STUDY HEART RATE BY TOOLS FROM COMPLEX NETWORKS*

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Heart rate measured as beat-to-beat time intervals varies in time. It is believed that time intervals between subsequent normal heart contractions carry information about the regulatory system of the heart. How to quantify such signals is not clear and because of that heart rate variability is still apart from the clinic routine. In the following, we propose a method for representing a heart rate signal as a directed network. Then we study the signal properties by complex network tools. The signals to study were collected from patients recovering after the heart transplantation. The aim is to classify the progress of adapting of the new heart — graft. Moreover, it is expected that the method allows for visual classification. Our investigations are preliminary, however the obtained results are promising.

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1. Introduction

Heart rate, measured as beat-to-beat time intervals, is not constant and varies in time. Each contraction is strongly influenced by autonomic nervous system. Vagal and sympathetic fibers — two branches of the autonomic nervous system, innervate the heart. Activity of neural cells modifies signal transduction between cardiac cells in many different aspects which in general lead to increase (sympathetic) or decrease (vagal) in the length of each heart cycle. It is believed that time intervals between subsequent normal heart

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contractions carry information about the regulatory system of the heart [1]. Moreover, it is possible to relate these signals properties with events affecting the cardiac regulatory system [2].

The heart transplantation breaks the autonomous control over the heart beating. It is said that the heart loses its variability. Whether cardiac reinnervation occurs after transplantation remains controversial [3] but progress in reinnervation is a survival prognosis. There are evidences that autonomic reinnervation occurs within a year after surgery [4].

The activity of the heart can be easy analyses thanks to the popular and easy measurement called ECG which provides the electrocardiogram. Each heart cycle is identified by the R peak on the electrocardiogram (R peak corresponds to the most evident change in the electric potential). The distance in time between two subsequent R peaks is assumed as the measure of the cardiac cycle. The sequence of such intervals is called RR series. However, since not every R peak corresponds to the proper heart contraction, a specialist labels (*i.e.* annotates) if a given R represents a normal contraction or it represents a contraction of the other type. Only intervals between two subsequent normal contractions are used in standard investigations of the heart variability. Such series are called NN signals.

Changes in NN signals have been investigated for more than a hundred years, basically by linear methods, see [1] for standards. Recently, thanks to the huge progress in our understanding of complex systems, non-linear approaches have been intensively developed [1, 5, 6, 7]. Most of these concepts are still away from clinical medicine with one exception. The so-called Poincaré plots — a graphical representation of a time series, where the values of each pair of successive elements from a signal defines a point in a Cartesian plane, are included into the clinical routine [8, 9, 10, 11, 12]. Roughly speaking, a Poincaré plot can be seen as an attractor of a dynamical system. The success of a Poincaré plot is partially due to the fact that main analysis can be performed by a simple visual inspection of the shape of the attractor.

In the following, we consider tools with roots in complex networks. Our aim is to estimate progress in adapting the new heart — graft, in patients recovering after the heart transplantation (HTX). At present, basic clinical methods involve tests which are sharply suffering. Therefore, developing other methods, especially of the non-invasive type, is extremely important. ECG recording is a non-invasive measurement and its ability to assess the autonomic regulation of the heart is believed. Our aim is two-fold: to test if one-hour ECG recording can be representative for the reliable assessment of the graft state, and to find an attractive graphical way which represent changes in the state of the graft when time is passing.

2. Method to represent NN-signal

34 ECG signals from 21 patients (3 signals from 1 patient, 2 signals from 11 patients and 1 signal from 9 patients) after heart transplantation and 12 from matching group of normal subjects without past history of cardiovascular diseases were collected. Data were recorded and digitized at 256 Hz using a Delmar Reynolds Holter monitoring system by 24 h ECG monitoring. Annotation files were manually corrected to exclude supraventricular and ventricular extrasystoles as well as artifacts.

A standard ECG recording provides values for NN-intervals with at least 128 Hz accuracy. Therefore, the set of NN-intervals, denoted by $\mathcal{N}$, is a discrete series. We shall note that $\mathcal{N}$ is finite $|\mathcal{N}| = N$ also, what allows to represent a sequence of NN-intervals $\mathcal{N} = \{nn_j\}_{j=1,\ldots,N}$ as a directed network, denoted as $\mathcal{NN}$-net:

- Let M be the number of different values in $\mathcal{N}$ ordered from the lowest to greatest value and denoted as $\{RR_i\}_{i=1,\ldots,M}$. The nodes of $\mathcal{NN}$-net are given the following labels

$$RR_1 = \min \mathcal{N} < \ldots < RR_i < \ldots < RR_M = \max \mathcal{N} .$$

- A directed edge between a pair of nodes (RR_i, RR_j) is established if these nodes are subsequent values in a sequence $\mathcal{N}$.

- If the subsequent elements in $\mathcal{N}$ have the same value then a loop is established at the corresponding node.

- By construction, there are multiple connections between nodes. Therefore, all edges and loops are attributed by weights — numbers of events which their represent.

It appears that the sequence $\mathcal{N}$ looks like wandering over the ordered set of nodes of $\mathcal{NN}$-net — the subsequent values from $\mathcal{N}$ are about to be neighboring in $\mathcal{NN}$-net. Therefore, for each RR_i we name its neighbors depending on the distance to i as follows, see Fig. 1:

— neighbors: $\{RR_{i-1}, RR_{i+1}\}$,

— next-neighbors: $\{RR_{i-2}, RR_{i+2}\}$,

— second-next-neighbors: $\{RR_{i-3}, RR_{i+3}\}$,

— others: $\{RR_j, |j - i| > 3\}$.

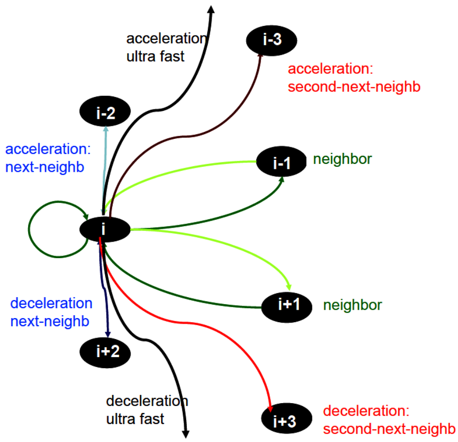

Fig. 1. An illustration of the notation used in the article to describe $\mathcal{NN}$-net.

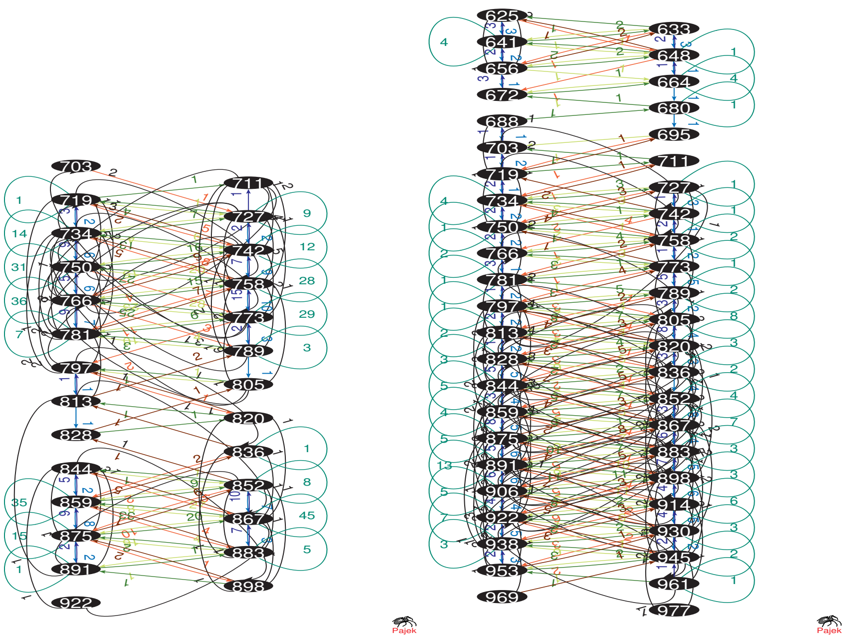

Fig. 2. Typical networks representing 1,000 subsequent NN-intervals received from a patient 13 years after HTX (left), and a healthy person (right). The node labels are NN intervals. By different edge colors: green (grey loops and connections between neighbors), blue (straight lines connecting next-neighbors), red (straight lines connecting second-next-neighbors) and black (curved lines representing all remaining transitions) different types of transitions between neighbors in $\mathcal{NN}$-net are coded. Diagrams are received thanks to [13].

In Fig. 2 two examples of networks are shown. They are constructed from sequences of 1 000 points. Node labels denote the lengths of particular NN-intervals, edge labels describe numbers of corresponding events. The transitions among different classes of neighbors are coded by different colors: green, blue, red, black, respectively. Notice that the graph structures can be compared to a linear network where the network order coincides with the node labels order. Because of that observation, in the following, the networks are presented in the form of a ladder. The networks are plotted with the help of `Pajek 1.26` software [13].

Fig. 2 is provided also to compare a typical network received from ECG of a healthy person to a network representing a heart rate of a patient which is 13 years after heart transplantation. It appears that even after so many years after HTX the network is evidently distinct from a network describing a healthy man rhythm.

3. Properties of $\mathcal{NN}$-nets

Let us concentrate on networks constructed from 5 000 subsequent points. Such amount of data covers approximately one hour of a ECG recording. Having 24-hour recordings we could, at first, study the representativeness of one hour recordings. Results of statistical characteristics of basic properties of one-hour networks for each person separately are collected in Sec. 3.1. Then, the graphical method to show the one hour network is proposed (Sec. 3.2). Finally, the presence of subsequent accelerations and decelerations are investigated in order to get information about the emergence of respiratory sinus arrhythmia — the strongest autonomic regulation in the case of the healthy heart rate.

In the analysis we considered networks resulting from 5 000 NN-intervals received from ECG signal where the first 5 000 points were skipped to avoid signals which are related to the adaptation of a patient to the Holter equipment attached to his/her body.

3.1. Statistical properties of one-hour networks

The first and evident difference between healthy people heart rate and the heart rate of patients after HTX is in number of nodes in the received networks, see Fig. 2. The analysis of the mean values of nodes in networks constructed from 5 000-length pieces of 24-hour recordings is plotted in Fig. 3 (top). The data is arranged according to the period of time passed after HTX. The first 3 letters of the data label code the patient. The last 3 numbers in the label denote time after HTX in months. So, we discuss signals received from patients being from two weeks to 156 months after HTX. The data of a healthy person is denoted by a gender (w — a woman, m — a man) and his/her age in years. The total mean of all healthy people is denoted as HEALTHY.

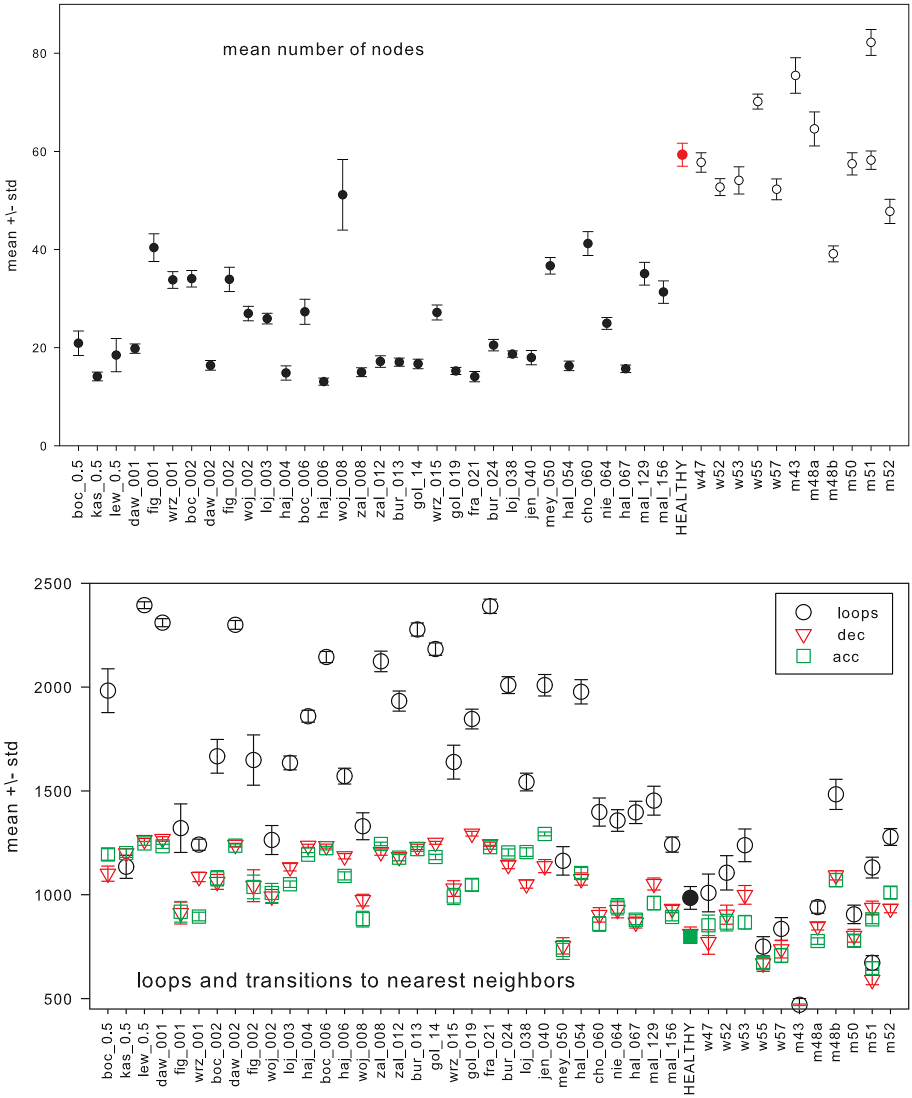

Fig. 3. Mean values of number of nodes (top), number of loops and transitions to nearest neighbors (bottom) in a one-hour network. The statistic (mean ± std error) is done according to 24-hour recording. Results from patients are arranged according to time passing after transplantation, then healthy people data is plotted. The red dot (black dot with label HEALTHY) in the top figure represents the mean of the group of healthy. The filled marks in the bottom figure denote the means of the group of healthy.

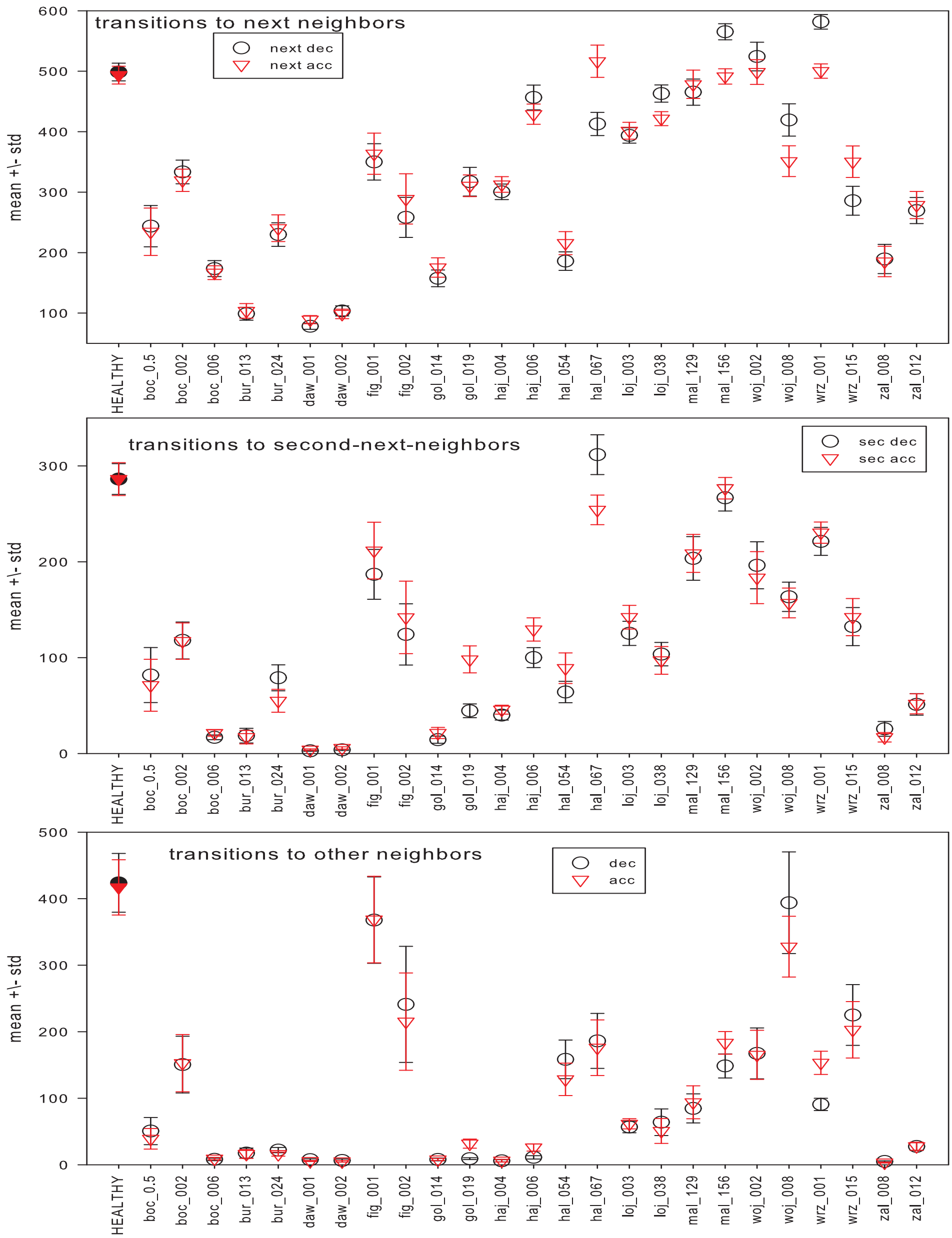

Fig. 4. Mean values of (from the top) number of transitions to next neighbors, second-next-neighbors, and other nodes in a one-hour network received from 24-hour recording. Results are arranged according to a patient, the mean value for a healthy person is plotted at HEALTHY label.

From Fig. 3 (top), one can see that even years after the operation the diversity of NN values is two times smaller than in the case of a typical healthy man. Moreover, this diversity does not appear to change in a systematic way with time passing what disables this characteristics from the diagnostic usage.

The number of loops and transitions to the nearest neighbors seems to have slightly better properties for the prognostic purpose, see Fig. 3 (bottom). After 5 years after HTX the significant decrease in presence of these events is observed. Notice, that the mean number of loops is still about 1.5 times greater than in a healthy man rhythm. Unfortunately, this characteristics does not differentiate patients that are just few months after HTX.

There are many reasons why a person is qualified for the heart transplantation. The basic disability is related to deficiency in the blood delivery to other parts of the body, and to the heart itself. However, usually this is caused by impairment of other organs. Therefore, the results that characterize changes that appear due to the time passed after HTX only cannot be satisfactory. However, if these changes in time are observed for each person separately, we can find indicators whether the recovery goes towards the right direction, namely, to the healthy individual characteristics. Therefore, the other network properties: transitions to next- second- and other neighbors, are presented after ordered them according to a patient, see Fig. 4. Such follow-up studies allow to divide patients into two groups: heart rate changes go towards values typical for a healthy man, or not. The systematic change in the number of transitions to the next-neighbors and second-next-neighbors with time passing after HTX, when we observe progress in each patient individually, seems to indicate at the proper index of recovery.

3.2. One-hour network

By plotting a network of transitions we should get a tool for a quick evaluation of the dynamics of a given heart rate. But at the increasing number of points to plot, readability of a network established in the way as in Fig. 2 is lost. By many trials we found that the following network plots are the most illustrative for heart rate dynamics, and the most eye catching:

(a) the ladder order of verticies is modified by shifting to the center of a graph every second horizontal step;

(b) the edge labels are visualized by the edge width but, because of the huge variability among edge labels, each label is represented by its square root;

(c) in order to emphasize the presence of transitions to the next-neighbors and second-neighbors, the signal is shown by two networks: as the complete graph and as a graph where loops and transitions to neighbors are omitted.

As consequence of (b) we lose an easy insight into the direct relationships between different edges. However by comparing the widths of edges we still can comfortably distinguish important edges from others. Thanks to (a) and (c) the changes in RR significantly different from each other are visible.

In Fig. 5 a typical network for a healthy person is plotted. The complete network is shown on the left. This network can be seen as a core consisting of about 40 nodes, where loops and edges to the neighbors are almost uniformly distributed. The presence of other transitions is also visible but hardly. The network on the right does not contain loops and changes to the neighbors — green edges. Again a uniform structure of transitions to the next-neighbors (blue) and the second-next neighbors (red) is noticeable.

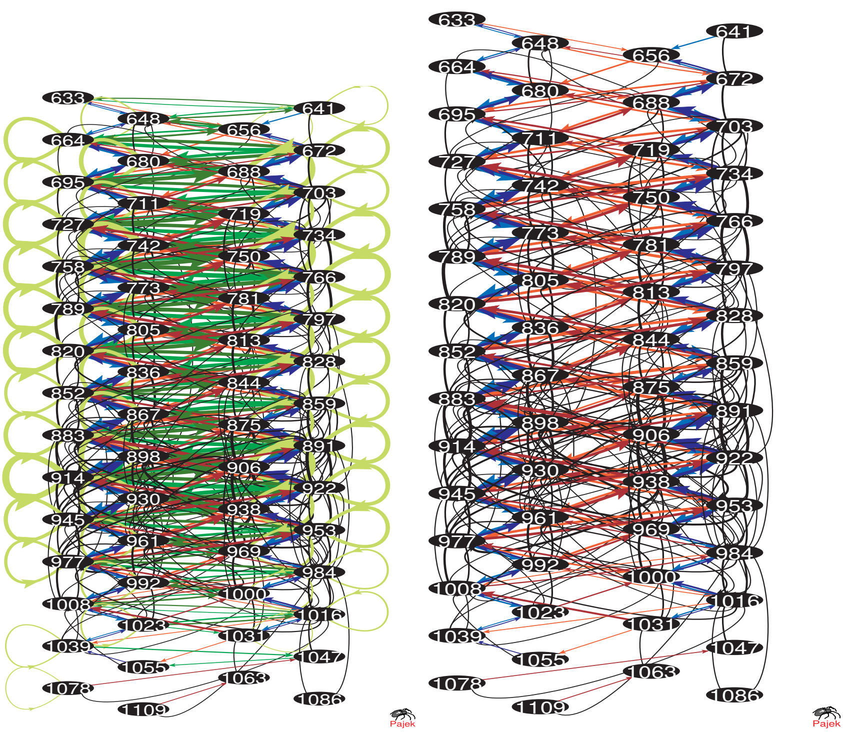

Fig. 5. Double network representation of one hour heart rate for patient `m52` complete (left) and without green (grey loops and connections between neighbors) edges (right).

To estimate the progress in adapting of the new heart we propose to compare networks received from two recordings separated by at least a month. In Figs. 6–9 we show networks received from recordings from patients which were shortly after HTX. The left figures correspond to the earlier moment of time.

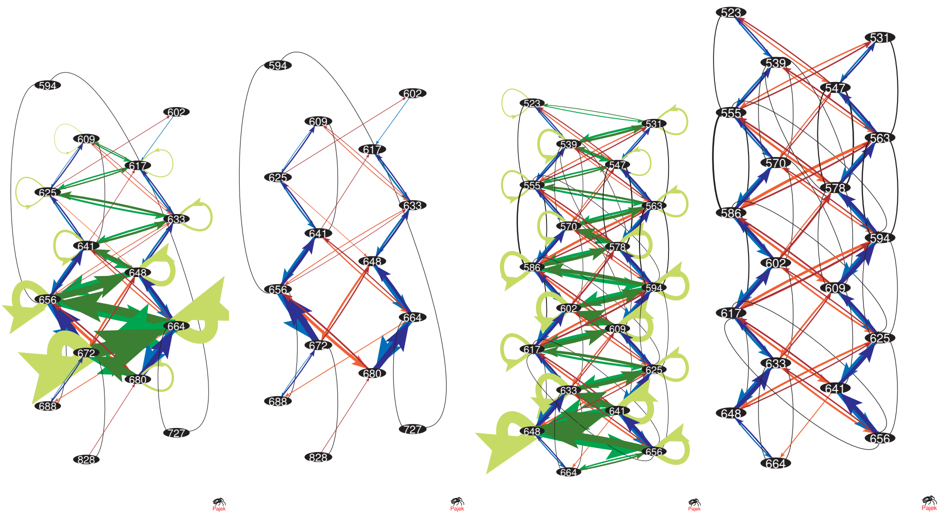

Fig. 6. Double network representation of the heart rate changes after HTX of the patient `haj`: `haj_004` (left) and `haj_006` (right).

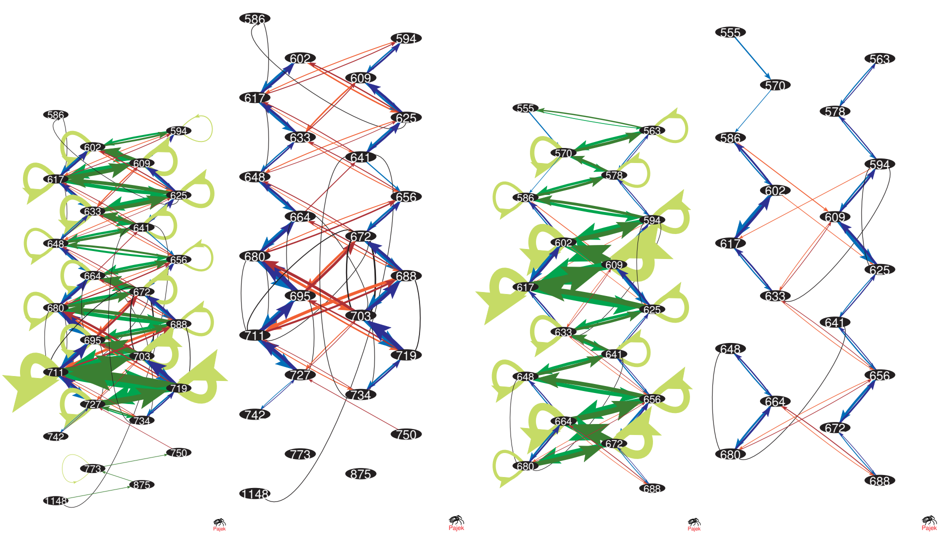

Fig. 7. Double network representation of the heart rate changes after HTX of the patient `boc`: `boc_002` (left), and `boc_006` (right).

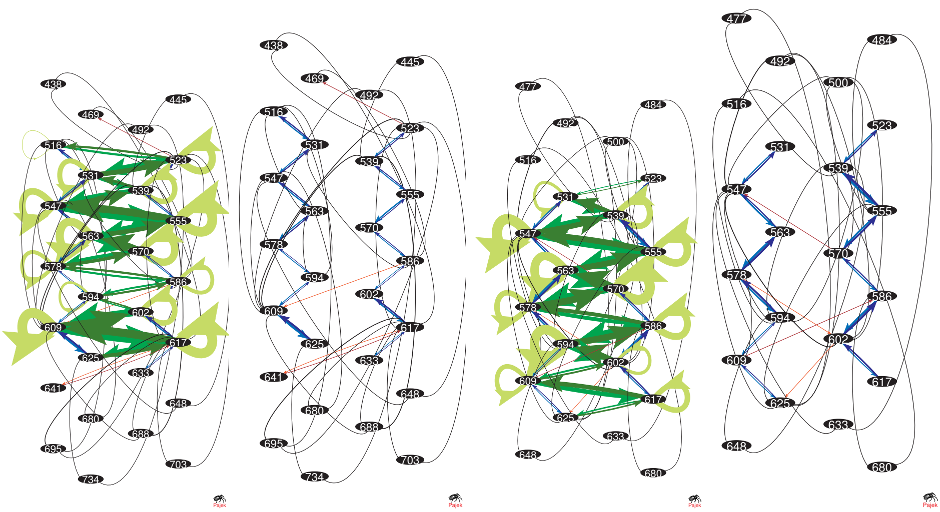

Fig. 8. Double network representation of the heart rate changes after HTX of the patient `daw`: `daw_001` (left) and `daw_002` (right).

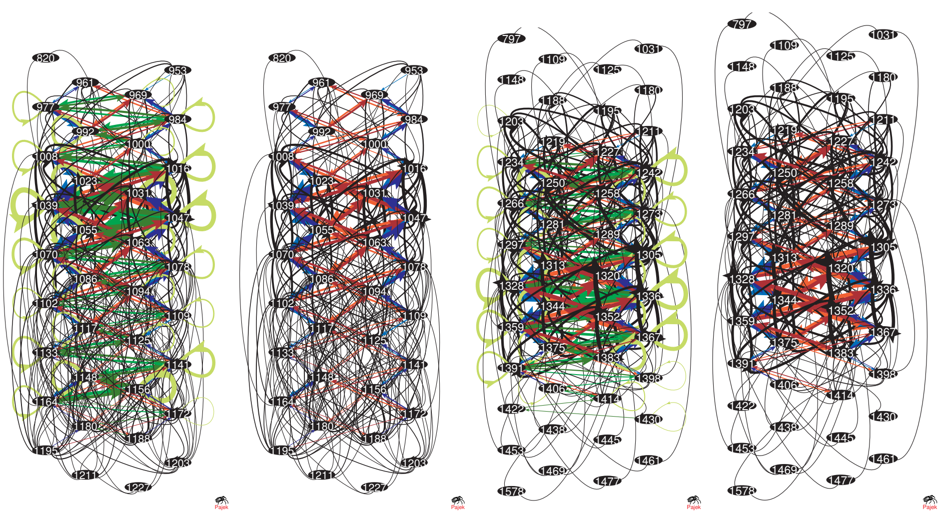

Fig. 9. Double network representation of the heart rate changes after HTX of the patient `fig`: `fig_001` (left) and `fig_002` (right).

The increasing complexity is evident in the case of a patient `haj`, Fig. 6 and, the evident loss of complexity is found for a patient `boc`, Fig. 7. There is not any obvious change in the networks representing the heart rate dynamics of the patient `daw`, Fig. 8. The dynamics of the patient `fig`, Fig. 9 looks like dominated by flights — transitions to rather distant nodes. But the transitions to next neighbors and second- next neighbors are also largely present. However, this patient heart rate dynamics differs from the healthy one significantly because the node labels are extraordinary large, namely RRs are about 1 000 milliseconds (the labels are readable after zooming the electronic version of plots).

3.3. Double-events statistics

Respiratory sinus arrhythmia (RSA) describes changes in a heart rate which are related to the breathing cycle. RSA is the primary natural reason for heart rate variability in a healthy man. During inhalation the heart accelerates, and during exhalation decelerates. This phenomena is often related to the autonomic regulation. Therefore, by considering subsequent events of accelerations and decelerations we can observe the emergence of autonomic control after HTX. The following subsequent events we found as good indicators which identify variability due RSA:

- no change $RR_i \to RR_i \to RR_i$,
- slow accelerations: $RR_i \to RR_{i-1} \to RR_{i-2}$
  or decelerations $RR_i \to RR_{i+1} \to RR_{i+2}$,
- middle fast accelerations:
  $RR_i \to \{RR_{i-1}, RR_{i-2}\} \to \{RR_{i-3}, RR_{i-4}\}$
  or $RR_i \to \{RR_{i-3}\} \to RR_{i-4}$
  and corresponding middle fast decelerations
  $RR_i \to \{RR_{i+1}, RR_{i+2}\} \to \{RR_{i+3}, RR_{i+4}\}$
  or $RR_i \to \{RR_{i+3}\} \to RR_{i+4}$,
- fast accelerations:
  $RR_i \to \{RR_{i-2}, RR_{i-3}\} \to \{RR_{i-5}, RR_{i-6}\}$
  or $RR_i \to \{RR_{i-1}, RR_{i-4}\} \to RR_{i-6}$
  and corresponding fast decelerations
  $RR_i \to \{RR_{i+2}, RR_{i+3}\} \to \{RR_{i+5}, RR_{i+6}\}$
  or $RR_i \to \{RR_{i+1}, RR_{i+4}\} \to RR_{i+6}$.

In Fig. 10 we show the mean counts calculated from our data. The results are ordered by a patient. At the label HEALTHY the mean value is plotted for a healthy person. We see that for each person when time is passing the value of the particular property goes towards or against the value of a healthy man. Notice that all indices go in the proper direction in the case of patient `haj`, and all of them go oppositely in the case of patient `boc`. Considering the patient `daw` we observe the right direction of changes in the number of double slow transitions. In case of patient `fig` all double-event counts go wrongly, suggesting that the huge variability observed is rather of different origin.

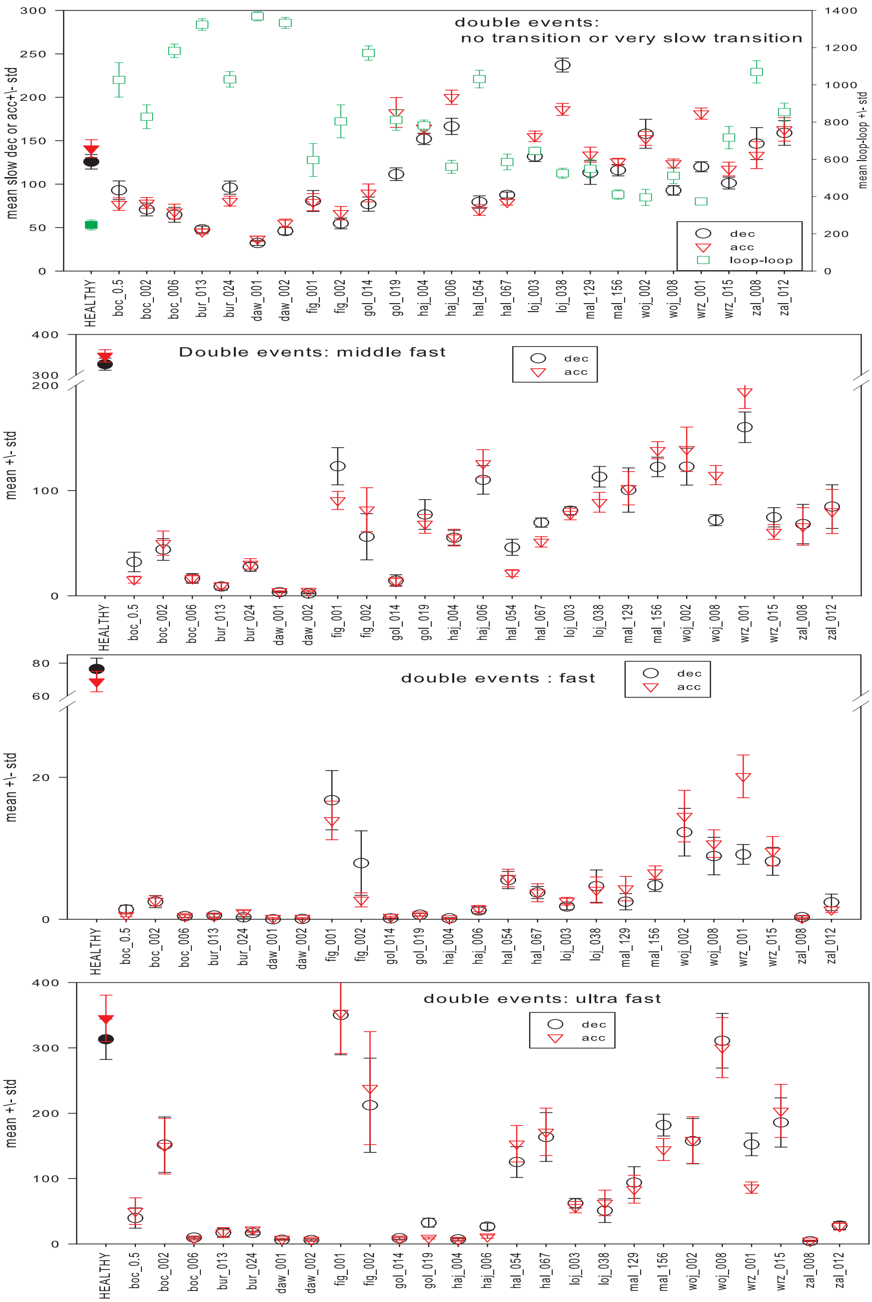

Fig. 10. Mean ± standard deviation error values of counts of double events for a one-hour ECG recording, received from 24-hour recording.

The observations from double-event statistics can be compared to results received by the method called symbolic dynamics. From such considerations we know [14] that the slow dynamics denotes the increased sympathetic modulation and vagal withdrawal. The increase of cardiac parasympathetic modulation effects as appearance of larger changes.

4. Summary and discussion

An early detection of the beginning of rejection is crucial for redirecting the process and patient survival. Therefore, it is of highest interest to determine patterns which allow to separate effects of the proper reinnervation of the heart from development of the rejection process. By visualizing the dynamic dependences between subsequent heart contractions, we received a method for the assessment of reestablishing of autonomic control in the myocardium. We have found that changes in the heart rate of the patients: `bur, haj, hal, gal, loj, mal, zal` develop properly, namely go toward characteristics of a typical healthy man. For some other patients (here: `boc, fig, woj, wrz`) the opposite direction of changes is noticed. It appears that our results agree with the clinical observations. Two patients (`boc` and `woj`) had died because of the rejection of the graft while for the two others the worsening of their clinical state was observed at the time of Holter recording.

Our considerations are only preliminary. We hope that deeper analysis of networks should allow to put forward the problem of differentiation between properly developing cooperation of the body and the graft from discovering a possible rejection.

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REFERENCES

[1] Heart Rate Variability. Standards of Measurement, Physiological Interpretation, and Clinical Use Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology, *Circulation* **93**, 1043 (1996).

[2] E. Buccelletti *et al.*, *Eur. Rev. Med. Pharmacol. Sci.* **13(4)**, 299 (2009).

[3] I. Izrailtyan *et al.*, *J. Thorac. Cardiovasc. Surg.* **120**, 737 (2000).

[4] D.A. Murphy *et al.*, *Ann. Thorac. Surg.* **69**, 1769 (2000).

[5] J. Yasha Kresh, I. Izrailtyan, A.S. Wechsler, *InterJournal Complex Systems* **221**, (1998).

[6] A. Dudkowska, D. Makowiec, *Physica A* **336**, 174 (2004).

[7] D. Makowiec *et al.*, *Physica A* **388**, 3486 (2009).

[8] M.A. Woo *et al.*, *Am. Heart J.* **123(3)**, 704 (1992).

[9] C. Lerma, O. Infante, H. Perez-Grovas, M.V. Jose, *Clin. Physiol. Func. Im.* **2003**, 72 (2003).

[10] J. Yasha Kresh, I. Izrailtyan, *Am. J. Physiol. Regulatory Integrative Comp. Physiol.* **275**, 720 (1998).

[11] P.W. Kamen, A.M. Tonkin, *Internal Medicine J.* **25**, 18 (2008).

[12] J. Park, S. Lee, M. Jeon, *BioMedical Engineering OnLine* **8**, 38 (2009).

[13] V. Batagelj, A. Mrvar, *Pajek — Program for Large Network Analysis*, home page: `http://vlado.fmf.uni-lj.si/pub/networks/pajek/`

[14] S. Guzzetti *et al.*, *Circulation* **112**, 465 (2005).