COST EMF - MED (Action BM1309):
European network for innovative uses of EMFs in biomedical applications

STSM Report:

Non-linear modeling of the body's response to vagus nerve stimulation

Researcher: Ryszard S. Gomółka, PhD. email: rgomolka@ibib.waw.pl

Home Institution: Nalecz Institute of Biocybernetics and Biomedical Engineering Polish Academy of Sciences, Poland.
Contact: Ryszard S. Gomółka, PhD. email: rgomolka@ibib.waw.pl

Host Institution: Institute of Electrodynamics, Microwave and Circuit Engineering Technische Universität Wien, Austria.
Contact: Ao.Univ.Prof. Eugenijus Kaniusas. email: kaniusas@tuwien.ac.at
Dipl.-Ing. Stefan Kampusch. stefan.kampusch@tuwien.ac.at

STSM Reference: ECOST-STSM-BM1309-37233

STSM dates: FROM **19th April 2017** TO **28th April 2017**

Abstract:

Analysis of heart rate variability (HRV) is frequently applied to assess the autonomous nervous system (ANS) activity. Since the activity of sympathetic and parasympathetic ANS is difficult to evaluate with standard linear methods, we proposed an application of Higuchi fractal dimension (HFD) algorithm for assessment of the ANS action.
The aim of the present COST STSM was to evaluate whether, based on HRV sequences analysis, HFD is able to: 1) discriminate healthy subjects from patients with diabetes mellitus type II; 2) assess the ANS activity in normal and diabetic conditions; 3) prospectively provide the information about the current ANS activity in patients subjected to percutaneous auricular vagal nerve stimulation.

List of abbreviations:

ANS - autonomous nervous system
HFD - Higuchi fractal dimension
HRV - heart rate variability
SD - standard deviation
VNS - vagal nerve stimulation

A. Purpose of the STSM

The main purposes of the Short Term Scientific Mission of Ryszard Gomolka in the Biomedical Sensing Group head by Prof. Eugenijus Kaniusas at the Institute of Electrodynamics, Microwave and Circuit Engineering of Vienna University of Technology in Austria were:

1) training in the field of vagus nerve stimulation (VNS) and application of the VNS in treatment of diabetic foot ulcers (diabetes mellitus type II) and spasticity;

2) development and application of computational methods for estimation of a degree of sympathetic and parasympathetic autonomous nervous system (ANS) activity during neuromodulation of vagus nerve.

Project proposal has been initiated during the last COST EMF-MED meeting in Warsaw, on 14-17.02.2017, during the workshop on the VNS. The STSM project was accepted by the COST Committee on 20 March 2017.

B. Work Description

Introduction

Analysis of heart rate variability (HRV) states a common tool for assessment of autonomous nervous system (ANS) influence on regulation of heart and frequently gives information about pathophysiological changes appearing in various diseases. Based on evaluation of HRV, the Biomedical Sensing Group of Vienna University of Technology has recently suggested that percutaneous auricular vagal nerve stimulation (VNS) positively alters the ANS by activation of its parasympathetic branch**.** However estimation of a relative sympathetic and parasympathetic ANS activation is necessary for accurate and controllable regulation of the VNS, the task is difficult to achieve with standard linear methods.

The Group conducted by Prof. Wlodzimierz Klonowski at the Nalecz Institute of Biocybernetics and Biomedical Engineering Polish Academy of Sciences proposed an application of Higuchi fractal dimension (HFD) method**,** for assessment of the ANS activity. Hence, the aim of our research was to estimate whether, based on HRV sequences analysis, HFD is able to: 1) discriminate healthy subjects from patients with diabetes mellitus type II; 2) assess the ANS activity in normal and diabetic conditions; 3) provide information about the current ANS activity in patients subjected to percutaneous auricular vagal nerve stimulation.

Materials and methods

All calculations and statistical analyses were performed by means of MATLAB®/2016b.

Patients and HRV signals

We retrospectively investigated 45 artifacts-free RR time series, of approximately 84 minutes duration each, from an open-label pilot study registered at ClinicalTrials.gov (no. NCT020984447), approved by the local ethics committee of The University of Vienna (Austria, no. 1924/2013). The results of the study are currently in review in a scientific journal. The RR time series were recalculated from ECG recordings originally obtained from 9 healthy (H) and 5 diabetic (D) subjects with clinically confirmed long-term diabetes mellitus type II, and diabetic foot ulcer (ulcus cruris) lasting for more than 6 weeks. The original ECGs were acquired by means of MP36 recording system (BIOPAC Systems Inc., CA USA) between 24.12.2014 and 03.04.2015, for further calculation of HR and HRV signals. Each of the H and D subjects underwent four consecutive stimulation sessions of two different stimulation patterns applied twice in a random order during four days. Therefore, each of the time series consisted of five consecutive phases: B- baseline measurement (10 min), S1- first VNS (22 min), P1- baseline measurement after the first VNS (20 min), S2- second VNS (22 min), P2- baseline measurement after the second VNS (10 min).

Higuchi fractal dimension algorithm

Calculations were performed by means of an in-house implementation of the HFD algorithm in Matlab 2016b. The HRV signal was analyzed in 100 samples window (approximately 1.5 min) displaced by a 50 consecutive samples across the signal, which resulted in having 99 HFD values for each of the RR time series. Subsequently, the following tasks were performed:

1) estimation of the optimal 'k_{max}' parameter of the HFD, allowing clear identification between the HRV signal from H and D subjects;

2) computation of aggregated distributions of HFD values in H and D groups separately;
3) application of the Shapiro-Wilk normality test, to confirm non-normal distribution of the HFD values;
4) calcualtion of percentiles, means, medians, standard deviations, skewness and kurtosis from the HFD aggregated distributions from H and D, for subsequent comparison;
5) comparison of mean representative vectors of HFDs(t) from H and D, by means of Wilcoxon matched-pairs signed rank test;
6) comparison of the mean HFD values in the B, S1, P1, S2 and P2 phases of the experiment, by means of two-way analysis of variance (ANOVA);
7) comparison of aggregated distributions of HFD values between the experiment phases.

C. Results

Task 1. The optimal k_{max} parameter, allowing clear differentiation between H and D groups, was found as 5 (Figure1A, B). The mean values of HFDs aggregated from H and D time series were found as the most statistically different for k_{max}=5, by means of two-sided Wilcoxon ranksum test (p<7.97e-25).

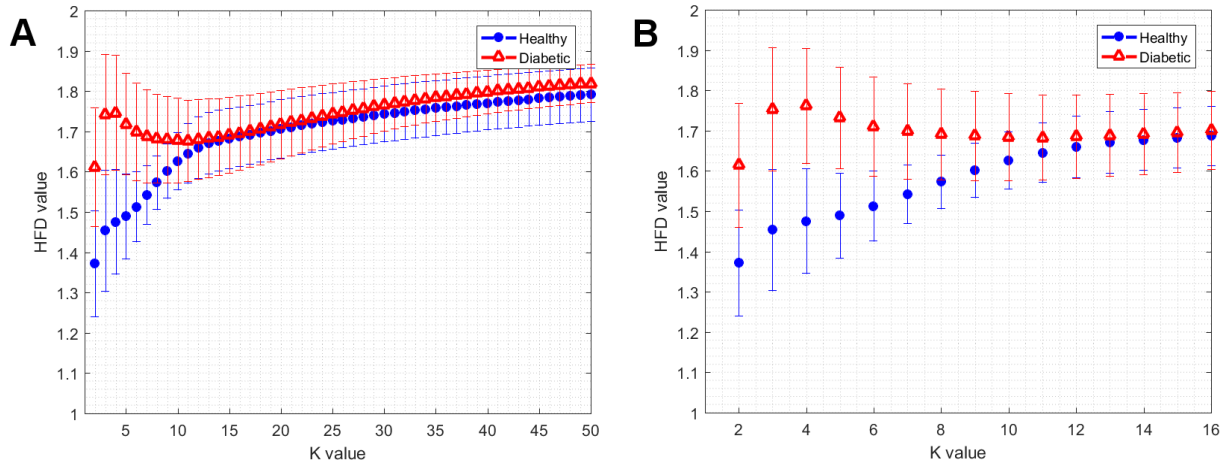


Figure 1
HFD values, in function of k_{max} parameter, calculated in 45 RR time series of healthy and diabetic subjects: A - for k_{max} from 2 to 50; B - for k_{max} from 2 to 16.

Tasks 2 - 4. Shapiro-Wilk normality test revealed that HFD values, aggregated jointly from H and D subjects, do not form a normal distribution (W=0.9745, p<0.05). Characteristics of HFD aggregated distributions (i.e. 5th, 25th, 75th and 95th percentiles, means, medians, SDs, skewness and kurtosis) are presented in the Table 1 ('Overall').

Task 5. Wilcoxon matched-pairs signed rank test revealed statistical differences between the mean HFD(t) values in H and D (W=4950, 99 pairs, p<0.0001). The mean(median) difference between H and D was 0.226(0.230). Absolute Pearson's linear correlation coefficients between the mean HFD(t) values and the time was larger in D (r=-0.56, p<0.0001), than in H group (r=-0.44, p=0.0002; Figure 2).

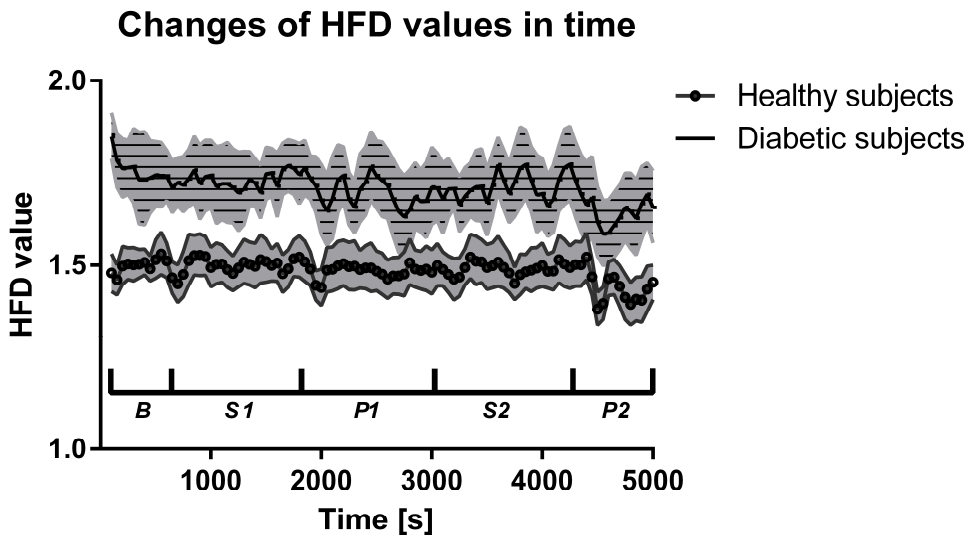


Figure 2
Mean±95% confidence intervals of HFD values during the course of experiment, for H and D separately. B, S1, P1, S2, P2 - phases of the experiment.

Task 6. Two-way ANOVA showed significant differences between the mean HFD's from different experiment phases, in H and D subjects. The differences were visible between the H and D groups ($F(1, 43)=60.79$, $p<0.0001$), and between the experiment phases ($F(4, 172)=10.80$, $p<0.0001$). Bonferroni's multiple comparisons test showed significant differences in mean HFD valuesbetween B and P2, S1 and P2, and S2 and P2 phases both in H ($p<0.05$, $p<0.01$ and $p< 0.05$, respectively) and D ($p<0.001$, $p<0.01$ and $p< 0.05$, respectively) groups. The mean HFD values were significantly different between H and D among all of the phases (largest $p<0.05$) except the P2 in D subjects, which was not different from B, S1 and S2 in H (Figure 3).

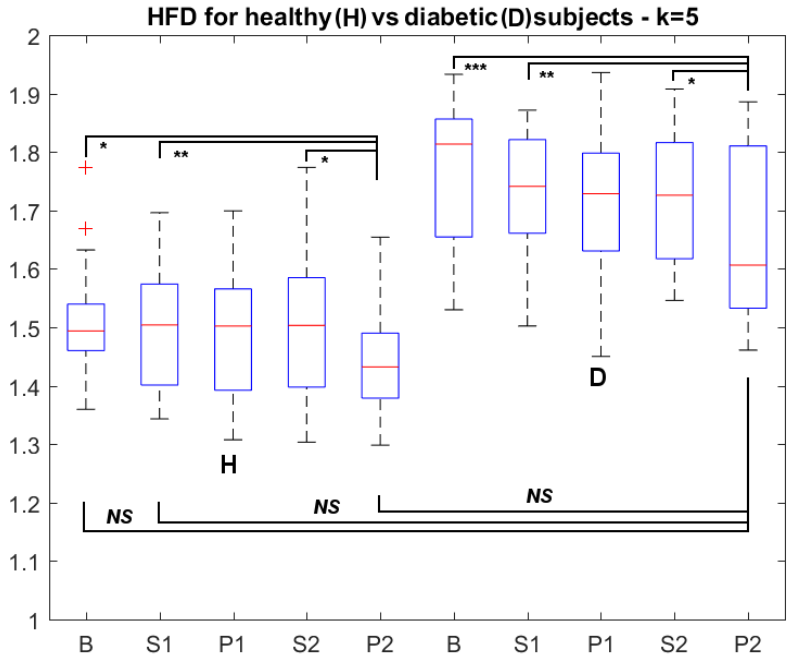


Figure 3
Whiskers-box plot for HFD values aggregated in respect to the phase of experiment, for H and D separately. Whiskers represent the range of min-max HFD values. B, S1, P1, S2, P2 - phases of the experiment.

Task 7. In total, all of the HFD distributions jointly were computed based on 4455 HFD values. Overall mean(median)±SD HFD values were found as 1.49(1.48)±0.14 and 1.72(1.73)±0.17 for H and D, respectively. In D subjects, skewness of aggregated HFD distributions was observed to changed from negative (-0.64) to

positive (0.18) between the experiment phases (r=0.98, R^2=0.96). The opposite, but not monotonic effect was observable in the H group (Table 1).

Table 1. Numerical characteristics of HFD aggregated distributions for the B, S1, P1, S2, P2 phases, in H and D subjects. SD - standard deviation.

	H (healthy subjects)						D (diabetic subjects)					
	Overall	B	S1	P1	S2	P2	Overall	B	S1	P1	S2	P2
5th percentile	1.29	1.34	1.30	1.28	1.29	1.26	1.42	1.45	1.44	1.37	1.44	1.37
25th percentile	1.38	1.42	1.39	1.37	1.38	1.33	1.60	1.65	1.64	1.59	1.59	1.51
75th percentile	1.59	1.57	1.61	1.59	1.59	1.55	1.85	1.92	1.85	1.83	1.85	1.80
95th percentile	1.76	1.75	1.75	1.76	1.78	1.70	2.00	2.00	1.98	1.98	2.00	1.99
Mean	1.49	1.50	1.51	1.49	1.50	1.45	1.72	1.77	1.74	1.71	1.72	1.65
Median	1.48	1.49	1.49	1.48	1.48	1.43	1.73	1.77	1.76	1.72	1.72	1.63
SD	0.14	0.12	0.14	0.15	0.15	0.15	0.17	0.17	0.16	0.18	0.17	0.19
Skewness	0.42	0.75	0.33	0.42	0.52	0.37	-0.30	-0.64	-0.53	-0.38	-0.12	0.18
Kurtosis	2.80	3.48	2.42	2.48	2.83	3.35	2.44	2.99	2.87	2.59	2.27	2.17

Discussion

This study advances our knowledge in application of Higuchi's fractal dimension algorithm for analysis of heart rate variability (HRV) in healthy (H) and diabetic (D) subjects. By means of an in-house implementation of Higuchi's method, overall mean±SD of aggregated HFD values were found as 1.49±0.14 and 1.72±0.17, for H and D respectively. Significant difference in mean values of HFD aggregated distributions was found between the B, S1 and P2 phases both in H and D. It is worth to note, that the mean HFD from P2 in D was found as not different from that from B, S1 and P2 phases in H group (Figure 3). Moreover, skewness of the aggregated HFD distributions was rising significantly from negative to positive between the phases in D, while a clear trend was not observable in H (R^2=0.96, $p<0.01$ vs. R^2=0.29, $p=0.35$, for D vs. H).

Our results indicate a slight VNS-induced shift of HFD values from assembled close to 2 to lower values, in D. The shift was observed mostly for the HFDs above the 50th percentile of distribution and was confirmed by the change in the distribution's skewness and kurtosis (Table 1). In contrary, the VNS seems to affect the whole distribution of the HFD values equally in H but the shape of HFD distribution was not changing substantially over the experiment. As higher HFD values correspond to the presence of higher frequencies in the signals Fourier spectrum, our observations would suggest that VNS may increase the parasympathetic and decreases the sympathetic activity of ANS in diabetic conditions. It is worth to note that due to neuropathy a lower parasympathetic and lower sympathetic activity is generally observed in diabetes, compared to normal conditions.

As diabetic subjects are characterized by a lager SD of HFD values in all of the experiment phases ('more chaotic' RR signal), the VNS seems to have a 'fine-tuning' effect on their ANS activity. The effect in H is much weaker, but the VNS seems to alter here ANS activity in a different manner - within the range of auto regulation capabilities of the subjects.

Conclusion

We have shown that the HFD is able to assess the activity of ANS and differentiate healthy from diabetic subjects, based on HRV signal. Our result have potential implication on patients' care and application of the VNS.

D. Future collaboration with host institution

Further research on application of Higuchi's fractal dimension for assessment of HRV in normal and pathophysiological conditions is planned after conclusion of the STSM. As the STSM was constrained by the 10 days period, also an application and adaptation of a human body model from Pan Q. et al. considering VNS is planned as one of the topics for future collaboration.

E. Expected Publications

The results of the research carried during the STSM are planned to be jointly submitted and published in a peer-reviewed journal related to physiology, regulation of cardiovascular system or biomedical engineering, i.e. the 'Autonomic Neuroscience: Basic and Clinical' journal (IF=1.62). The submission will take place within 30 days after conclusion of the STSM.

F. Other Comments

Comment by RyszardS. Gomolka:

I would like to express my sincere gratitude to Ao. Univ. Prof. Eugenijus Kaniusas for a great hospitality, possibility of collaboration on a very interesting project of VNS, and introduction into the scientific procedures and experiments conducted in the Biomedical Sensing Group at the Technische Universität Wien. I would also like to express my thankfulness to Univ. Ass. Dipl.-Ing. BSc Stefan Kampusch for sharing and introducing into the data and into the latest, yet unpublished, results of research. Special thanks to Dipl.-Ing. Florian Thürk for many possibilities of scientific talk and very good scientific time spent at work. At the end, I would like to thank to all of the Collaborators jointly for keeping in touch before my arrival and many discussions.

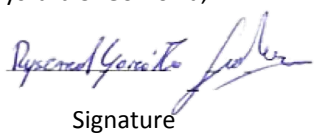
Confirmation by the host institution of the successful execution of the STSM:

We confirm that Ryszard Gomolka has performed the research work as described above.

Ao.Univ.Prof. Eugenijus Kaniusas

Signature

Ryszard S. Gomolka, PhD



Signature