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EDITORIAL

Waves, oscillations and optics in biomedical engineering: research in the Department of Biomedical Engineering 1994–2014

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Abstract. In this historical review the main topics of research in the Department of Biomedical Engineering of the Technomedicum of the Tallinn University of Technology are discussed.

Key words: coherent photodetection, microwave radiometry, microwave effect, brain oscillations, pulse wave, biofluid optics.

1. INTRODUCTION

The Department of Biomedical Engineering (DBME) of the Technomedicum of the Tallinn University of Technology (TUT) was formally created as the Centre of Biomedical Engineering on 15 March 1994. The DBME celebrates its 20th anniversary in this year.

Biomedical engineering is a branch of science employing the principles of exact sciences and engineering methods in medicine and biology for diagnostic and therapeutic purposes. The DBME was based on the Chair of Radio and Laser Engineering of the Department of Radio Engineering. Therefore, it is essential that the research directions in the department follow previous study lines: electromagnetic waves, oscillations, and optics.

The DBME has been involved in an Estonian Centre of Excellence in Research, the Centre for Nonlinear Studies (CENS), during 2002–2007 and is currently involved in the Centre for Integrated Electronic System and Biomedical Engineering during 2008–2015.

2. INTERACTION OF WAVES IN LASER NONLINEAR ACTIVE MEDIUM

Last decades of the 20th century was the time of intensive development of laser technology and its implementation in telecommunication and measurement. The principles and methods for development of microwave devices were and are still fruitful for applications in coherent optics. The principle of heterodyne detection, very common for coherent detection in microwave receivers, requires high phase stability of the waves from the signal source and local oscillator. Therefore, application of coherent detection in optical region, at much shorter wavelengths, is highly complicated. The published studies reported first successful attempts of coherent photodetection using infrared lasers, particularly CO_2 lasers at 10.6 μ wavelength. Nobody has realized coherent photodetection in visible region.

Our experiments with a HeNe laser at 0.63 μ discovered an interesting phenomenon in visible region [1,2]. Reflecting a laser beam from a moving mirror back to the laser resonator, the signal at Doppler frequency was easily detectable. The unexpected simple realization of coherent photodetection might be explained only by the interaction of the reflected and initial laser radiations inside the laser tube [1]. Obviously, two waves, propagating simultaneously in the laser active medium, became synchronized. Most remarkable is that the Doppler signal was detectable even without an external photodetector using a wire, located parallel to the tube. We tried to explain this phenomenon as interaction of waves due to the nonlinearity of the laser active medium [1]. The coherent photodetection occurred at distances from the reflecting or scattering target much longer compared to the coherence length. The physics of the phenomenon was not fully understood.

The simple method of selfmixing in the laser resulted in various application ideas. Most promising were methods for the detection of small particles and pollutions aerosols [2–4]. We studied also a Gunn diode based self-oscillating mixer at microwave frequencies [5]. The effect of selfmixing in diode lasers was employed further for the detection of pulse wave parameters and find application in cardiovascular diagnostics [6,7].

Coherent photodetection with a laser was the topic of the PhD thesis by Kalju Meigas (supervisor H. Hinrikus), defended in 1997 as the first thesis in the department. Kalju Meigas is now Professor of biomedical engineering, Director of the Technomedicum of TUT.

3. MICROWAVE RADIOMETRY

The energy of thermal radiation is determined by the temperature of the radiation source and its radiation coefficient. Microwave radiometry, implemented in radioastronomy, is a passive technique for measuring thermal radiation, emitted by an object. The principle of noncontact measurement of temperature can be also adopted for clinical use. The application of microwave radiometry for early detection of cancer is based on the difference of the temperatures between cancerous and healthy cells. The anomalies in tissue temperature appear before morphological changes. The use of microwave radiometry as a noninvasive, passive technique for the early detection of cancer appears promising. However, wider acceptance of the method for diagnostics still awaits fundamental improvements in important and nontrivial problems of the antenna and interpretation of the radiometric signals in inhomogeneous medium.

A quasi-zero method of the radiometric measurement, which uses a probe with two identical antennas, was applied in the radiometer, developed in DBME. The 4.5 GHz Dicke radiometer was developed in cooperation with the companies MITEQ (NY, USA) and MITEQ Eesti (Tallinn, Estonia) [8,9]. The analysis of the signal flow over the antenna–tissue interface showed that a probe with two identical waveguide antennas, positioned close to each other against the tissues, eliminates the error caused by reflections [10]. The applied balanced measurement method significantly simplifies the hardware of the radiometer.

Fig. 1. Researchers Jevgeni Riipulk and Denis Karai demonstrate developed in the DBME devices at the Technology 2000: on the table left device Tensiotrace for blood pressure monitoring, on the table back laser device for cardiovascular diagnostics, and on the table right radiometric system for cancer exploration.

Fig. 2. PhD student Jevgeni Riipulk and Professor Hiie Hinrikus are testing microwave radiometer (1996). Microwave part of the device (two input waveguides, modulator, ferrite isolators, mixer, intermediate frequency amplifier) is located inside the white box.

Numerical modelling of the radiometric measurement on an inhomogeneous layered biological medium was used to find the influence of the parameters and the geometry of tissues on the radiometric signal and to calculate the signal for different sizes of the tumor [11,12]. The electromagnetic modelling was performed in cooperation with the Darmstadt Technical University employing their software MAFIA based on the Finite-Difference Time Domain (FDTD) method. Microwave radiometry for medical applications was the topic of the PhD thesis by Jevgeni Riipulk (supervisor H. Hinrikus), defended in 2000.

The radiometric system for cancer exploration was demonstrated at the Hannover Messe in 1998.

4. ELECTRICAL OSCILLATIONS OF HEART

Activation of the heart originates from the sinus node operating as an electrical oscillator, generating electric pulses at the frequency controlled by the highly complicated system of electric and chemical signals. If the sinus node or electric leads of the heart become distorted, the efficient pumping action of the heart may deteriorate or stop altogether. In this case an artificial pacemaker is needed that generates the appropriate electric pulses and keeps the heart rate in the normal range adapted to the physiological state of the person. The main problem in adaptive cardiac pacing is the reconstruction of normal heart rate.

The DBME participated in the European COPERNICUS project CP940202 Harmony "Application of hardware-based fuzzy logic controller to adaptive pacemaker" 1995–1998, cooperating with the scientists from Paris, Warsaw, and Stuttgart. The aim of the project was to develop an analog fuzzy logic controller for the reconstruction of the heart rate, based on the optimal system of selected physiological signals.

The role of the DBME in this project was the development of a model for a healthy man, based on the physiological parameters system, measured during exercise tests and evaluation of the quality of different physiological parameters for the reconstruction of the heart rate. The parameters like physical activity, ventilation, and characteristics of the electrocardiographic (ECG) signal, as QT interval, and their combinations were compared. Regarding the single-parameter system, the QT interval had higher reconstruction accuracy as compared to the activity and ventilation. All the double-parameter systems presented the error level of heart rate reconstruction around 10% that is within the limits suitable for clinical practice; the triple-parameter models appeared not to improve the quality of heart rate reconstruction. It was shown that linear and polynomial approximations for heart rate reconstruction practically coincided inside the range of interest for pacing in clinical practice 60–120 beats per minute [13]. The hardware-based fuzzy logic controller as a more dynamic and flexible one demonstrated advantages compared to the existing heart rate adaption algorithms and was protected by French and European patents.

5. MICROWAVE EFFECT

The worldwide applications of electromagnetic fields in telecommunication and information technology devices have resulted in public interest in the effects of microwave radiation on human health. Guidelines for limiting exposure to microwave radiation are based on thermal biological effects resulting from tissue heating. However, experimental findings have demonstrated the effect of microwave radiation at the field power densities levels much lower than the thermal limit. The mechanisms behind the low-level microwave effects have been under discussion in international scientific community for decades. Low microwave field strengths in tissues compared to intramolecular fields, high frequencies of radiation compared to physiological processes and contradictory experimental data have caused doubts in the low level of the effects. At present, heating still remains the only commonly recognized mechanism occurring in the microwave range. On the other hand, polarization of the living tissue by microwave radiation, related to the rotation of dipolar water molecules, does not cause any doubts.

The influence of microwave radiation on the human brain was selected for investigation in DBME because the nervous system is most sensitive to external stressors. Two methods were applied: electroencephalographic (EEG) signal analysis and psychological tests. The frequency of applied microwave radiation was 450 MHz in all experiments to provide deeper depth of penetration and comparability of results. All experiments were performed with low-frequency modulated microwave radiation at field power density level more than ten times lower compared to the officially recommended health protection limits.

Alterations related to microwave exposure in the EEG signal are small and hidden in the natural variability of the signal. A special method, integration of differences, for the detection of small alterations in EEG was developed [14]. Nonlinear methods, based on fractality analysis, demonstrated good sensitivity for the detection of microwave effect [15,16].

The problems of interpretation of biosignals from brain and heart were discussed in the PhD thesis by Jaanus Lass (supervisor H. Hinrikus), defended in 2002. Jaanus Lass is now Senior Research Scientist on biosignals analysis at the DBME.

Fig. 3. PhD student Jaanus Lass is receiving Ragnar Granit Young Scientists Award from Professor Jaakko Malmivuo, Chairman of the Board of the Ragnar Granit Foundation (1999).

The first experiments at 7 Hz modulation frequency demonstrated that the changes, caused by microwave radiation in the EEG alpha and theta frequency bands, varied strongly between subjects and, consequently, were not statistically significant [17]. Further investigation at the modulation frequencies of 7, 14, and 21 Hz showed statistically significant alterations at 14 and 21 Hz modulation frequencies in the EEG alpha and beta frequency bands [18,19]. Our findings suggest that the effect of microwave radiation, modulated at 7, 14, and 21 Hz, varies depending on the modulation frequency.

The question about individual sensitivity to microwave radiation was investigated at 7, 14, 21, 40, 70, 217, and 1000 Hz modulation frequencies [20–22]. The results indicated that the number of subjects, significantly affected by microwave radiation, depends on the modulation frequency. The rate of subjects, affected by microwave exposure, is about 30%. This number is even higher than the rate of population affected by nonspecific chemical pollution.

The results of performed psychological tests confirm the effect of low-level microwave radiation on the ability of the brain for correct information processing [23–26]. The numbers of correct answers decreased with microwave exposure. The effect was small, 5–7%, but statistically significant.

The dependence of the microwave effect on the level of the applied field power density was demonstrated to be much less critical than expected. The experiments showed that decreasing of the microwave field to 20 dB reduced the related changes in the EEG to 5–8 dB and the number of affected subjects, but did not exclude the effect [27].

Fig. 4. Maie Bachmann and Denis Karai in EEG laboratory (2012).

Microwave effect on EEG at different modulation frequencies was the topic of the PhD thesis by Maie Bachmann (supervisor H. Hinrikus) in 2008. Maie Bachmann is now Senior Research Scientist on EEG analysis at the DBME.

6. PARAMETRIC EXCITATION OF BRAIN OSCILLATIONS

Several possible mechanisms of the low-level microwave effect have been discussed in the DBME during years [28–31]. The specific behaviour of the microwave effect – its dependence on the modulation frequency whereas the effect is evident at the EEG frequencies close or lower than the modulation frequency – leads us to the idea that the parametric excitation would be a suitable mechanism for the effect. In the case of a nonlinear excitable system, the first zones of the parametric excitation are expected to occur at the EEG frequency f_0 to modulation frequency F ratios f_0/F equal to 0.25, 0.5, and 0.75. Results of the experimental study with microwave radiation, modulated at 7, 14, 21, 40, and 70 Hz, demonstrated that modulated microwave radiation causes excitation of the brain EEG rhythms exactly at the frequencies predicted by the nonlinear model of parametric excitation [32]. No significant alterations were detected at other EEG frequencies.

The parameter, periodically altered by modulated microwave radiation, should be related to the neurophysiologic processes in the brain. Neurophysiologic processes are based on the balance between the processes due to the electric field forces and the forces due to diffusion. The background electric field of external origin affects polarization of the medium, consequently changing electric forces in the medium. Alterations of temperature of the medium affect mostly diffusion. The question is, does microwave radiation affect diffusion also at constant temperature.

The data of experiments, performed in NaCl solution diffusion in water, demonstrated that microwave exposure makes faster the process of diffusion at constant temperature [33]. This result is consistent with the proposed mechanism of low-level microwave effect: microwave radiation, rotating dipolar water molecules, causes high-frequency alterations of hydrogen bonds between water molecules, thereby affects its viscosity and makes faster diffusion.

For the first time, the studies performed in DBME proposed the theory and experimentally proved the mechanism behind the low-level microwave effect on the nervous system. The proposed model of parametric excitation is helpful for the interpretation of the experimental results on the critical dependence of the effect on modulation frequency and noncritical dependence on the level of power density of the radiation.

7. BRAIN OSCILLATIONS

A huge number of neurons in the human brain are connected to form functionally specialized assemblies. Functionally, oscillations are a prominent feature of neuronal activity and the synchronization of oscillations, which reflects the temporally precise interaction of neural activities, is a likely mechanism for neural communication. Neural oscillations refer to periodic variations in the recordings of the neural activity and EEG signals. The emergence of oscillations and the frequencies of these oscillations depend on cellular pacemaker mechanisms and neuronal network properties. Lower EEG frequencies refer to life supporting physiological processes, whereas higher EEG frequencies are related to intellectual activity. The maximum of the oscillations spectrum power density is located in the EEG alpha band frequencies. Following the theory of switched oscillators, the alpha band frequencies would be considered as a resonance of unloaded, eyes closed, system of oscillators. Loading of the system by a large amount of information – eyes open – the maximum at alpha frequencies disappears.

The balance between EEG powers at frequencies higher and lower the alpha band is expected to provide information about the state of the brain. The EEG spectral asymmetry index (SASI) was proposed for the detection of depression and other mental disorders [34–36]. The method is defended by the patent US8244341B1. The principle of SASI is estimation of the spectral asymmetry of the EEG spectrum, regarding its maximum in alpha band. For this purpose, the relative difference of the powers in the frequency bands, selected higher and lower than the alpha band, is calculated at least in one EEG channel. The boundary frequencies of selected for the calculation frequency bands were adjusted taking into account the individual alpha for a subject and excluding alpha band from the analysis.

The linear SASI method demonstrated sensitivity of differentiation between depressive and healthy subjects comparable to that achieved by the nonlinear Higuchi's fractal dimension method [37].

The SASI algorithm was implemented as a FPGA based prototype for a portable EEG Analyser device in cooperation with the Department of Computer Engineering in the framework of the Centre of Excellence CEBE [38].

The algorithms for the detection of alterations in the EEG signal, caused by depression and microwave radiation at two different levels of exposure, constituted the content of the PhD thesis by Anna Suhhova (supervisors M. Bachmann and H. Hinrikus), defended in 2013.

8. PULSE WAVE

Pulse wave propagation through vascular tree is a complex process. The nature of mechanical wave propagation depends on elastic properties and geometry of the arteries and blood viscosity. Whereas arterial pulse wave velocity depends on intravascular pressure and artery viscoelastic properties, pulse wave parameters can be employed for getting information about blood pressure and arterial stiffness, useful in cardiovascular diagnostics. The aortic pulse wave velocity as an index of arterial stiffness has already been entered to the guidelines for hypertension as providing cardiovascular risk prediction. However, the process of obtaining sufficient information for pulse wave velocity calculations requires simultaneous measurement of many parameters. The measurement of parameters as vessel wall thickness, vessel radius, blood pressure, blood density, and viscosity requires employment of different methods. Additionally, the theory for the origin of pulse wave shape, traditionally proposed by medical researchers, does not seem to follow the theory of wave propagation in transmission lines. These are the main reasons why only few devices are available for pulse wave diagnostics nowadays; the process of measurements is very complicated and the dispersion of results is high.

Optical methods for pulse wave shape, pulse wave velocity, and blood flow measurement were developed in the DBME.

The coherent optical method for pulse wave profile measurement was based on recording the Doppler frequency shift related to a moving target – blood vessel walls or small blood particles [39–41]. The Doppler signal was detected using self-mixing that occurred in the diode laser cavity. An experimental device with a pigtail laser diode was developed for detecting pulsation of arteries. The simultaneously recorded pulse profile signal and electrocardiographic (ECG) signal include information, potentially useful for determining pulse wave shape and the pulse wave delay time.

Noninvasive cuff-free method for evaluation of blood pressure was developed [42]. The method was based on the calculation of blood pressure from the pulse wave velocity employing optical pulse wave signals from two fixed points on an artery. The geometry of the artery was counted as a vessel structure parameter (ratio of wall thickness to vessel radius). Utilizing the vessel structure parameter and presuming stability of the blood density, it was possible to get a singular relationship between blood pressure and arterial stiffness [43]. This idea was registered as an invention

Fig. 5. Kristjan Pilt (left) and Denis Karai are testing the novel device for the determination of arterial ageing (2014).

by the Estonian patent office. The method provided good stability during recordings. However, calibration was needed for getting absolute arterial blood pressure values.

The laser device for cardiovascular diagnostics was demonstrated at the Hannover Messe in 2000.

Further development of new ideas resulted in an advanced method and device for the determination of arterial stiffness, based on photoplethysmographic signal processing [44–47]. The novel algorithm of photoplethysmographic signal processing uses adaptive filtering for noise removal and adaptation of signal sampling frequency to the current heart rate [45]. The parameters of the pulse wave shape were calculated using the second derivative method [46]. Experimental investigations of the method demonstrated advantage of the novel algorithm: the method provides higher stability of results and lower standard deviation compared to the commercial devices [47].

The method for early detection of arthrosclerosis and determination of arterial ageing was developed in the PhD thesis by Kristjan Pilt (supervisors K. Meigas and M. Viigimaa), defended in 2014. Kristjan Pilt is now a Senior Research Scientist at the DBME.

9. BIOFLUID OPTICS

Hemodialysis is the only method of removing uremic toxins and therapy for the end stage renal disease patients. In clinical practice the quality of the dialysis process is monitored using laboratory chemical analysis. Today, there is no method available for on-line monitoring of uremic toxins with different molecular size for the quality assessment of renal disease therapy.

In principle, chemical analysis can be replaced by on-line optical analysis of biofluids. In tenuous optical media, like spent dialysate, all the incident light is either reflected, absorbed or transmitted and scattering from other regions of the medium can be ignored. Therefore, concentration calculation methods, utilized in absorbance spectroscopy, can be applied also for monitoring the spent dialysate. For the first time the techniques of online monitoring of solutes in dialysate using absorption of ultraviolet (UV) radiation, connected to dialysis dose estimation, was developed by Ivo Fridolin during his doctoral studies at Linköping University. His further studies demonstrated clearly that removal of urea can be successfully estimated by online measurement of the UV absorption in the spent dialysate [48,49]. Ivo Fridolin is now Professor of Medical Physics, Director of DBME.

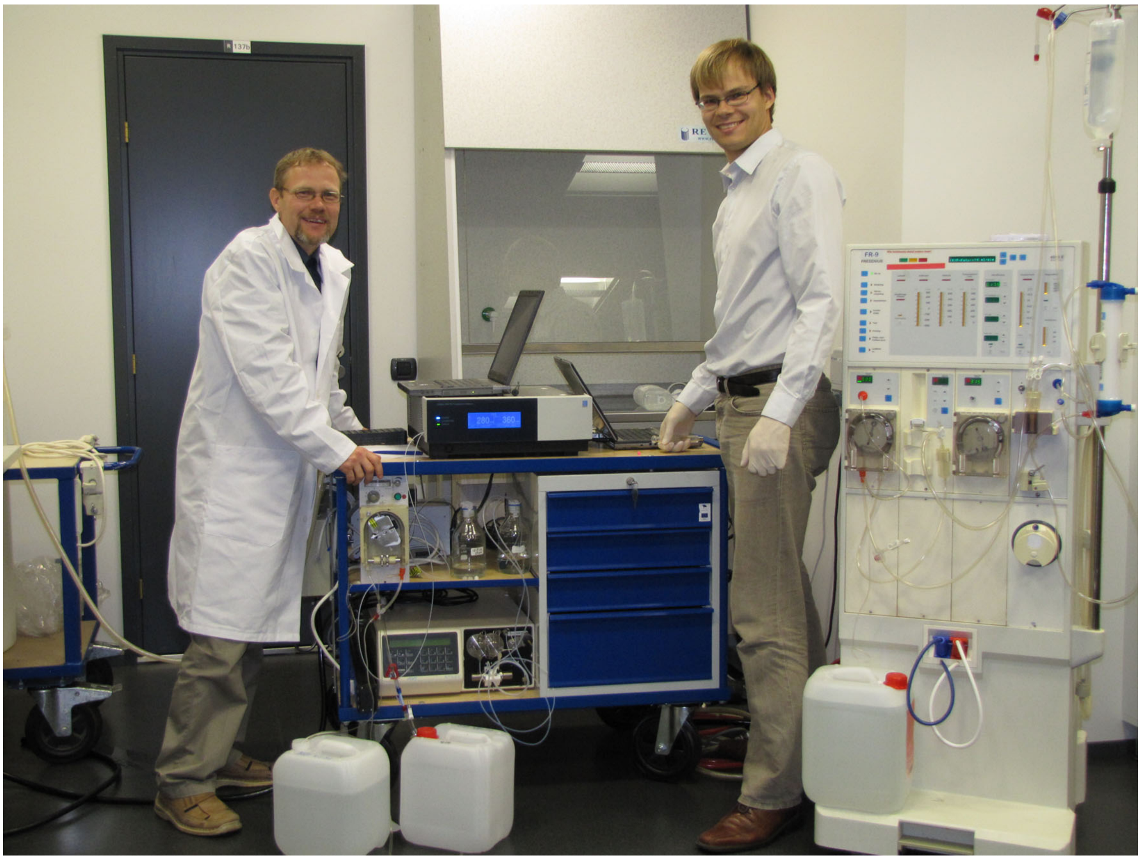

Fig. 6. Professor Ivo Fridolin (left) and PhD student Jürgen Arund in biofluids laboratory (2013).

Fig. 7. PhD student Jana Holmar is receiving the Young Scientists Award from the President of the International Federation for Medical and Biological Engineering, Prof. Herbert F. Voigt on the 5th European Medical and Biological Engineering Conference, 14–18 September 2011, Budapest, Hungary.

The biofluid optics research in the DBME is based on a novel concept of the multicomponent dialysis monitoring, using optical techniques. The multicomponent monitor incorporates online removal estimation of all the three uremic toxins' groups: small molecular weight, middle molecular weight, and protein bound large molecular weight toxins [50–60].

Novel algorithms for measuring concentration of water soluble small molecular weight uremic toxins, urea, uric acid, and creatinine, in the spent dialysate for the estimation of dialysis dose and nutritional status (protein nitrogen appearance and lean body mass) on dialysis patients were developed [51–53].

Accuracy of the estimation of uremic toxins concentration can be improved using information of the multispectral UV-absorbance in the spent dialysate. Introduced multi-wavelength algorithms enable reliable and more accurate calculation of the uremic toxins concentration from the spent dialysate compared to one wavelength calculations.

Merike Luman defended her PhD thesis on the assessment of dialysis dose and nutrion by an optical method in 2010 (supervisor I. Fridolin). She is the first medical doctor who got her PhD from the Tallinn University of Technology. Optical method for uric acid removal assessment during dialysis was discussed in the PhD thesis by Jana Holmar (supervisor I. Fridolin), defended in 2013. Jana Holmar is now a Senior Research Scientist at the DBME.

Method for determining middle and protein bound uremic toxins in the spent dialysate was proposed using fluorescence spectroscopy. The method was a subject for several Estonian and international patent applications. For the first time, it was confirmed that a light emitting diod based miniaturized optical monitor is capable to estimate dialysis dose and nutritional status without blood samples and offers a possibility for simplified mapping of the dialysis.

Many of the uremic toxins are candidates for being cardiovascular disease markers. For this reason an appropriate high performance liquid chromatography method was developed, capable to measure more uremic toxins compared to existing standard laboratory methods [58]. The method provided possibility to identify and quantify different uremic toxins in the serum and in the spent dialysate (uric acid, hypoxanthine, indoxyl sulfate, indole-3-acetic acid, hippuric acid, etc.) and determine the optical spectra for many chromophores in the uremic fluids.

10. PERSPECTIVE

The DBME has achieved a solid level of scientific knowledge and practical experience in smart technologies combining the principles of physical and mathematical models with the advanced processing of biomedical signals from brain, heart, vessels, and biofluids. The assessment of vital physiological parameters contributes to early detection of health disorders and evaluation of treatment efficiency.

However, human being is a highly complicated system where interactions between different organs and systems are highly important for its functioning. Therefore, combined analysis of physiological data from different organs is expected to provide more useful information for the interpretation of health disorders compared to single organ data.

Cardiovascular diseases have become the number one cause of death in the world, according to a WHO-supported investigation. A total of 260 million European citizens experience some form of brain related neurodegenerative disorders or mental disorders. According to WHO statistics, unipolar depressive disorder is a leading cause of burden of disease in high- and middle-income countries nowadays and it is projected to take the first place in the world in 2030. There is a strong evidence that persons with renal impairment are attributed to major cardiovascular risk factors for the development and progression of endothelial dysfunction and atherosclerosis and all-cause mortality. Furthermore, renal impairment is one of the leading causes of encephalopathy and other cerebral disorders. The persons with renal impairment (about 10% of population) have to be considered as very high-risk persons. Despite this, many patients remain undiagnosed and untreated.

The natural next step for the DBME is extending the research topic, involving interactions between the brain, cardiovascular system, and kidney. The new knowledge about processes in three physiological systems, cerebral, cardiovascular and renal, and interactions between the systems is highly valuable for medical diagnostics. Multiscale, multiorgan, and multivariate analysis makes it possible to get more information about the systems offering advantage in resolving the problem of early diagnosis of health disorders. Tight cooperation with hospitals, first of all with the North Estonia Medical Centre, is expected to promote medical aspects of the research.

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