CEBE | Centre for Integrated Electronic Systems and Biomedical Engineering

1918 TALLINNA TEHNIKAÜLIKOOL TALLINN UNIVERSITY OF TECHNOLOGY

Eesti tuleviku heaks

Euroopa Liit
Euroopa
Regionaalarengu Fond

Research on Biomedical Engineering: Cooperation with hospitals.

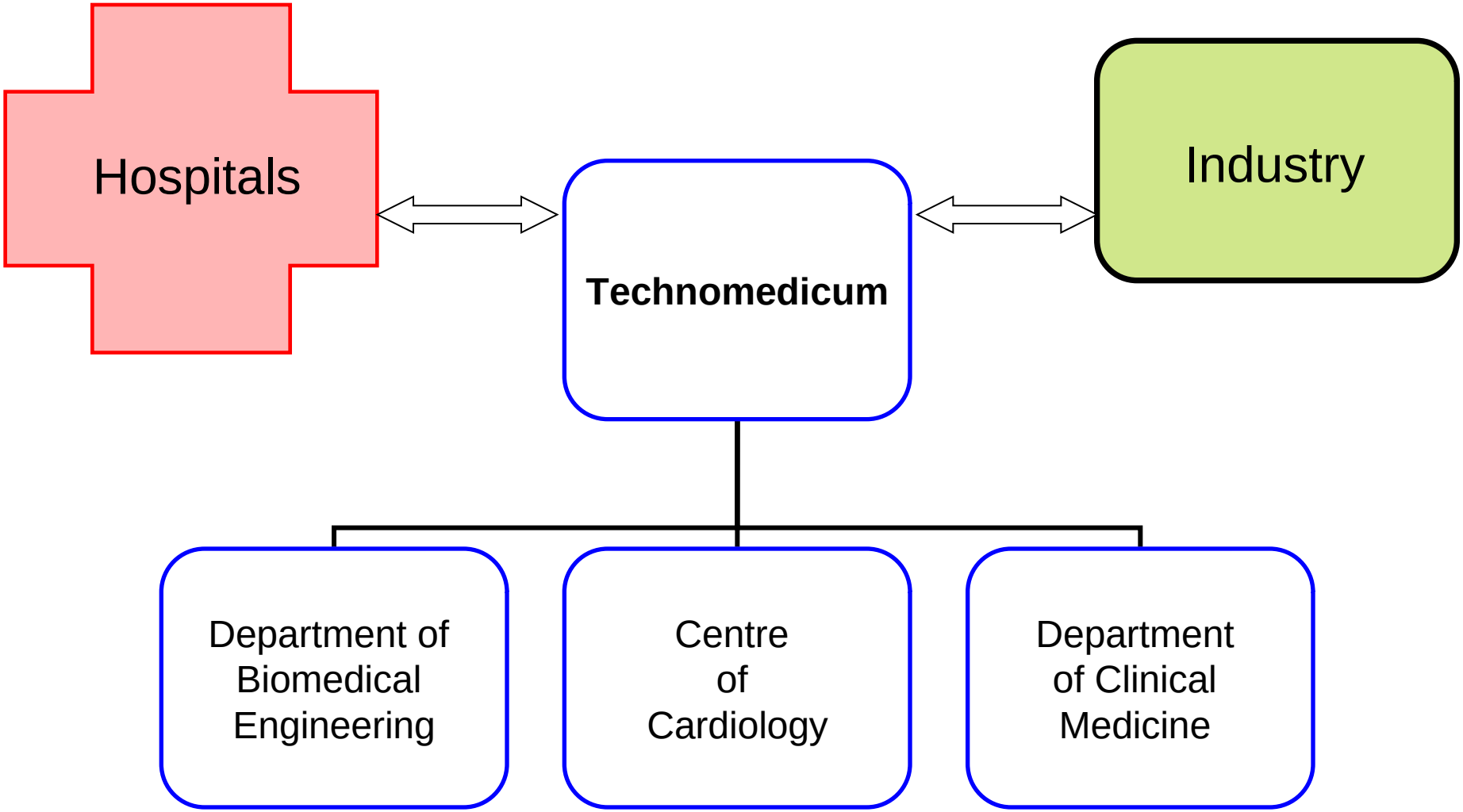
Ivo Fridolin

Department of Biomedical Engineering, Technomedicum

Centre for Integrated Electronic Systems and Biomedical Engineering (CEBE)
Tallinn University of Technology

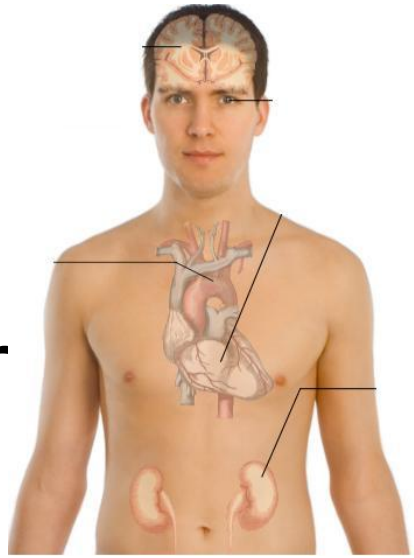
www.cebe.ttu.ee

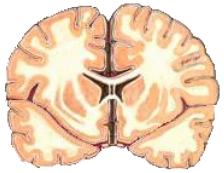
Technomedicum at Tallinn University of Technology



Biomedical Engineering research at TM

- ✓Topics:
  - Brain diagnostics
  - Diagnostics of cardiovascular diseases
  - Sleep apnea monitoring
  - Optical kidney dialysis monitoring





Brain Diagnostics: principle and problem

+ The brain bioelectrical activity (EEG signal) is a good source of knowledge about the functioning of the brain providing objective information related directly to its ability to process information.

- Useful diagnostical information is hidden in highly complex natural variability of the EEG signal

Brain Diagnostics: analysis of bioelectric signals of brain

Content of the research: detection and investigation of the characteristic features of the electroencphalographyc (EEG) signals related to

i) *Mental disorders (depression, stress etc.)*

- ✓ 25% of adults are diagnosable for one or more mental disorders (MD);
- ✓ 6.7% of population suffers from depression, and the rate is increasing.

(*Statistics by National Institute of Mental Health about US*)

ii) *Excitation of the brain by weak periodic external stressor (effect of modulated electromagnetic fields - EMF)*

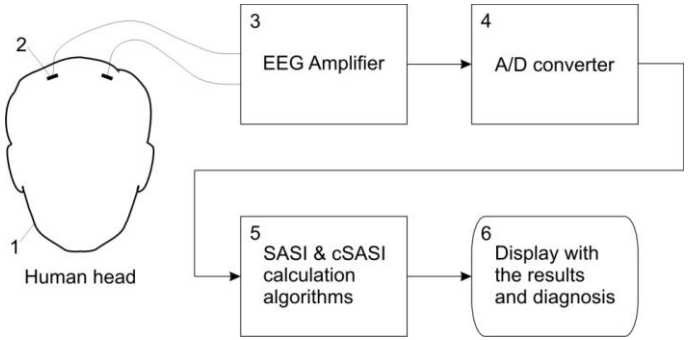
- ✓ Health concerns of population associated with EMF fields and potential danger of EMF (mobile phones, wifi, relay antenna etc)

(*Resolution by European Parliament from 2009 and Council of Europe 2011*).

Brain Diagnostics: principle and problem

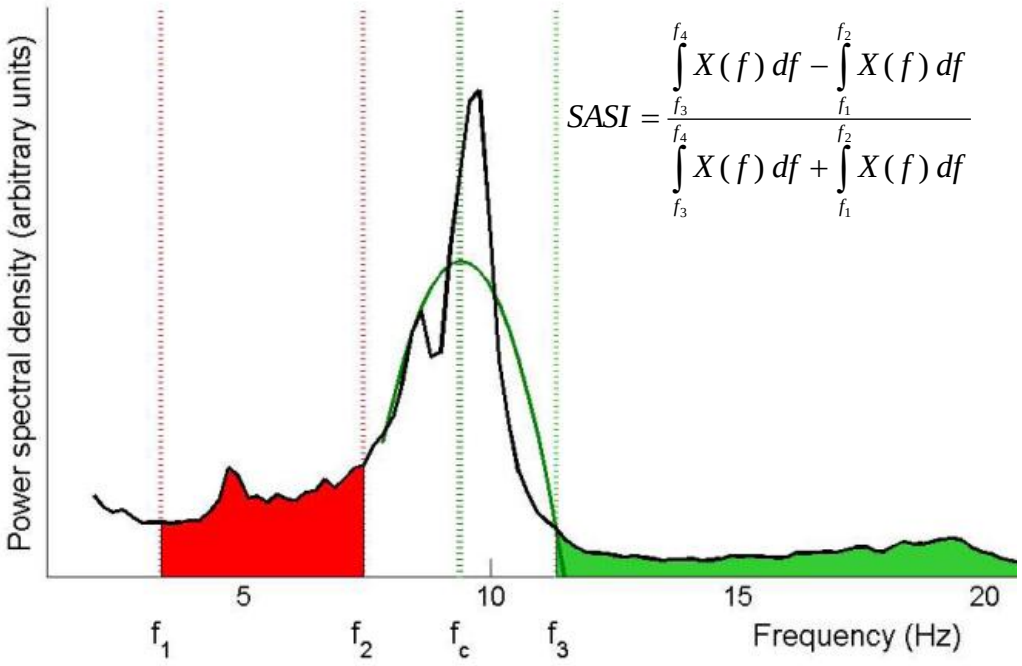
The research is aimed to

- develop new methods for detection of small hidden changes in the EEG signal
- find new measures for evaluation of the brain (mental) disorders



Cooperation:
Clinic of Psychiatry, NEMC
Center of Psychiatry, West Tallinn CH

New method – Spectral ASsymmetry Index (SASI)

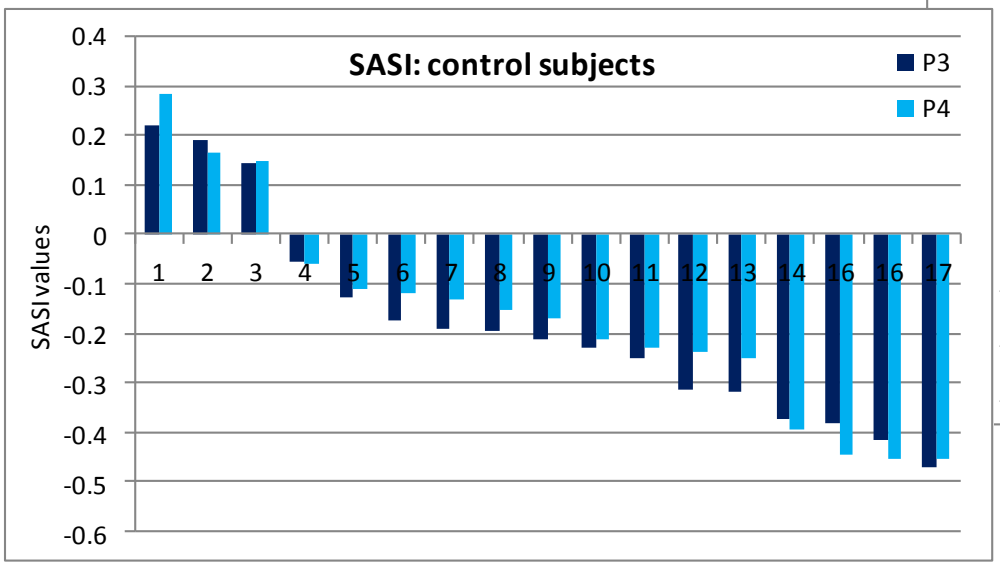


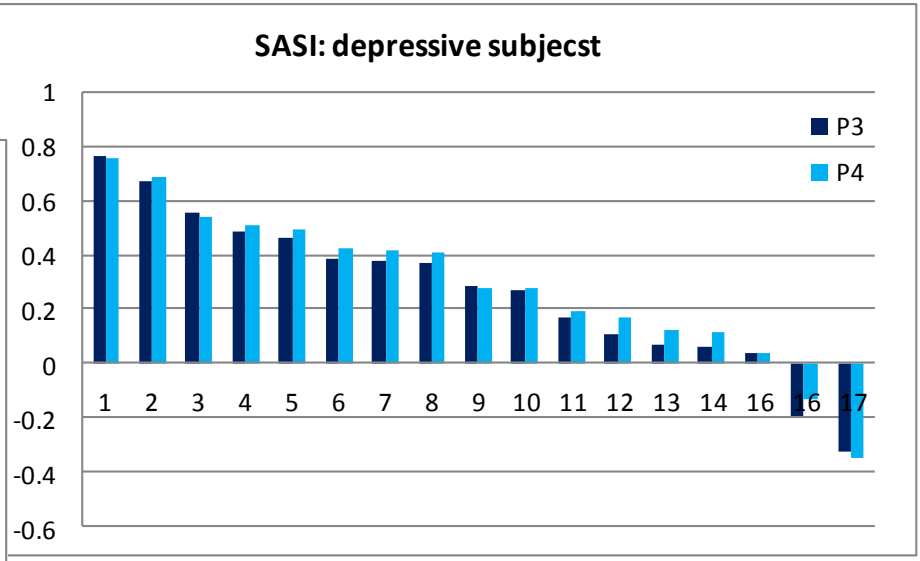
$$SASI = \frac{\int_{f_3}^{f_4} X(f)\,df - \int_{f_1}^{f_2} X(f)\,df}{\int_{f_3}^{f_4} X(f)\,df + \int_{f_1}^{f_2} X(f)\,df}$$

SASI bases on the balance of powers of two EEG frequency bands selected higher and lower than the EEG spectral maximum (alpha band)

Pat. US8244341B1 from 14.08.2012 “Method and device for diagnosing a mental disorder by measuring bioelectromagnetic signals of the brain,” Authors: H.Hinrikus, M.Bachmann, J.Lass, A.Suhhova, V.Tuulik (**TUT**), K.Aadamsoo, Ü.Võhma (**NEMC**)

New method – Spectral ASsymmetry Index (SASI)

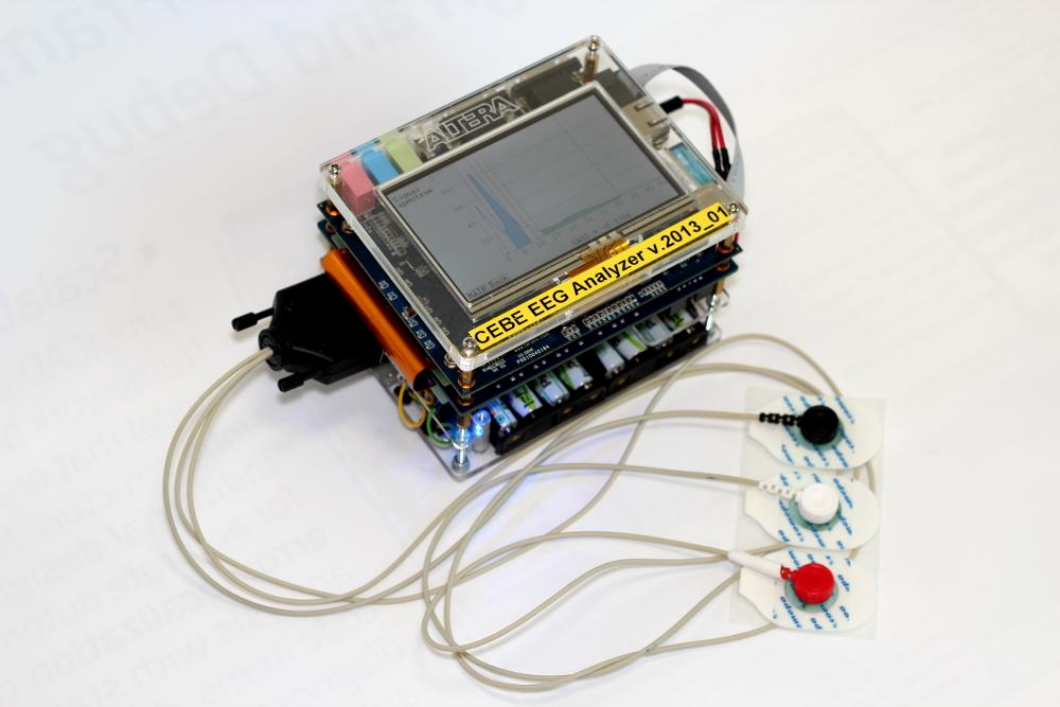




SASI is negative for healthy and becomes positive for depressed/disturbed brain.

Implementation of SASI – CEBE project P4

EEG Analyzer Prototype Based on FPGA



Cooperation with the Department of Computer Engineering

Jenihhin M, Gorev M, Pesonen V, Mihhailov D, Ellervee P, Hinrikus H, Bachmann M, Lass J. EEG Analyzer Prototype Based on FPGA. Proceedings of IEEE 7th International Symposium on Image and Signal Processing and Analysis, ISPA 2011, Dubrovnik, Croatia, September 4-6, 2011, pp. 101 - 106.

Results and *plans*

SASI

- ✓ differentiates correctly 85% of depressed/healthy subjects
- ✓ SASI inceases with depression and microwave exposure
- ✓ ***test for various brain disorders using SASI***

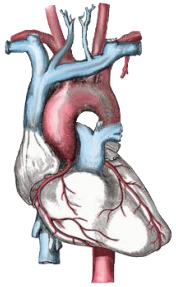
Bachmann et al., *Mat Computer Met Medicine*, 2013 (in press)
Hinrikus et al., *Med Biol Eng Comput*, 2009, 47:1291-1299

Microwave effect

Experiments on 5 groups, 77 subjects:
450 MHz MW modulated at F=7, 14, 21, 40, 70, 217, 1000 Hz;
field power density **1.6** W/m^2 and **0.016** W/m^2 (EC limit **10** W/m^2);

- ✓ **30% of healthy young subjects were affected**
- ✓ MW radiation increases EEG power at frequencies $f=n0.25F$
- ✓ **First time the parametric mechanism of the MW effect on brain oscillations was proposed and proved by experiment**

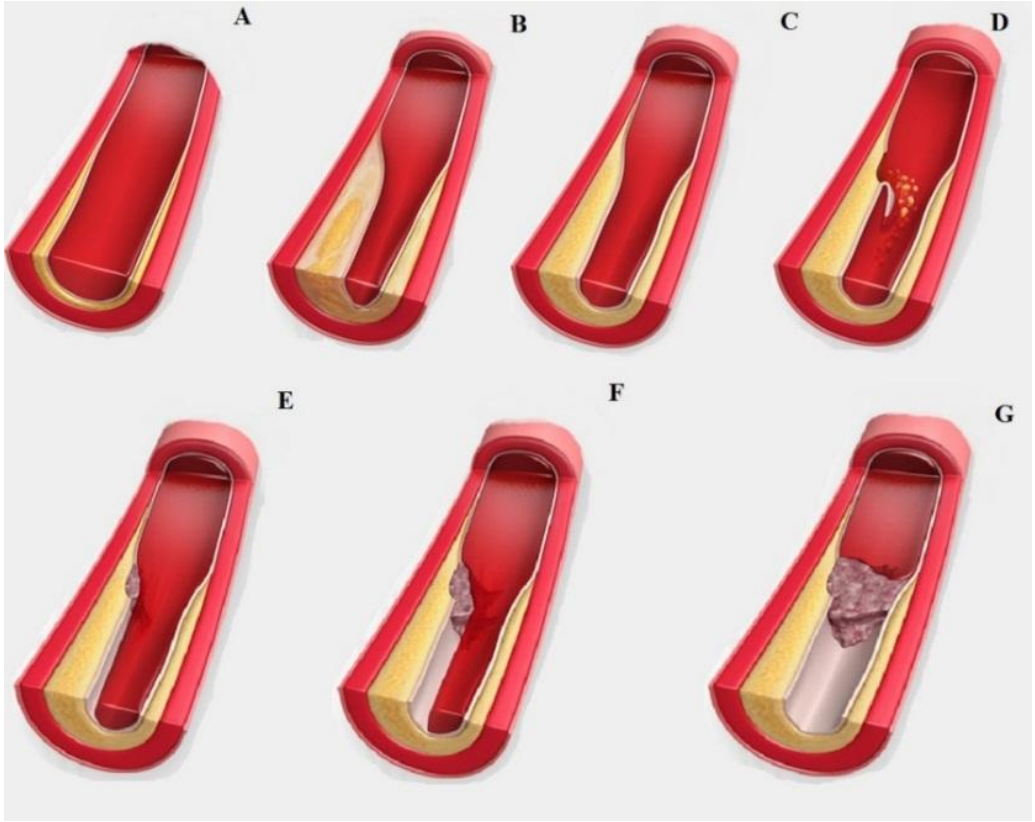
Suhhova et al., *Bioelectromagnetics,* 2013, 34:264-274
Hinrikus, et al., *Int J Radiat Biology*, 2011, 87:1077-1085
Hinrikus et al. *Int J Radiat Biology*, 2008, 84:69-79



Diagnostics of cardiovascular diseases

- ✓ The ability to identify premature arterial stiffening is of considerable value in the prevention of cardiovascular diseases.

Different stages of atherosclerosis:



(American Heart Association, Learn and Live)

Diagnostics of cardiovascular diseases: Aim

Development of innovative non-invasive methods and devices for the early diagnosis of atherosclerosis through:

- Continuous non-invasive monitoring of arterial blood pressure by non-invasive and non-oscillometric way (by pulse wave velocity - PWV)
- Inexpensive and noninvasive methods (e.g. signal analysis algorithms and PPG technology) for studying elastic properties of the vascular system

Diagnostics of cardiovascular diseases

- ✓ There is collaboration with North Estonia Medical Center (Tallinn Estonia) in order to carry out studies on diabetes, coronary artery, and chronic kidney disease patients:

- ✓ Center of General Internal Medicine:
  - Dr. Anu Ambos
- ✓ Centre of Nephrology:
  - Dr. Merike Luman
- ✓ Center of Cardiology:
  - Dr. Marika Heinpalu-Kuum
- ✓ Laboratory:
  - Dr. Galina Zemtsovskaja
  - Dr. Marika Pikta

Regionaalhaigla

Diagnostics of cardiovascular diseases

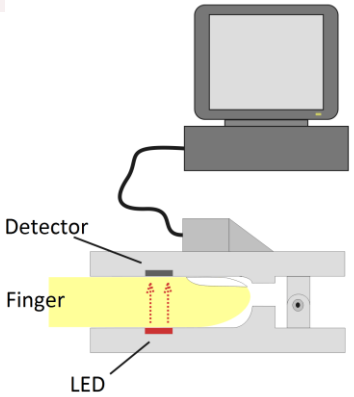
The setups of physiological signal recording system in hospital.

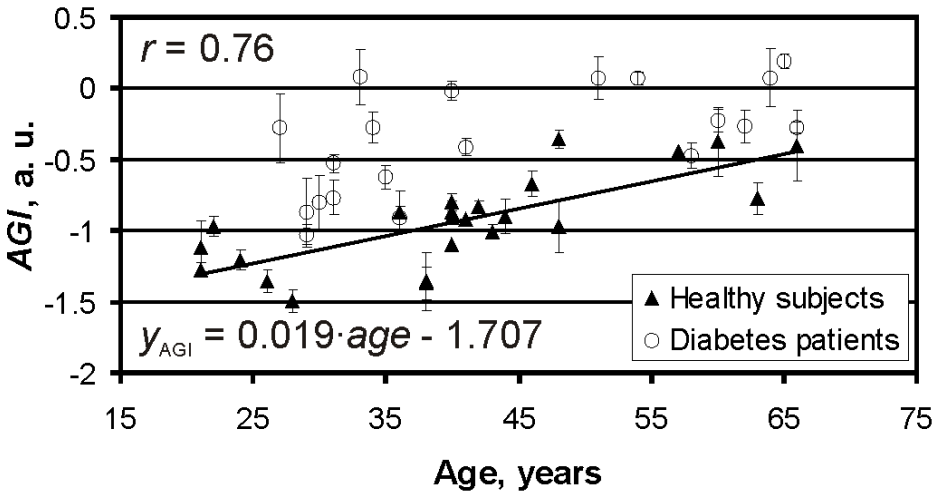
The setup in Centre of Cardiology

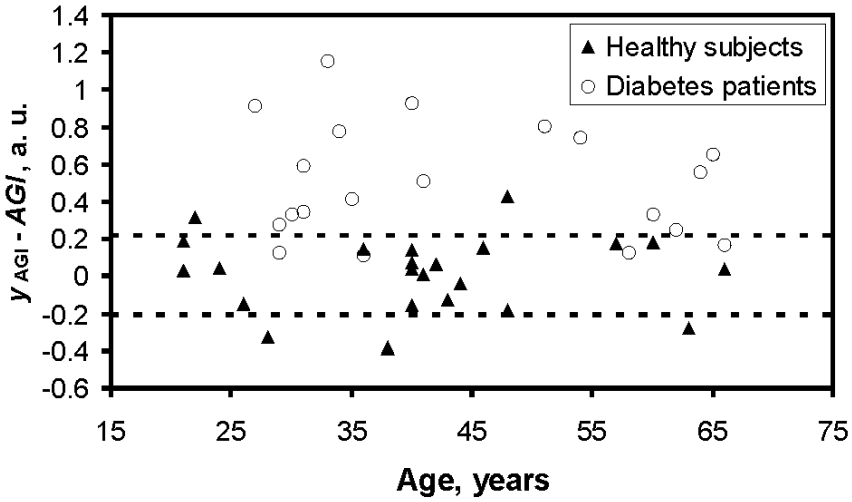
The setup in DialysisForum

Diagnostics of cardiovascular diseases: Results

The subjects, with increased arterial stiffness can be more easily differentiated from healthy subjects by using developed signal analysis algorithm ('ageing index' – AGI) with inexpensive PPG technology.





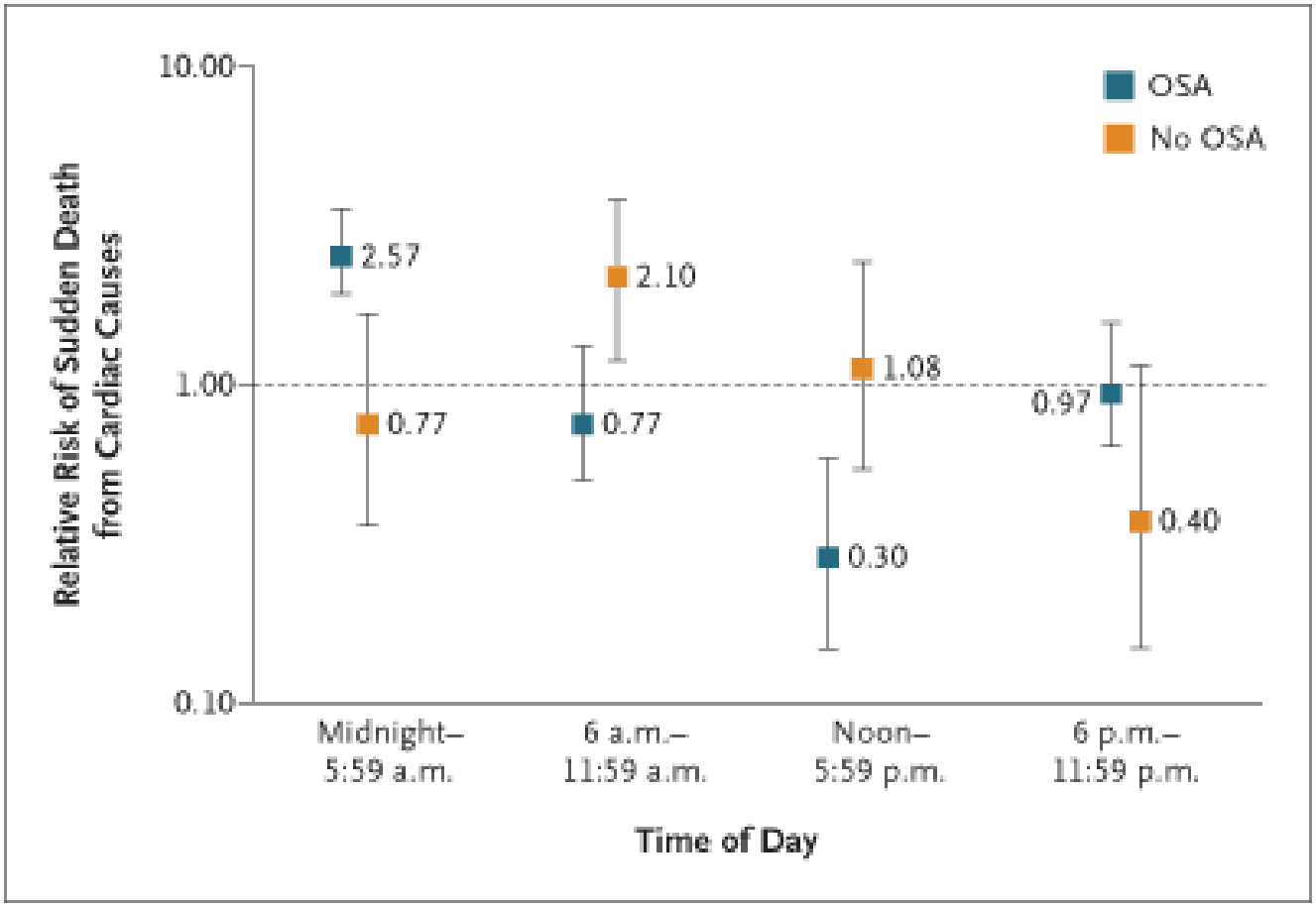


K. Pilt, R. Ferenets, K. Meigas, L-G. Lindberg, K. Temitski, M. Viigimaa. New Photoplethysmographic Signal Analysis Algorithm for Arterial Stiffness Estimation. The Scientific World Journal, Vol 2013, Article ID 169035, http://dx.doi.org/10.1155/2013/169035.

Sleep apnea

- ✓ **The most important problem in sleep medicine is sleep apnea.**
- ✓ Sleep apnea (also Obstructive Sleep Apnea (OSA)) is defined as a more than 10-second pause in respiration during sleep and 5 to 10 such episodes in an hour is the upper limit of the physiological norm.
- ✓ **The number of episodes above that limit** – there can be tens or hundreds episodes of sleep apnea in an hour, each could last for up to several minutes – **is an important risk factor for cardiovascular diseases**.

Sudden death risk in OSA and no-OSA patients



Gami et al NEMJ 2005

Sleep apnea monitoring: aims

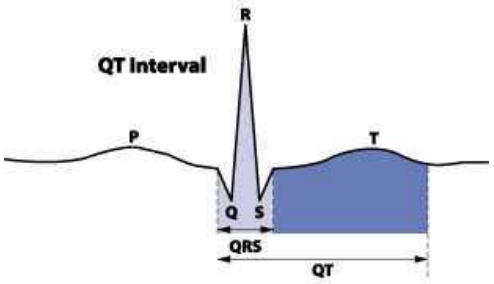
- ✓ **Development of a novel system enabling the sleep quality and sleep disorder occurrence continuous remote monitoring** which creates a new set of medical services for people with different sleeping disorders.
- ✓ Develop and validate the **small-sized portable model device** for physiological signal detection and registration and the responsive **remote diagnostic center** which collects and processes the received information and enables feedback opportunities.

Sleep apnea monitoring: method

Original algorithms developed in Technomedicum of TUT for assessment of QT interval variability to identify possible regularities in VR parameters before and during OSA episodes, which could serve as a basis for:

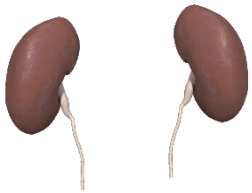
- ✓ determining the predisposition to life threatening arrhythmias in every single OSA patient both during sleep and when awake;

- ✓ interpolating repolarization peculiarities specific to high sudden death risk to the routine ECG 24-hour recordings in general population, i.e. using the physiological changes of the patient coming out of a prolonged OSA episode as a model of sudden death- like state.



Sleep apnea monitoring: Cooperation

Centres of sleep medicine:
Estonia: Mae Pindmaa Sleep Clinic, North-Estonia Medical Centre(Department of Pulmonology), Tartu University Hospital (Department of Psychiatry, Department of Otorhinolaryngology),
Finland: Tampere University (Department of Respiratory Medicine), Turu University (Sleep Research Unit), Helsingi-Turu-Tampere Sleep Medicine Centre
Russia: Almazov Federal Research Centre for Heart, Blood and Endocrinology
Medical equipment producers - Girf Ltd, Tensiotrace Ltd, (Estonia), Unesta Ltd, RESMED Finland (Finland), Biosignal Ltd (Russia),
Scientific societies: Nordic Sleep Medicine Association, European Sleep Research Society, European Space Agency



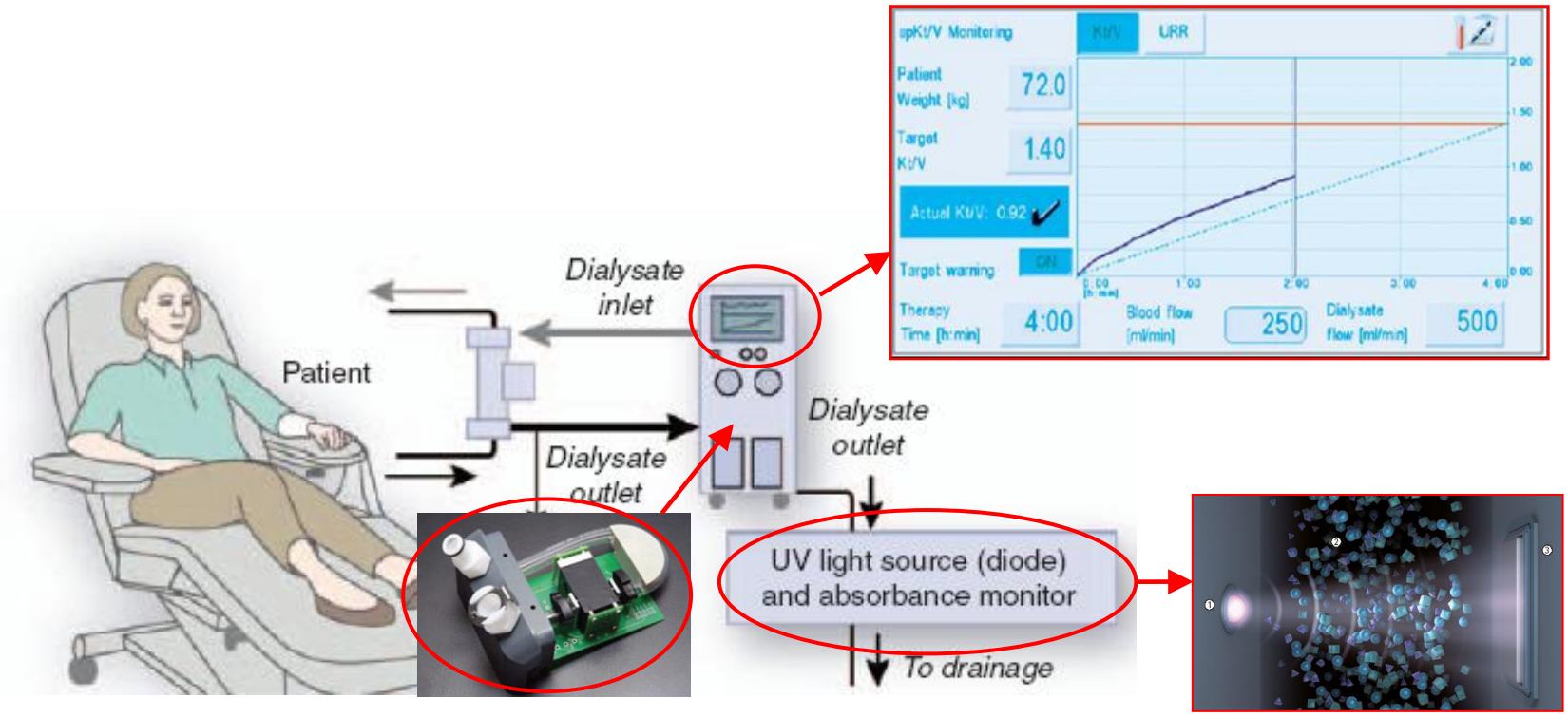
Optical kidney dialysis monitoring

Kidney dialysis - treatment of the end stage renal disease (ESRD) patients by the artificial kidney (dialysis machine) in order to replace all main kidney functions.

Kidney dialysis: status quo

- 3.1 million ESRD patients worldwide (about 2.1 million HD patients) – 7 % annual growth rate
- Time consuming (3 times x 5 hours / week)
- Complications (hypotension, dizziness, etc)
- Complex medical and dietary regimen
- Expensive – ca 50 billion $ annually (among 20 % technical)

Optical kidney dialysis monitoring



Commercially available options:

- Option Adimea, B. Braun Avitum AG
- Dialysis Dose Monitor, Nikkiso Co, Ltd.

Clinical kidney dialysis dose

Dialysis dose should be expressed in terms of equilibrated Kt/V (eKt/V) with the rate equation based on the regional blood flow two-pool urea kinetic model (evidence level: B).

European Best Practice Guidelines Expert Group on Haemodialysis. Nephrol Dial Transplant 2002: 17(Suppl 7): S16–S31

4. Minimum adequate dialysis: Guideline 4.1
In anuric patients, treated by three times per week dialysis, the prescribed target eKt/V should be at least 1.2.

Tattersall, J., A. Martin-Malo, et al. (2007). "EBPG guideline on dialysis strategies." Nephrology Dialysis Transplantation 22: 5-21.

Current dialysis dose quality parameters are based only on a singel markermolecule – urea!

Optical kidney dialysis monitoring: paradigm shift

nature genetics

Okada et al, Nature Genetics 2012

Meta-analysis identifies multiple loci associated with kidney function–related traits in east Asian populations

Our meta-analysis identified 17 loci newly associated with kidney function–related traits, including the concentrations of blood urea nitrogen, uric acid and serum creatinine and estimated glomerular filtration rate based on serum creatinine levels (eGFRcrea) ($P < 5.0 \times 10^{-8}$). We further examined

Biofluid Optics Team:Cooperation

- Centre of Nephrology, North-Estonian Medical Centre in Tallinn (M. Luman, MD, PhD)
- Department of Dialysis and Nephrology, Linköping University Hospital, Linköping , Sweden (A. Fernström, MD, PhD, F. Uhlin, PhD)
- The biochemical laboratories at North-Estonian Medical Centre and Quattromed HTI Laborid OÜ
- Laboratory of Chemical Physics, National Institute of Chemical Physics and Biophysics
- P5:Dept. Of Computer Engineering, TUT

Optical kidney dialysis monitoring

Do Only Small Uremic Toxins, Chromophores, Contribute to the Online Dialysis Dose Monitoring by UV Absorbance?

Jürgen Arund [1,*], Risto Tanner [1,2], Fredrik Uhlin [1,3] and Ivo Fridolin [1]

toxins

ISSN 2072-6651

registered between 200 and 400 nm. Nearly 95% of UV absorbance originates from solutes with high removal ratio, such as uric acid. The contributions of different solute groups vary at different wavelengths and there are dynamical changes in contributions during the single

Arund et al, Toxins 2012

Research Article

Optical Method for Cardiovascular Risk Marker Uric Acid Removal Assessment during Dialysis

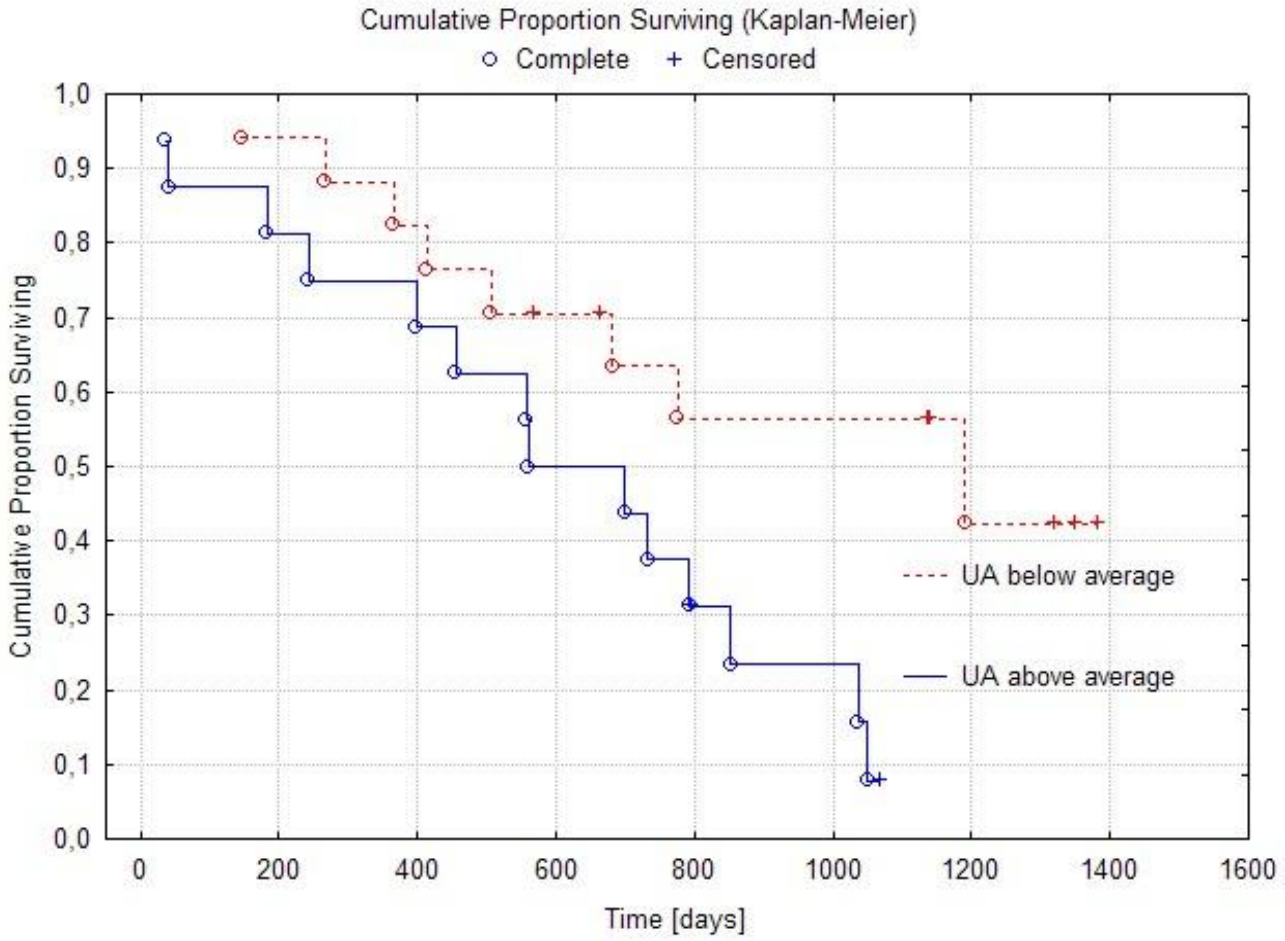
The ScientificWorldJOURNAL

Jana Holmar,[1] Ivo Fridolin,[1] Fredrik Uhlin,[1,2,3] Kai Lauri,[1] and Merike Luman[1,4]

Holmar et al, The Scientific World J 2012

Optical kidney dialysis monitoring

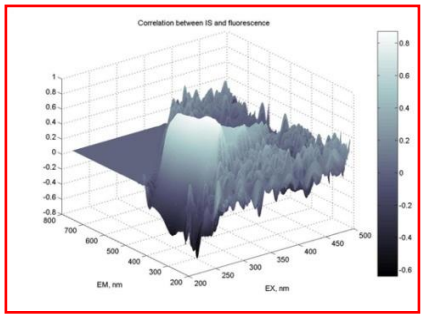
4-year survival analysis of dialysis patients (N=33).



Holmar et al, Submitted to Clin Nephrology 2013

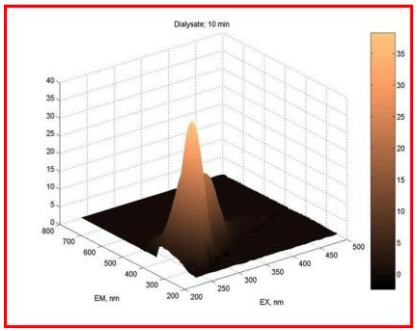
Optical kidney dialysis multi component monitoring

Enhanced Vision for Dialysis Quality Monitoring via Multi component monitoring

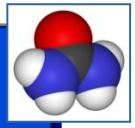


MCM:

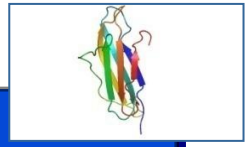
- Uremic toxins
- Cardiovascular markers



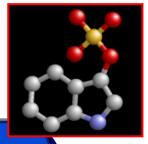
Small Molecules < 500 Da



Middle Molecules 500 .. 12 000 Da

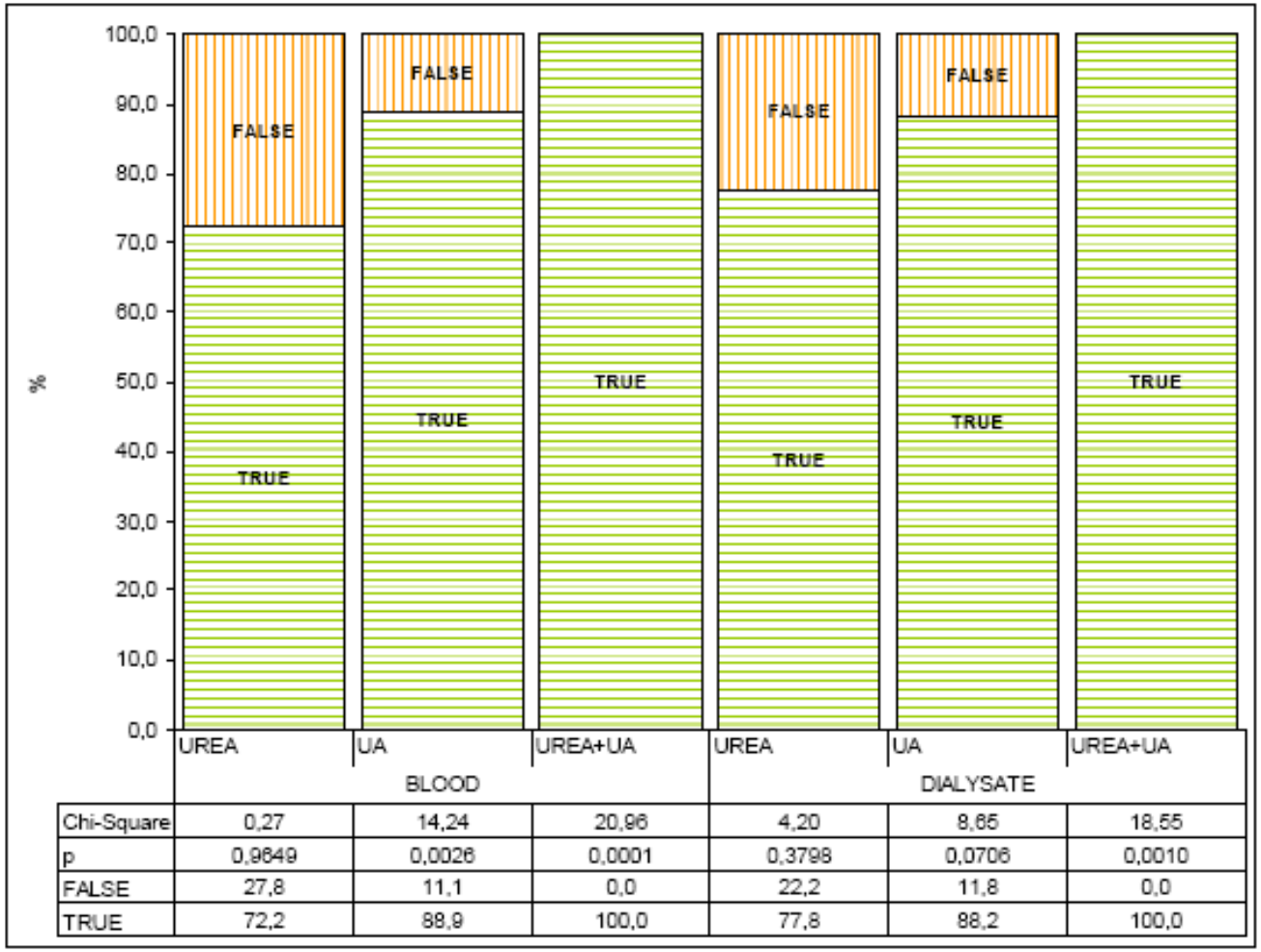


Protein Bound Molecules < 500 Da



Optical kidney dialysis monitoring

Prediction of 3-year survival of dialysis patients (N=18).

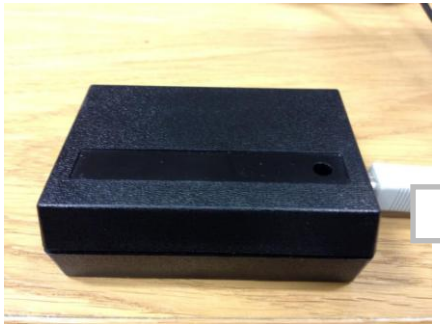


	UREA	UA	UREA+UA	UREA	UA	UREA+UA
	BLOOD			DIALYSATE		
Chi-Square	0,27	14,24	20,96	4,20	8,65	18,55
p	0,9649	0,0026	0,0001	0,3798	0,0706	0,0010
FALSE	27,8	11,1	0,0	22,2	11,8	0,0
TRUE	72,2	88,9	100,0	77,8	88,2	100,0

Holmar et al, Submitted to Clin Nephrology 2013

Multicomponent (MCM©) Sensor concept

OFT OPTOFLUID TECHNOLOGIES



MCM© sensor
Built-in module

Dialysis machine

Benefits

- Enhanced dialysis dose quality monitoring
- Cardioprotective therapy assurance
- Improved dialysis care
- Improved life quality
- Longer life expectancy
- Lower healthcare costs

Optofluid Technologies OÜ (OFT) is a spin off company based on the research from CEBE. MCM© sensor is an official trade mark of OFT.

CEBE Cooperation Project P5

IEEE TRANSACTIONS ON BIOMEDICAL ENGINEERING, VOL. 60, NO. 5, MAY 2013 1371

Accurate Dialysis Dose Evaluation and Extrapolation Algorithms During Online Optical Dialysis Monitoring

Ivo Fridolin*, *Member, IEEE*, Deniss Karai, Sergei Kostin, and Raimund Ubar, *Member, IEEE*

The advantages of the SMART algorithm compared to the L-M algorithm are that:

- data processing is done without any time delay providing instantly exact information about the treatment process;
- it allows for extrapolating at any time moment the current knowledge about the treatment process to predict the end for the treatment.

Conclusions

(Engineers + Doctors)*Collaboration = Happy patients!

Thank you for your attention!