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3D packaging for an implantable hemodynamic control system

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In this presentation, the 3D packaging for an implantable hemodynamic control system is proposed. The system consists of a pressure sensor, an ASIC for data and energy management, an accelerometer for measuring the position of the patient and an interposer as a base. The interconnects of a MEMS accelerometer, the integration of all components on the interposer and the encapsulation were elaborated within the Fraunhofer Lighthouse Project "Theranostic Implants" by Fraunhofer ENAS. The ASIC and the pressure sensor were developed by Fraunhofer IMS.
The base of the system, the interposer, features an LTCC technology with 75 µm line/space and 13 layers. It also contains a coil for inductive energy supply and data transmission. The ASIC and the MEMS accelerometer are mounted on the interposer either by flip-chip bonding with gold studbumps or by glueing and wire bonding. The bonds are stabilized with an underfiller and the wire bonds are protected by a glob top with a high thixotropy. The MEMS accelerometer is fabricated using deep reactive ion etching. After fabricating the MEMS core, it is wafer-level packaged with through-silicon vias. These through-silicon-vias are produced by etching square shaped holes in the silicon cap wafer. The buildup is investigated regarding bond quality and voids with micro computer tomography (Micro-CT) equipment and scanning acoustic microscopy (SAM). An Al_2O_3/Parylene system is used as a biocompatible and hermetic encapsulation. The system is highly miniaturized (length: 15 mm, diamter: 3 mm) due to the packaging technologies used and proved to be functional in first tests at Fraunhofer IMS.

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An auscultatory non invasive blood pressure equivalent without PEP?

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Puls transit time (PTT) is a non invasive method for estimating blood pressure. PTT is defined as the period of time, which the pulswave needs from systolic ejection to a certain point in the arterial system. Conventionally PTT is determined between the R-spike of the ECG and the arrival from the pulswave in the forefinger. Applying this method the pre-ejection period (PEP) is included in the PTT. PEP essentially depends on the sympatic activation of ventricle and negatively correlates with the heart period. Via an invasive animal experiment (canine) Zhang et al. 2011 proved, that 1/(PTT-PEP) is a better predictor for the diastolic blood pressure than 1/PTT. For the determination of the ejection time, phonocardiography and impedance cardiography have been applied.
Through temporary segmentation from the first heart sound into its internal acoustic components, events within the S1 can be defined and assigned to heart dynamics. Therefore the end of isovolumetric contraction of the left ventricel and the beginning ejection into the aorta ascendens can be indicated. Through the continous wavelet transformation and segmentation of pseudo spectrogram, we could isolate the acoustic components and fit them with bivariat models. By modeling and its proof of goodness of fit, it is possible to avoid misinterpretation and suppress potential outliers. The isohypse determined by bivariat modelling, enables us to detect the events of the heart dynamics.
First synchronised recordings of ultra sound doppler spectrums of the aorta ascendens and an intercostal parasternal auscultation show a high coincidence in time between the acoustic model and the starting point of the doppler spectrum.
By reducing the acoustic PEP from the PTT, the demonstrated method is an improvemend compared to the conventinal long term monitoring of the blood pressure equivalent via PTT.

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A chip-based biosensor for the detection of glycosylphosphatidylinositol-anchored proteins in serum as stress biomarkers

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The function of the post-translational modification of eucaryotic proteins with the glycolipidic structure glycosylphosphatidylinositol (GPI) remained enigmatic so far. Here a novel strategy is presented for the elucidation of the role of GPI-anchored proteins (GPI-AP), equipped with the complete GPI anchor and associated with phospholipids and cholesterol in extracellular complexes (GAPEC) which are assumed to be released in response to (metabolic) stress, such as prevalent during type 2 diabetes (T2D). The putative correlation of GAPEC in serum with (pre-)diabetic states has not been studied so far.
A chip- and microfluidic channel-based biosensor relying on surface acoustic waves (SAW) was used, which detects capturing of the GAPEC by the chip gold surface via the GPI-binding molecule, α-toxin, and monitors phospholipids of the GAPEC via binding of annexin-V. Time-resolved phase shifts and amplitude reductions of the SAW (signatures) reflected alterations in mass loading of the GAPEC to the chip surface and in their viscoelasticity, respectively, as validated with exosomes from primary rat adipocytes, which represent a subspecies of GAPEC. Pairwise comparison of SAW signatures produced by the GAPEC in pooled or individual serum samples in the presence of PIG enabled differentiation according to either genotype (between insulin-sensitive lean Wistar and ZF or insulin-resistant obese Wistar and ZDF or insulin-resistant obese ZF and diabetic obese ZDF rats) or body weight (between ZF lean and insulin-resistant obese or insulin-resistant ZDF lean and obese rats or Wistar lean and obese rats). Loss of the differentiating SAW signatures in course of elimination of GPI-AP, phospholipids or cholesterol and exposure toward physical stress, which was used for the delineation of critical threshold values for the differentiation, is compatible with serum GAPEC constituted by weak interactions between their components within a non-vesicular configuration. Thus, GPI-AP in serum GAPEC may be correlated to early stages of T2D, in particular, and regarded as phenomenological biomarker for the prediction of stress-related disorders, in general.

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Impaired autonomic regulation in ideopathic sudden sensorineural hearing loss patients - Does it depend on hypertension?

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The causes of idiopathic sudden sensorineural hearing loss (ISSHL) still remain uncertain, as does the specific site of inner ear disease. There is a high variability of severity of hearing loss, its spontaneous improvement, and response to medical treatment. Probably, this high variability expresses that ISSHL is a collective term for a multicausal disease. It is known that ISSHL influences the autonomic regulation (AReg).
The aim of this study was on the one side to validate the presence of an impaired AReg in ISSHL patients, differing from the AReg in normal-hearing controls (CON) and on the other side to investigate the influence of hypertension on the impaired AReg in ISSHL.
Firstly we investigated 19 CON (10 male, 9 female, age: 38.6 ± 8.3 years) and 14 ISSHL (8 male, 6 female, age: 48.6 ± 16.1 years) without hypertension. Secondly we investigated an age matched group of 27 ISSHL subdivided into two groups - hypertension (8 male, 4 female, age: 59.7 ± 7.3 years) and no hypertension (7 male, 8 female, age: 52.3 ± 14.1 years). Time and frequency domain analysis, segmented Poincaré plot analysis (SPPA) and joint symbolic dynamics (JSD) analysis were performed on 30 minutes beat-to-beat (BBI), systolic (SBP), and diastolic (DBP) blood pressure time series.
The results indicate significant differences in BBI (p=0.0008), SBP (p=0.004) and DBP (p=0.001) as well as JSD (p=0.0007) between CON and ISSHL. These indices were not affected by hypertension. However, a few and different parameters from DBP, SPSS and JSD revealed significant differences between the hypertension and no hypertension groups.
In conclusion, ISSHL patients clearly show an impaired AReg in different domains. The indices which characterize this impairment are independent from the co-morbidity hypertension. Hypertension leads also to an impairment of AReg that is, however, characterized by other indices.

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Correlation of Mayer waves in arterial blood pressure and retinal vessel diameter

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Static and dynamic retinal vessel analysis are promising tools for the early risk evaluation of cardiovascular diseases. Mayer waves are temporal biological variations visible in retinal vessel diameter and lead to uncertainties in this analysis. A correlation to blood pressure is described in literature. We investigated the temporal correlation of retinal vessel diameters and arterial blood pressure in the range of the low frequency waves in a multimodal measurement study to understand the temporal relation.
In accordance with the Declaration of Helsinki we performed measurements on 15 young and healthy subjects. Six repeated measurements with a duration of six minutes each were performed within a time period of 90 minutes. Retinal vessels were recorded by Dynamic Vessel Analyzer and the arterial blood pressure was recorded by means of a continuous blood pressure measurement device simultaneously. From the retinal vessel diameters, the equivalent values of arterial and venous vessel diameters CRAE and CRVE were calculated, the Mayer waves around 0.05Hz as well as 0.1Hz were extracted by filtering and the temporal dependencies were determined by cross correlation. Cross correlation yielded clear dependencies in most of the 90 datasets. The following time shifts are determined for the strongest correlations: For 0.05 Hz the minima of arteries are median -3.83 s / IQR 3.38 and the minima of veins are median -6.03 s / IQR 3.94. Around 0.1Hz the minima of arteries are median -4.01 s / IQR 1.90 and the maxima of veins are median -0.16 s / IQR 0.86. Distribution of the time shifts around 0.1Hz is much narrower than around 0.05Hz. Most of the outliers are shifted by one period. Randomly shifted outliers have lower correlation coefficients. Most outliers are concentrated on a few subjects. Outliers for arterial and venous correlation are not necessarily related.

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Empirical mode decomposition and time varying modelling for carotid audio signal analysis

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Auscultation is the acoustic diagnosis of the internal sounds of the body, using a stethoscope. It is performed for examination of the sounds of the circulatory and respiratory systems. Experienced clinicians can hear the flow of blood e.g. in the carotid arteries. We assume that this sound will change over the human life time due to changes inside the vessels. If it is possible to hear the blood flow, it should also be possible to automatically measure changes in the sound of the blood flow. The main problem is that it is necessary to detect dynamical changes at a really long term in a signal that is highly short-term nonstationary. In this work a time-varying (TV) Empirical Mode Decomposition (EMD) analysis was performed to find a trace in the carotid audio signal that is invariable in long-term spaced recordings. EMD has been proposed in the literature as an adaptive time-frequency signal analysis method for dealing with processes involving nonlinear and nonstationary characteristics. Here EMD is used to identify dynamical changes of the carotid blood flow that could be characteristic of each subject through the decomposition of the carotid audio signal in different modes. For that a stethoscope with a microphone were combined with a smartphone for the acquisition of carotid audio signals from five volunteer subjects at different dates in an interval of two months. The recorded signals were first filtered using a wavelet based band-pass filter. The signals were then decomposed using EMD and for some selected modes TV AR models were computed. Finally the TV spectrum and poles were calculated for analysis. Preliminary results show that the TV poles of some modes of the audio signal can be different from subject to subject, and the idea is to further investigate these patterns for patient specific very long-term monitoring.

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Nonparametric modeling of quasi-periodic signals – application to esophageal pressure filtering

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The pressure measured in the esophagus is an important quantity used for the assessment of patient-ventilator interaction during mechanical ventilation. Unfortunately, the esophageal pressure signal is subject to cardiogenic pressure oscillations, which may complicate diagnosis. This work addresses the separation of the respiratory and the cardiac signal component. The two signals can be discriminated by their fundamental frequency, however, conventional lowpass filtering is inappropriate due to band-overlap between the harmonics. Here we consider a nonparametric modeling approach via Gaussian processes. The quasi-periodicity of both signals in the mixture is described by their second order statistics, thus enabling the reconstruction of each source. The chosen kernel covers a wide range of respiratory and cardiogenic waveforms. Information about periodicity is incorporated from reference signals: the respiratory frequency is given by ventilatory data, the cardiac frequency by the electrocardiogram. The remaining hyperparameters of the covariance function are learned through maximization of the marginal model likelihood using gradient descent. We demonstrate the effectiveness of the method on esophageal pressure recordings of patients under assisted spontaneous ventilation. Compared to previous approaches for cardiogenic artifact removal, which merely incorporate the cardiac frequency, the proposed technique takes advantage of the additional information given by the periodicity of the respiratory signal. It provides a generic framework for the separation and denoising of respiratory-cardiac signal mixtures and thus may also be applied to related problems.

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Using functio-anatomical prior knowledge in linear EEG/MEG source reconstruction methods

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Reconstructing brain activity from electro-/magnetoencephalographic (EEG/MEG) data requires the solution of the bioelectromagnetic inverse problem. This problem, however, cannot be solved based on EEG/MEG data alone. Additional assumptions are needed to obtain a unique solution. A common class of methods is based on distributed source models, where a large number of sources (i.e., dipoles) with fixed orientations and locations cover the region of interest (e.g., the cortex). The task is to estimate a spatial distribution of the source strengths. As this is usually a strongly underdetermined problem (many more source strength than measurement channels), often spatial smoothness is used as an additional constraint. This is equivalent to the prior assumption of a particular source covariance structure.
Recent publications have suggested to alter this spatial correlation structure such that it reflects available knowledge on the functio-anatomical organization of the brain. In particular, it is possible to derive borders between different brain areas from various types of brain images. This allows assuming that sources located within the same area exhibit similar activity and sources in different areas are mutually uncorrelated. Here, we present Monte-Carlo simulations, which provide a systematic evaluation how such functio-anatomical prior knowledge influences the estimate of different linear inverse procedures. The study aimed at answering questions like "What happens if the course of boundaries is uncertain?", "What if our knowledge on functional areas is limited to certain cortical regions?" and "Can prior knowledge improve source localization?". We found that it is crucial that the incorporated boundaries and the underlying activity are consistent. Omitting boundaries or using additional boundaries expresses a believe on the source correlation structure that is not supported by data. Moreover, we demonstrate our method to localize auditory N100 activity from experimental EEG/MEG data. The results clearly suggest that spatially informed linear inverse methods provide very plausible reconstruction results.