Abstract of the PhD dissertation

"Analysis of biosignals in joint time-frequency domain"

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Cerebral blood circulation control mechanisms are responsible for stabilizing cerebral blood flow at a level adjusted to metabolic needs of the brain. Cerebral autoregulation (CA) is a complex process which exhibits non-stationary behaviour. Diseases related to impaired CA, such as ischaemic strokes, intracerebral haemorrhages, or traumatic brain injuries, are frequent causes of disability and death, particularly among people in working age.

The most popular non-invasive method of CA assessment is the analysis of mutual relation between arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV). The most common tool to model and analyse this relation is the transfer function. The spectral transfer function analysis yields three parameters: gain, phase shift, and coherence. Among these parameters, the phase shift between ABP and CBFV is of the greatest clinical importance. Even though these parameters provide a rather basic description of CA, their physical and physiological interpretation is straightforward, and hence they are widely accepted in clinical practice. The transfer function approach assumes that the system linking the input (ABP) and the output (CBFV) is linear and time-invariant. It is the simplest tool for modelling dynamic systems.

There exist complex non-linear models based on Volterra series which allow describing changes in CBFV in response to changes in ABP as well as to changes in other factors if multiple-input models are considered. These models are computationally inefficient, difficult to interpret, and appear to be impractical in clinical applications. From the physicians' point of view, it is important to draw reliable conclusions about patient's clinical state and verify or potentially adjust the therapeutic strategy on this basis.

Methods that account for non-stationarity of CA are a good compromise between the simplicity of the classical spectral approach and accurate modelling of cerebral blood flow. The wavelet transform has already been employed to investigate CA. It leads to the so-called scalogram, i.e., time-scale representation. Although interpretation of the scalogram in the time domain is straightforward, it is less intuitive to retrieve information in the frequency domain from this representation, compared to time-frequency representations. In the dissertation, CA is assessed by means of the Zhao–Atlas–Marks transform, which leads directly to a time-frequency representation [1, 2], and the multichannel matching pursuit, which decomposes signals using Gabor atoms of known location in time-frequency plane [3]. Both methods allow estimating phase shift between considered signals, a measure which provide clear interpretation and is thus accepted by clinicians.

Part of the following dissertation is devoted to the aspect of complexity of physiological signals. According to the decomplexification (reduction of complexity) theory of illness, high complexity of physiological signals is a manifestation of the working mechanisms

that control an organism and adjust it to the changing environment. A decrease in complexity is attributed to an impairment of these mechanisms, which often occurs in diseases as well as with ageing and may be linked to a poor outcome of a treatment. The term *complexity* has not yet been strictly defined, hence there is no single universal index of complexity. Numerous clinical studies, including those of the Author [4, 5], indicate usefulness of complexity estimators in the analysis of signals carrying information on cerebral haemodynamics.

The aim of this dissertation was to apply time-frequency methods to analyse physiological signals carrying information on CA and to investigate how complexity and asymmetry of those signals depend on the occurrence of intracranial pathologies.

An alternative method, based on the Zhao–Atlas–Marks transform, for calculating the CA index was proposed and discussed in detail in [1], where controlled hypercapnia was used as a model of disturbed CA. In that work, non-stationarity tests showed that in more than half of the cases, ABP and CBFV as well as the phase shift between them cannot be deemed stationary. The method was also used to study CA in healthy volunteers during controlled respiratory rate [2] and to study baroreflex sensitivity during postural changes and hypercapnia [6]. In [1], it has been shown that the method based on the Zhao–Atlas–Marks transform led to lower dispersion of phase estimates, compared to the classical method. Furthermore, the proposed method, unlike the spectral approach, does not require data rejection, even in the case of low average spectral coherence between considered biosignals. Results of performed analyses confirm the hypothesis no. 1 stating that applying time-frequency methods to describe the relationship between ABP and CBFV allows assessing CA better than the spectral approach.

Results of the studies presented in [4, 5] concern analysis of complexity of physiological signals. In [4], complexity of ABP and CBFV signals, registered in patients after aneurysmal subarachnoid haemorrhage, was evaluated indirectly via their time-frequency representations. This way of estimating complexity is novel, as previous studies focused on calculating entropy of these signals directly from their time courses. Paper [5] is the first work where complexity of cerebral oxygenation signals were investigated in critically ill preterm infants. Previous studies on complexity of physiological signals in babies focused mainly on analysing electrical signals, such as EEG or ECG. Obtained results confirm the thesis no. 2 stating that impaired ability of the brain to control cerebral blood flow correlates with decreased complexity of cerebral oxygenation signals, CBFV, and ABP in the low frequency band (slow waves). Low complexity of brain signals may serve as an early-warning indicator for prediction of upcoming narrowing of cerebral artery in patients after aneurysmal subarachnoid haemorrhage [4] and unfavourable outcome of treatment in preterm infants [5].

In [3], a novel asymmetry index — the phase shift estimated between slow waves of CBFV recorded in the main cerebral arteries on both sides of the patient's head — was proposed. In order to account for non-stationarity of analysed signals, a method based on the multichannel matching pursuit was applied to estimate the phase shift between left and right CBFV. Another advantage of the multichannel matching pursuit is the ability to

eliminate the so-called cross terms without worsening the time-frequency resolution, which is generally not possible in the case of the Zhao–Atlas–Marks transform. A progressive asymmetry, manifested by a gradual increase in the phase shift on consecutive days after aneurysmal subarachnoid haemorrhage, was observed in patients who developed vasospasm. Patients who had positive average value of the asymmetry index were more likely to develop vasospasm. Obtained results confirm the thesis no. 3 stating that the asymmetry of cerebral blood flow slow waves after aneurysmal subarachnoid haemorrhage correlates with the occurrence of cerebral vasospasm. It has also been shown that the phase shift estimated using the method based on the multichannel matching pursuit reflects the cerebral blood flow asymmetry better than the phase shift calculated by the conventional spectral analysis.

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[1] **Placek M.M.**, Wachel P., Iskander D.R., Smielewski P., Uryga A., Mielczarek A., Szczepański T.A., Kasprowicz M., „Applying Time-Frequency Analysis to Assess Cerebral Autoregulation during Hypercapnia", *PLOS ONE*, **2017**, 12(7): e0181851; doi: 10.1371/journal.pone.0181851, IF_{2017}: 2.766, MNiSW points: 40.

[2] Uryga A., **Placek M.M.**, Wachel P., Szczepański T., Czosynka M., Kasprowicz M.; „Phase shift between respiratory oscillations in cerebral blood flow velocity and arterial blood pressure", *Physiological Measurement*, **2017**, 38(2): 310–24; doi: 10.1088/1361-6579/38/2/310, IF_{2017}: 2.006, MNiSW points: 20.

[3] **Placek M.M.**, Smielewski P., Wachel P., Budohoski K.P., Czosnyka M., Kasprowicz M., "Can interhemispheric desynchronization of cerebral blood flow anticipate upcoming vasospasm in subarachnoid haemorrhage patients?" *Journal of Neuroscience Methods*, **2019** (under review), IF_{2017}: 2.668, MNiSW points: 25.

[4] **Placek M.M.**, Wachel P., Czosnyka M., Soehle M., Smielewski P., Kasprowicz M.; „Complexity of Cerebral Blood Flow Velocity and Arterial Blood Pressure in Subarachnoid Hemorrhage Using Time-Frequency Analysis", *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, **2015**: 7700–3; doi: 10.1109/EMBC.2015.7320176, Web of Science points: 15.

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