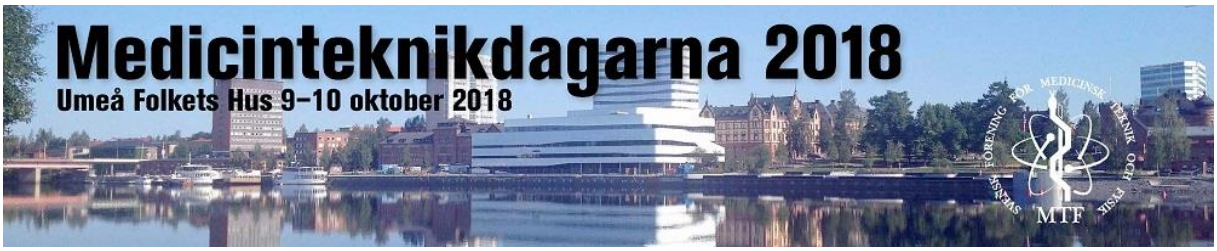


PROJEKT MED STÖD FRÅN VETENSKAPSRÅDET

Tisdag 9 oktober 15.15 – 17.00

Abstract: 102

Laser-based real-time breath gas analysis coupled to gas exchange modelling

*R. Ghorbani, *F. Schmidt*; Umeå University, Applied Physics and Electronics, Umeå*

Breath gas analysis is a rapidly evolving research field and increasingly used in medical diagnostics for non-invasive assessment of the physiological and metabolic state of the body [1]. Applications range from critical care, treatment and biological monitoring to stable isotope tests, breathomics and validation of physiological models. However, only a handful of breath tests are used clinically.

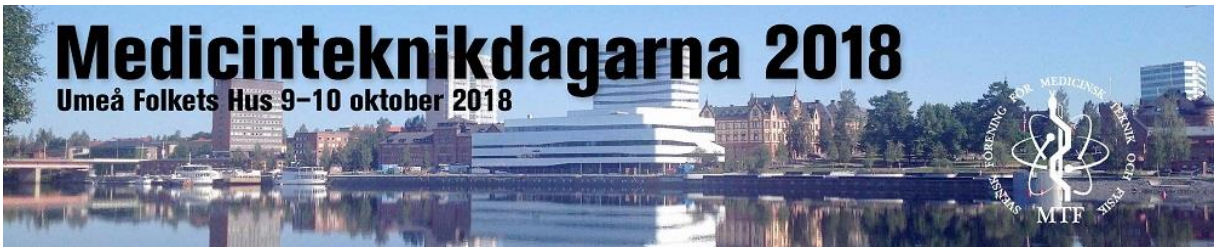
The main reasons is the lack of compact, user-friendly instruments that can perform state-of-the-art breath analysis, which implies online sampling, selective real-time detection of individual breath cycles (exhalation profiles) with high sensitivity, and requires good knowledge about biomarker origin, gas exchange and chemical pathways. Single-exhalation profiles measured with high precision and time-resolution also carry spatiotemporal information about the respiratory tract and can be coupled to gas exchange models to facilitates data interpretation and retrieve physiological parameters [2]. Exhaled breath carbon monoxide (eCO) is a promising biomarker for non-invasive assessment of (systemic and local) oxidative stress and respiratory diseases.

However, conventional end-tidal eCO analysis with electrochemical sensors cannot distinguish, whether eCO reflects blood CO, exogenous sources or lung diffusion properties, and it cannot discriminate airway from alveolar contributions. In this work, eCO exhalation profiles are measured using mid-infrared tunable diode laser absorption spectroscopy (TDLAS) [3, 4]. The system combines an interband cascade laser operating at 4.7 µm, a compact, low-volume multipass cell and wavelength modulation spectroscopy to achieve a detection limit of 9 ppbv at 5 ppbv precision and 0.1 s acquisition time [4].

A trumpet model with axial diffusion (TMAD) is employed to simulate the CO gas exchange dynamics in the respiratory tract and corresponding eCO profiles. Calculated expirograms are then least-squares fitted to the experimental data to extract TMAD parameters, such as maximum fluxes, diffusing capacities and expected equilibrium concentrations of CO in airways and alveoli. Using measured respiratory data and inhaled CO as model input, good fits are achieved for expirograms recorded during tidal breathing and after breath-holding.

A simulation study shows that changes in alveolar flux and diffusing capacity affect the profile shape in a unique way, and that a small increase in airway flux can be distinguished from an increase in alveolar flux. Clinical studies were conducted to establish the healthy-population baseline and diurnal variation of the eCO TMAD parameters, and to investigate the effects of 2 hour exposures to 10 ppm CO and wood smoke (400 µg/m3 PM0.4, ~10 ppm CO) on healthy non-smokers. Extended real-time breath gas analysis opens up for novel breath tests with improved diagnostic value.

References *[1] A. Amann, D. Smith. Volatile Biomarkers: Non-invasive Diagnosis in Physiology and Medicine. 2013 (Elsevier). [2] J. E. Mountain et al. Potential for noninvasive assessment of lung inhomogeneity using highly precise, highly time-resolved measurements of gas exchange. J. Appl. Physiol. 2018; 124:615-631 [3] R. Ghorbani, F. M. Schmidt. Real-time breath gas analysis of CO and CO2 using an EC-QCL. Appl. Phys. B 2017; 123:144 [4] R. Ghorbani, F. M. Schmidt. ICL-based TDLAS sensor for real-time breath gas analysis of carbon monoxide isotopes. Opt. Express 2017; 25:12743-12752*



Abstract: 108

B-tensor encoding is clinically feasible and may add relevant information in the work-up of patients with brain tumors

**J. Brabec*1, F. Szczepankiewicz2, C.-F. Westin2, A. Golby3, D. van Westen4, P. C Sundgren4, M. Nilsson5; 1Lund University, Medical Radiation Physics, Lund, 2Harvard Medical School, Brigham and Women's Hospital, Laboratory for Mathematics in Imaging, Boston, 3Harvard Medical School, Brigham and Women's Hospital, Department of Neurosurgery, Boston, 4Lund University, Radiology, Lund, 5Lund University, Clinical Sciences Lund, Department of Radiology, Lund*

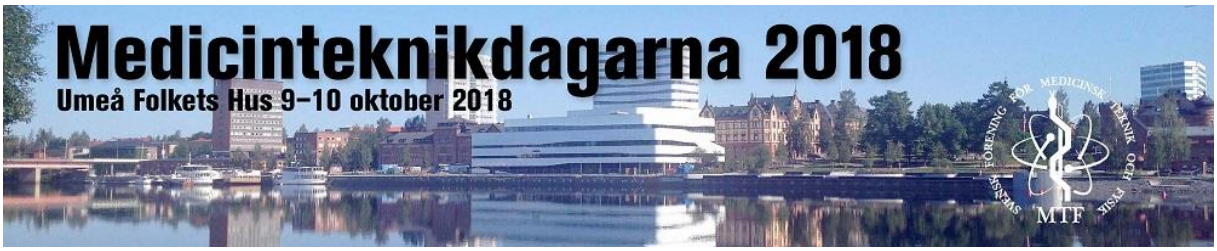
Background:
Diffusion MRI (dMRI) is a non-invasive method that is uniquely sensitive to tissue microstructure. However, dMRI methods that utilize a conventional Stejskal-Tanner encoding may convolve several interesting features. These may be disentangled using the additional information from the novel B-tensor encoding concept. It has been shown to improve discrimination shapes or orientation dispersion within tissues[1][2]. Here, we studied dMRI-derived quantities related to microstructural features, namely tissue heterogeneity MKI and microscopic anisotropy MKA. We applied B-tensor encoding to 4 brain tumor types and describe them in terms of their MKI, MKA, and mean diffusivity maps. Importantly, we showed that it is feasible to acquire the data in under 3 minutes and thus B-tensor encoding may be added to the work-up of patients with brain tumors.

Material & Methods:
Patients were scanned on a 3 T MAGNETOM Prisma (Siemens Healthcare, Germany) with a 20-channel coil array with a prototype spin-echo sequence that enables B-tensor diffusion encoding. TE=80 ms, TR=3.2 s, FOV=230x230 mm2, slices=21, resolution 2.3x2.3x2.3 mm3, iPAT=2, partial-Fourier=6/8 and four equidistant b-values between 0.1 and 2.0 ms/μm2. Gradient waveforms were optimized to minimize the TE. The signal was modelled by: $S(b,b\Delta)=\exp(-b\ MD + b2\ MD2\ MKI/6+b\Delta 2b2MD2MKA/6)$. Where b is the classical b-value, bΔ b-tensor shape, MD mean diffusivity, MKI tissue heterogeneity and MKA microscopic anisotropy. Analysis was implemented in Matlab (The Mathworks, USA) available at https://github.com/markus-nilsson/md-dmri. Nine high-grade glioma (grade III and IV), two metastases, one pituitary adenoma and five meningiomas were studied. Regions of interests (ROIs) were chosen manually in the contrast-enhanced regions. Necrotic parts were discarded. For comparison, additional ROIs were chosen in a normal-appearing white matter in the frontal lobe.

Results:
Post-Gadolinium T1-weighted images of the different tumors were compared to tissue heterogeneity and microscopic anisotropy maps that were acquired under 3-minute-long scan time. Normal-appearing white matter showed high microscopic anisotropy and low tissue heterogeneity, which supports their interpretations as the elongation of cell shapes and cell density variance, respectively. Glioblastoma and metastasis showed low microscopic anisotropy but higher tissue heterogeneity. Pituitary adenoma and meningioma showed both higher microscopic anisotropy and tissue heterogeneity.

Conclusions:
It is possible to add B-tensor encoding to clinical protocols since the high-quality images can be acquired under 3 minutes of scan time[1]. Such short scan time was achieved by gradient waveform optimization. B-tensors encoding allows to separate microstructural parameters that were previously confounded when using conventional dMRI methods[2]. Specifically, microscopic diffusion anisotropy and tissue heterogeneity both lead to high diffusional kurtosis although they describe various aspects of the microstructure.

References: *[1] M. Nilsson et al. "Tensor-valued diffusion MRI in under 3 minutes: An initial survey of microscopic anisotropy and tissue heterogeneity in four brain tumor types." Proceedings of the 27th Annual Meeting of ISMRM. 2018. [2] F. Szczepankiewicz et al. "The link between diffusion MRI and tumor heterogeneity: Mapping cell eccentricity and density by diffusional variance decomposition (DIVIDE)." NeuroImage 142 (2016): 522-532.*



Abstract: 74

Tidsserie av Ramanspektra - biokemisk aktivitet från enskilda celler vid olika syrehalter

**J. Wahl*1, K. Ramser2, F. Knöpp3, A. Andersson1, J. Borg4; 1Teknikvetenskap och matematik, Strömningslära och experimentell mekanik, Luleå, 2Department of Engineering Sciences and Mathematics, Luleå, 3Excellence Cluster Cardio-Pulmonary System, Giessen, 4CMS, London*

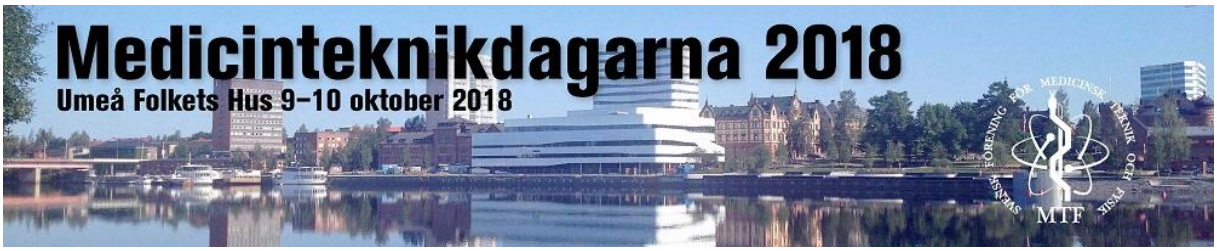
Bakgrund
Det är viktigt med effektiv syretransport från våra lungor till blodflödet. Akut syrebrist i lungornas alveoler kan leda till Pulmonell Arteriell Hypertension (PAH), där pulmonella arteriella glattmuskelceller (PASMCs) är effektorceller. Vid hypoxi drar cellerna ihop sig, vilket gör att blodflödet omfördelas till områden med större syremängd för att maximera syreupptagningen. För den som lider av sepsis, lunginflammation, leversvikt eller genomgår anestesi kan PAH blir livshotande. En kronisk ökning av flödesmotståndet i lungornas artärer leder till att hjärtats högra kammare behöver arbeta hårdare. Vilket ofta leder till hjärtsvikt. Det har föreslagit att PAH kan utlösas av reaktiva syreföreningar, som produceras av NADPH-oxidas eller mitokondrier [1,2]. Raman-spektroskopi har visat sig vara ett värdefullt hjälpmedel för att studera mitokondriella biomarkörer. Vi presenterar ett gastätt mikroflödessystem som tillåter mätningar med Raman-spektroskopi och patch-clamp samtidigt som syremängden i provet kan kontrollera.

Material och metoder
Mikroflödessystemet designades i ett CAD program. Computational Fluid Dynamics (CFD) simuleringar av mikroflödessystemet gjordes i Ansys CFX 16 för att undersöka olika utflödes geometrier. Därefter var kanalsystemet konstruerat från polykarbonat med hjälp av CNC-automatiserad borrning. Nyligen isolerade PASMCs från C57BL/6J-möss fick växa på botten av petriskålar i 7 till 10 dagar innan experiment. Tre olika experiment genomfördes där flödesvätskan ändrades (i) efter de första två mätningarna och (ii) efter 4 min för att sedan avslutas efter ytterligare 4 min. Lösningarna av experiment 1 var (a) en normoxisk (21 % O2, 5,3 % CO2 och resten N2) och (b) en hypoxisk Tyrode-lösning (1 % O2, 5,3 % CO2 och resten N2). I experiment 2 byttes flödes från (a) till en lösning med väteperoxid. I kontrollexperimentet (samma tidsram) byttes vätskan inte ut. En grön (532nm) laser användes för att göra resonans Raman mätningar parallellt med flödesförloppet. Differensspektra och t-test (signifikansnivå: 5 %) användes för att identifiera statistiskt signifikanta förändringar i Raman-spektra. Dessa förändringar jämfördes sedan automatiskt med en databas, som bestod av tidigare identifierade relevanta Raman-toppar.

Resultat
Mikroflödessystemet gjorde det möjligt att snabbt ändra syretillståndet till en stabil nivå på under 2 % i området intill PASMCs. Ett litet stegsvar i det resulterande Raman-spektrat kunde mätas, som inte observerades för kontrollmätningarna. Signal-brus-förhållandet som härrörde från flödet och fysiologisk aktivitet i PASMCs försvårade analysen av mätningarna för isolerade Raman-toppar, men flera statistiskt signifikanta förändringar vid kända Raman-toppar identifierades ändå för bland annat cytokrom c, mitokondrier och lipider. Totalt observerades 14st signifikanta förändringar för kända Raman-toppar för hypoxi, 10st för väteperoxid och 6st för kontroll (normoxi).

Slutsats
Det verkar möjligt att följa redox stadierna hos mitokondriella och andra biomarkörer med resonans Raman-spektroskopi.

Referenser *[1] Almohammedi, A., et al., Spectroscopic analysis of myoglobin and cytochrome c dynamics in isolated cardiomyocytes during hypoxia and reoxygenation. Journal of the Royal Society Interface, 2015. 12(105). [2] Erjavec, N., G. Pinato, and K. Ramser, Raman spectroscopy as a tool for detecting mitochondrial fitness. Journal of Raman Spectroscopy, 2016: p. n/a-n/a.*



Abstract: 72

Computed Tomography Image Estimation by Statistical Learning Methods

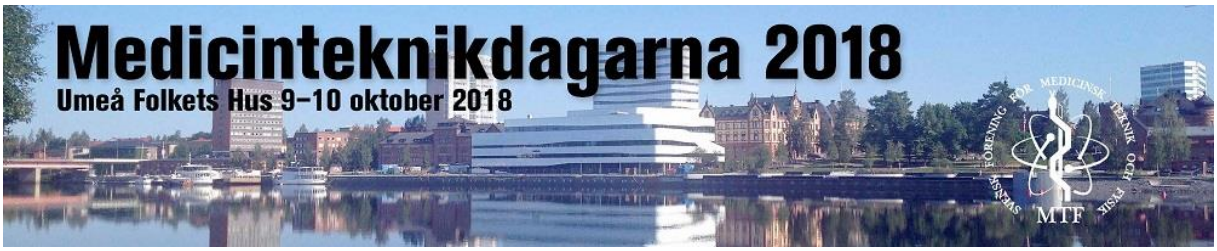
**J. Yu*; Umeå University, Mathematics and Mathematical Statistics, Umeå*

Purpose:
There is increasing interest in computed tomography (CT) image estimations from magnetic resonance (MR) images. The estimated CT images can be utilised for attenuation correction, patient positioning, and dose planning in diagnostic and radiotherapy workflows.

Methods:
This study presents a statistical learning method for CT image estimation. We have used predefined tissue type information in a Gaussian mixture model to explore the estimation. The performance of our method was evaluated using cross-validation on real data.

Results:
In comparison with the existing model-based CT image estimation methods, the proposed method has improved the estimation, particularly in bone tissues.

Conclusions:
Evaluation of our method shows that it is a promising method to generate CT image substitutes for the implementation of fully MR-based radiotherapy and PET/MRI applications. Keywords: computed tomography; magnetic resonance imaging; CT image estimation; pseudo-CT image; supervised learning; Gaussian mixture model



Abstract: 109

Iso-acoustic focusing for flow cytometry and cell isolation

*P. Augustsson, *M. Rezayati Charan*; Lund University, Biomedical Engineering, Lund*

A major challenge in both label-based and label-free cell detection and isolation methods is to discriminate rare sub-populations of cells from an abundant background of other cells. An example of this is to detect circulating tumor cells in the blood of cancer patients to monitor the effect of treatment where just a few cancer cells per milliliter blood must be isolated from a background of billions of blood cells. It is the overall purpose of this VR-funded project to address this hurdle by microfluidic ultrasound-based separation.

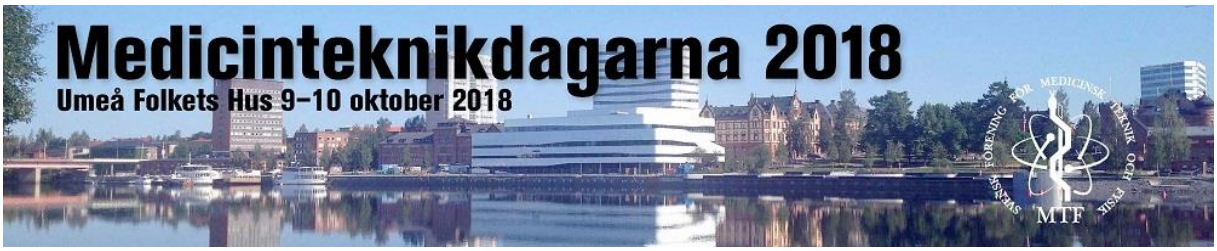
This can lead to faster cell-based assays, enabling continuous monitoring or treatment of patients and enables measurement of biophysical properties at single cell level. Increasingly size, density, deformability, morphology and electrical properties of cells are being utilized to fraction cells that are viable and accessible for further culturing and assessments.

Methods that do not rely on pre-treatment using chemical labels can lead to faster analysis in cell-based assays enabling continuous monitoring or treatment of patients. In the extension of this we can envision panels of mechanical and optical properties that can be combined to perform multidimensional tunable cell filters to analyze or isolate target cells with minimal sample preparation.

We are developing a microfluidic instrument, an iso-acoustic flow cytometer [1], that enables measurement of the acoustic properties of thousands of single cells in minutes. In iso-acoustic focusing cells are flowing through a microfluidic chip and are exposed to an ultrasound standing wave that deflects their trajectories in a predictable manner based on their mass and size.

With this instrument we can chart the distributions and correlation between properties for a panel of different cell types and cell states related to detection and isolation of rare cells from blood. In addition we are developing an instrument to isolate rare target cells directly from blood and route them to a specific outlet of an acoustic microfluidic chip and thus enabling fast and label-free acces to these cells.

References *[1] Augustsson et al., Iso-acoustic focusing of cells for size-insensitive acousto-mechanical phenotyping, Nature Communications 7, 11556 (2016)*

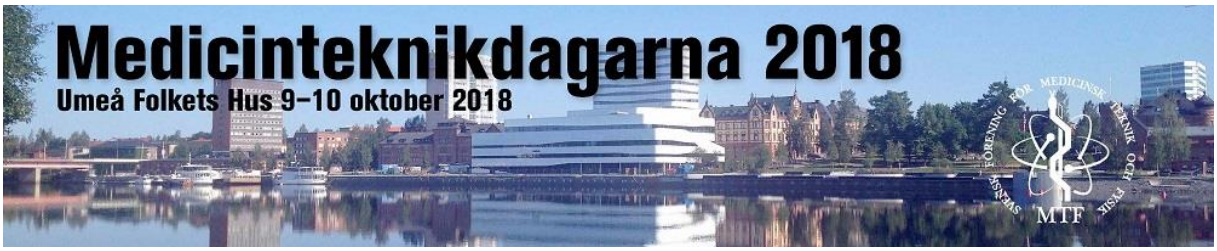


Abstract: 37

Swedish guidelines for registry-based randomized clinical trials

*P. Hedman, *F. Kåver*; Uppsala Clinical Research Center, Uppsala Universitet, Uppsala*

During the last decade Sweden has invested in a national infrastructure for collection of structured clinical data in the form of healthcare registries (in Sweden known as Kvalitetsregister). This data can be combined with other public data using the national personal identifiers that is issued to Swedish citizens. The healthcare registries have an almost complete coverage of Swedish healthcare and a large network of clinicians is involved in the quality assurance and continuous improvement of healthcare using these registries. Uppsala Clinical Research Center (UCR) has been a technology provider of large scale national registries and has a strong background in clinical trial management. This effort combines the areas of healthcare registries and clinical trials into a novel way of performing clinical trials to be able to 1) run clinical trials as an integrated part of normal clinic workflow and 2) leverage the nationwide network of outcome reporting. This strategy was proven a tremendous success in the TASTE (Thrombus Aspiration in Myocardial Infarction) study (see 4. Case study). After TASTE was published the New England Journal of Medicine wrote a perspective on the study calling it "The randomized registry trial – the next disruptive technology in clinical research?" The registry-based RCT is an efficient and effective mechanism to assess hard clinical endpoints in large patient cohorts. Hitherto, registry based randomized trials have evaluated treatments strategies and devices or simples pharmaceutical agents, but there is no strict limit to what therapy can be evaluated with the registry link as long as patient safety is assured and there is adherence to existing regulations. Registry-based RCTs with more efficient and streamlined trial conduct may also be possible for evaluation of approved pharmaceutical agents for new indications and labels. The benefit of the RRCT is related to the ability to identify patients, enroll larger proportions of patients in relative short time and a possibility of indefinite follow-up. Together with the fact that a RRCT often is much more inexpensive than an ordinary RCT has made the RRCT renown on a global scale. Since then several studies has been conducted this way with great success. UCR has been appointed, by Clinical Studies Sweden and the Swedish Research Council, to develop the Swedish national guidelines for registry-based randomized clinical trials in order to ensure the possibility for more organization to run this kind of studies. The guidelines consists of documentation on the specifics on running a clinical trial as an RRCT as well as a technical framework. The framework specifies the domain of Clinical Trials and defines business rules for legal compliance. The building blocks of the framework are combined to support the clinical trial at hand and coupled to the registry after being validated against the study protocol. The clinical trial implementation is treated as a stand-alone application which shares life-cycle with the registry. This architecture handles the incompatible legal requirements between clinical trials and registries with regard to patient/participant opt-out.



Abstract: 107

Minimalistic complexity analysis for feature-based classifiers of atrial fibrillation

*A. Abdukalikova1, D. Kleyko1, E. Osipov1, *U. Wiklund*2; 1Luleå University of Technology, Luleå, 2Umeå University, Radiation Sciences, Umeå*

Background
The 2017 Computing in Cardiology conference challenge was devoted to automatic atrial fibrillation (AF) classification based on short ECG recordings [1]. The proposed data-driven solutions concentrated on maximizing the classifiers' mean F1-score, whereas the number of features used for classification was not considered. We believe that the deployment of AF classifiers should be done on resource-limited devices. Local processing is preferable because of intermittent connectivity and data privacy. However, this demands simple computations (preprocessing, feature extraction, classification), i.e., the practical limitation is the computational complexity of the solution.
We argue that the complexity of the classifier must be addressed as it places restrictions on the applicability of inexpensive devices for AF monitoring outside hospitals. Therefore, we investigated the feasibility of complexity reduction by analyzing one published classifier from the competition [2].

Materials & Methods
We focused on a random forest classifier, where complexity was analyzed in terms of number of features extracted according to (. Each of the 8528 recordings in the published data from the competition was represented by 171 features. The performance was measured with accuracy and mean F1-score using 5-fold cross-validation. The most important featureswere identified by using Recursive Feature Elimination method [3], which is based on a feature ranking criterion. Results
Results showed that the best set of 5 features worsened accuracy by 6.0% and F1-score by 6.7% (compared to results for the full classifier using all 171 features). The difference to the full classifier when using 10 features was only 2.4% and 1.3% respectively. There was no performance degradation for 15&20 features. Accuracy for 8 temporal features was comparable to 5 best features but F1-score was 7.1% worse.

Conclusions
We postulate the feasibility of using Recursive Feature Eliminationfor decreasing the AFclassification complexity (both the number of features and the need for signals transformations), thus increasing the possibility of deployment on resource-limited devices.

References *[1] G Clifford. et al. AF Classification from a short single lead ECG recording: the PhysioNet/Computing in Cardiology Challenge 2017. In Computing in Cardiology 2017. Rennes (France). [2] F Andreotti, et al. Comparing Feature Based Classifiers and Convolutional Neural Networks to Detect Arrhythmia from Short Segments of ECG. In Computing in Cardiology 2017. Rennes (France). [3] I Guyon, et al. Gene Selection for Cancer Classification using Support Vector Machines. Machine Learning, 2002;46:389-422*.