Model based analysis of multimodal data sets for quantitative molecular and microcirculatory imaging

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Background and Aim

The well-being of all biological organisms relies on a sufficient supply of nutrition and oxygen. In the human tissue, the smallest vessels of the microcirculatory network fulfill this demand. Consequently, there is a clinical demand for objective methods that rapidly and accurately characterizes the microcirculatory perfusion and the blood oxygen saturation.

The long-term aim for this project was to devise new algorithms for mapping the microcirculatory perfusion and the blood oxygenation in tissue using a combination of hyper/multi spectral imaging (HSI/MSI) and laser speckle imaging (LSI/LASCA) techniques. To solve this our project work has focused on novel inverse-model algorithms based on extensive computer simulations that accurately predict how photons propagate thru tissue. Within the project, we have also focused on refining the imaging setup to improve the signal quality and data acquisition speed to allow for accurate and fast imaging of the microcirculation.

Scientific results

The main scientific achievements within the CENIIT project are within the development of algorithms for an optical assessment of the microcirculatory perfusion and blood oxygenation. The applicability of these algorithms has been demonstrated in hardware setups including both laser speckle based techniques (LDF, LSI and LASCA) and diffuse spectroscopy techniques (MSI, HSI and DRS). In addition, an MSI setup for assessing skin auto-fluorescence has been developed and evaluated.

Algorithm development

The CENIIT project initially focused on how the theoretical framework for modeling and simulating LDF and DRS spectra could be used effectively to assess the microcirculation. This work resulted in a refined algorithm capable of quantifying booth blood oxygenation and speed resolved perfusion. The algorithm is based on inverse Monte Carlo simulations for model identification. The model is individualized and can automatically adapt to tissue differences including both chromophore content, scattering amount and geometrical properties. We have shown that by introducing a novel layer-based discrimination of pre-simulated photon pathlengths, real-time inverse Monte Carlo calculations of probe-based DRS and LDF data can be achieved. In collaboration with Perimed, three prototype instruments running this software has been put together. This instrument, denoted EPOS, has been used in more than five minor studies (about 200 examinations in total) with promising results. Currently the instrument is being further evaluated both in lab experiments and in the SCAPIS study (Swedish CardioPulmonary bioImage Study, Hjärt-Lungfonden) where about 1000 subjects has been examined during 2016 using the EPOS system, and more than 3000 examinations are scheduled for the coming two years. We are confident that this work will not only be of scientific value but also serve as key reference for Perimed when introducing production EPOS systems.

Multi Spectral Imaging – MSI

We have demonstrated theoretically that blood oxygenation can be accurately estimated (2.2% rms error) using only four wisely selected wavelength bands. This finding was used in the SEMEOTICONS project (EU FP7-ICT-2013-10 STREP) were a low-cost MSI system based on four separate cameras were built and integrated in a smart mirror for wellness self-assessment. Occlusion tests have shown that this setup can clearly distinguish between tissue with normal and critically low oxygenation using simplified fast algorithms suitable for image applications. During the last year of the CENIIT project a new type of MSI snapshot camera have been available. This camera make use of a custom mosaic band pass filter allowing hyper-cubes with 16 wavelength bands to be acquired in 170fps. Results from a comparative study on 24 subjects undergoing standard provocations have shown that this camera enables us to capture both spatial and temporal variations in blood oxygenation. These results were achieved using algorithms tailored for the complex spectral characteristics of the mosaic bandpass filters.

An additional two-camera MSI system for remote measurement of AGE-related tissue autofluorescence has also been designed and evaluated. Results from a comparative study using our image based algorithms and a reference probe-based system have shown a significant correlation (R=0.68, p=0.005) between the two methods. This system has been integrated in the SEMEOTICONS smart mirror.

Multi Exposure LASCA/LSI

Starting in 2015 our group was given a four year grant by the Swedish Research Council (Vetenskapsrådet; Dnr 2014-6141) for exploring how a novel multi-exposure scheme could be used for significantly improving the LSI technique. During 2015 and 2016 we have been able to theoretically demonstrate how the simplified LASCA technique is related to the classical and well established LDF technique. Our work shows that with a multi-exposer scheme it is possible to attain virtually the same information as is given by the more complex LDF technique.

In parallel to our theoretical work, results using off-line processing of laser speckle images acquired at 1000fps using our initial camera setup have demonstrated large improvements in image quality and acquisition speeds as compared to traditional multi-exposure setups. The initial hardware setup did however not enable us to fully implement our algorithms into the FPGA logics for a real-time on-line image processing. During 2016 a new hardware solution based on a CoaxPress communication interface between the camera and the FPGA was evaluated. With this setup, we could demonstrate, for the first time, an FPGA implementation capable of processing and delivering multi-exposure LSI images (1 to 64 ms) at the theoretical maximal speed of 15.6fps. Currently we are working on a tailored hardware setup where the CMOS sensor is directly connected to the FPGA, in collaboration with Perimed. This setup will drastically reduce the hardware cost (about 20000 SEK) while improving its performance even further, making it a viable solution for further research and product development.

Degrees and promotions

Main applicant Marcus Larsson became Senior Lecturer (Universitetslektor) in October 2012. In June 2016 Hanna Jonasson (formerly Karlsson) toke her PhD degree. Hanna has been working on algorithm development within the project. Her thesis is titled: "*Model-based quantitative assessment of skin microcirculatory blood flow and oxygen saturation*".

Master's thesis

Three master thesis on LASCA and multi exposure LASCA have been conducted in collaboration with Perimed AB. Two of them (1 and 2) in collaboration with Professor Atila Alvandpour (ISY/LiU):

[1] Hultman, M. and A.Z. Bexell, *High speed image processing for LASCA on an FPGA*, Master Thesis, Linköping University, 2016.
[2] Hallberg, C., *High Performance Multiple Exposure LASCA - Implementation on a Xilinx Spartan-6 FPGA*, Master Thesis, Linköping University, 2016.
[3] Kusch, J., *Connecting laser speckle contrast analysis and laser Doppler flowmetry perfusion values*, Master Thesis, Linköping University, 2014.

Persons funded by the project

The project has funded two PhD students, Hanna Jonasson (formerly Karlsson) and Maria Ewerlöf, in addition to the main applicant Marcus Larsson.

Industrial collaborations

The research group at IMT has a strong connection to the main collaborating company, *Perimed AB*. Thru out the project the technology transfer between both partners has been facilitated by having a senior researcher, Ingemar Fredriksson, that works part-time at both IMT and Perimed. During our collaboration Perimed has mainly benefited in three different areas:

1) Transfering knowledged in classical LASCA theory when designing their original Laser Speckle imager.
2) Adopting our novel algorithms for simultaneous calculation of blood perfusion and blood oxygenation estimations. These algorithms are currently being used in their new prototype instrument, denoted EPOS.
3) Designing a new multi-exposure LASCA algorithm and hardware solution, based on an FPGA and a high-speed 1000fps camera. Perimed and IMT is currently exploring the possibility to make use of these results when designing a new enhanced imager for the next generation of LASCA instruments.

Our research group at IMT has also collaborated with other companies within an FP7 EU project (SEMEOTICONS, EU FP7-ICT-2013-10 STREP) that aims to design a smart mirror for individual wellness self-assessment. Within this project our group was responsible for designing algorithms and hardware solution for a multi spectral camera integrated in the smart mirror setup. During 2016 a second prototype mirror have been manufactured and evaluated in a multi-center study.

Connections with other CENIIT projects

Our project group at IMT has collaborated with Oleg Burdakov, MAI (CENIIT project: *A novel approach in multilinear least-squares with application to design of filter networks*) on inverse-model optimization algorithms, resulting in a joint journal publication:

[1] Fredriksson, I., O. Burdakov, M. Larsson, and T. Strömberg, *Inverse Monte Carlo in a multilayered tissue model: merging diffuse reflectance spectroscopy and laser Doppler flowmetry.* Journal of Biomedical Optics, 2013. **18**(12): p. 127004.

The research group at IMT

The CENIIT project, and the main applicant Marcus Larsson, has strongly contributed to widen the scope of the IMT research group towards an imaging application track. Previous research was mainly focused on probe-based applications, but with the new research track additional external funding has been attracted for microcirculatory imaging research. This include an FP7 EU grant (SEMEOTICONS, EU FP7-ICT-2013-10 STREP) and a VR grant (Swedish Research Council; Dnr 2014-6141) where Marcus Larsson is project leader. The CENIIT project has not directly resulted in a new research group at IMT but rather a new viable research track with new PhD students and projects that adds to the already existing group.

Publications in Journals, Books and Proceedings

[1] Ewerlöf, M., M. Larsson, and E.G. Salerud. *Spatial and temporal skin blood volume and saturation estimation using a multispectral snapshot imaging camera* in *SPIE Photonics West*. 2017. San Francisco: SPIE proceeding.

[2] Jonasson, H., S. Bergstrand, F.H. Nystrom, T. Länne, C.J. Östgren, N. Bjarnegård, I. Fredriksson, M. Larsson, and T. Strömberg, *Skin microvascular endothelial dysfunction is associated with type 2 diabetes independently of microalbuminuria and arterial stiffness.* Diabetes & Vascular Disease Research, 2017. *Accepted for publication*.

[3] Larsson, M., R. Favilla, and T. Strömberg, *Assessment of advanced glycated end product accumulation in skin using auto fluorescence multispectral imaging.* Computers in Biology and Medicine, 2017.

[4] Fredriksson, I. and M. Larsson, *On the equivalence and differences between laser Doppler flowmetry and laser speckle contrast analysis.* J Biomed Opt, 2016. **21**(12): p. 126018.

[5] Milanic, M., A. Bjorgan, M. Larsson, T. Strömberg, and L.L. Randeberg. *Detection of hypercholesterolemia using hyperspectral imaging of human skin*. in *Clinical and Biomedical Spectroscopy and Imaging IV*. 2015. SPIE.

[6] Milanic, M., A. Bjorgan, M. Larsson, P. Marraccini, T. Strömberg, and L.L. Randeberg. *Hyperspectral imaging for detection of cholesterol in human skin*. in *Optical Diagnostics and Sensing XV: Toward Point-of-Care Diagnostics*. 2015. SPIE.

[7] Jonasson, H., I. Fredriksson, A. Pettersson, M. Larsson, and T. Strömberg, *Oxygen saturation, red blood cell tissue fraction and speed resolved perfusion — A new optical method for microcirculatory assessment.* Microvascular Research, 2015. **102**: p. 70-77.

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[9] Ewerlöf, M., E.G. Salerud, T. Strömberg, and M. Larsson. *Estimating skin blood saturation by selecting a subset of hyperspectral imaging data*. in *SPIE Photonics West*. 2015. San Francisco: SPIE proceeding.

[10] Andreu-Cabedo, Y., P. Castellano, S. Colantonio, G. Coppini, R. Favilla, D. Germanese, G. Giannakakis, D. Giorgi, M. Larsson, P. Marraccini, M. Martinelli, B. Matuszewski, M. Milanic, M. Pascali, M. Pediaditis, G. Raccichini, L. Randeberg, O. Salvetti, and T. Strömberg. *Mirror mirror on the wall...; An intelligent multisensory mirror for well-being self-assessment*. in *Multimedia and Expo (ICME), 2015 IEEE International Conference on*. 2015.

[11] Strömberg, T., M. Larsson, G. Salerud, and K. Wårdell, *Laser Doppler Perfusion Monitoring and Imaging*, in *Biomedical Photonics Handbook*. 2014, CRC Press.

[12] Strömberg, T., H. Karlsson, I. Fredriksson, F.H. Nystrom, and M. Larsson, *Microcirculation assessment using an individualized model for diffuse reflectance spectroscopy and conventional laser Doppler flowmetry.* Journal of Biomedical Optics, 2014. **19**(5): p. 057002.

[13] Fredriksson, I., M. Larsson, and T. Strömberg, *Model-Based Quantification of Skin Microcirculatory Perfusion*, in *Computational Biophysics of the Skin*. 2014, Pan Stanford Publishing: Singapore. p. 395-420.

[14] Strömberg, T., H. Karlsson, I. Fredriksson, and M. Larsson. *Experimental results using a three-layer skin model for diffuse reflectance spectroscopy*. 2013. SPIE proceeding.

[15] Fredriksson, I., O. Burdakov, M. Larsson, and T. Strömberg, *Inverse Monte Carlo in a multilayered tissue model: merging diffuse reflectance spectroscopy and laser Doppler flowmetry.* Journal of Biomedical Optics, 2013. **18**(12): p. 127004.

[16] Briers, D., D.D. Duncan, E. Hirst, S.J. Kirkpatrick, M. Larsson, W. Steenbergen, T. Strömberg, and O.B. Thompson, *Laser speckle contrast imaging: theoretical and practical limitations.* J Biomed Opt, 2013. **18**(6): p. 066018.

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[19] Fredriksson, I., M. Larsson, and T. Strömberg, *Inverse Monte Carlo method in a multilayered tissue model for diffuse reflectance spectroscopy.* Journal of Biomedical Optics, 2012. **17**(4): p. 047004-12.

[20] Lindbergh, T., E. Häggblad, H. Ahn, E. Göran Salerud, M. Larsson, and T. Strömberg, *Improved model for myocardial diffuse reflectance spectra by including mitochondrial cytochrome aa3, methemoglobin, and inhomogenously distributed RBC.* Journal of Biophotonics, 2011. **4**(4): p. 268-276.

[21] Karlsson, H., A. Pettersson, M. Larsson, and T. Strömberg. *Can a one-layer optical skin model including melanin and inhomogeneously distributed blood explain spatially resolved diffuse reflectance spectra?* 2011. San Francisco, CA: SPIE proceeding.

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