Tunable Quantum Cascade Laser based Blood Sensor for Clinical Application

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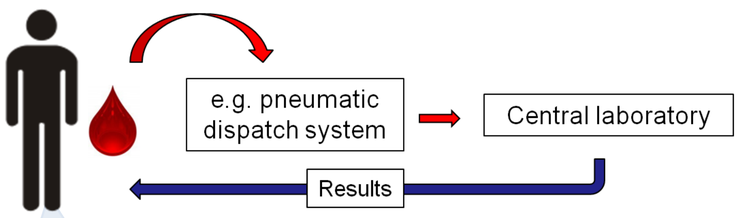
Introduction

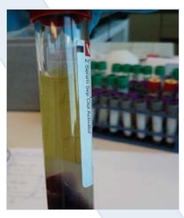
We report on the simultaneous quantification of multiple blood parameters in human blood plasma facilitated by a mid-infrared laser based approach. The sample set consisted of aliquotes of **68 routinely taken blood samples from critically ill patients**. In order to reduce the effects of clogging and sample adsorption in the transmission cell, thereby improving the robustness, the optical pathlength was set to **165 µm**. This is a major improvement compared to standard mid-infrared spectroscopy with pathlength-limits below 100 µm.

The enabling technology are External Cavity Quantum Cascade Lasers (EC-QCLs), which offer high emission power combined with a tuning range of several hundred wavenumbers. As previously shown in [1] and [2], it is possible to quantify the physiologically relevant parameters glucose and lactate in aqueous solutions as well as glucose and triglycerides in human blood serum utilizing an EC-QCL with 200 cm^{-1} tunability in the range between **1030 and 1230 cm^{-1}**. This approach was now extended towards a clinical application of the sensor system for quantification of multiple parameters in human blood plasma.

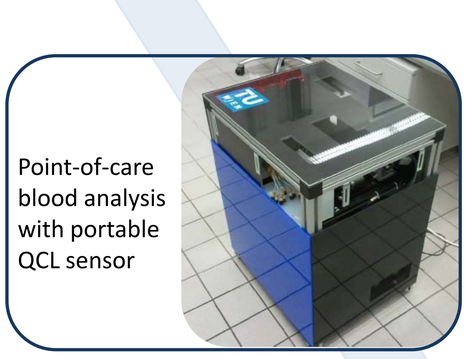
Automated Quantum Cascade Laser – based sensor



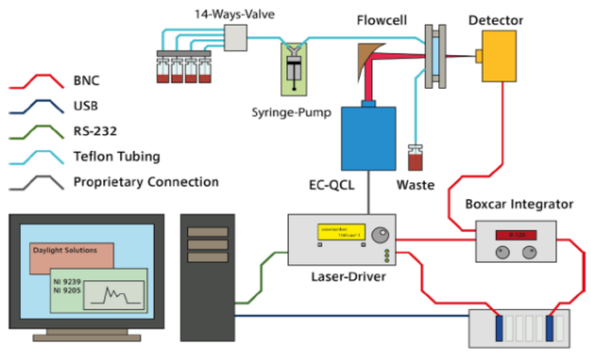
Standard clinical blood analysis is very often dominated by time-consuming sample handling procedures.



Point-of-care blood analysis: A fully automated sampling system supplied a broadly tunable Quantum Cascade Laser based mid-infrared transmission set-up with blood plasma samples, thus enabling point-of-care application:



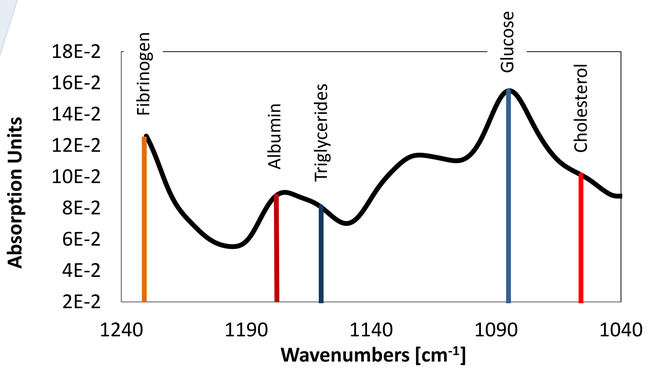
Point-of-care blood analysis with portable QCL sensor



The pulsed EC-QCL was operated at 350 mW peak power, 100 kHz repetition rate and 500 ns pulse length [3].

Simultaneously quantified blood parameters:

- Glucose
- Albumin
- Total Protein
- Fibrinogen
- Cholesterol
- Triglycerides

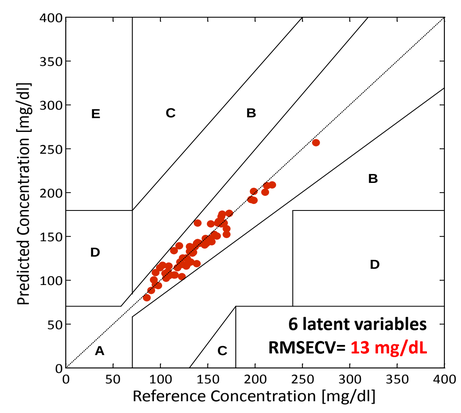


Typical spectrum of human blood plasma; the spectral positions of the absorption maxima of the pure analytes of interest are denoted in the spectrum.

Simultaneous multianalyte detection

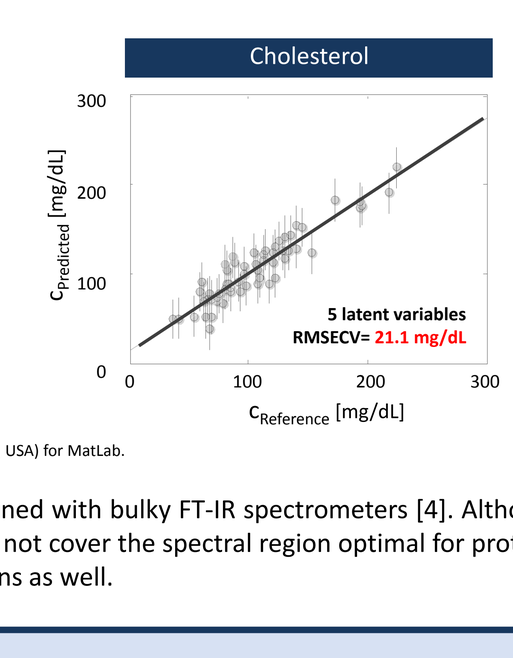
Spectral tunability of the laser facilitated the simultaneous determination of 6 blood parameters by multivariate calibration. Standard Partial Least Squares (PLS) regression analysis was used for quantitative analysis in a set of 68 blood plasma samples.
Reference concentrations were supplied by the hospital's laboratory. Therefore, quantification errors of the reference values have to be taken into account when looking at the resulting root-mean-square errors of cross-validation (RMSECV).

Glucose: Clarke error grid analysis

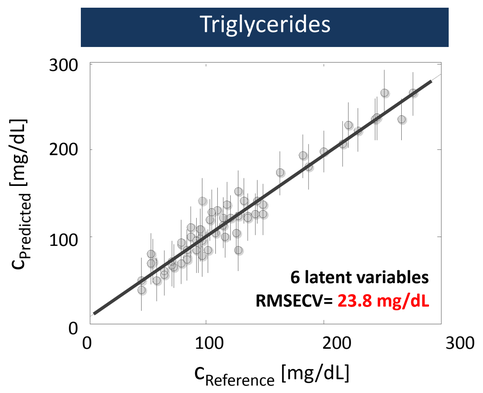


Clotting factor Fibrinogen

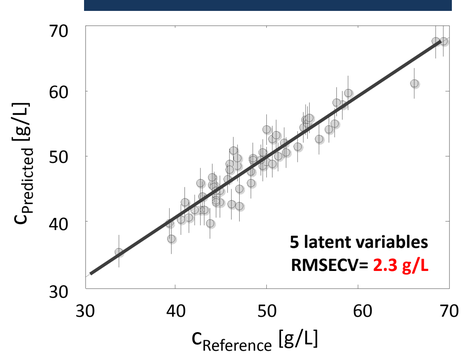
- Fibrinogen level is an indicator for the development of inflammation processes in the human body
- Increased levels are associated with risk of thromboembolism



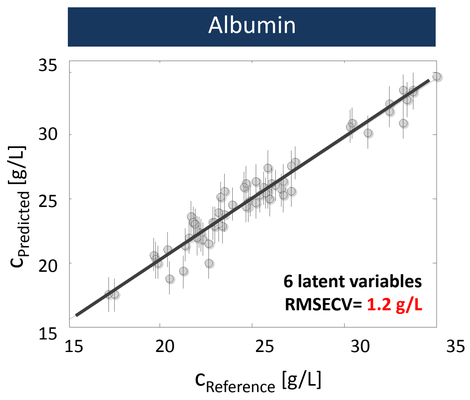
Triglycerides



Total Protein



Albumin



Cholesterol

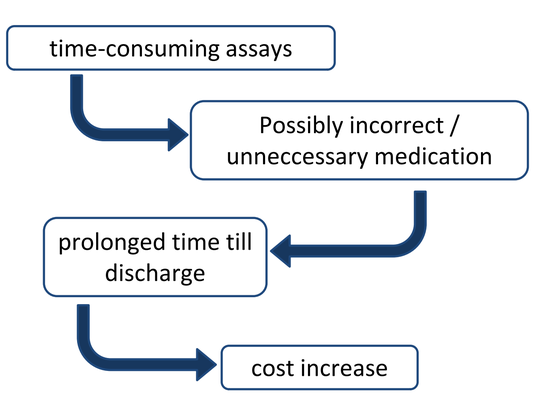
PLS regression was performed with the PLS Toolbox (Eigenvector Research, USA) for MatLab.

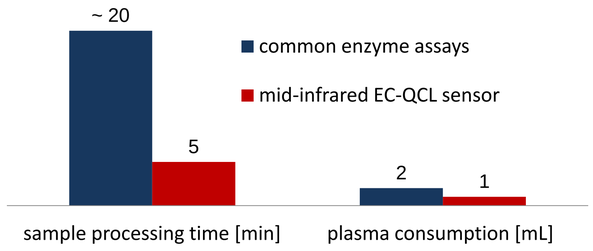
The achieved results can compete with those gained with bulky FT-IR spectrometers [4]. Although the EC-QCL's tuning range (1030 – 1230 cm^{-1}) did not cover the spectral region optimal for proteins it was possible to establish calibrations for proteins as well.

Benefits compared to standard clinical analysis

In contrast to standard enzyme based assays, mid-infrared spectroscopy is a direct and label-free detection method facilitating a reduction of the running costs. The sensor system benefits from the three major features of Quantum Cascade Lasers:

- High spectral power density → Large optical pathlength enhances sensitivity and robustness
- Spectral tunability → Multivariate data analysis possible = simultaneous multianalyte detection
- Small size of QCLs → Ideal for portable point of care devices





Due to the non-destructive nature of mid-infrared absorption measurements even continuous blood monitoring is feasible.

References

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[2] M. Brandstetter, L. Volgger, A. Genner, C. Jungbauer, B. Lendl, "Direct determination of glucose, lactate and triglycerides in blood serum by a tunable quantum cascade laser based mid-IR sensor", *Appl. Phys. B*, DOI: 10.1007/s00340-012-5080-z

[3] M. Brandstetter, B. Lendl, „Tunable mid-infrared lasers in physical chemosensors towards the detection of physiologically relevant parameters in biofluids", *Sensors and Actuators B – Chemical* **170**, pp. 189-195 (2012)

[4] H.M. Heise, U. Damm, O. Vogt, V. Konderpati, "Towards reagent-free blood glucose monitoring using micro-dialysis and infrared transmission spectrometry", *Vib.Spec.* **42**, pp. 124-129 (2006).

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