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Non-invasive blood glucose measurement by mid-infrared spectroscopy: Principle and validation

- Mid-IR Quantum Cascade Lasers (QCL)
- Proprietary photothermal detection
- IP Protection
- Clinical validation
- Contact with Industry Partners
- Table-top device with CE mark
- Clinical Tests for Applicability and Reliability
- Hand-held medical device

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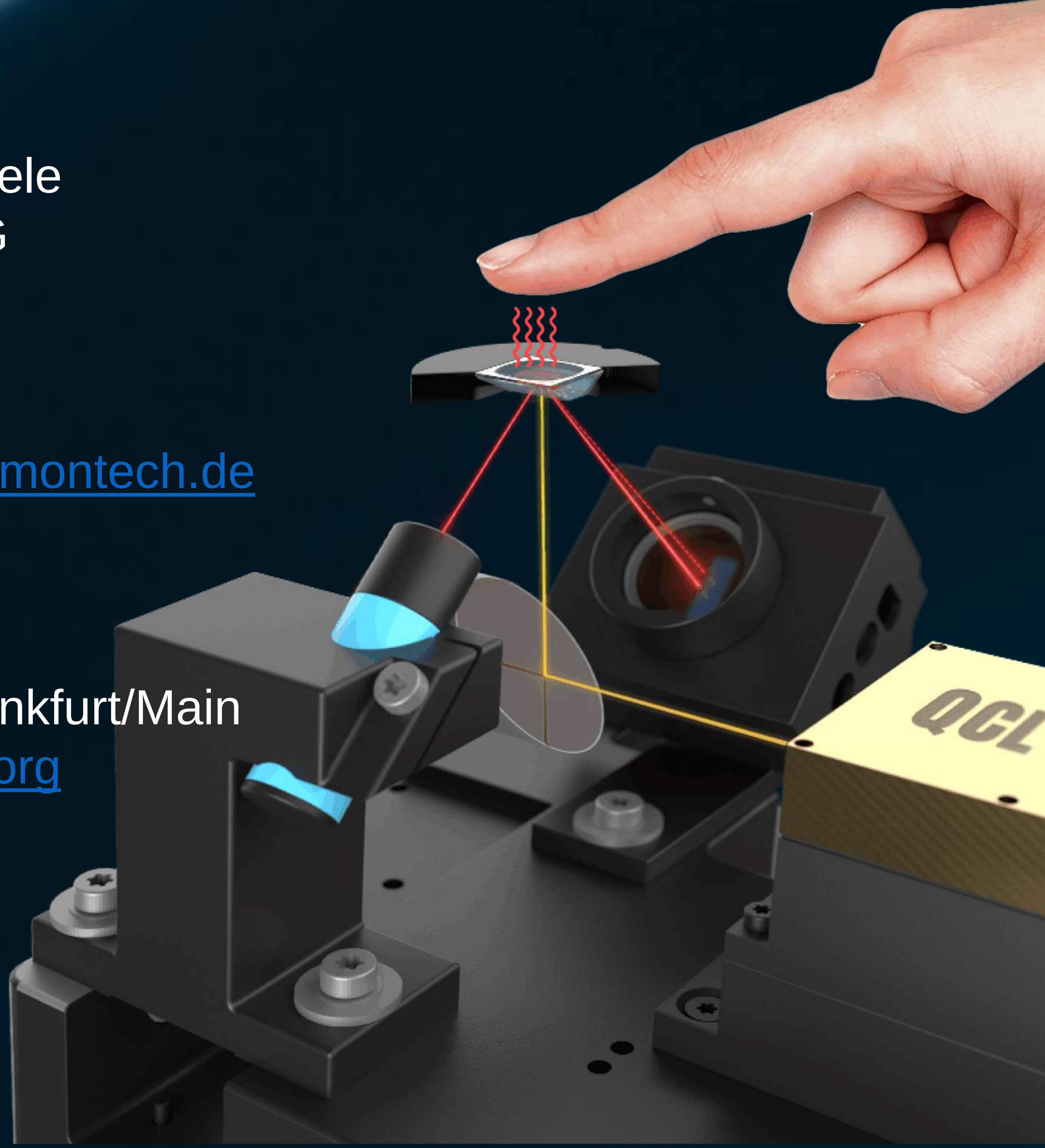

Diabetes: A worldwide disease

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Over 800 million adults live with diabetes

(The Lancet, November 13, 2024)

- Prevalence up to 30% of population in some countries
- An important driver of the rise in type 2 diabetes rates is obesity and poor diets
- More than half of the patients are not receiving treatment, global study suggests
- For many LMICs: over 90% of people with diabetes do not receive treatment

Diabetes cannot be cured – but managed

Management today:

Measuring blood glucose level several times a day:

- invasive: finger pricking
- test strips
- painful
- uncomfortable

↓

- adaptation of food intake
- physical activity
- medication
- insulin injection

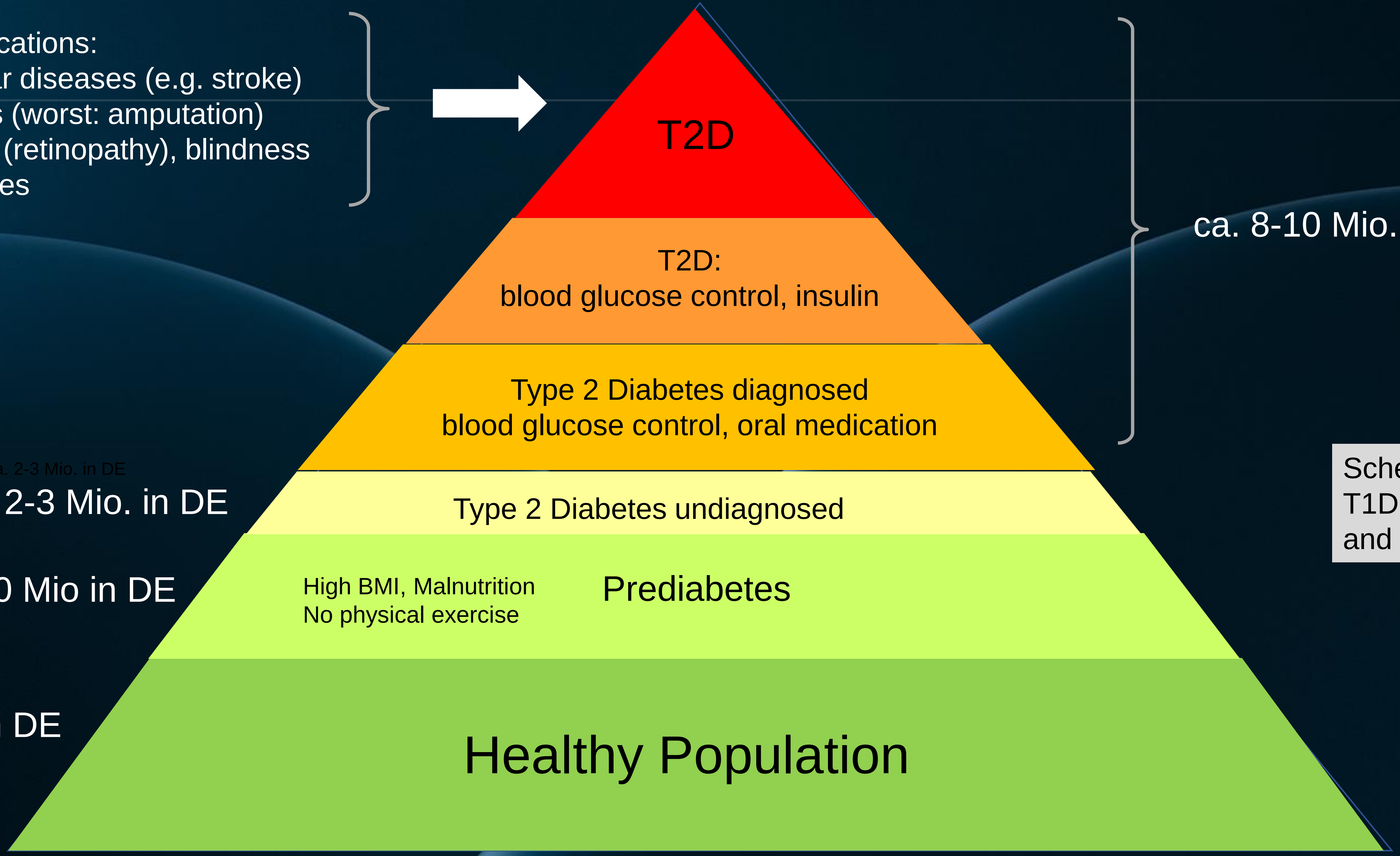
- test strips with immobilized enzymes and electrochemical detection:
- encoded: Activity of the enzymes used
- limited shelf lifetime
- Prize 0,30 – 0,60 €/piece

- continuously measuring minimally invasive sensors sensor lifetime: <2 weeks
- sensor prize: ≈ € 60.-
- frequent failures, allergies

Enzymatic measurement of blood glucose with test strips is used by 8-10 Mio. diabetes patients in Germany

approx. 10-15 Mio. measurements total per day.

Serious complications:
- Cardiovascular diseases (e.g. stroke)
- Foot problems (worst: amputation)
- Eye problems (retinopathy), blindness
- Kidney diseases
- ....



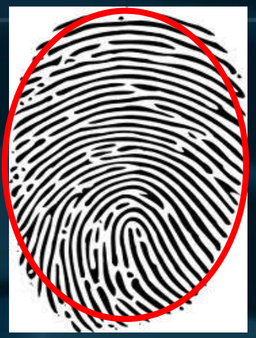
Scheme does not include T1D patients and gestational diabetes

Numbers from:
- Diabetes Surveillance (RKI)
- Deutsche Diabetes Gesellschaft DDG)
- Deutsches Diabetes-Zentrum (DDZ)

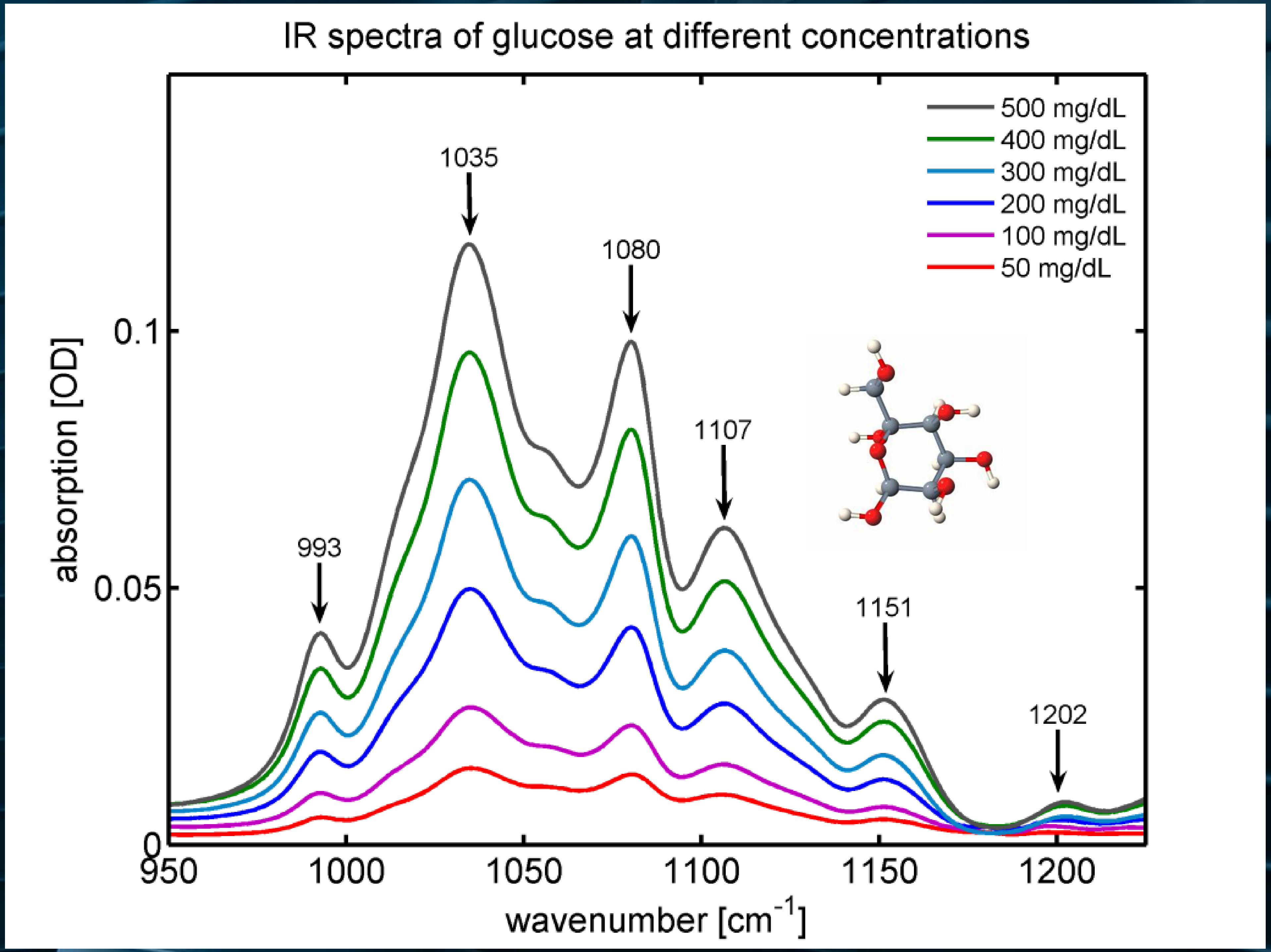
DiaMonTech‘s motivation for a reagent-free, non-invasive glucose monitoring system for diabetes patients based on IR spectrosocpy.

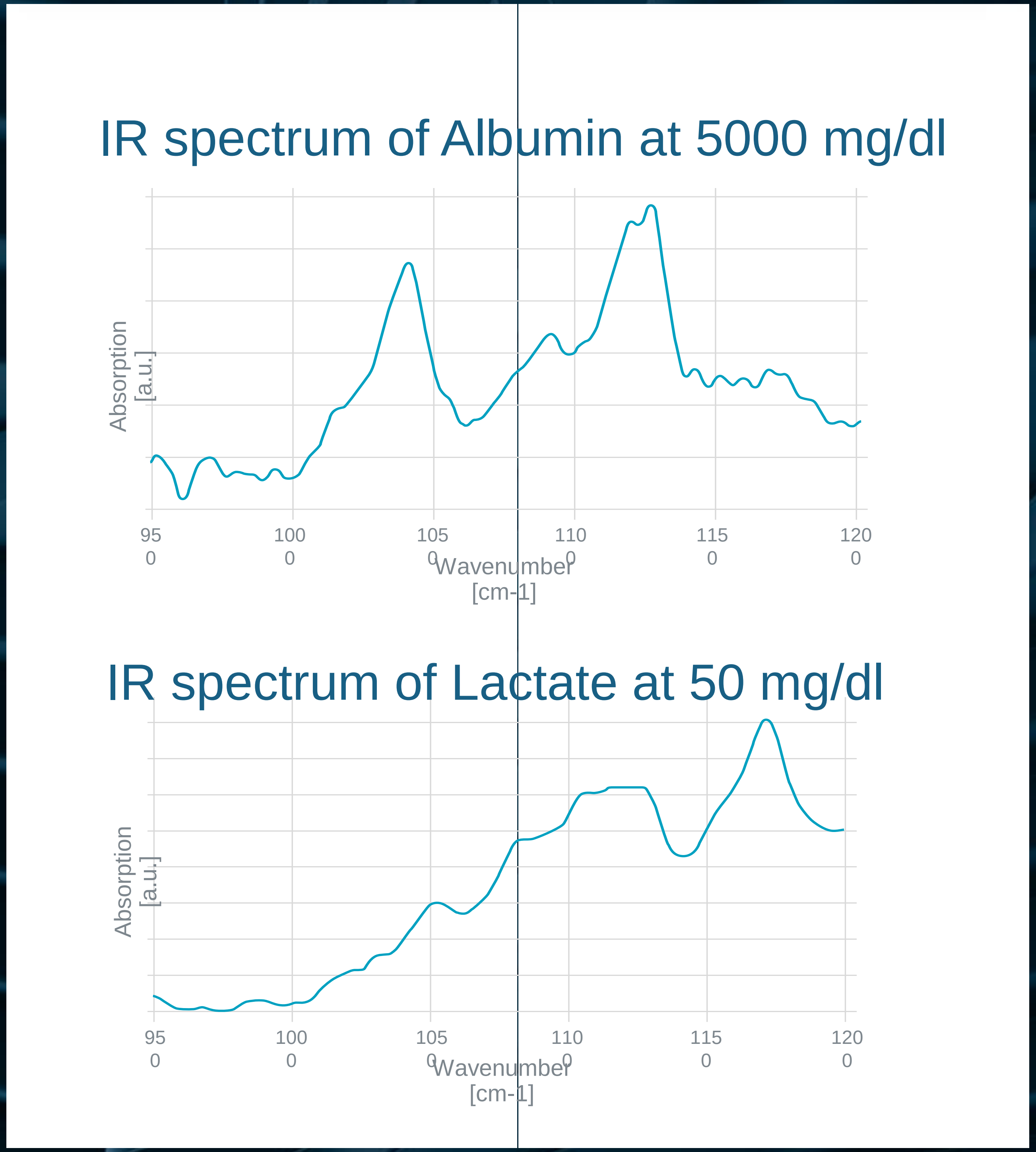
The Idea: Targeting a molecular fingerprint of glucose with high specificity

DiaMonTech's technology targets a specific glucose fingerprint in the Mid-IR…



…where glucose is clearly distinguishable from other molecules in the skin





Body fluids and what they tell us about blood glucose:

Blood: venous, arterial, capillary: Only minor differences in glucose level

Urine: contains glucose only for very high blood glucose levels

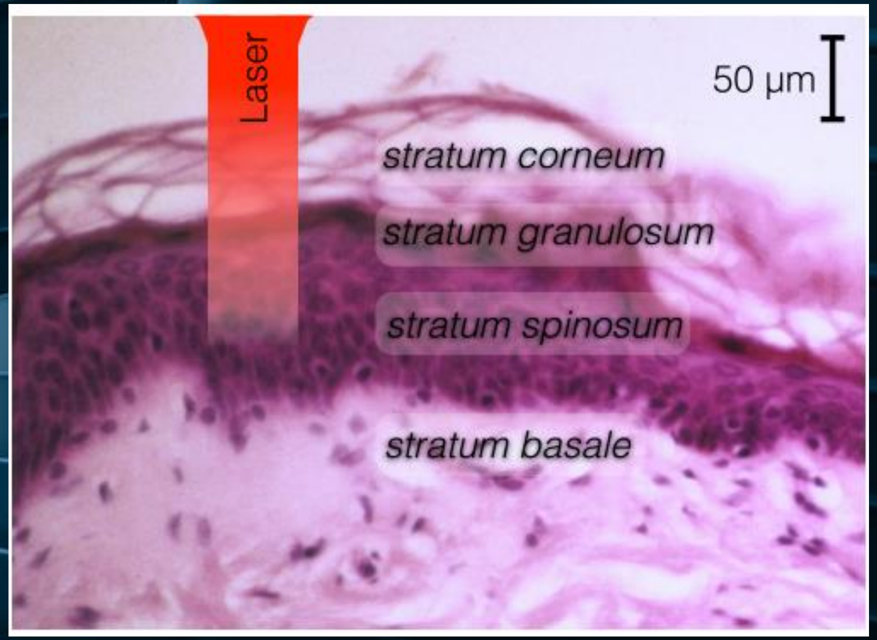
Saliva: only traces of glucose, no fixed correlation with blood glucose

Sweat: only traces of glucose, no fixed correlation with blood glucose

Tears: small amounts of glucose, no fixed correlation, delayed

(e.g. the „Google Lens“, project stopped 11/2018) 

Interstitial fluid (ISF), skin fluid: An ideal target for an optical non-invasive glucose measurement



- liquid surrounding cells in skin, muscle,..
- approx. twice the blood volume (i.e. around 10-12 l in an adult)
- appears on skin as yellowish liquid after shallow scratches
- appears slightly modified in blisters
- simple matrix: water, ions, albumin, glucose, phosphate
- good correlation with blood glucose (85-90 %), low delay

M. Pleitez, H. von Lilienfeld-Toal, W. Mäntele (2012) Spectrochim. Acta A 85, 61-65.

Infrared Spectroscopy of Skin Layers: A Challenge

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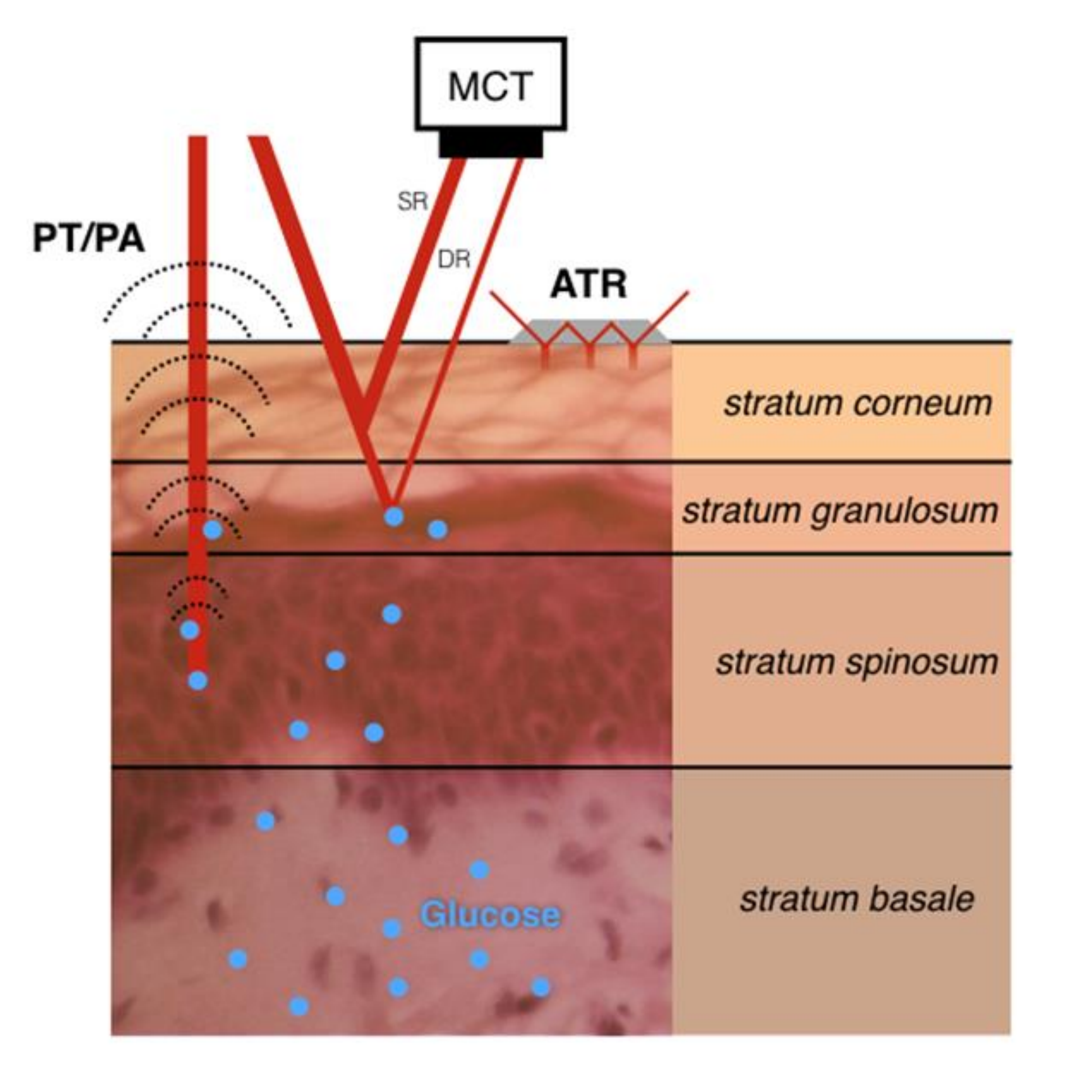


Pleitez et al. (2017) Spectrochimica Acta Part A **184**, 220–227

Optical penetration depth for 10 µm MIR radiation in skin is around 60-100 µm:

No chance for a transmission measurement

ATR (attenuated total reflection) measurement:

- evanescent wave penetrates only in the order of one wavelength or less

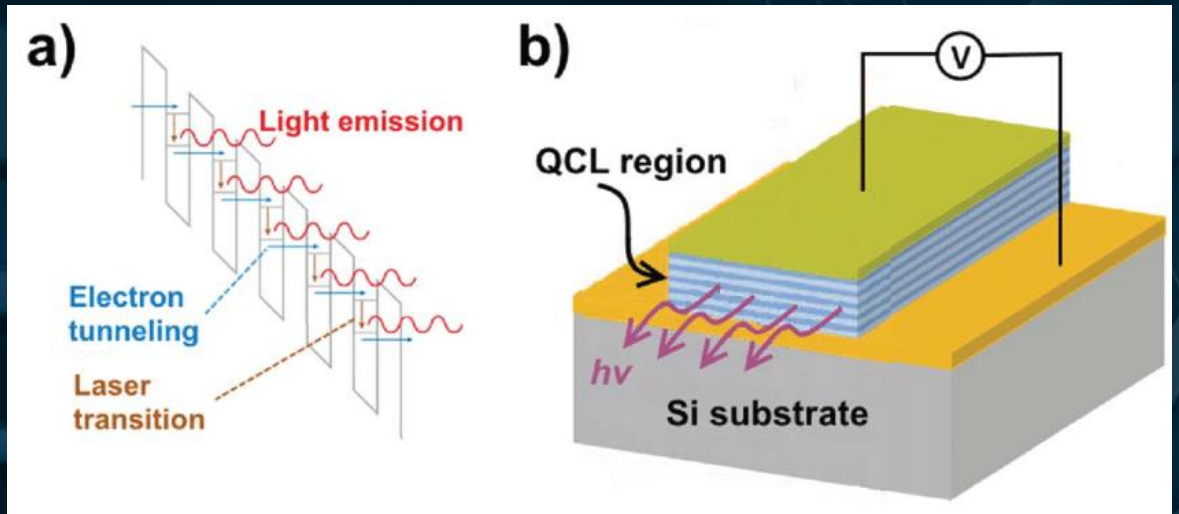
- Backscattered IR light:
  - Specular reflectance (SR): Only top layers are probed
  - Diffuse reflectance (DR): Only shallow layers are probed

Way out:

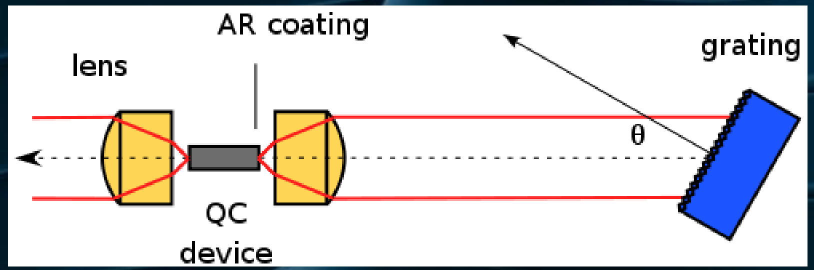
- Direct measurement of the absorption process by photoacoustic or photothermal detection

Quantum Cascade Lasers (QCL) as MIR Sources for Sensors

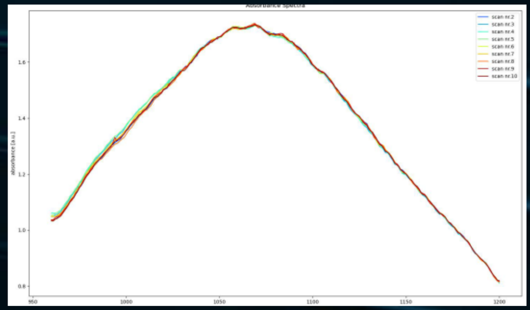
- Unipolar lasers (no electron-hole pairs)
- Emission from intersubband transitions
- Repeated stack of semiconductor multiple quantum well heterostructures
- Compact, powerful MIR sources
- CW or pulsed operation
- Wide MIR tuning range (>300 cm^{-1}) for EC-QCLs
- QCL arrays: Compact multi-wavelength emitters



External Cavity tunable QCL (EC-QCL)

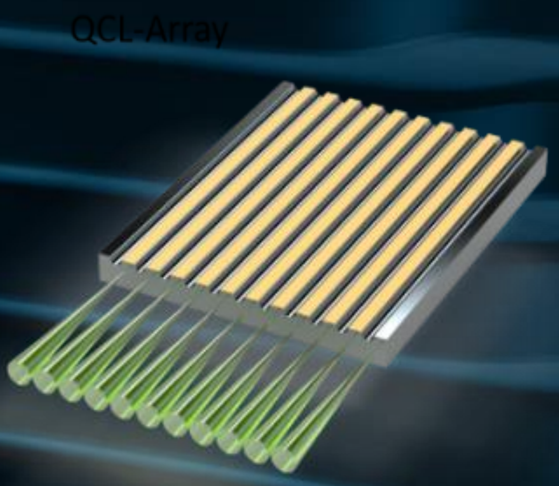


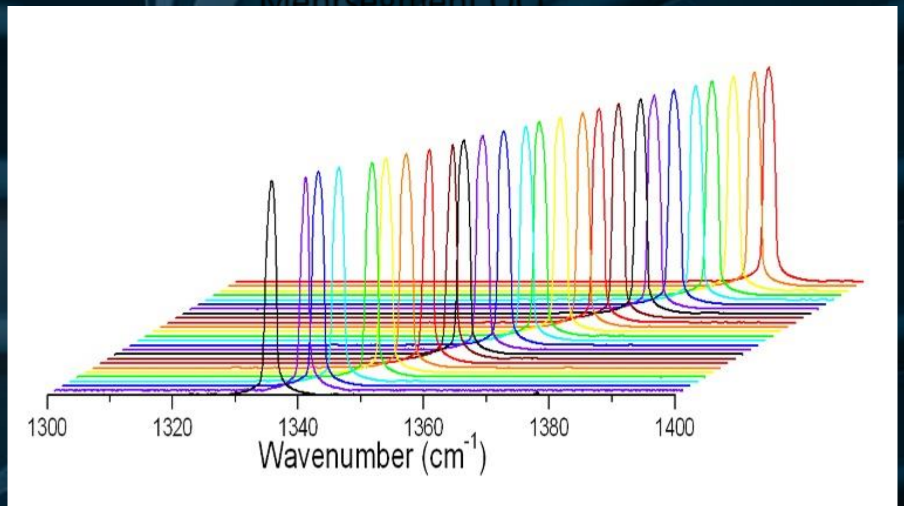
©Daylight Solutions



Emission spectrum

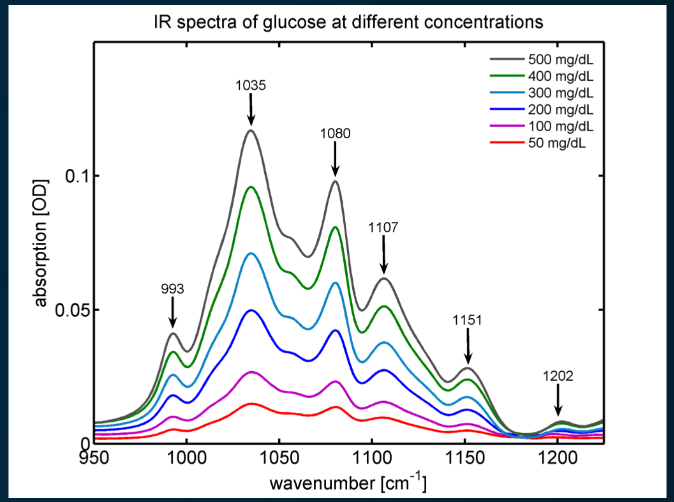
QCL Arrays for up to 25 emitters



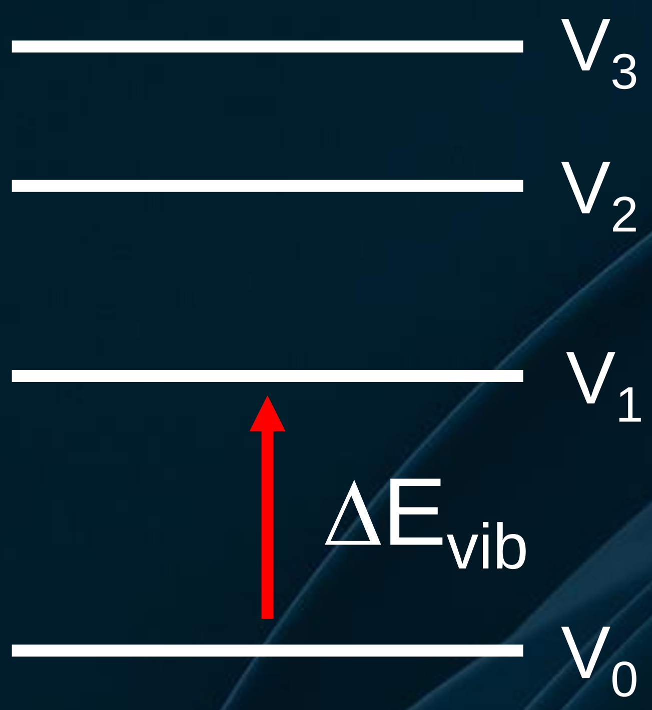


The physics of a photoacoustic/photothermal measurement

Vibrational modes of glucose

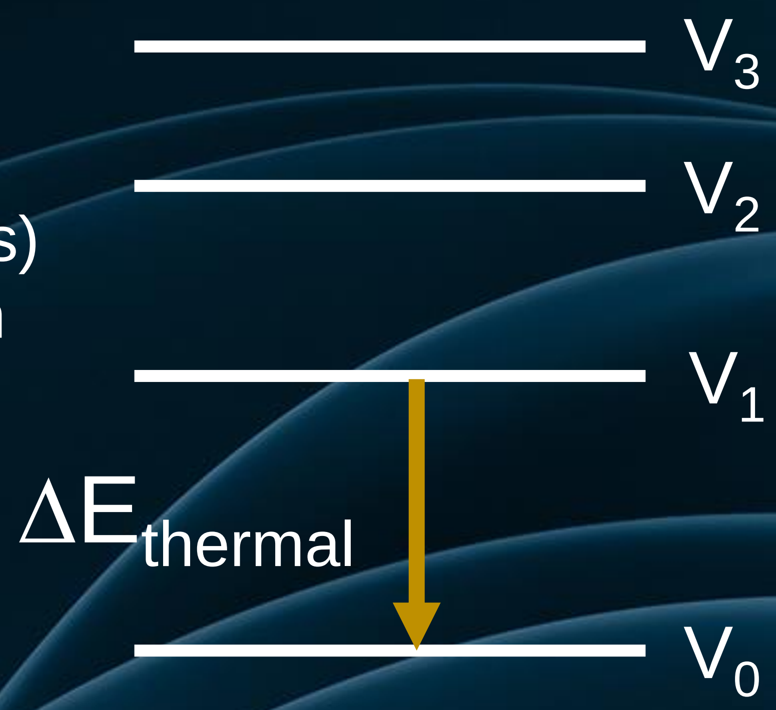


Vibrational Energy Levels



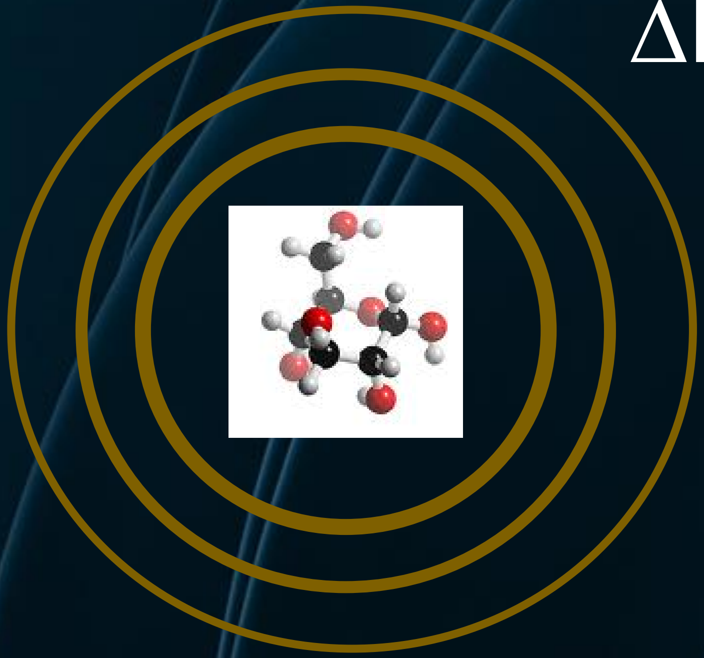
Immediate (10^{-12} s) thermal relaxation

Vibrational Energy Levels



Excitation with IR photon from Quantum Cascade Laser

$$E = h \cdot \nu$$



$\Delta E_{thermal}$

- dissipated into the molecule‘s surrounding
- heat gradient spreads out slowly (ms)
- adiabatic expansion leads to a photoacoustic signal spreading out at speed of sound

IRE-PTD: Internal Reflection Element PhotoThermal Deflection

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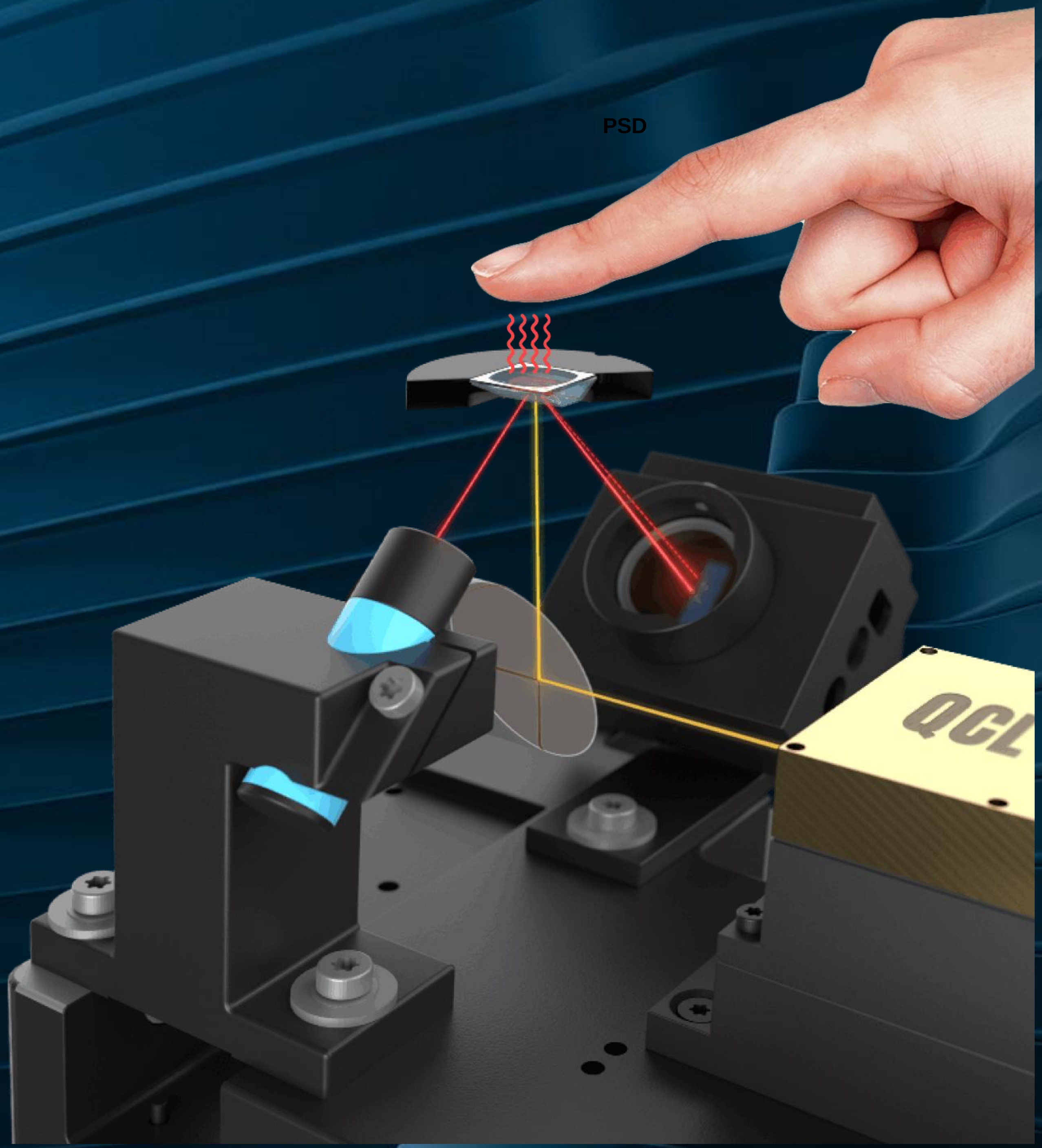

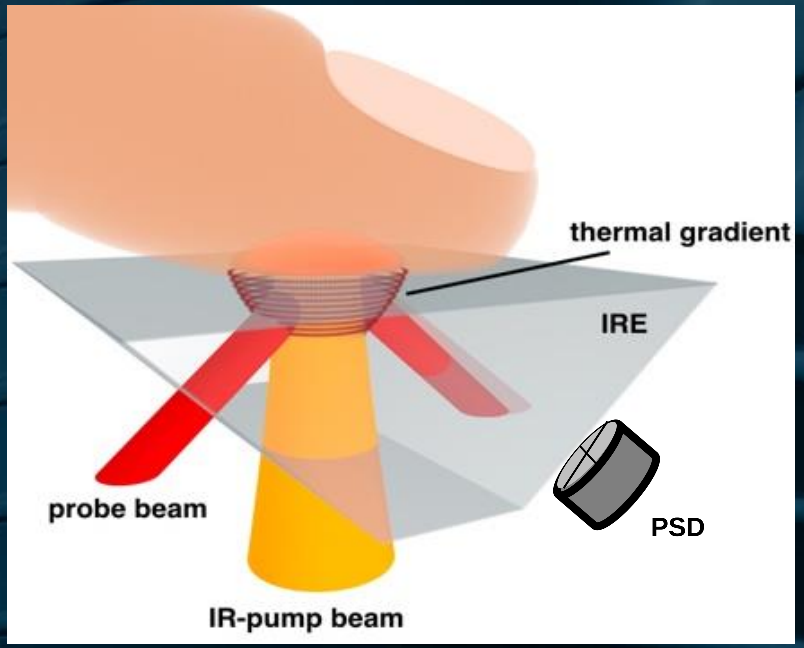

The quantum cascade laser (QCL), termed “pump beam”, emits light pulses in the glucose fingerprint range in the mid-infrared (8-11 µm), either at several discrete wavelengths or tuneable through this wavelength range.

In skin, absorbance of MIR light from the QCL pump beam generates a tiny amount of heat, specific for the glucose molecule and its concentration. This heat gradient migrates to the skin surface and into the IRE.

The material of this IRE is locally warmed at the contact surface with skin, thus changing optical parameters such as the refractive index. This is called a “transient thermal lens”.

Readout of the thermal lens is performed with a second laser beam (“probe beam“), sent through the thermal lens.

Its deflection for excitation at specific MIR wavelengths is measured with a Position Sensitive Detector (PSD).

M. A. Pleitez, O. Hertzberg, A. Bauer, M. Seeger, T. Lieblein, H. v. Lilienfeld-Toal, W. Mäntele (2015), Analyst **140**, 483
A. Bauer, O. Hertzberg, D. Strobel, A. Küderle, M. Pleitez, W. Mäntele (2017) J. Biophotonics **9**, 1-12
O. Hertzberg, A. Bauer, A. Küderle, M. Pleitez W. Mäntele (2017) Analyst **142**, 495-502

IRE-PTD: Internal Reflection Element PhotoThermal Deflection

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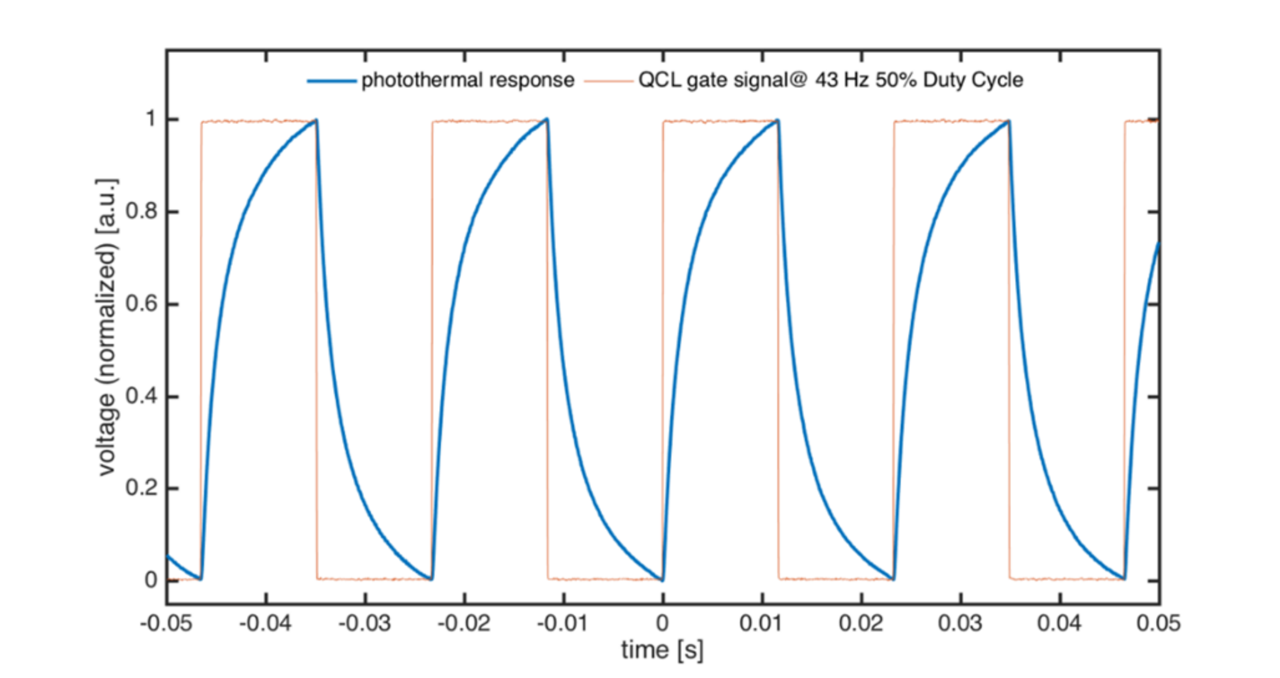
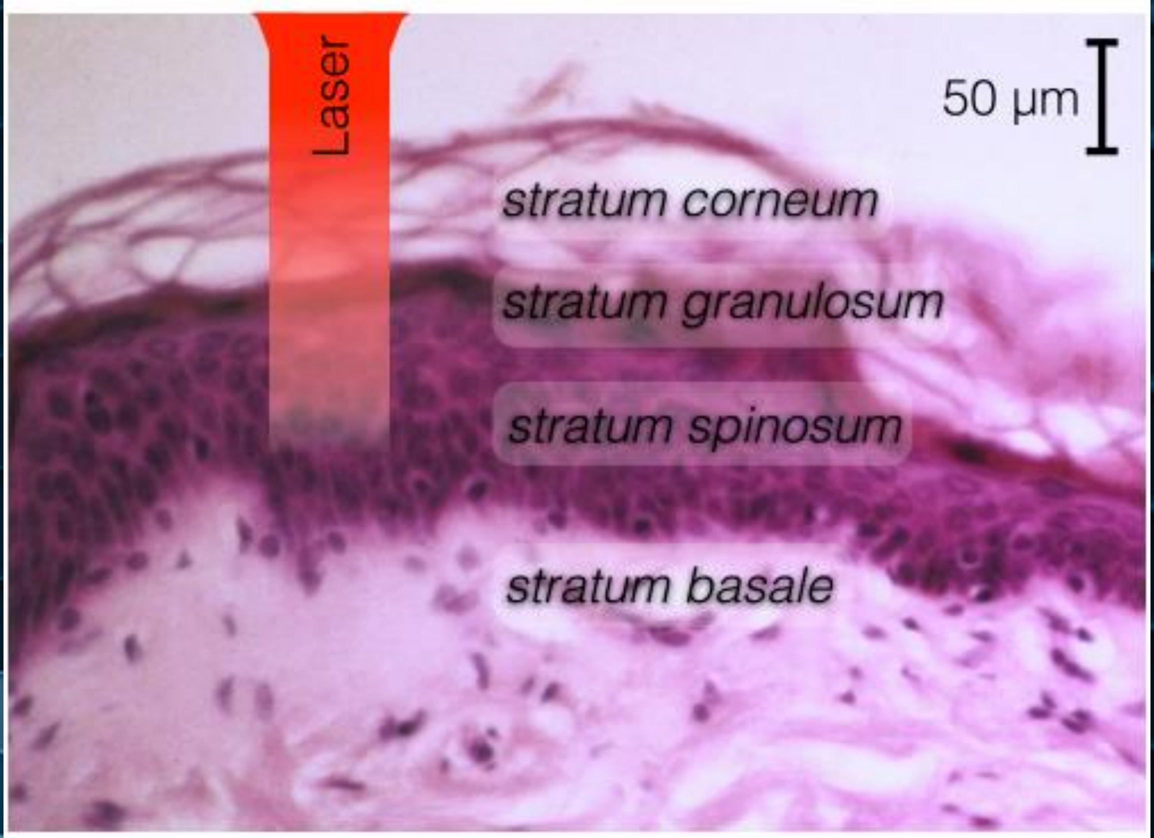


IR pump signal (red line) generates probe beam deflection signal (blue line):

- Evaluation of signal amplitude
- Evaluation of phase shift

Depth-selective IR spectroscopy of skin:



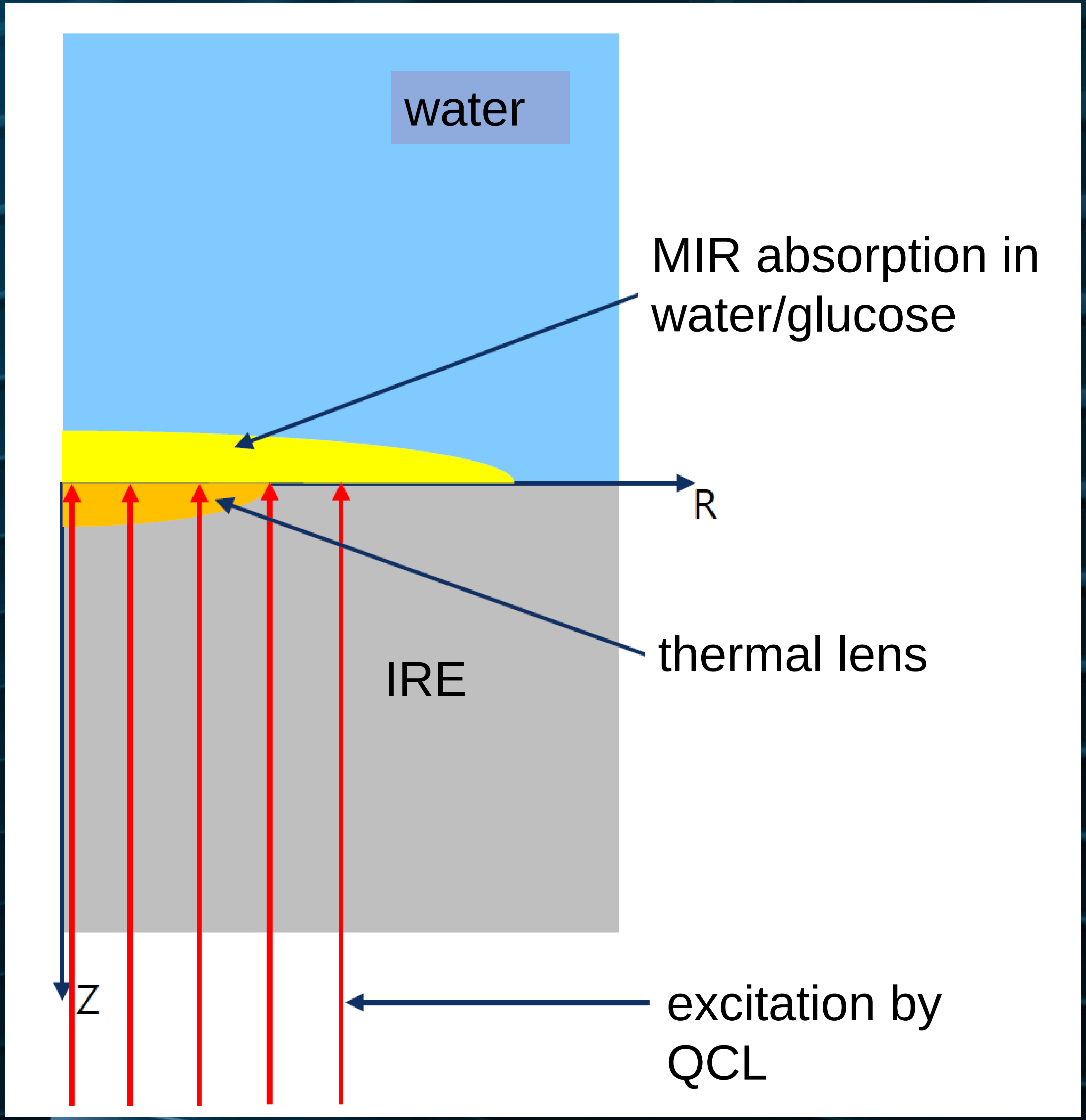
$$\mu_s = \sqrt{\frac{\alpha_s}{i2\pi f}}$$

μ_s: thermal diffusion length
f: modulation frequency
α_s: thermal diffusivity

- spectral depth profiles are obtained by varying the thermal diffusion length μ_s that depends on the modulation frequency f and the thermal diffusivity α_s of the sample;
- spectra at different modulation frequencies (approx. 20 – 500 Hz) are recorded;
  - low frequencies: total optical penetration depth (all layers)
  - high frequencies: only shallower layers

A. Bauer, O. Hertzberg, D. Strobel, A. Küderle, M. Pleitez, W. Mäntele (2017) J. Biophotonics **9**, 1-12
O. Hertzberg, A. Bauer, A. Küderle, M. Pleitez W. Mäntele (2017) Analyst **142**, 495-502

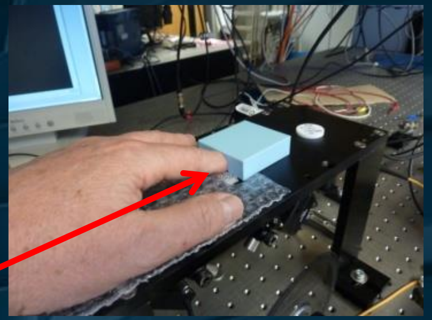
Steady-State Thermal Simulation of IRE-PTD



Improved detection technology by optimized:

- IRE materials:
  - refractive index n; n(T)
  - thermal conductivity
  - heat capacity
- IRE size and geometry
- QCL pulse shape and duration
- Probe laser geometry
- ……….

Validation of MIR-based photothermal glucose measurement during **O**ral-**G**lucose-**T**olerance-**T**ests (OGTTs) and Oral Glucose Correlation Tests



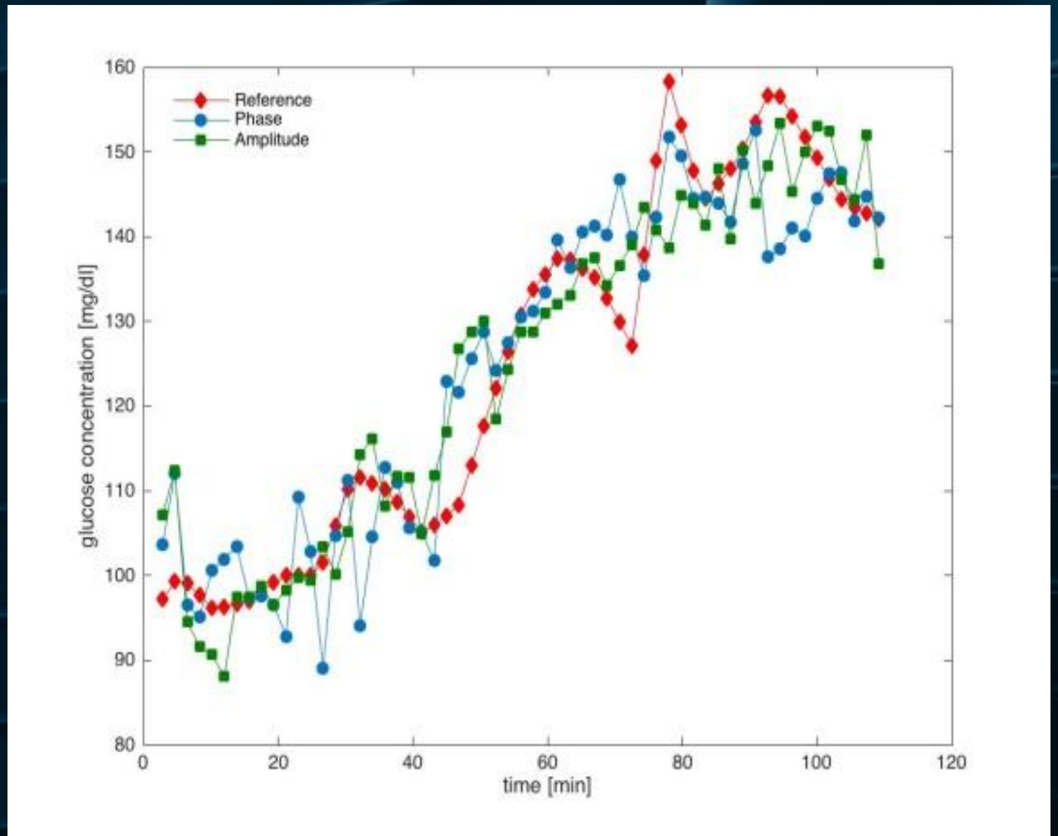
Non-invasive

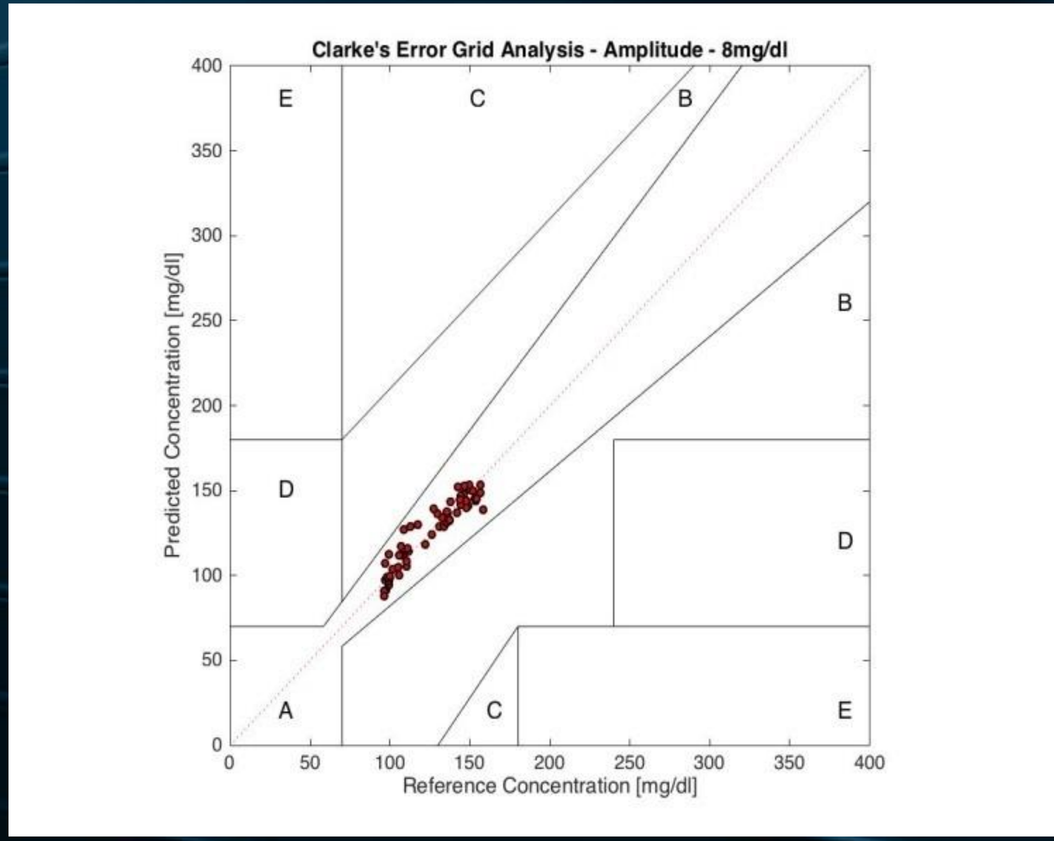
vs.

Reference

Modulation of blood glucose:

- Oral glucose uptake: 75 g glucose in 250–300 ml water) (for healthy volunteers only)
- food intake (for diabetes patients)
- my personal alternative: Assorted Niederegger Marzipan (100 g) in < 5 minutes

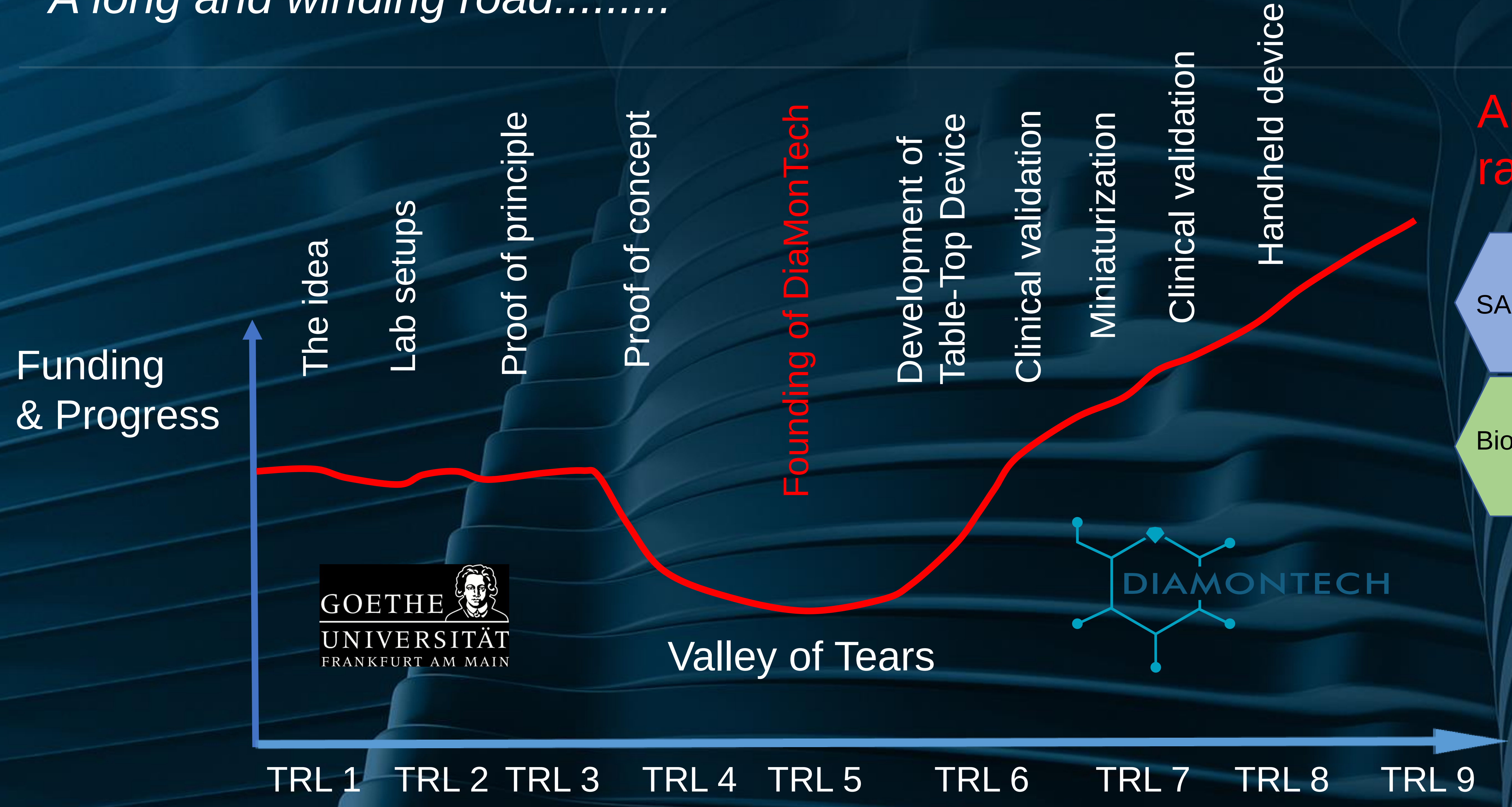




Reference data:

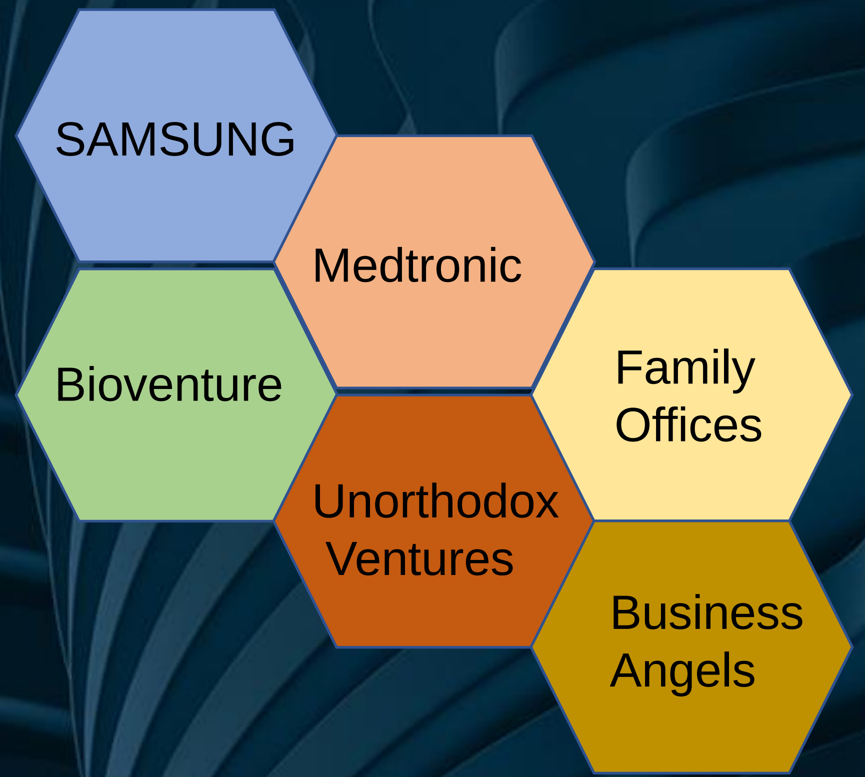
- Invasive test strip devices (such as: Aviva Accu-Check)
- professional Glucose measuring device B-Glucose (B-G)
- continuous measurement with a minimally invasive subcutaneous sensor (if used by diabetes patient)

A long and winding road.........



Technology Readiness Level

Around 20 M€
raised up to now:



2005 - 2015

- Basic Research at Frankfurt University
- Funding by Public Money (DFG, BMBF)
- Initial IP protection

2015-2024

- R&D in Startup
- Funding by investors
- Several funding rounds
- Strong IP protection (~100 filed; ~40 issued)
- Clinical Tests

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Regular clinical tests for validation:

Name	Location	Year	Participants	Reason	Results (MARD*)	Publication
Study 100	Goethe University	2019/20	100	Feasibility of technology	11,3 % (retrospective)	Journal of Diabetes Science and Technology, 2021, Vol. 15(1) 6–10
Interplay	DiaMonTech	2022/23	12	Ongoing validations	<10% (retrospective)	Internal presentations
Freckmann	IfDT Ulm	2023/24	36	External validation	18-20 % (prospective)	https://www.clinicaltrials.gov/study/NCT06088615

Questions that can only be answered by clinical tests:

- How can calibrations be performed by the user ?
- How long will a calibration be valid: days, weeks, months ?
- What are the factors that determine precision and reliability in practical use and in daily life ? (e.g. humidity or cosmetics on skin, skin diseases, medication, outside temperature,….)

IfDT: Institut für Diabetes-Technologie (Ulm)

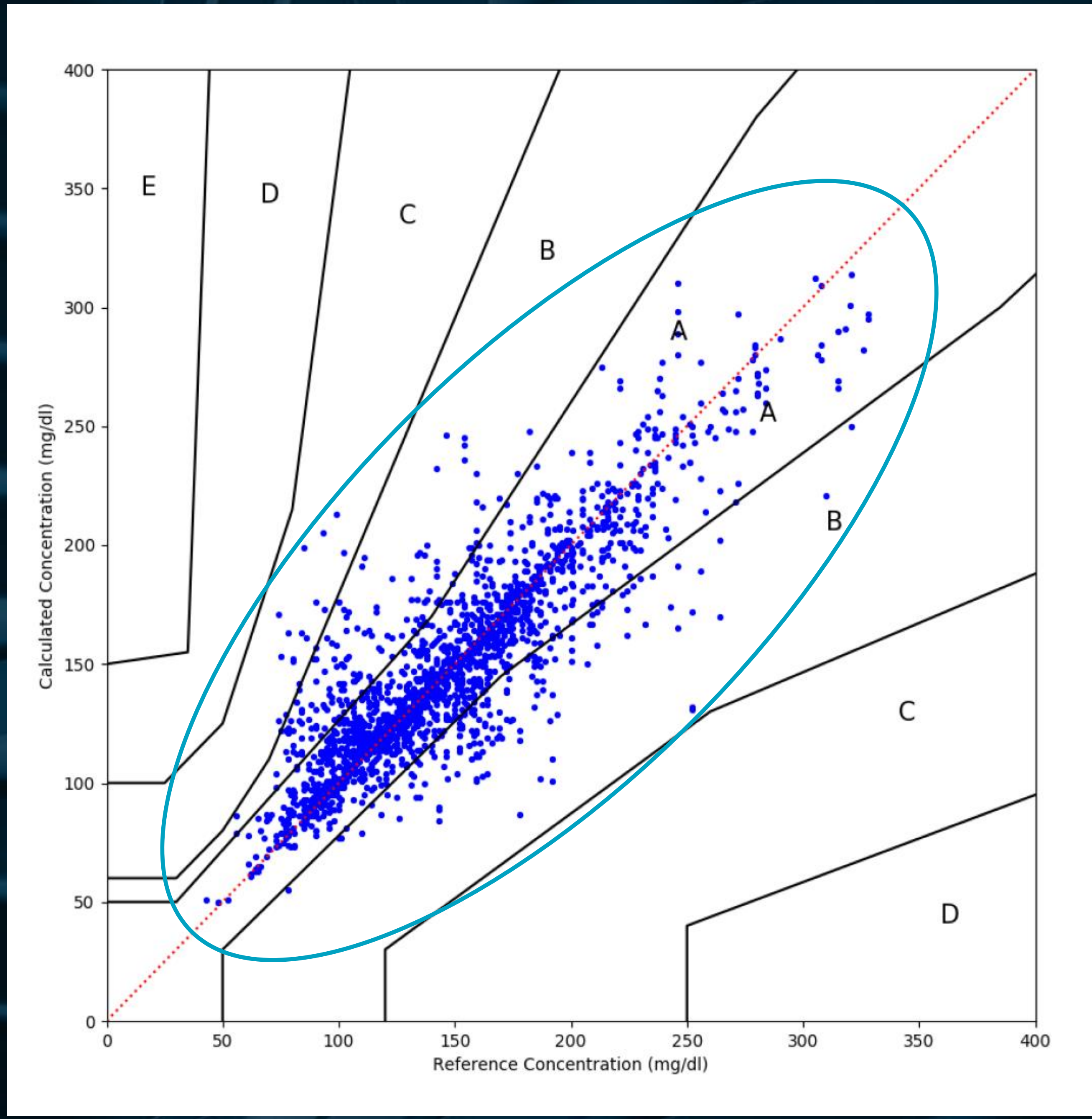
Average error (MARD) should be around 10% retrospective and lower than 25% prospective

From Lab setups to instruments

D-Base (2019)
- Multi-User Device
- EC Tunable QCL
- CE Certified
- Clinical Validation

Study 100: A retrospective test with healthy and diabetic volunteers

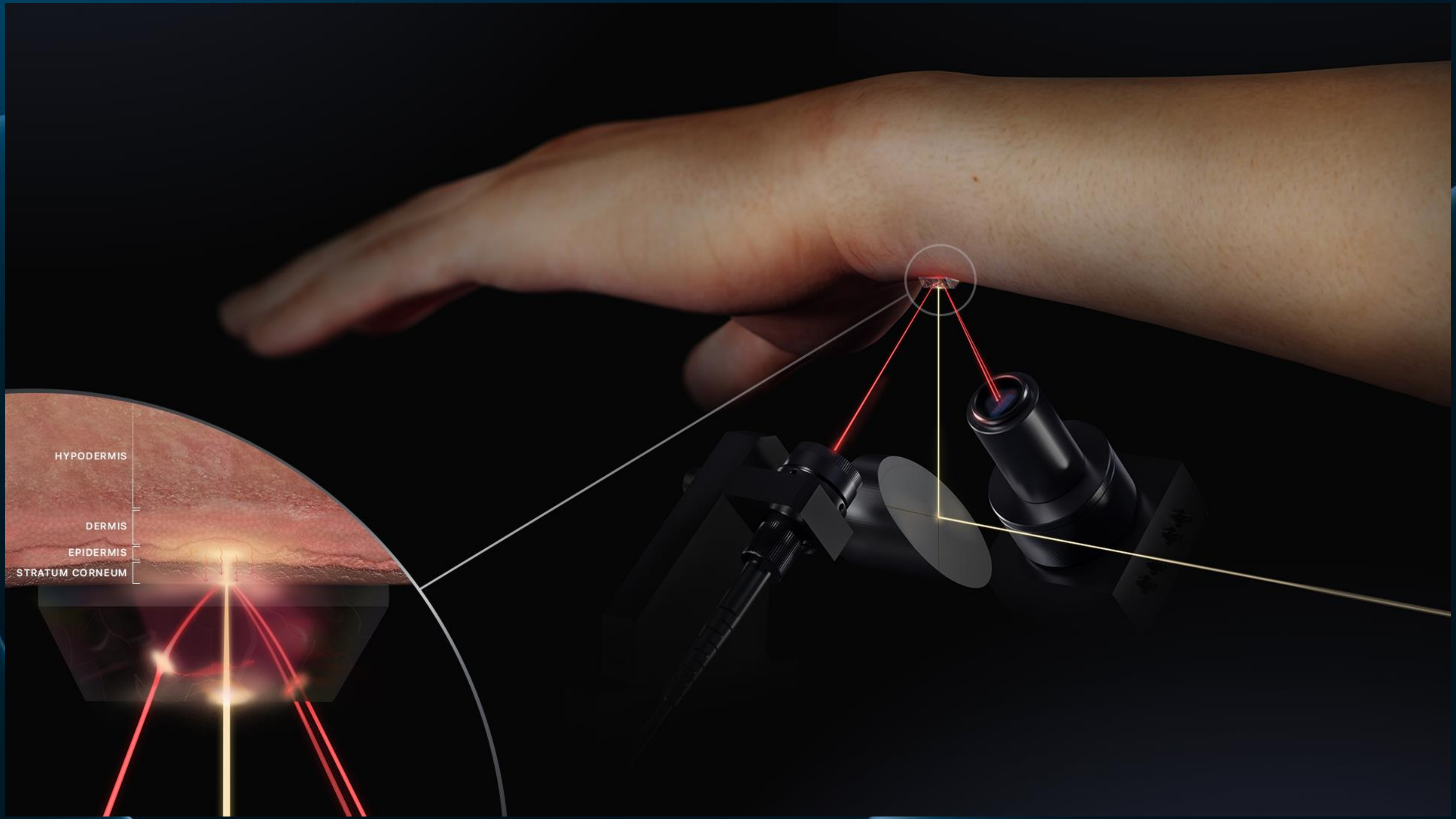
- 08/2018 – 02/2019
- 41 diabetes patients Type 1/Type 2
- 59 healthy volunteers
- approved by Ethics Commission of Frankfurt University (Ref. Nr. 27/2017)
- age:18 to 70+
- 55% male/ 40% female/ 5% not specified
- supervised by diabetologist
- measurement in 5-minute-intervals over 2-3 hours
- about 20-25 data pairs/volunteer (Ref. *invasive vs*. IR *non-invasive*)
- total 1.943 data pairs: 99,1 % in Zones A und B
- 0,9 % in Zone C
- No data in zones D and E



Accuracy corresponds to commercially available minimal invasive glucometers

Journal of Diabetes Science and Technology, 2021, Vol. 15(1) 6–10

Preferred measuring site: The inner side of the wrist



- Thin *stratum corneum* (20-30 µm)
- Low interperson variabitity
- Low variability over time
- Test site for future wearable

Clinical validation by an independent institute (IfDT Ulm (Germany)

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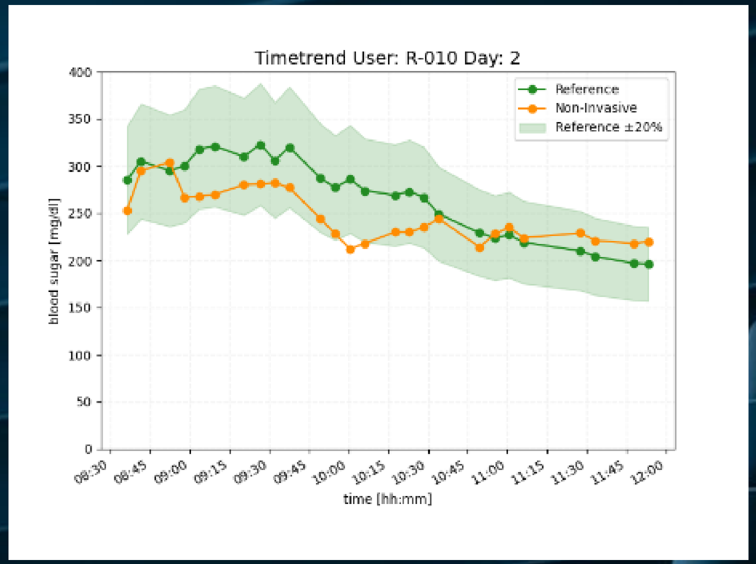
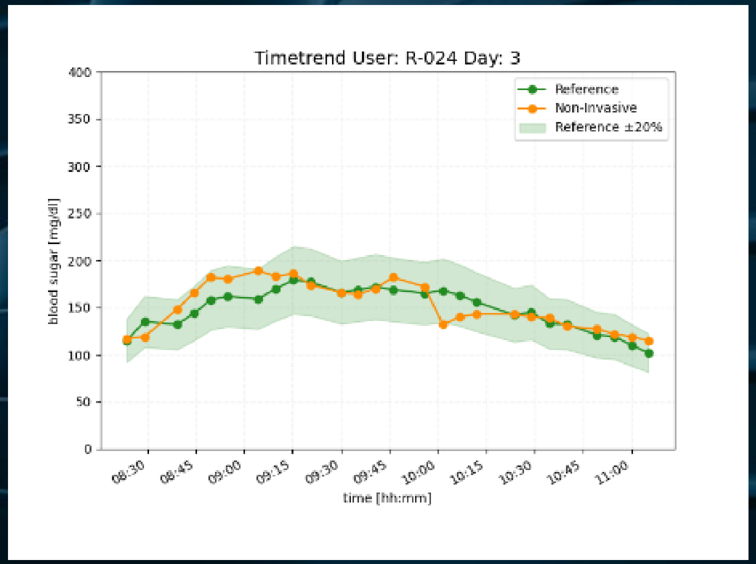
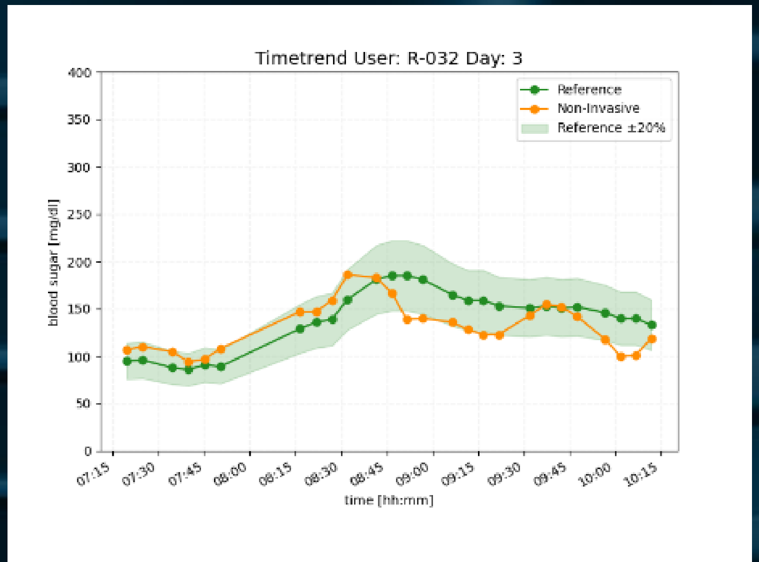
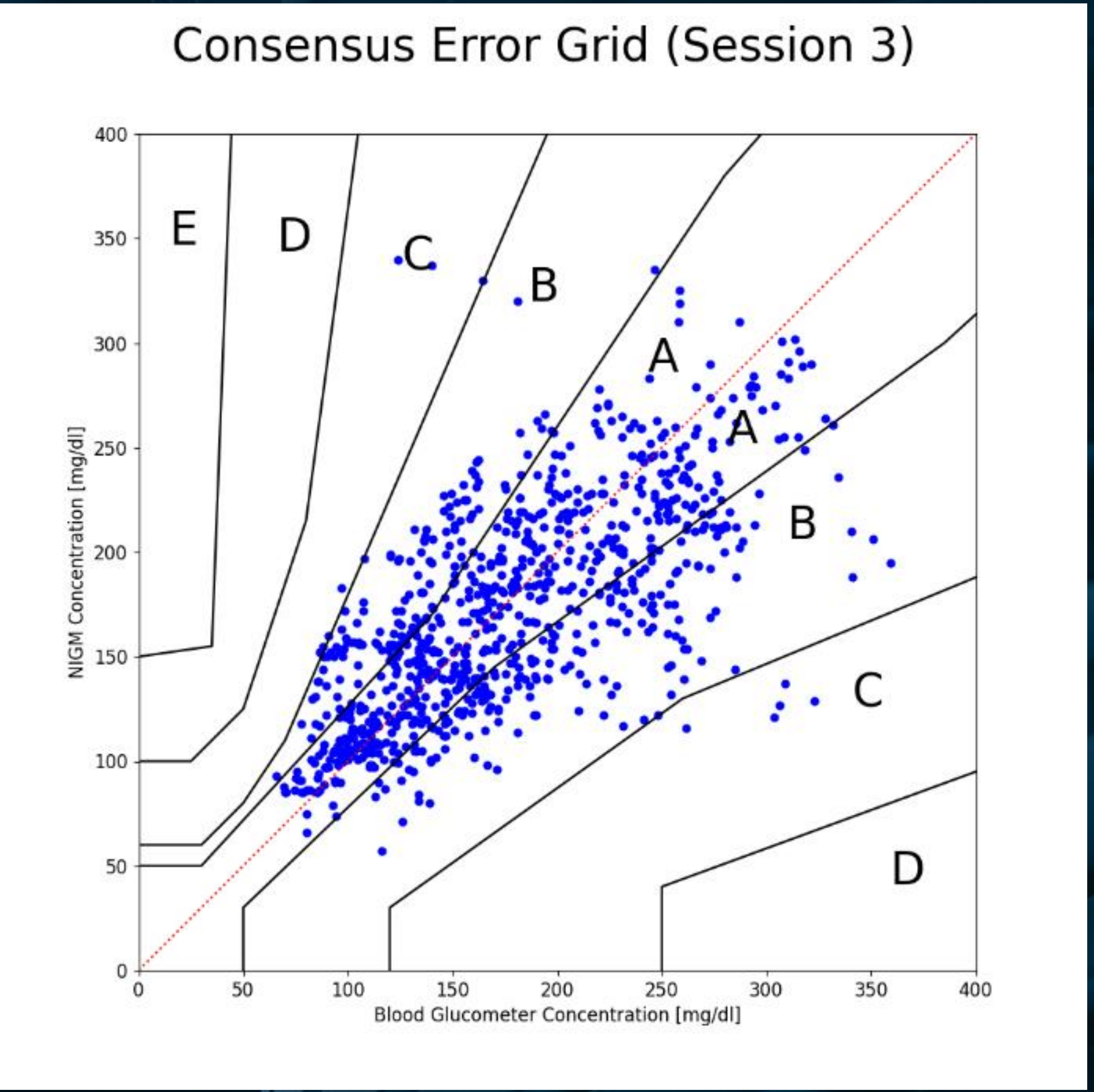
A prospective test with Type 1 and Type 2 diabetes patients

- 11/2023 – 02/2024
- 36 diabetes patients Type 1/Type 2
- Three sessions each 3-5 days apart:
  Session #1 for calibration; Session #2 for control; Session #3 for precision
- Four different algorithms tested









- 98.6 % of the values are within clinically accurate zones A+B
- Only one measurement in zone D; no measurement in zone E.
- Performance is close to the requirements for invasive blood glucometers
- MARD (Mean Absolute Relative Difference): 19,6 % for Session #3
- Minimum calibration effort

Manuscript submitted to
Nature Communications Medicine

From a table-top device to a handheld device for the diabetes patient

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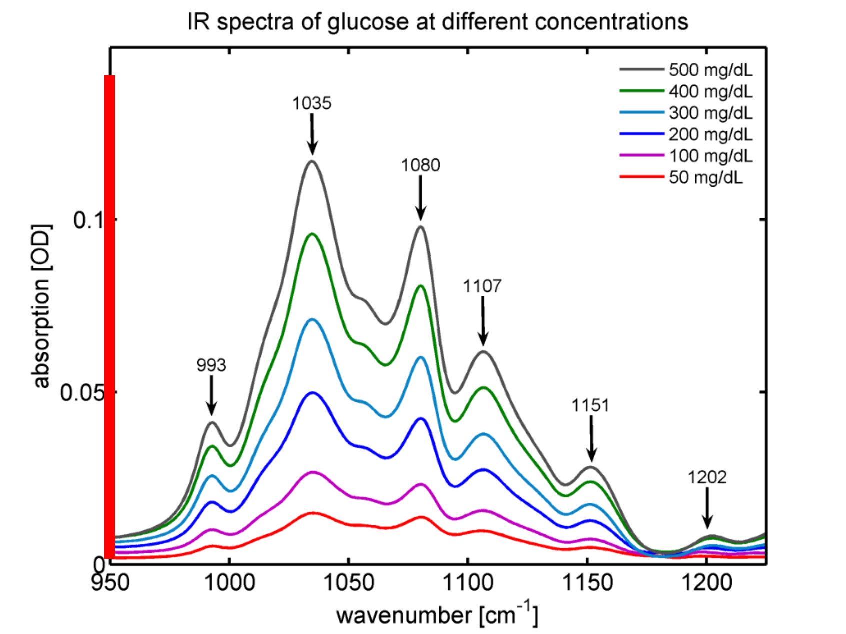
D-Base

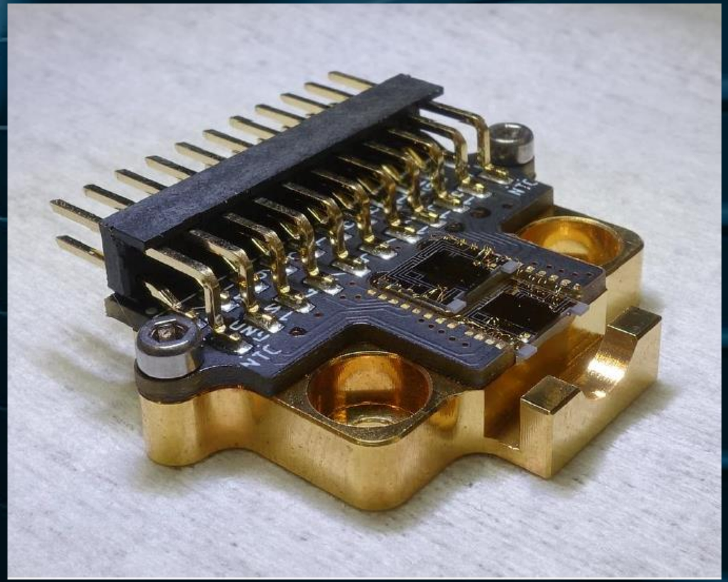
EC Tunable QCL

©Daylight Solutions

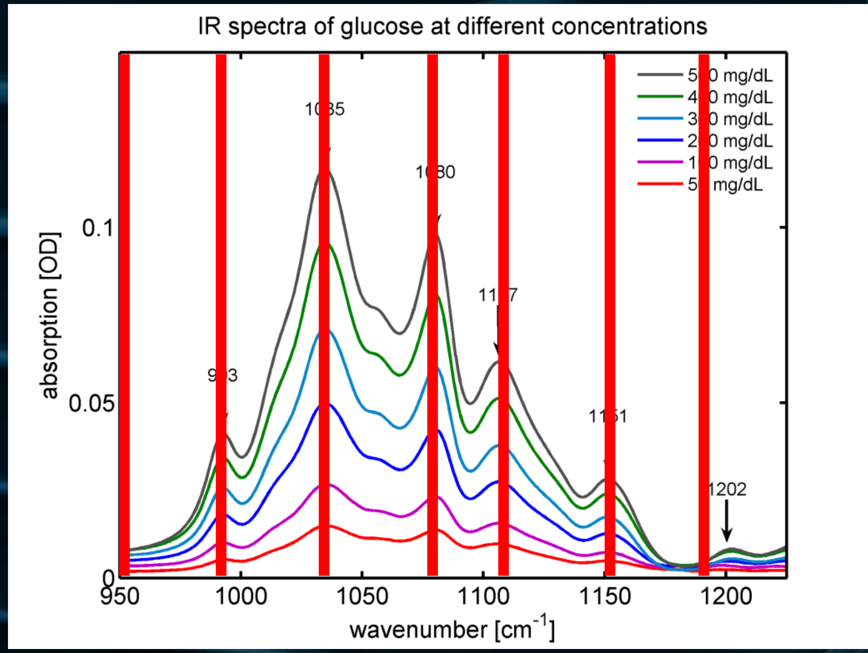


- Scanning of entire glucose range
- Relevant / less relevant wavelengths
- Scanning instabilities
- Time for scan/detection

D-Pocket

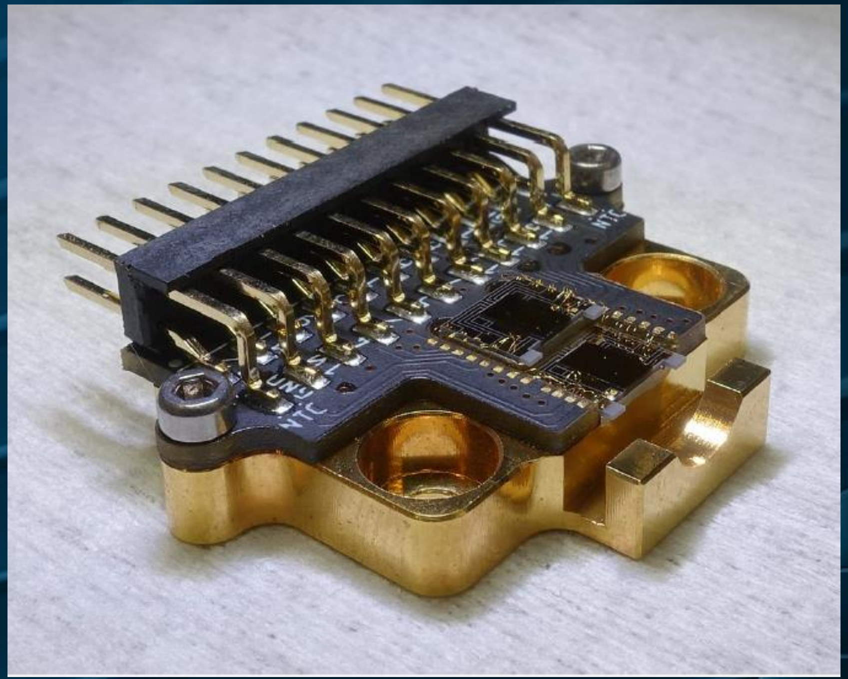


Array of DFB QCL chips



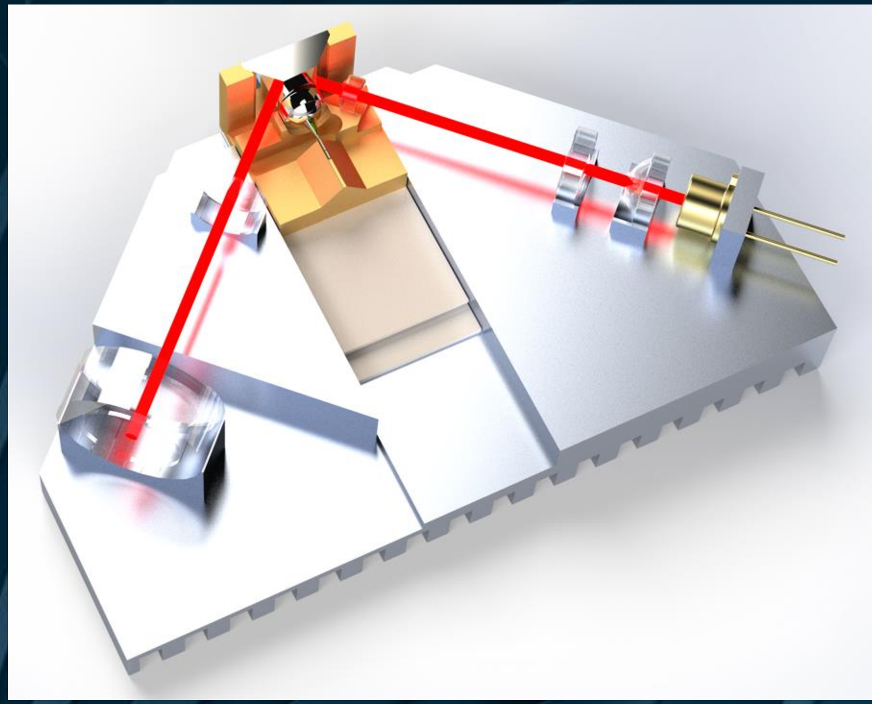
- Scanning of relevant glucose wavelengths
- Wavelengths for water background
- Wavelengths for interfering compounds / molecules
- Stable wavelengths
- Faster

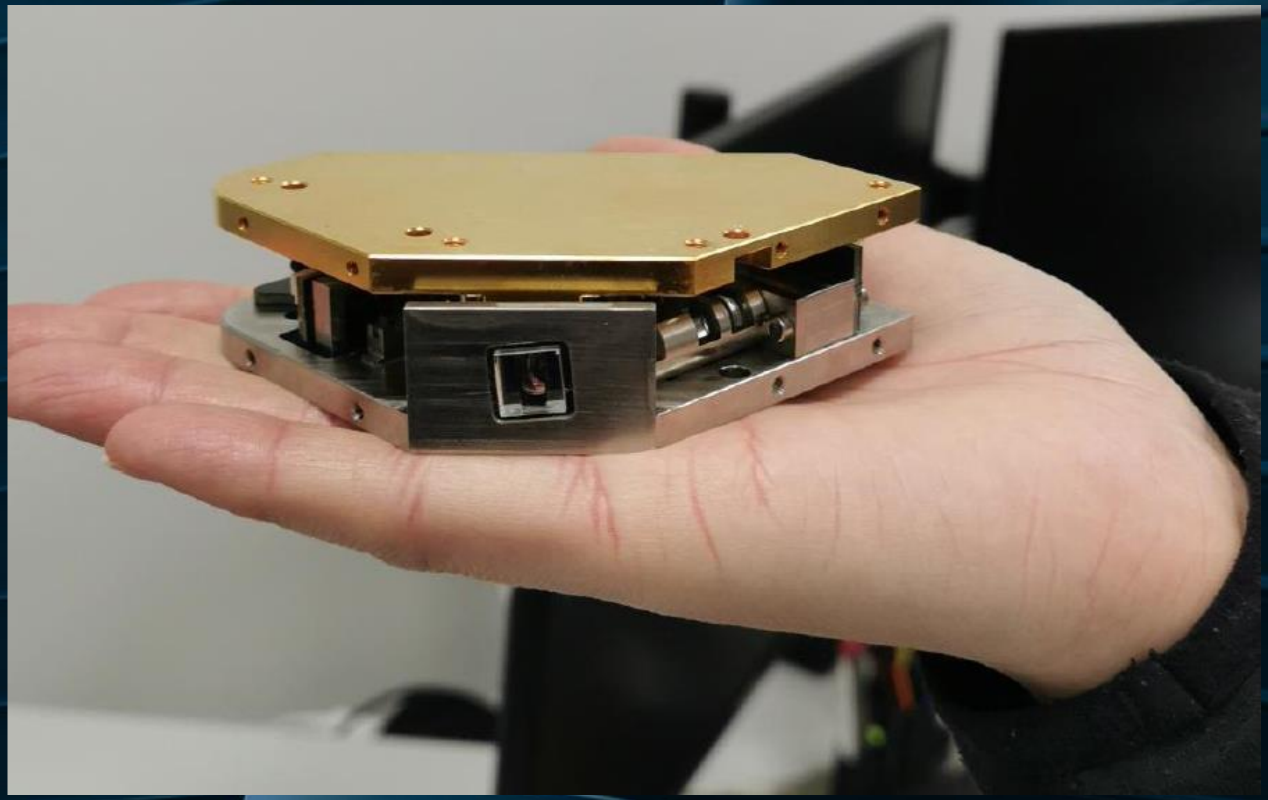
QCL Array: discrete wavelengths instead of broad tunability



16-wavelength QCL array developed in cooperation with Nanoplus

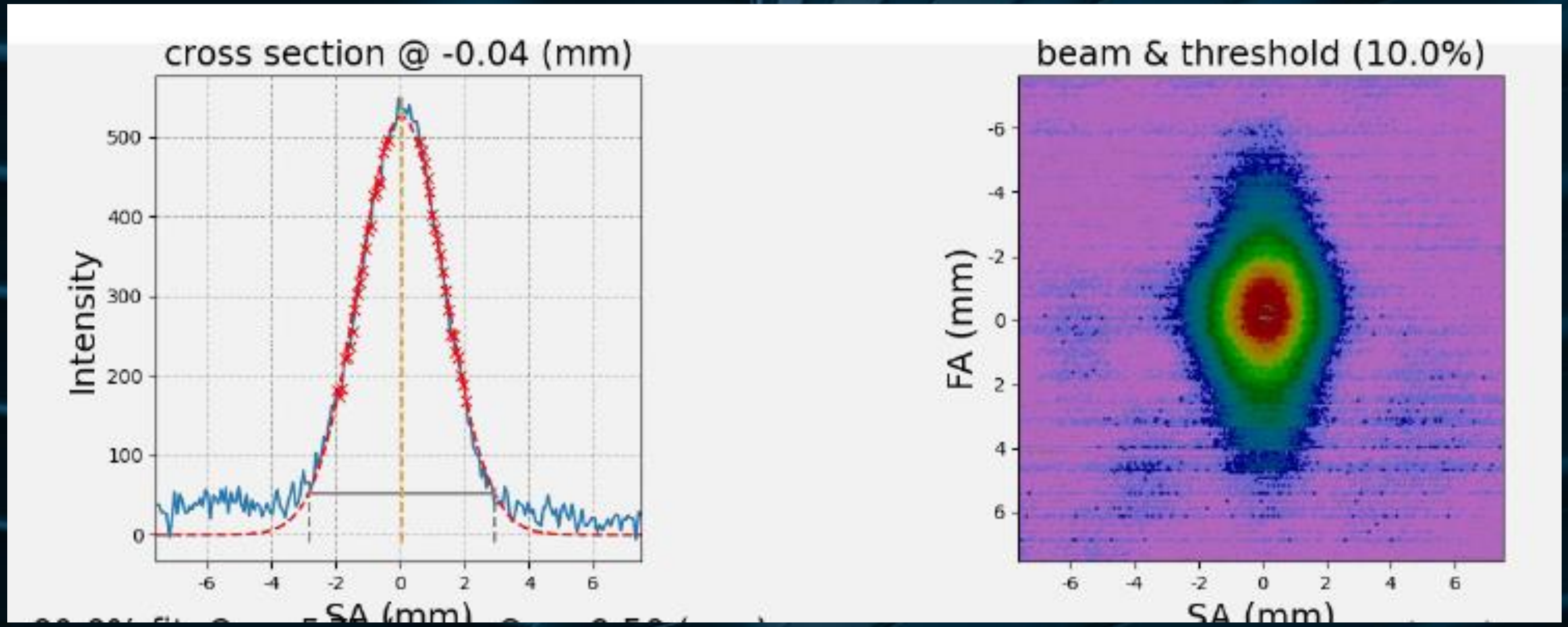
QCL pump beam and readout laser





assembled sensing unit

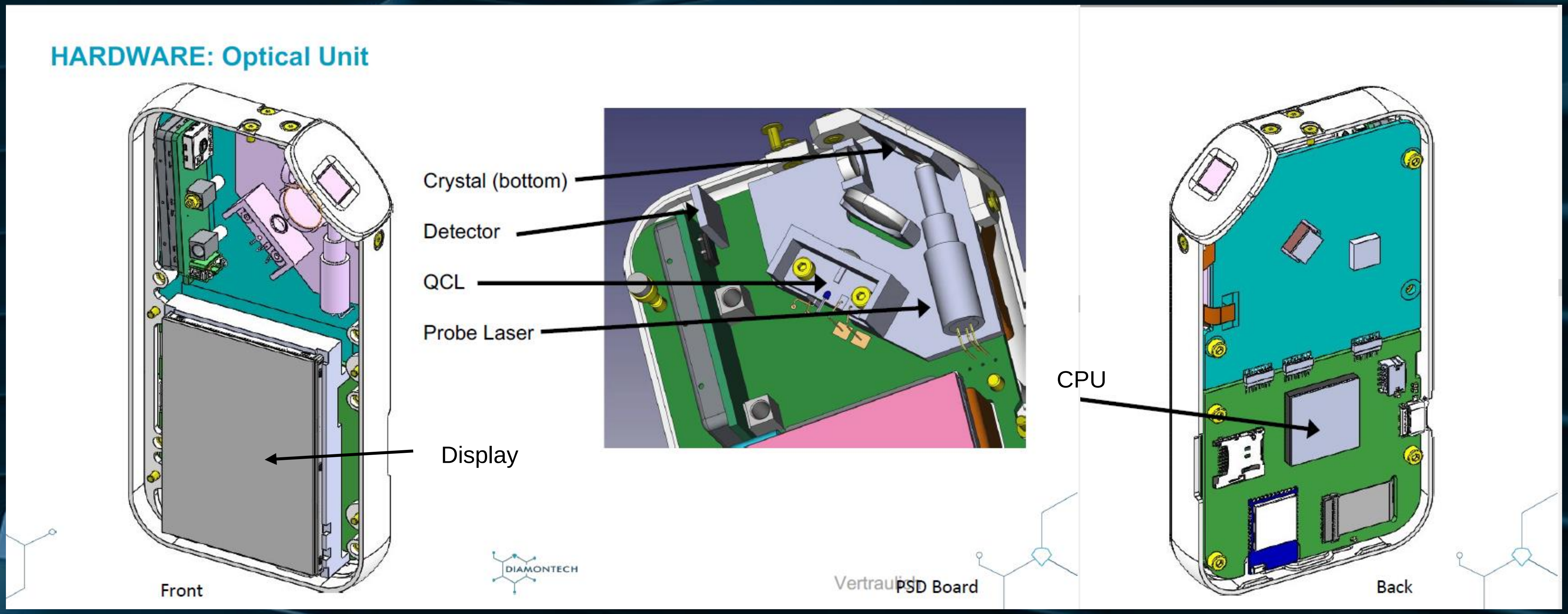
Sufficient output power and beam quality



Minaturization: D-Pocket, a handheld device for the diabetes patient

Features:

- Same technology as D-Base
- Discrete Mid-IR wavelengths in the glucose range
- Miniaturized QCL array for excitation
- Microlens array for beam collimation
- Miniaturized photothermal detection
- Measuring time approx. 10 seconds
- Allows 50+ measurements with one battery charge
- Works autonomous, but can connect to smartphone via BT
- Communication with diabetes app developed by us



D-Pocket (in development)

Individual companion for the diabetes patient

D-Pocket: Regulatory approval and certifications

DIAMONTECH

2024 | 2025 | 2026

- Q3 – Pre-Sub FDA
- Clinical Study US/EC
- Start CE/FDA-Process
- CE-Sign
- FDA-Approval

DiaMonTech is certified as developer for medical devices.

MEDICAL DEVICES ISO ISO 13485:2016 QUALITY MANAGEMENT

Medical Device Classification CLASS IIa EU Directive 93/42/EEC

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And our vision: D-Band

- wearable device (wrist band)
- continuously measuring blood glucose (e.g. in 10 minute-intervals)
- includes data logging and alarm functions to track glucose levels
- communication with DMT’s Diabetes App *Diamoki* ®

Complementary Team


Thorsten Lubinski
CEO

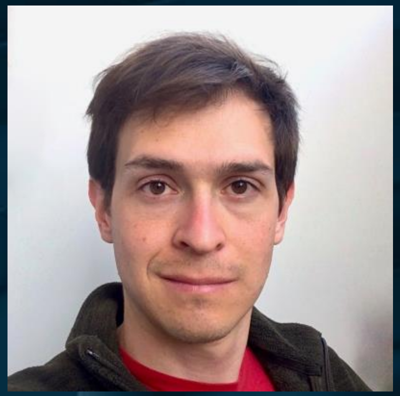

Sergius Janik
COO


Dr. Michael Kaluza
CTO


Dr. Jenny Kegel
Regulatory Expert


Mengzhi Guo
Software Developer


Dr. Luca Canini
Data Analyst


Daniel Rojas
Mechanical Engineer


Dr. Yigit U. Mahsereci
Electronic Engineer


Dr. Mattia Saita
Optics & Photonics

+ others (total 20 employees)

R&D Partners:
- Samsung
- Nanoplus
- Medtronic
- IfDT Ulm

Funding from BMBF: KMU Innovativ


Prof. Dr. Werner Mäntele
CSO

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THE NEXT GENERATION OF BIOSENSING

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