Noninvasive Blood Glucose Monitoring in the 2.0-2.5μm Wavelength Range

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Outline

Introduction to Diabetes

- What is diabetes?
- Why is noninvasive glucose monitoring valuable?

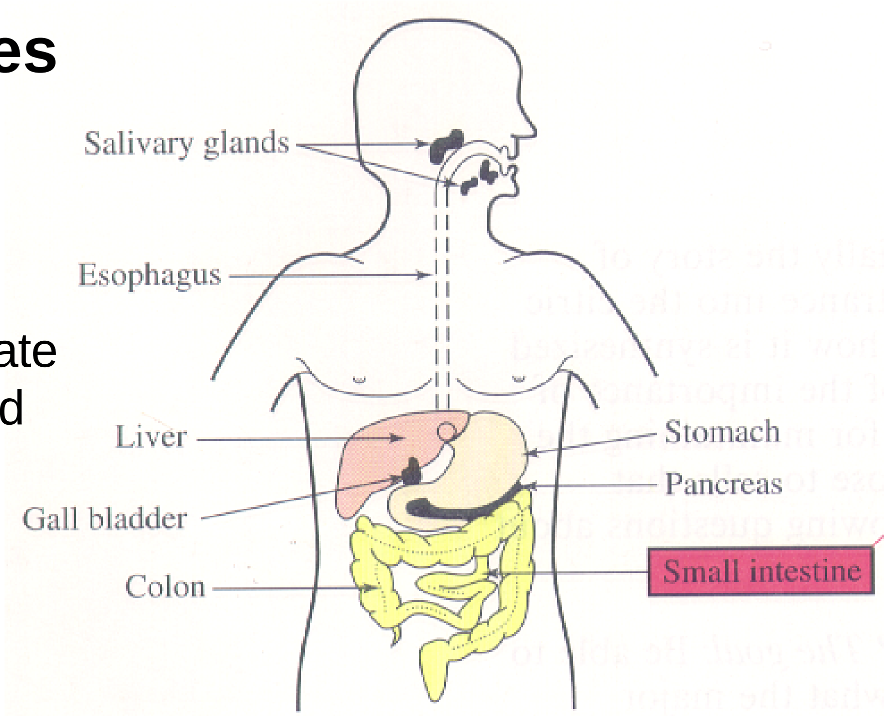
Noninvasive Monitoring

- How does noninvasive glucose detection work?
- What are the current limitations?

Mid-IR Technology

- How can IR semiconductor technology help?
- What are the key requirements for glucose sensing using laser diodes?

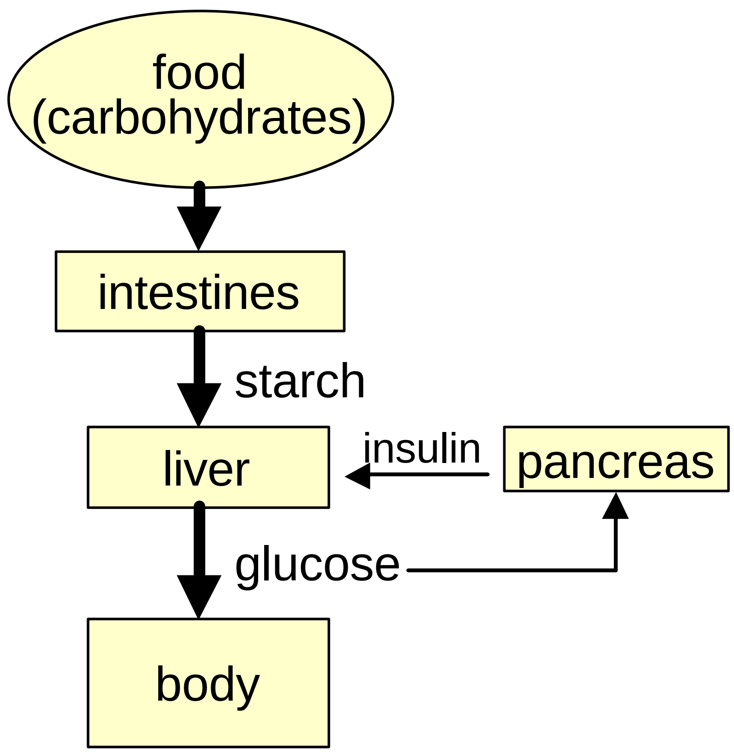
Diabetes



Affects 16 million Americans

What is diabetes?

- Breakdown of the body's ability to regulate the amount of glucose (sugar) in the blood stream



Glucose

- Produced in liver from digested carbohydrates
- Distributed to cells in the body by way of the blood stream

Insulin

- Hormone produced in the pancreas
- Regulates amount of glucose in blood
    - Tells liver to slow down glucose release
    - Tells cells to increase glucose intake
- In diabetics, insulin is not produced or is ineffective

Normal glucose level ~5.5 mM (100 mg/dL)

Manual Control of Glucose Levels

What happens when glucose is not regulated?

- Too much glucose (*hyperglycemia*):
  - Long-term danger
  - Excess glucose reacts with amine groups on proteins
    - eyes (blindness)
    - nerve damage
    - kidney (renal failure)
- Too little glucose (*hypoglycemia*):
  - Acute danger
  - Brain dependent on continuous glucose supply
    - confusion, coma, death

Self-regulation

- Draw blood and measure glucose 4-6 times per day
- Administer insulin manually

Problems with self-regulation

- Painful, risk of infection
- Cost of lancets, test strips
- Can’t do it while asleep

Goal of our work:

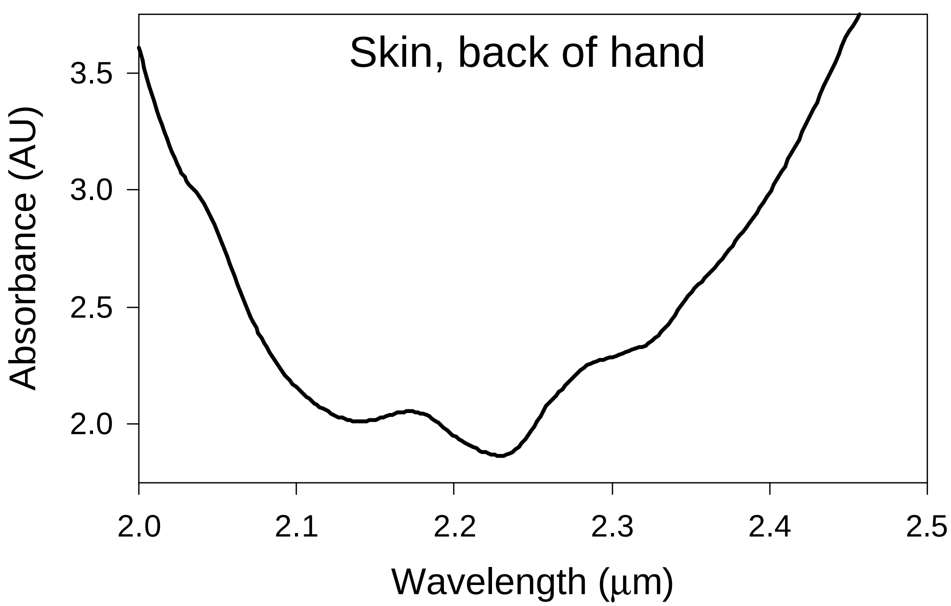
- Tools for measuring blood glucose without having to draw blood

Strategies for Optical Glucose Monitoring

- Near-infrared spectroscopy
- Raman spectroscopy
- Rotation of polarized light
- Light scattering
- RF impedance

Near-infrared transmission spectroscopy

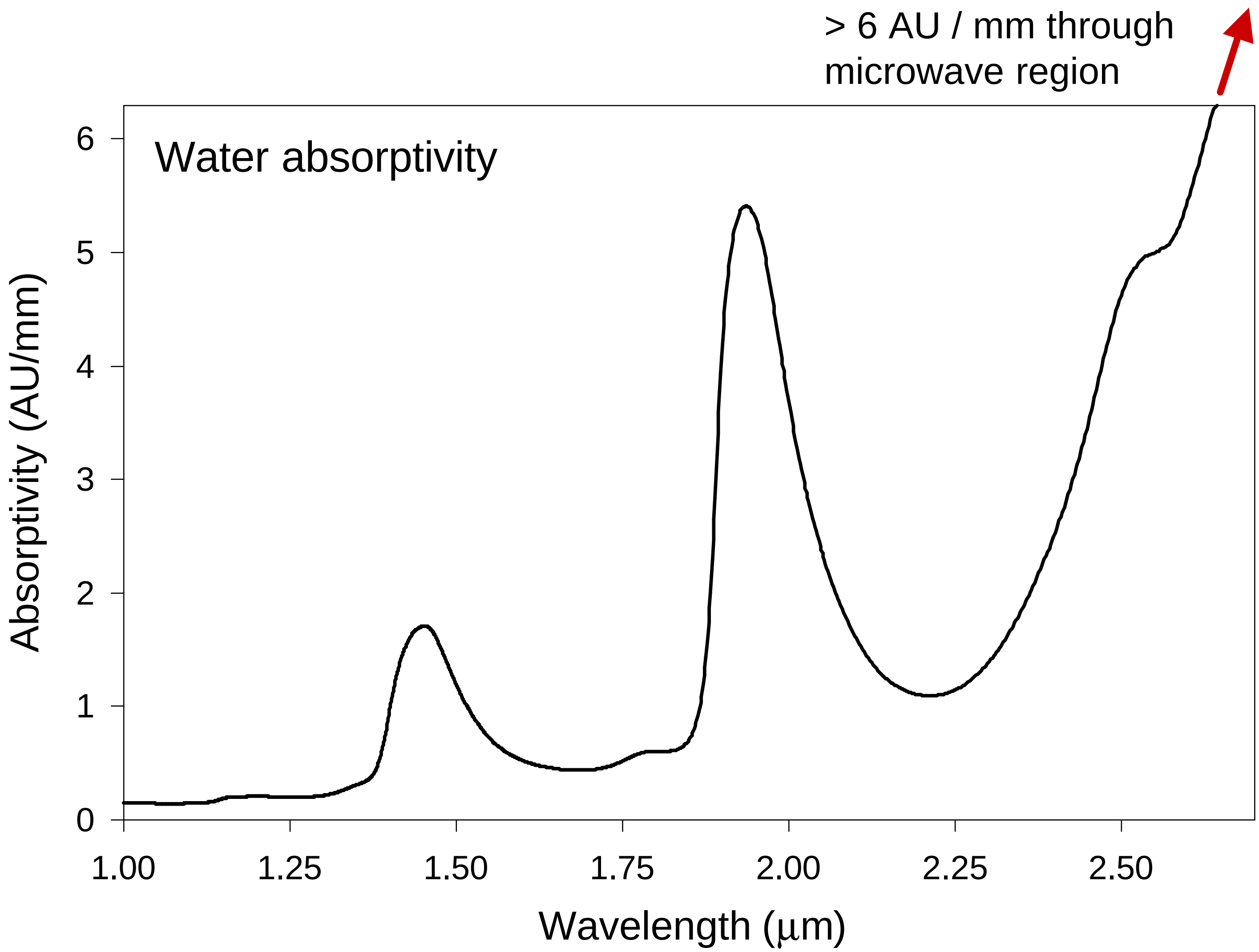
Incident near-IR radiation → Body → Transmitted radiation



Spectral processing → Glucose Concentration

Partial least squares regression

Water Transmission Windows

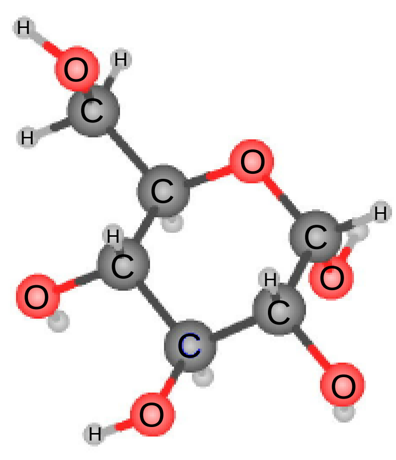


Absorptivity = $-\log_{10}$(transmission) / length

1 AU = 1 unit of optical density (OD)

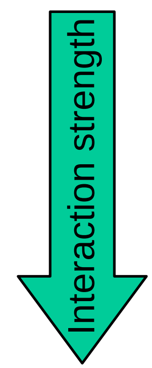
Interaction of Glucose with Light

Glucose molecule: $C_6H_{12}O_6$



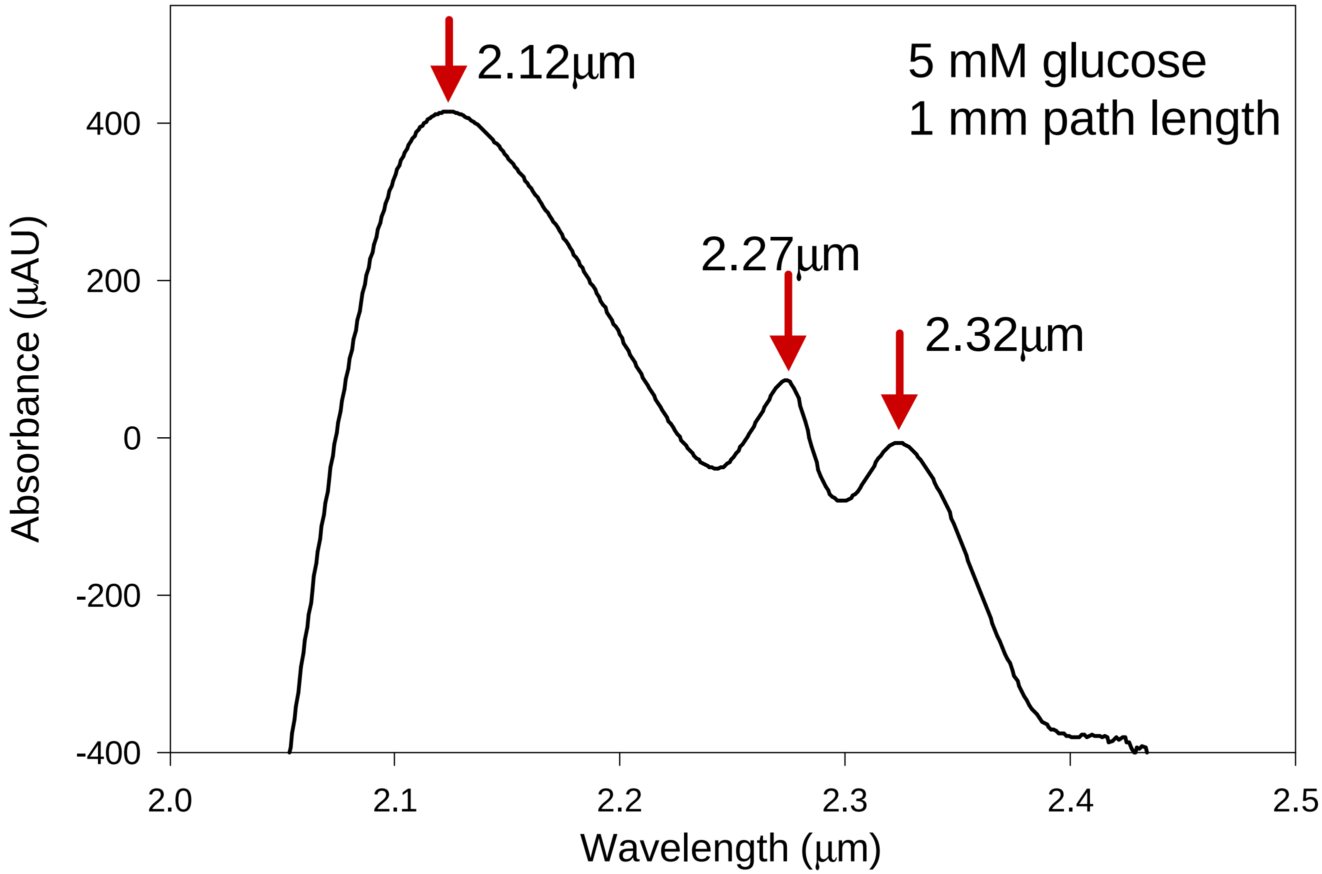
Vibrational spectroscopy

- Bending and stretching modes of C-H, N-H, and O-H bonds (4-10µm)
- Nonlinear combinations of stretching and bending modes (2.0-2.5µm)
- First overtone of C-H stretching modes (1.5-1.8µm)
- Second overtones and higher-order combinations (0.8-1.2µm)



The 2.0-2.5µm wavelength range has the best analytical information of any of the available water transmission windows

Glucose Absorbance Spectrum

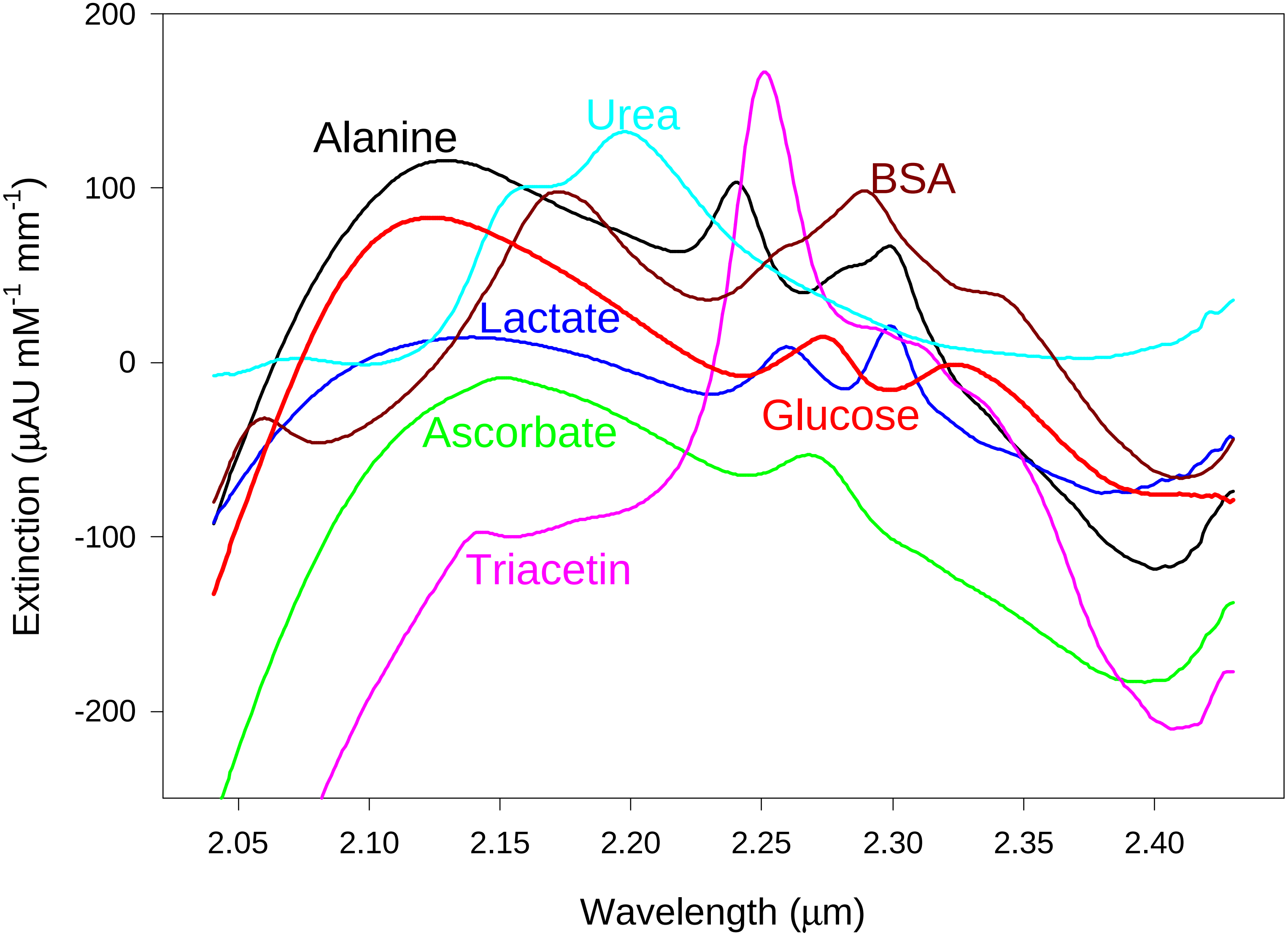


Spectral uniqueness

- The wavelength and width of absorption features depend on the local chemical environment surrounding the bonds

Absorbance Spectra of Other Components

The glucose absorption spectrum is unique…
but it is overlapped with many other unique spectra



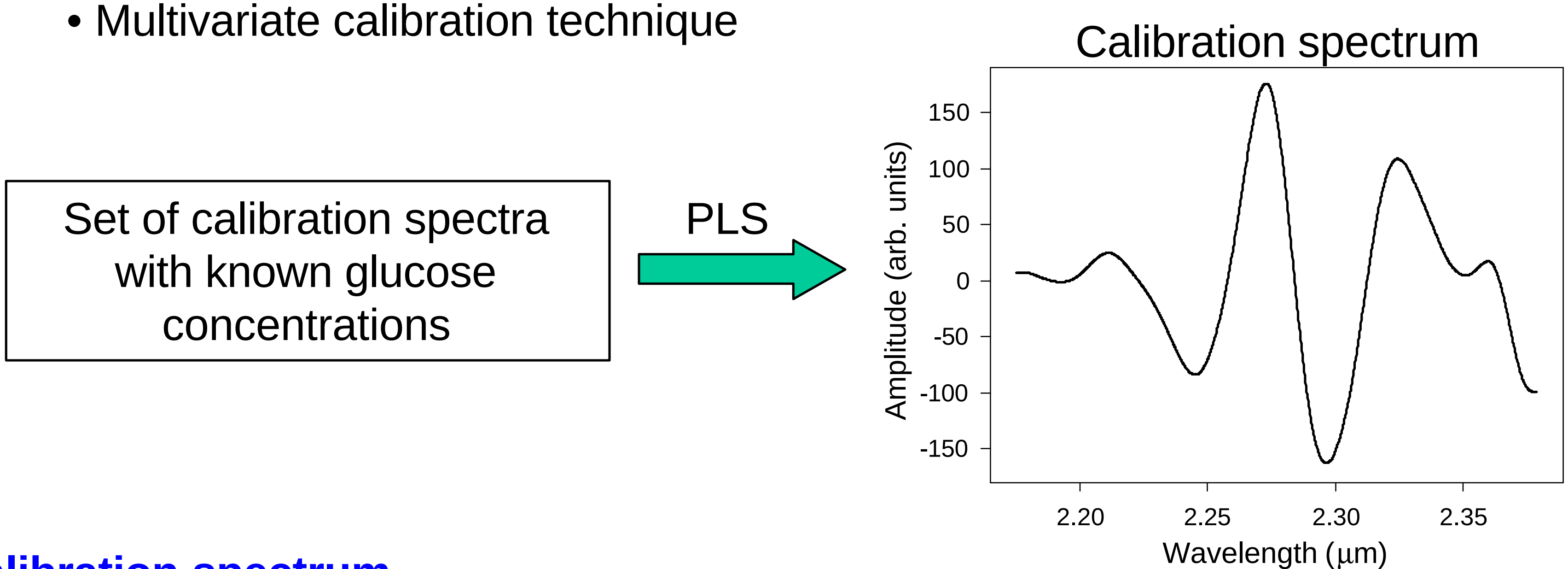
Information at *multiple* wavelengths is required to uniquely identify glucose

Seeing Through Interference

How do we isolate the glucose information from a spectral measurement?

Partial Least Squares Regression (PLS)

- Multivariate calibration technique

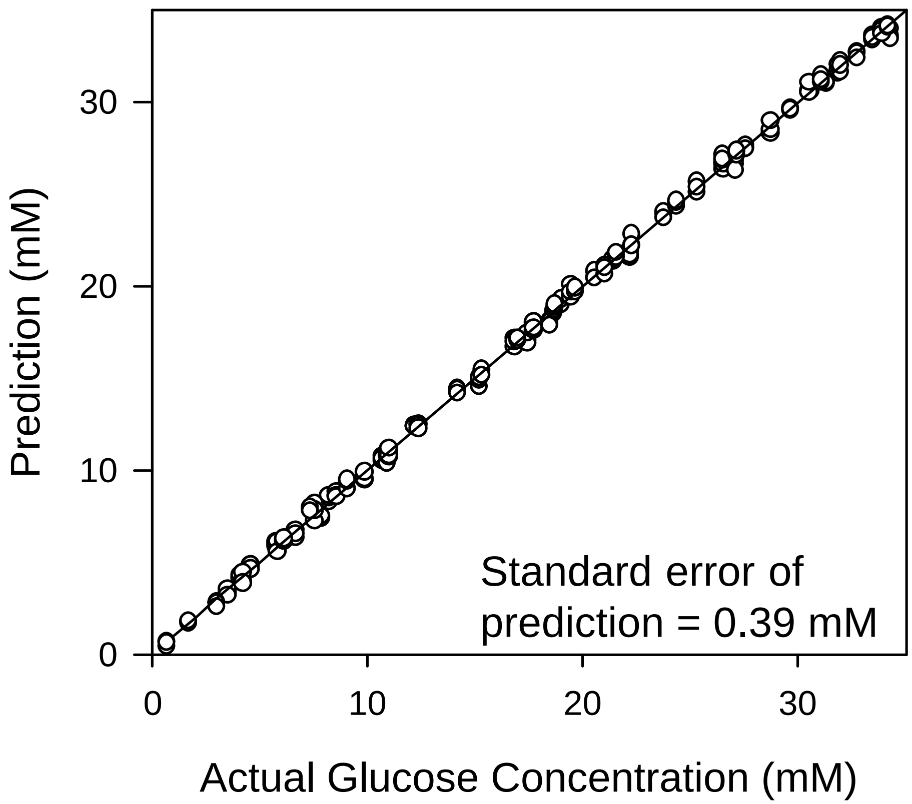


Calibration spectrum

- Calibration describes the systematic variation in the calibration spectra that is the most highly correlated with glucose concentration
- Inner product of calibration spectrum and the spectrum of a sample gives the glucose concentration
- Calibration spectrum is orthogonal to non-glucose spectral variations (e.g., due to other skin components, hemoglobin, urea, lactate, skin temperature, etc.)

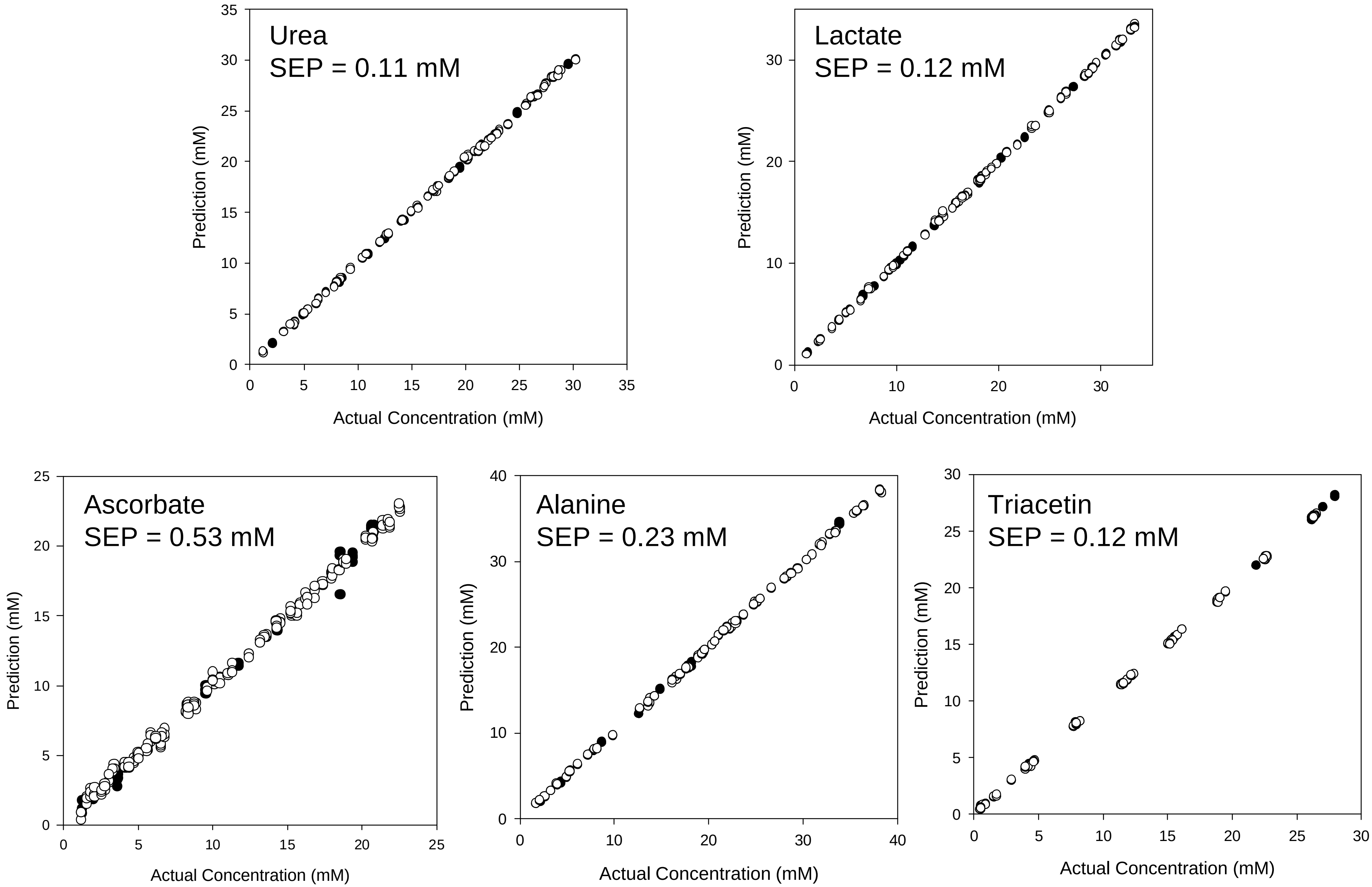
In Vitro Measurement of Glucose

- 80 samples containing glucose, lactate, alanine, ascorbate, urea, and triacetin
- Sample set designed to avoid correlations between component concentrations
- 2.0-2.5µm wavelength range



The analytical information needed to extract glucose concentration in the presence of other analytes is present

Other Analytes



The Danger of False Calibrations with PLS

Partial least squares regression is a very powerful technique, but it must be handled carefully

Great care is required to avoid bogus calibrations that *seem* to work well

- Experimental protocols must eliminate correlation between glucose concentration and all other parameters, *including time*

Calibrations based on glucose tolerance tests are problematic

Arnold, *et al.*, Analytical Chemistry 70, 1773 (1998)

From *In Vitro* to *In Vivo* Measurements

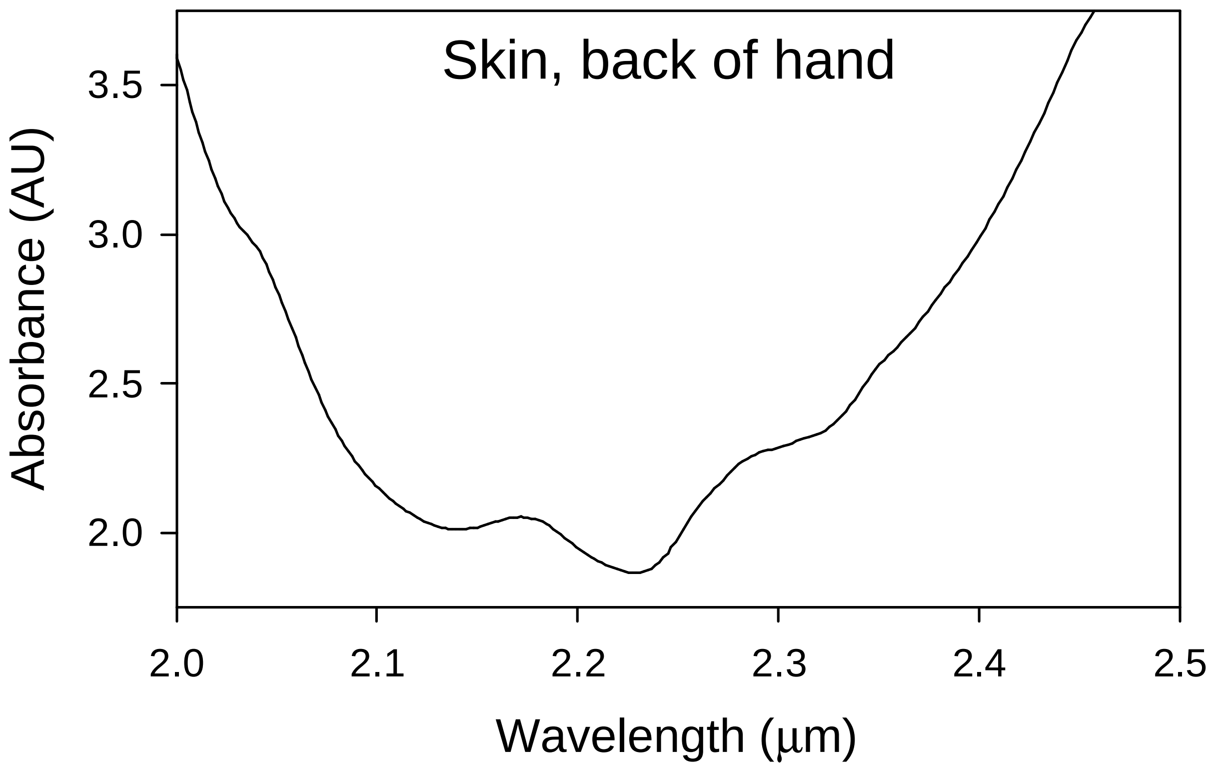
Increased sample complexity

- Greater number of chemical components

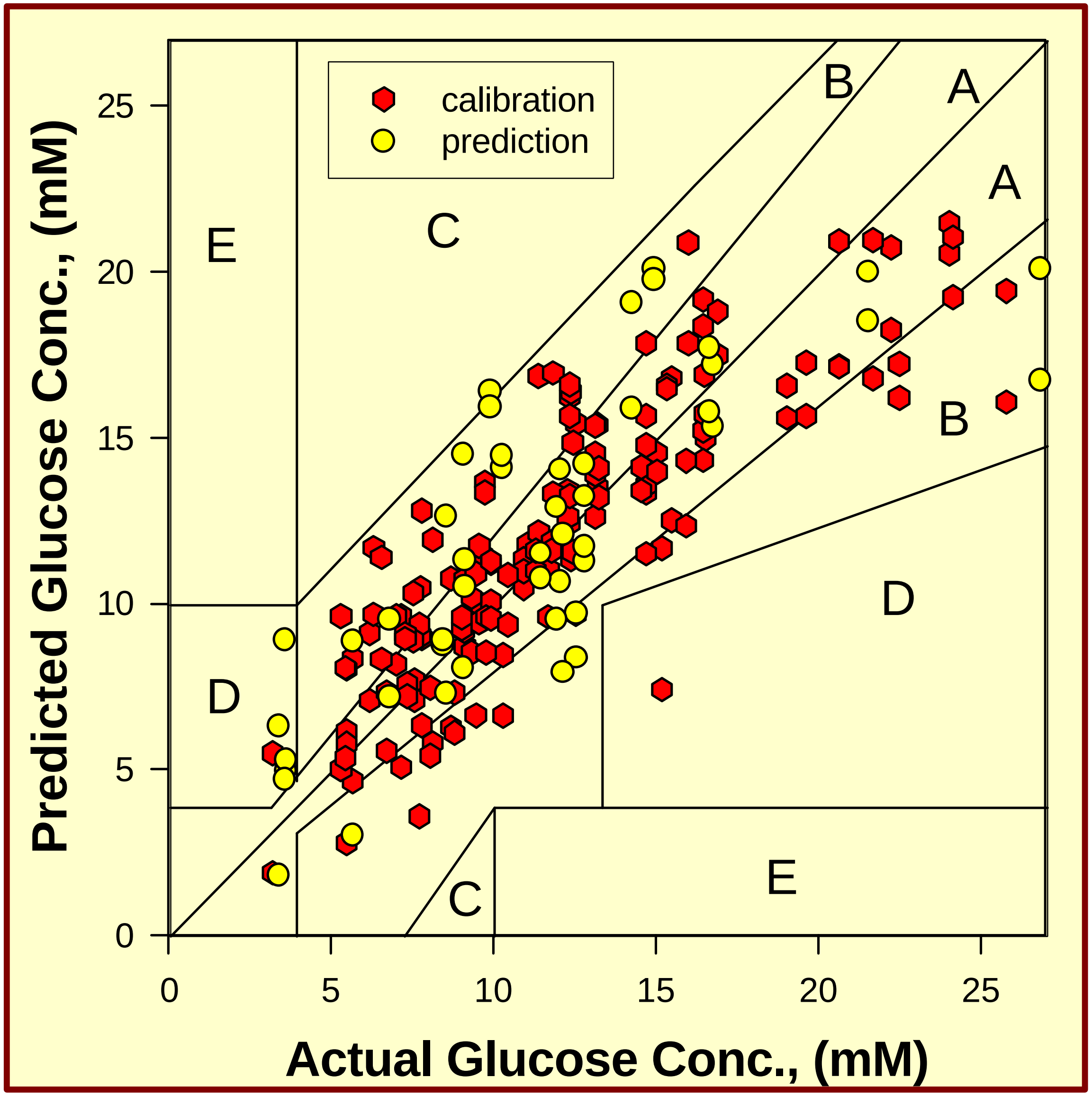
Decreased sample throughput

- Water absorptivity at 2.2μm ~ 1 AU/mm
- Skin absorptivity at 2.2μm ~ 2 AU/mm

Factor of 10x reduction in signal with respect to water



In Vivo Measurement of Glucose



Noninvasive measurement

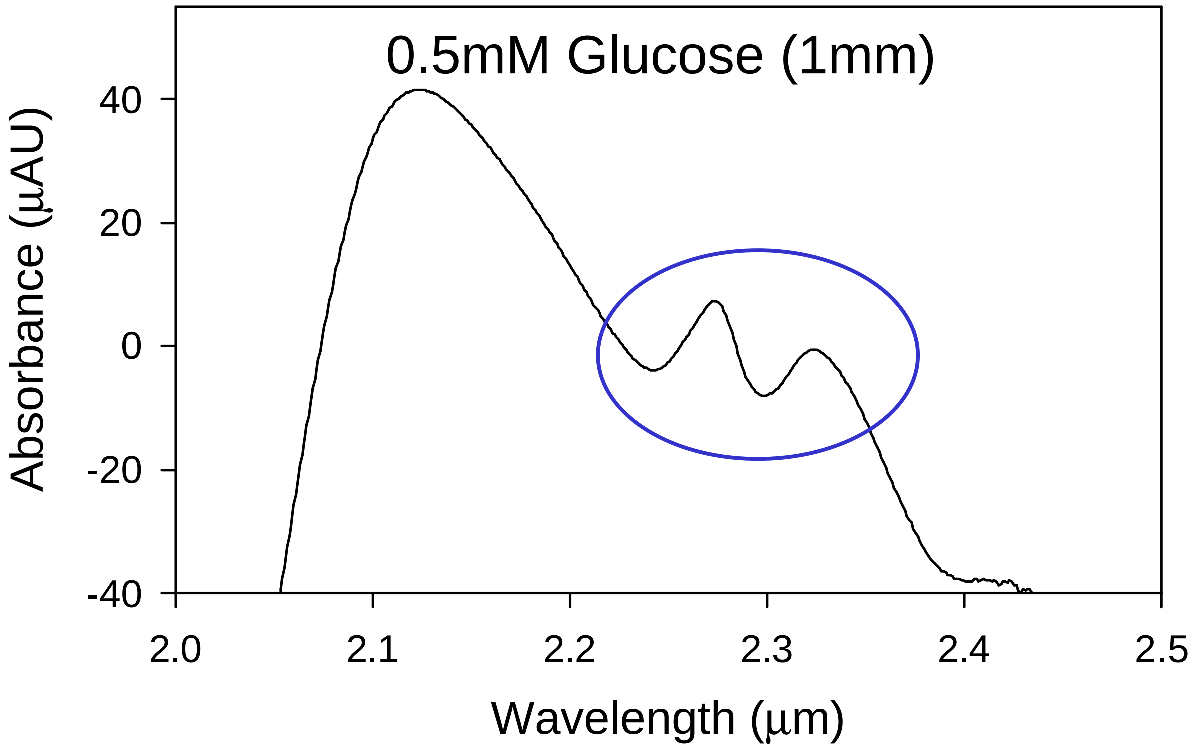
- 1.5-1.8μm wavelength range
- Measurements through tongue
- Calibration based on 29-day period
- Results are for the subsequent 10-day period
- Prediction error 3.4 mM

What can be improved?

- Spectral range
- Signal-to-noise ratio

Burmeister, Diabetes Technology and Therapeutics 2, 5 (2000)

Target Signal-to-Noise Ratio



Target signal-to-noise ratio

- Assume 1mm path length, 0.5mM change in glucose
- Resolving a change in absorbance of 10μAU requires detecting a change in transmission of 1 part in 50,000 (20ppm)
- Require a signal-to-noise ratio of ~50,000.

Looking for a *very small* signal in the presence of a *very large* absorption background

Current In Vivo Measurement System

Broadband optical source

- Tungsten lamp

FTIR spectrometer

- High resolution
- Excellent wavelength stability
- High throughput

Single-element detector

- Extended wavelength InGaAs
- 2.6µm cutoff
- 1mm diameter
- 2-stage TE cooled (-40ºC)
- D^* = 2×10^{12} cmHz$^{1/2}$/W (NEP ~ 50fW/Hz$^{1/2}$)

How Can Mid-IR Semiconductor Technology Help?

Key wavelength range: 2.2 - 2.4mm

Detectors

- Present work using FTIR spectroscopy is detector-noise limited
- Unstrained Sb-based detectors can potentially outperform highly-strained InGaAs materials

2-stage TE cooled InGaAs: $D^* = 2\text{x}10^{12}$ cmHz$^{1/2}$/W

LED's

- High-brightness for coupling into fiber optics with limited apertures
- Commercially available 2.3µm LED's (~1/4 mW)
- Need an improvement of factor of 4 to outperform tungsten lamps

Laser Diodes

- High-power sources can help overcome low skin throughput (10's mW)

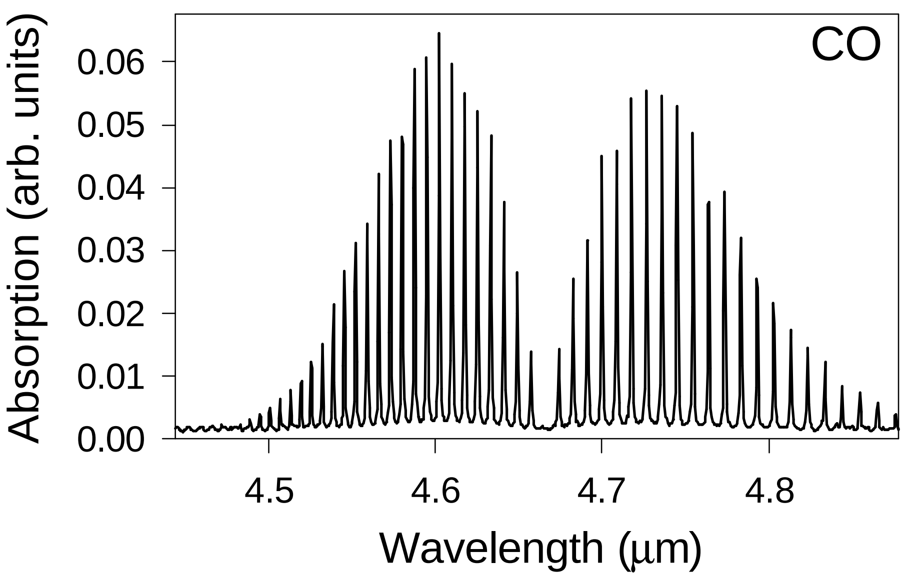
Laser Diode Spectroscopy

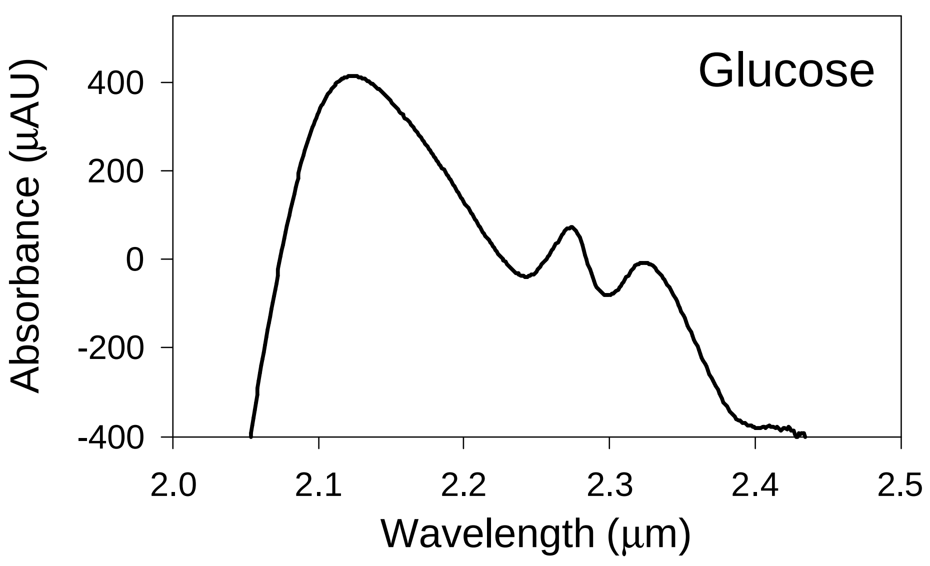
Requires tunability or integration of many single-wavelength diodes

- Multiple wavelengths required to distinguish between many skin components with overlapping spectral signatures

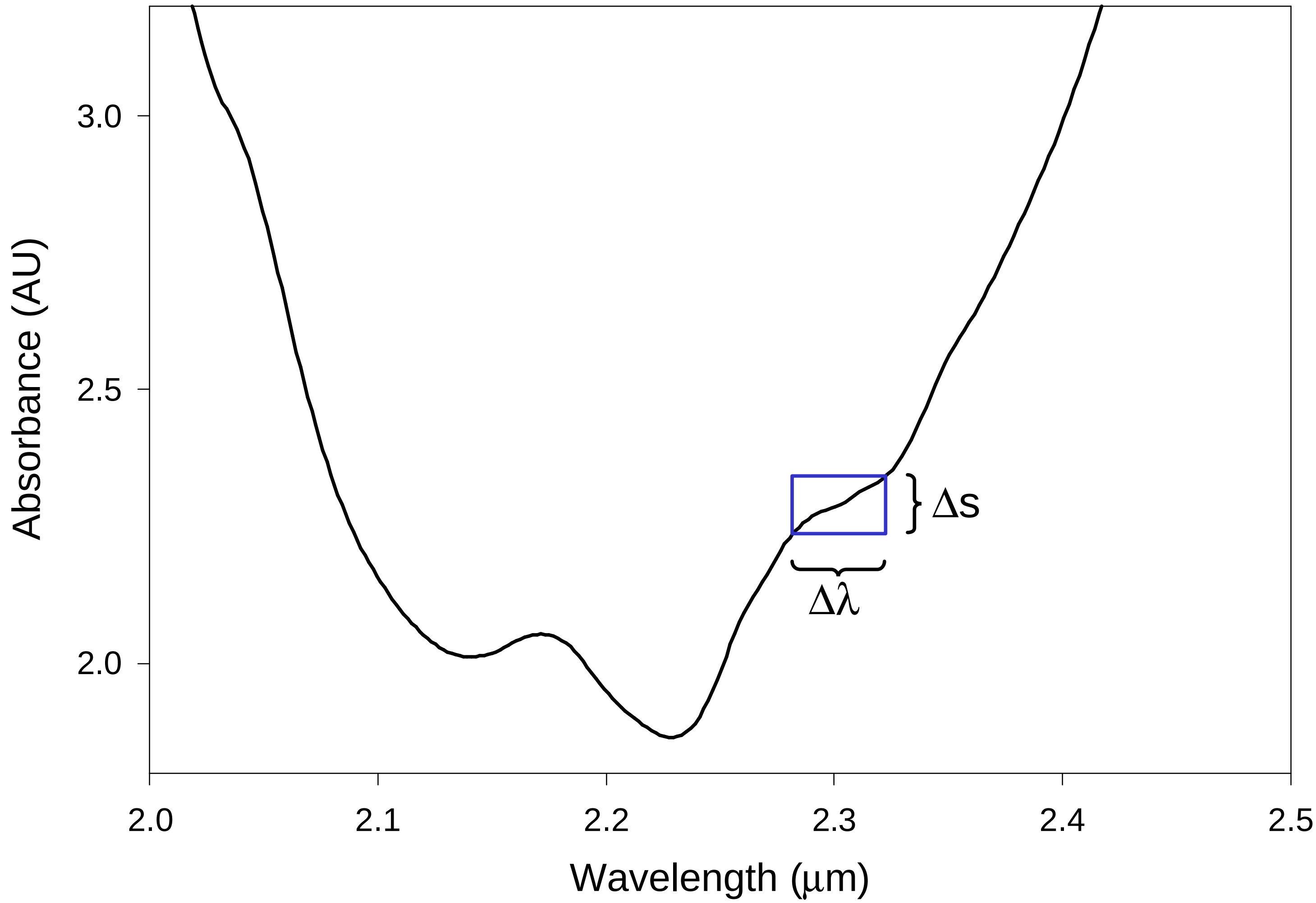
Very different from gas sensing

- Broad bands rather than narrow features
- Require 200nm tuning range (2.2-2.4μm)
- Line width is not important, but wavelength stability and reproducibility are





Wavelength Reproducibility



- Variability in wavelength produces variability in signal by Δs = ds/dλ Δλ
- In order to achieve a SNR of 50,000, we require Δλ = 0.01-0.05nm

Consequence of *large* SNR requirement

Tuning Strategies

Temperature

- Wide tuning range
- Slow tuning
- Imprecise

Electronic

- Variation of drive current or variation of index of refraction with injected charge density
- Convenient
- Fast tuning

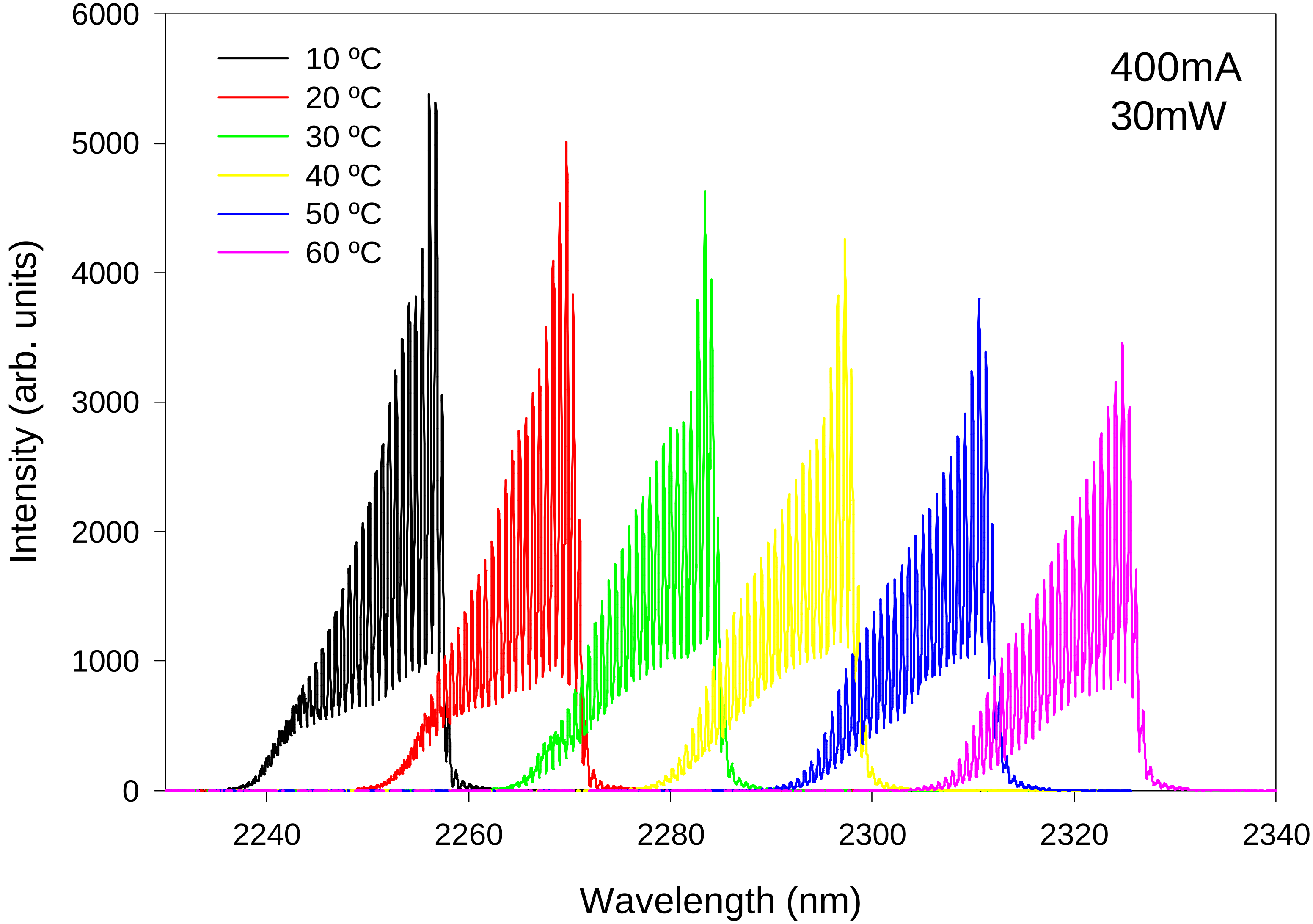
External cavity

- Bulky, not as convenient as electronic tuning
- Wide tuning range
- Grating-based approaches have moving parts, moderate tuning speeds

Temperature Tuning

Laser diodes provided by the Fraunhofer Institute

- *Appl. Phys. Lett. 77, 1581 (2000)*
- Strained GaInAsSb quantum wells



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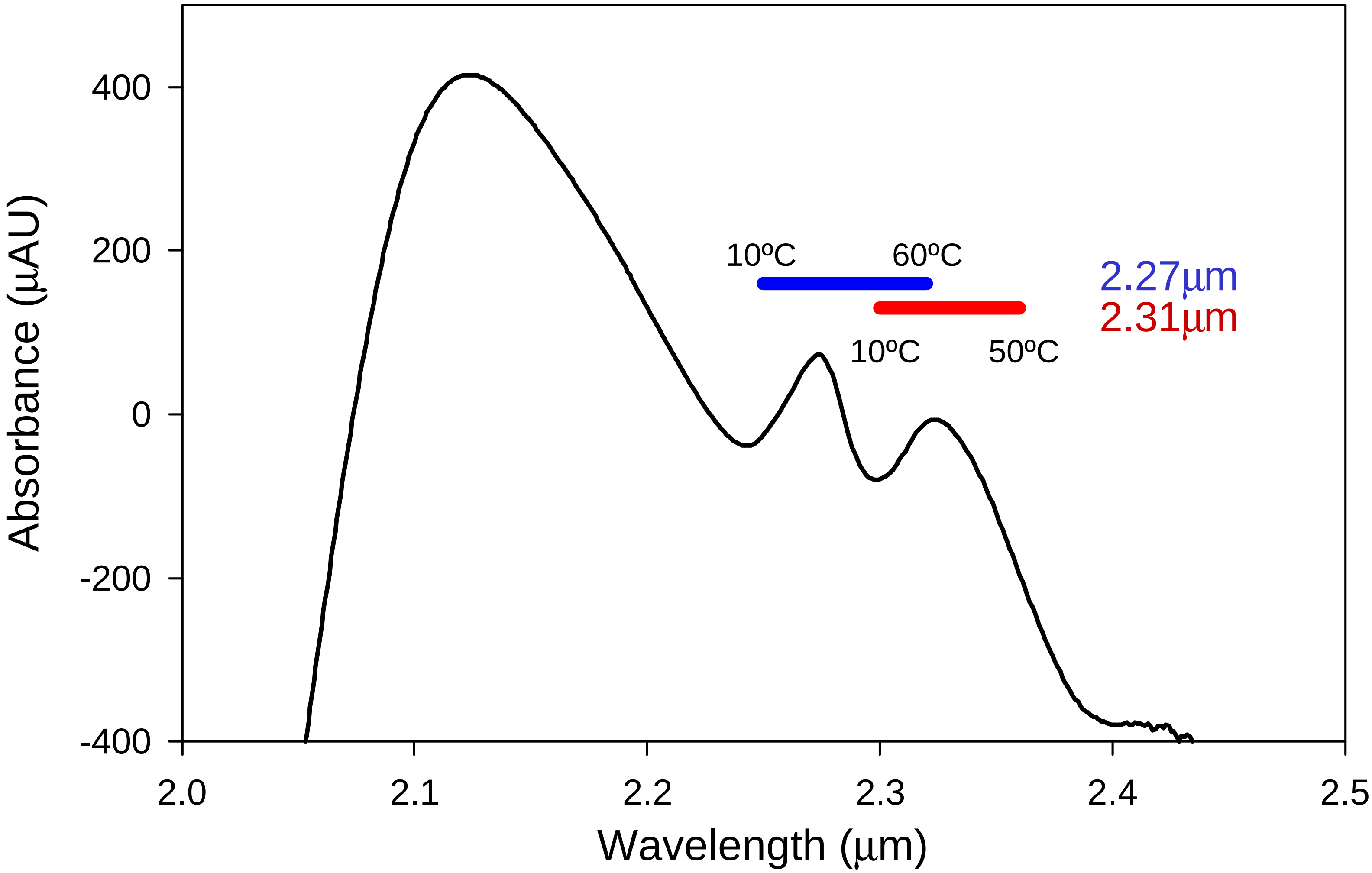
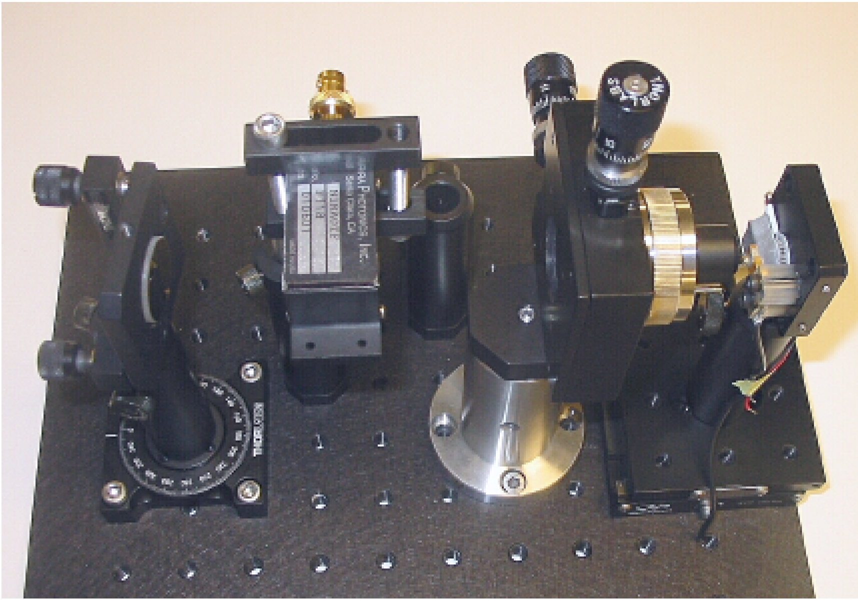
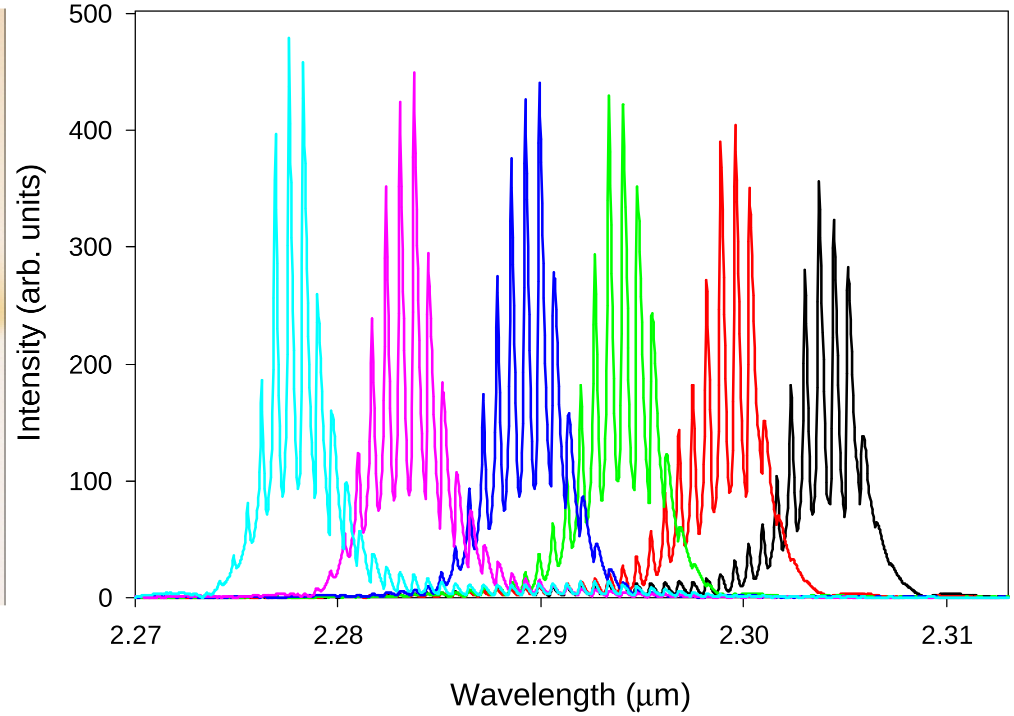


External Cavity Tuning With an AOTF





Acousto-optic tunable filter (AOTF)

- No moving parts
- High wavelength precision (1ppm)
- Fast tuning, random wavelength access

- Tuning range of 25nm has been obtained with 2.3µm devices
- Wider tuning should be available with stronger AR coating on front facet and shorter stripe lengths

Conclusions

The analytical information required to determine glucose concentration is available in near-IR wavelength range

- Best information is in the 2.0-2.5μm range
- Glucose spectrum is unique

Noninvasive monitoring of glucose is difficult

- Many overlapping spectral contributions
- Optical throughput of skin is small
- Glucose absorbance is small

Accurate glucose determination requires

- Very large SNR's
- Measurement at many wavelengths

Mid-IR semiconductor technology can help in this effort

- Improved detector performance
- High-brightness LED's
- Laser diodes
  - Moderate powers
  - Reproducible tunability