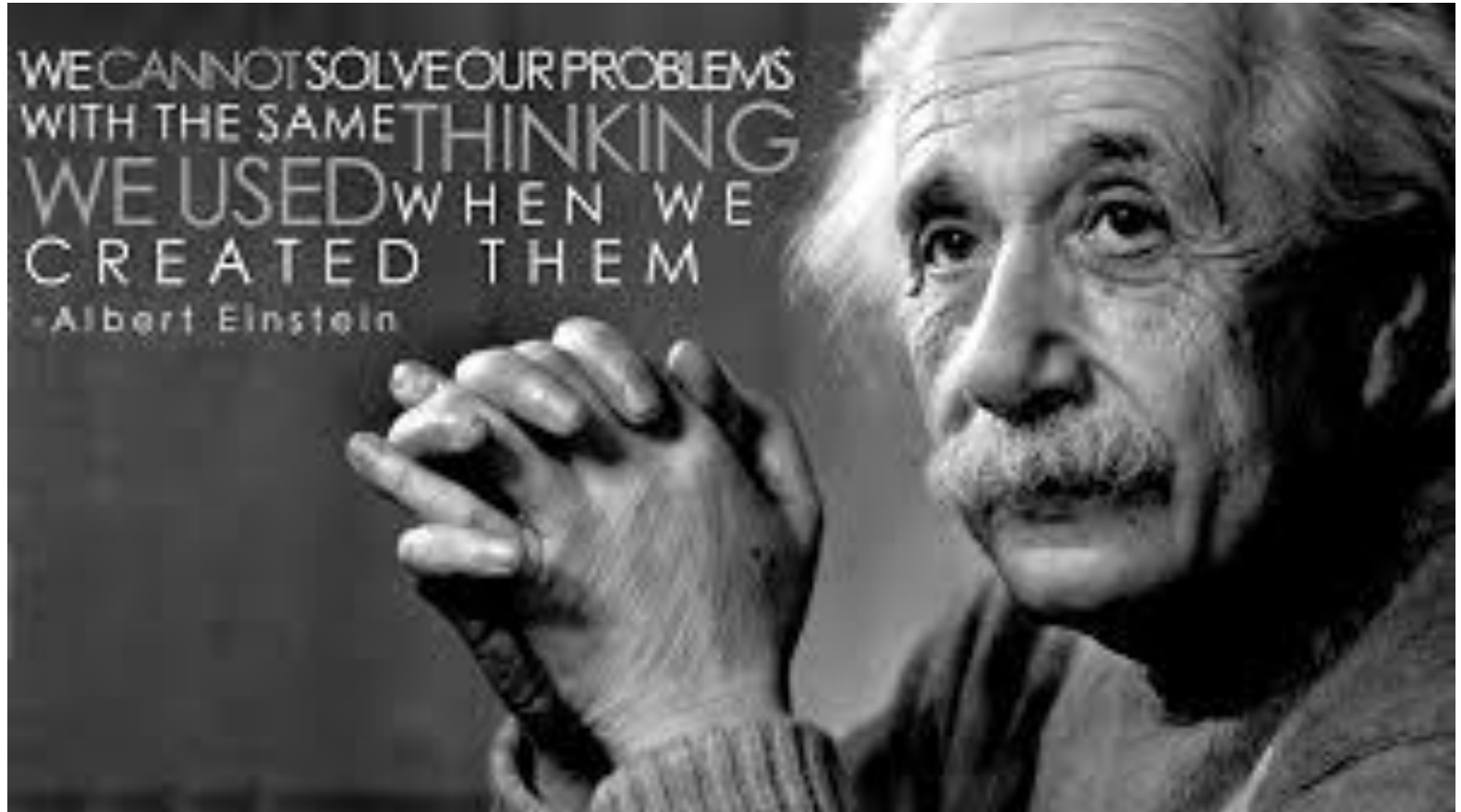


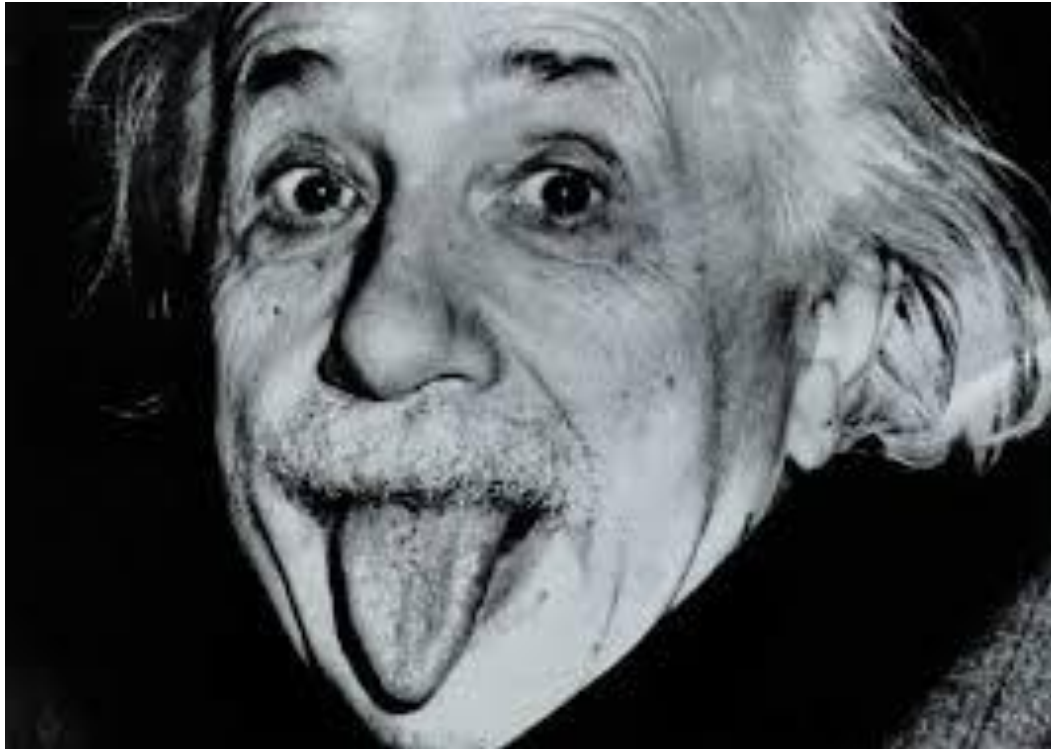
Outline

- Introduction
- TAS Instrumentation
- Applications

Preface



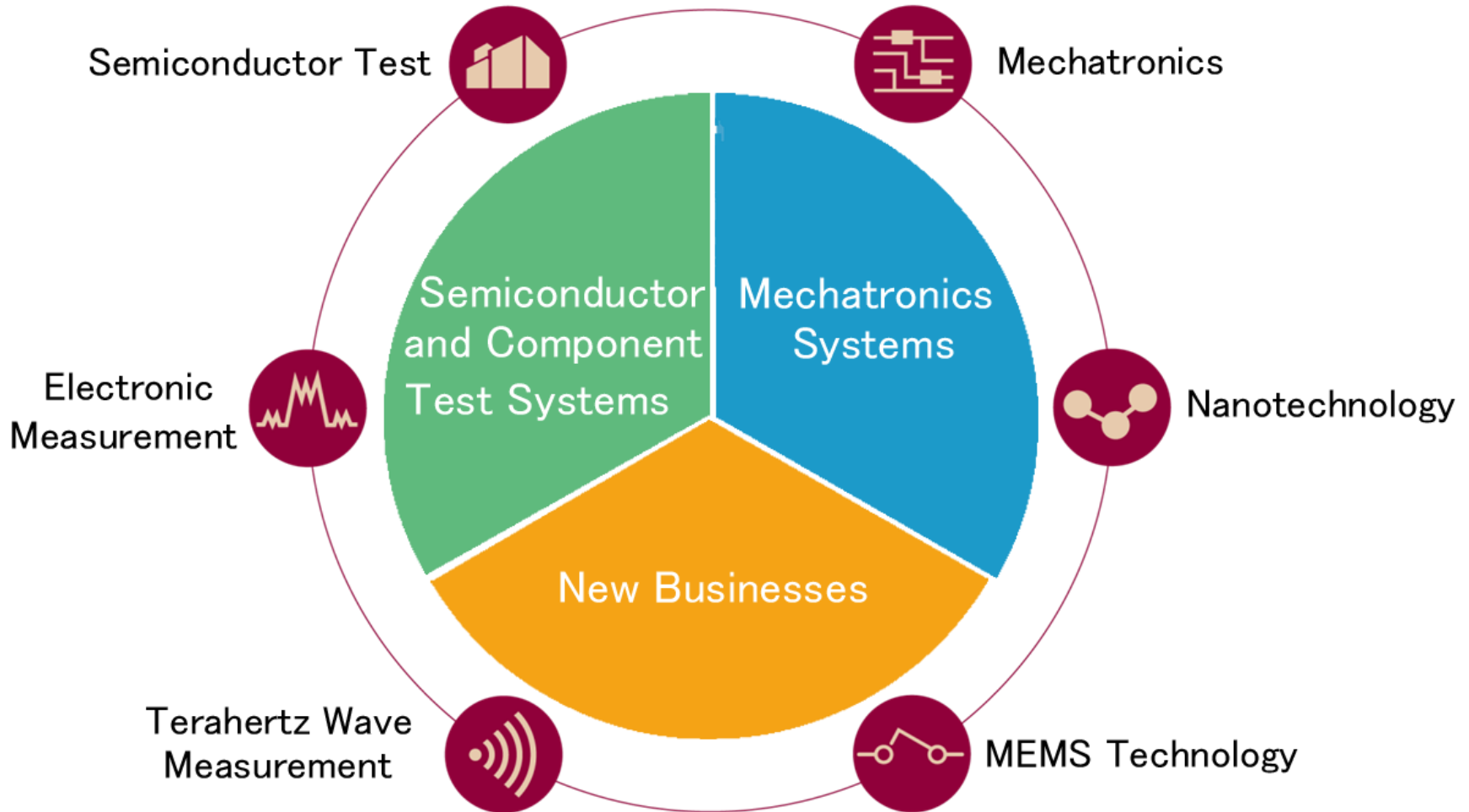
Preface



Company Overview



- HQ Founded** : 1954, Tokyo, Japan
- U.S. Subsidiary** : 1982, Santa Clara, CA
- European Subsidiary** : 1983, Munich, Germany
- Asian Subsidiaries** : China, Taiwan, Korea, Singapore
Malaysia
- Business** : Semiconductor ATE
Mechatronics Systems
Services ,Support & others
(Terahertz Technologies)
- Publicly Traded** : Tokyo Stock Exchange (6857)
New York Stock Exchange (ATE)
- Capital** : /32.4Billion
- Revenue (FY2012)** : Appx. \$1.7B
- No. of Employees** : Globally Approximately 5000
- Annual R&D Spend** : \$ 365M – 8 facilities



Introduction of TAS7500 Series and Applications



For more inquiries

ADVANTEST CORPORATION

508 Carnegie Center, Princeton, NJ 08540 USA

Tel.: +1-609-897-7326

Anthony.Petrolonis@advantest.com

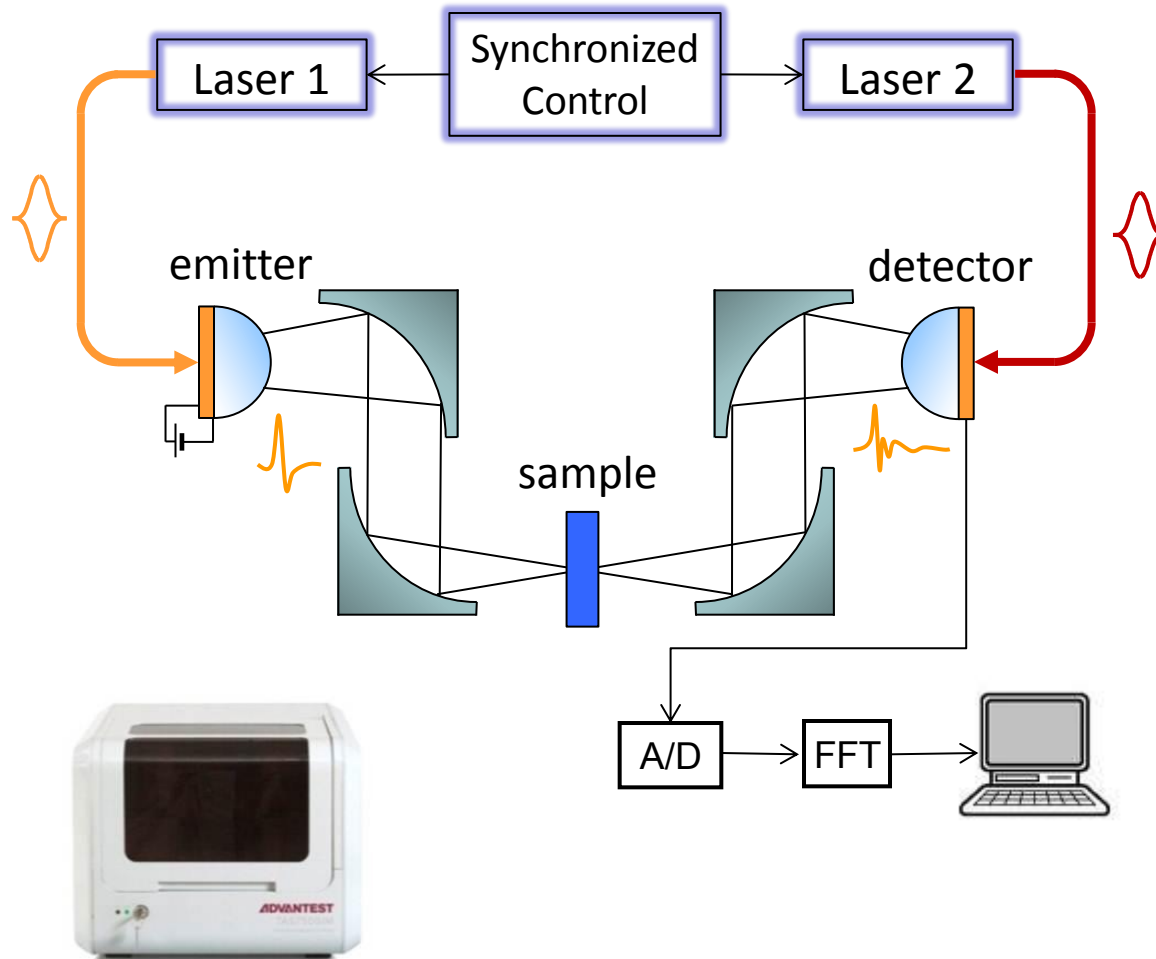
June 2013



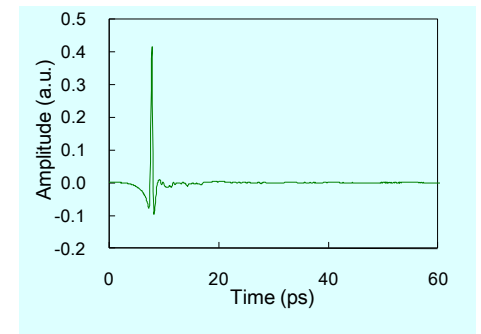
Sample compartment
(dry air purged)

	<p>Reflectance</p> <p>Sample</p>	<p>Multi-layer analysis</p> <ul style="list-style-type: none"> • Layer thickness • Refractive index
	<p>Transmission</p> <p>Sample</p>	<p>Bulk analysis</p> <ul style="list-style-type: none"> • Powders • Tablets • Liquids • Suspensions
	<p>ATR *</p> <p>Sample</p>	<p>Surface analysis</p> <ul style="list-style-type: none"> • Highly absorbing samples (Aqueous) • Rapid powder analysis
	<p>Linear Polarization Transmission</p>	<p>Polarization analysis</p> <ul style="list-style-type: none"> • Anisotropic solids • Chiral molecules

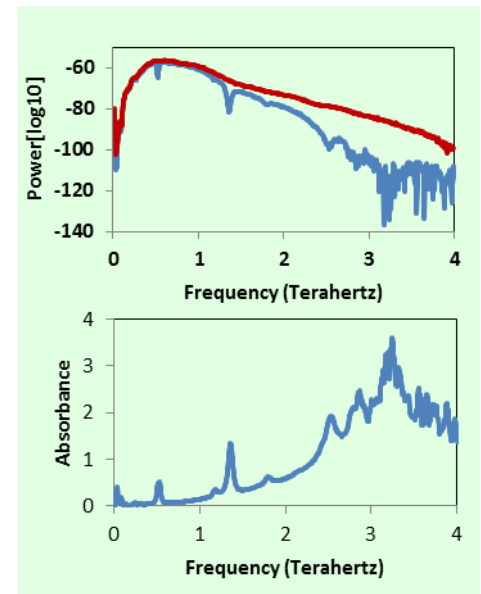
TAS7500SP unit block diagram



Time domain waveform



Frequency domain spectrum





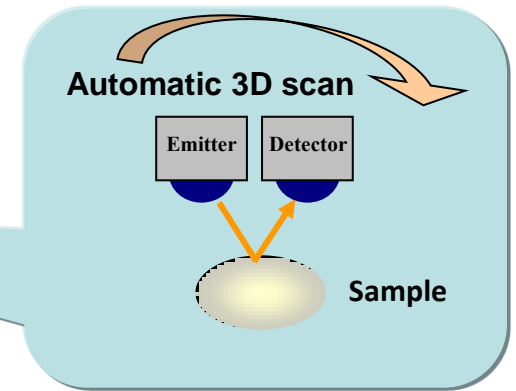
1. Measure sample dimensions



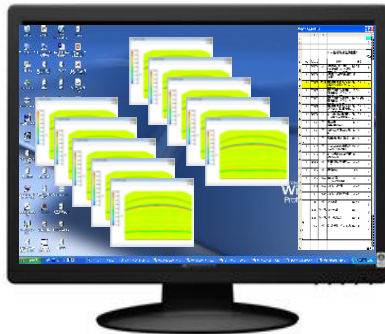
2. Select cassette and load samples



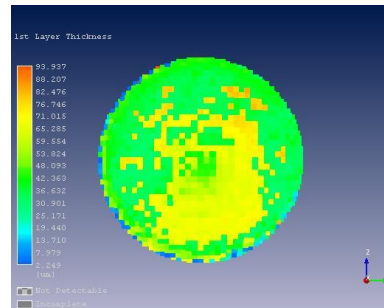
3. Select point spacing and data averaging



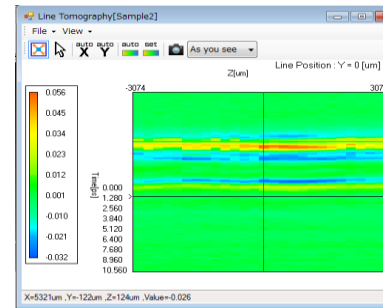
4. Automated data collection on up to 10 tablets



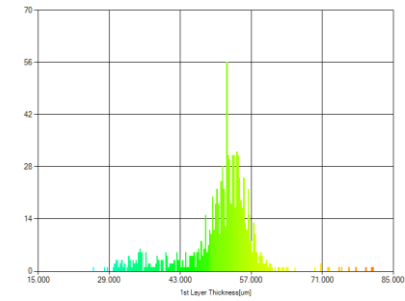
5. Define calculation file and run automated data processing



Spatial mapping of coating thickness

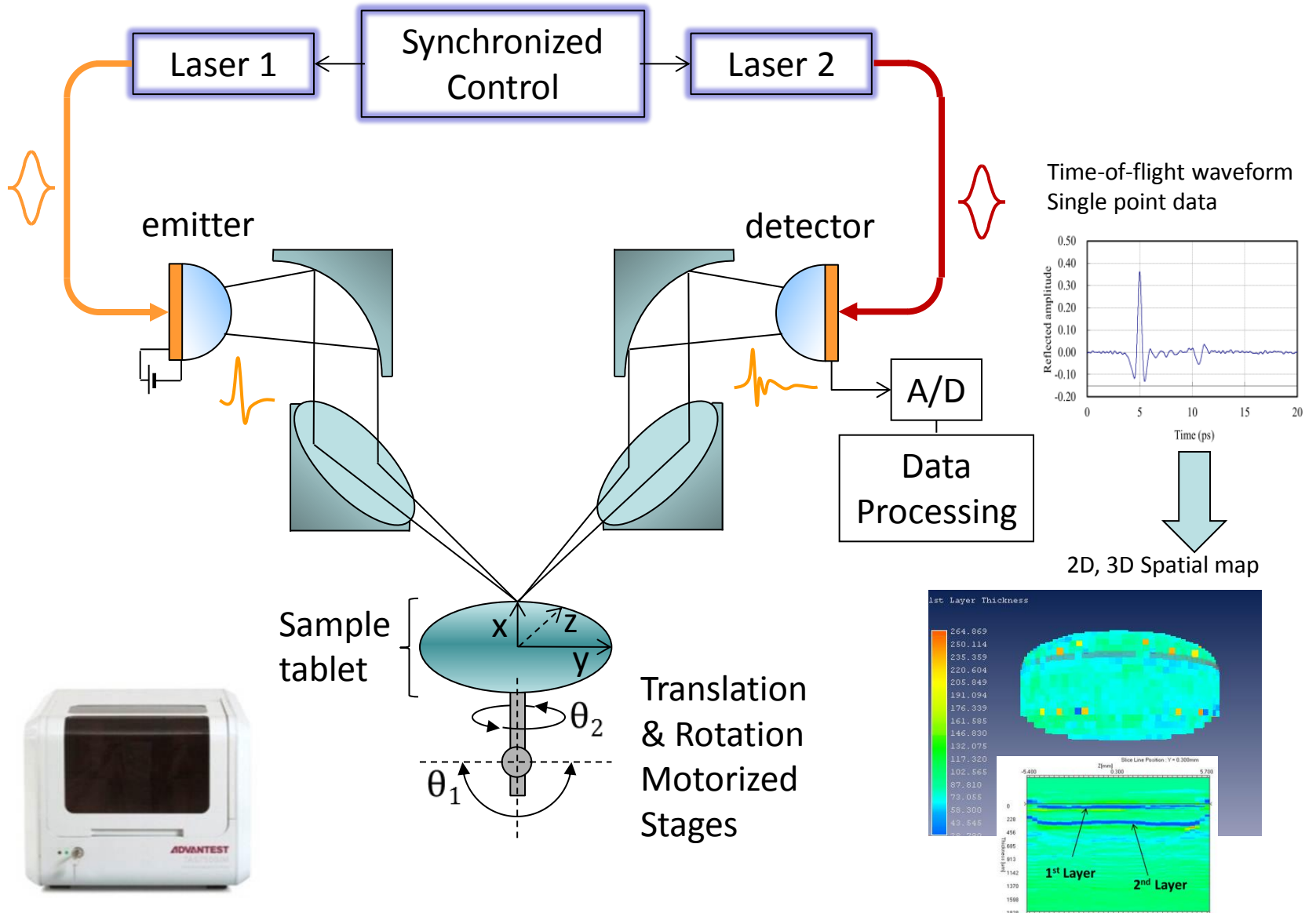


Cross-sectional depth profiling

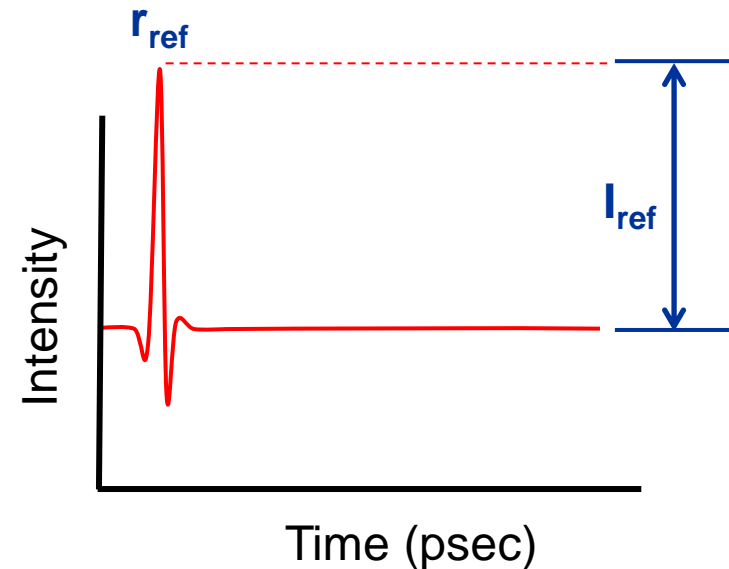
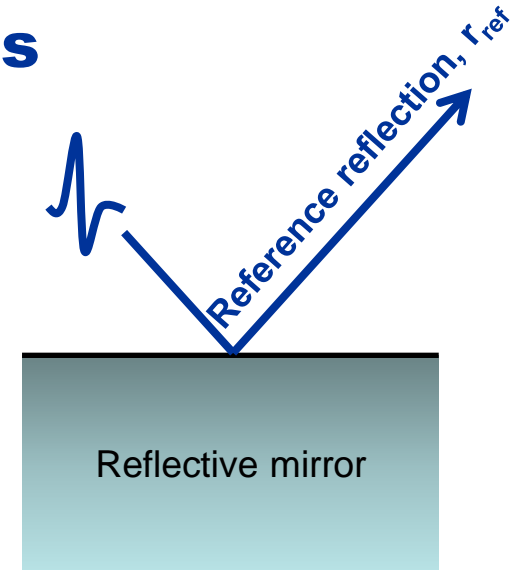
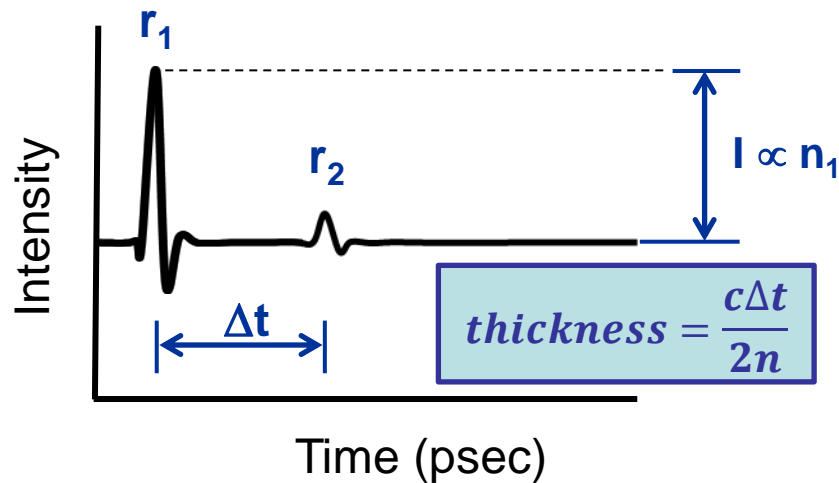
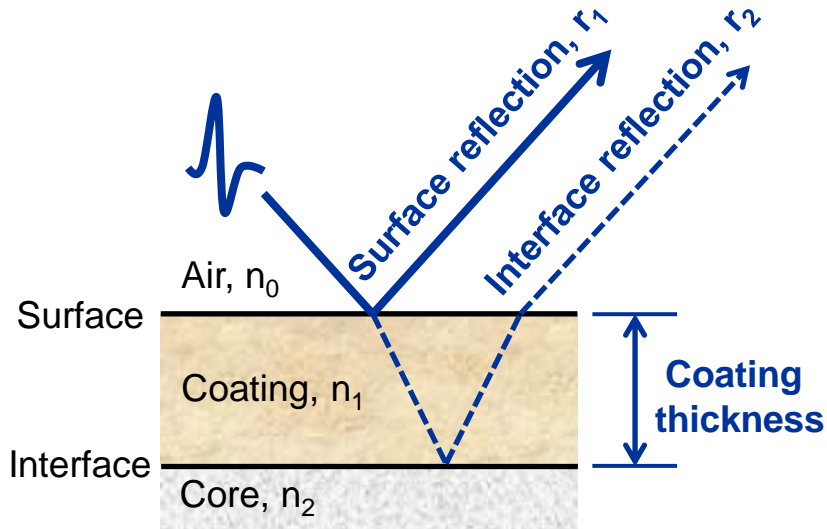


Layer thickness distribution

6. Display analysis results



Layer Thickness Measurements



The **TAS7500** can be configured as a complete system or as individual units

TAS7500 - Spectroscopy & Imaging



TAS7500SP - Spectroscopy only



TAS7500IM - Imaging only



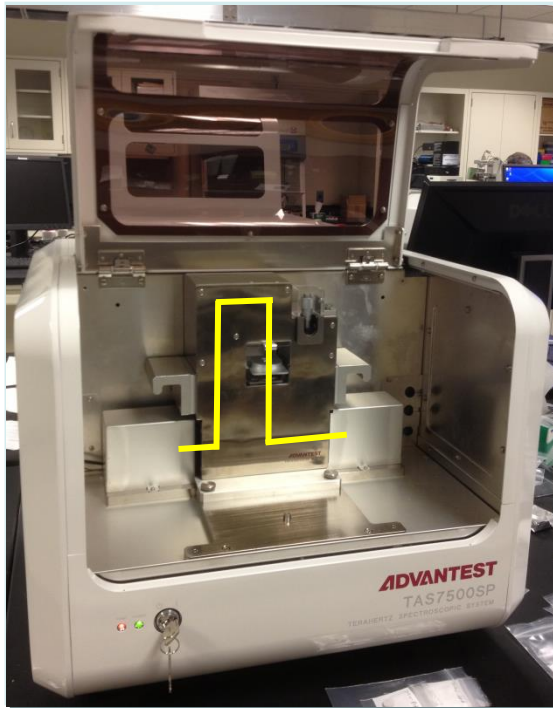
System controller/
analysis PC

Analyzer unit

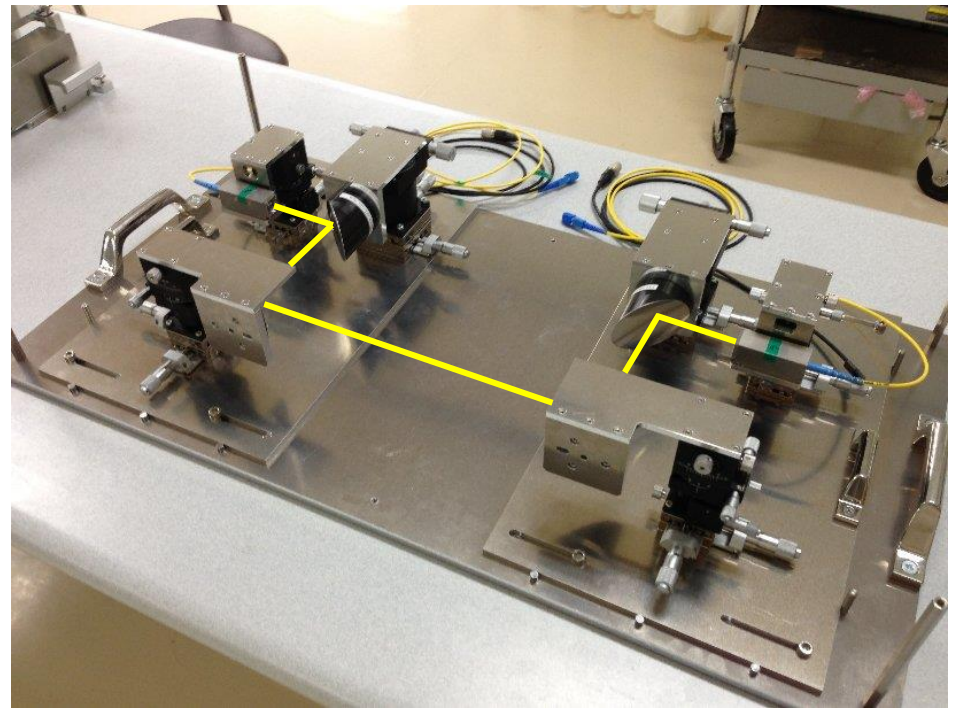


Common parts for all configurations

Variable Optical Path Length



Sample Compartment
for the
Spectroscopy System SP



Configurable Optical Bench
for the
Optical Sampling System TS

New Terahertz Technology

- Dual Fiber Launch System brings the THz beam to your sampling system
 - Taking spectroscopy “out of the box”
- Choice of Emitters
 - Wide Choice of Optimized THz Emitters
 - Ultra Broadband Coverage
- Variable Optical Path Length
 - Continuously Variable Up to 10 meters
- Variable Acquisition Speed and Resolution
 - Minimum 1 msec/scan





TAS7500TS

Terahertz Wave Optical Sampling System

Flexible Terahertz wave measurement and analysis platform



TAS1110 **0.1 - 4THz (basic type)**

TAS1120 **0.03 - 2THz (low-frequency type)**

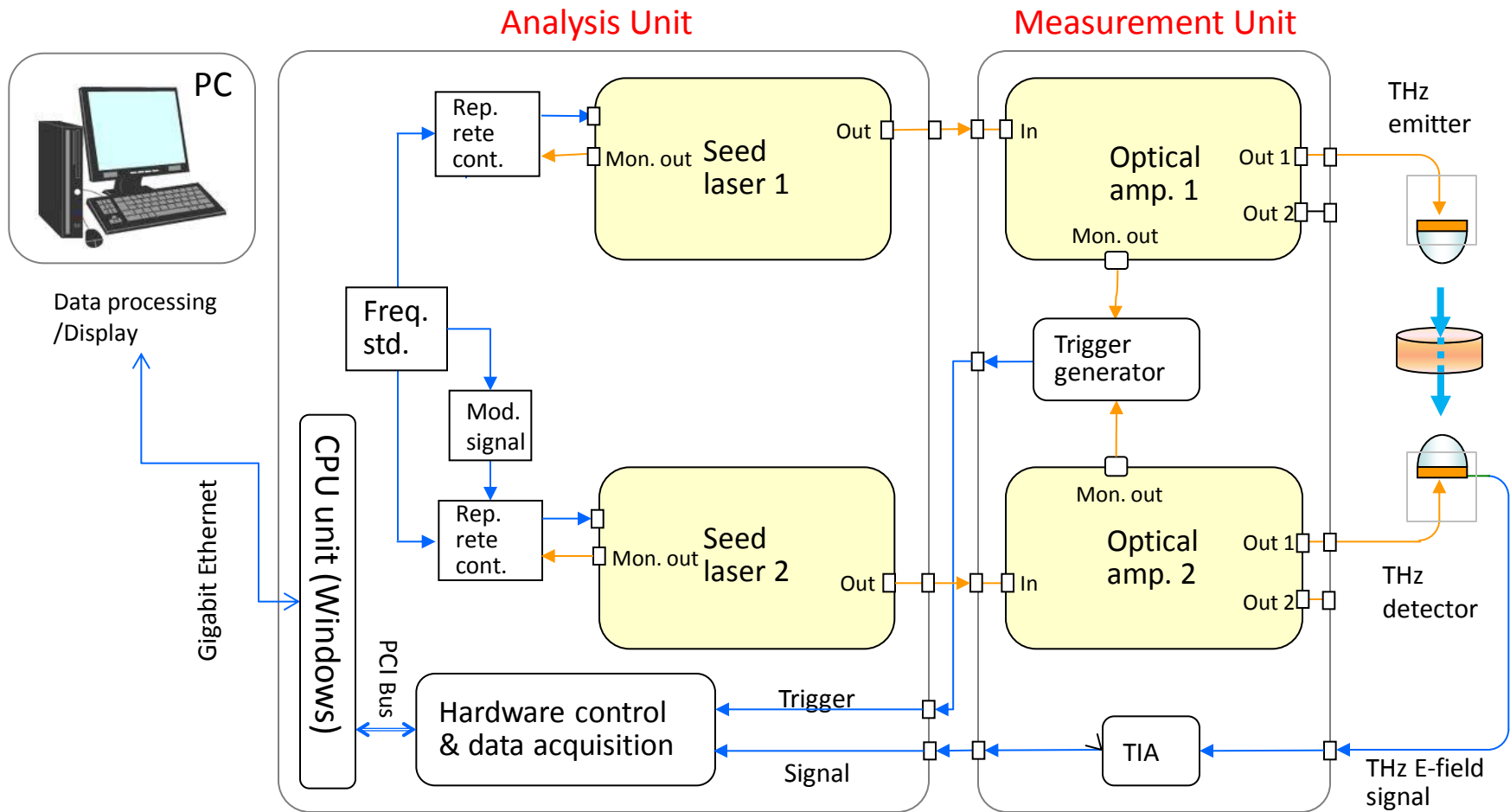
TAS1130* **0.5 - 7THz (broadband type)**

TAS1110, TAS1120, TAS1130 Terahertz Source Modules



TAS1230 **0.03 - 7THz (broadband type)**

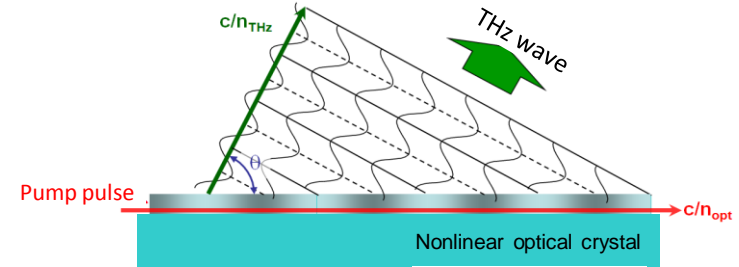
Fiber coupled compact terahertz wave detector with transimpedance amplifier



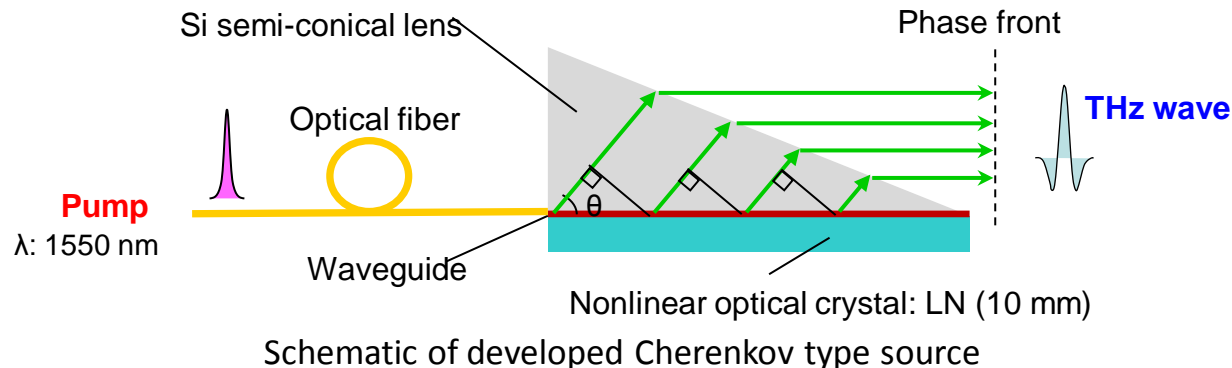
Technology breakthrough

Introduction of the Cherenkov type phase matching^{*1, 2}

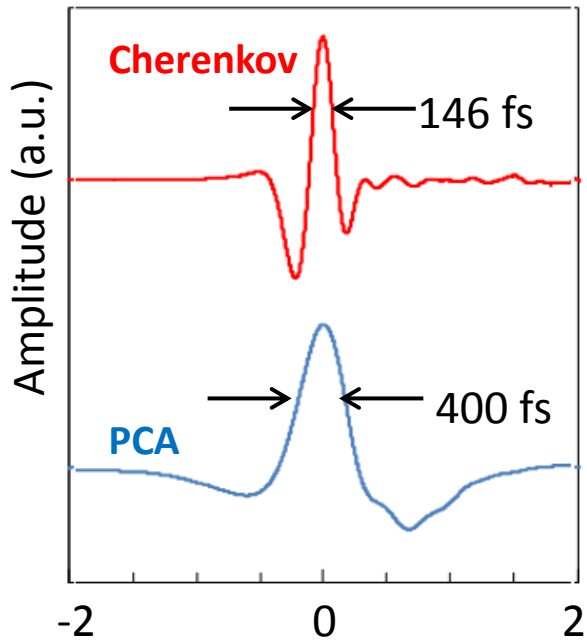
- Phase matching condition independent
- Waveguide structure enables surface THz generation in the nonlinear crystal, which minimize absorption loss of THz wave in the crystal.
- Shorter pump pulse width generates shorter THz pulse width with broad spectral range



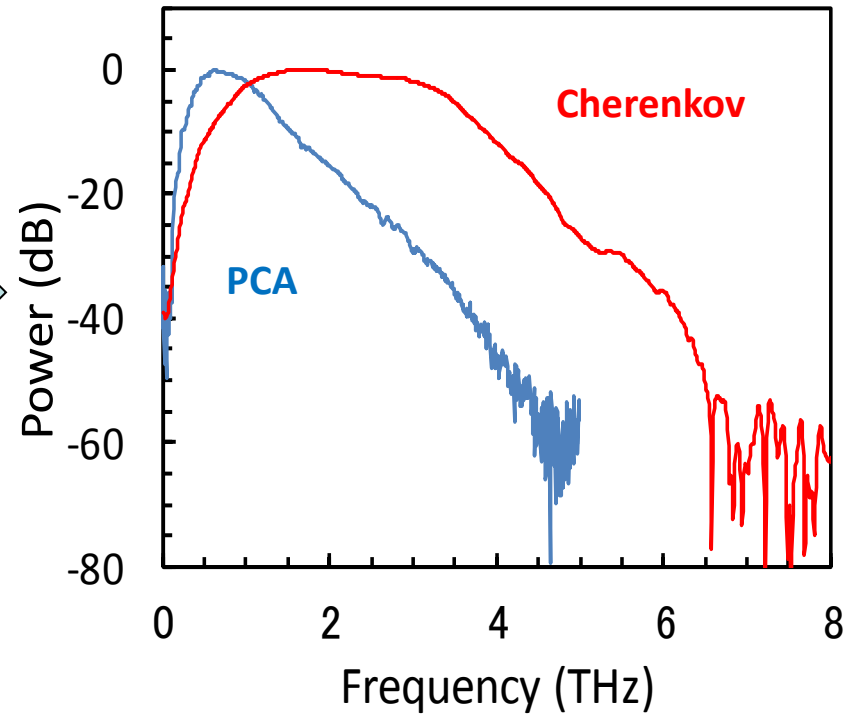
Cherenkov type phase matching and THz wave generation



1 K. Suizu et al., Opt. Express, **16**, 7493 (2008)
 2 K. Suizu et al., Opt. Express, **17**, 6676 (2009)



Fourier Transform



Power spectra

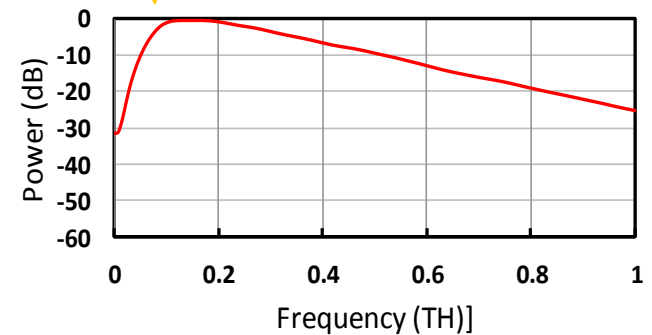
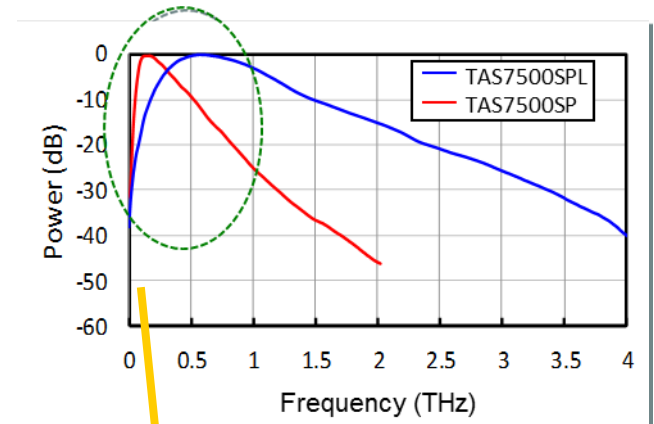
Signal-to-noise ratio in higher frequency range region (> 30 dB @4THz) was dramatically improved relative to conventional photoconductive antenna (PCA) source

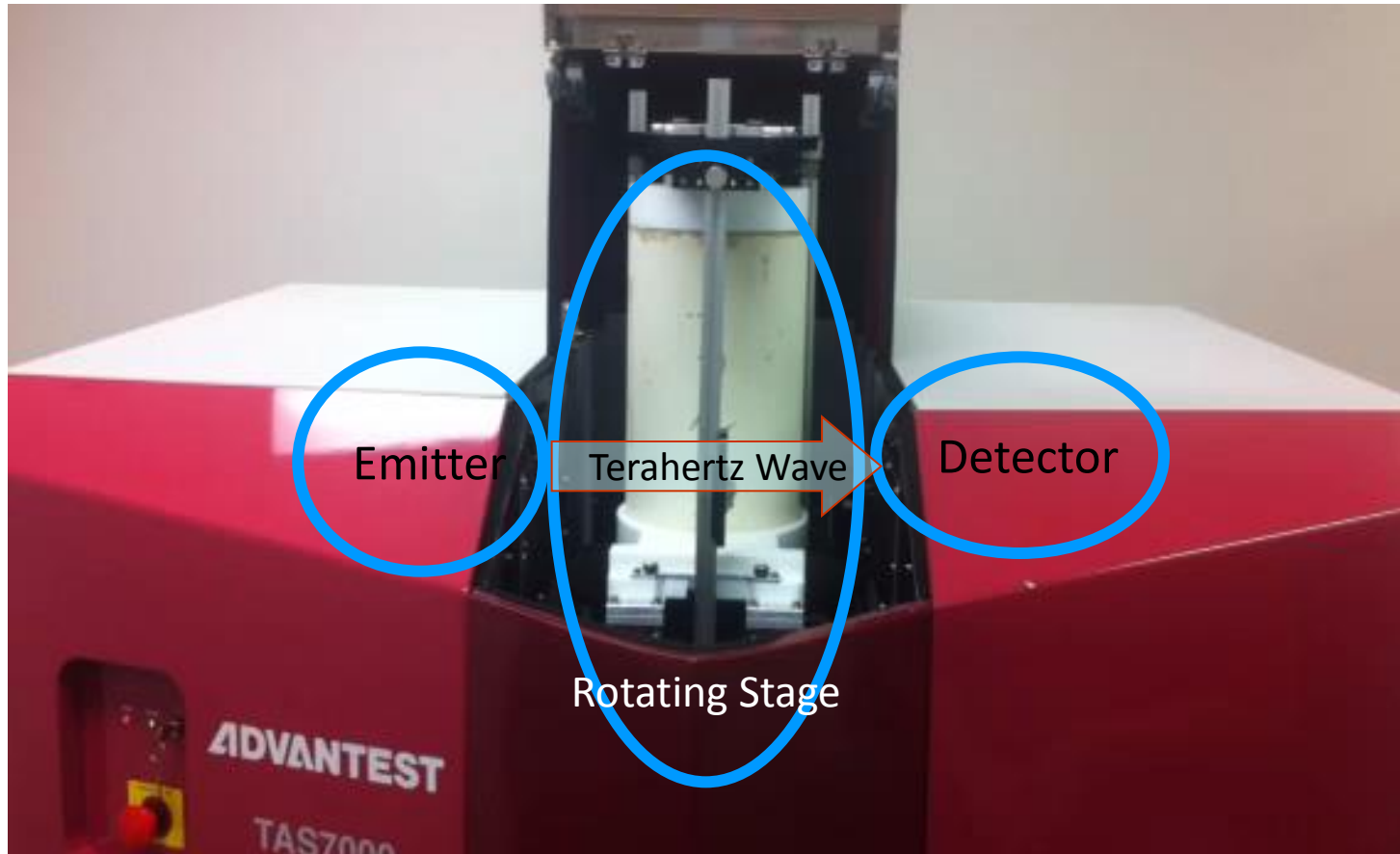
- Lower band spectroscopy from 30 GHz with high sensitivity
- Suitable for material development of MMW* / Sub-MMW communication devices

* Millimeter wave

■ Features

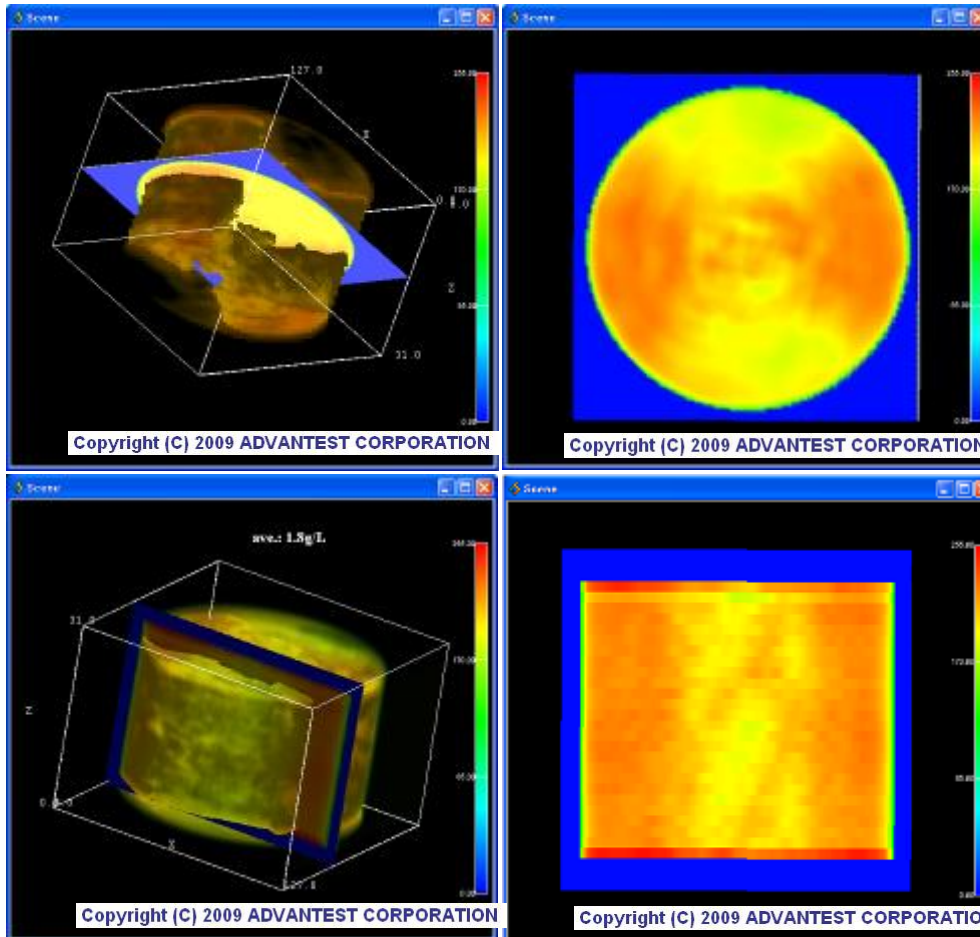
- Low frequency (~30 GHz) sensitive terahertz emitter and detector
- Industry's fastest waveform scan (8ms / scan)
- Easily interchangeable sampling accessories (transmittance / reflectance)
- Software enables comprehensive spectroscopic analysis
- Excellent performance in a small footprint





Sample Moves Through Fixed Focal Point

Measurement analysis and design factor optimization 3D analysis (operational example)

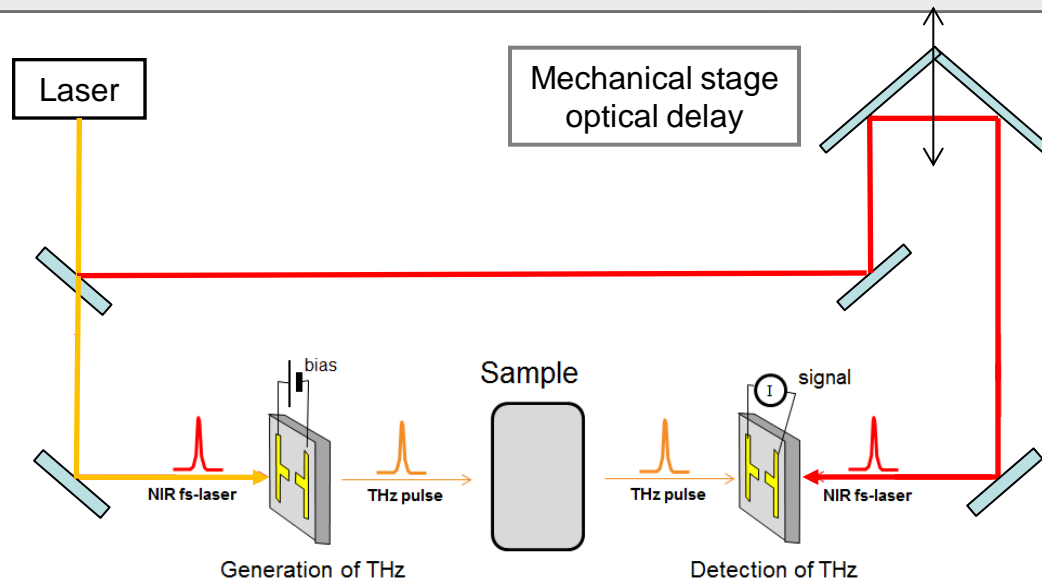


XY cross section scan

Z cross section scan

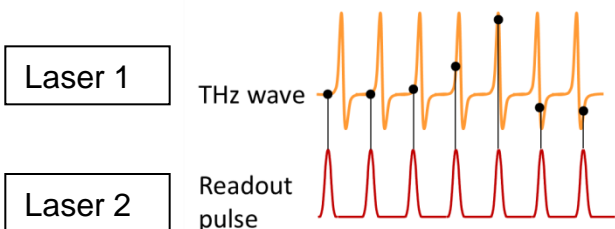
Mechanical

- Slow sweep rate
- Sensitive optical alignment
 - Temperature
 - Mechanical vibration
- Ti-sapphire laser
 - External power supply
 - Chiller

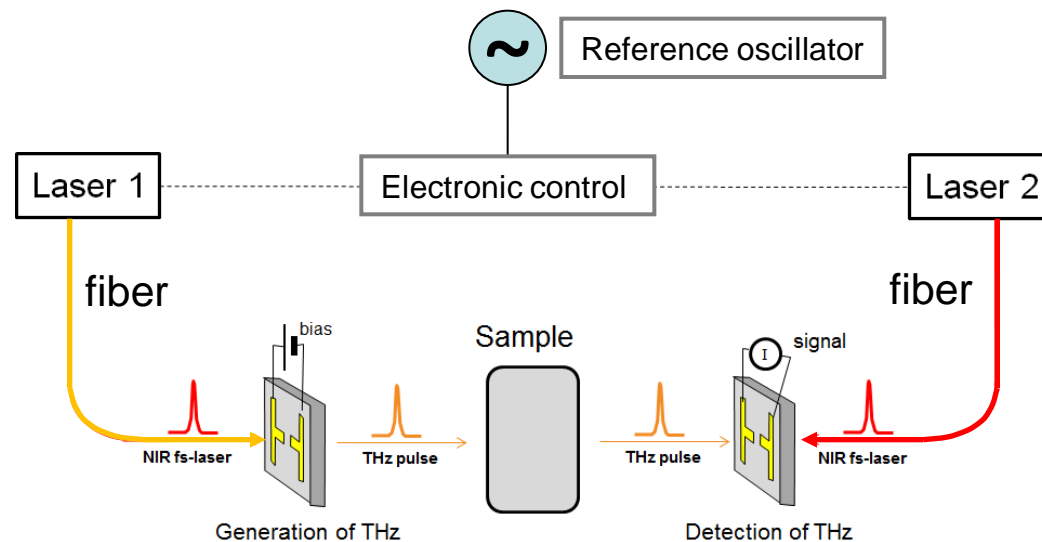


ADVANTEST All electronic

- Fast pulse rate (50 MHz)
- Advantest manufactured fiber laser
- Dual laser sampling technology



Phase control: Slightly different repetition rate



Features	TAS7500TS /Advantest
THz module dimensions	Emitter & Detector: 55mm × 20mm × 19mm
Measureable frequency range	0.03 THz - 2 THz / 0.1 THz - 4 THz / 0.5 THz - 7 THz are selectable by changing emitter module
Frequency resolution (after FFT)	3.8 GHz / 7.6 GHz / 61 GHz
Frequency accuracy	±10 GHz
Scan rate	16 ms / 8ms / 1ms
Dynamic range (required time)	60dB (30 s) at 7.6 GHz resolution
THz module fiber length	1.5 m - 10 m (To be determined at the time of order)
Automatic adaptive trigger delay adjustment function	Available
Remote control function	Available
External measurement synchronization control	Available
System size	Table-top /rack mountable
Number of measurement channels	- 1 measurement channel (standard) - 2-channel system is optionally available

THz Instrumentation Summary

- TAS7500Sx
 - Terahertz Spectroscopy
 - Multiple Sampling Modules
 - Multiple Emitters
- TAS7500IM
 - Terahertz Imaging optimized for pharmaceutical tablets
- TAS7500TS
 - Flexible Fiber Probe Based Spectrometer
 - User Configurable Optical Design
 - Remote Sampling
- TAS7000
 - Automotive/Industrial Terahertz Tomography
 - Large Sample Sizes

Product pipeline

- TAS7400 Spectroscopy
- BIOATR Live cell analysis
- OEM THz Product B2B
- THz Power meter
- And more...

ADVANTEST ADVANTEST ADVANTEST

Applications



Advantages of the Terahertz Frequency Range

- Non-destructive
 - Changes with time can be measured on a single sample
 - The sample is available for physical testing (e.g. dissolution)
- Non-ionizing radiation
 - No concerns about altering product integrity
 - No engineering controls are required
- No sample heating
- High depth of penetration
 - Transmission spectroscopy
 - Multilayer imaging
- Penetrate optically opaque materials

Distinguishing Characteristics of Pulsed Terahertz Vibrational Spectroscopy

- Measures fundamental inter-molecular vibrations
 - Specific for crystallinity
 - Hydrogen bonding
 - Weak dipolar and van der Waals interactions
 - Low frequency 5-150 cm⁻¹
- Measures dynamics on a picosecond timescale
 - Time-of-flight
 - Femtosecond pulsed THz emitter
- Measures fundamental material properties
 - Refractive Index, Absorption Coefficient, dielectric constants, conductivity...
 - Phase sensitive detection
- Measures orientation
 - Anisotropy
 - Optical activity
 - Polarized beam

3 Scales of Terahertz Measurements

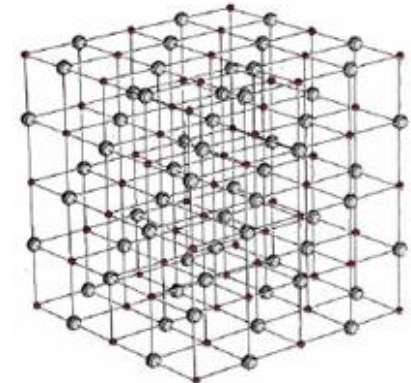
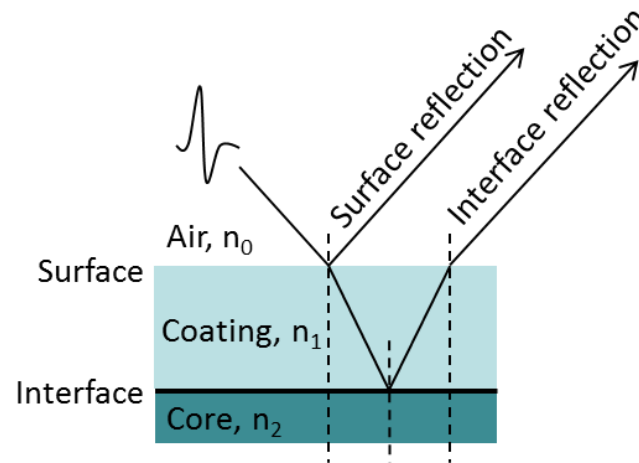
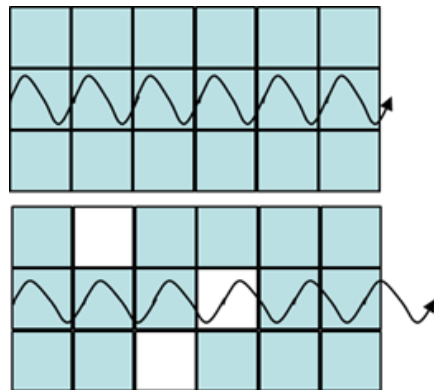
- Bulk properties
 - Density/porosity
 - Tablets
 - Roller Compaction Ribbon
 - Layer thickness
 - Multi-layer tablets
 - Packaging materials – e.g., filled polymers
- Microscopic examination of coatings and interfaces
 - Coating thickness – spatial uniformity in 3D imaging
 - Correlation with performance properties
 - Component migration
 - Interface strength
 - Voids and defects
- Molecular properties
 - Crystallinity, polymorphism, hydration/solvation
 - Content uniformity
 - Specificity based on crystalline form
 - Physical stability
 - Co-crystal formation, Crystalline/amorphous content

Microscopic/Imaging Applications

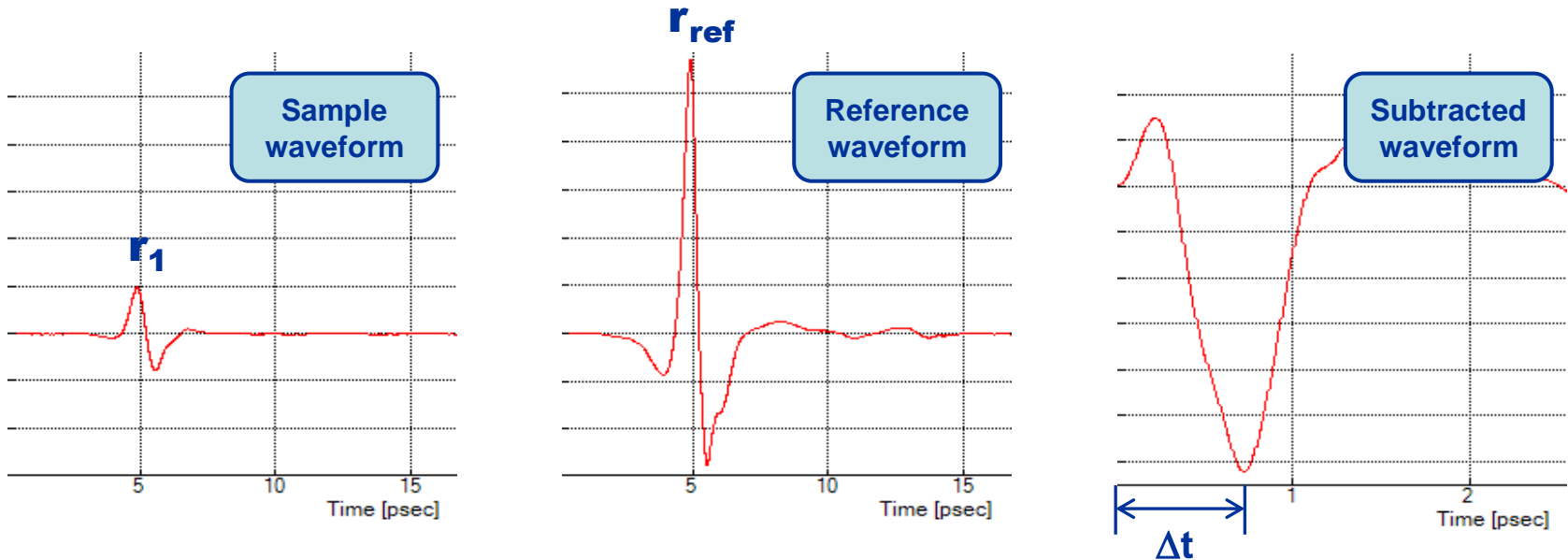


Important Applications of Terahertz Imaging

- Density/Porosity of materials
- Layer thickness and spatial uniformity



Method of Data Analysis

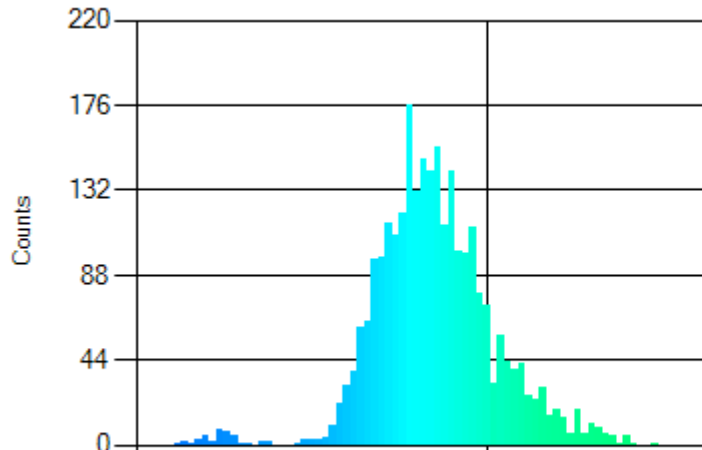


Subtracted waveform = sample waveform - normalized reference waveform

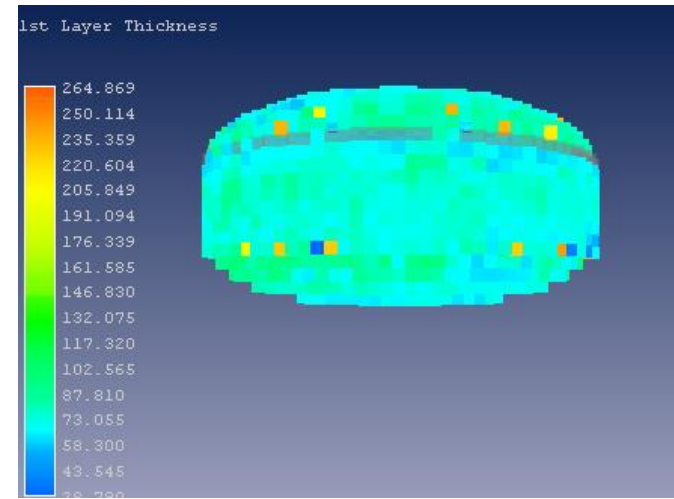
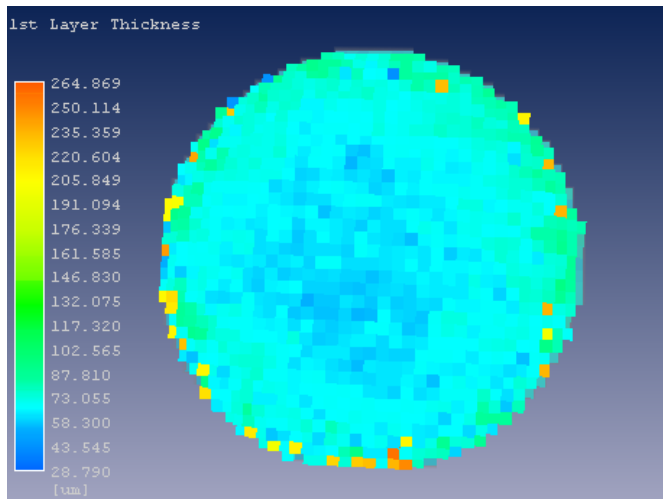
- Reference waveform is normalized in time and amplitude to that of the sample
- Normalized reference waveform is subtracted from the sample waveform
- Coating thickness $\propto \Delta t$ and refractive index
- Refractive index of coating \propto (amplitude of r_1) / (amplitude of r_{ref})

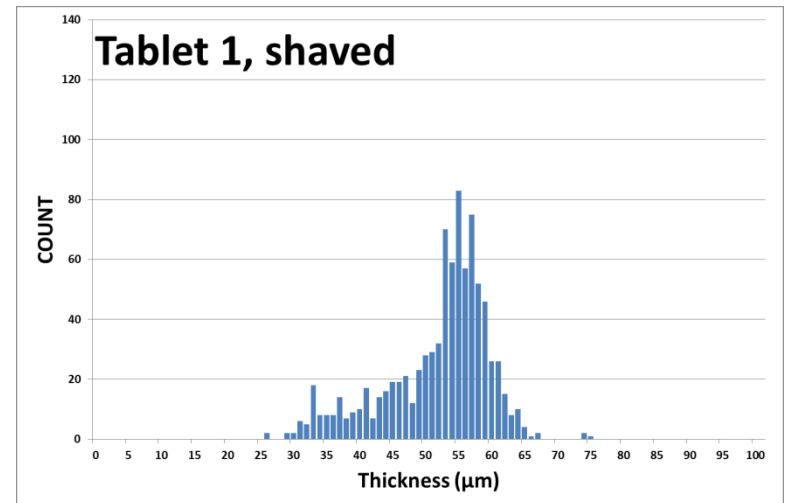
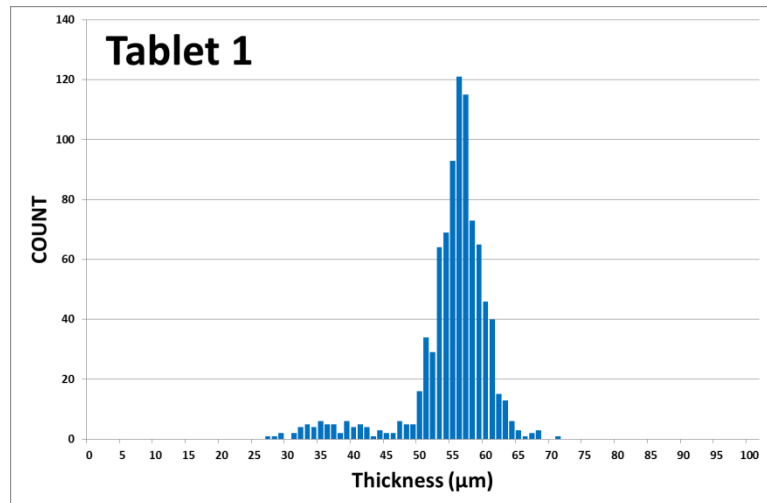
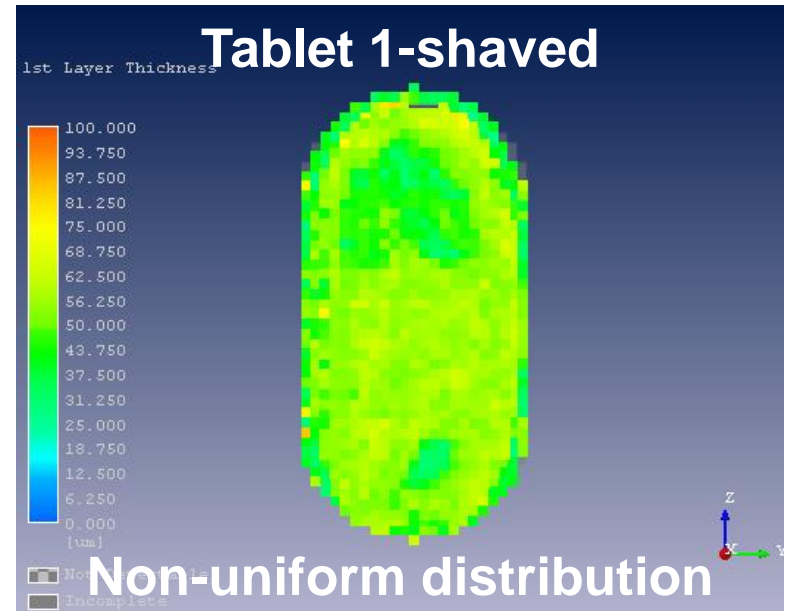
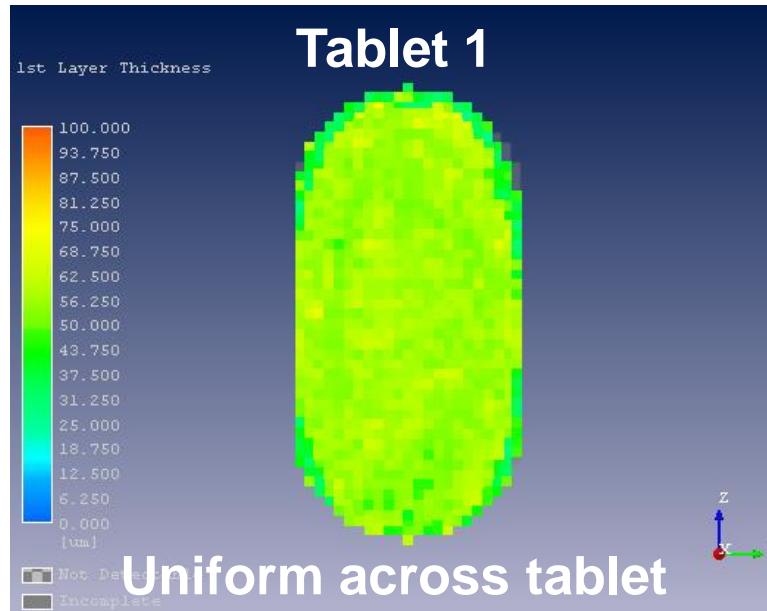


Advantages of THz 3D Imaging



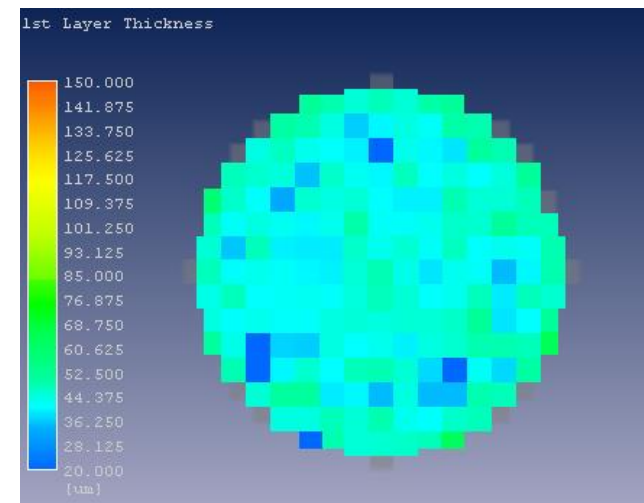
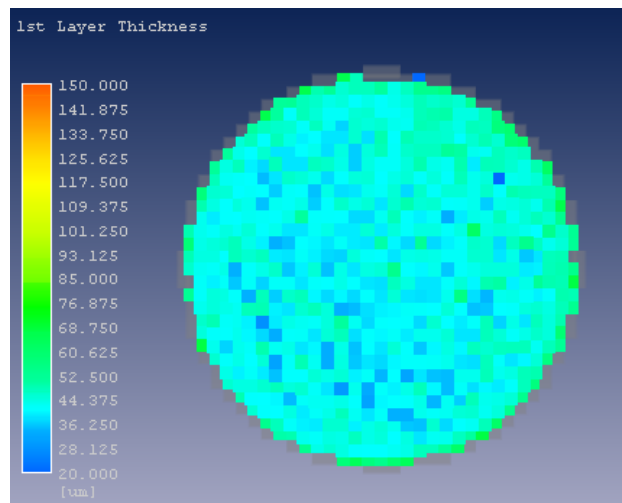
- 2-dimensional sampling yields 3-dimensional information
- Spatial information on coating
 - Layer thickness and spatial uniformity
- Coating properties
 - Surface density
- Interface properties
 - Interface strength and integrity



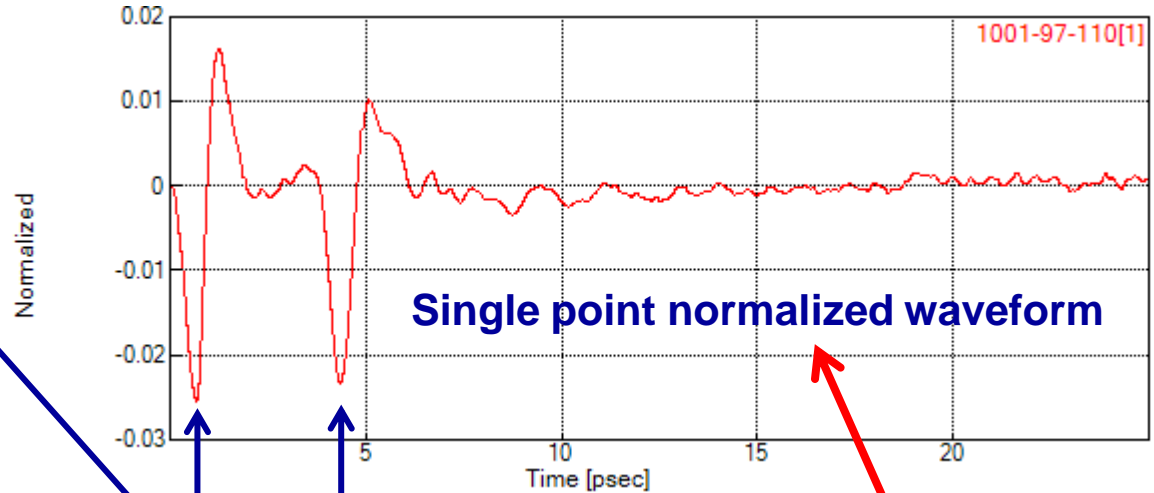
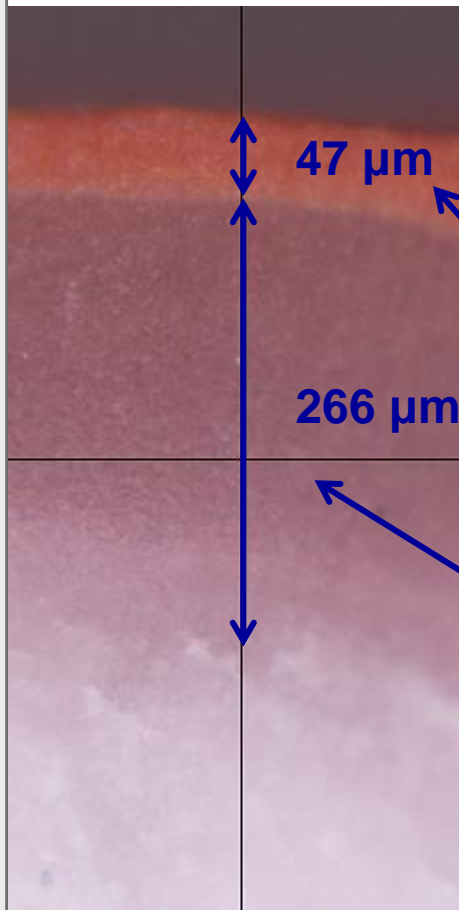


Spatial Resolution vs. Scan speed

	High Resolution	Low Resolution
Resolution	0.3 mm	0.6 mm
# of Points	732	182
Data averaging	512 scans/point	32 scans/point
Scan time	70 min	8 min



Penetrating Multiple Layers

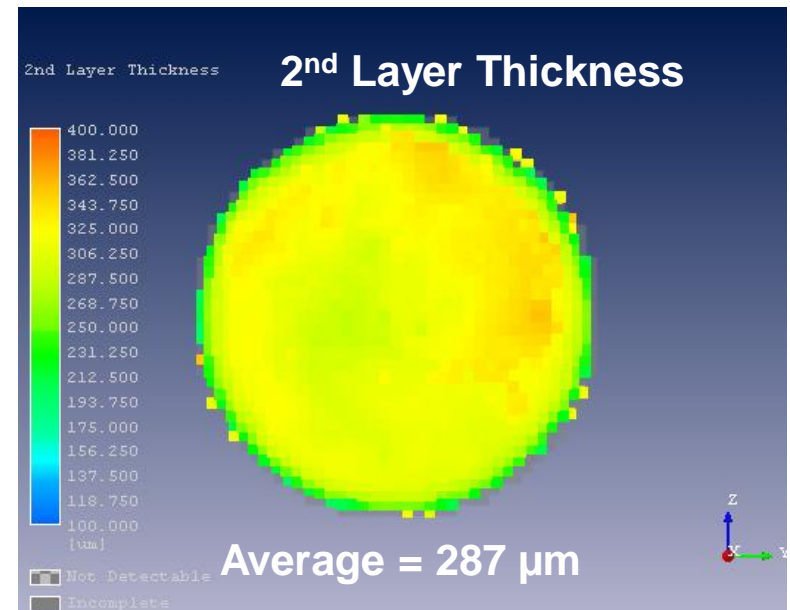
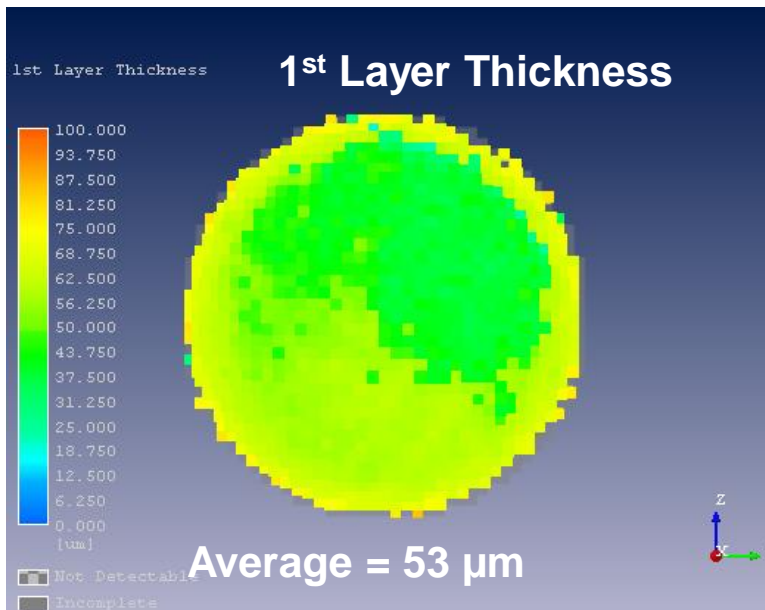


1st Layer

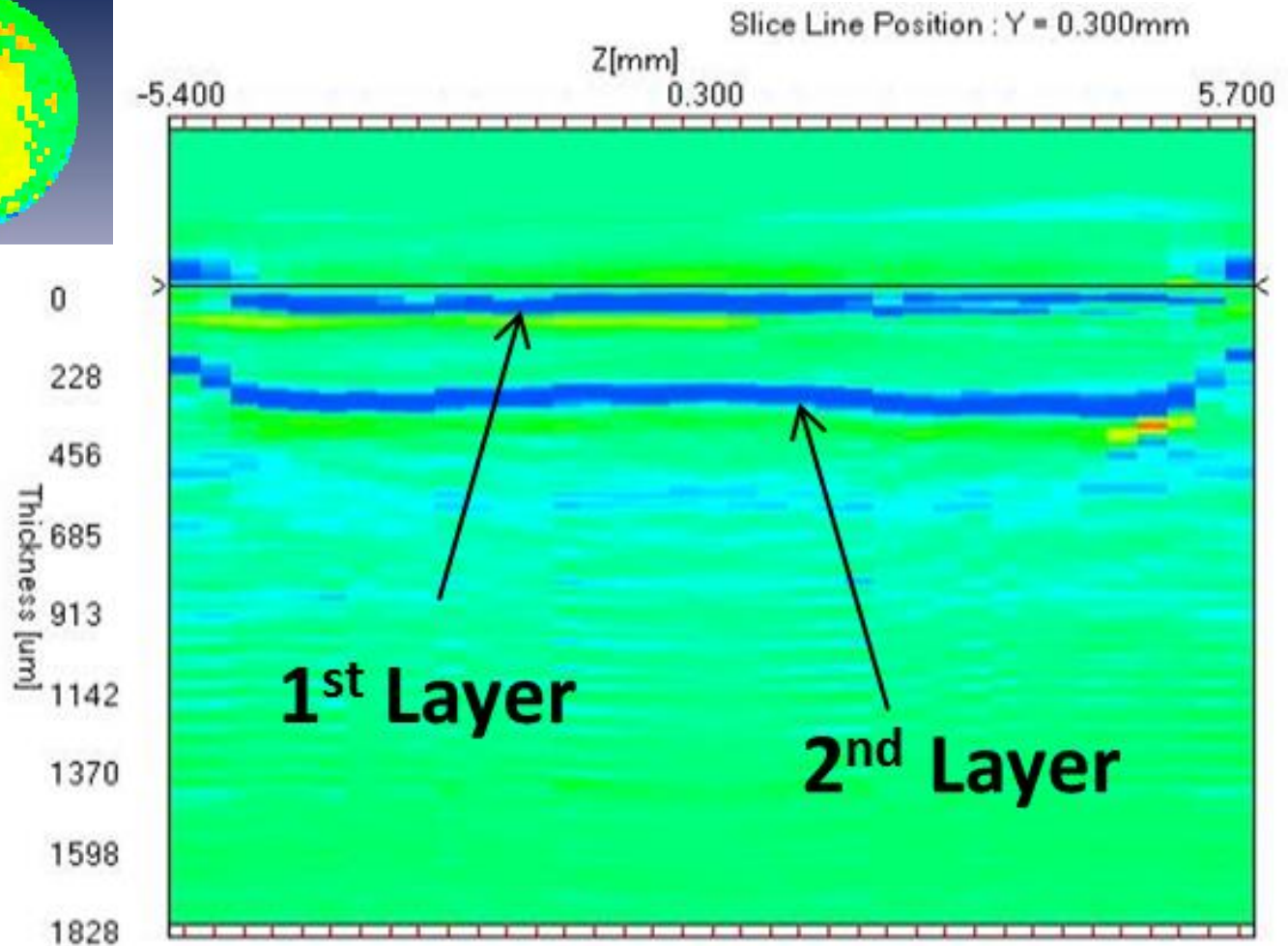
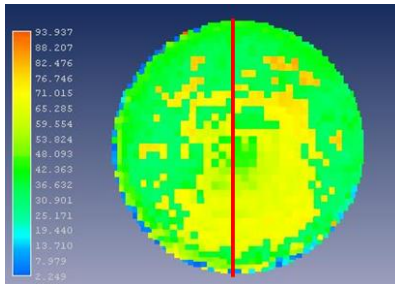
2nd Layer



Spatial Mapping of Layer Thickness



Cross-sectional Imaging



Profiling a Multi-layer System

The TAS75000 series has the unparalleled ability to probe several millimeters into the core of a multilayer tablet to reveal its internal dimensions

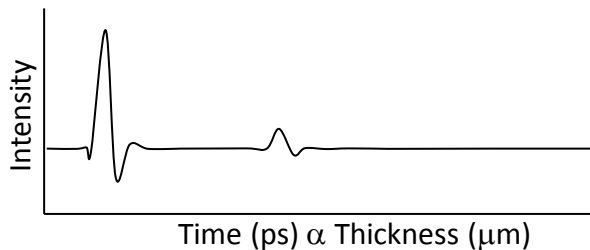
Dry-Coated Tablet



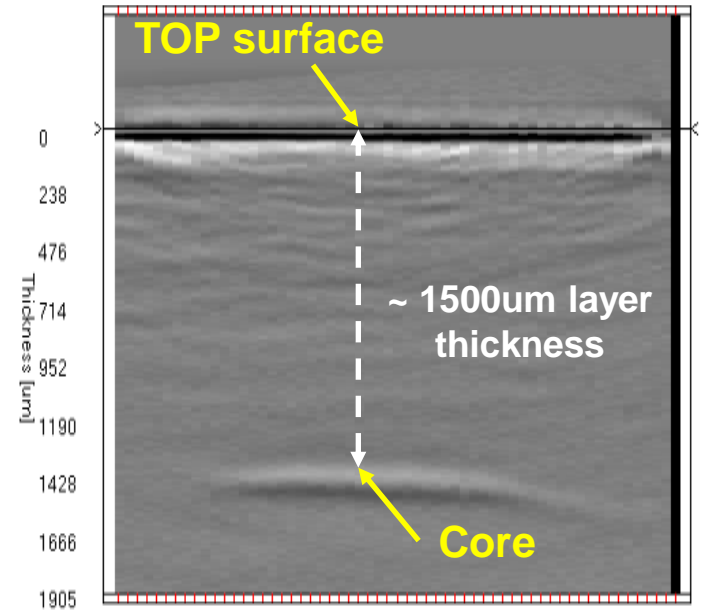
Intact



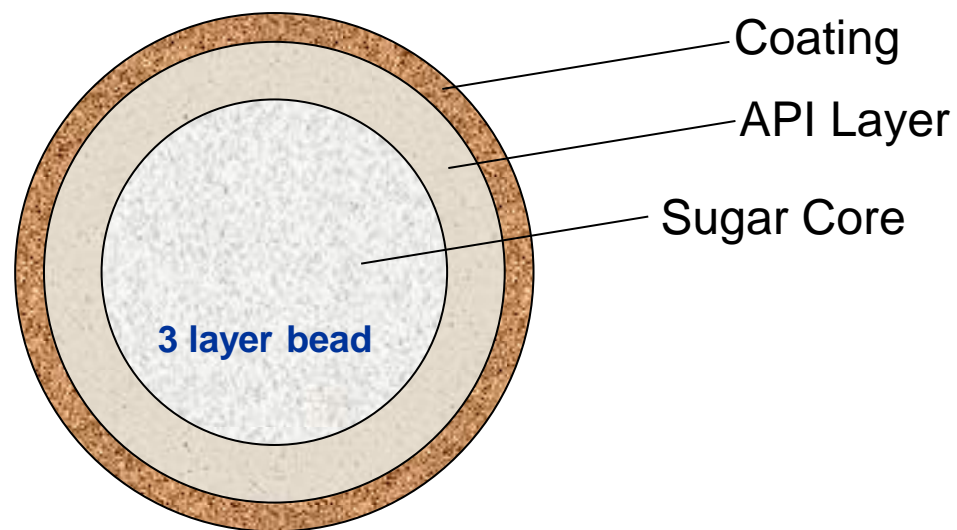
Sectioned



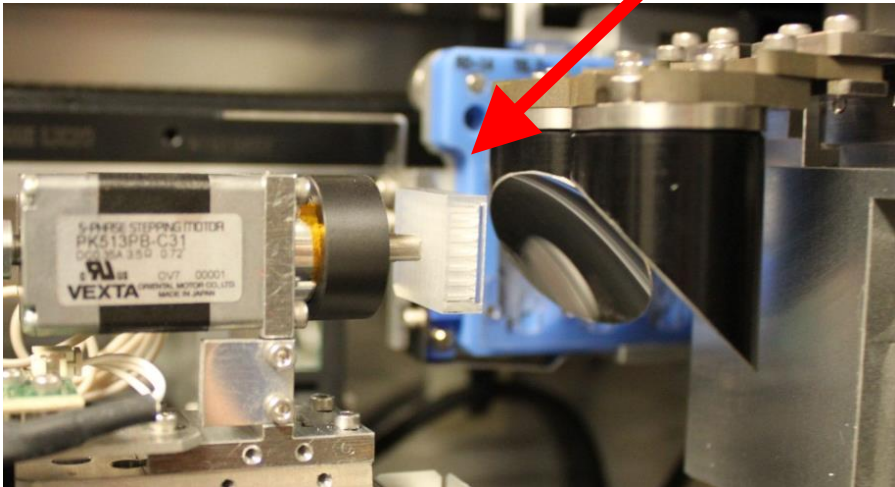
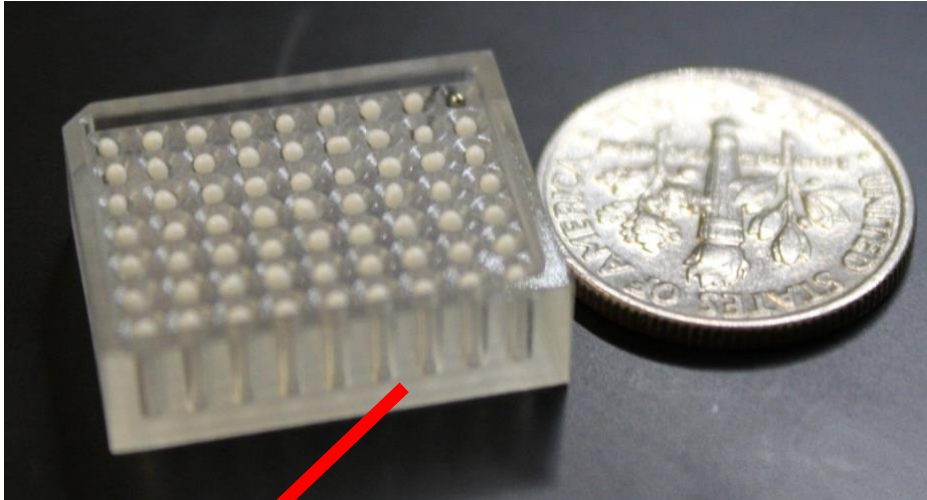
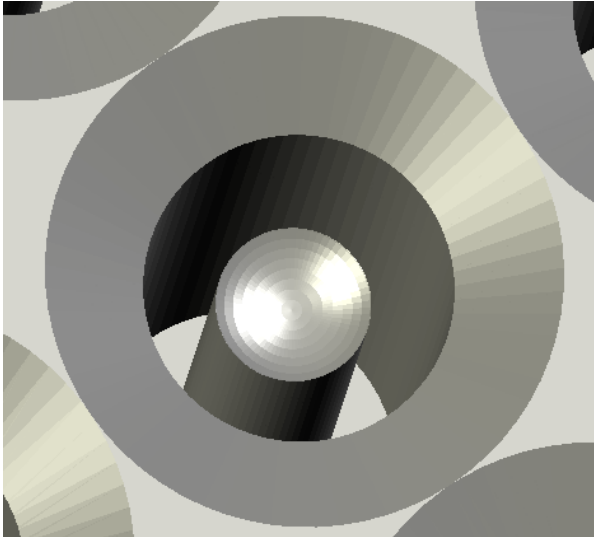
2D Cross-section



Samples < 1 mm

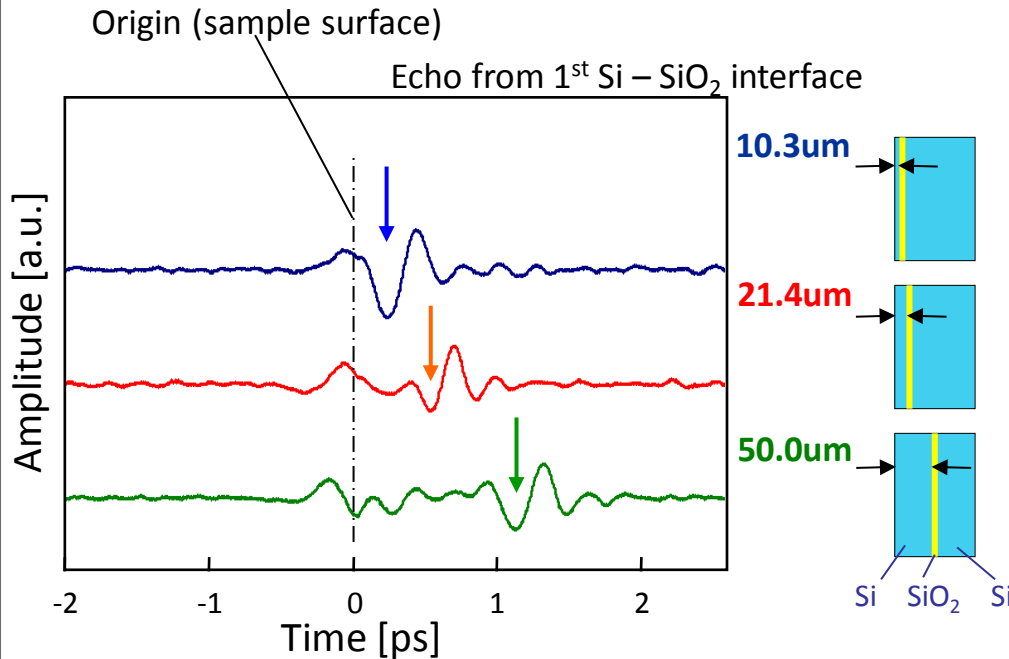


Enabled by Custom Bead Holder

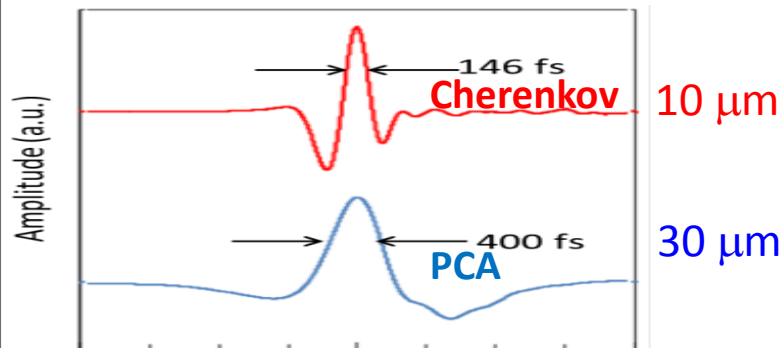
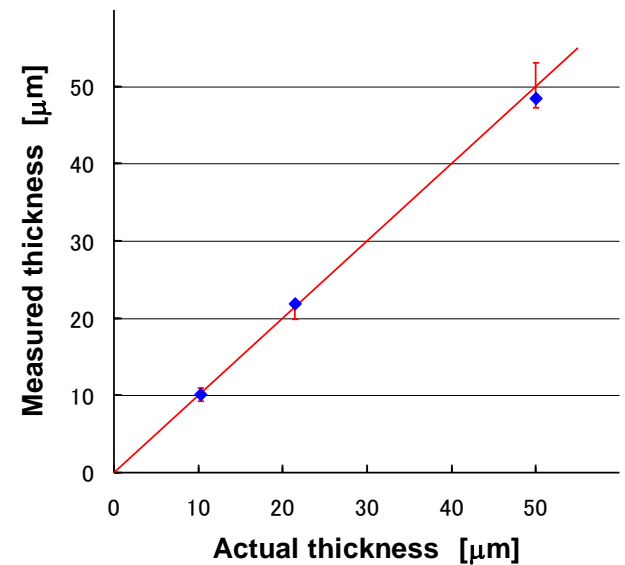


Sample: Silicon on an Insulator Chip

Detected waveforms

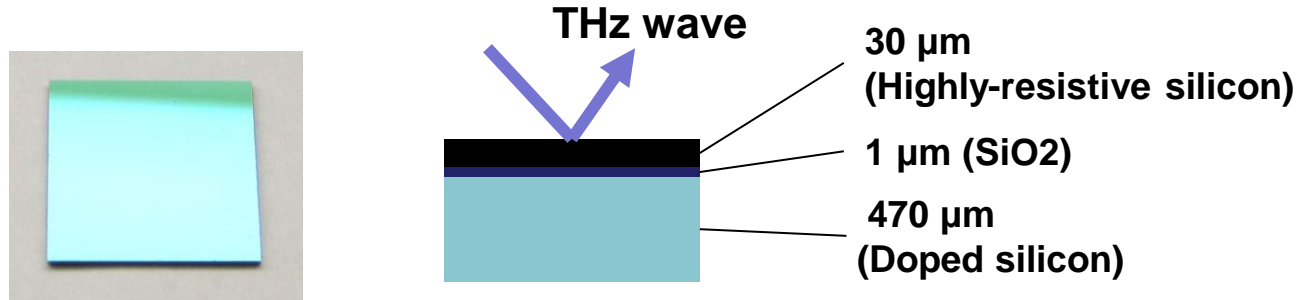


Correlation of actual vs. measured

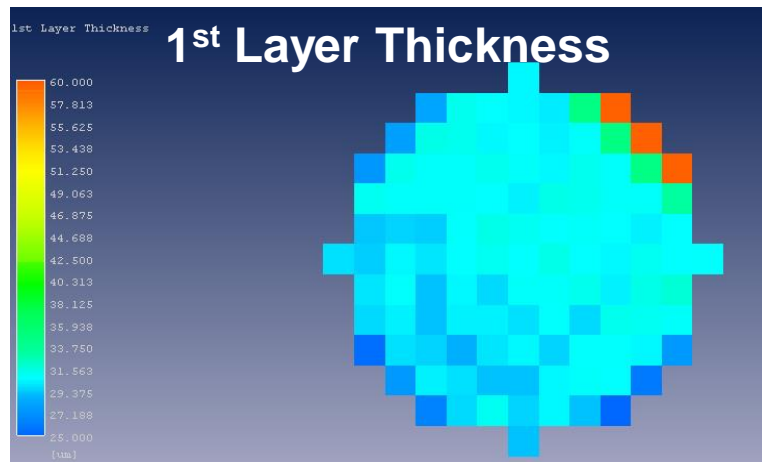


Realized Nondestructive thickness measurement down to 10um

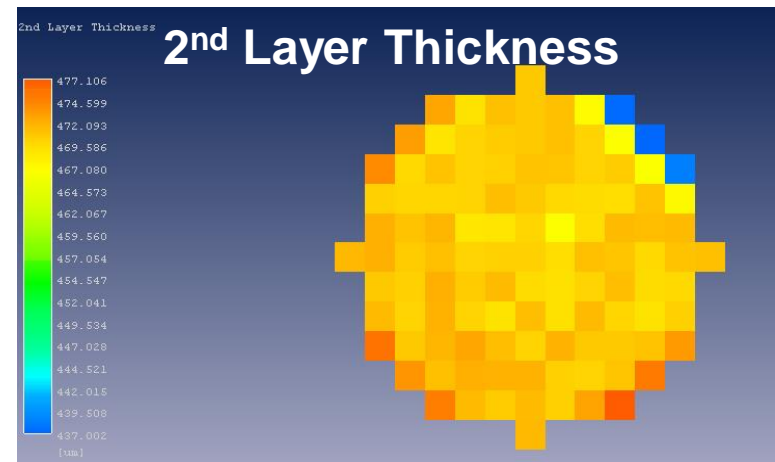
System Measurement Accuracy



OQ standard uses SOI (Silicon On Insulator) chip



Average = 30.3 μm
 $\sigma = 0.73 \mu\text{m}$



Average = 470.6 μm
 $\sigma = 1.3 \mu\text{m}$

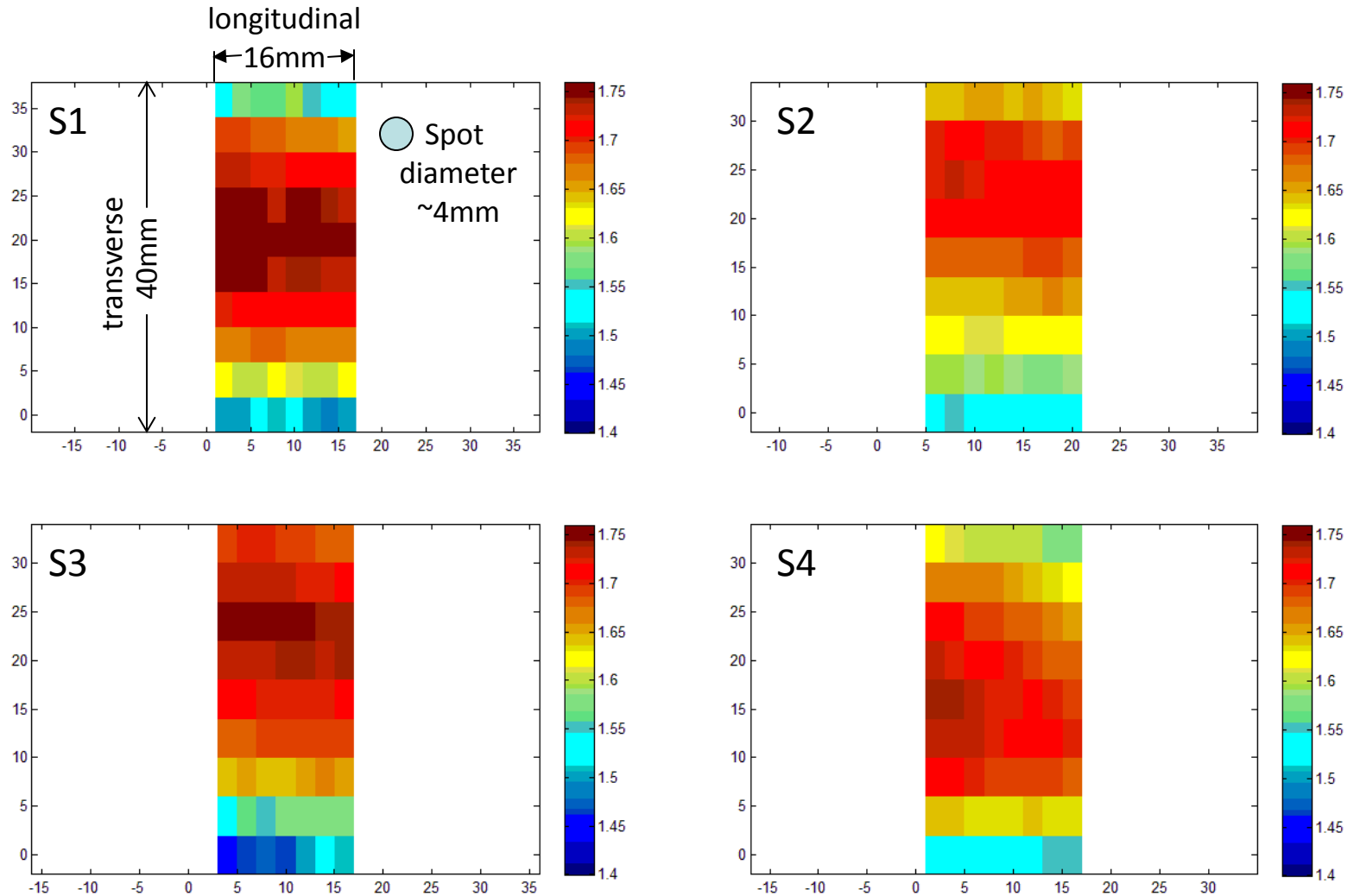
Analysis of Larger Samples

- Analyzed on other Advantest instruments
- Robotic stage/ optical bench combined with TAS7500TS system in transmission, reflection orientations
- Samples can include:
 - Large ceramic discs
 - Rock core samples
 - Bottles and other multi-layer plastics
 - Other packaging materials
 - Syringes (determine filling state)
 - Biologics

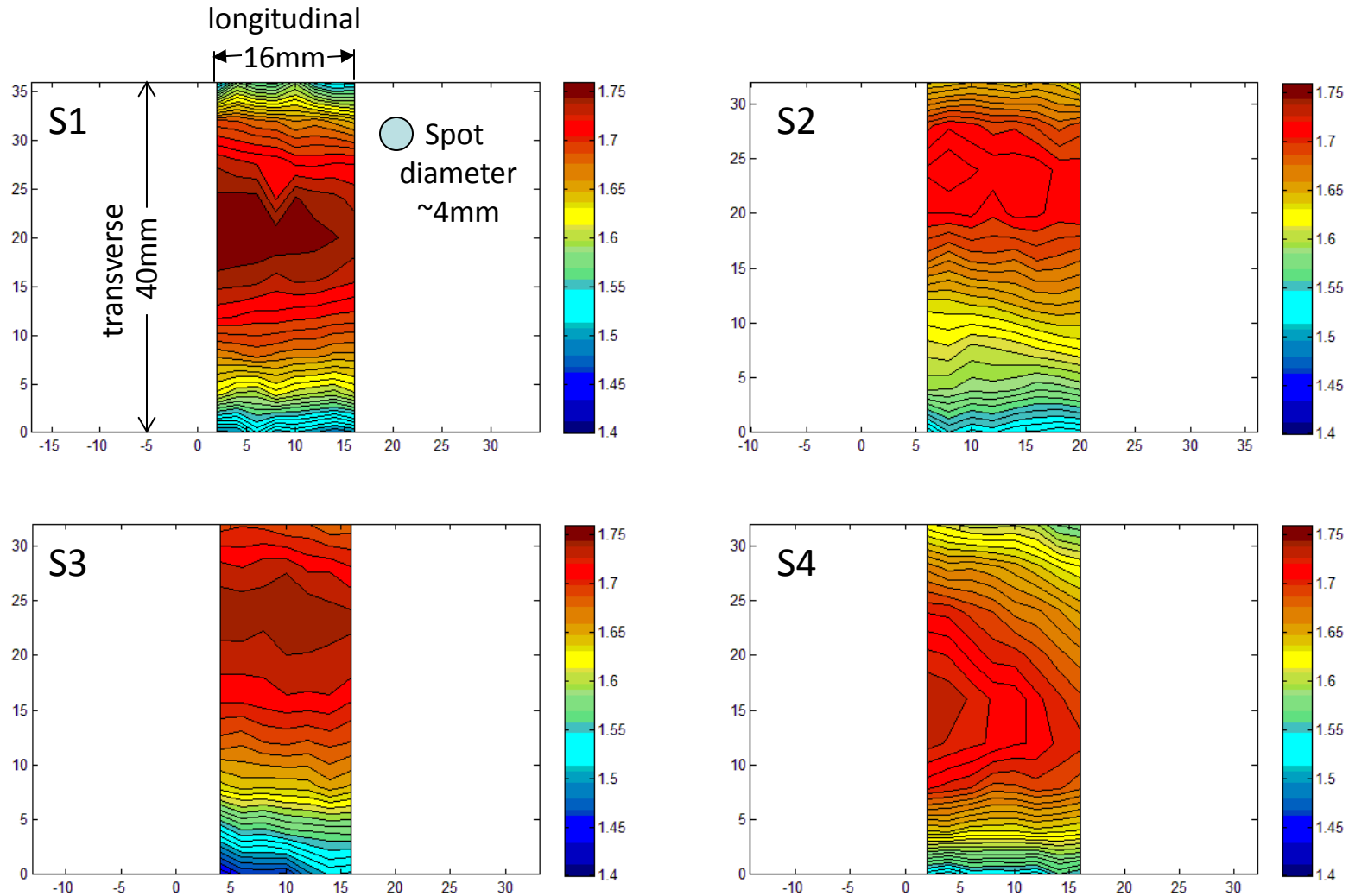
Spatial Mapping of Bulk Properties



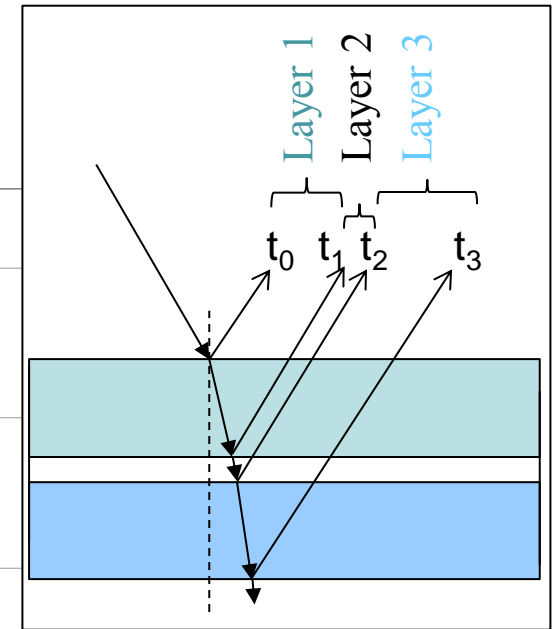
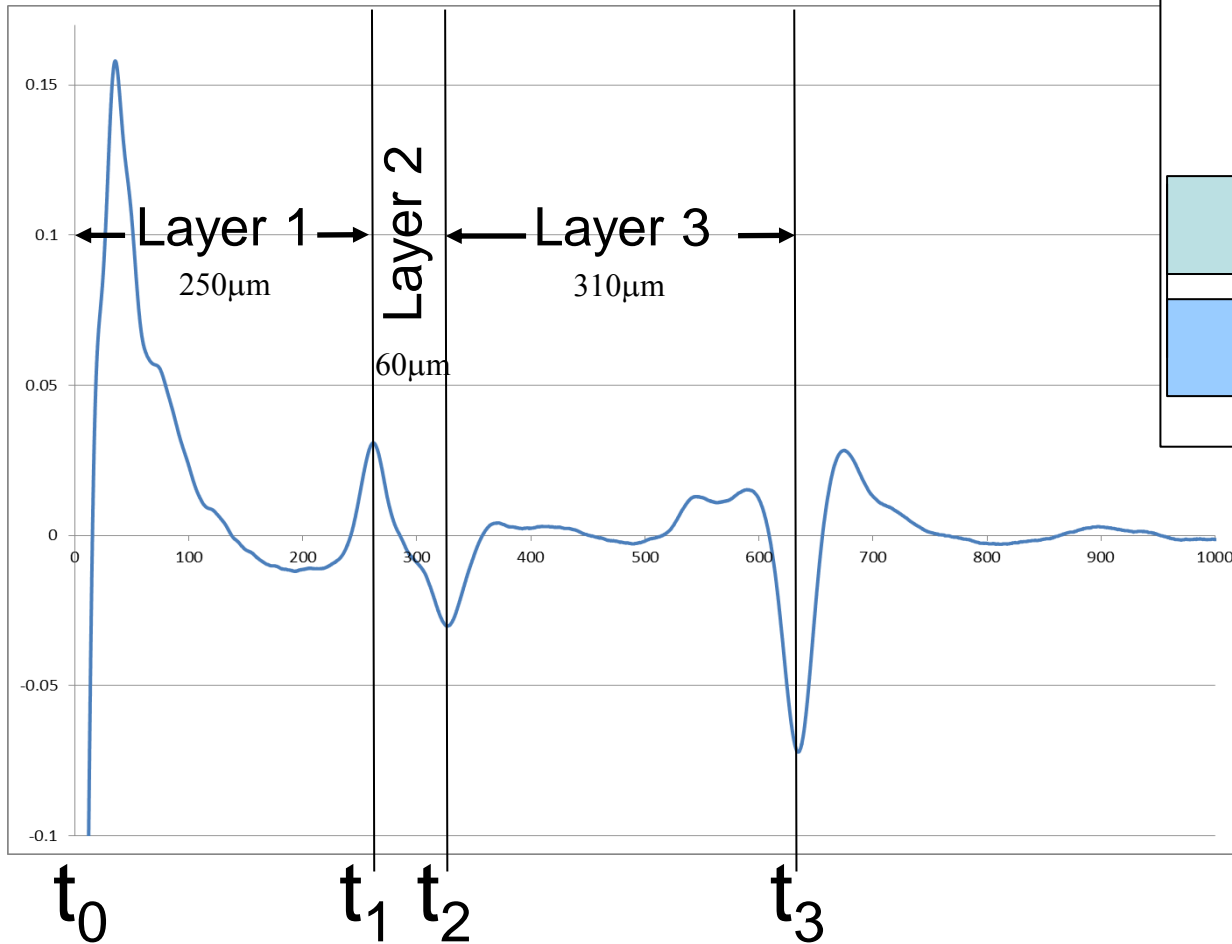
Roller Compaction Ribbon Spatial Density Mapping



Spatial Density Heat Map Representation



Controlled atmosphere packaging integrity

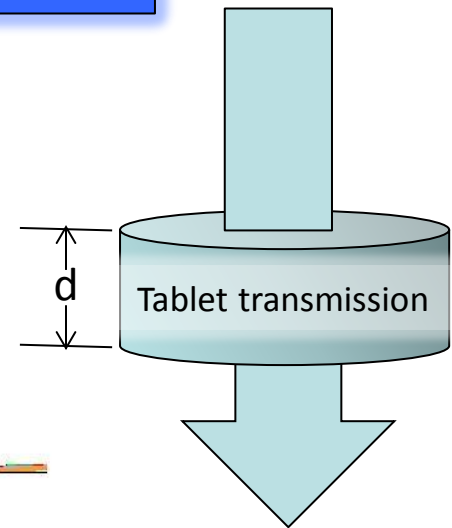
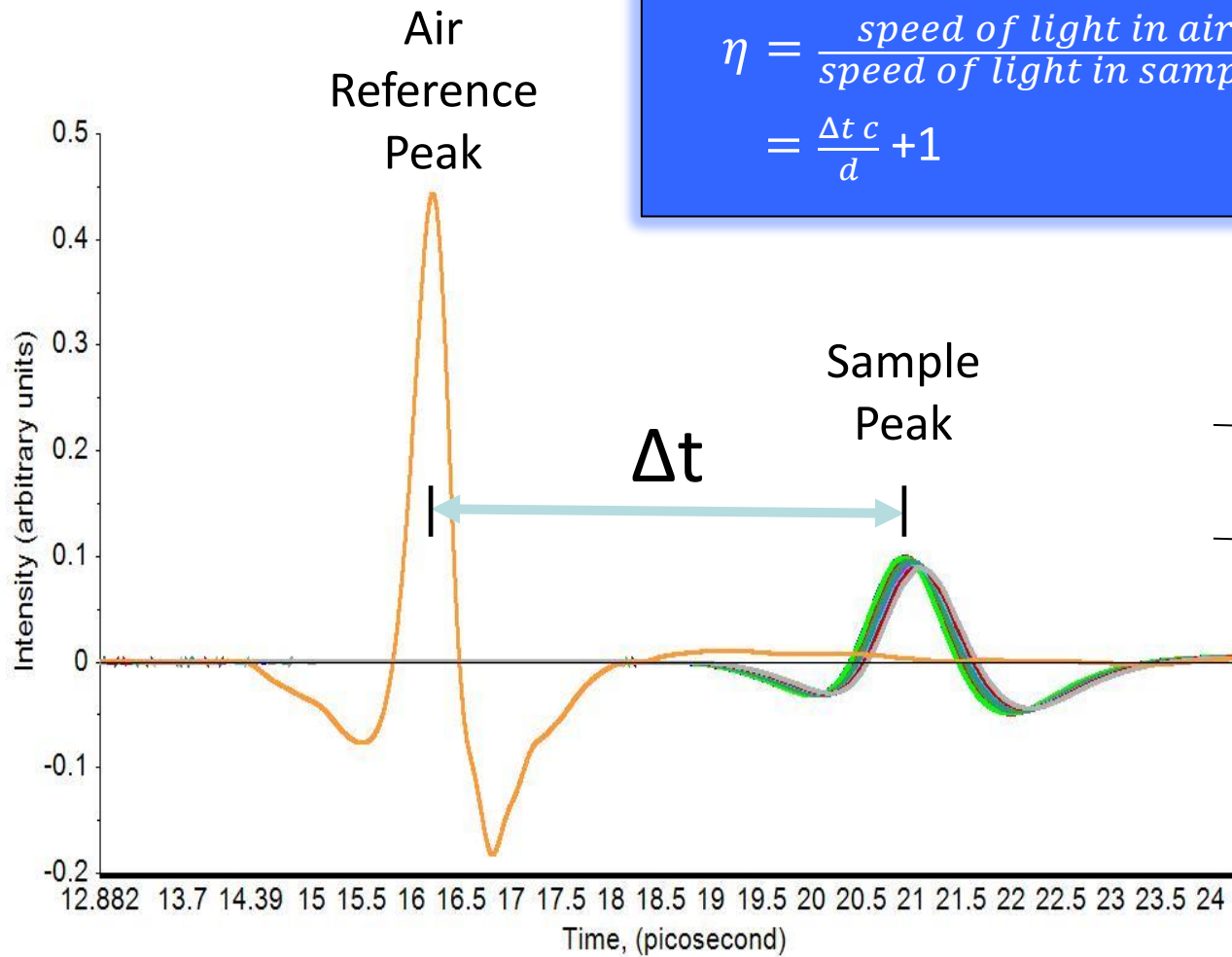


Bulk Properties

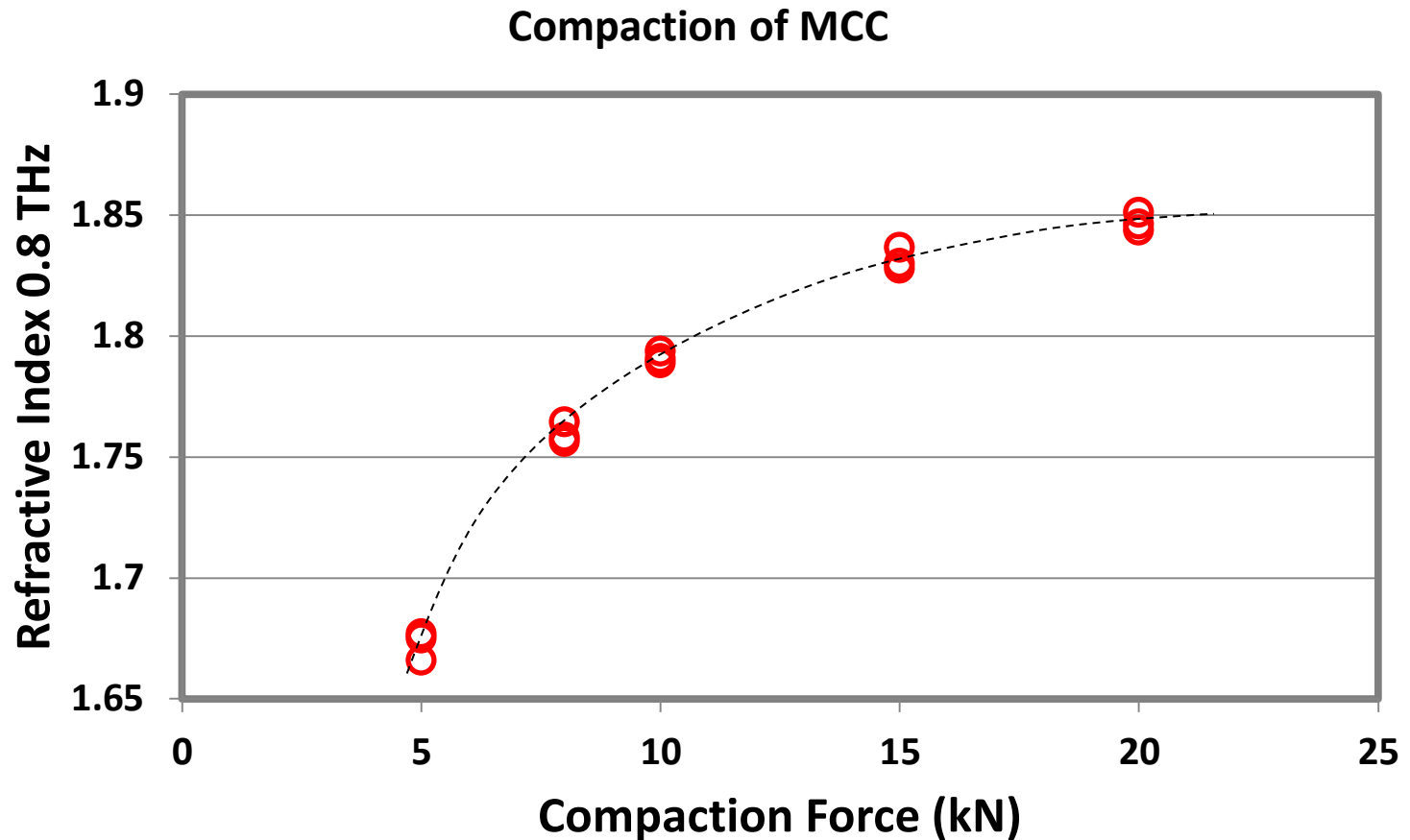


Measurement of Refractive Index

$$\eta = \frac{\text{speed of light in air}}{\text{speed of light in sample}} = \frac{\Delta t c}{d} + 1$$

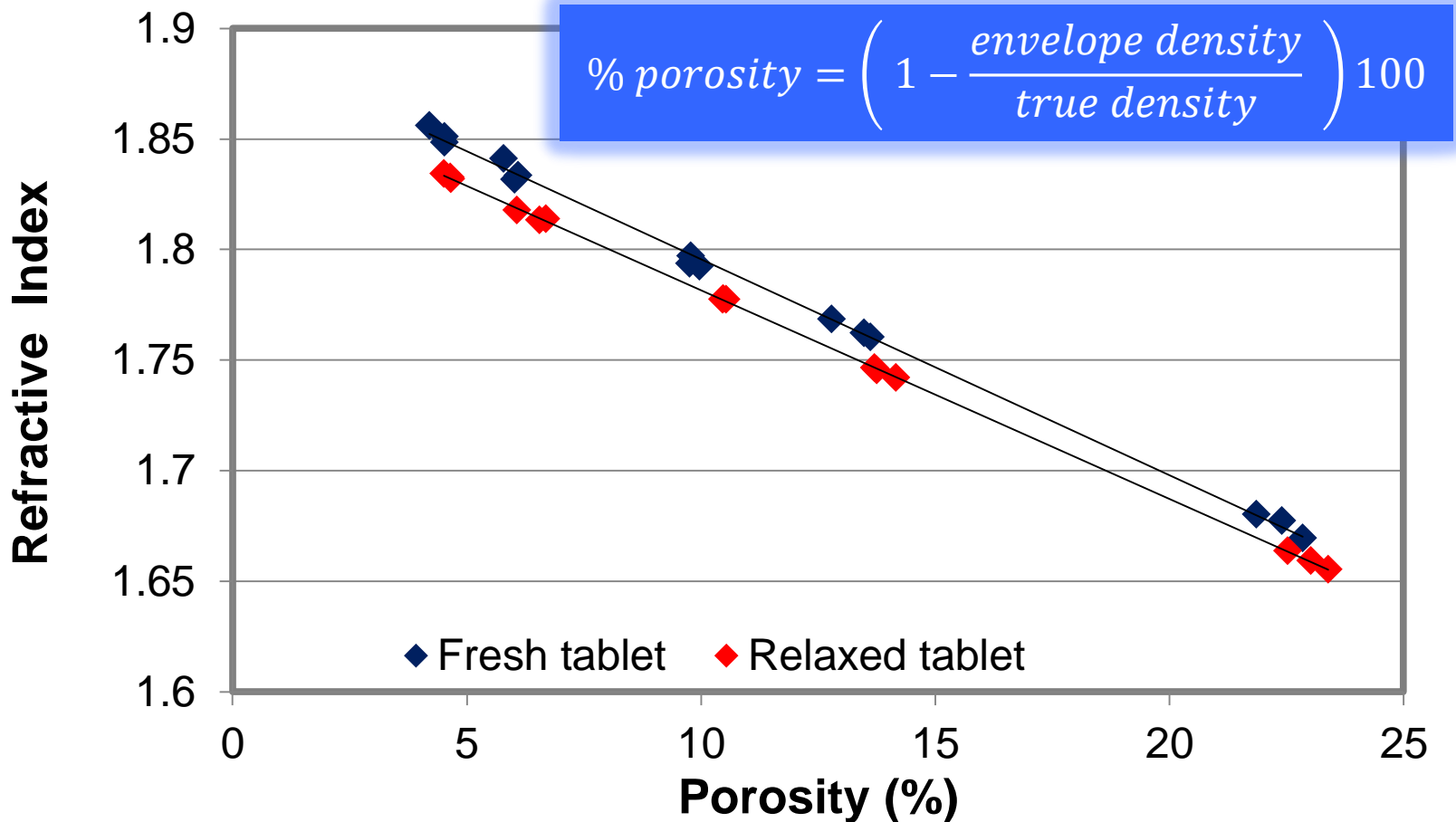


Change in Refractive Index with Compaction Force

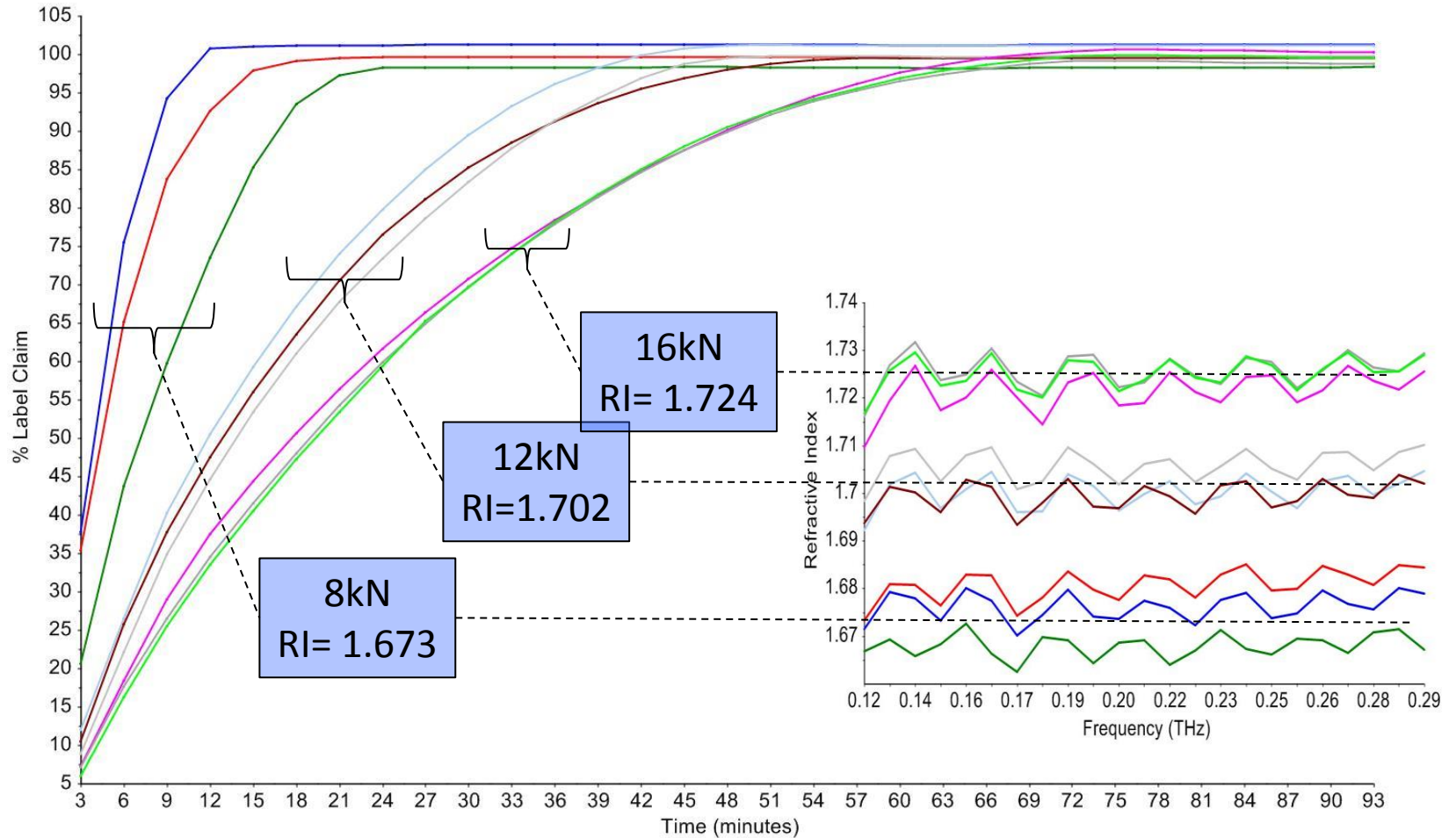


Calibration of Refractive Index vs. Porosity

Compaction of MCC



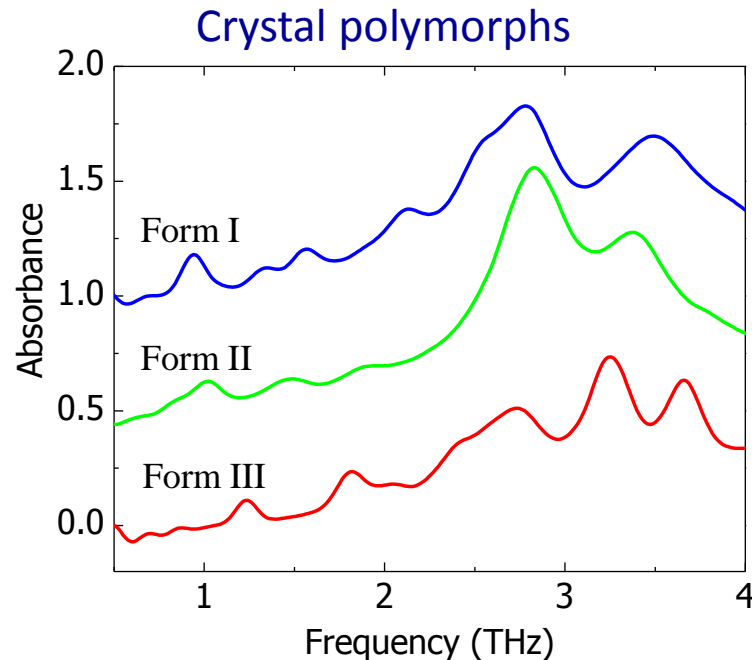
Correlation of Refractive Index to Dissolution Rate of Powder Compacts



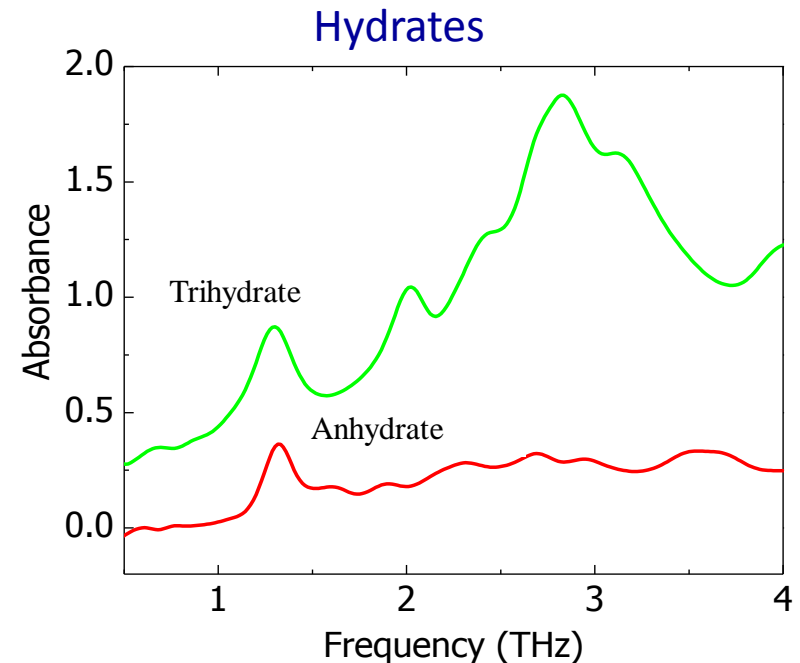
Molecular/Spectroscopic Applications



Polymorph, hydrate, and co-crystal analysis

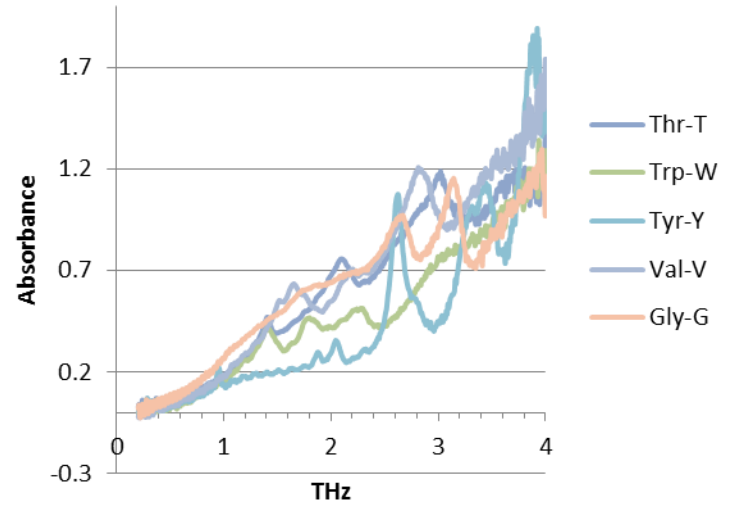
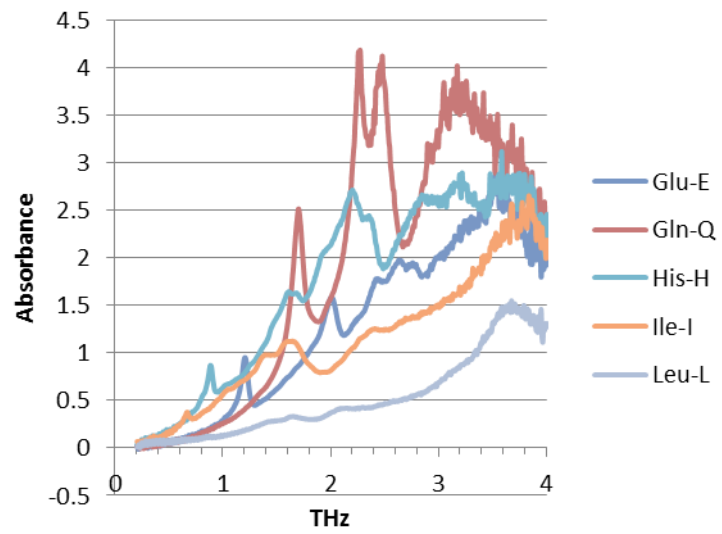
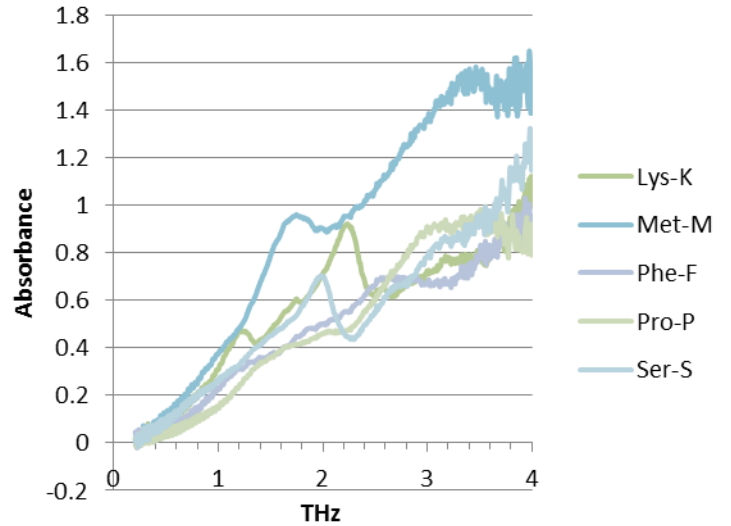
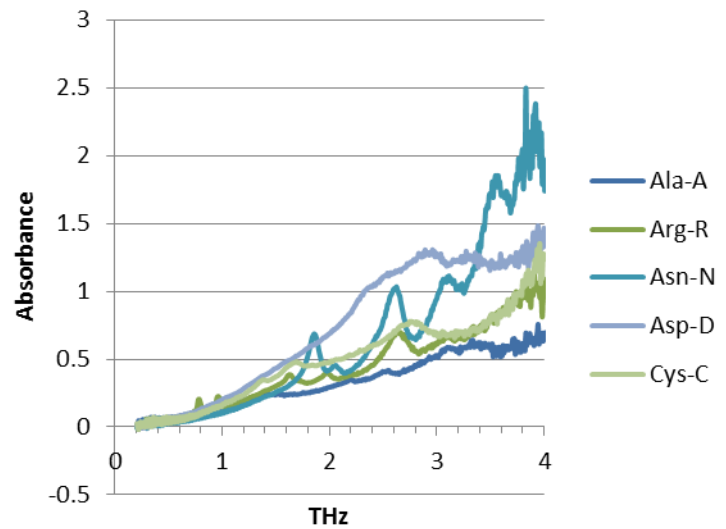


Spectra of carbamazepine polymorphs (I – III)

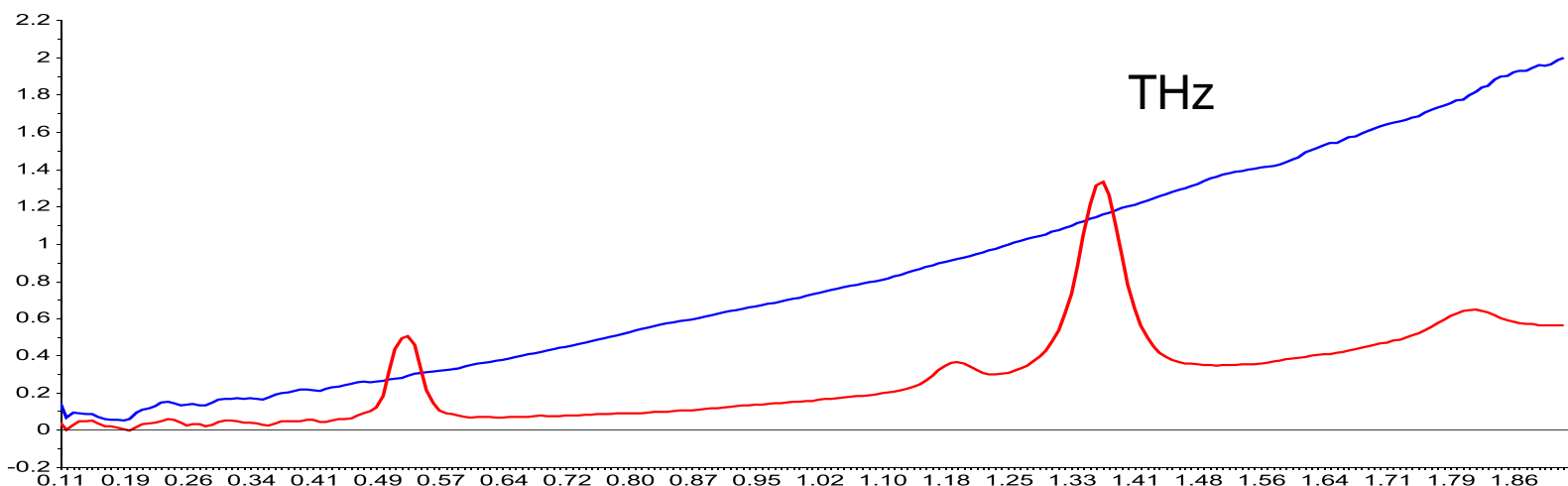
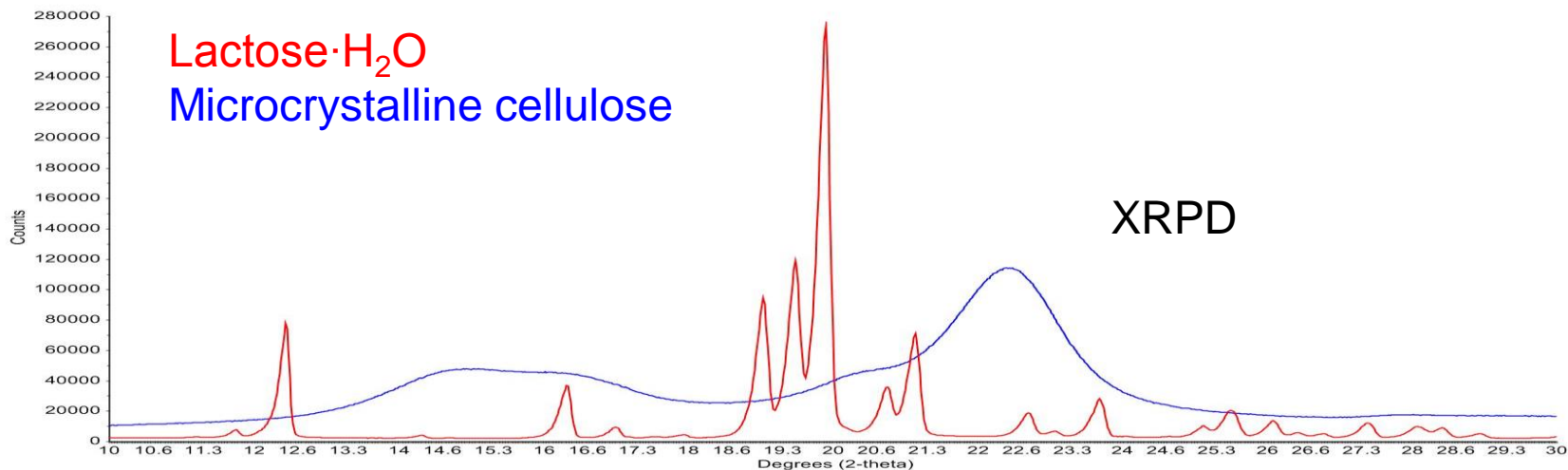


Spectra of pipemidic acid anhydrate and trihydrate

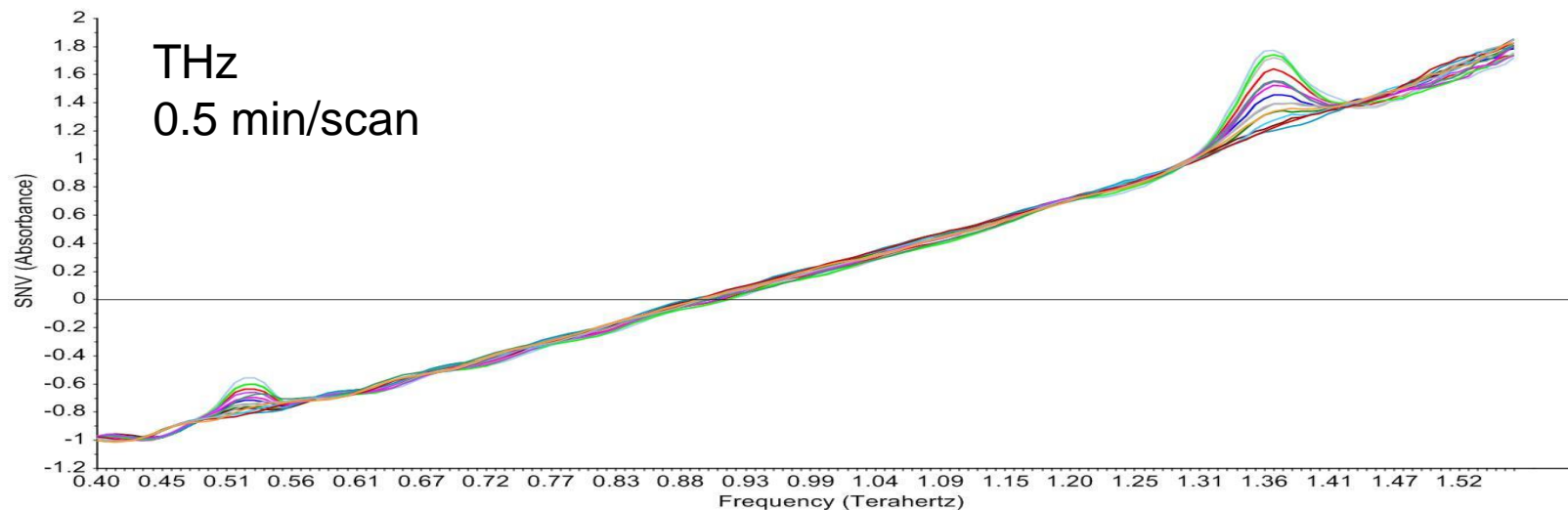
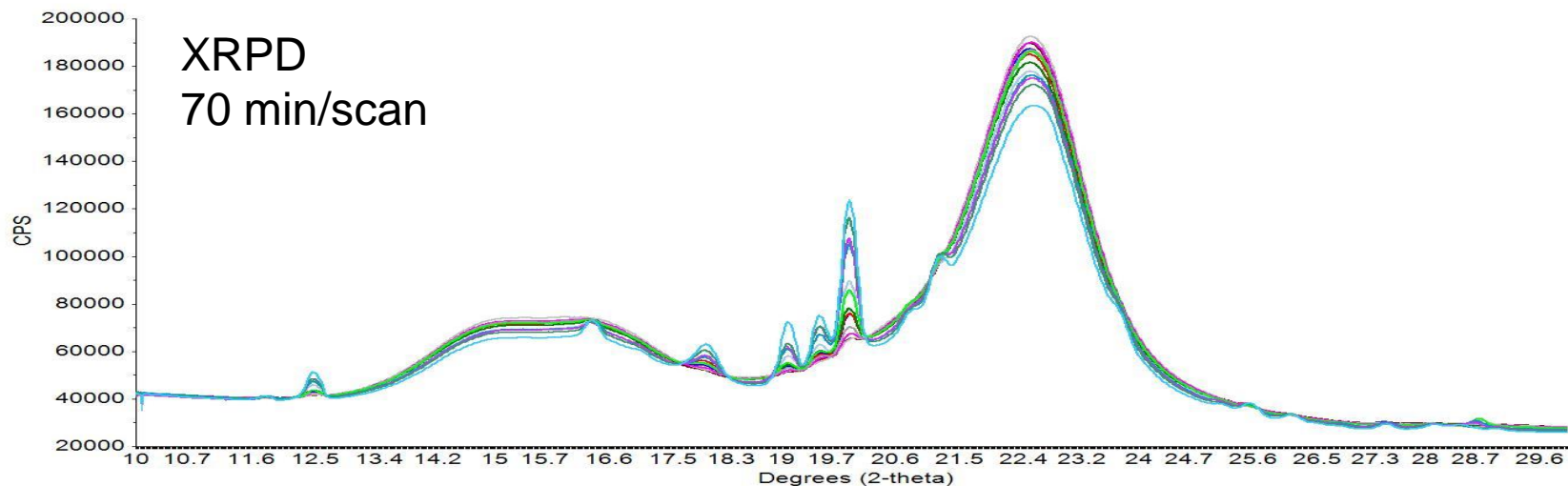
*Samples provided by Prof. Katsuhide Terada, Pharmaceutical Department, Toho University



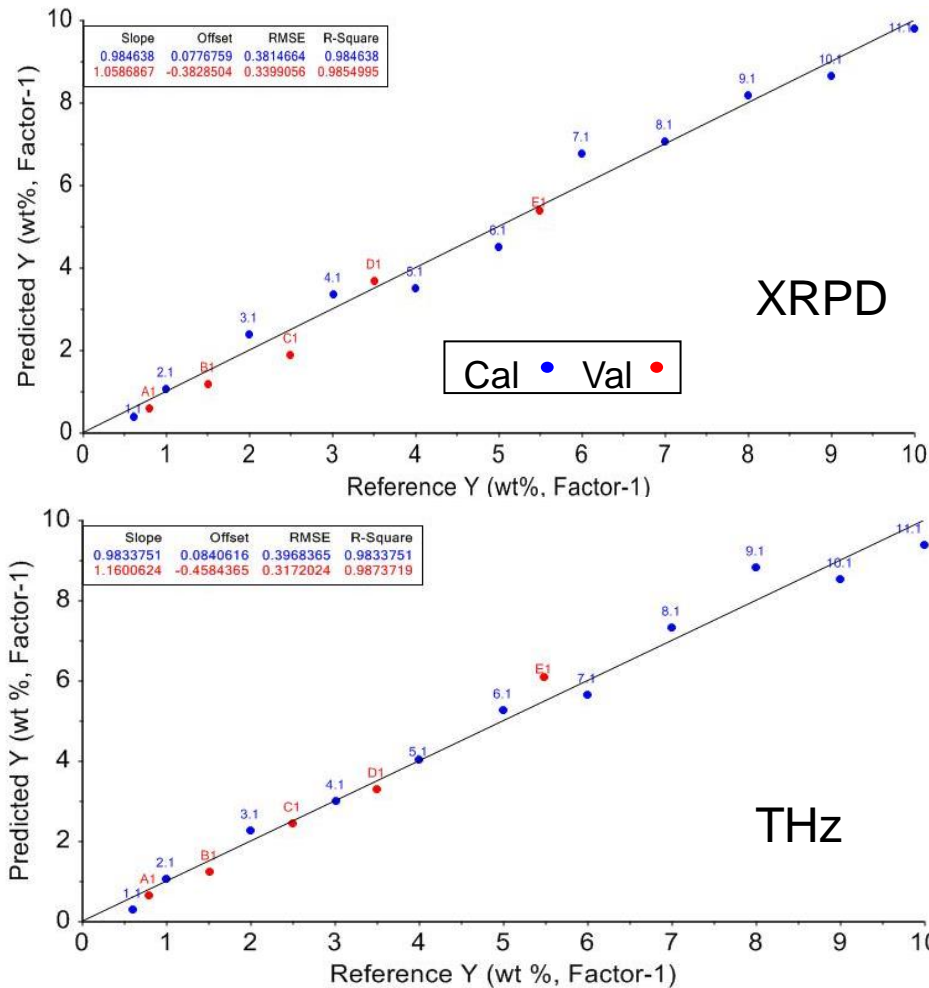
XRPD and THz Spectroscopy measure crystallinity directly



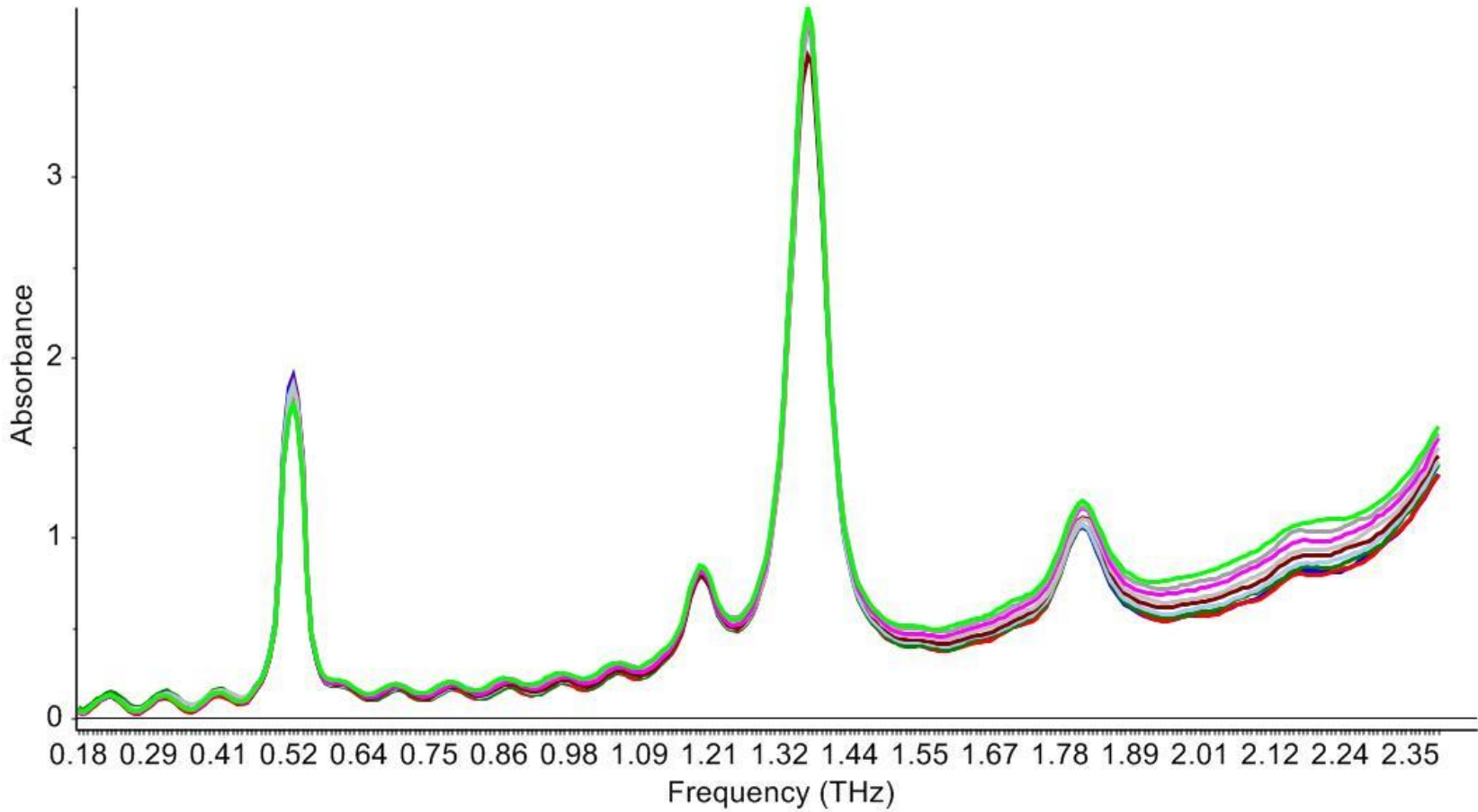
XRPD and THz Quantitative Calibration Data



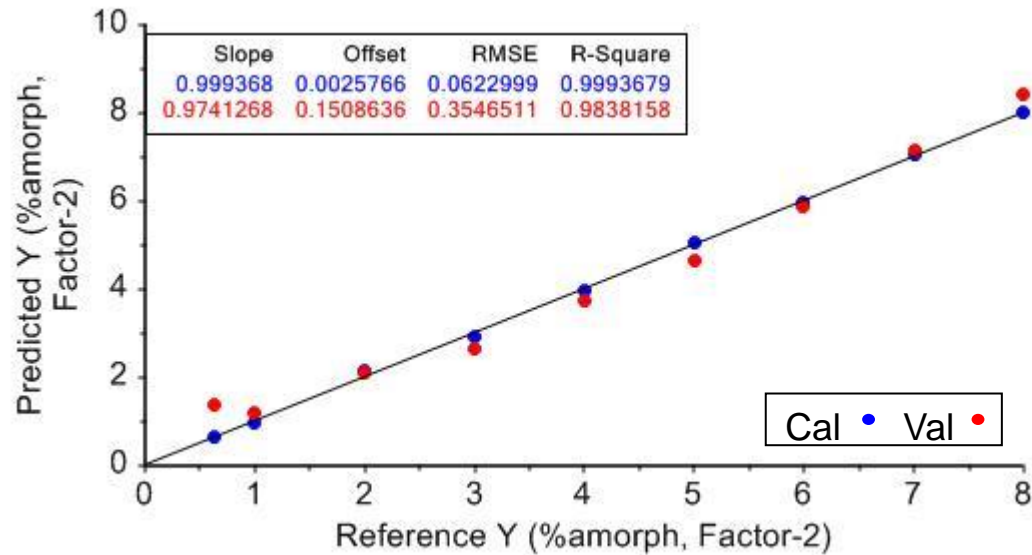
XRPD and THz yield comparable PLS calibration results



THz PLS Calibration Data



THz PLS Calibration Results



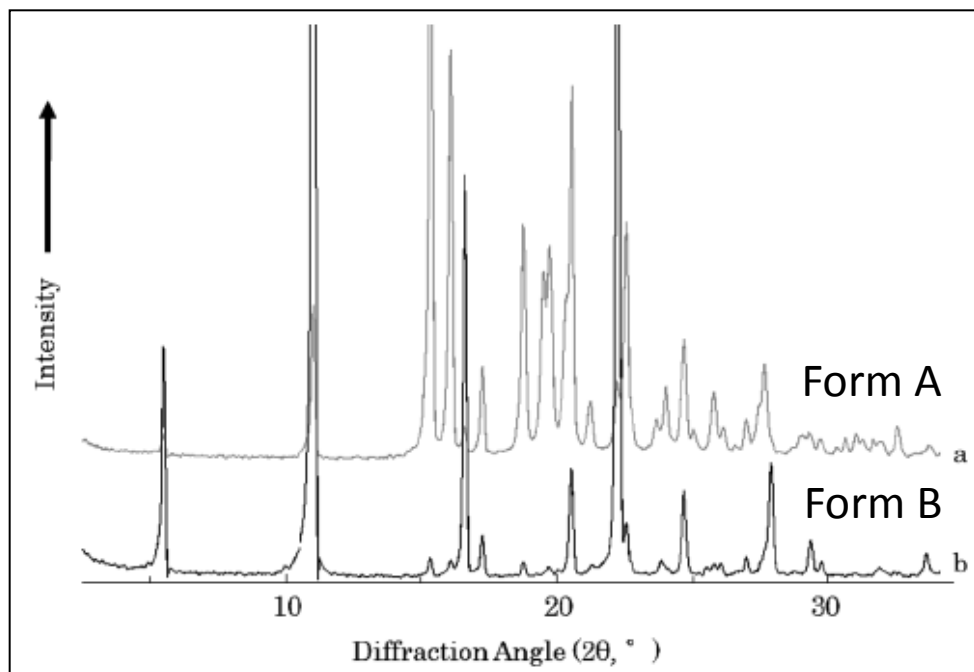
ADVANTEST ADVANTEST ADVANTEST

Physical Stability

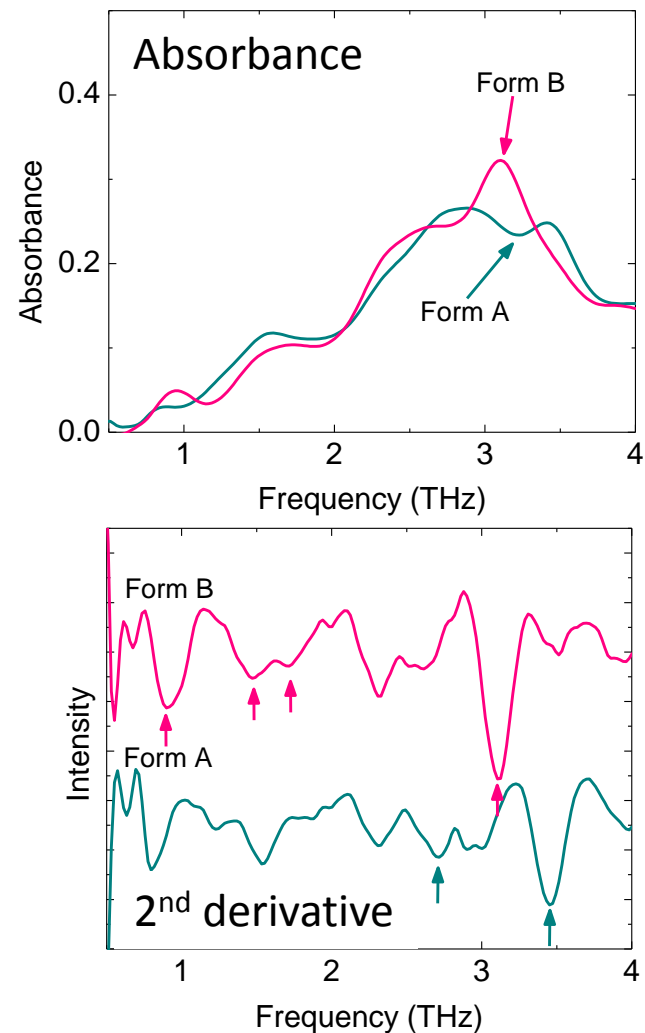


Drug Substance polymorph identification

X-RAY POWDER DIFFRACTION

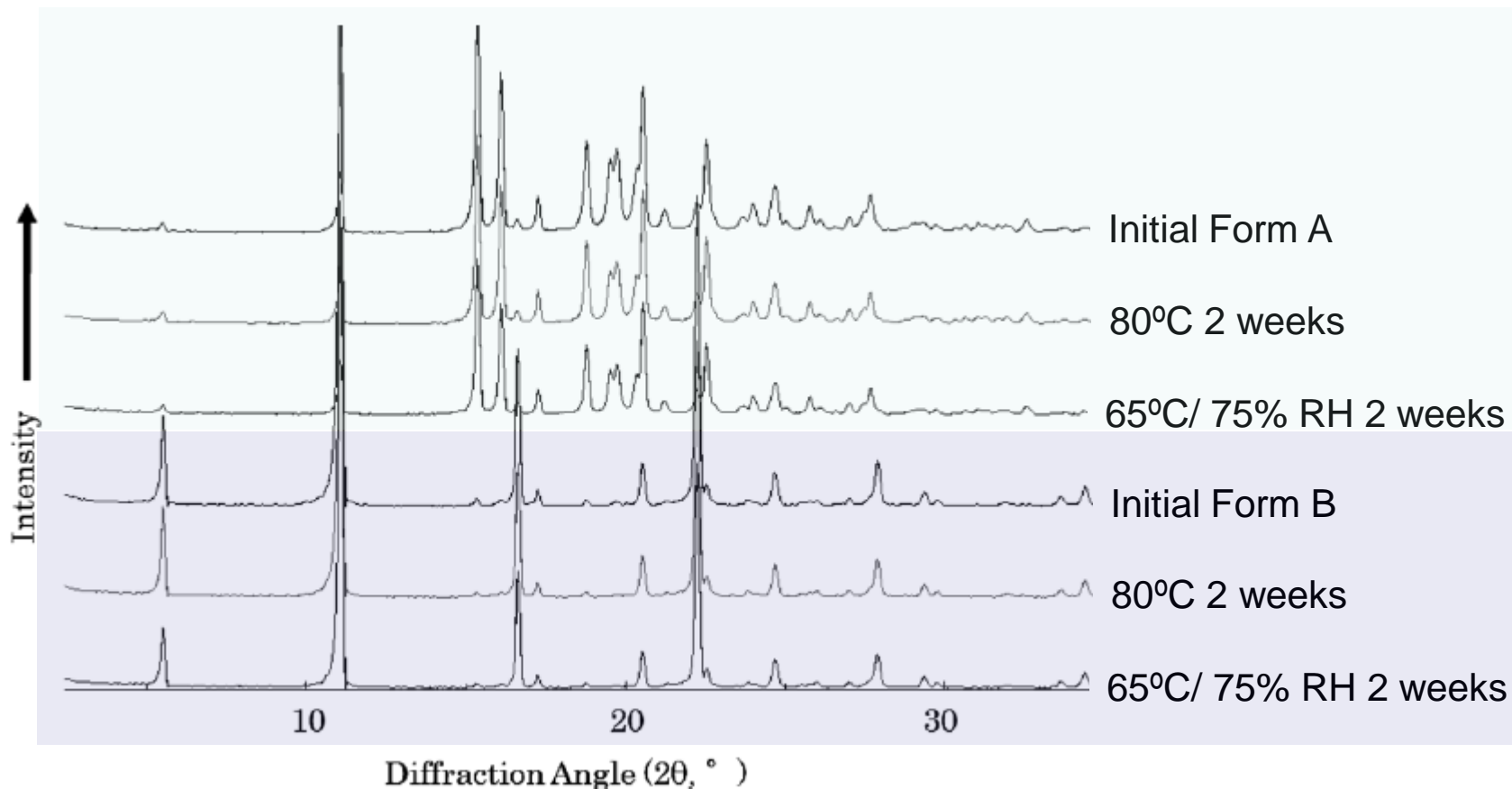


TERAHERTZ SPECTRA



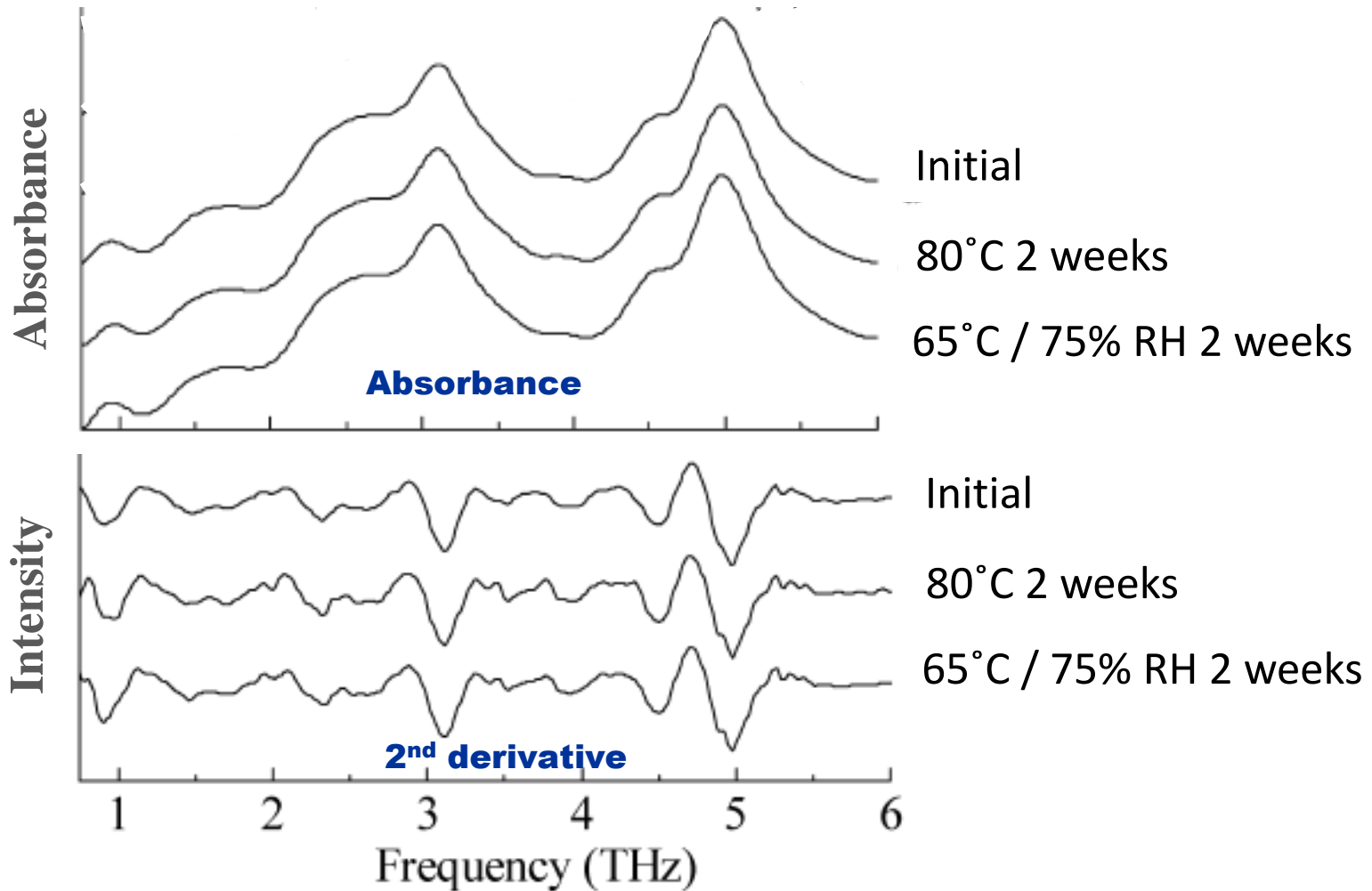
Y. Ikeda, E. Kato, K. Terada et al., Chem. Pharm. Bull., 58 (2010) 76.

XRPD

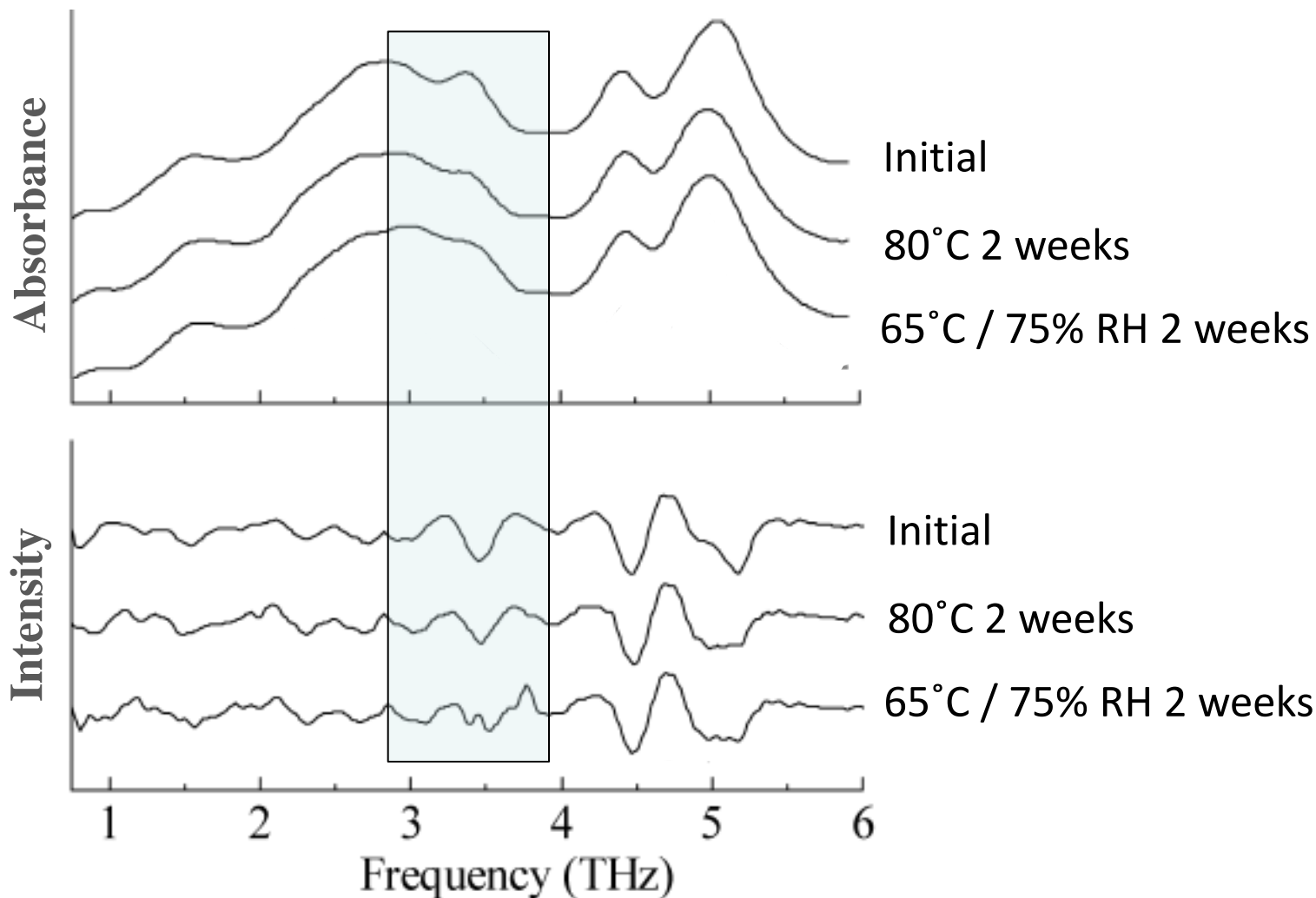


Y. Ikeda, E. Kato, K. Terada et al., Chem. Pharm. Bull., 58 (2010) 76.

Drug Substance Polymorph Form B



Drug Substance Polymorph Form A



1. Fast and Compact

- Advantest designed resulting in fastest commercially available measurement system
- *TAS7500TS: 1ms/scan, wave form effective measurement 2fs

2. Flexible (Multifunctional and Broadest Bandwidth)

- Fiber length option, adaptive trigger delay, external and remote control
- 2 channel system offering simultaneous measurement option
- Wideband spectral coverage: 0.03 to 7 THz
 - i. Low-frequency: 30 GHz to 2 THz
 - ii. Standard: 100 GHz to 4 THz
 - iii. Ultra-wideband: 500 GHz to 7 THz

3. Engineering and hardware excellence: (High Resolution and low cost of ownership)

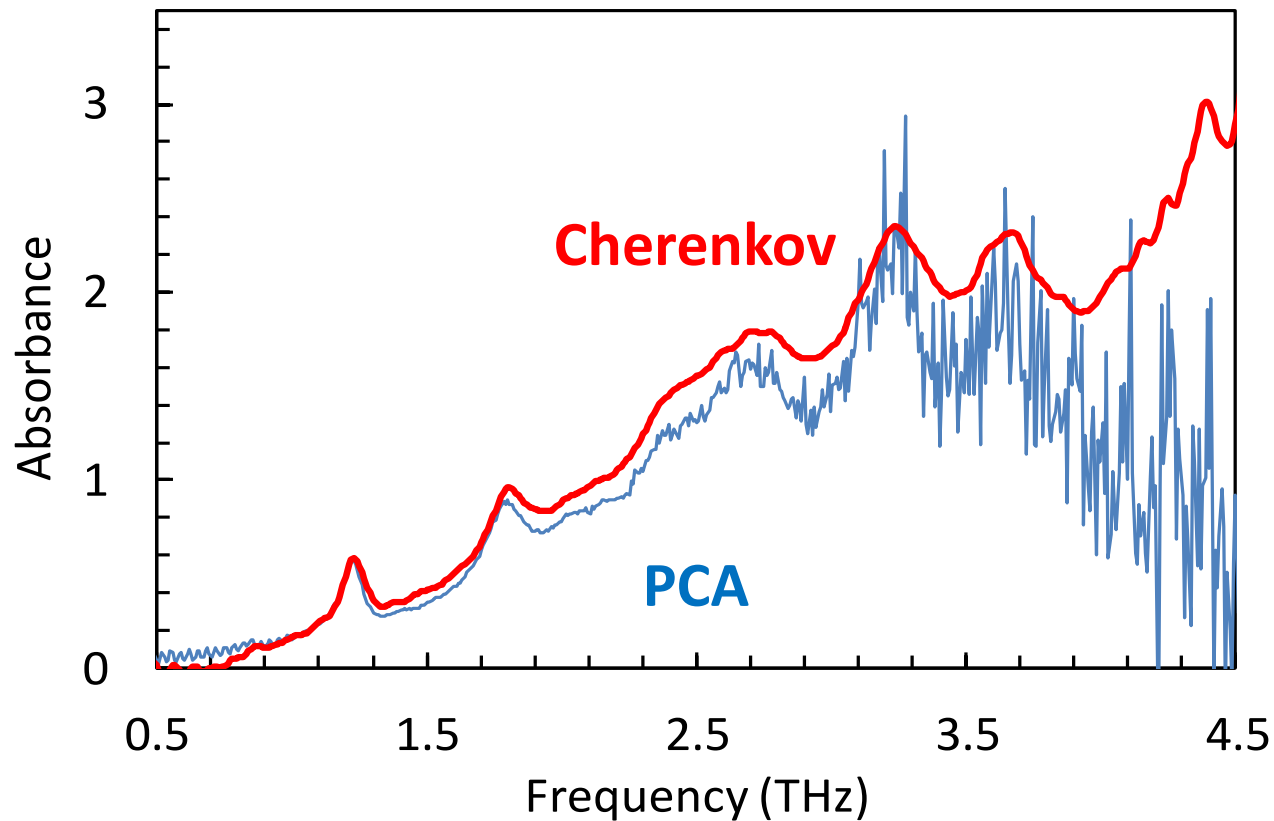
- 100% Solid state with no moving parts to fail
- Increased instrument availability
- Low voltage

**Thank you
for your attention**

Questions?



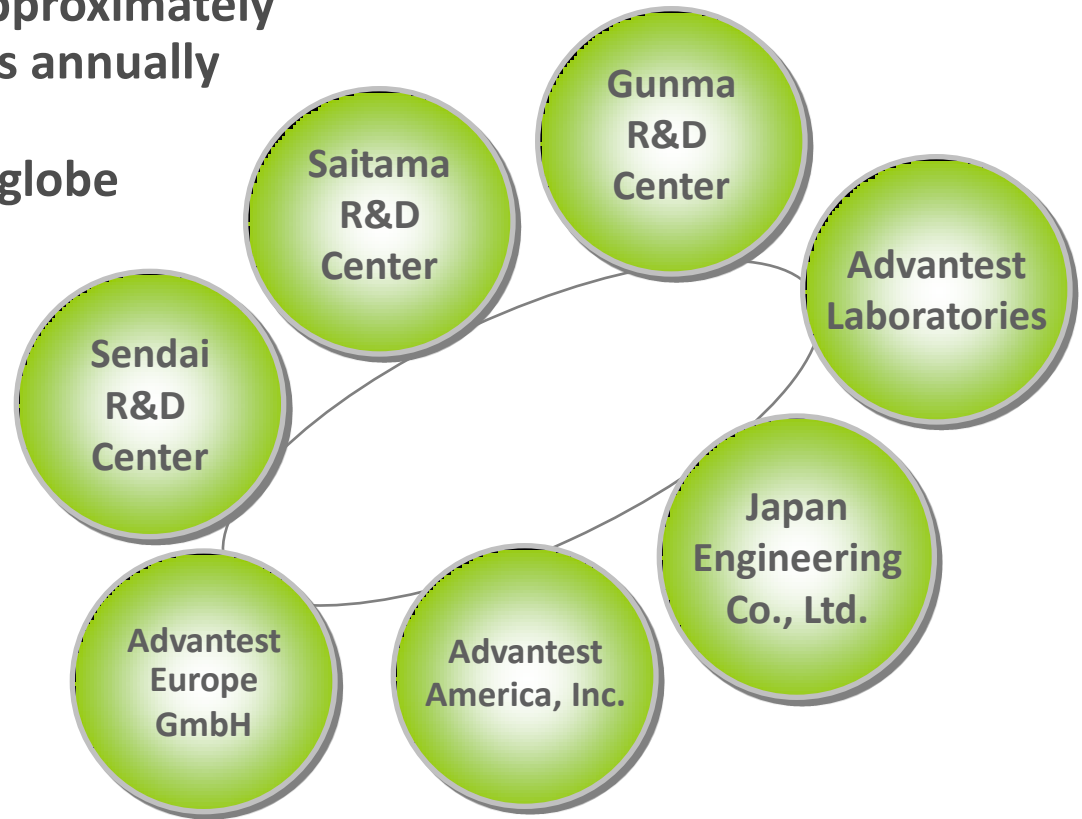
- **Sample:**
 - Carbamazepine, Form III (CBZ (III)), 20mg
 - Mixed with 200 mg polyethylene powder and compressed into a flat faced tablet
- **Measurement**
 - Transmission geometry



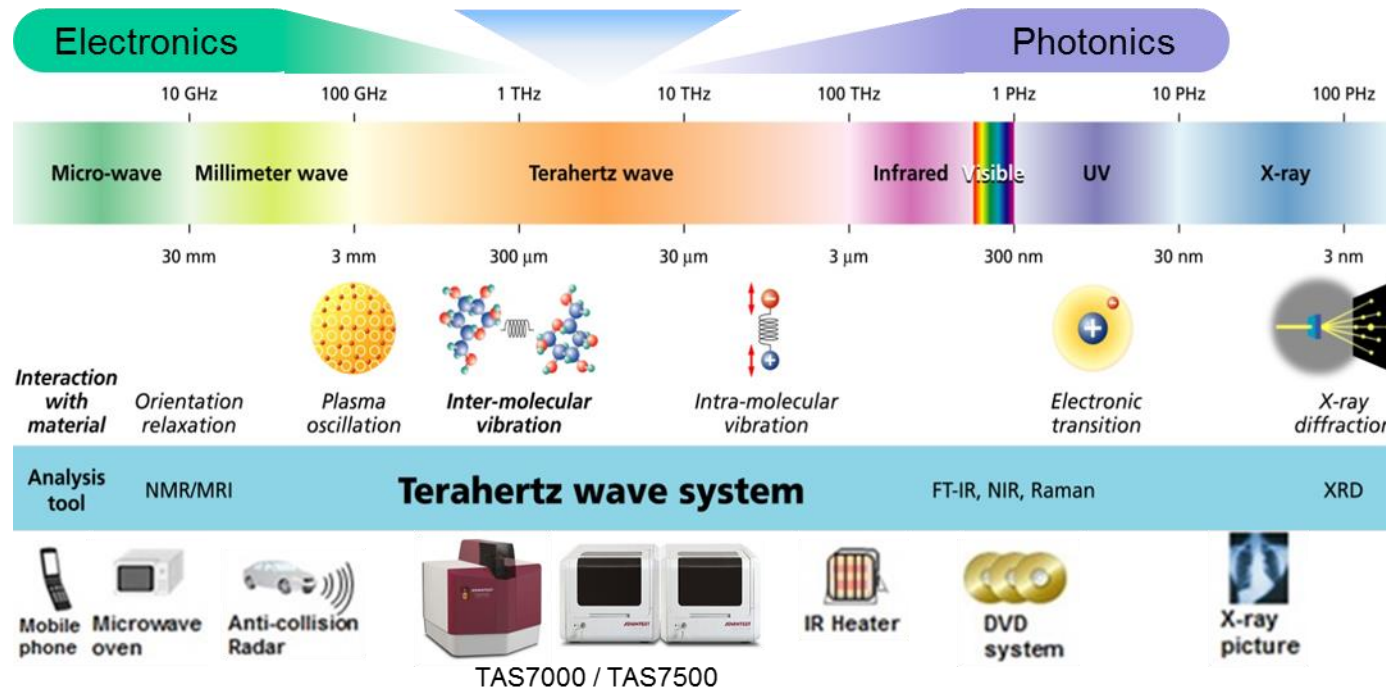
Technology Support on the Leading Edge:

Measurement Sciences Company

- Committed to investing ~20% of annual revenue into R&D
- Rich pipeline generates approximately 10 new product launches annually
- R&D facilities around the globe



Advantages of the Terahertz Region



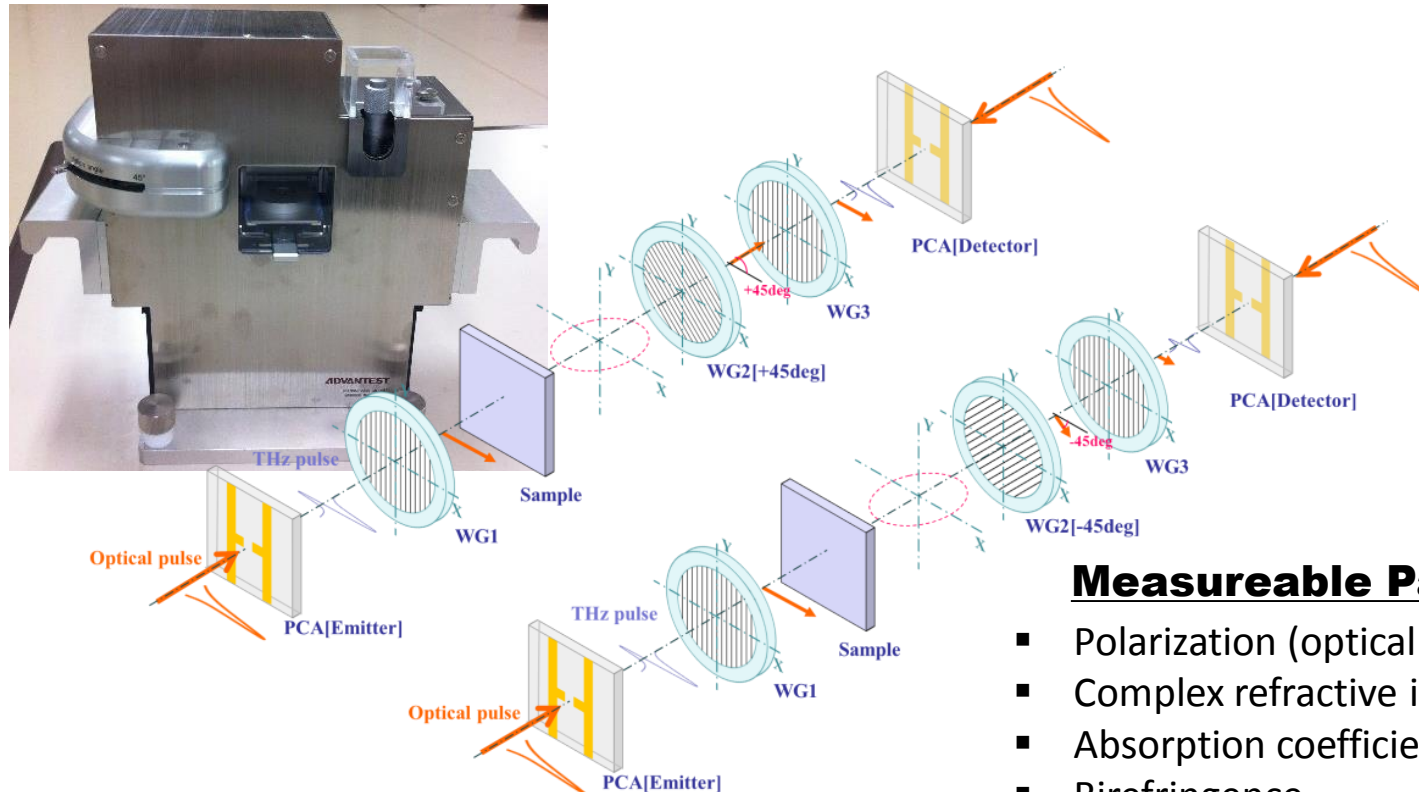
Low photon energy

- Crystal lattice vibration, hydrogen-bond, intermolecular interaction
- Non-ionizing radiation
- No sample heating

Technological advantage

- High transparency for non-conducting materials
- Time-domain spectroscopy

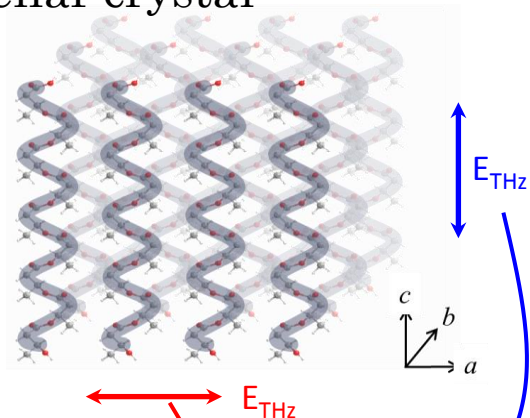
Transmission polarization accessory



Measureable Parameters

- Polarization (optical rotation) change
- Complex refractive index
- Absorption coefficient
- Birefringence
- Retardation
- Jones vector
- Ellipticity

Lamellar crystal

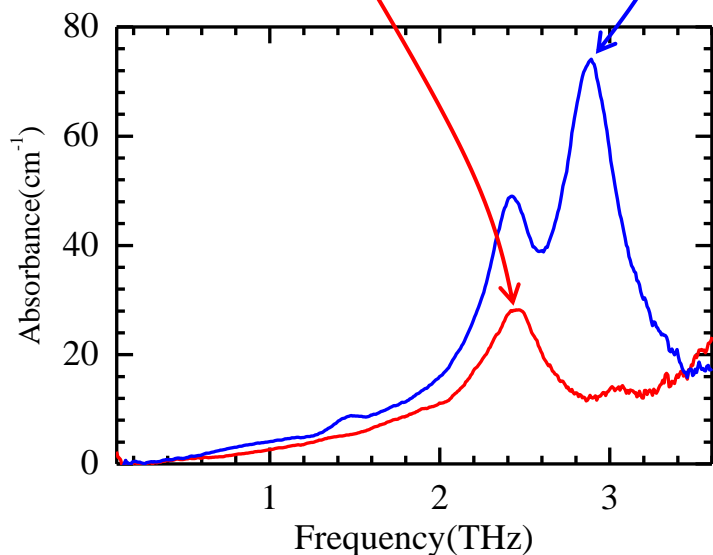


Vibration along helix structure
→ skeletal vibration

2.9THz

Vibration between helicies
→ hydrogen bonds

2.3THz



Measured by TAS7500SP (ADVANTEST)

Hoshina et al. Appl. Phys. Lett. **96**,
101904 (2010)
Hoshina et al. PCCP, **13**, 9173 (2011)

TAS7500TS Remote Fiber Probe

