Molecular Structure and Dynamics in the Solid State - Terahertz Spectroscopy of Pharmaceuticals

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The Heidelberg PAT Conference 2007

The FDAs "'Desired State"' and the Pivotal Role of Spectroscopy

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Outline

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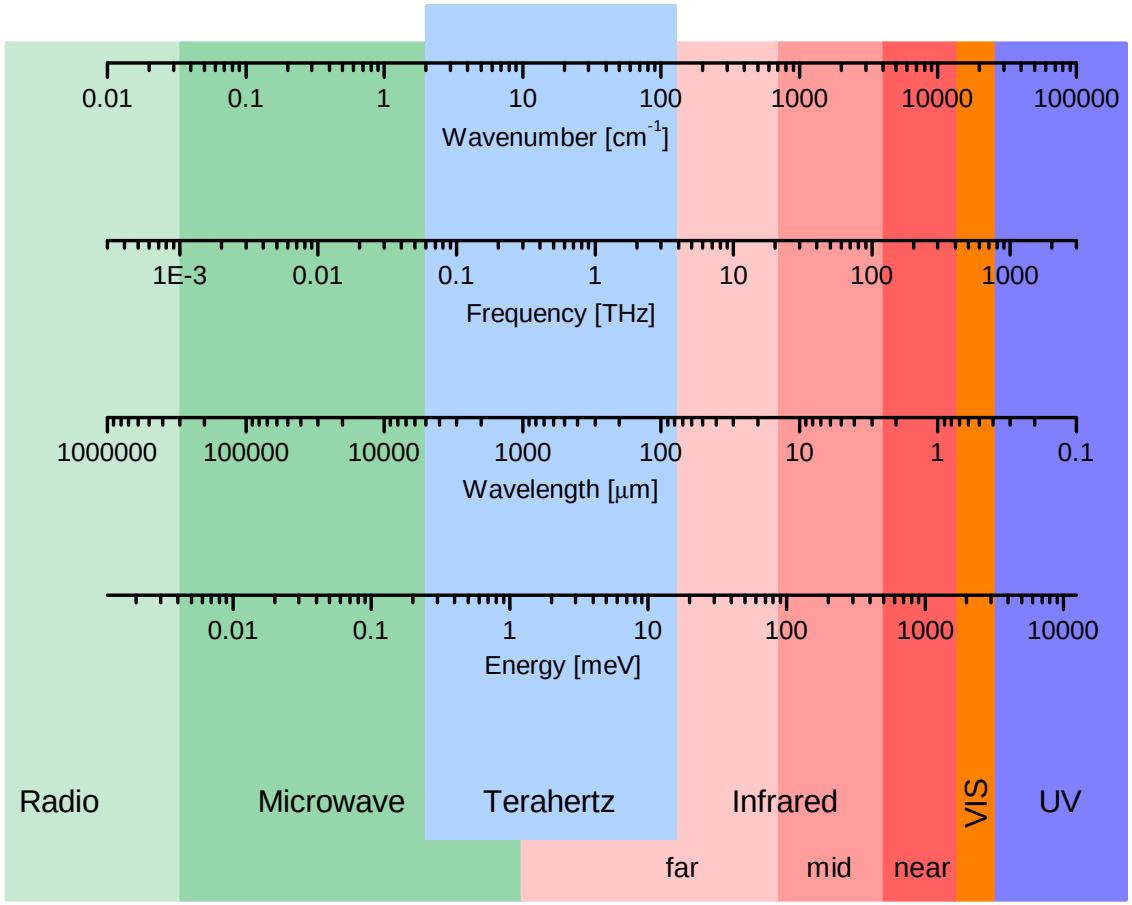
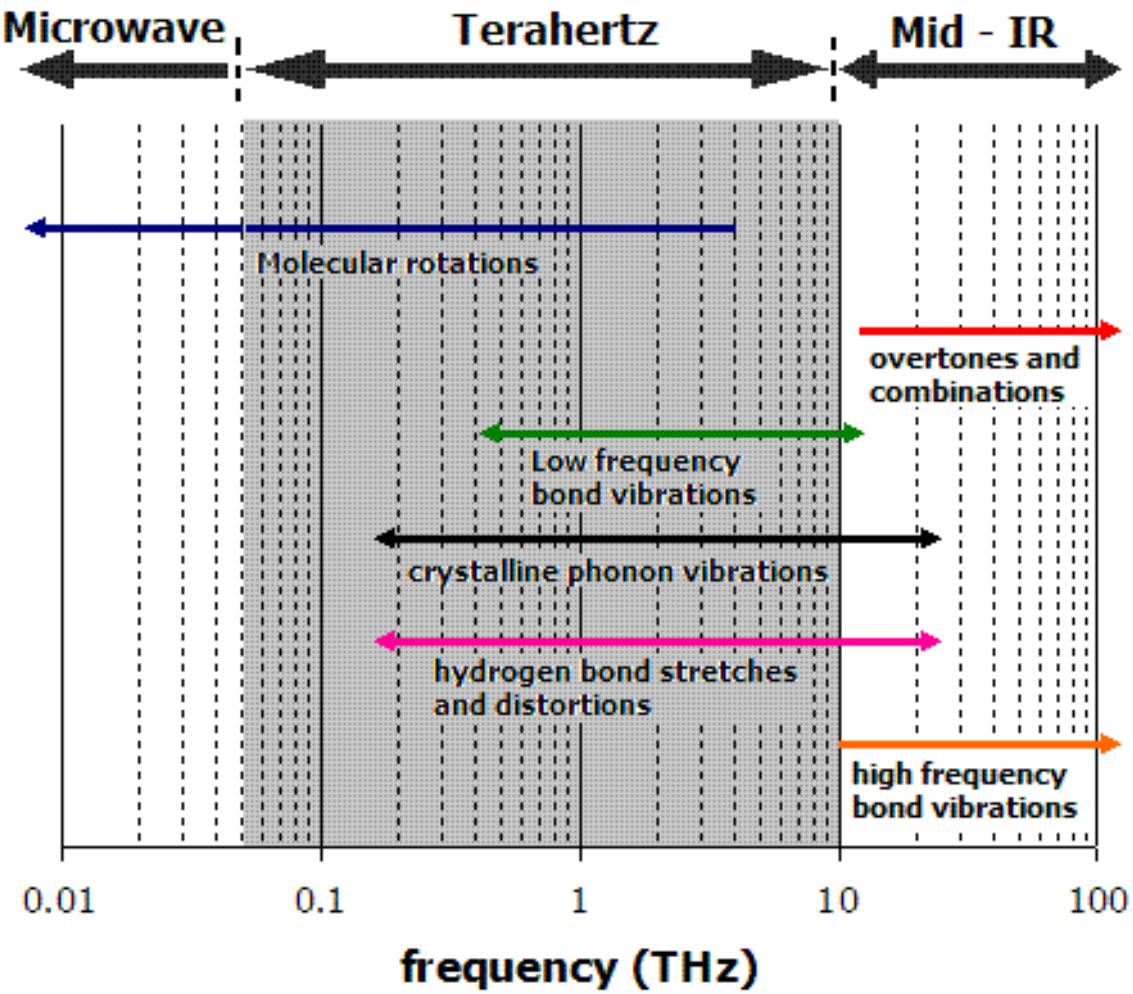
What is Terahertz Radiation?



Terahertz radiation – frequency regime adjacent to optical and electronic techniques

What is Terahertz Radiation?



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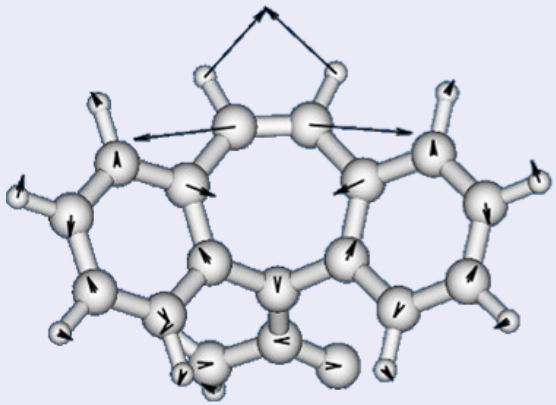
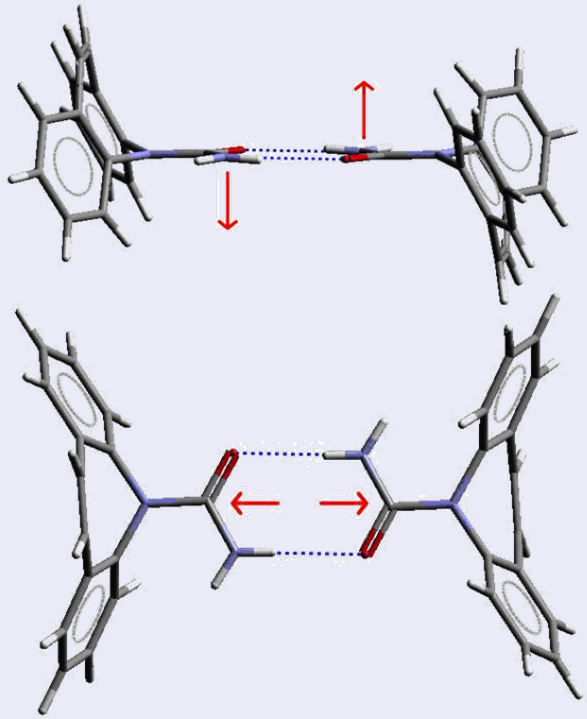
Inter- vs. intramolecular vibrations

Mid Infrared



Intramolecular modes

Terahertz



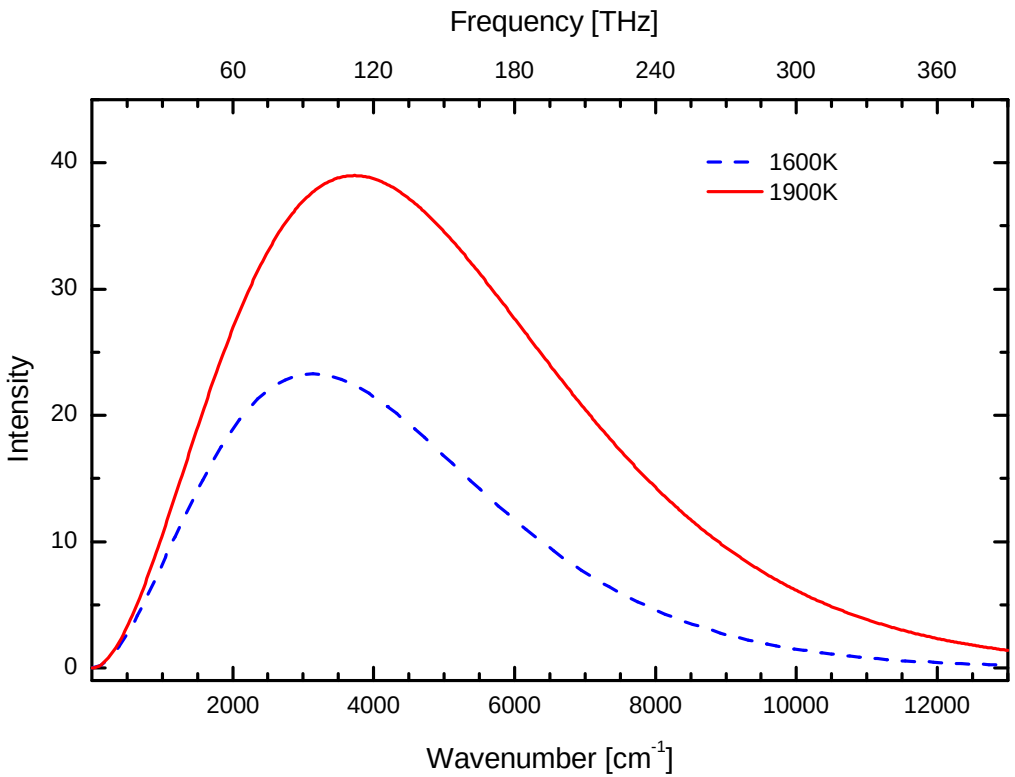
Intermolecular modes

THz Radiation

Characteristics

- 2 to 133 cm^{-1} / 60 GHz to 4 THz, μW output power – intrinsically safe
- Probes vibrational modes that extend across large domains of the lattice in organic molecular crystals
- Most polymeric materials are (semi-)transparent in this frequency range
- Ultrashort pulsed radiation readily available
- Coherent detection scheme using detectors operating at room temperature
- Measurement of the electric field rather than just its amplitude

Terahertz pulse



Radiation intensity from a blackbody radiation source

Limitations

- Very low intensity below 500 cm^{-1}
- Difficulties to distinguish thermal background from signal
- Cryogens needed to cool the detectors

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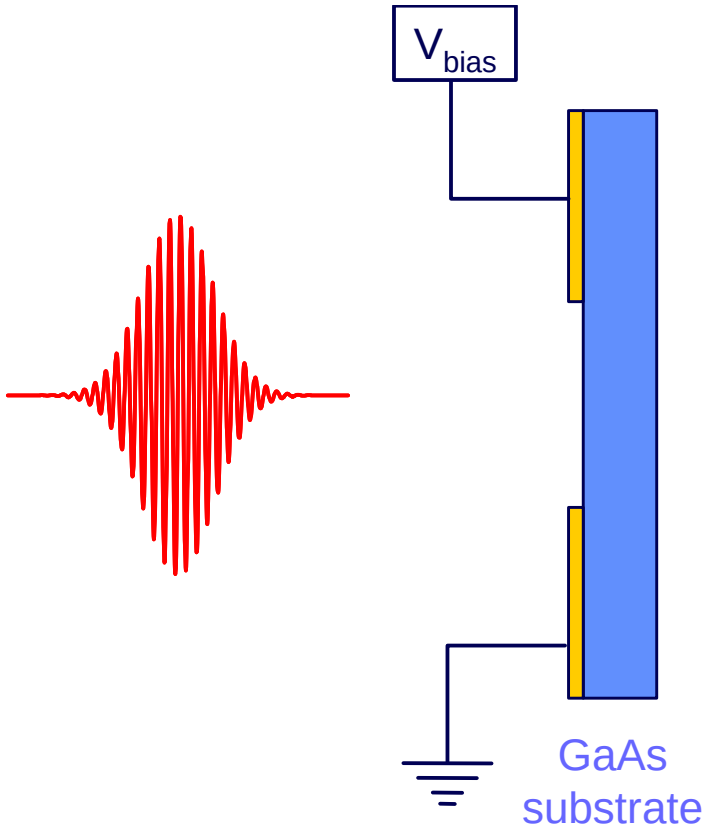
Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



Generation of Terahertz Pulses

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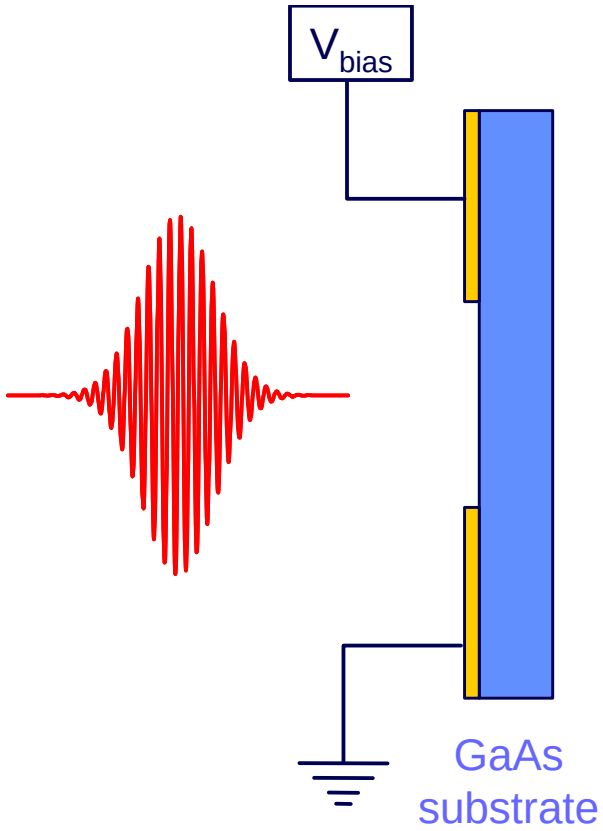
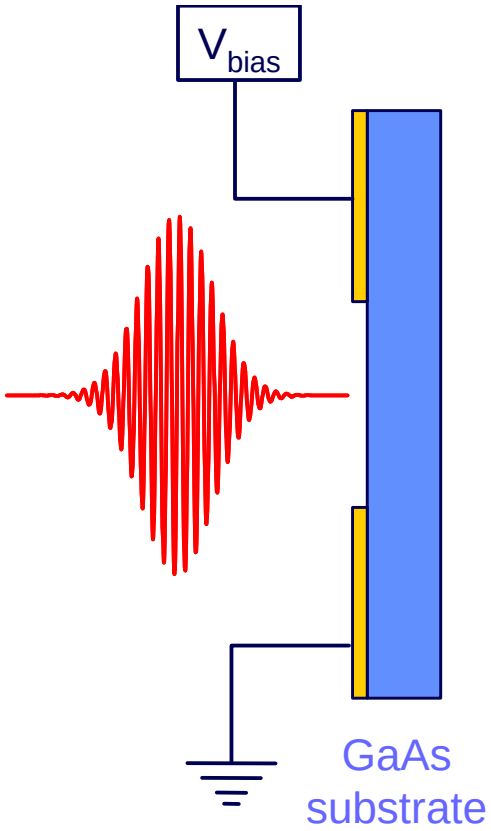


Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



Generation of Terahertz Pulses

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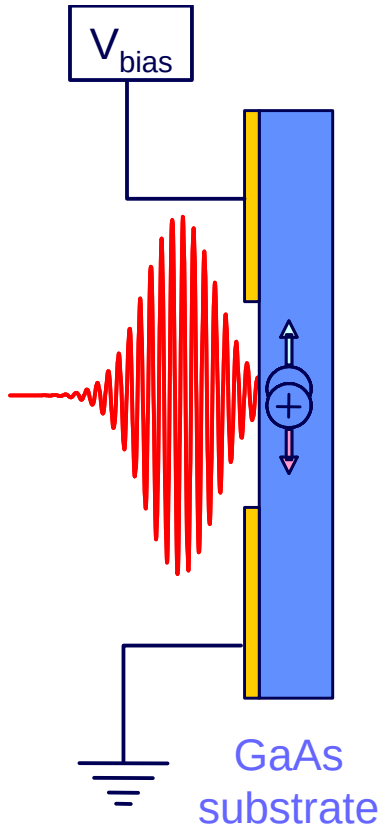

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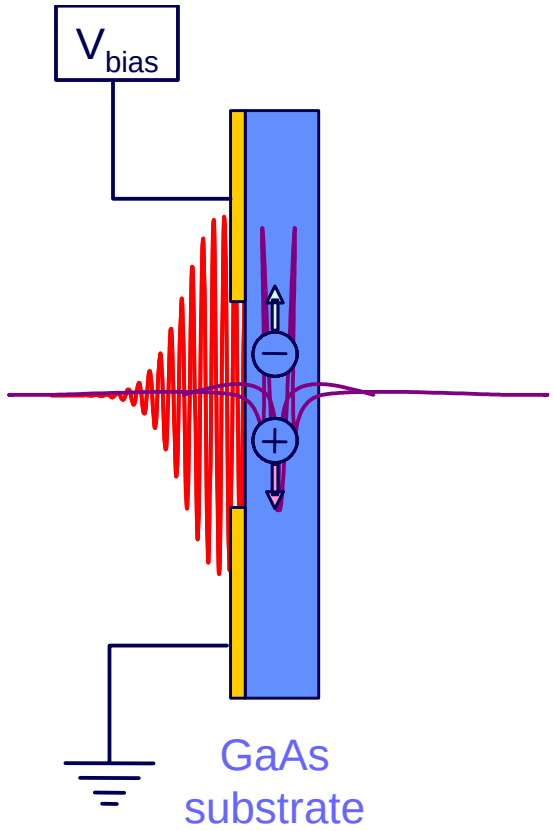
Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



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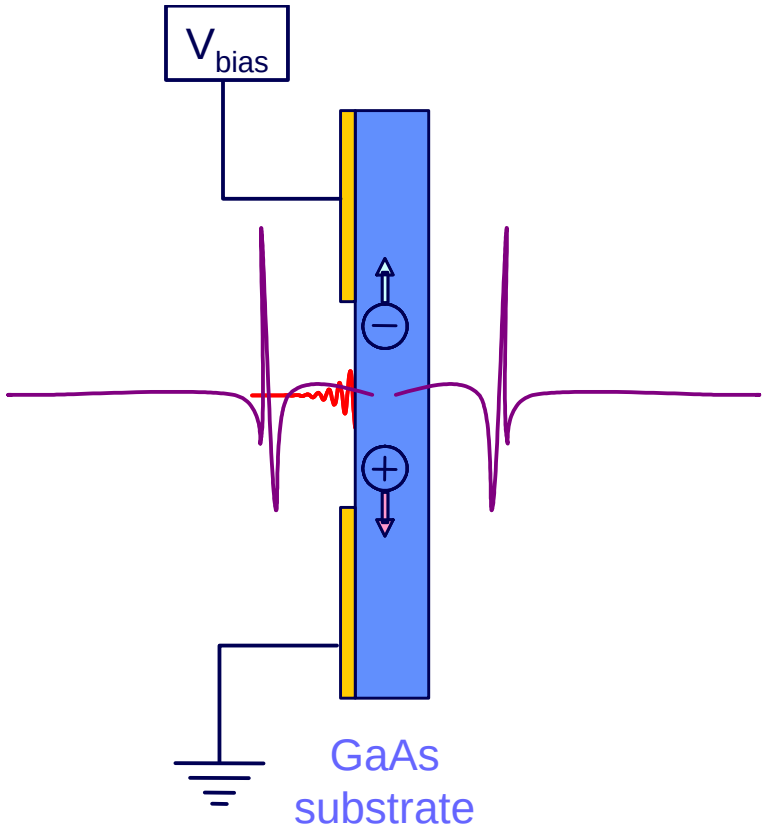
Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



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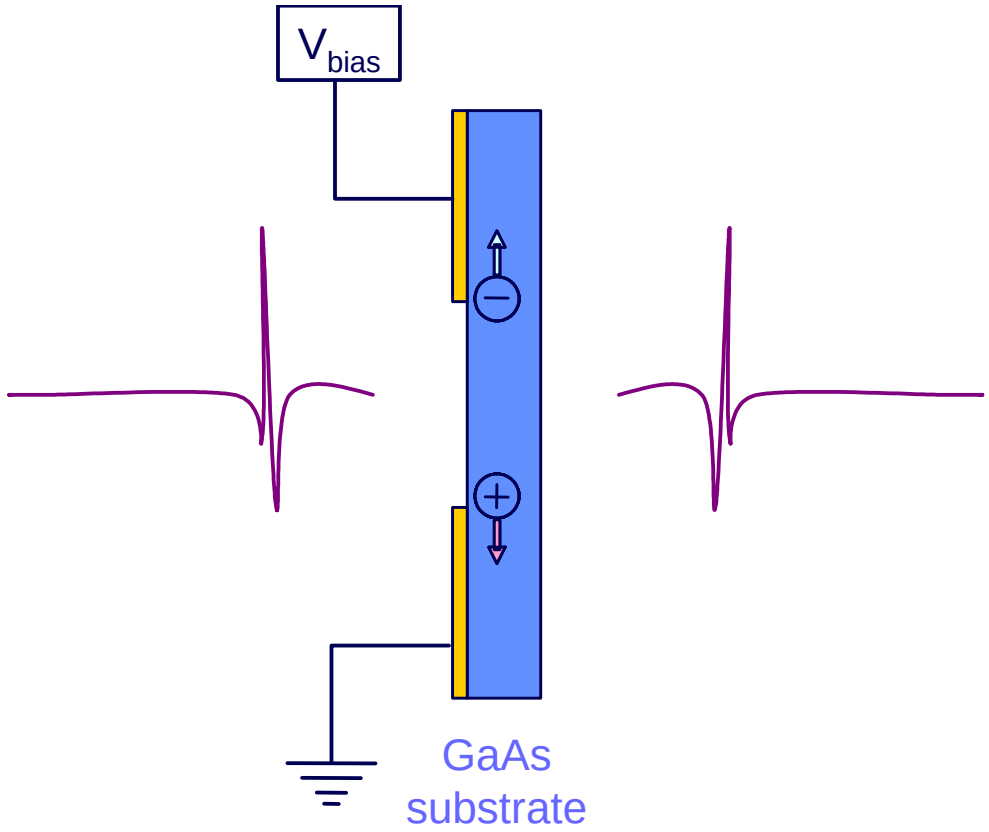
Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



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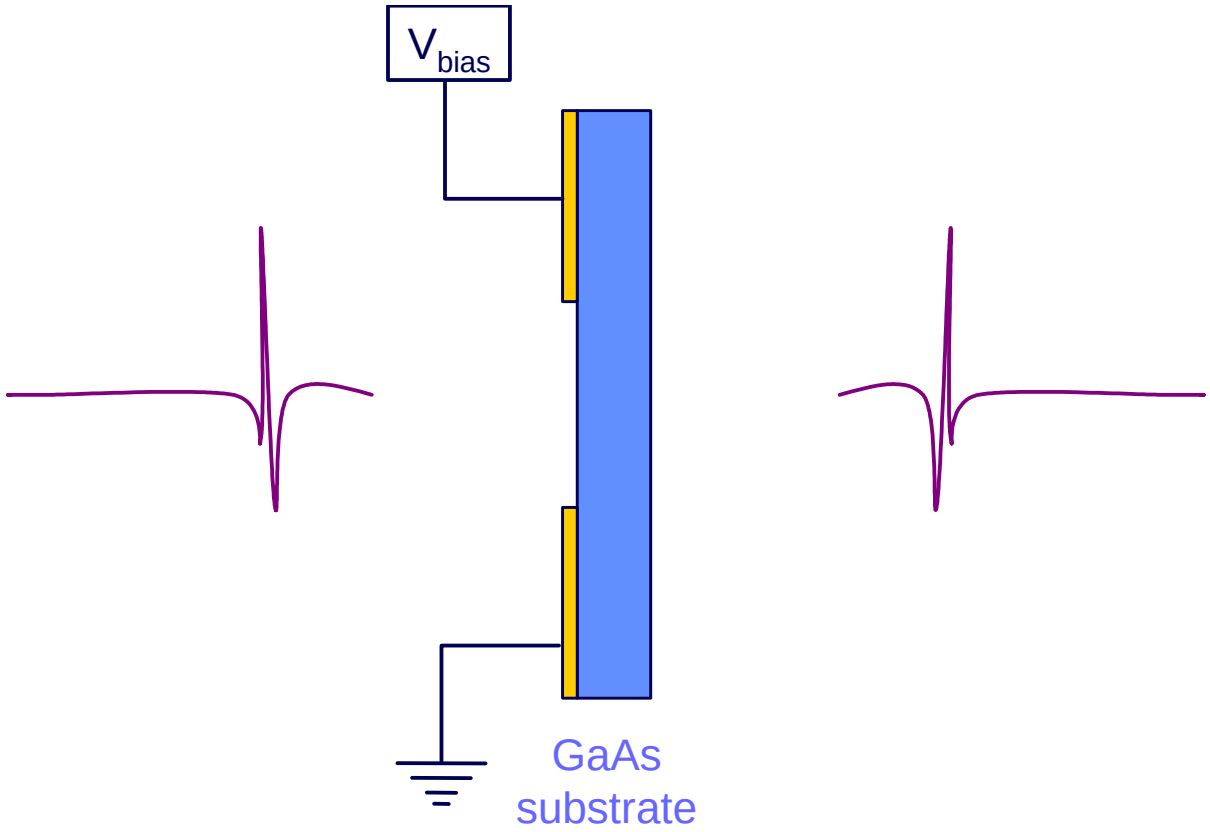
Generation of Terahertz Pulses

Pulsed coherent radiation from femtosecond switched photoconductive antennas



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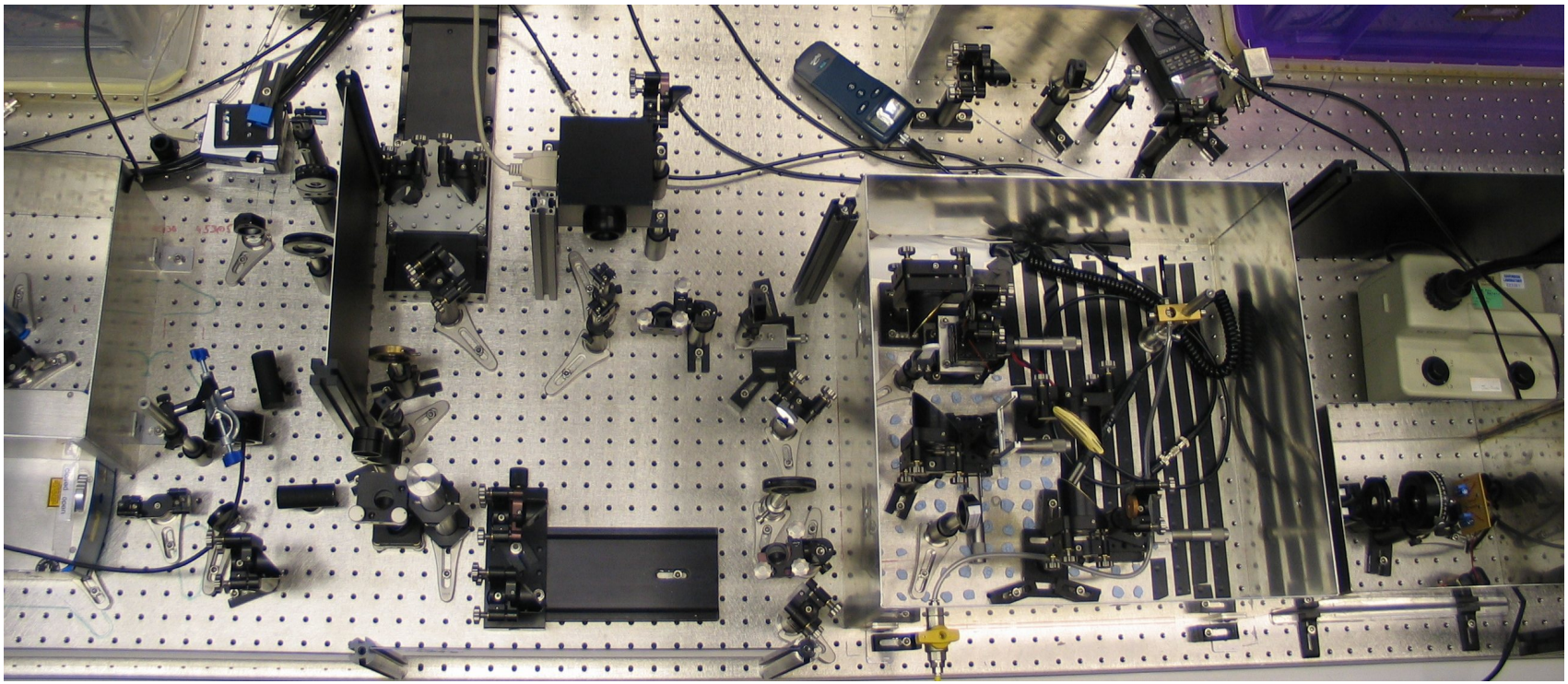
THz-TDS setup in our lab



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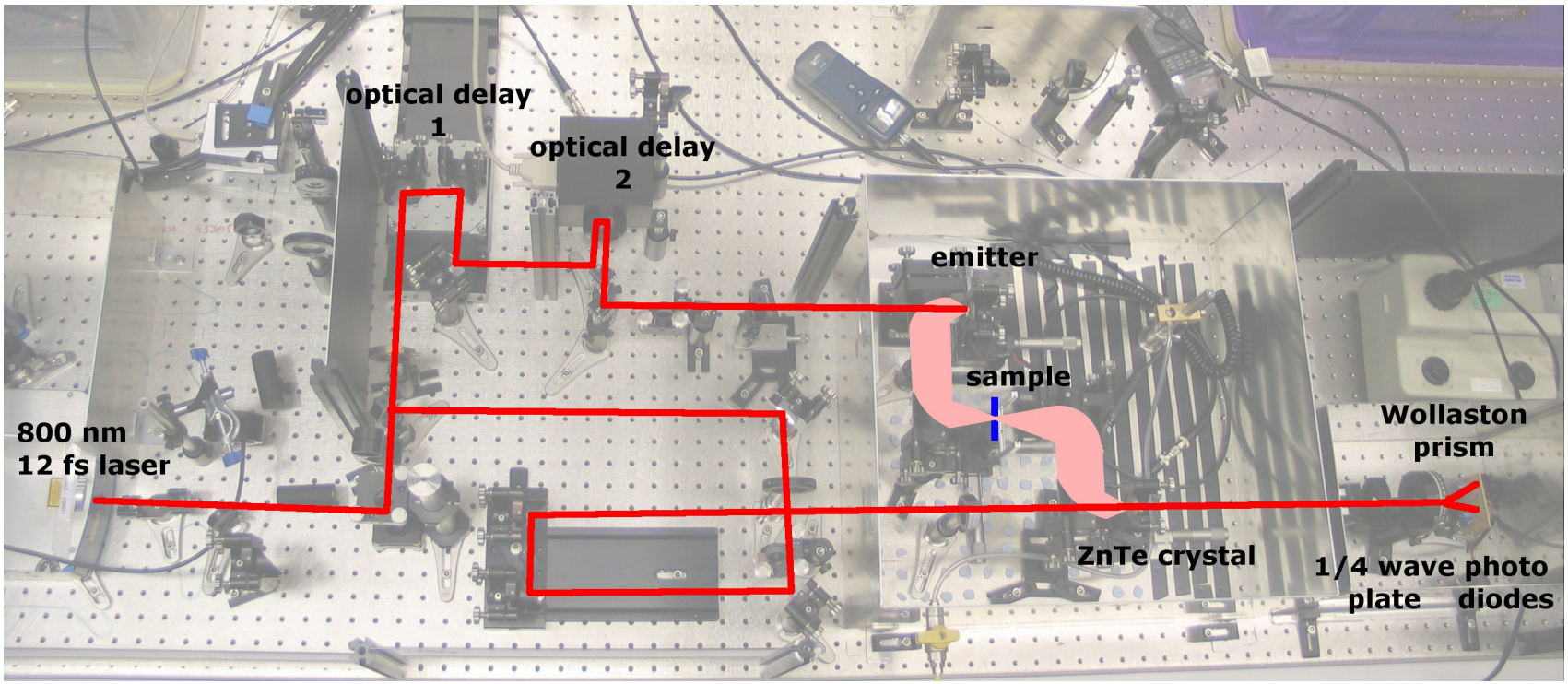

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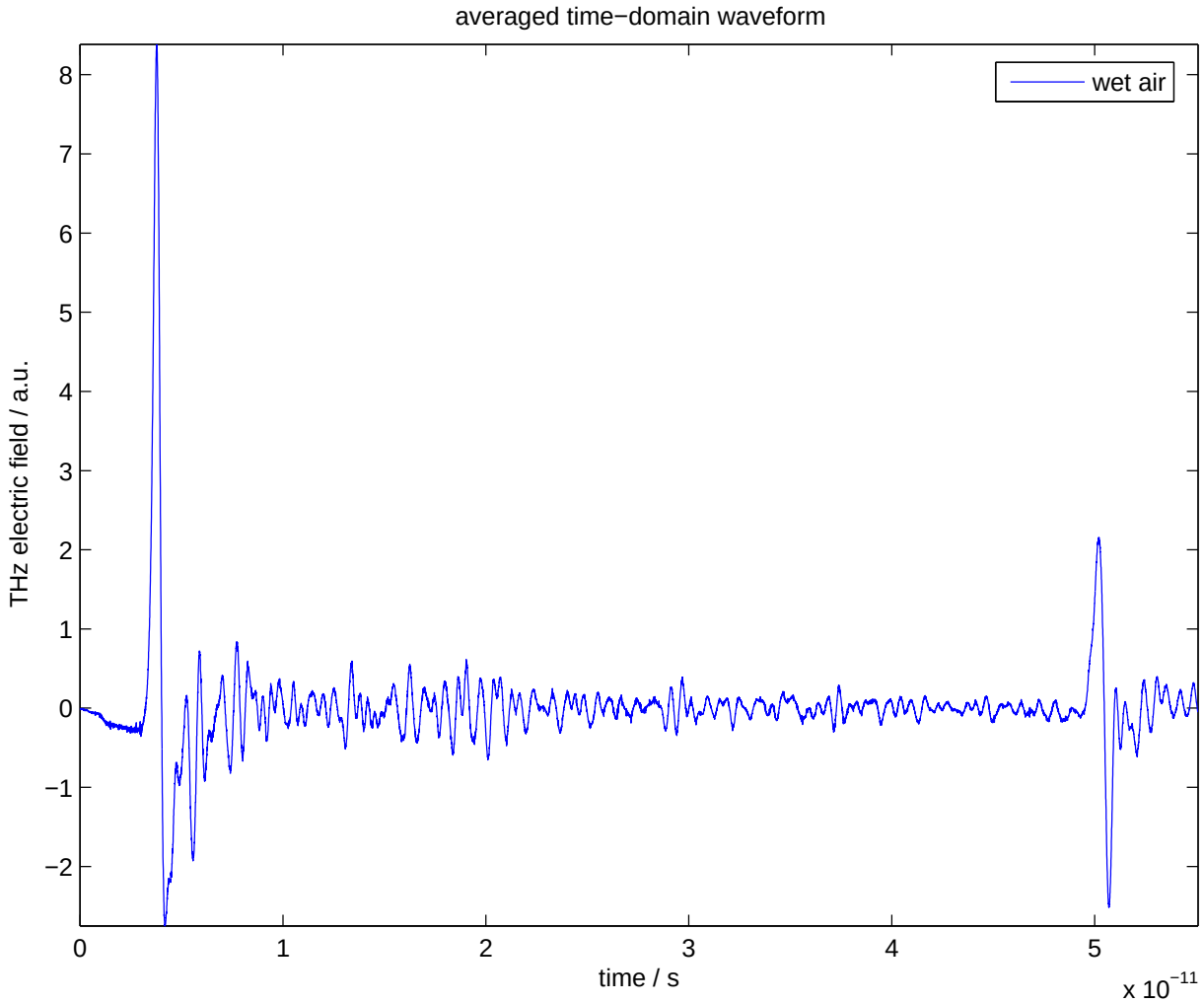
Terahertz pulse



Time-domain signal of the terahertz pulse from a LT-GaAs device surface emission detected by electro-optical sampling (0.5 mm ZnTe crystal)

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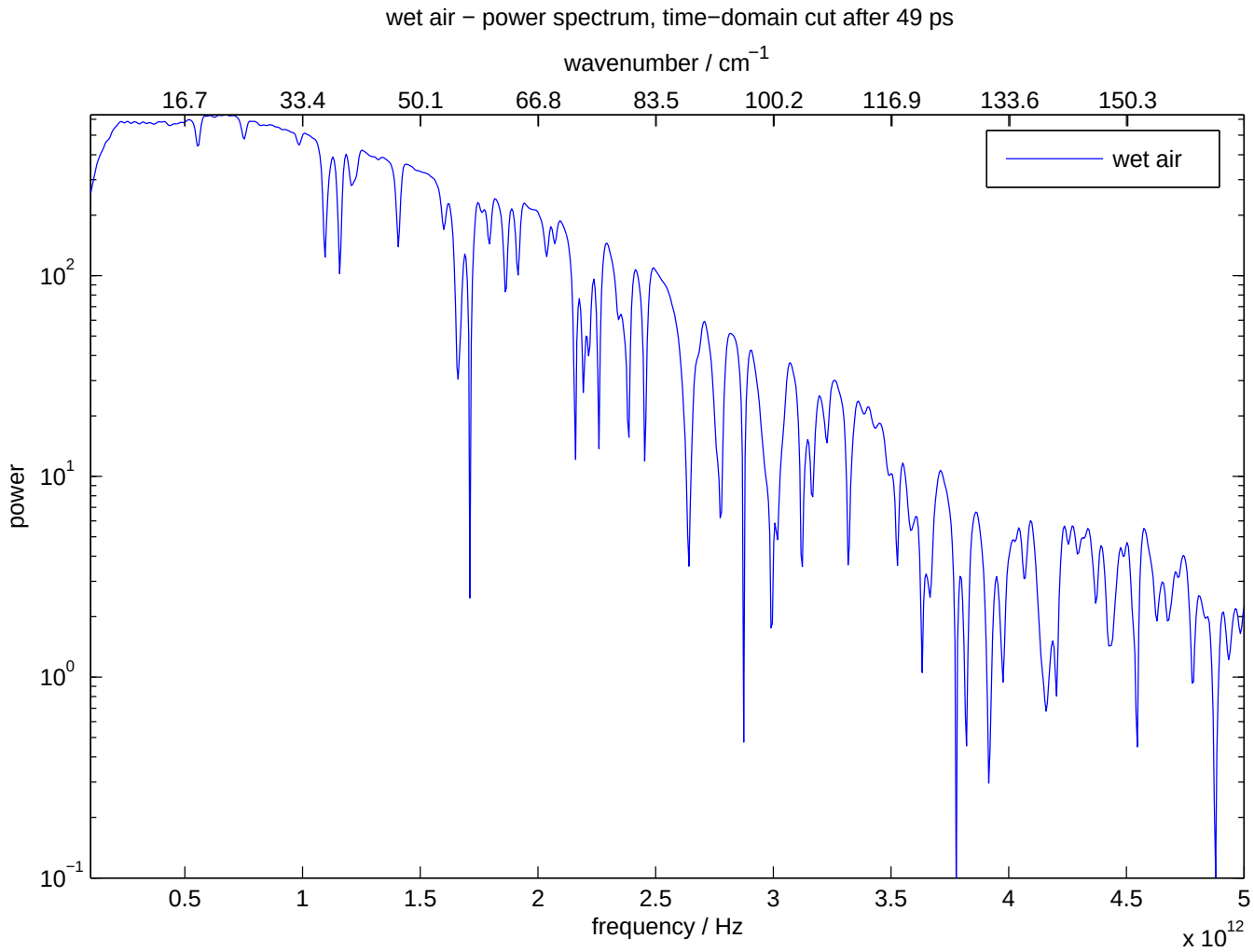
Photoconductive Antenna Bandwidth



Power spectrum of the pulse FFT

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Commercial THz-TDS setup

Commercial turn-key alternative (TeraView Ltd)

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Outline

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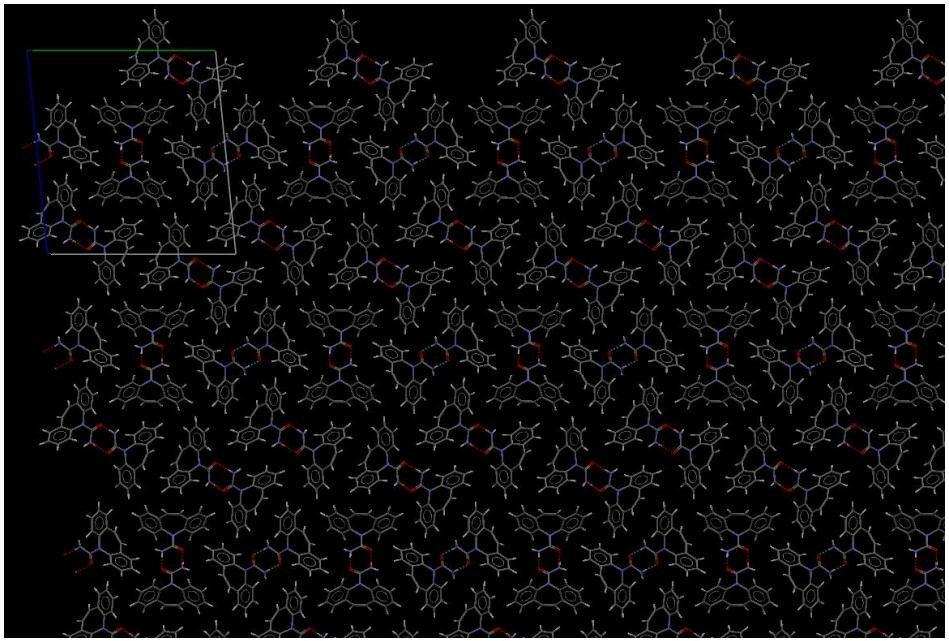
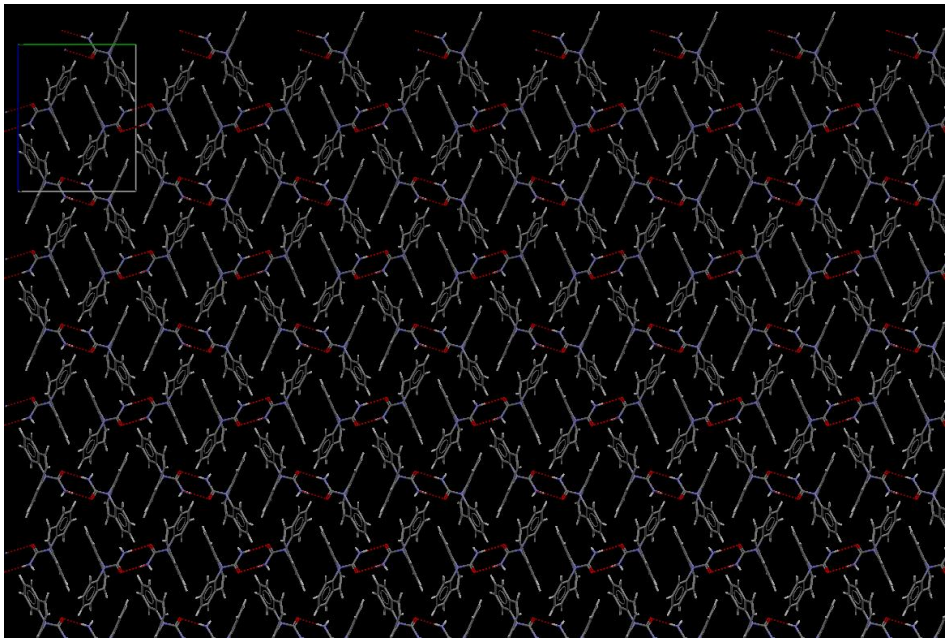
Polymorphism – Crystal Structure



Carbamazepine form I



Carbamazepine form III

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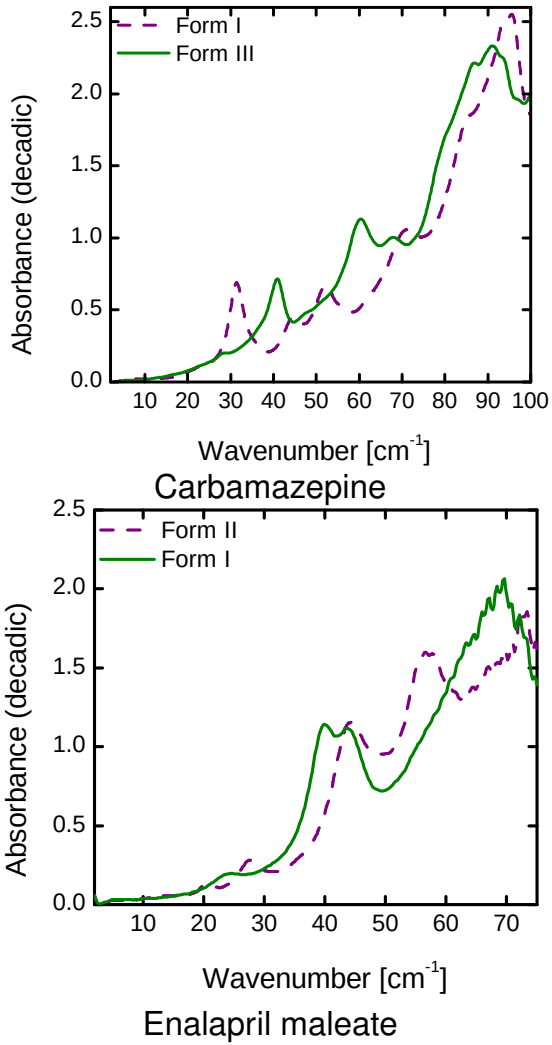
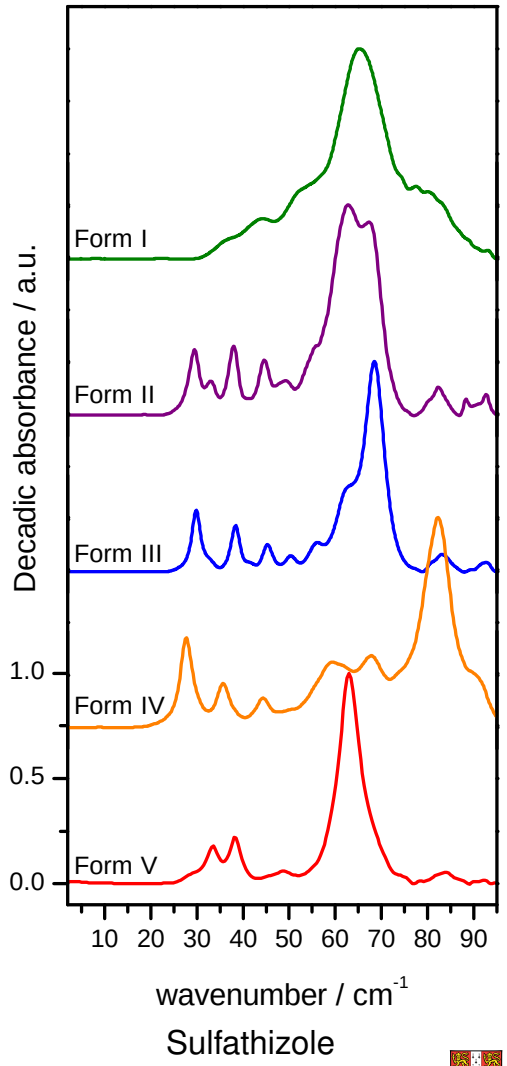
Polymorphs





C. J. Strachan *et al.*, Chem. Phys. Lett. 390, 20 (2004); J. A. Zeitler *et al.*, J. Pharm. Sci. 95, 2486 (2006).

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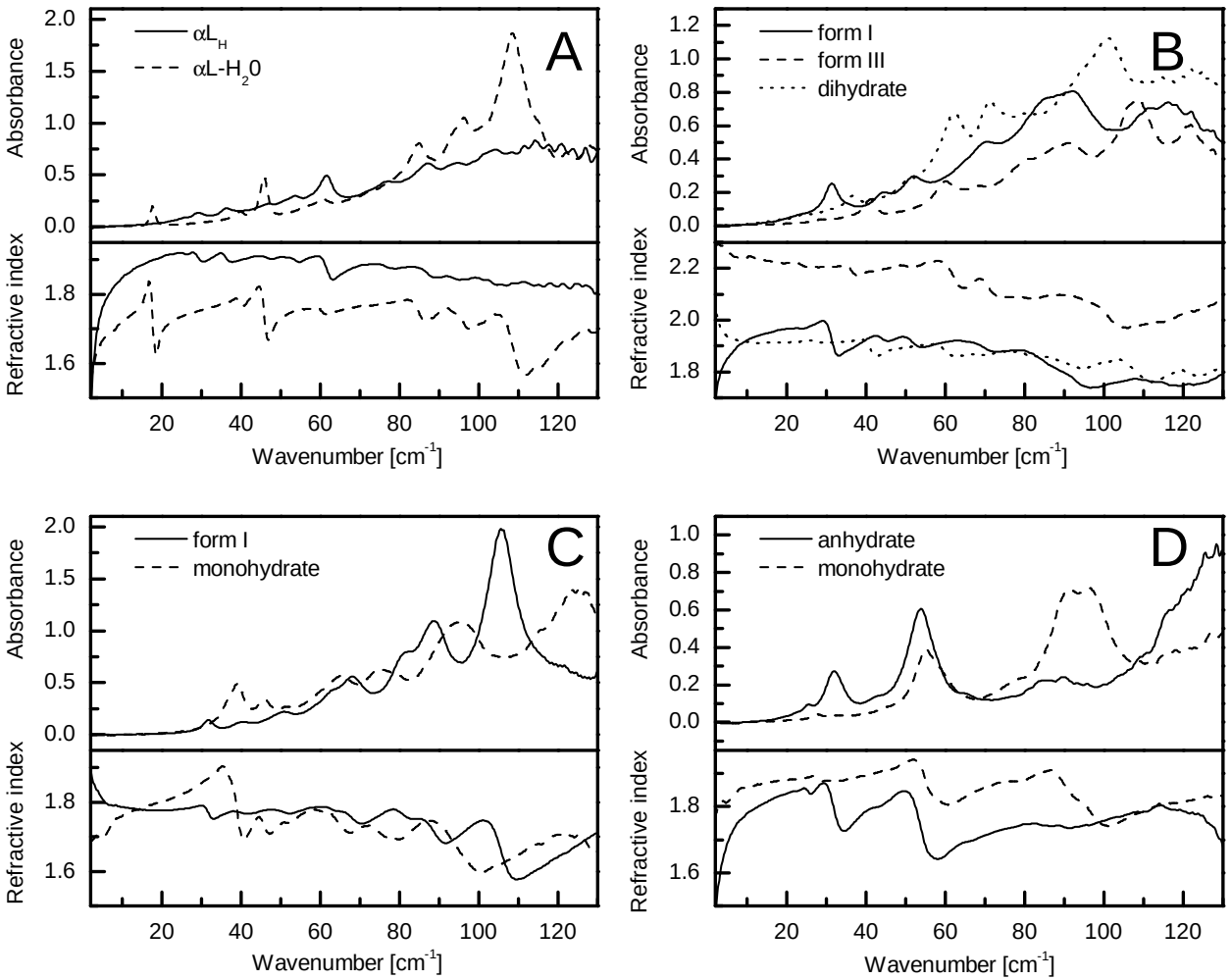
Hydrates



A) Lactose, B) carbamazepine, C) piroxicam and D) theophylline
J. A. Zeitler *et al.*, Int. J. Pharm. 334, 78 (2007).

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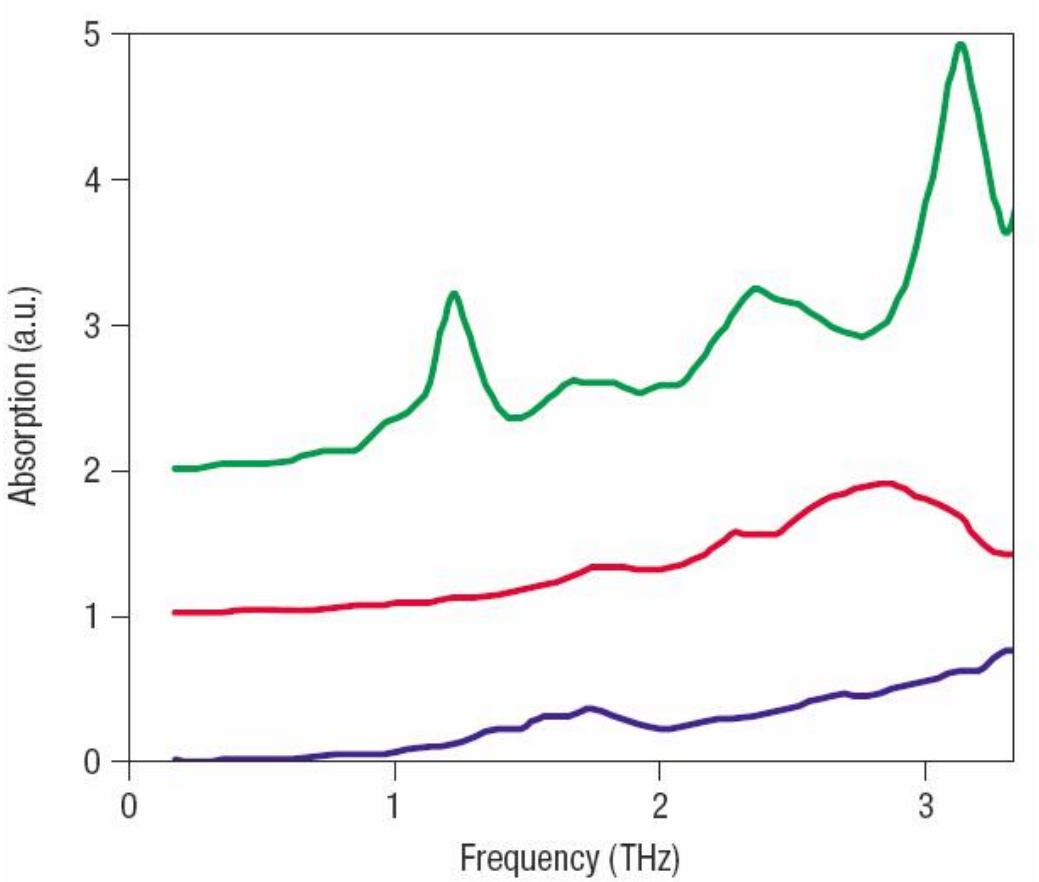
Cocrystals



The cocrystal constituents phenazine (blue), mesaconic acid (green) and the cocrystal (phen)·(mes)

K. L. Nguyen *et al.*, Nat Mater 6, 206 (2007).

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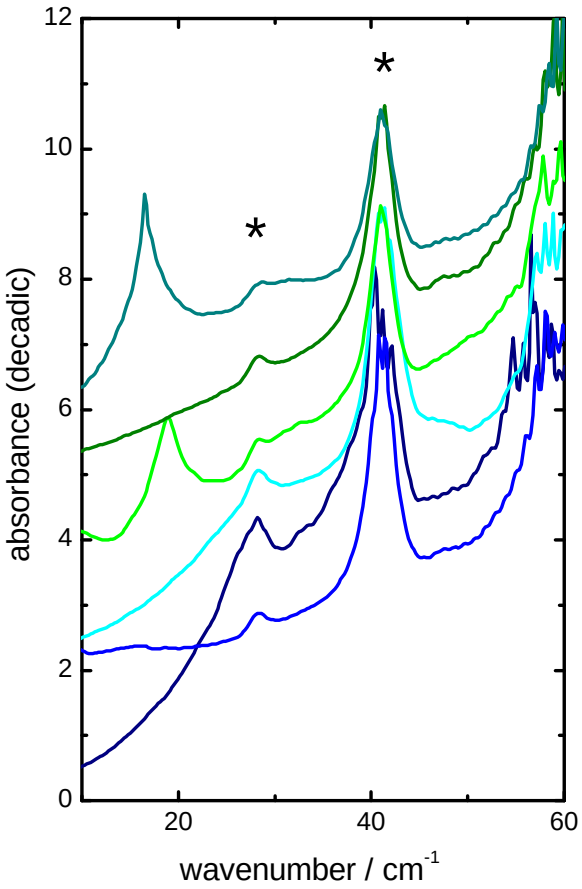
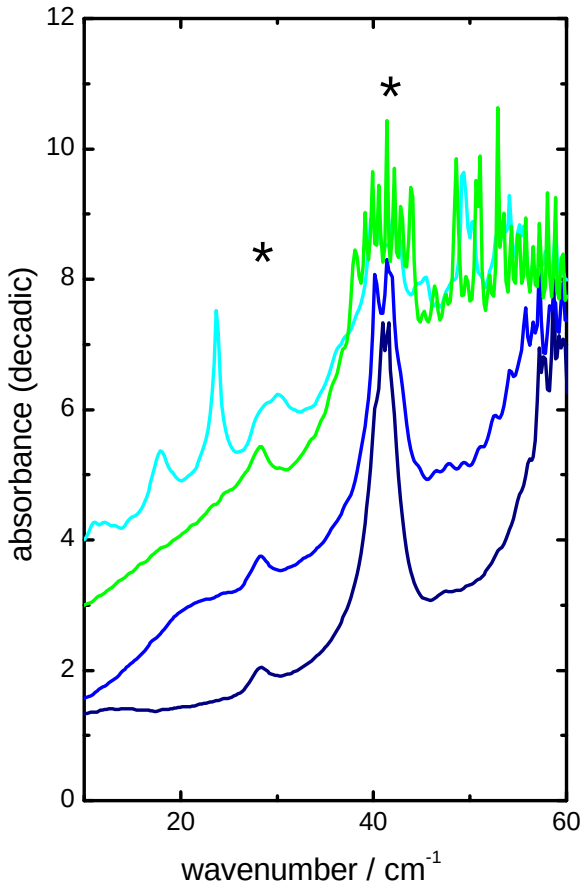
Commercial Tablets



Tablets containing 200 mg CBZ



Tablets containing 400 mg CBZ

J. A. Zeitler, T. Rades, and P. F. Taday, in THz Spectroscopy: principles and applications, edited by S. L. Dexheimer (Taylor & Francis, New York, 2007 in press), pp. 299.

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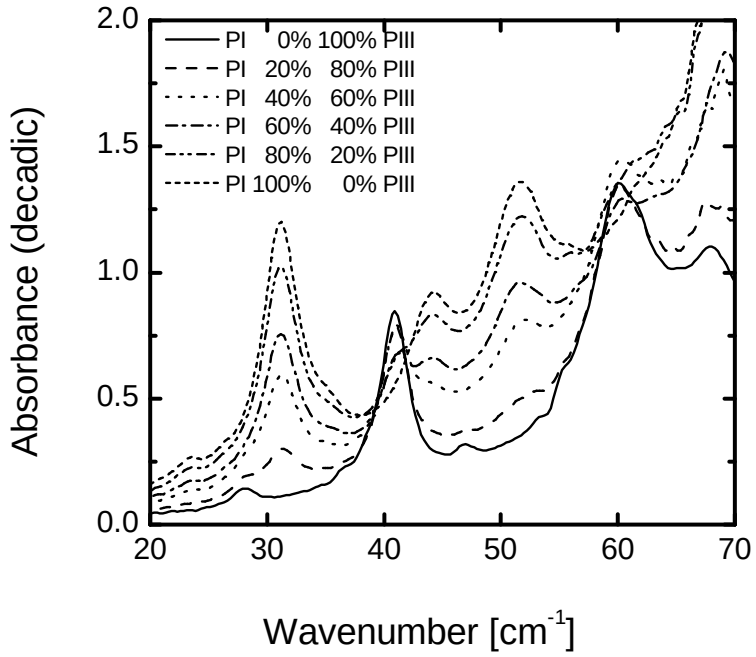
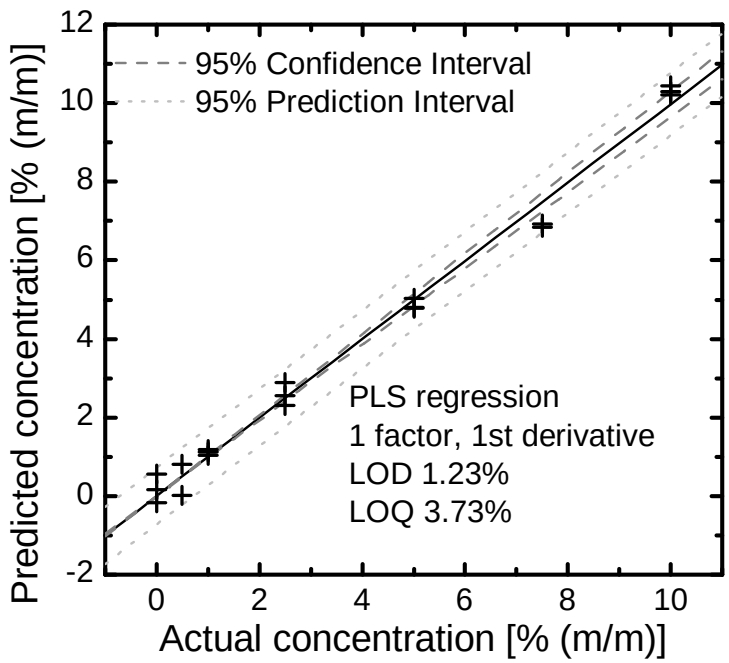
Polymorphic Mixtures





Physical mixture of carbamazepine form I and III

C. J. Strachan et al., J. Pharm. Sci. 94, 837 (2005).

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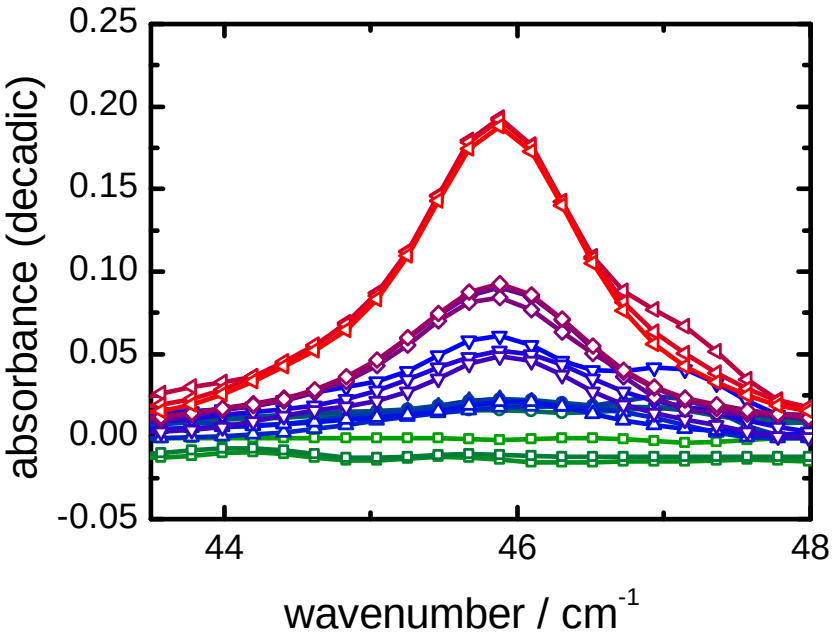
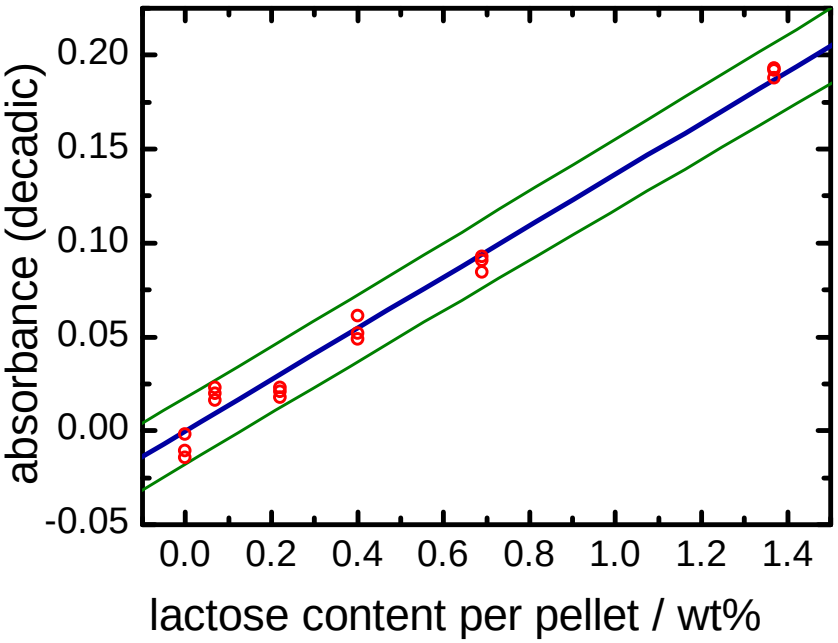
Detection of Crystalline Materials



Absorption feature of lactose α-monohydrate for pellets containing a 0 to 5 mg sample material



Linear fit of the absorbance reading against the amount of lactose α-monohydrate

J. A. Zeitler, T. Rades, and P. F. Taday, in THz Spectroscopy: principles and applications, edited by S. L. Dexheimer (Taylor & Francis, New York, 2007 in press), pp. 299.

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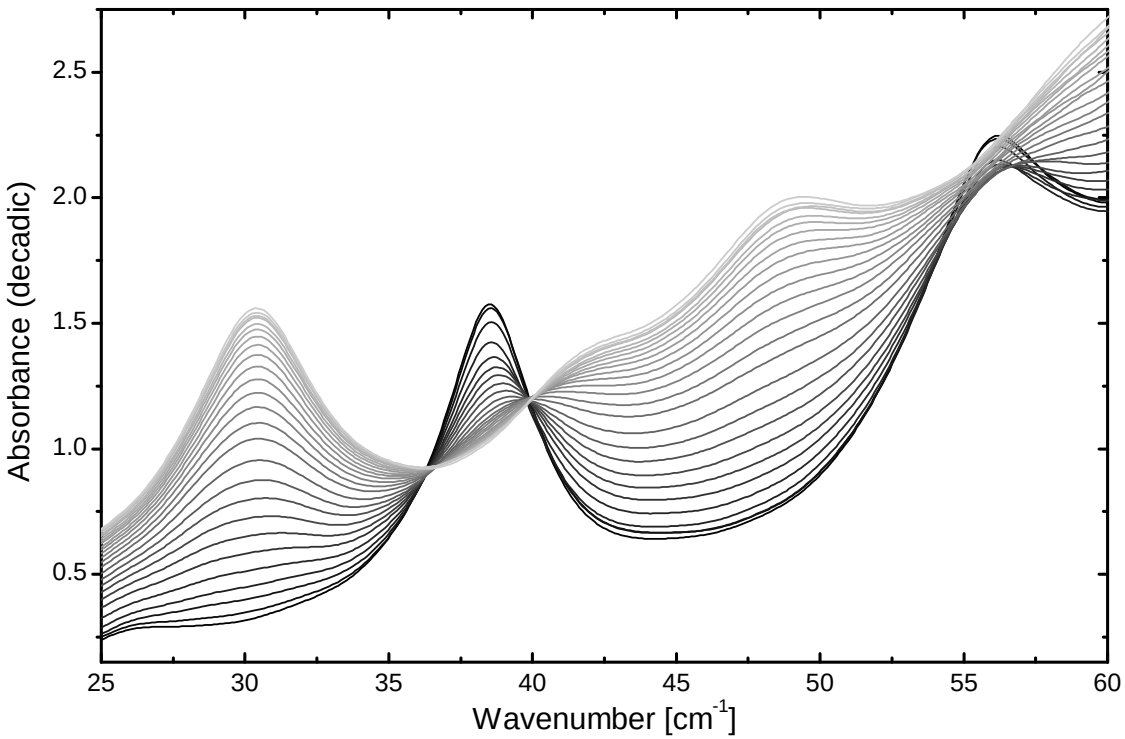
Polymorph Conversion - *in situ* Spectra



Conversion of carbamazepine form III to I at 433 K

J. A. Zeitler et al., Thermochim. Acta 436, 71 (2005).

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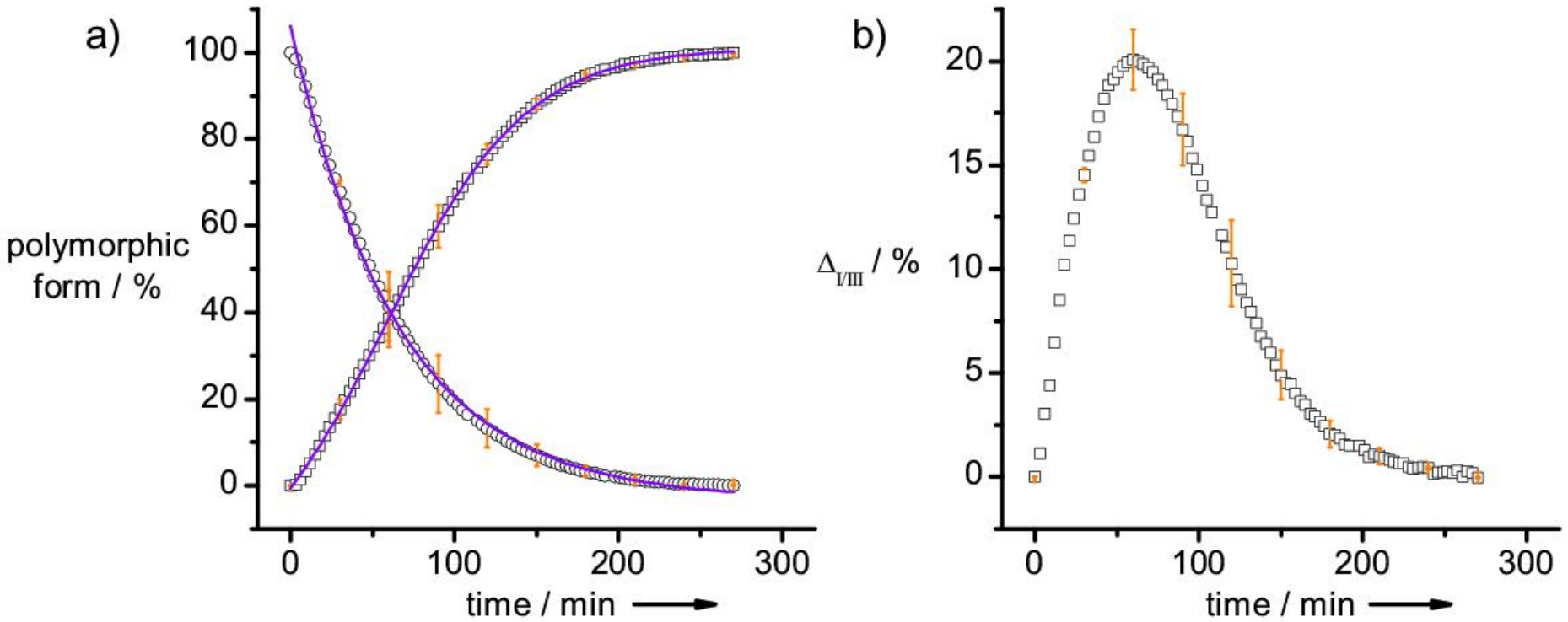
Polymorph Conversion - Kinetics



Kinetics of solid state conversion (carbamazepine form III to I at 433 K)
Mechanism was found to occur via the gas phase

J. A. Zeitler et al., ChemPhysChem 8, 1924 (2007).

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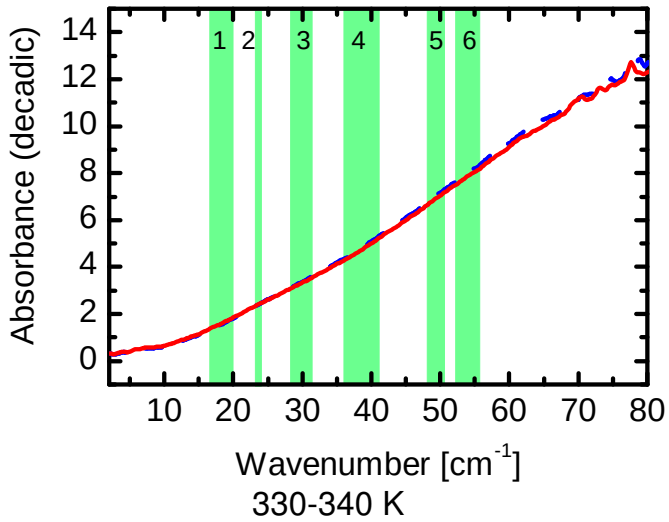
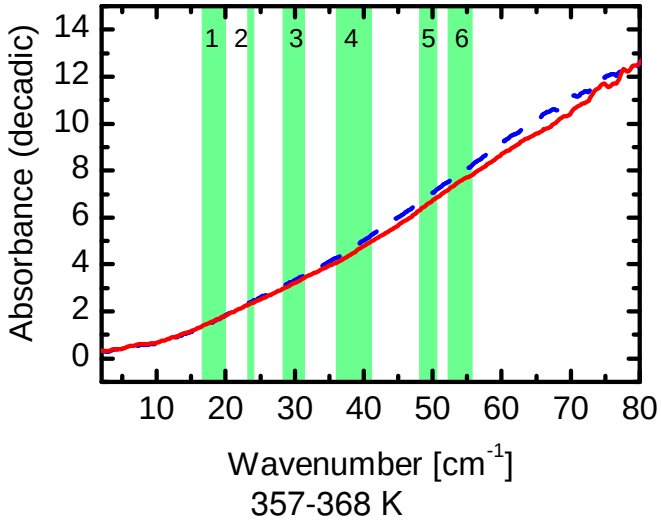
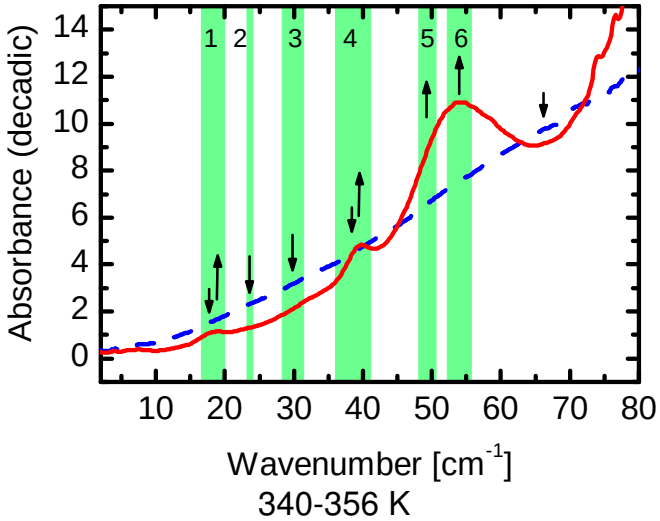
Relaxation and Crystallisation of Amorphous Materials



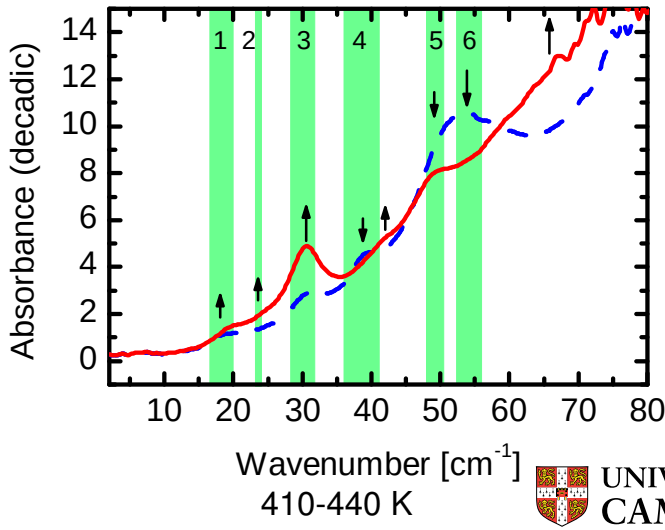
330-340 K



357-368 K



340-356 K



410-440 K

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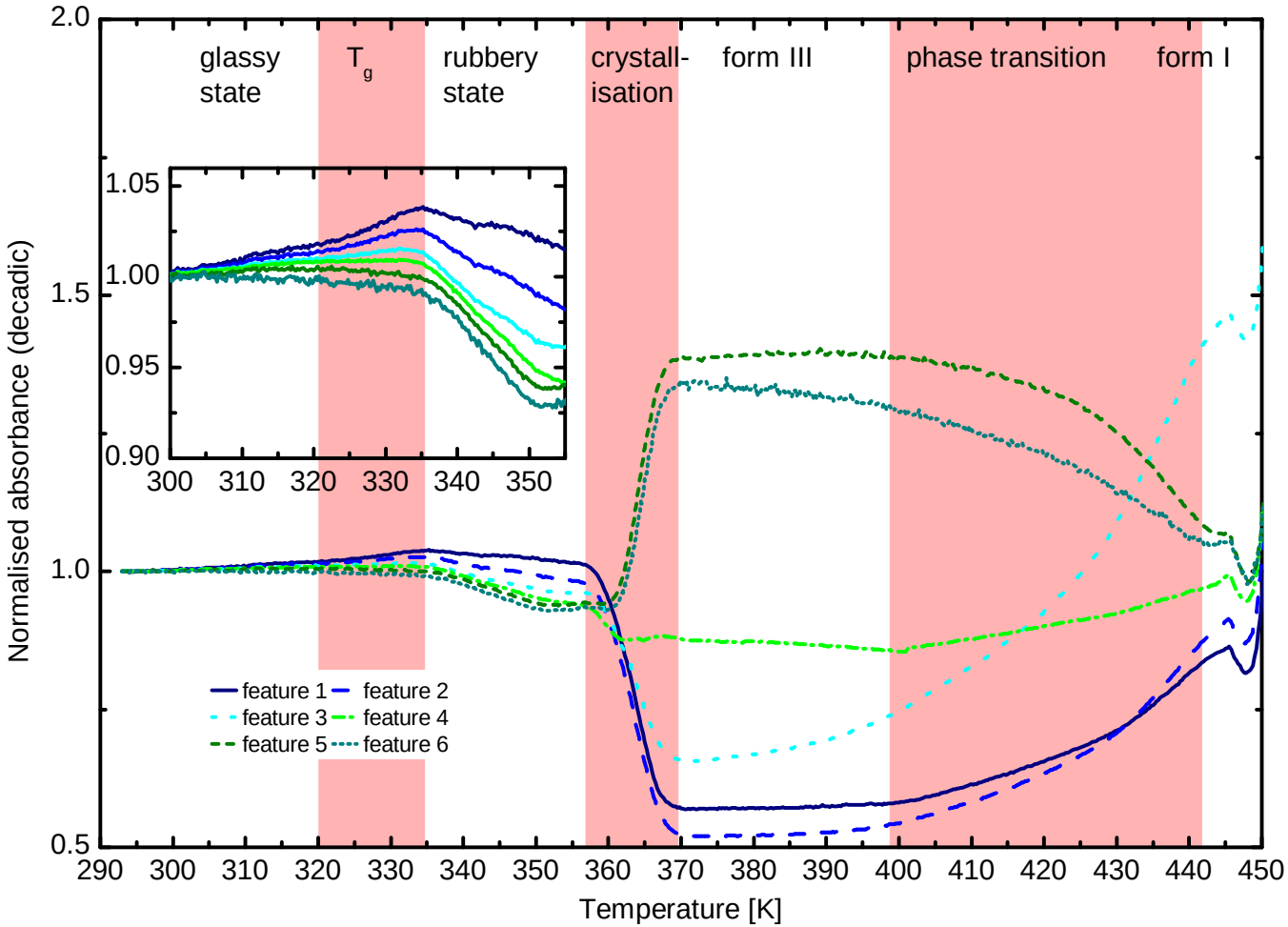
Change in Absorbance



J. A. Zeitler et al., J. Pharm. Sci. 96, 2703 (2007).

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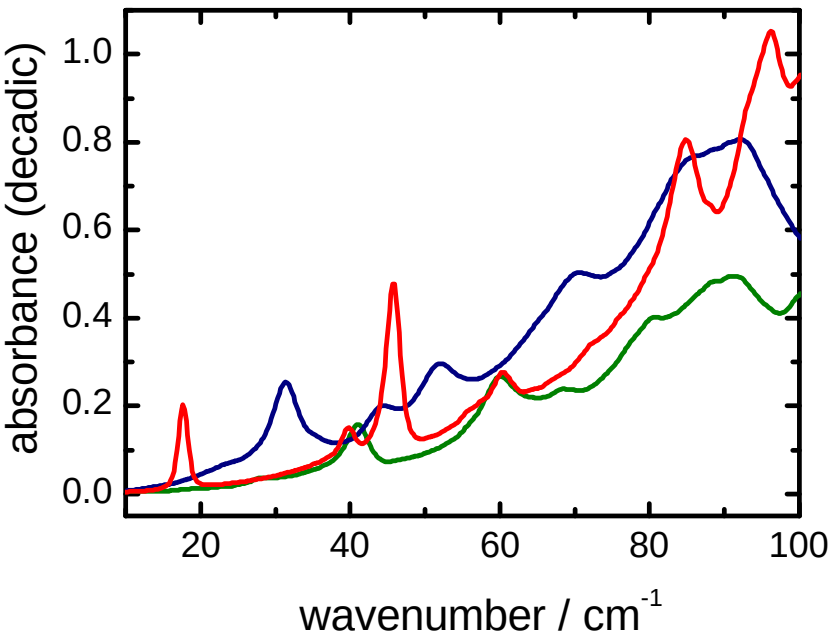
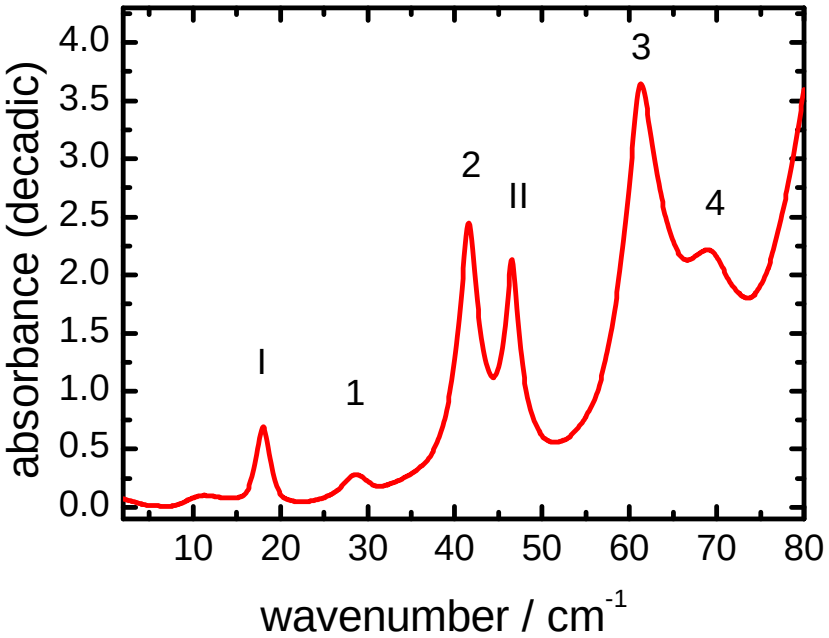
Direct Compressed Tablet – Constituents



Spectrum of lactose α-monohydrate (red), carbamazepine form III (green) and form I (blue)



Terahertz spectrum of the tablet – Roman numbers refer to spectral features of the lactose α-monohydrate and Arabic numbers refer to spectral features of carbamazepine form III

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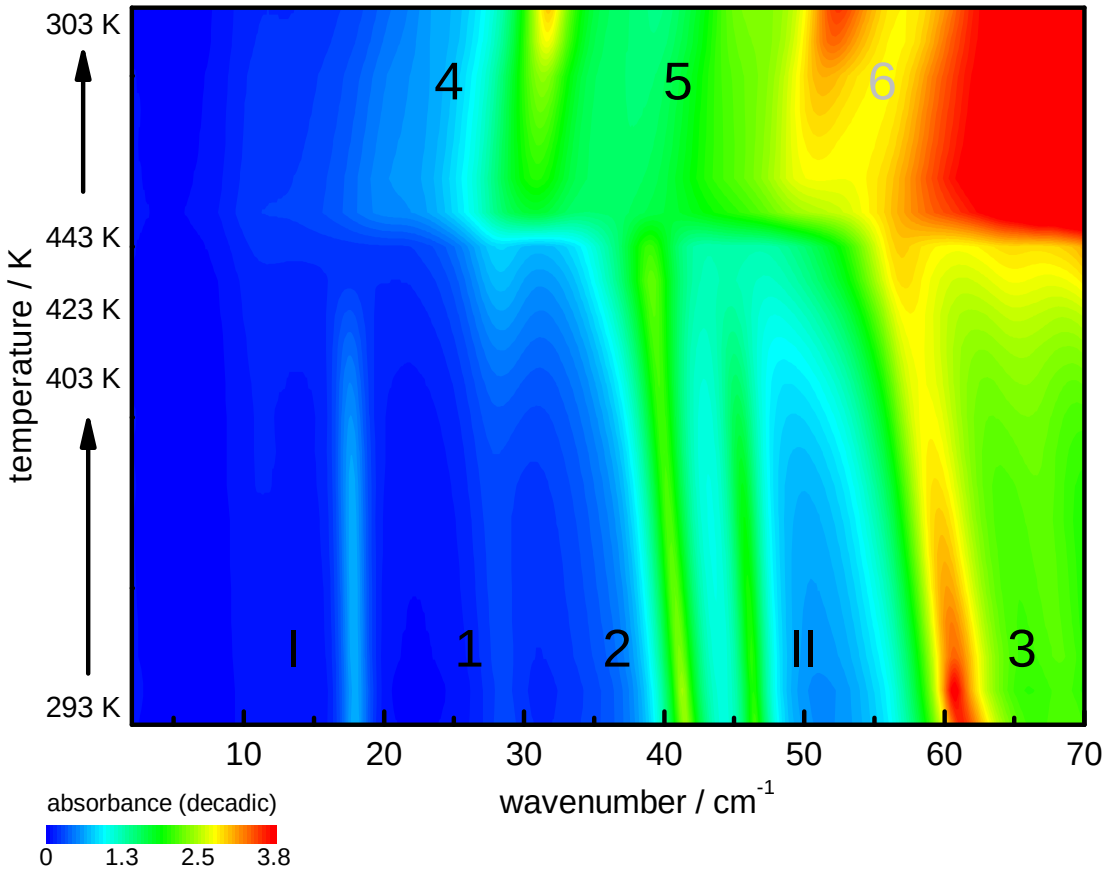
Direct Compressed Tablet – Phase Transition



Contour plot of the transmission terahertz spectra acquired during heating of a 200 mg carbamazepine tablet

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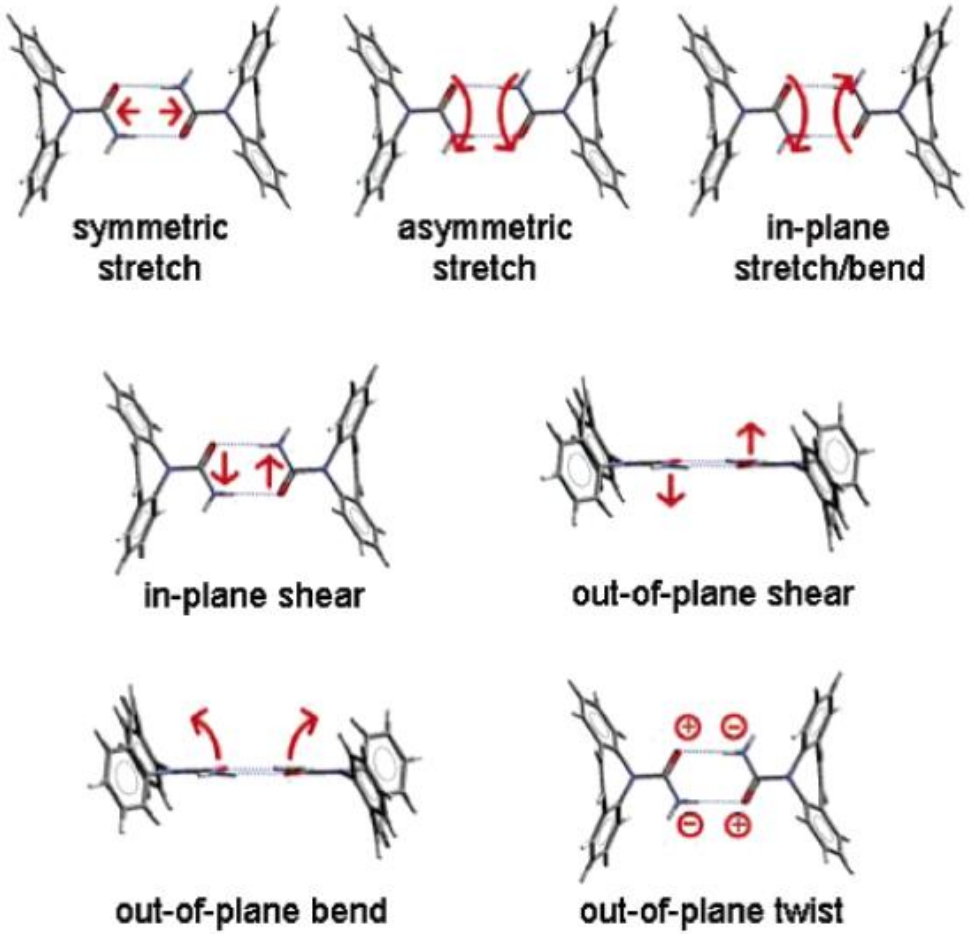
Intermolecular Interactions



Possible rigid molecule distortions and descriptors of the carbamazepine dimers

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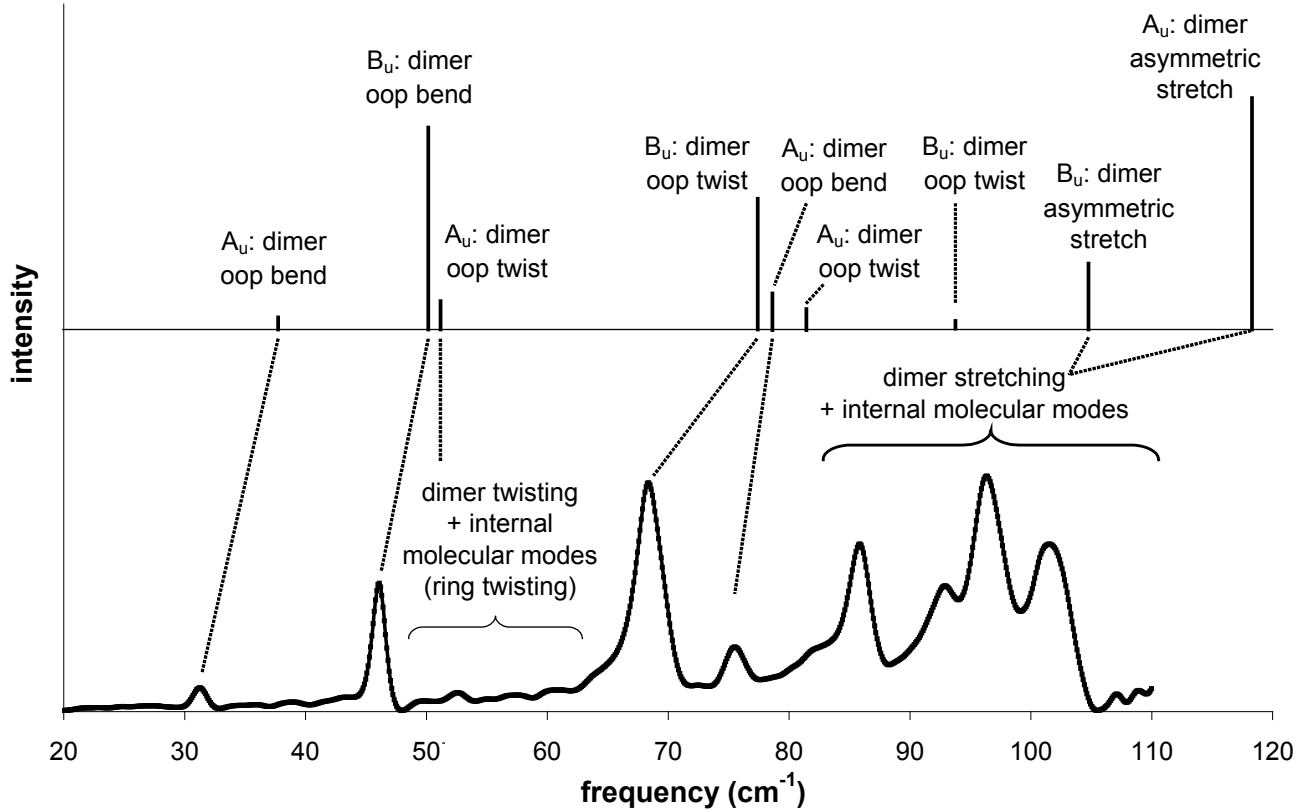
Tentative Assignments in CBZ



Calculations were performed using a computationally cheap force-field approach

G. M. Day et al., J. Phys. Chem. B 110, 447 (2006).

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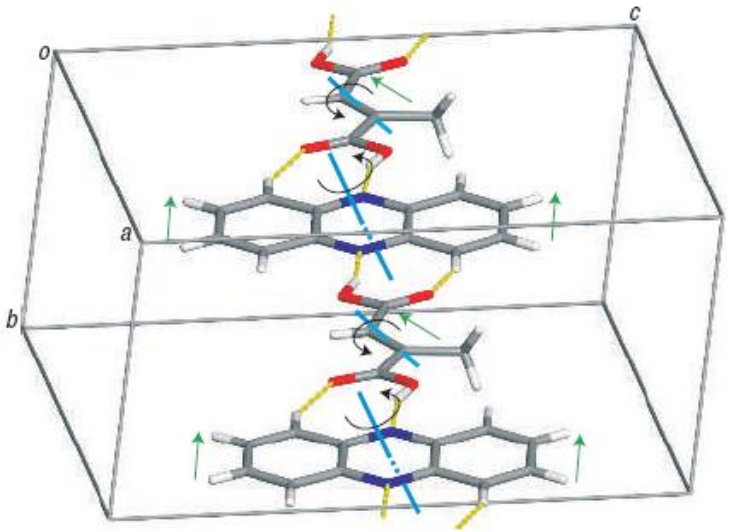
Tentative Assignments in Cocrystals



Distortion of the hydrogen-bonded chain leading to an absorption peak at 1.2 THz. The feature is a combination of wagging motions of the components in each chain (the chains propagate parallel to the crystallographic 110 direction)

K. L. Nguyen *et al.*, Nat Mater 6, 206 (2007).

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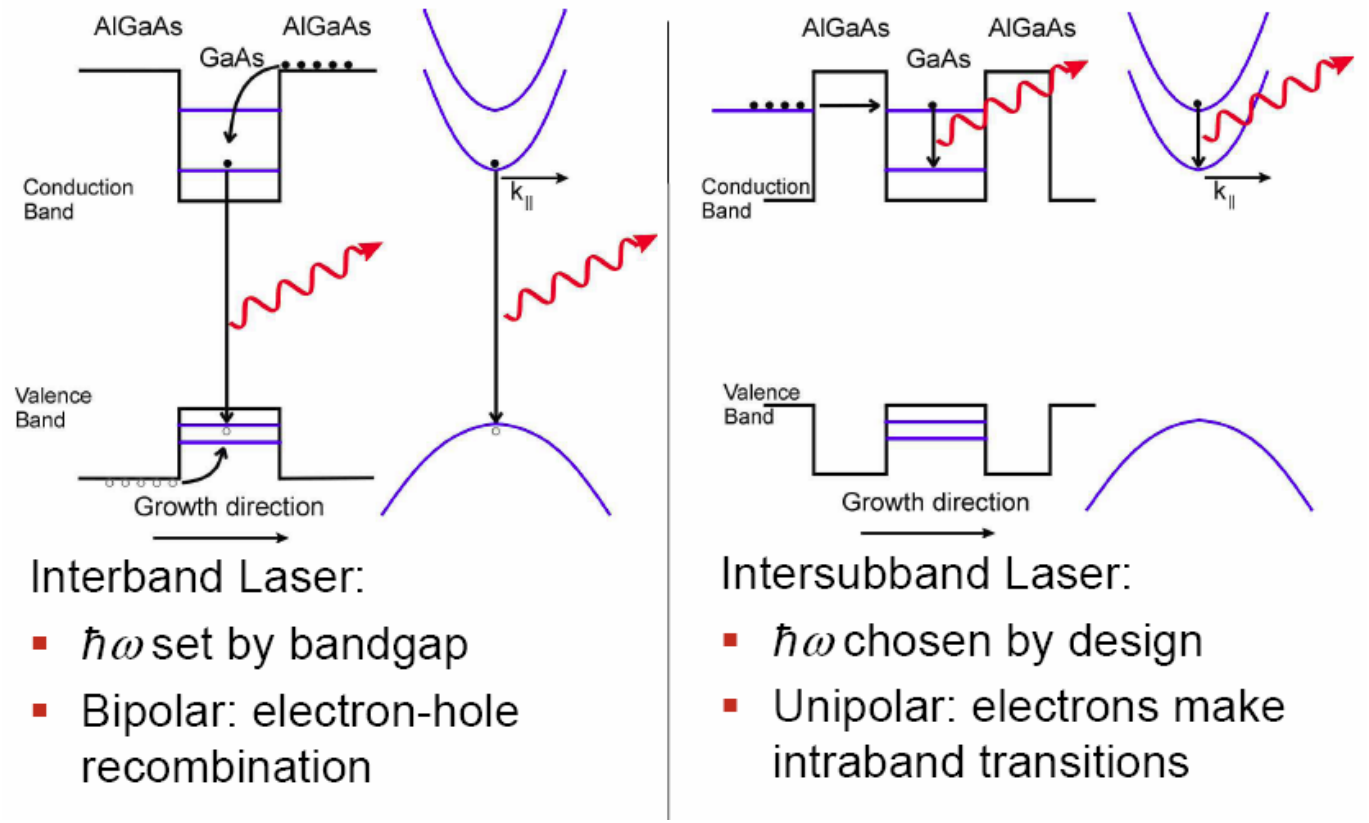
Alternative Approaches

- CRYSTAL
- CASTEP
- VASP
- CHARMM
- ... and many more

Intersubband Transitions



In contrast to a normal semiconductor laser the photons are emitted from transitions within the conduction band

Schematic courtesy of B.S. Williams, 2005

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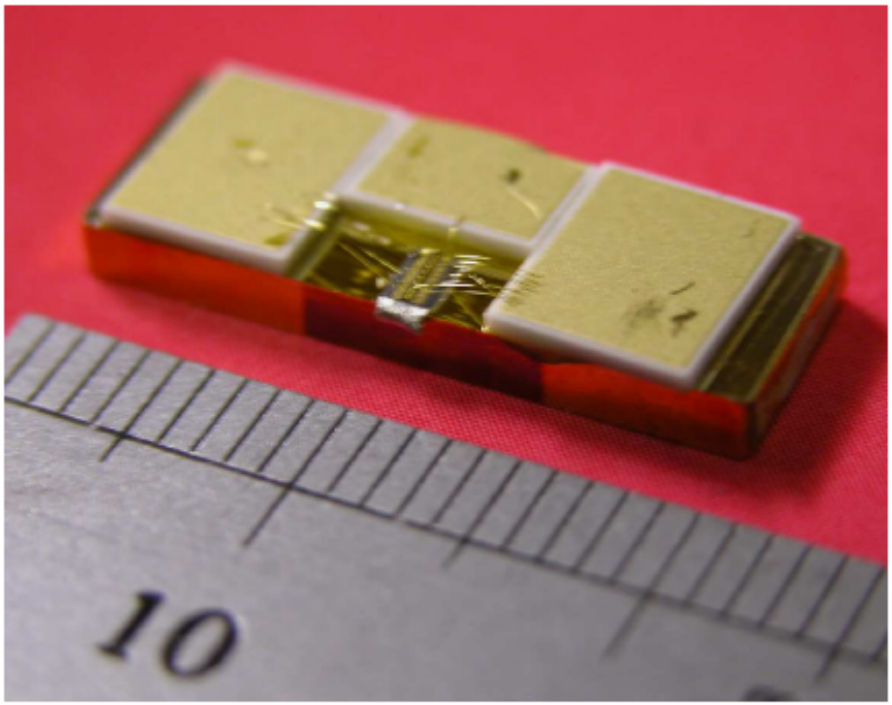
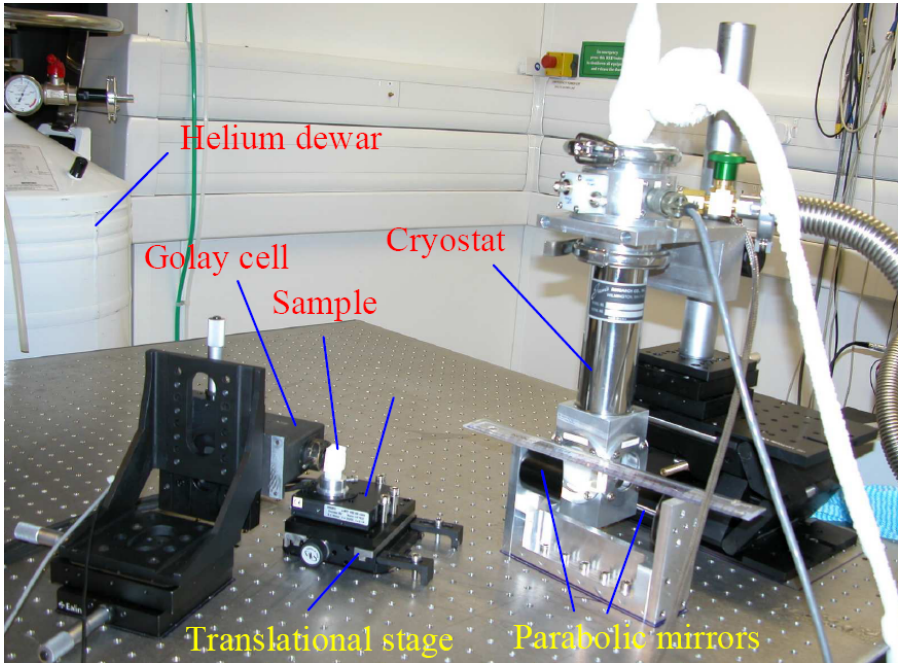
Quantum Cascade Laser (QCL) Device



QCL mounted on copper block



Experimental setup

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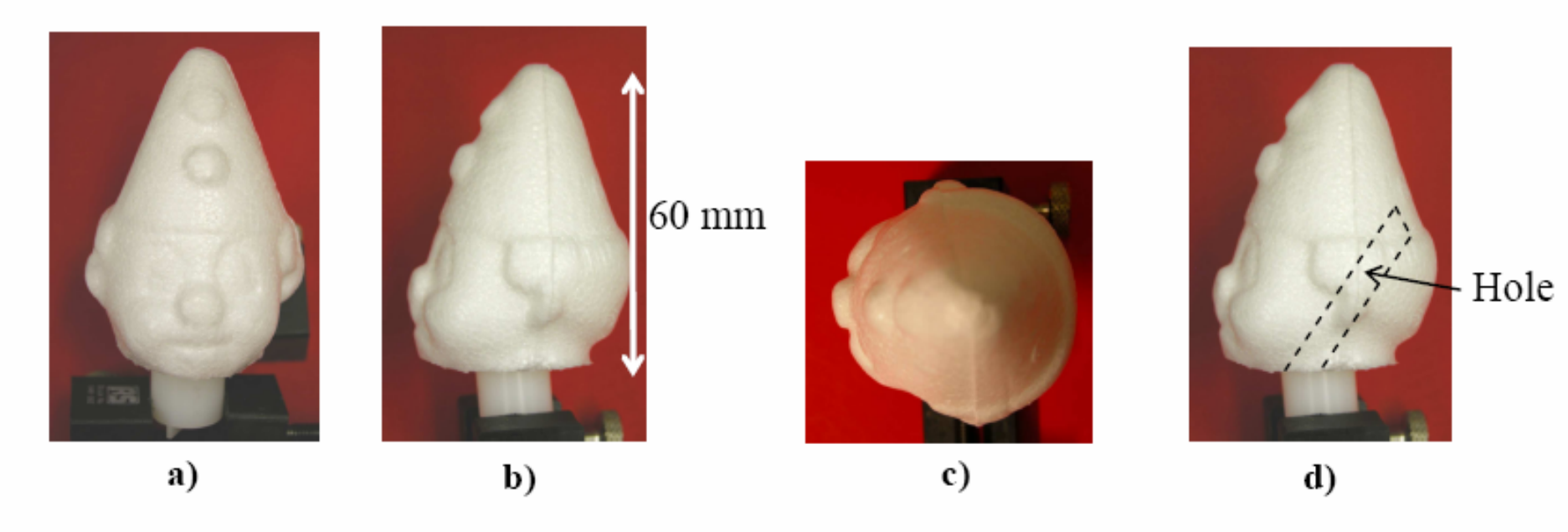
Polystyrene Phantom



Polystyrene phantom in the shape a clown's head

K. L. Nguyen *et al.*, Opt. Express 14, 2123 (2006).

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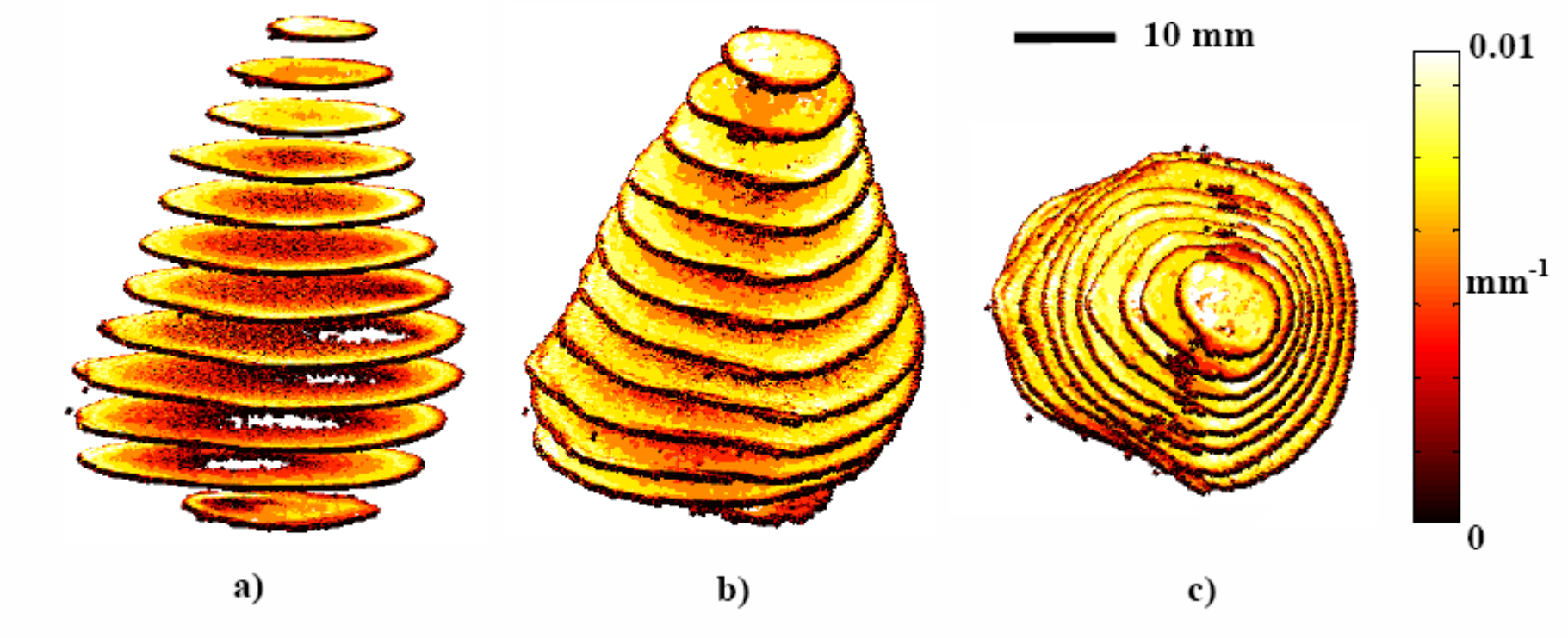
Polystyrene Phantom



Some views of the reconstructed 3D image

K. L. Nguyen *et al.*, Opt. Express 14, 2123 (2006).

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THz QCL imaging

Advantages

- High power source (up to 50 mW)
- Microbolometer arrays are possible
- Uncomplicated optics setup
- Array detectors possible

Current Limitations

- Optimum operation temperature at 4-10 K (max. 150 K)
- Lack of readily available optics at THz frequencies (lenses, filter)
- Very immature waveguide technology
- Limited range of operating frequencies

Outline

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Advantages of Terahertz Spectroscopy

Highlights

- Spectral signature represents unique fingerprint that directly originates from the molecular interaction in the crystal lattice (hydrogen bonding, phonon modes)
- No artefacts due to preferred orientation
- Very fast technique, time resolved measurements are possible
- Many experiments can be performed in transmission (large sampling volume)
- Detection of the signal with room temperature detectors
- FT-IR and Raman sampling accessories such as ATR can be readily used

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Current Limitations

Major challanges

- No diffuse reflectance sampling possible to date
- Limited bandwidth and power
- Cost and maintenance of fs lasers
- Signal processing can be tricky due to echo pulses and multiple reflections
- Limited understanding of the vibrational modes at THz frequencies

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New literature in the field from 2007 - I

Our group:

- J.A. Zeitler *et al.*, Terahertz pulsed spectroscopy and imaging in the pharmaceutical setting – a review, J. Pharm. Pharmacol., 2007, 59, 209-223
- K.L. Nguyen *et al.*, Terahertz time-domain spectroscopy and the quantitative monitoring of mechanochemical cocrystal formation, Nat. Mater., 2007, 6, 206-209
- J.A. Zeitler *et al.*, Drug Hydrate Systems and Dehydration Processes Studied by Terahertz Pulsed Spectroscopy, Int. J. Pharm., 2007, 334, 78-84
- J.A. Zeitler *et al.*, Solid-state transition mechanism in carbamazepine polymorphs by time-resolved terahertz spectroscopy, ChemPhysChem, 2007, 8, 1924-1927
- J.A. Zeitler *et al.*, Relaxation and crystallization of amorphous carbamazepine studied by terahertz pulsed spectroscopy, J. Pharm. Sci., 2007, 96, 2703-2709
- J.A. Zeitler *et al.*, Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging, J. Pharm. Sci., 2007, 96, 330-340
- L. Ho *et al.*, Analysis of sustained-release tablet film coats using terahertz pulsed imaging, J. Control. Rel., 2007, 119, 253-261
- J. Obradovic *et al.*, The use of THz time-domain reflection measurements to investigate solvent diffusion in polymers, Polymer, 2007, 48, 3494-3503

New literature in the field from 2007 – II

Other groups:

- H.B Liu *et al.*, Characterization of anhydrous and hydrated pharmaceutical materials with THz time-domain spectroscopy, J. Pharm. Sci., 2007, 96, 927-934 (X.C. Zhang's group, US)
- J.A. Spencer *et al.*, Delayed release tablet dissolution related to coating thickness by terahertz pulsed image mapping, J. Pharm. Sci., 2007, in press, doi:10.1002/jps.21051 (FDA and TeraView)
- H. Wu *et al.*, Process analytical technology (PAT): Effects of instrumental and compositional variables on terahertz spectral data quality to characterize pharmaceutical materials and tablets, 2007, Int. J. Pharm., 343, 148-158 (FDA and NIST)
- H. Wu *et al.*, Process analytical technology (PAT): quantification approaches in terahertz spectroscopy for pharmaceutical application, 2007, J. Pharm. Sci., in press, doi:10.1002/jps.21004 (FDA and NIST)

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