Dendrimer Terahertz Technology: Applications in Life Sciences

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Outline

- Introduction
- Electro-optic Dendrimer nanomaterial
- Terahertz generation and Spectroscopy
- Future of terahertz technology
- Value proposition and market potential
- EO rectification: DNA identification
- Difference Frequency Generation
- Other photonic components
- Concluding Remarks

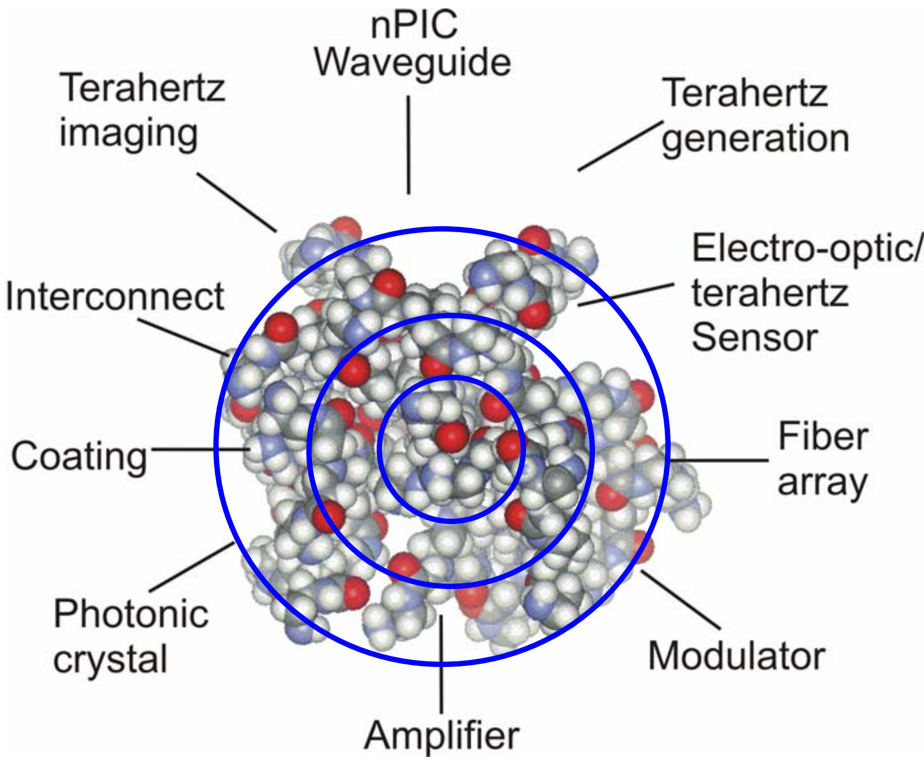
NanoPhotonics

- **An opportunity to create smart devices by combining <u>nanotechnology</u> and <u>photonics</u>**
- **1880 Bell: *Photophonic transmitter***

- **1905 Einstein: *measured sugar molecule size ~ 1 nm***
- **1985 Tomalia: *successful synthesis of star burst polymer (dendrimer)***
- **2003 ARP: dendrimer based photonics technology that resulted in a high power terahertz source and applications**

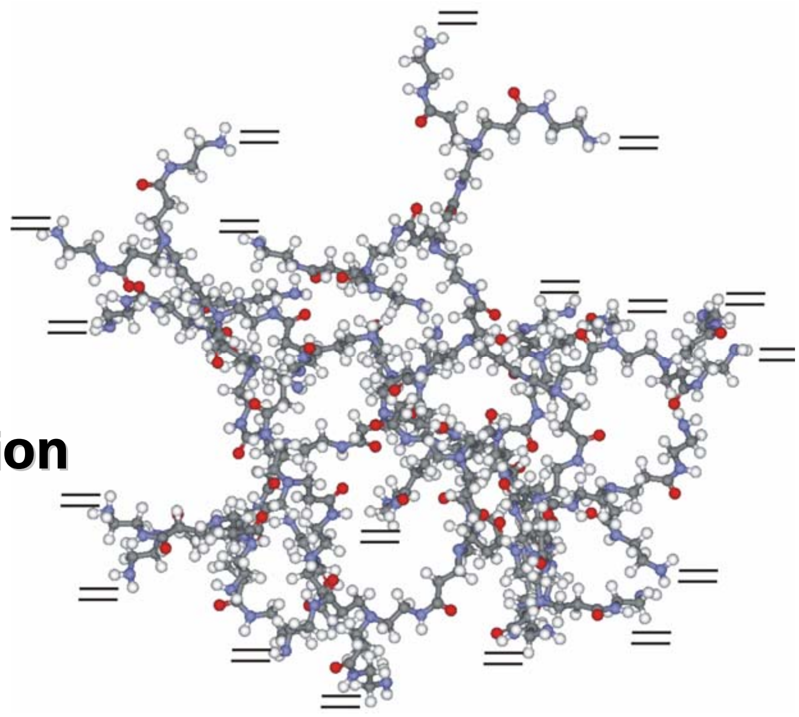
Dendrimer: A polymeric nanomaterial

- **3-D core-shell molecule**
- **Generation: G0-G11**
- **Size: 4-12nm**
- **Multiple functionality: terahertz emitter, waveguide, modulator, amplifier, and band gap**
- **Established route for transition to production**
- **Cost-effective**



ARP: Electro-optic Dendrimer

- High $\chi^{(2)}$ material required for THz generation: Inorganics → low $\chi^{(2)}$
- Dendrimer's EO properties can be enhanced by doping
- Potentially 64 fold increase of $\chi^{(2)}$ for *G*3; higher for higher generation
- High field poling required
- There are many chromophore and / or dopants to choose from

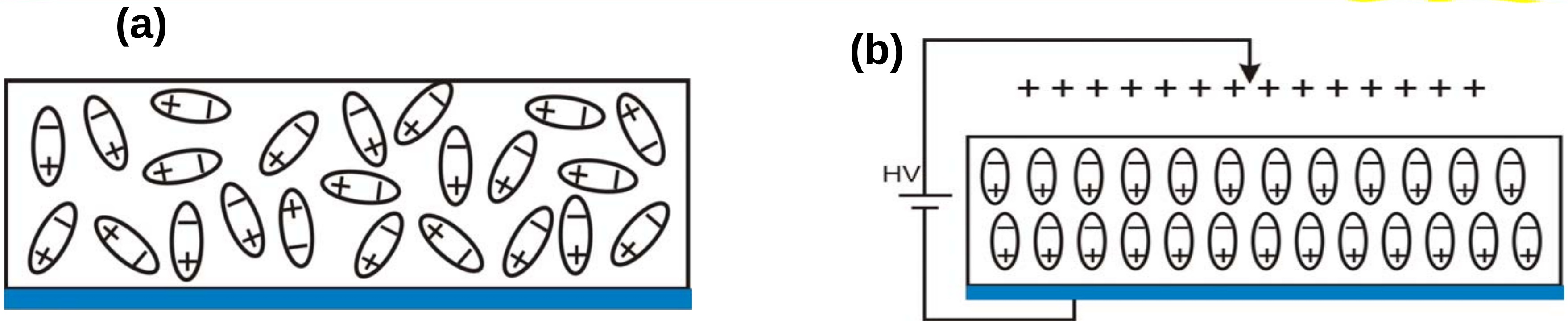


$$\chi^{(2)} = n\, f\, \beta\, \langle \cos^3\theta \rangle$$

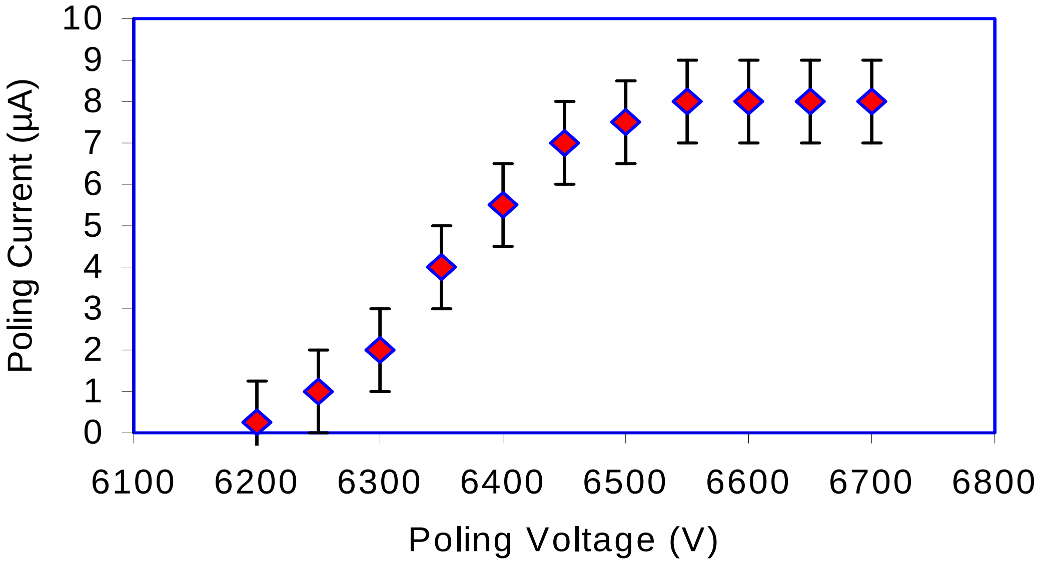
n = dipole density

f = local field, β = hyperpolarizability

Dendrimer EO properties



Sketch of dipole orientation in (a) unpoled and (b) corona poled dendrimer film.



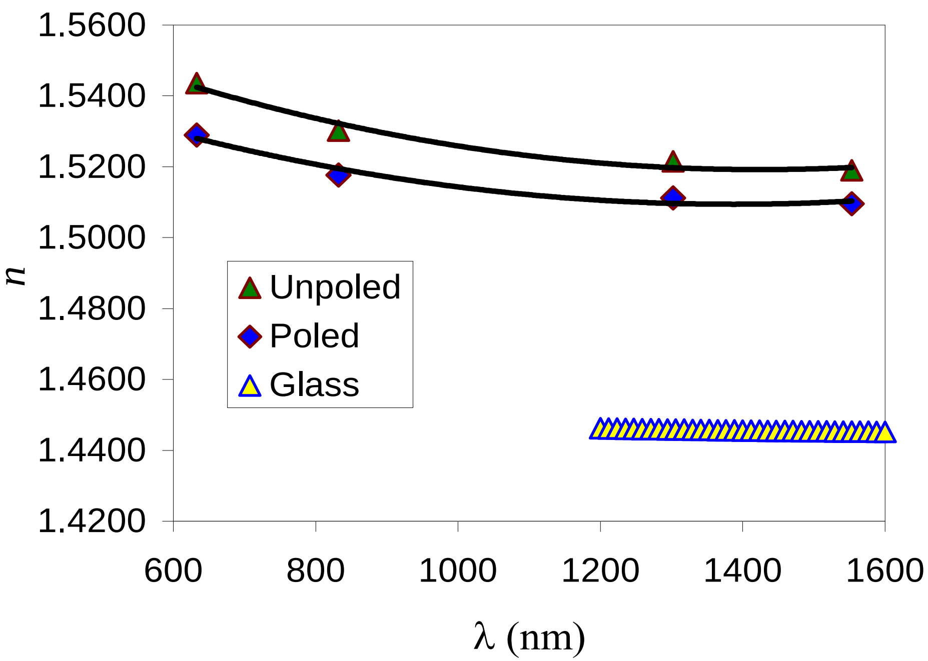
Poling I-V: poling current in dendrimer film.

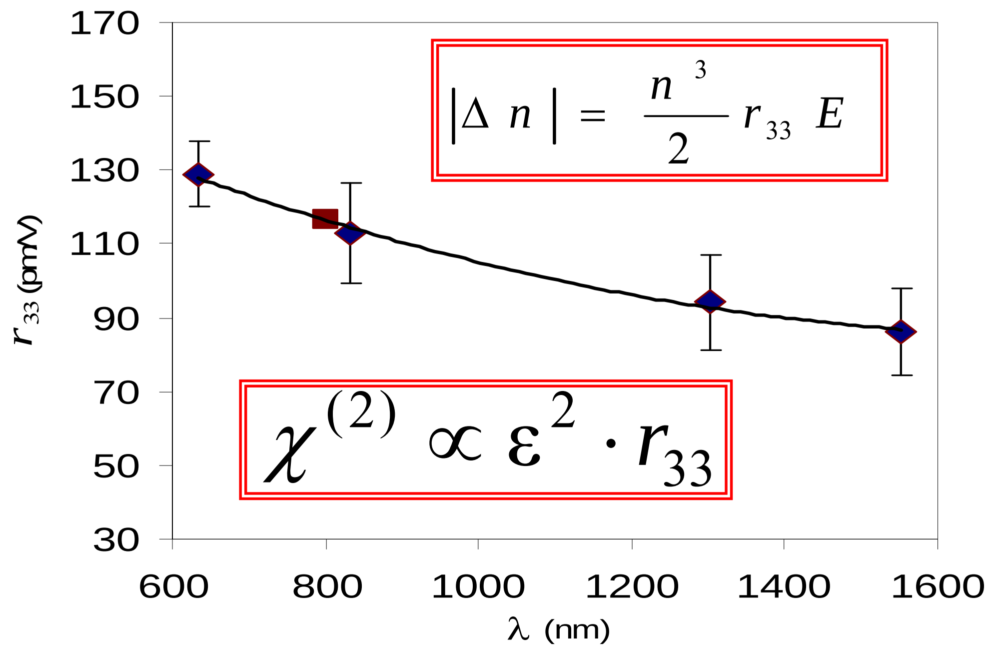
Stabilized current indicates maximum orientation of the dipoles; cosθ ~ 1.

Under this condition, the material is a uniaxial polar material.

Refractive Index & EOC

Pockels effect

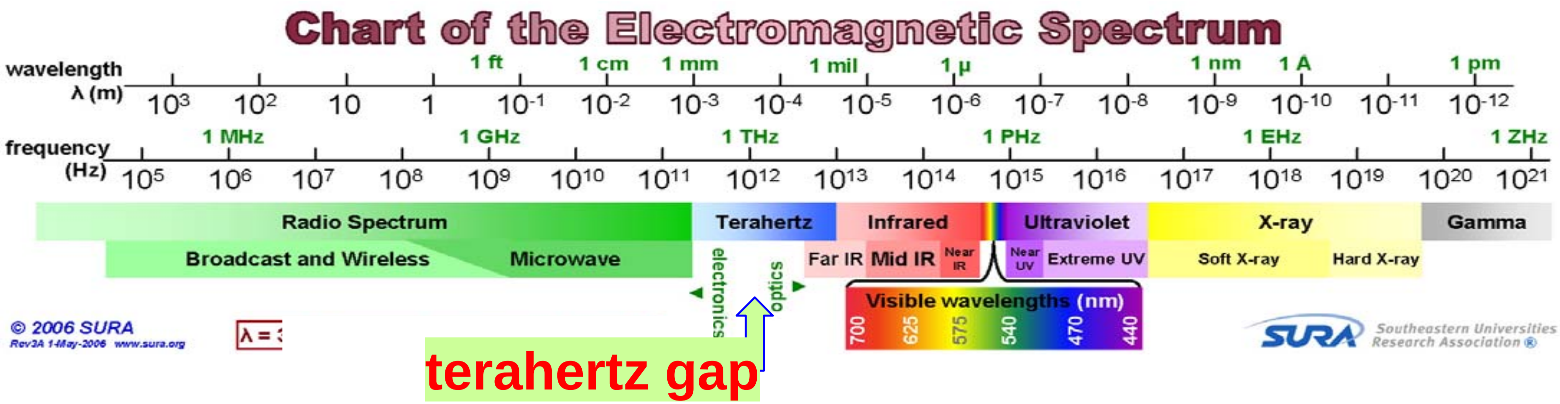




Refractive index difference between poled and unpoled dendrimer (Metricon 2010).

r_{33} ~130 pm/V @ 633nm >> $LiNbO_3$ (~33 pm/V)

Terahertz Radiation (T-Rays)



- Terahertz spectroscopy (THz-TDS) has unique applications
- 1 THz = 33.33 cm^{-1} (wave numbers) or 0.004 eV photon energy.
- THz spectroscopy covers 0.3 THz to ~20 THz (from 10 to 600 cm^{-1}); most work done between 0.3 and ~3 THz range.
- THz can detect “intra-molecule” vibrations as well as “inter-molecule” vibrations
- THz can detect changes in individual bonds in protein complexes ➔ monitoring structural and conformational changes in biological reactions.
- T-rays can see through obstacles: fog, mist, box, wall, etc.
- THz technology has a sound market potential.

Future of Terahertz Technology

- **Medicine/Biological Sciences:**
  - Biomolecular interactions, Label-free DNA analysis, Pharmaceutical process, Drug discovery, Medical diagnostics, Early detection of skin cancer, bone density, Endoscopy, Mammography, Dentistry (detection of tooth decay), Food industry process control (moisture detection), pill inspection, etc.
- **Scientific:**
  - Earth remote sensing, Environmental sensing (pollution detection), Plasma diagnostics, molecular signature spectroscopy
- **DOD, NASA, Security and Screening**
  - Active and passive imaging through dust, smoke, fog etc; all weather active and passive seekers; secure communications; spectrographic sensing of explosives, gases and biologicals.
  - high rate and secure data transfer, flame analysis (rocket or jet engine burn optimization)
  - Homeland Security - concealed weapon identification, biological threat detection
  - detection of voids in the space shuttle foam
  - passenger screening, hidden weapons detection, contraband detection

THz Biosensing

- Theoretical calculations predict many resonances in the THz frequency range associated with inter-backbone excitations of DNA molecules, such as propeller-twist, hydrogen-bond breathing, and base-roll and base-shift vibrational modes (Van Zandt & Saxena 1989; Zhuang *et al* . 1990).
- The presence of these modes indicates a unique potential of THz technologies for the label-free detection of the DNA binding state.
- Investigations by Raman and Fourier-transform techniques on hybridized DNA molecules can not address binding state specific analysis (see, for example, Urabe & Tominaga 1982; Woolard *et al* . 1997)
- Recently, we demonstrated the use of the THz Spectroscopy of the binding state of DNA at THz frequencies as a potential method for label-free gene detection.

National Initiatives

Comprehensive, consistent, and high quality THz spectral libraries are required to support further development of THz sensing systems and to support spectral sensing applications – **Battelle Science and Technology Center, MD**.

National Signatures Program (NSP)

- NSP is a joint service, multi-agency venture initiated by the DIA
- Objective: to meet increased demand for signatures intelligence
  - Support our soldiers on the battlefield
  - Monitor the proliferation of WMD
  - Support Homeland Defense and the Global War on Terrorism
- NSP catalogs and disseminates signatures to end users

THz Activities/news

- **[Radiation source to further cancer research]**

  Thursday, July 6th, 2006 Plans to construct Europe's most intense terahertz (THz) radiation source to further development of cancer research are underway at the University of Liverpool.

- **Terahertz Biochip for Detecting Illicit Drug Powders, High-speed Terahertz Imager at 2006 CLEO/QELS Meeting**

  Wednesday, April 26th, 2006 Researchers from around the world will present new results in optics, photonics and their applications at the 2006 CLEO/QELS meeting from May 21-26, 2006.

- **SPEC 2008: Shedding Light on Disease: Optical Diagnosis for the New Millenium** Sao Jose dos Campos, Sao Paulo, Brazil. October 25-29, 2008

- **Terahertz success relies on research investment**

  Tuesday, October 14th, 2008 Terahertz radiation holds great promise for enhanced security systems, industrial inspection and sophisticated spectroscopy. Marie Freebody speaks to Hartmut Roskos to find out about the progress that has been made so far and the key challenges that remain.

Source: THz Science & Technology Network: http://www.thznetwork.org/

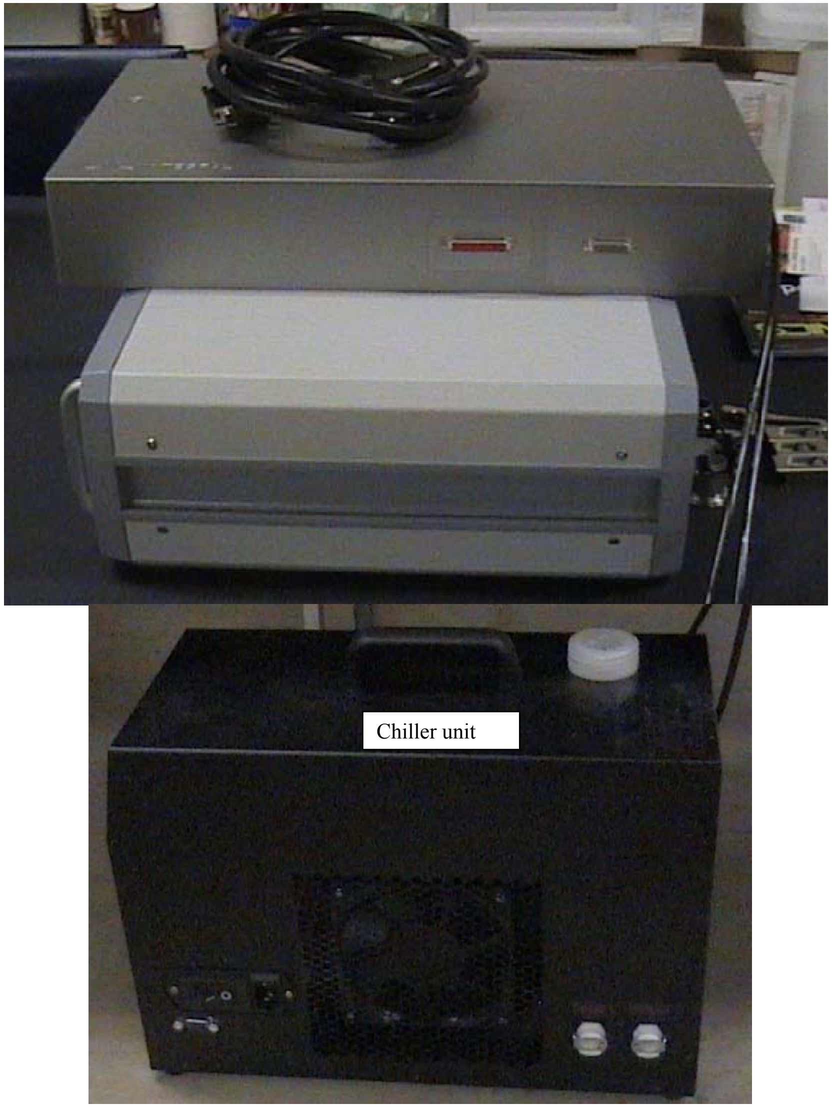
Terahertz generation

Technology	Advantages	Challenges
Electro-optic rectification (EOR)	• Easy alignment • Broadband spectrum • High time resolution • Power scalable	• Needs femto pulsed laser • Output power depends on electro-optic properties • High cost
Diff. Freq. Gen. (DFG)	• Narrow line widths • Tunable, Pulsed or CW • Lower cost	• Two lasers needed • Difficult alignment • Many unknowns
Waveguide	• Can use both **EOR, DFM**	• Alignment and packaging
Photo-conductor	• Commercially available	• Low output power, ~ nW-μW
Reactor/ Accelerator/ Synchrotron	• Higher output power	• Huge size and cost • Needs dedicated facility, staff

EOR: big, expensive

Main drawback:
Cost and Size

Requires femto-second pump laser (not too many supplier). The femto-laser needs a pump laser of its own, an active water cooling system, and also a big bulky power supply.

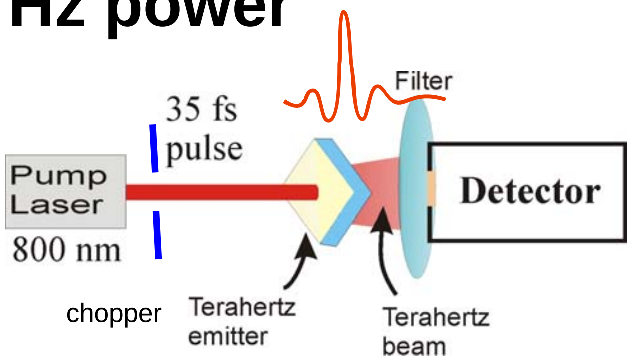


Value Proposition

- **Femto-second laser (EOR) route is expensive yet limited in power**
- **DFG based spectrometer is a new disruptive route**
- **Label-free molecular (DNA) identification and quantitation**
- **Label-free SNP detection**
- **Expandable to scanning spectrometry, THz Imaging and THz Microscopy products**

Terahertz generation by Electro-optic Rectification

THz power



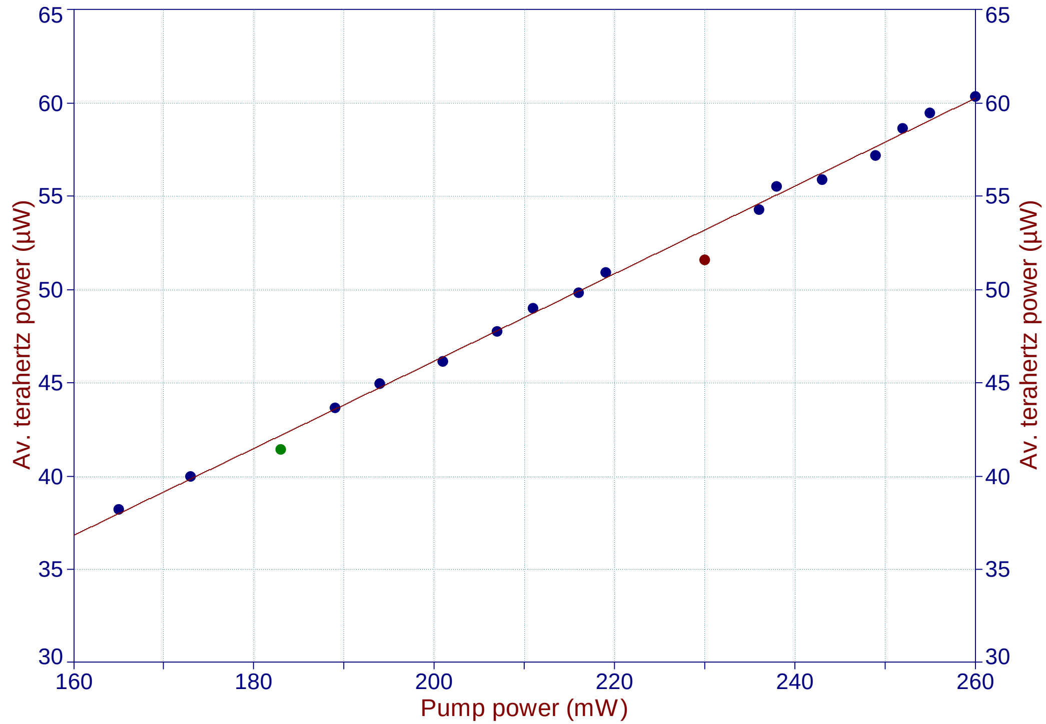
$$E_{THz} \propto d_{14} E_{pump}^2$$

$$d_{14} = \tfrac{1}{2}\chi^{(2)}$$

$$\chi^{(2)} \propto \varepsilon^2 \cdot r_{33}$$

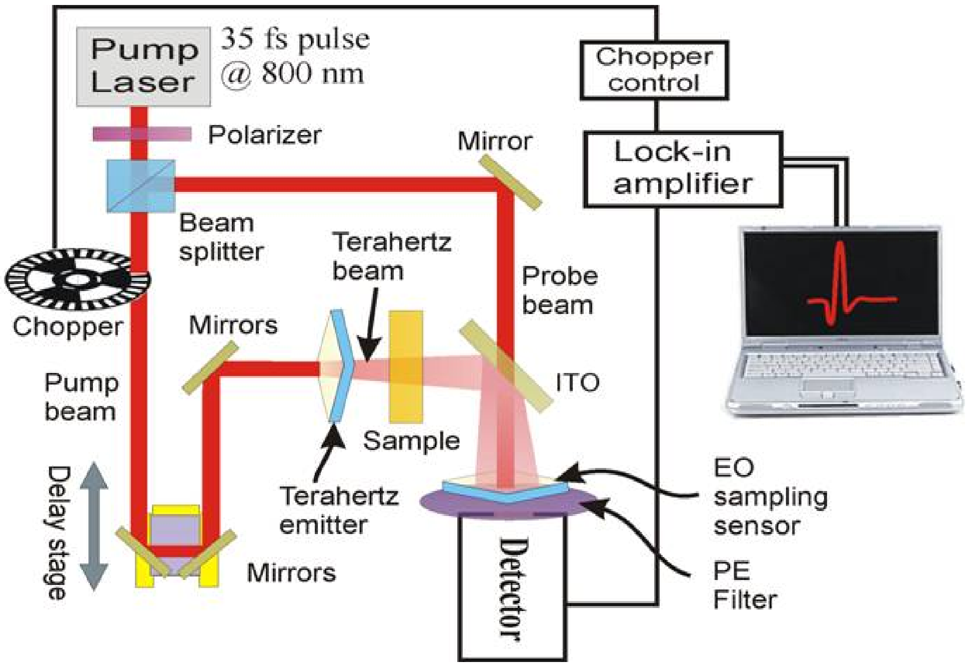
$$\boxed{E_{THz} \propto r_{33} E_{pump}^2}$$

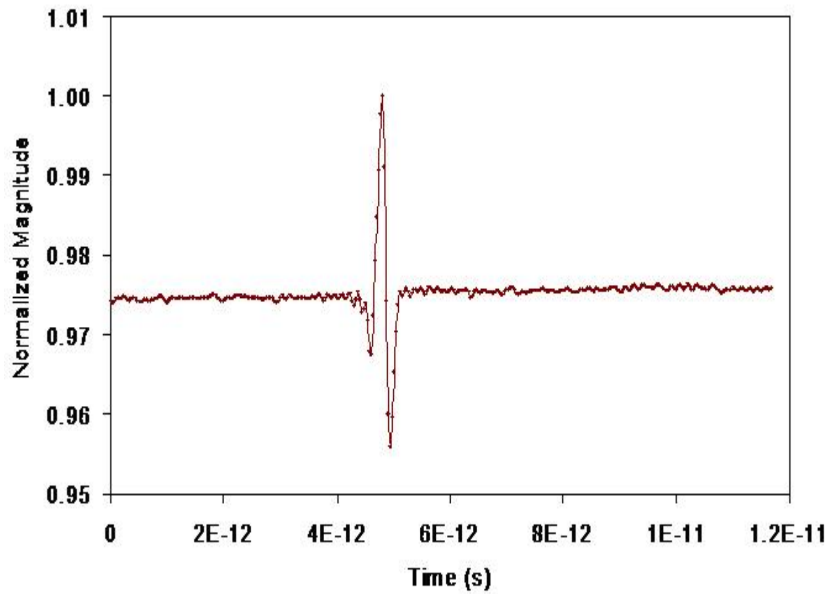
$$\boxed{w_{THz} = a_{dend} w_{pump}^2 + C}$$



Measured average terahertz power. The solid line is the fit of Eq. (4) with *a* = 1.593×10^{-5} and *C* = 0.228.

THz-Time Domain Spectroscopy (EOR)





A setup for THz-TDS with femto-second laser. The ITO acts as a THz reflector while it is highly transparent to the probe beam.

Typical temporal pulse envelope detected by a lock-in amplifier (without specimen)

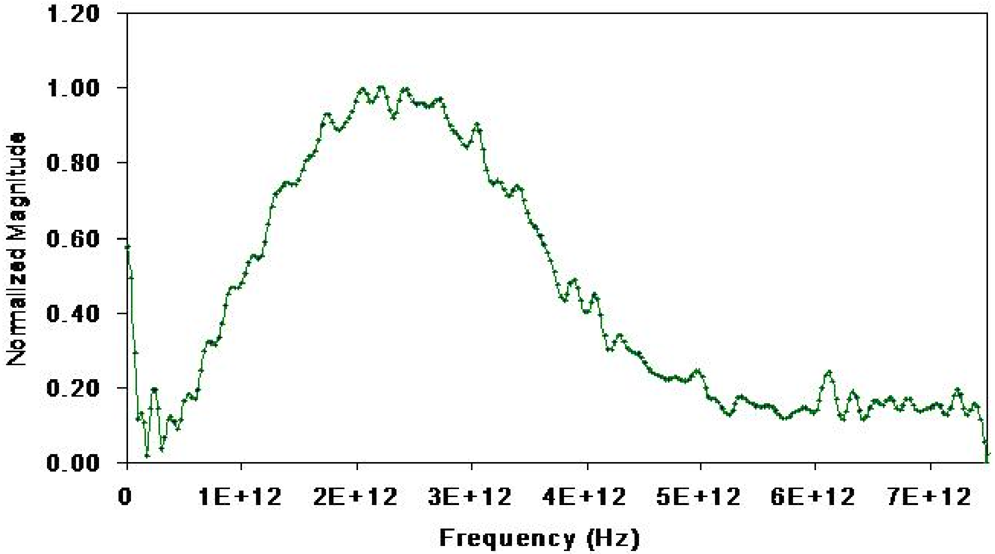
TDS – Fourier Spectrum

Top: Broadband magnitude spectrum generated from the temporal pulse

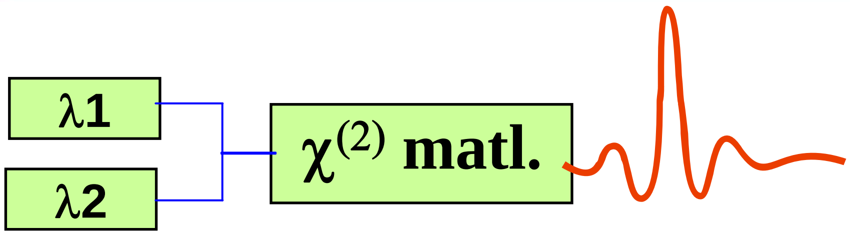
Bottom: Absorbance spectrum of the same

$$\left|\Delta f_{THz,Max}\right| = c\left|\Delta\lambda\right| / \lambda_0^2$$

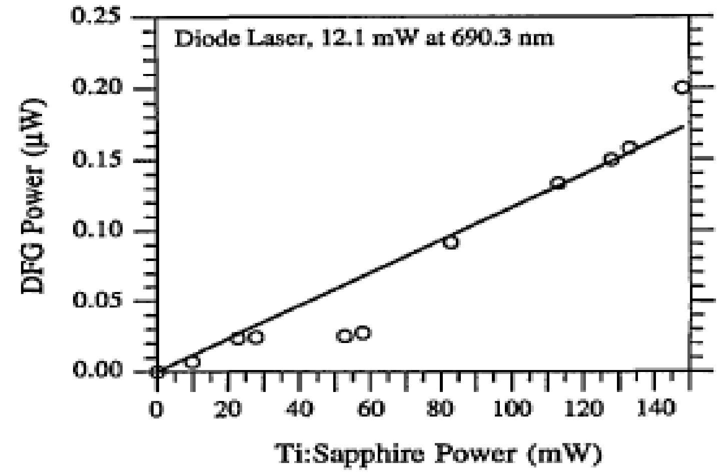
$\Delta\lambda$ = 26 nm
λ_0 = 800 nm
$\Delta f_{THz,Max}$ ~ 12 THz



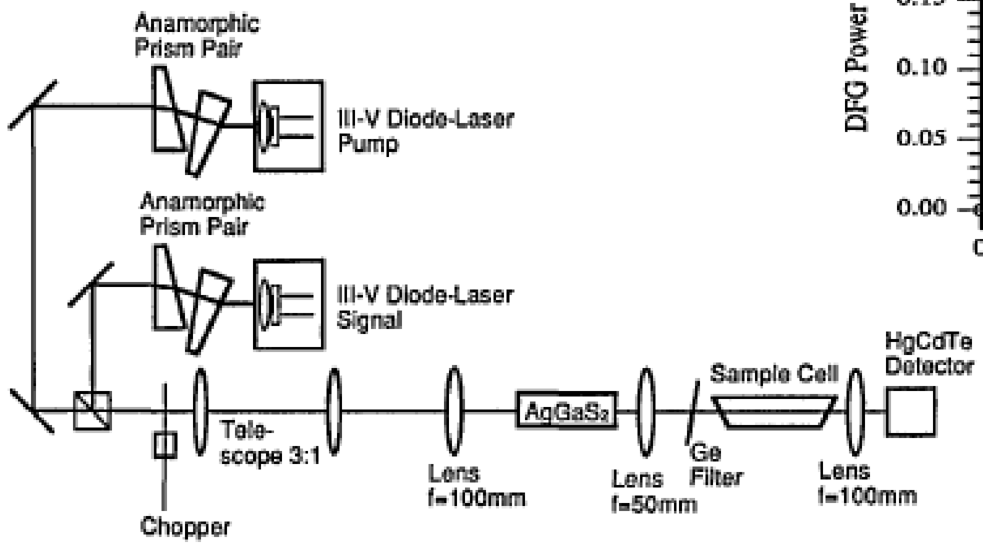
Difference Frequency Mixing



$$f_{THz} \propto \nu_2 - \nu_1$$

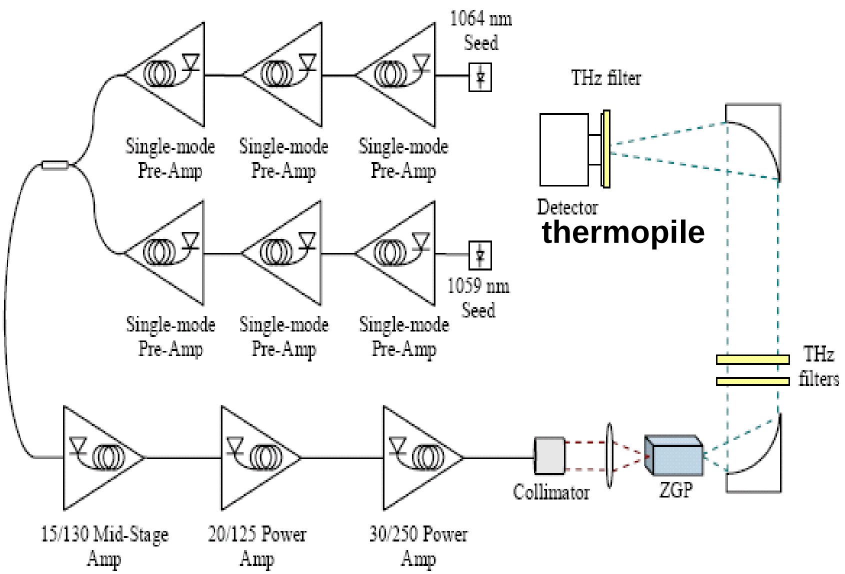


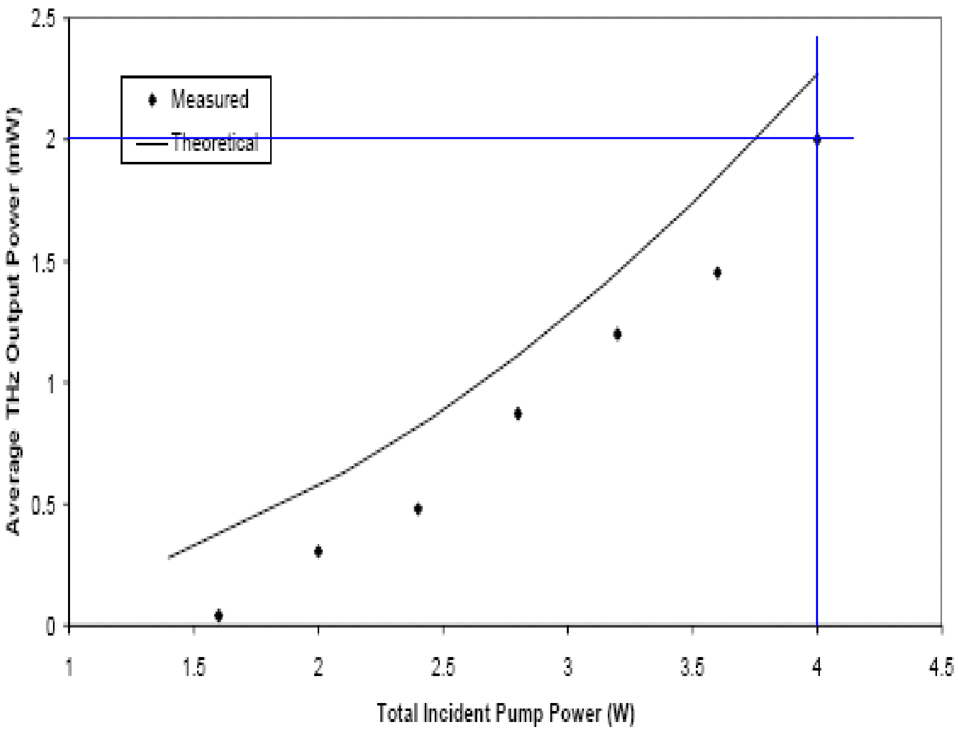
Setup used by Simon et al., 1993



U. Simon, C. E. Miller, C. C. Bradley, R. G. Hulet, **R. F. Curl,** and F. K. Tittel, "Difference-frequency generation in $AgGaS_2$ by use of single-mode diode-laser pump sources," OPTICS LETTERS / Vol. 18, No. 13 / July 1, 1993, p 1062–1064.

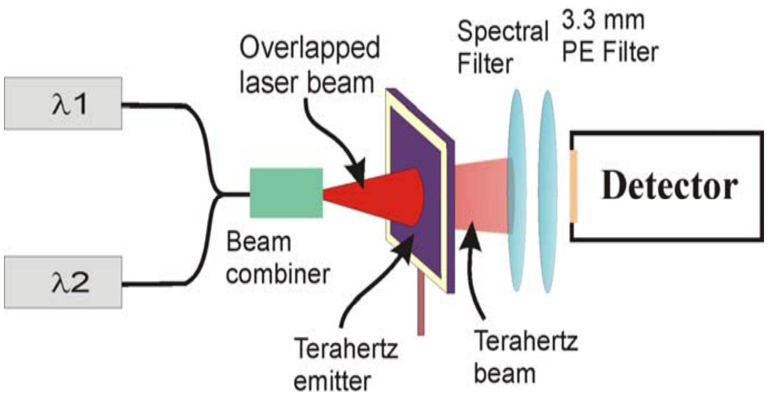
Difference Frequency Example





D. Creeden, J. C. McCarthy, P. A. Ketteridge, P. G. Schunemann, T. Southward, J. J. Komiak, E. P. Chicklis, “Compact, high average power, fiber-pumped terahertz source for active real-time imaging of concealed objects,”
14 May 2007, Vol. 15, No. 10, OPTICS EXPRESS, p. 6478

Difference Frequency Mixing in Dendrimer

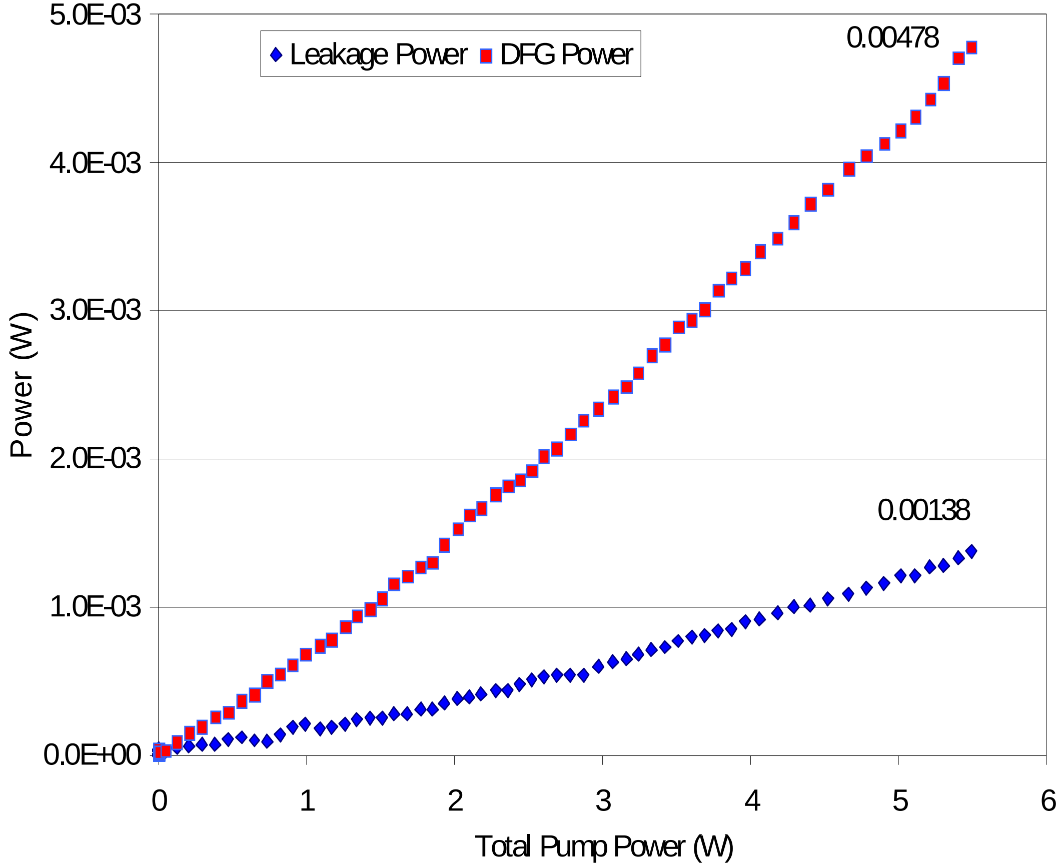


Difference frequency power measurement.

$\lambda 1 \sim 975$ nm

$\lambda 2 \sim 940$ nm

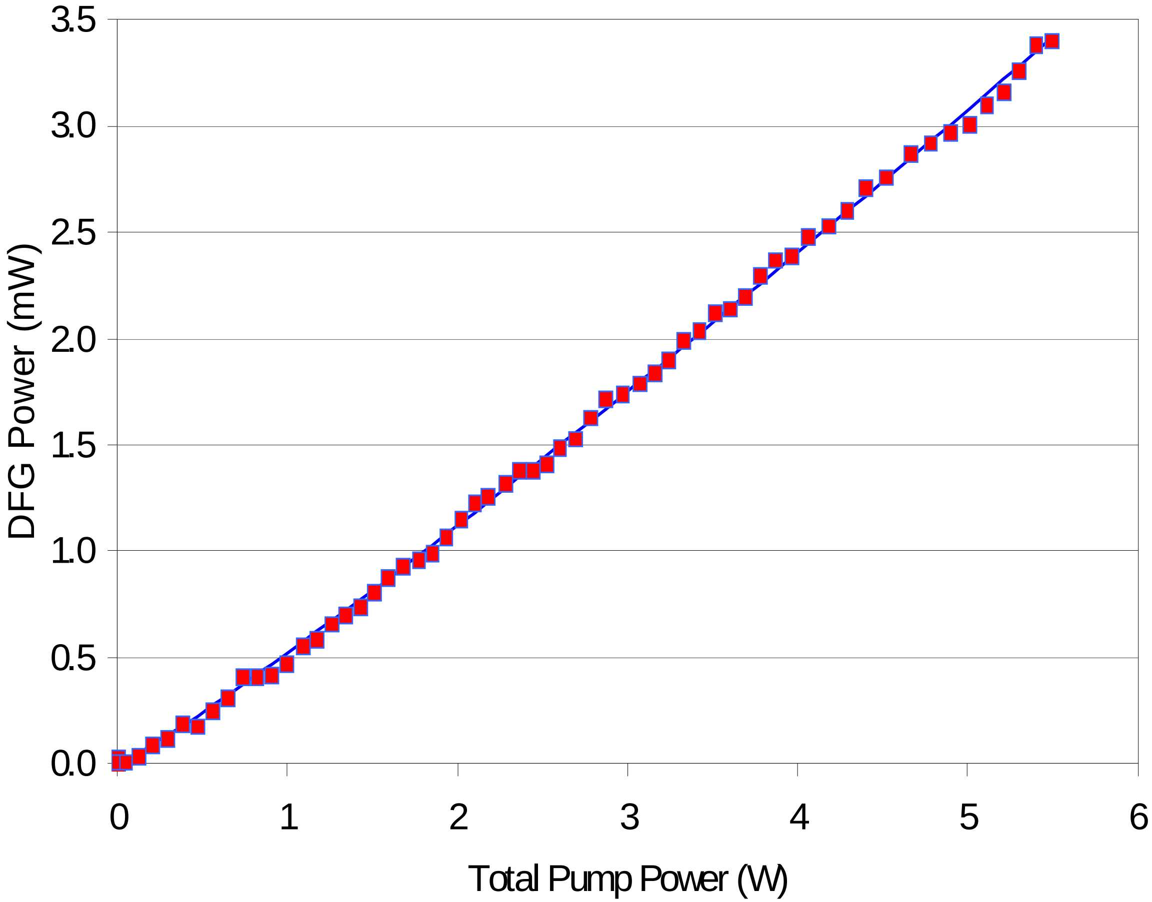
$f_{\mathrm{THz,\ max}} = 35$ THz



Filter leakage and THz power vs. total pomp power

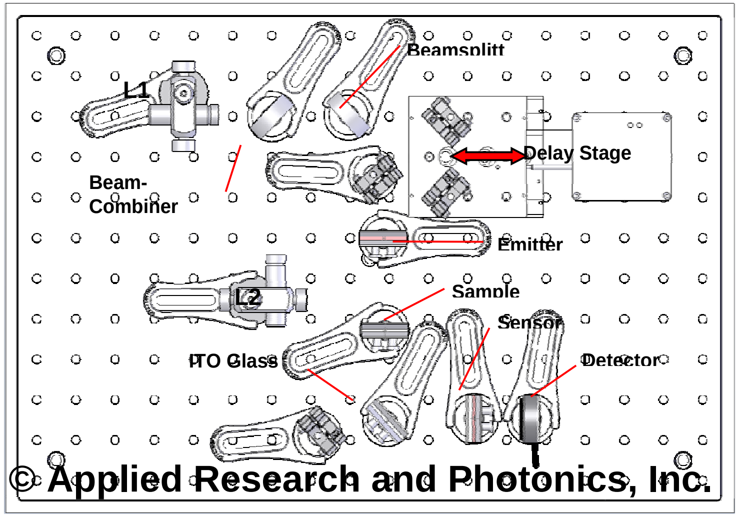
DFM Power

- **3.4 mW DFM power generated from dendrimer emitter at 5.49 W combined pump power (diode1 + diode2).**
- **This power can be increased with higher pump power**
- **Further increase in power is possible via waveguide structure proposed by ARP.**

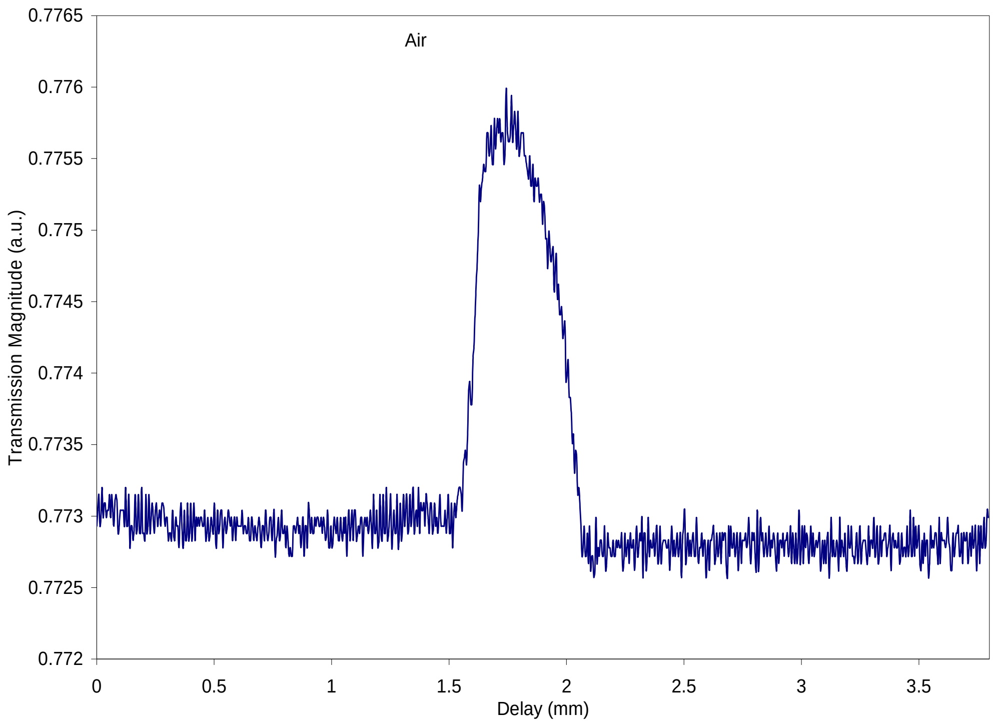


DFG = a*w^{n}_{pump}

THZ-TDS (DFG)

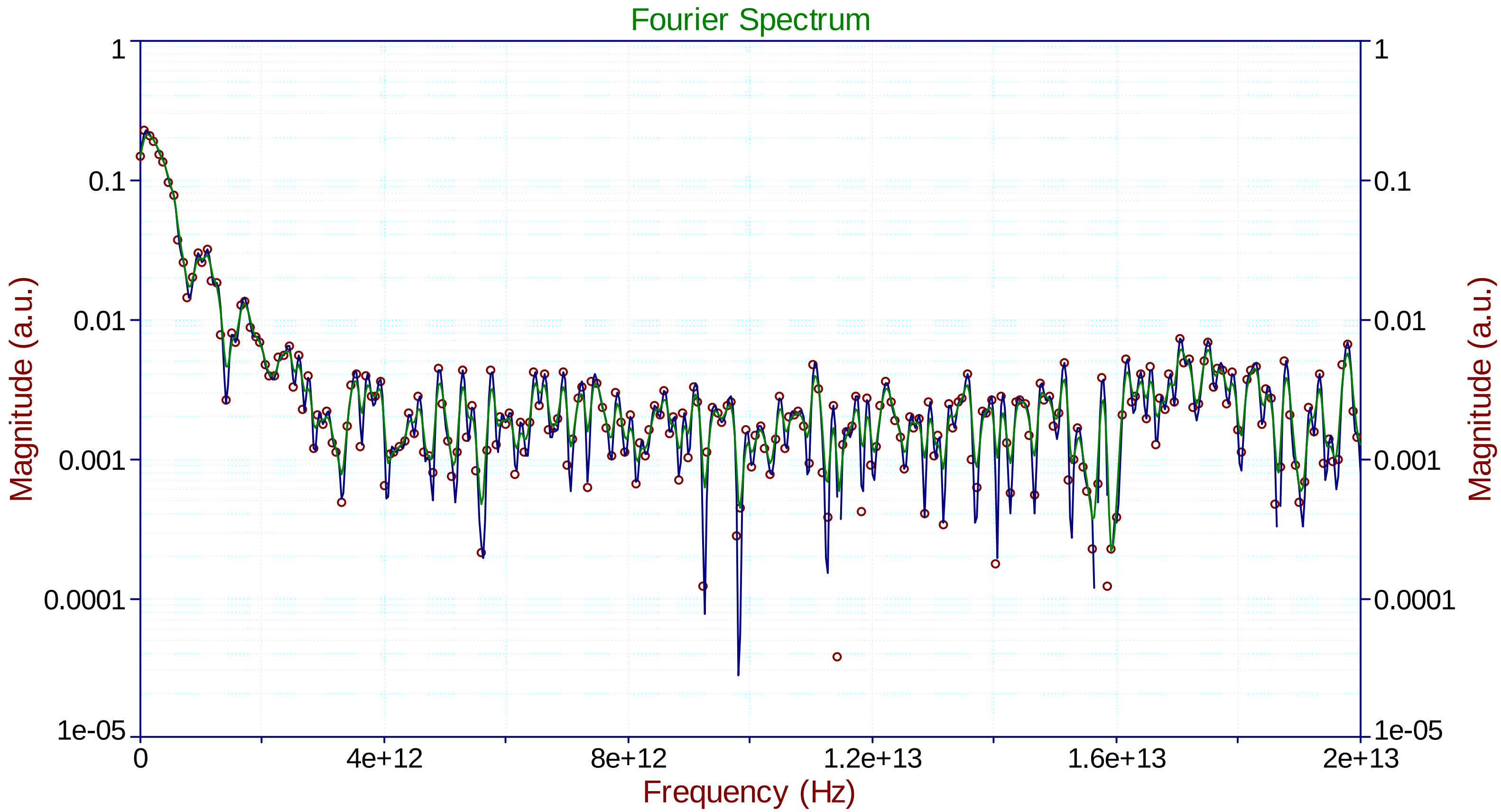


Layout of a THz time domain spectrometer (THz-TDS) based on difference frequency generation.



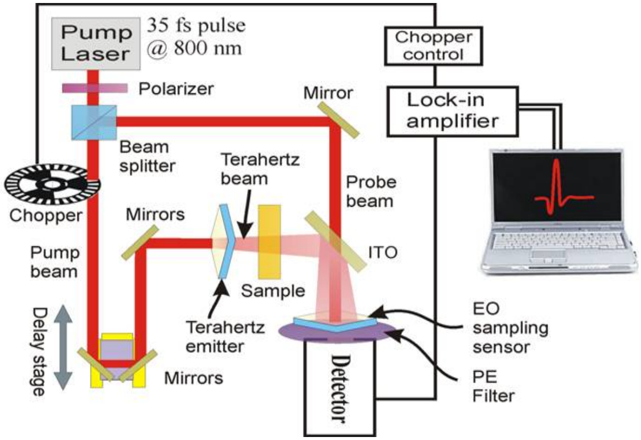
Temporal pulse (transmission vs. delay stage translation). Transmission data from the detector's analog output were collected with a high speed voltmeter.

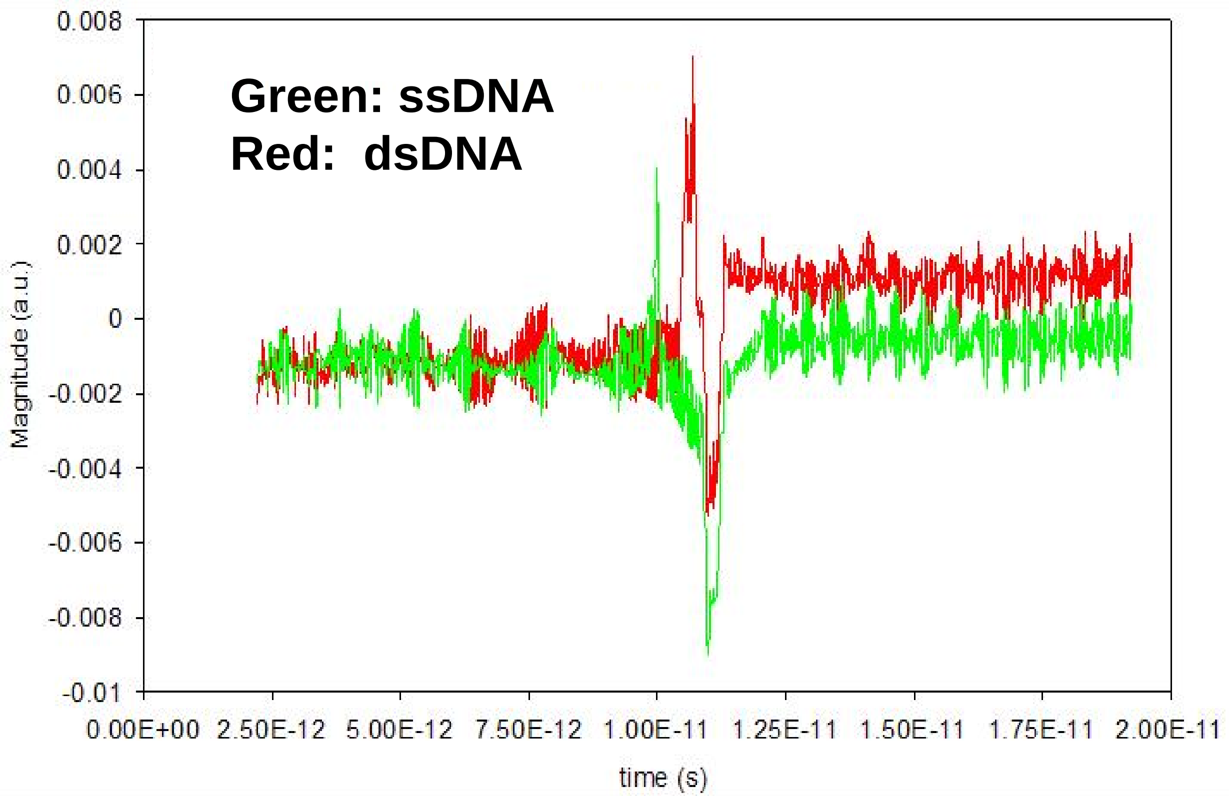
DFM Fourier Spectrum



Fourier transform frequency spectrum of the temporal pulse. The frequency spans a wider broadband up to 20 THz.

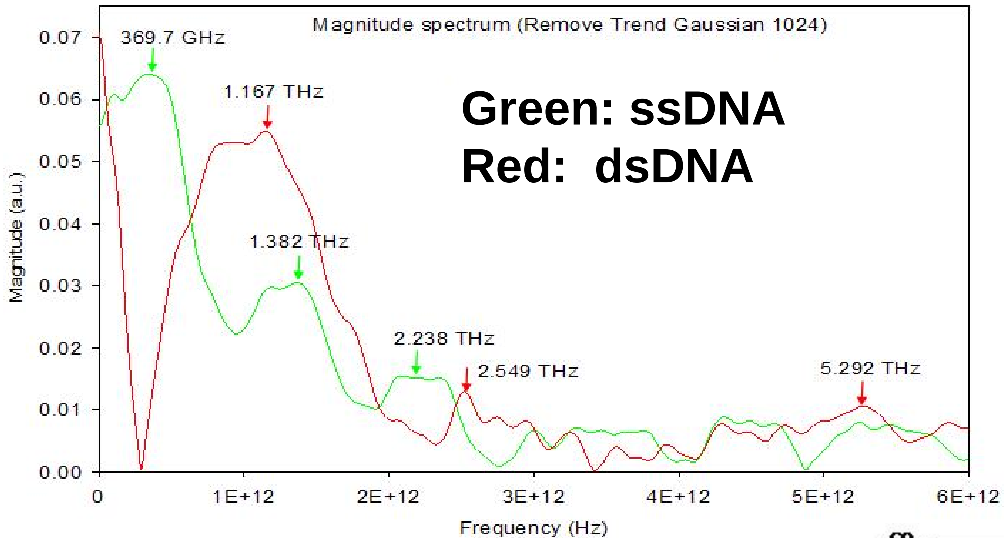
Label-free DNA Detection (EOR)





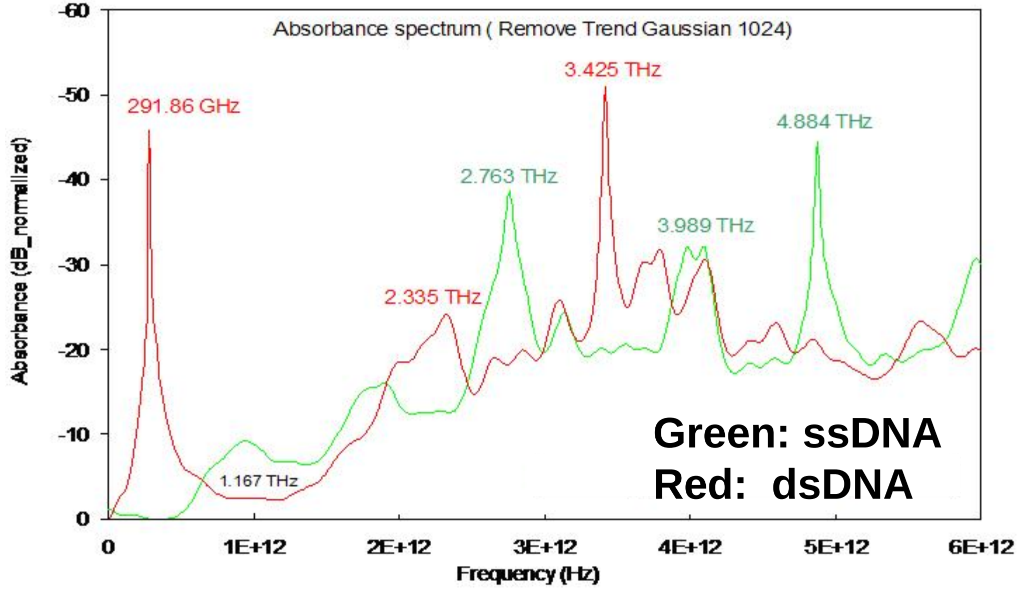
Temporal pulses of a 25-mer oligonucleotide, 2.72 pMole ssDNA (green) and dsDNA (red) obtained by subtracting the Blank substrate pulse from the respective samples. (Samples courtesy of Penn State Molecular Synthesis Facility).

25-mer DNA Spectra (EOR)

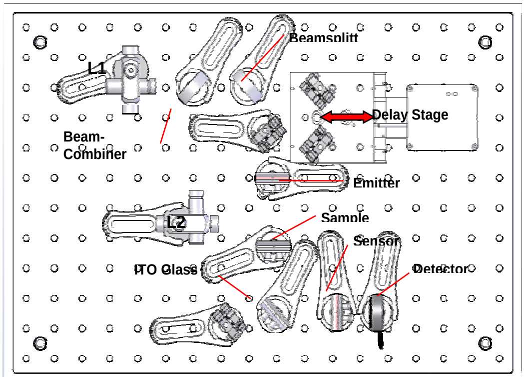


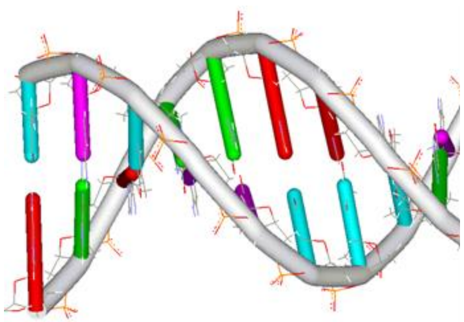
Magnitude spectra of the ssDNA (green) and dsDNA (red). For each species, three different peaks can be identified for both ssDNA and dsDNA; however, the peaks are significantly shifted compared to each other, thus allowing distinct comparison.

Absorbance spectra of the ssDNA (green) and dsDNA (red). Sharp absorbance peaks are present that are shifted with respect to each other.

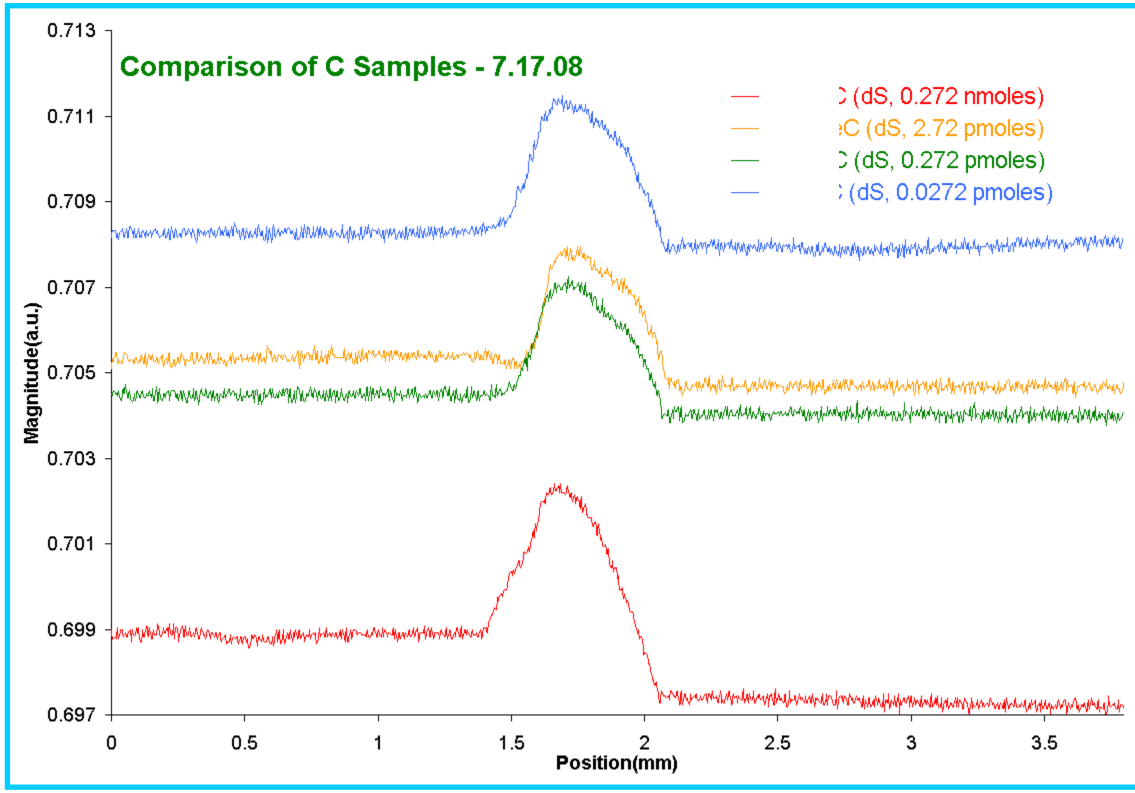


Temporal signal of DNA samples (DFG)





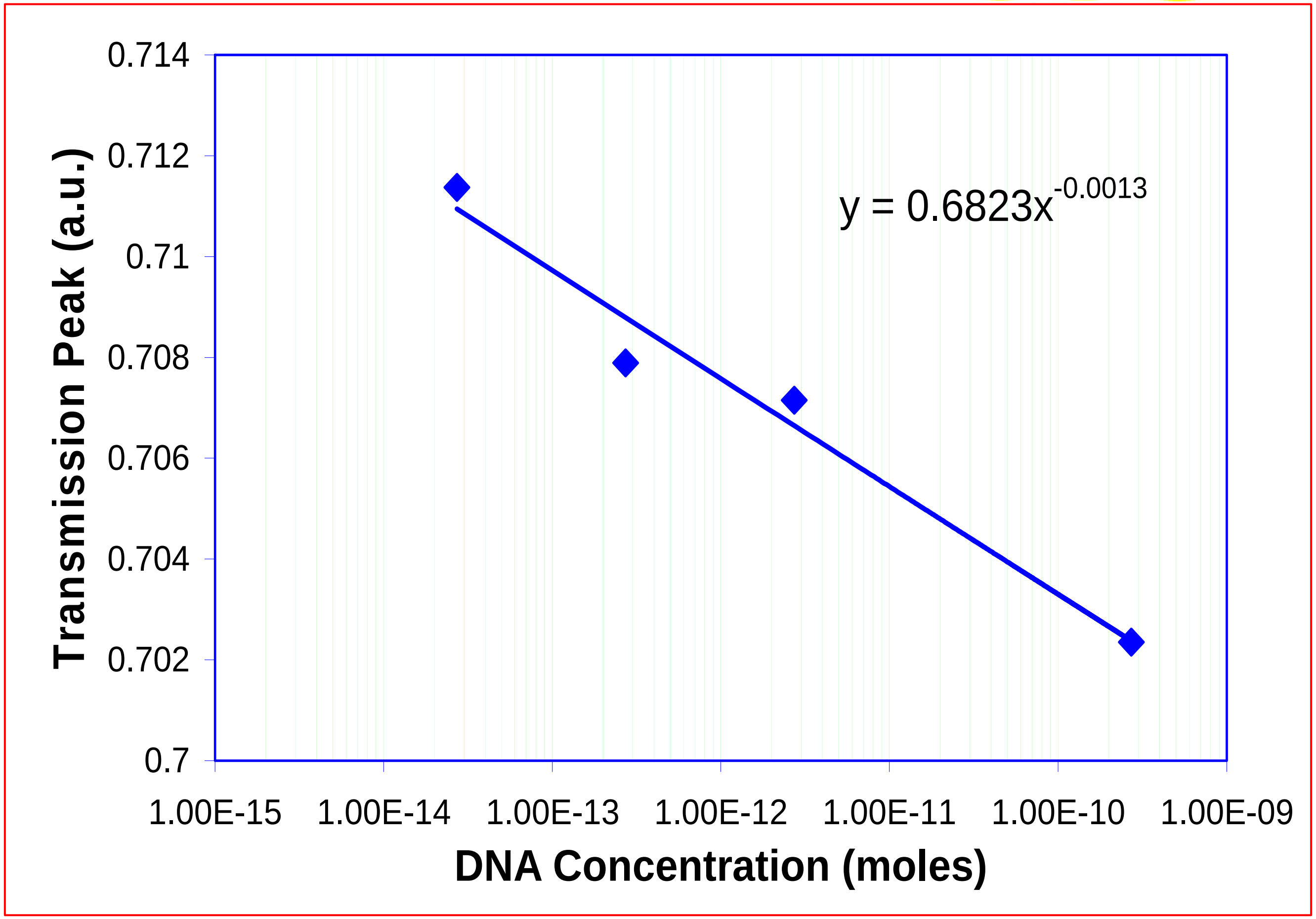
Double stranded DNA molecule showing 9 base pairs.



Temporal spectra of 25-mer oligonucleotides at different concentrations. Systematic concentration dependent transmission peak (absorption) is observed. *(Samples courtesy of Dr. Bruce Stanley of Penn State Molecular Synthesis Facility).*

DNA Quantitation (DFG)

- **Transmission exhibits concentration dependence over wide range: nanoMole to femtoMole**
- **Can be calibrated for other molecular species**
- **Combined with the Fourier spectra, this allow unique identification and quantitation tool**



Concentration dependence of transmission peak of DNA samples. The data follow the Concentration dependent power law within the experimental error.

Significance of DNA measurements

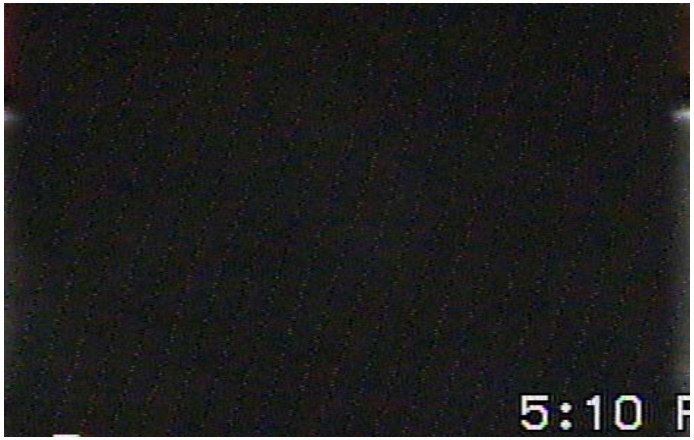
- The results clearly demonstrate the ability of the spectrometer to discern a minute amount of biomolecules.
- From measurements of known concentration, calibration curves can be established for different molecular species.
- The importance of this ability is in the fact that it will be able to identify a disease causing pathogen that may bind to the DNA causing mutation that can not be identified by any other method.
- This capability can be used as a diagnostic tool, as well as for studying molecular reactions such as mutation.
- (a) quantitative mRNA expression analysis without expensive fluorescent labeling or (b) "presence/absence" type experiments e.g., for biodefense field sensors for biological toxic's like cholera or viruses.

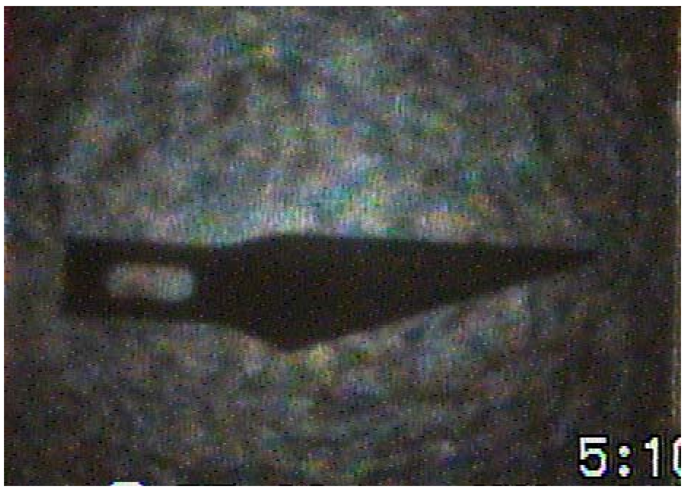
Single-base mutation

"As THz sensing is a direct measure for the amount of hybridization in a DNA sample, it was also demonstrated that this identical approach can be used to observe even ***single-base mutations in DNA samples*** (Nagel *et al* . 2002*a*)."

P. Bolivar, M. Nagel, F. Richter, M. Brucherseifer, H. Kurz, A. Bosserhoff and R. Buttner, **Label-free THz sensing of genetic sequences: towards 'THz biochips',** *Phil. Trans. R. Soc. Lond.* A (2004) **362**, 323–335.

Imaging with DFM T-rays

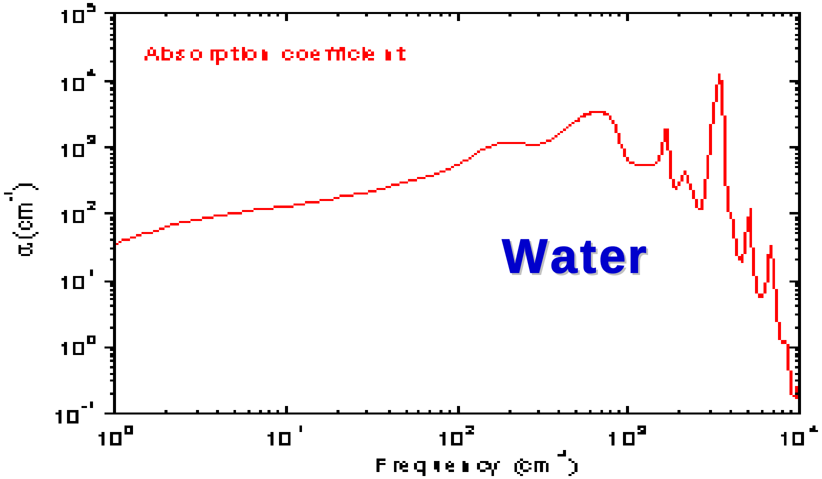


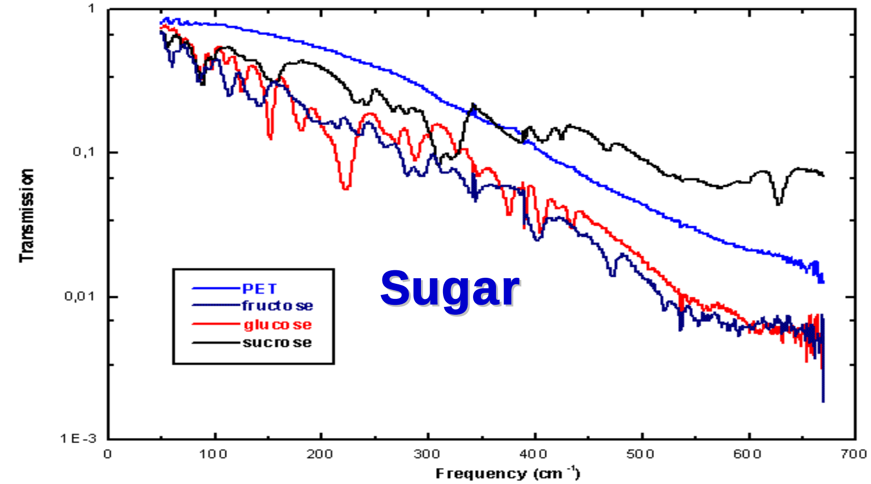


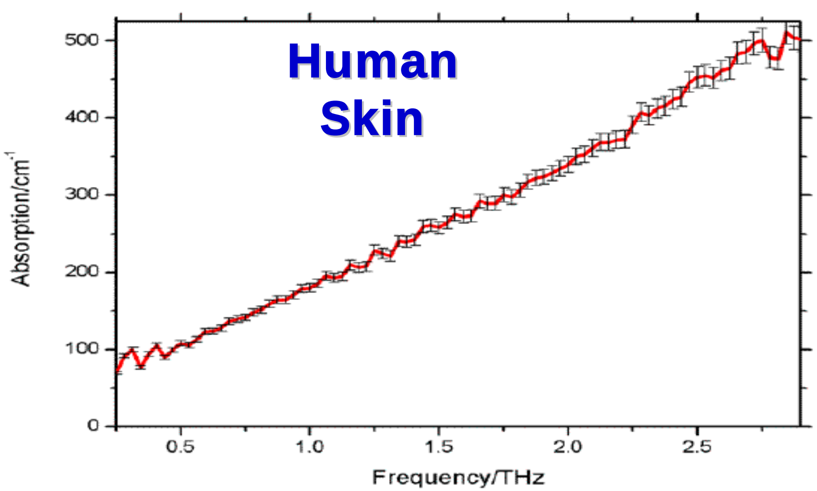
A hidden blade behind a cardboard is revealed with the terahertz source.

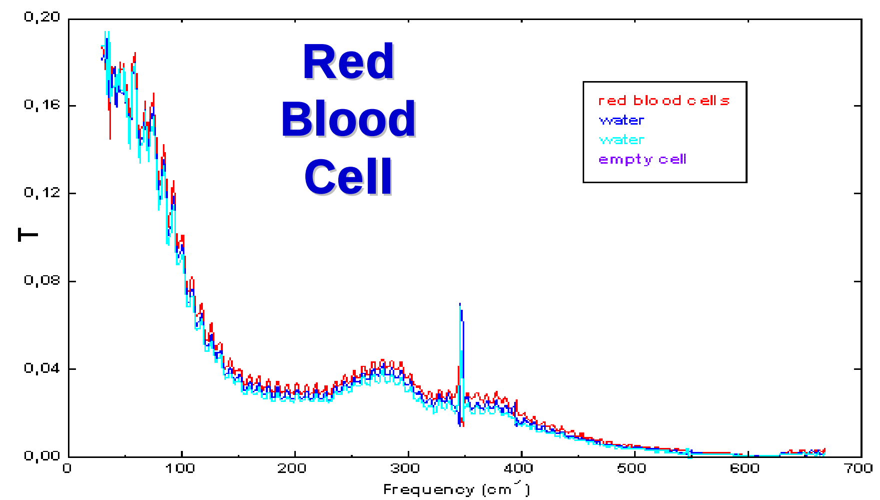
A metallic knife hidden behind a thick dark cloth is revealed by the terahertz beam.

Molecular Signature Spectra





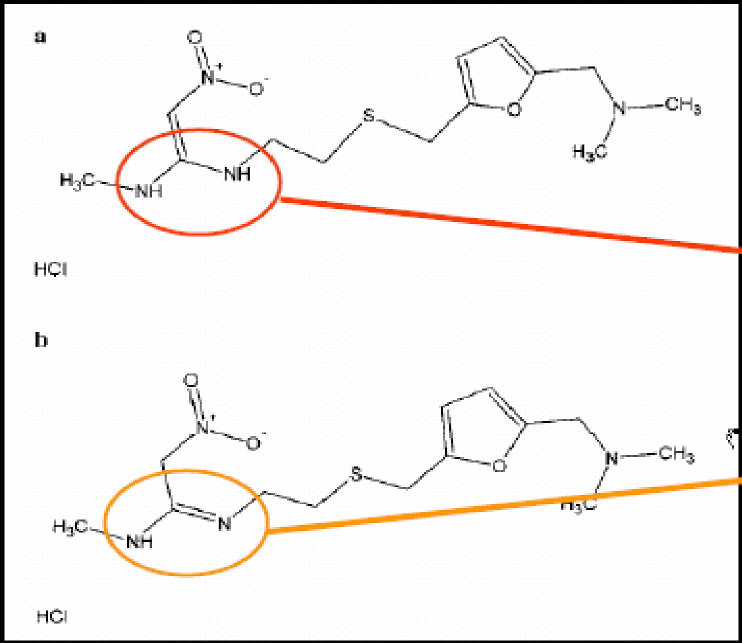


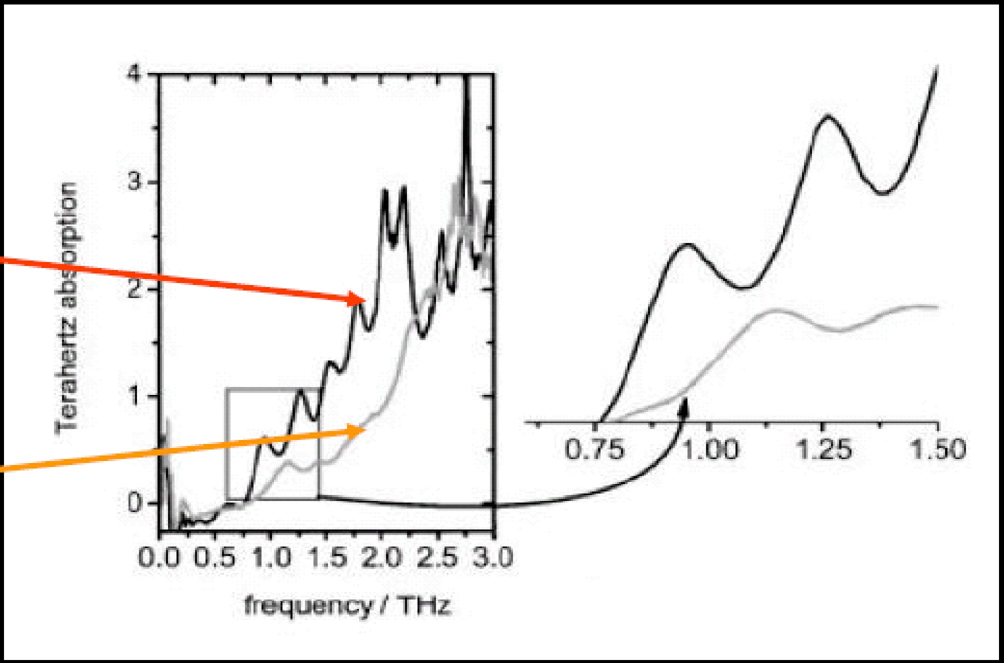


Ref: http://www.frascati.enea.it/THz-BRIDGE/database/spectra/searchdb.htm

Pharmacological Applications: Polymorphs

P.F. Taday, I.V. Bradley, D.D. Arnone and M. Pepper, "Using Terahertz Pulse Spectroscopy to Study the Crystalline Structure of a Drug: A Case Study of the Polymorphs of Ranitidine Hydrochloride," Journal Of Pharmaceutical Sciences, vol. 92, no. 4, pp. 831-838, April 2003. TERAVIEW





T-Ray observations by Teraview of the two conformationally distinct polymorphic forms of ranitidine hydrochloride (a primary constituent of common heartburn medication) have been made on commercial pressed tablets with definite distinguishing spectral characteristics that might be attributed to vibrational phonon modes.

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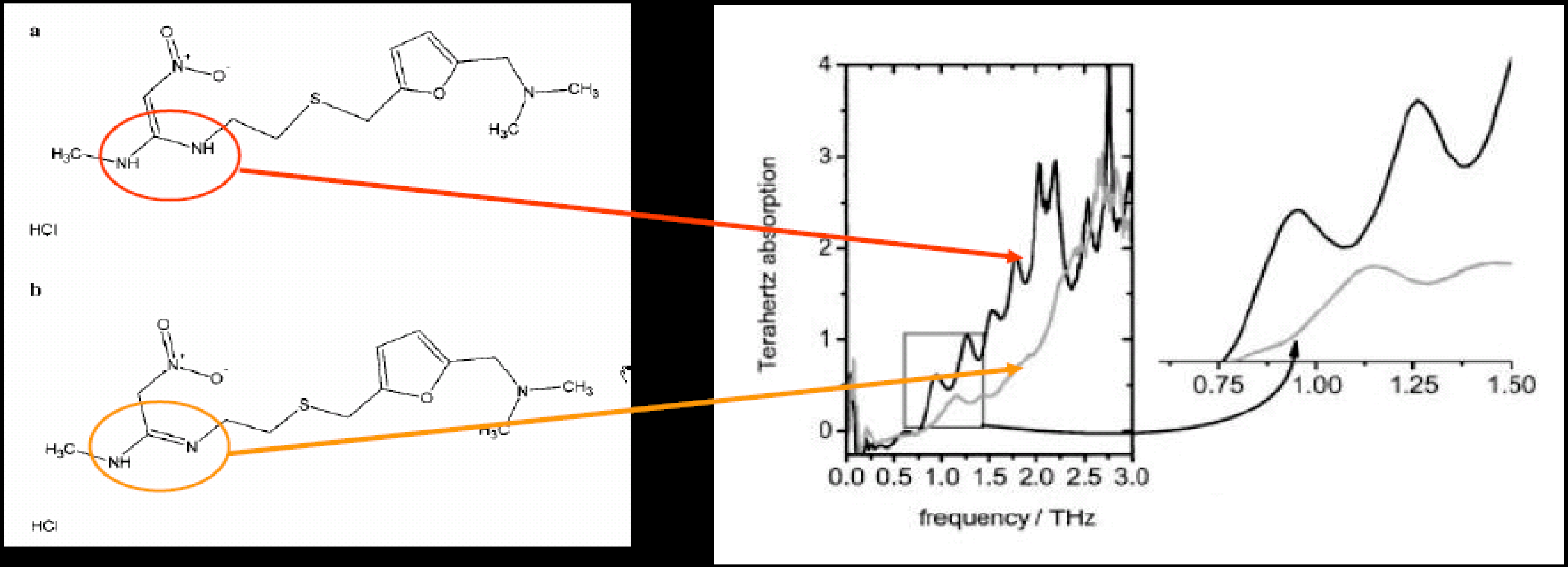
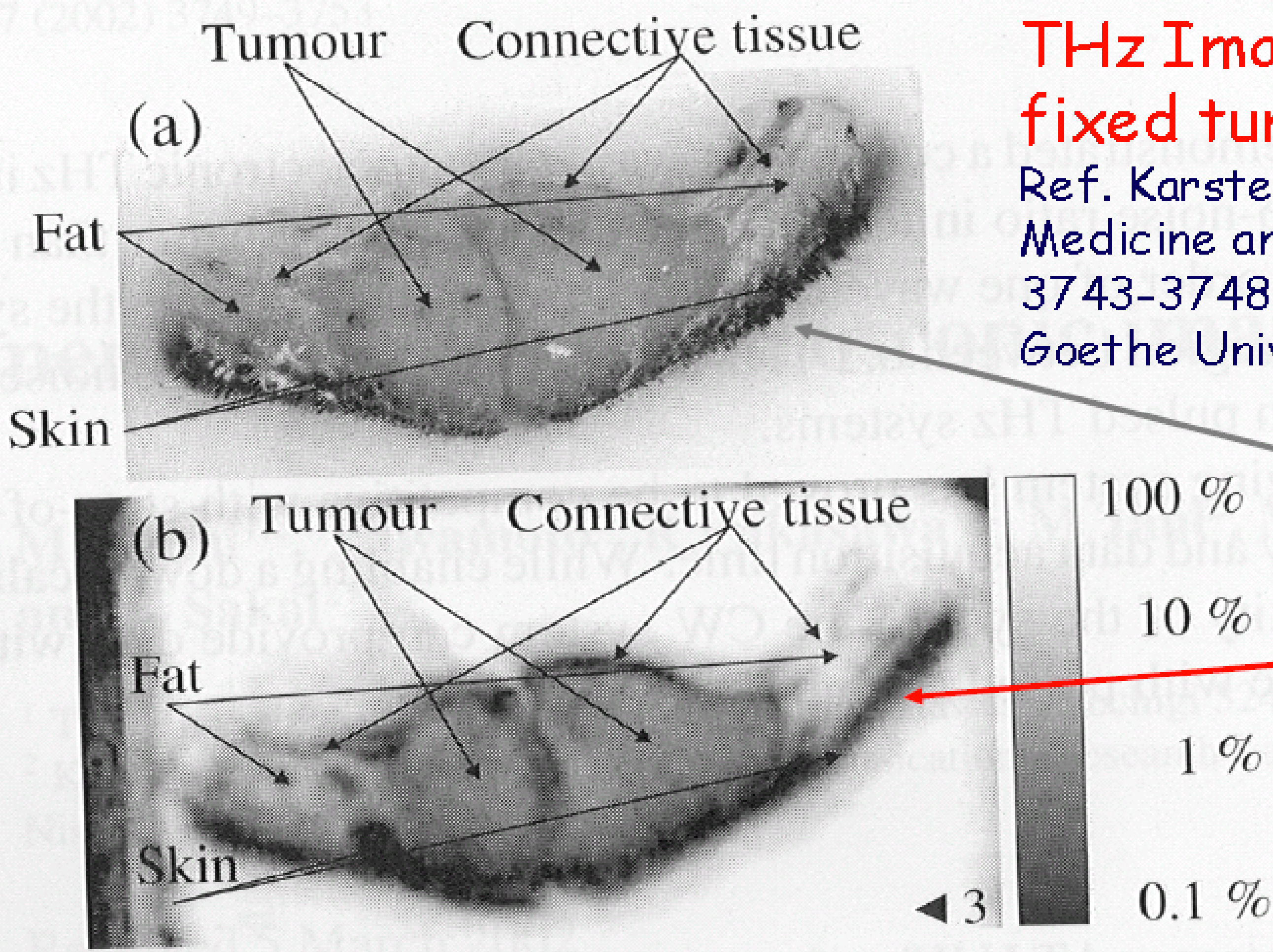


T-Ray observations by Teraview of the two conformationally distinct polymorphic forms of ranitidine hydrochloride (a primary constituent of common heartburn medication) have been made on commercial pressed tablets with definite distinguishing spectral characteristics that might be attributed to vibrational phonon modes.

Imaging of Biological Tissues



THz Image of excised and fixed tumor using TDS

Ref. Karsten et.al. , Physics in Medicine and Biology, v.47, 2002, pp. 3743-3748

Goethe Univ., Germany

OPTICAL IMAGE

THZ IMAGE

Figure 3. (a) Photograph of the sample, a wax-mounted thin-cut canine's basal cell tumour; object size: 32 mm × 24 mm × 3 mm. (b) CW THz power transmission image at 1 THz.

Medical Application: THz Imaging of Basal Cell Carcinoma in-vivo by TeraView

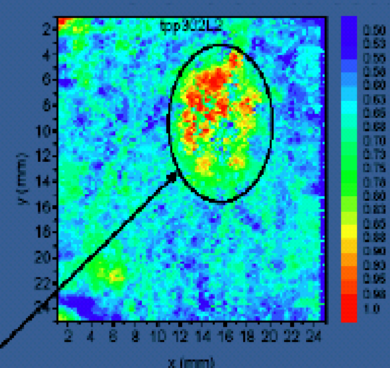
T-Ray Imaging is being applied for the first time to medical diagnostics

Below: In Vivo and Ex Vivo imaging of Basal Cell Carcinomas using the transportable TPI System developed by TeraView Ltd.

In vivo TPI™ images of basal cell carcinoma recorded with TPI scan

BCC on upper forearm

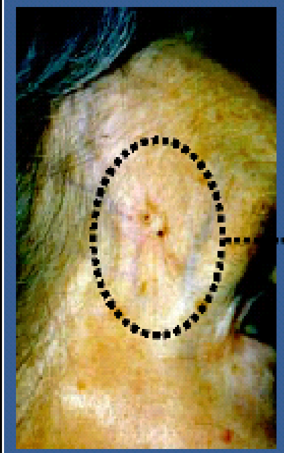
TPI shows buried tissue



Tumor

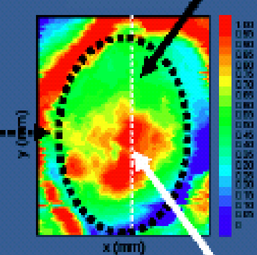
Ex vivo TPI™ images of basal cell carcinoma recorded with TPI scan

Visible picture of patient forehead with suspect lesion



Where is the lesion?

TPI image



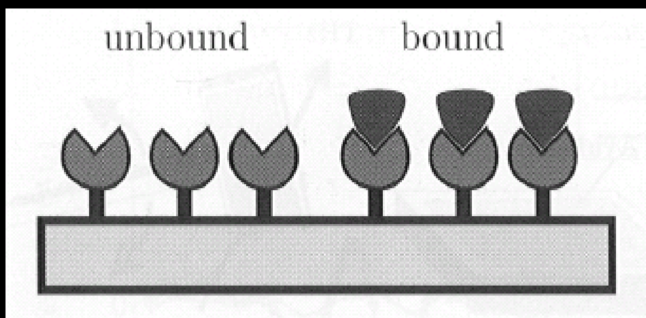
Uniform low absorption (green) by healthy tissue

Large 'hot spots' show huge, invisible tumour under surface of skin

Avidin-Biotin Binding/Disassociation

Disassociation of Avidin-Biotin using TDS

Ref. Mickan, X-C Zhang et.al. , Physics in Medicine and Biology, v.47, 2002, pp. 3789-3795, RPI



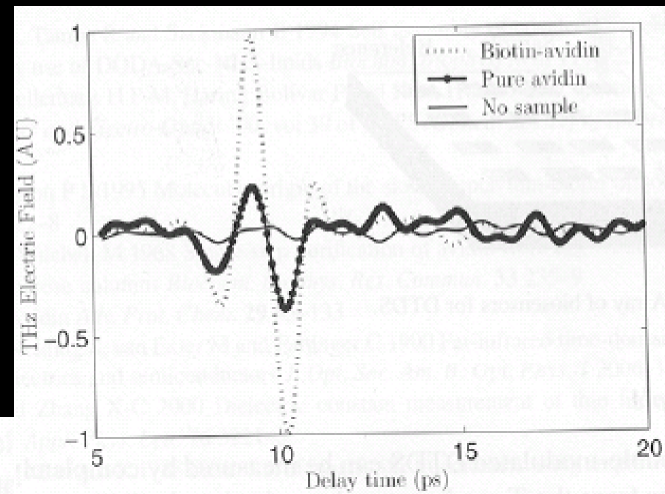


Figure 4. Time-domain differential T-ray pulses (output from LIA2). These waveforms have been normalized to the peak of the biotin–avidin waveform and smoothed using a 0.15–0.95 THz band-pass filter. The three cases shown are (1) the signal from the biotin–avidin interface, (2) noise from topographic variations in the pure avidin film and (3) inherent noise in the DTDS system 'no sample'. The variability in the biotin–avidin over multiple scans is less than the thickness of the plotted line. Each waveform shown was measured with a time constant of 1 s on LIA2.

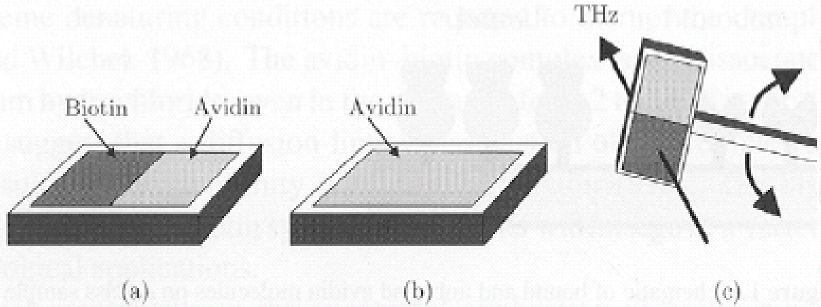
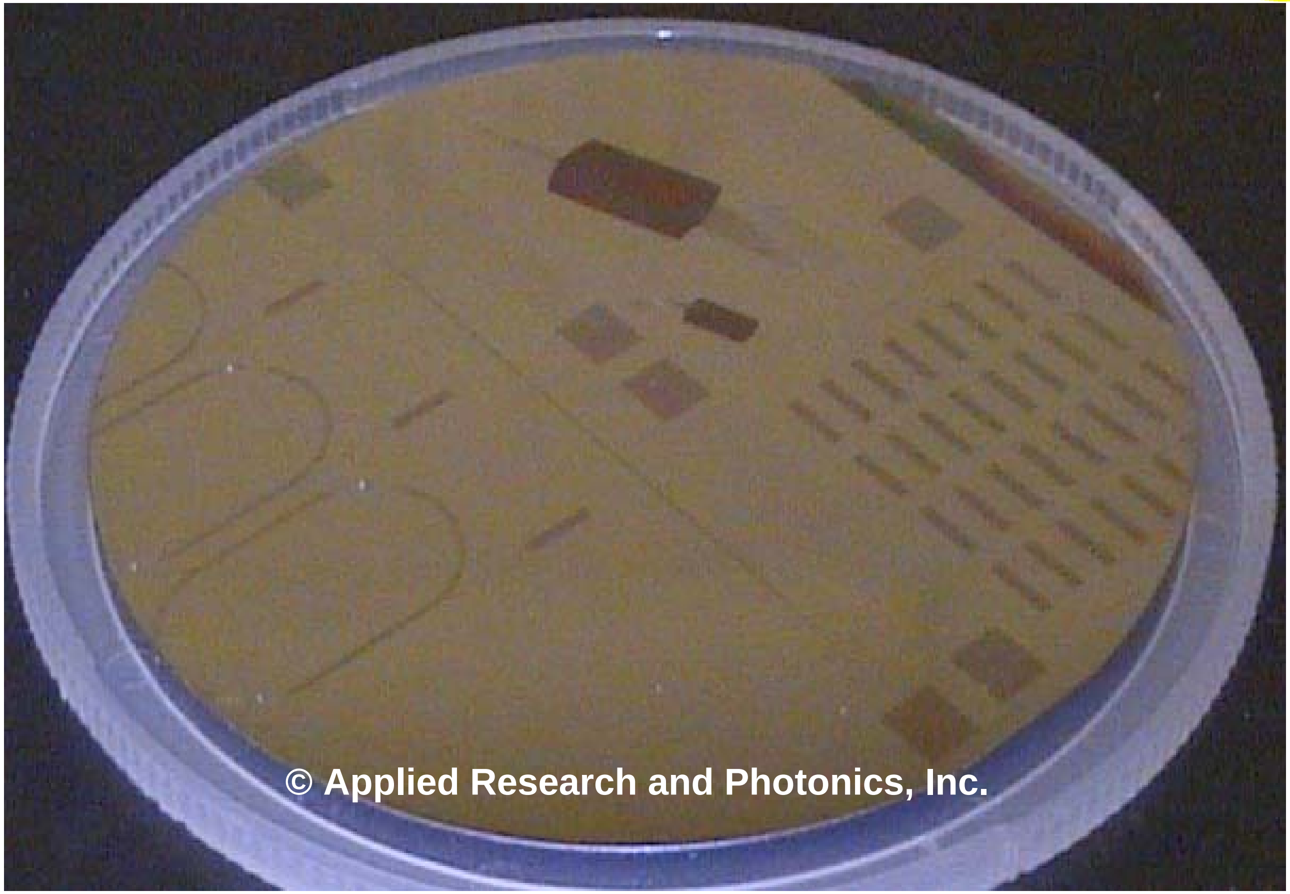


Figure 3. Biosensor slide configurations used in DTDS. The two slides, (a) biotin–avidin slide and (b) pure avidin test slide, were prepared as detailed in section 2, and mounted for DTDS as in (c).

Concluding remarks

- Creating value from innovation.
- Solving problems in biomedical, pharmaceutical, proteomics, genomics, and other ‘omics.
- Dendrimer based system can bring the cost down and improve the performance
- Opportunity for investment to tap into unmet market needs
- Ample opportunity of economic growth

Photonic components



Demonstration of photonic components from dendrimer

Fabricated at Penn State University Nanofab Facility