LAMELIS 2017
Lasers in Medicine and Life Sciences

Terahertz photonics for biomedical applications

Dr. Mikhail K. Khodzitsky
PhD student Tianmiao Zhang
THz Biomedicine Laboratory

ITMO UNIVERSITY
THz Bio Lab
University of Szeged Where knowledge and challenge meet
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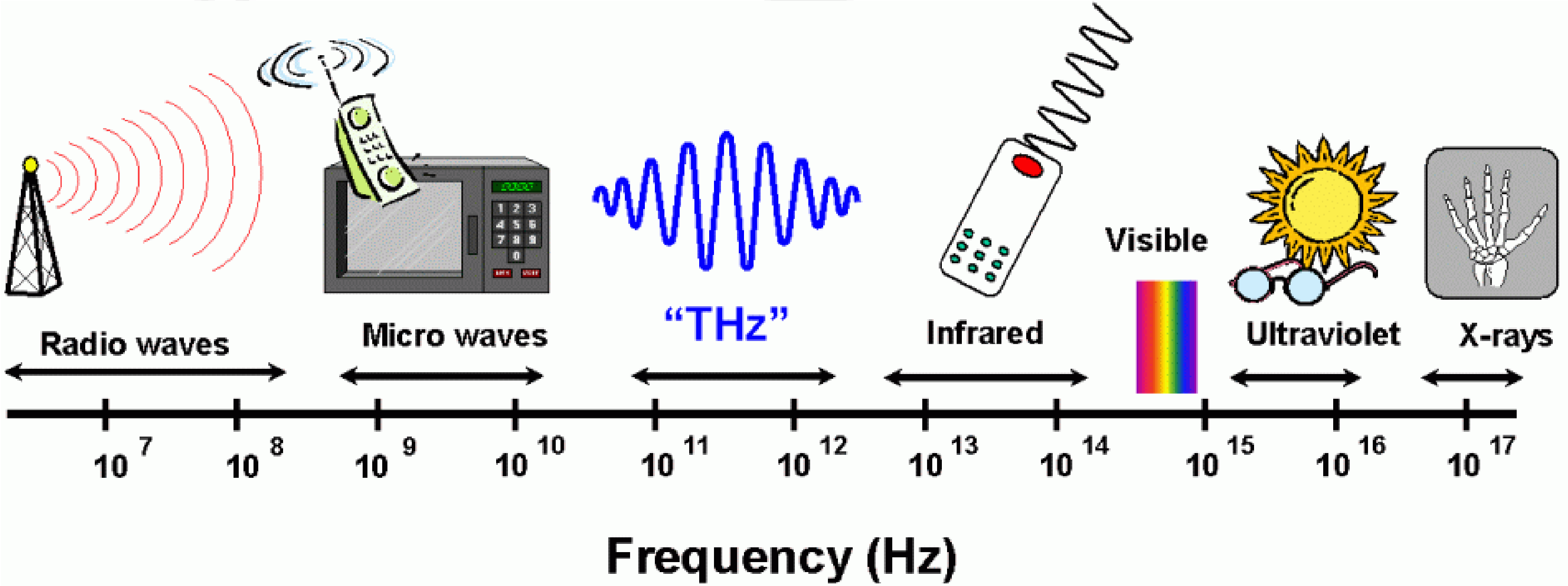
Outline

- **THz photonics:**
  - Benefits and disadvantages of THz waves;
  - THz generators and detectors;
  - THz time-domain spectroscopy;
  - THz time-domain imaging
- **Biomedical applications:**
  - Spectroscopy of small & macro biomolecules;
  - Spectroscopy and imaging of cells and tissues;
  - Hydration of Molecules and Its THz Response;
  - Quality control of pharmaceutical products
- **Our results:**
  - Diagnosis of glucose level in blood and gastric cancer;
  - Determination of water concentration;
  - Influence of THz radiation on glial cells;
  - Development of tunable THz filters and absorbers

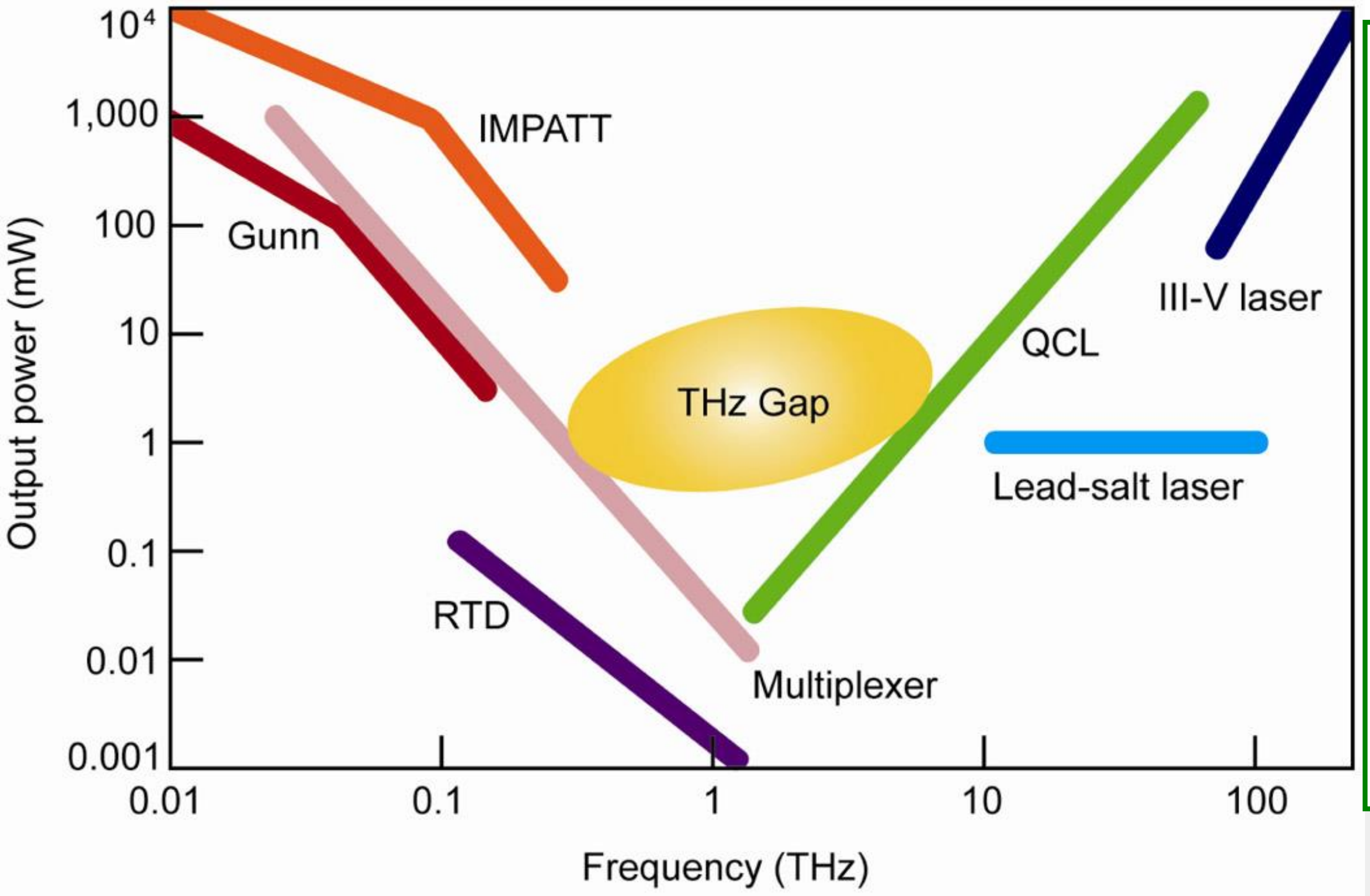
Terahertz radiation

Frequency range: 0,1 - 10 THz
Wavelength range: 3 mm – 30 microns
Equivalent temperature: 1 – 100 K



Tera is a unit prefix in the metric system denoting multiplication by 10^{12} or 1000000000000 (one trillion short scale; one billion long scale). It has the symbol **T**. *Tera* is derived from Greek word τέρας *teras*, meaning "monster". The prefix *tera-* was confirmed for use in the SI in 1960.

Terahertz frequency gap



Terahertz (THz)-power performance of different sources around the THz gap.

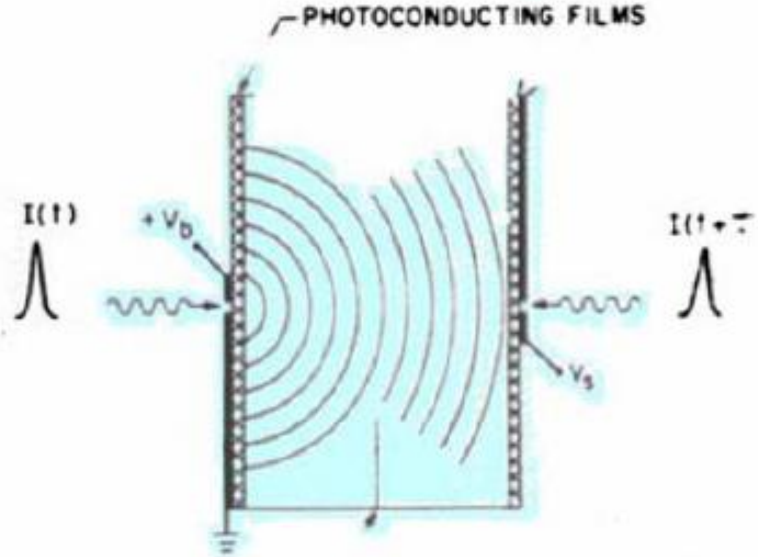
RTD: Resonant tunnel diode.
IMPATT: Impact ionization avalanche transit-time diode.
Gunn: Gunn laser.
QCL: Quantum-cascade laser.
III–V: Denotes groups III and V in the periodic table of elements.

Invention of THz time-domain spectroscopy

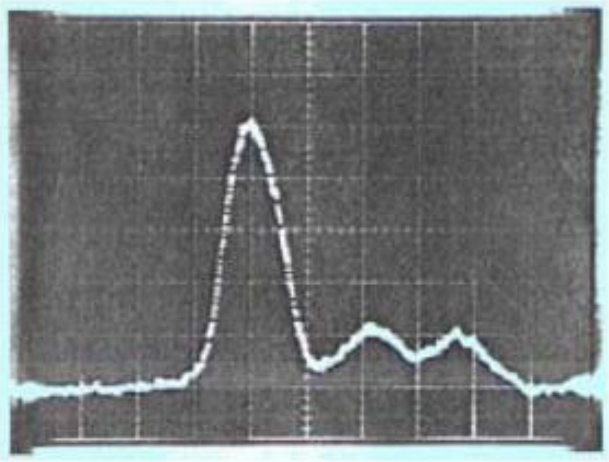
Picosecond photoconducting Hertzian dipoles

Appl. Phys. Lett. 45 (3), 284 (1984)

D. H. Auston, K.P. Cheung, and P. R. Smith



Experimental configuration.



Measured response.

The unique nature of THz waves

- ✓**Low photon energies:** thus cannot lead to photoionization in biological tissues as can X-rays. As a result, THz waves are considered safe for both the samples and the operator.
- ✓**Extreme water absorption:** THz waves cannot penetrate into the human body like microwaves can. Therefore, even if THz waves do cause any harm, it is limited to skin level.
- ✓**Longer wavelengths than visible and IR waves:** this means THz waves are less affected by Mie scattering. THz waves are transparent to most dry dielectric materials, such as cloth (or bandages), paper, wood, and plastic. THz waves are considered very promising in nondestructive evaluation applications.
- ✓**Strong absorption by molecules**: At THz frequencies, many molecules exhibit strong absorption and dispersion due to dipole-allowed rotational and vibrational transitions. These transitions are specific to the molecule and therefore enable spectroscopic fingerprinting in the THz range.
- ✓**Time-domain:** Coherent THz signals can be detected by mapping the transient electric field in amplitude and phase. This gives access to absorption and dispersion spectroscopy.

The main applications of THz waves

Disadvantages of THz photonics

- ✓Current pulsed THz wave emitters offer **extremely low-conversion efficiency** from the input laser power into THz wave power, and a lock-in amplifier has to be used to increase the SNR and time constants around ms are usually set.

- ✓**The high water-vapor absorption** significantly weakens the THz wave signal during its propagation in air and, therefore, it is a challenge to accomplish remote sensing with THz waves in air over several meters

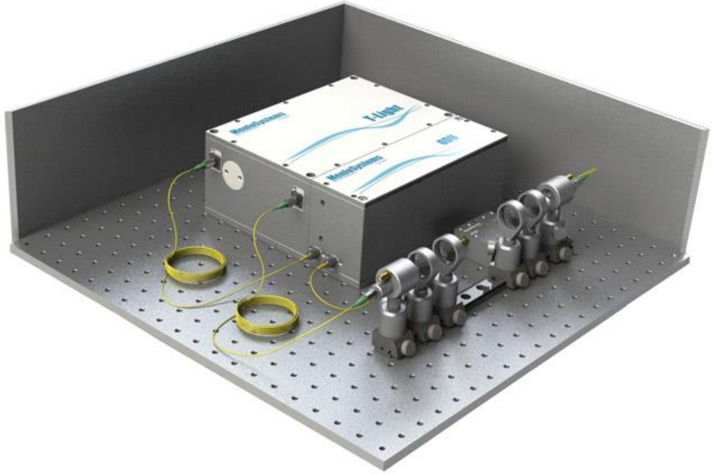
- ✓**Thick samples**, or samples with a high absorption coefficient in the THz range, greatly attenuate the transmitted THz wave and in some cases only the reflected or scattered THz wave signal can be collected and analyzed, although the signal is very weak.

Terahertz commercial systems

Teraview

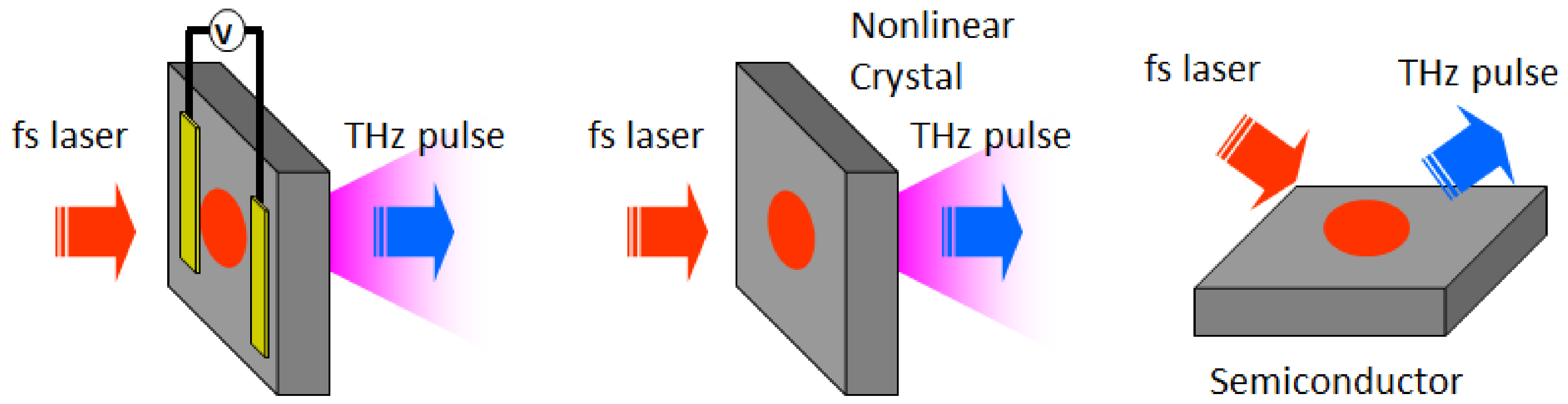
Ekspla

Toptica



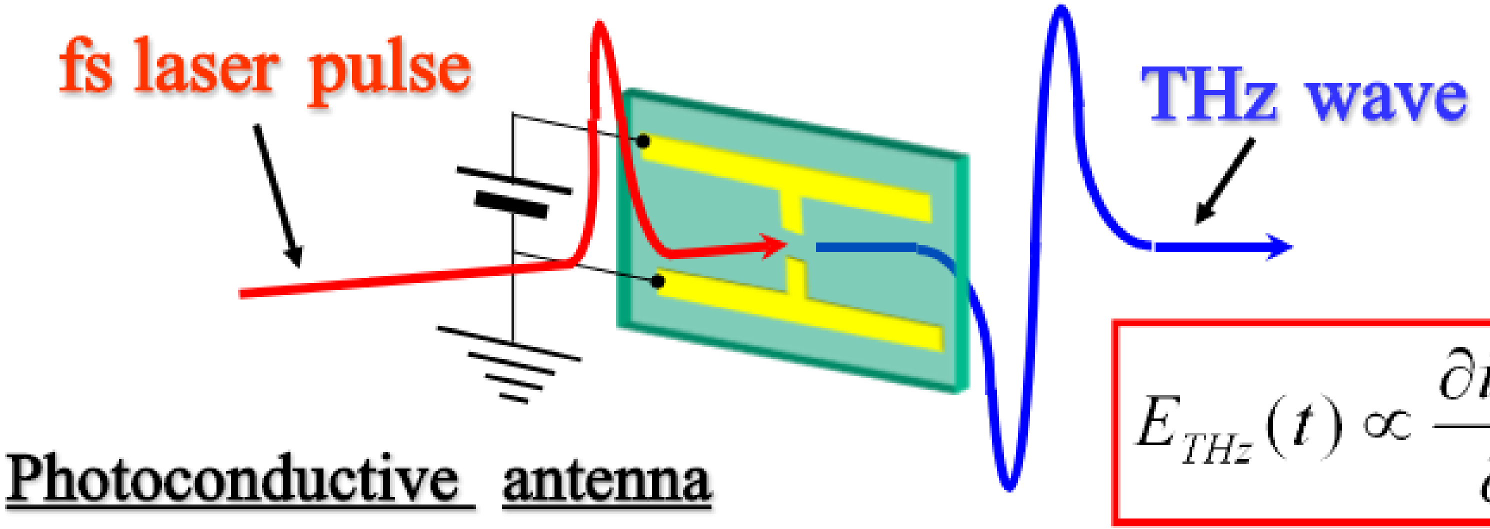
MenloSystems

THz pulse generation

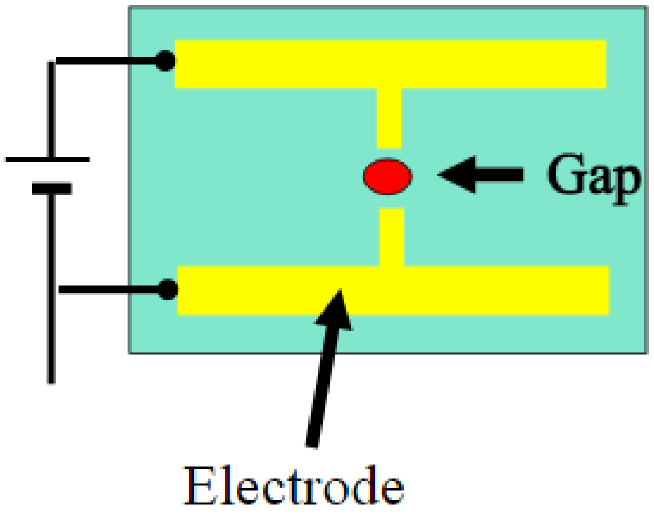


Photoconductive Antenna **Optical Rectification** **Semiconductor Surface**

THz pulse generation: photoconductive antenna



$$E_{THz}(t) \propto \frac{\partial i(t)}{\partial t}$$



fs laser pulse is focused on the gap

↓

Generation of carriers

↓

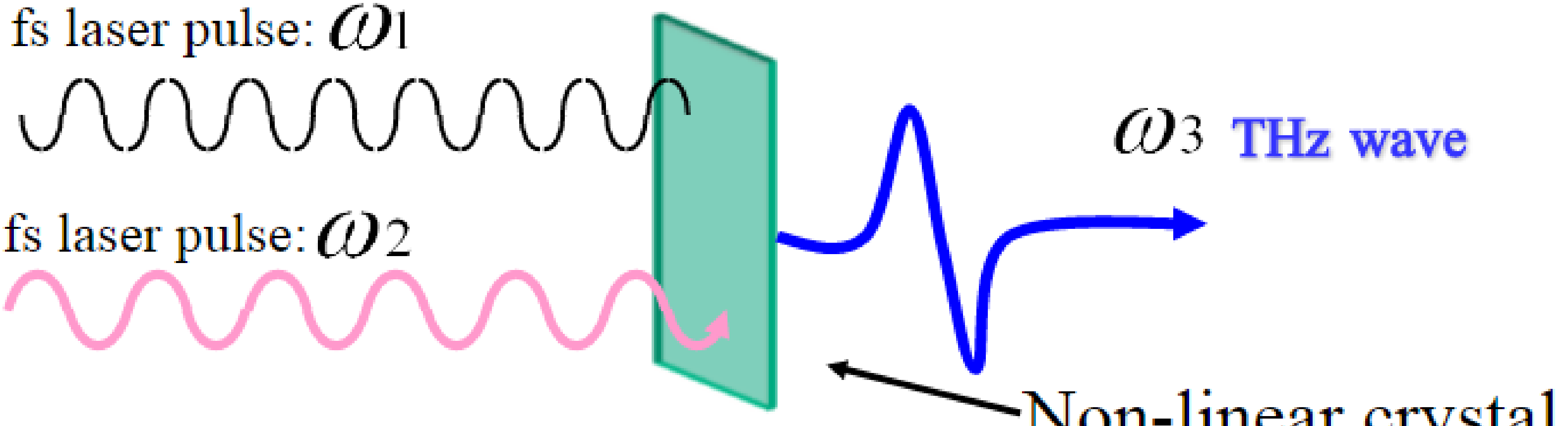
Transient current

↓

Emission of THz wave

THz pulse generation: optical rectification

Optical rectification ➡ <u>second-order non-linear optical effects</u>



①fs laser pulses falls on the NL-crystal

②Nonlinear polarization generates

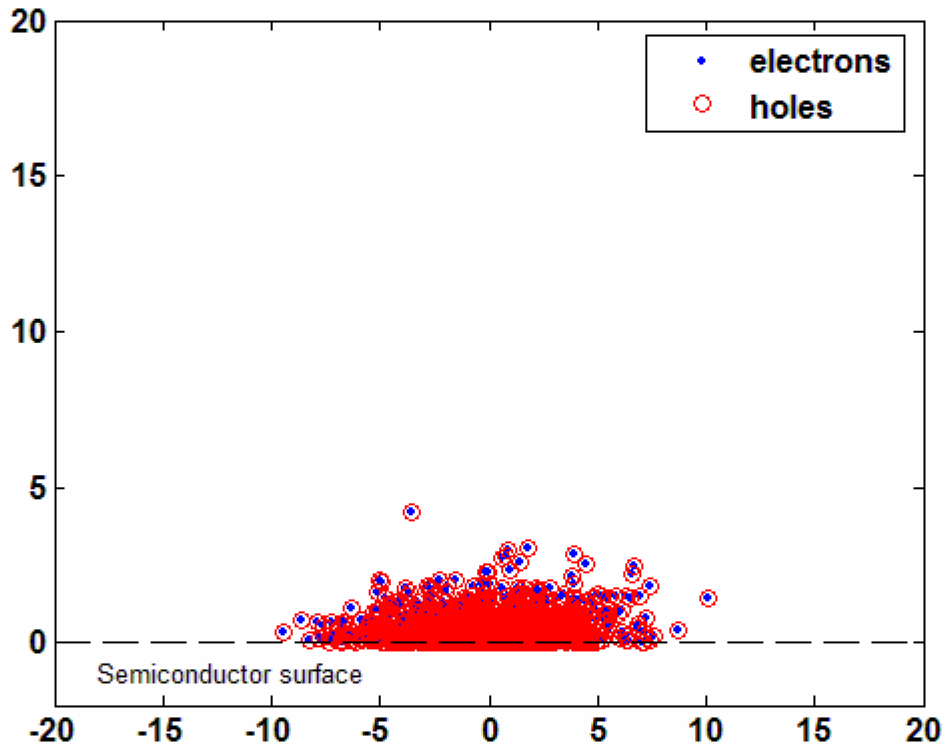
$$p_i(\omega_3) = \sum_{j,k=x,y,z} \chi^{(2)}_{ijk}(\omega_3;\omega_1-\omega_2)E_j(\omega_1)E^*_k(\omega_2)$$

③Electromagnetic wave ω_3 is emitted

* $\omega_3 = \omega_1 - \omega_2$

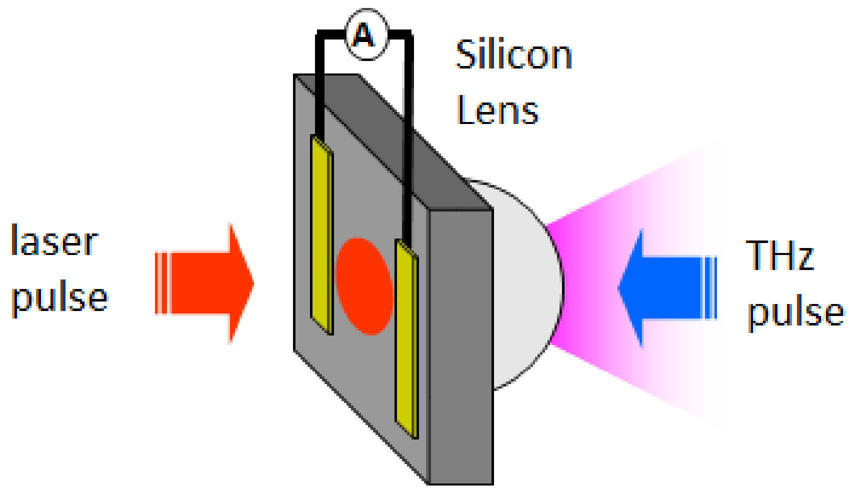
Because a femtosecond pulse contains many frequency components, any two frequency components contribute to the difference-frequency generation

THz pulse generation: Photo-Dember effect

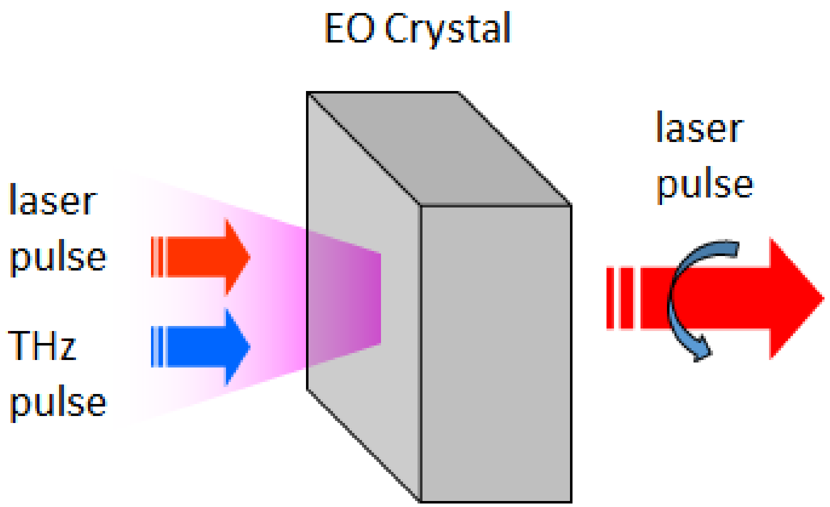


In semiconductor physics, the **Photo–Dember effect** is the formation of a **charge dipole** in the vicinity of a semiconductor surface after ultra-fast photo-generation of charge carriers. The dipole forms owing to **the difference of mobilities** for holes and electrons which combined with the break of symmetry provided by the surface lead to an effective charge separation in the direction perpendicular to the surface.

THz pulse detection

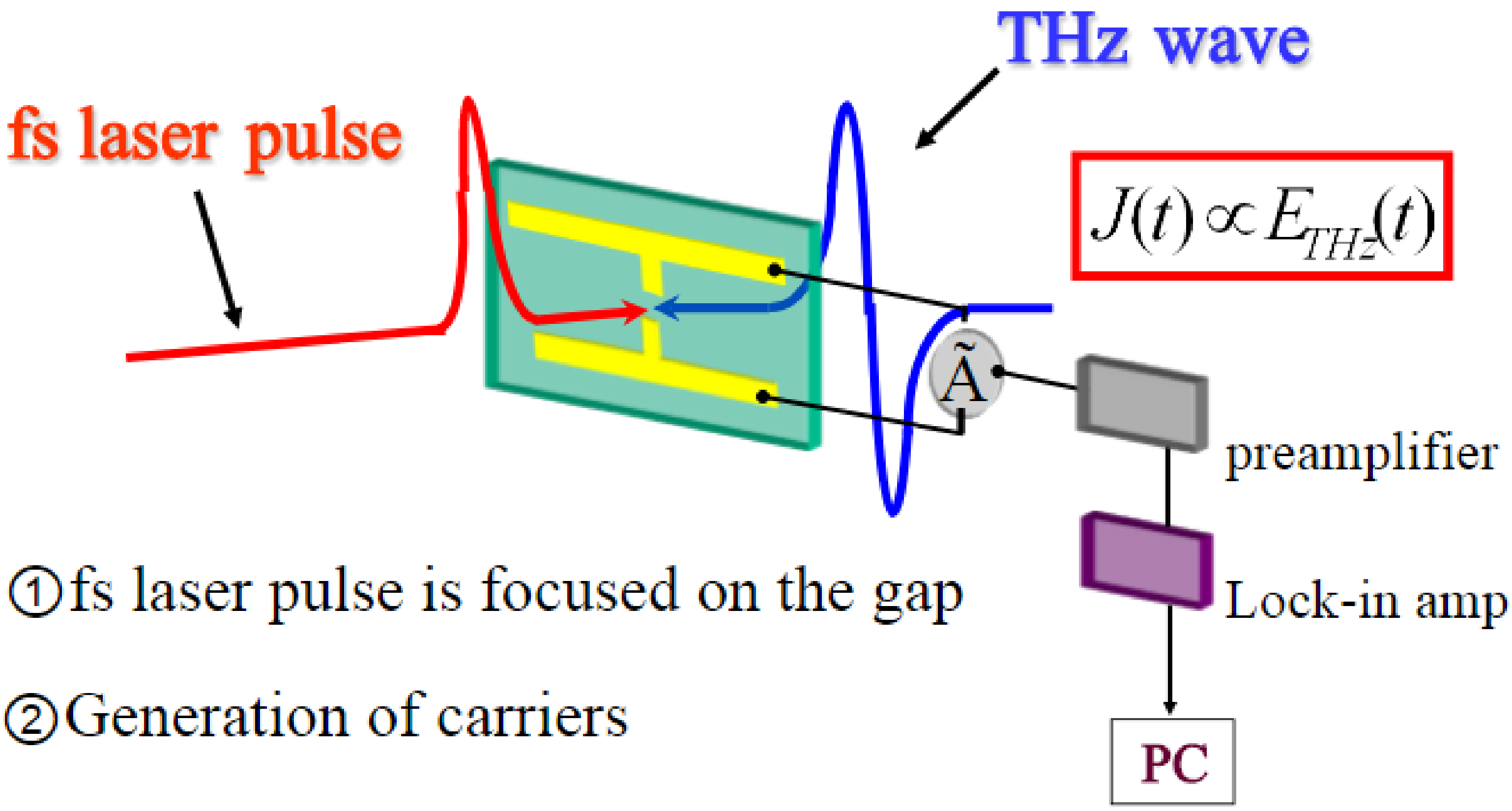


Photoconducting Antenna



Electro-Optic Detection

THz pulse detection: photoconductive antenna



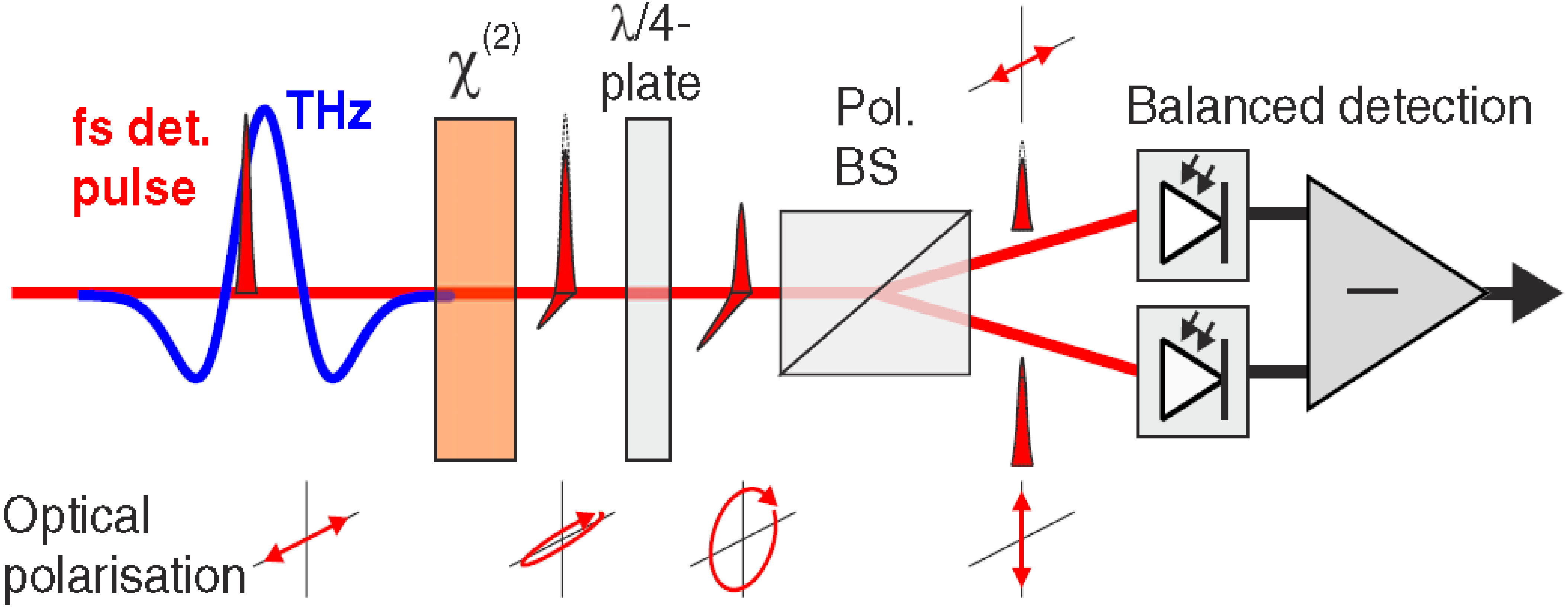
①fs laser pulse is focused on the gap

②Generation of carriers

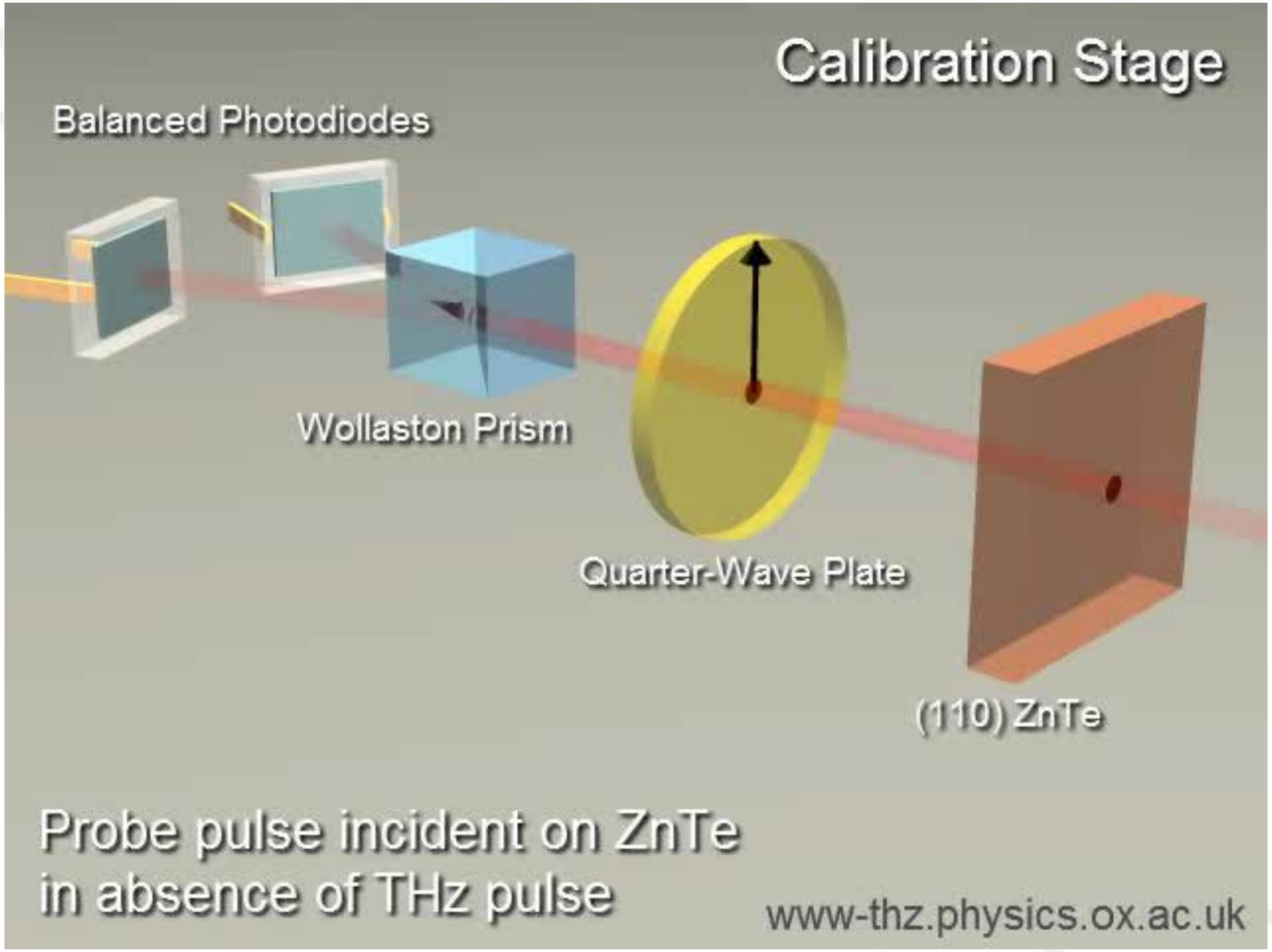
③Carriers are accelerated by THz electric field

Carriers movement → Current signal of $E_{THz}(t)$

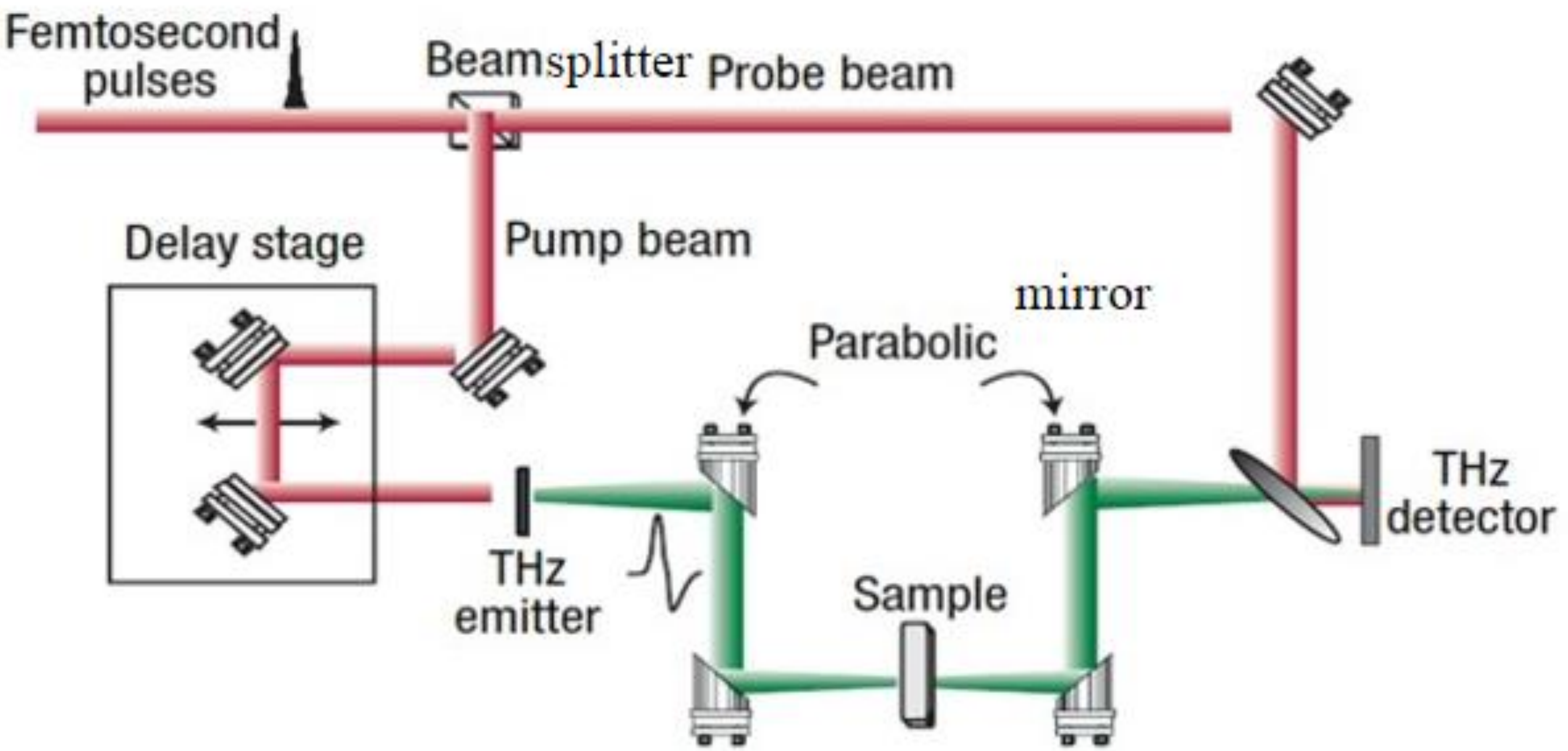
THz pulse detection: electro-optic detection



THz pulse detection: electro-optic detection

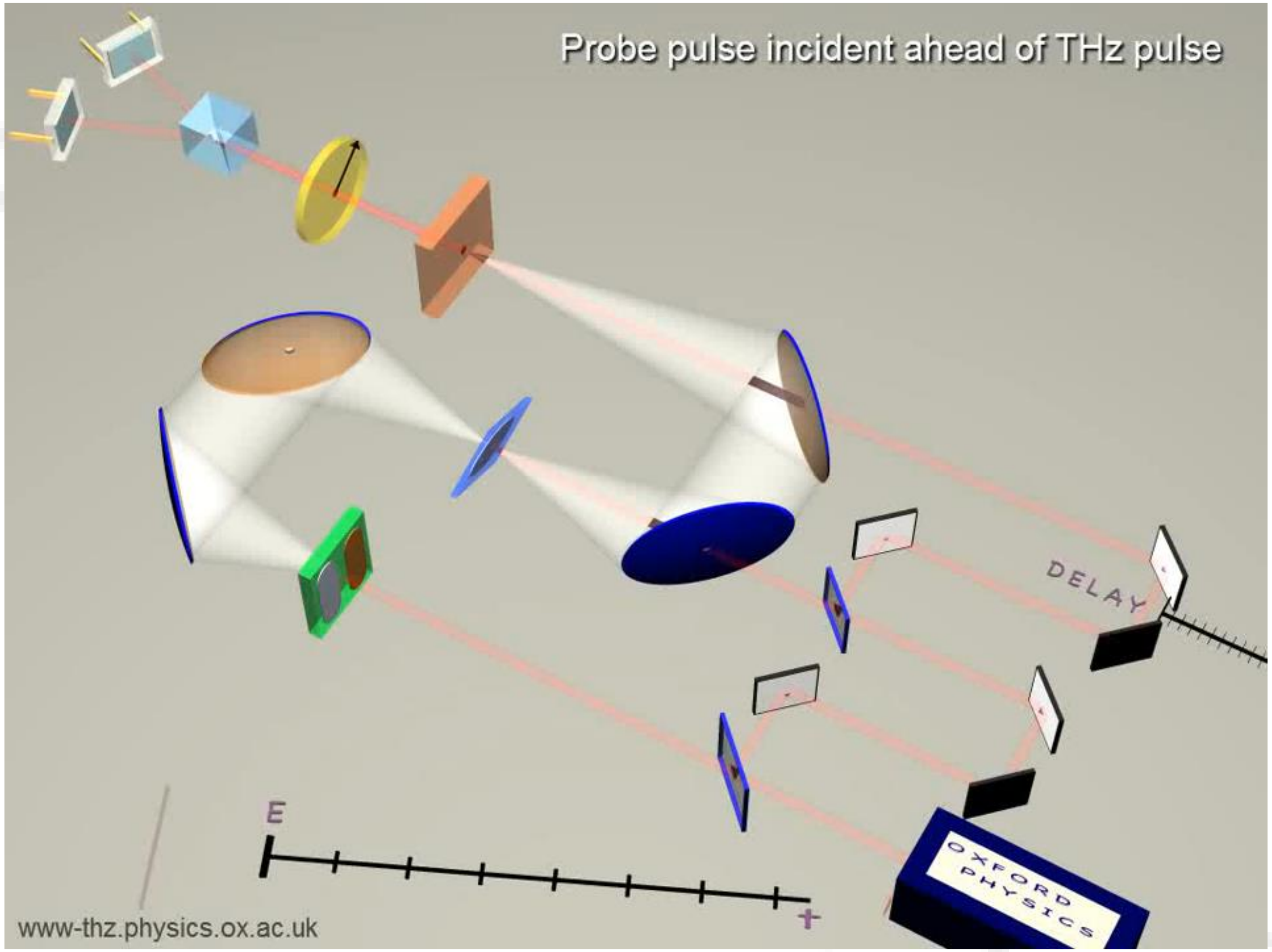


THz Time-domain Spectrometer (THz TDS)

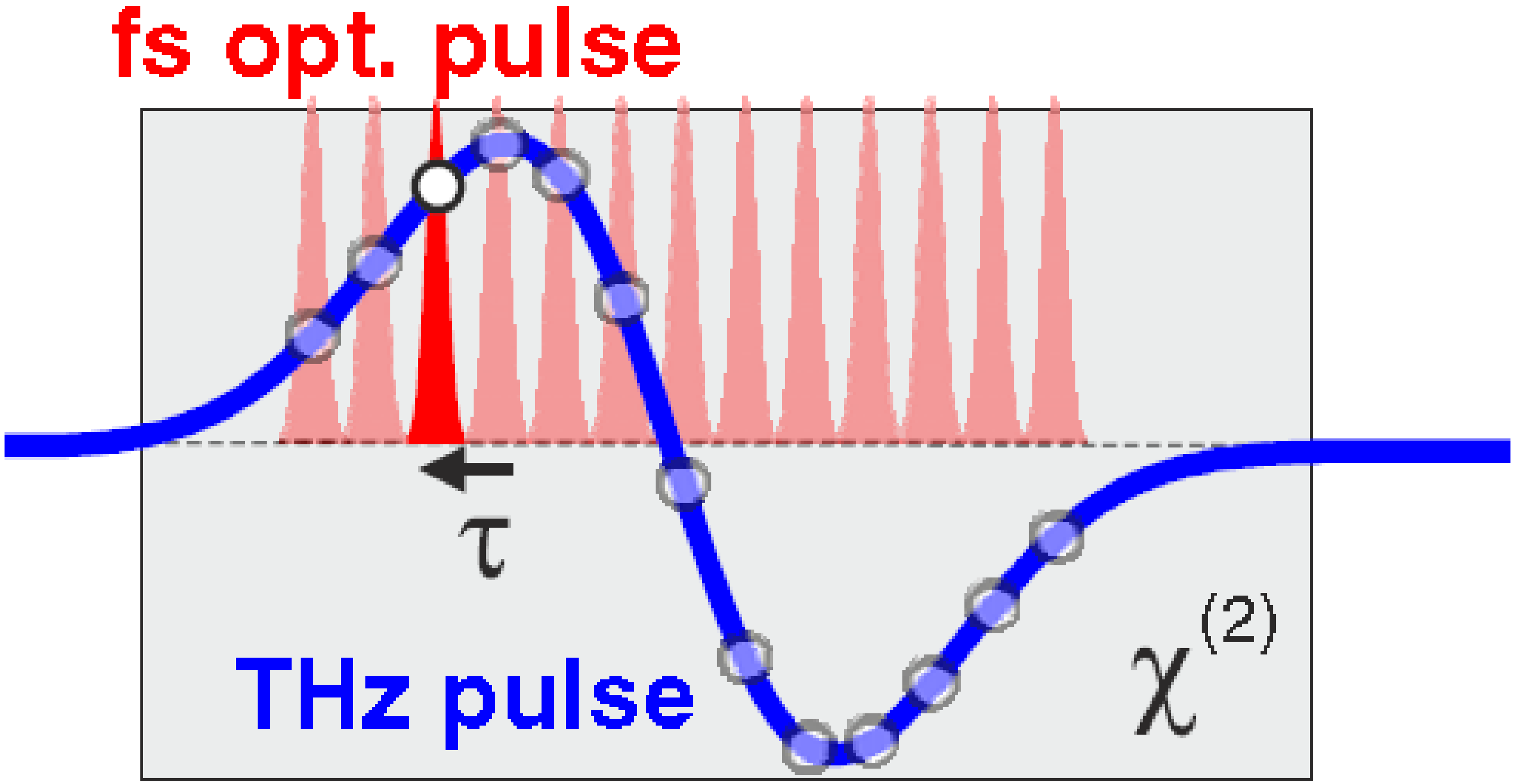


We can get the **amplitude** and **phase** of electromagnetic wave at the same time!!

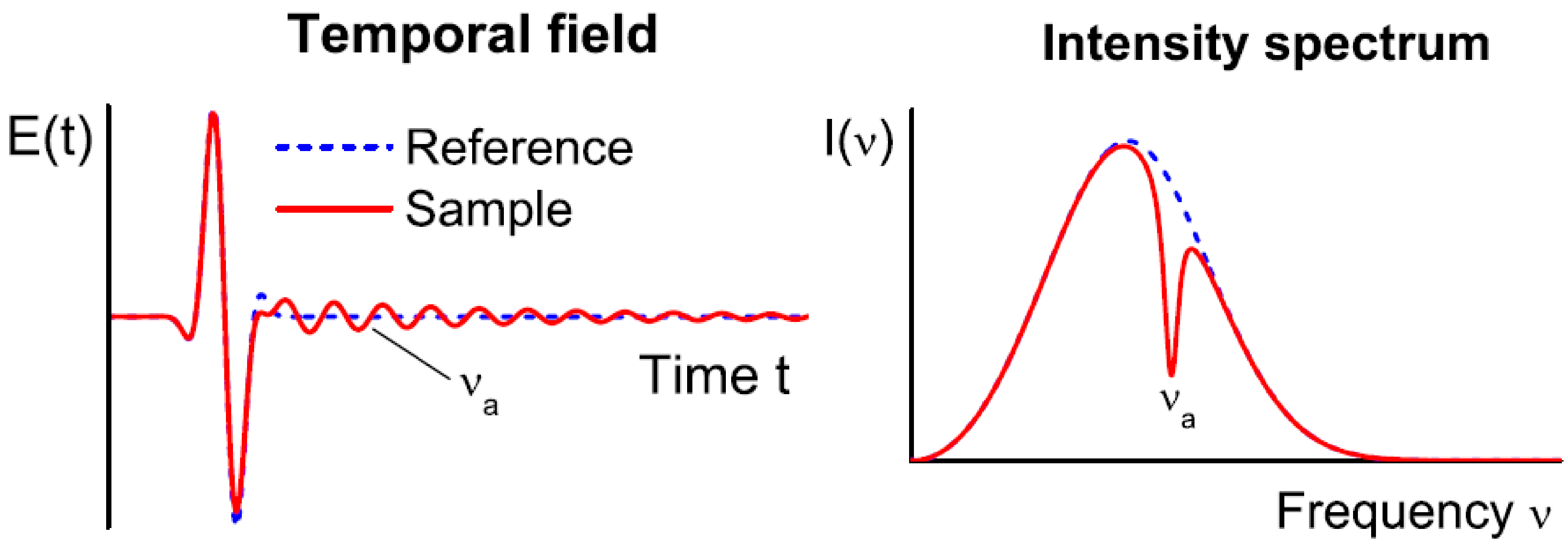
THz time-domain spectrometer



Electro-optic sampling



Terahertz spectral analysis



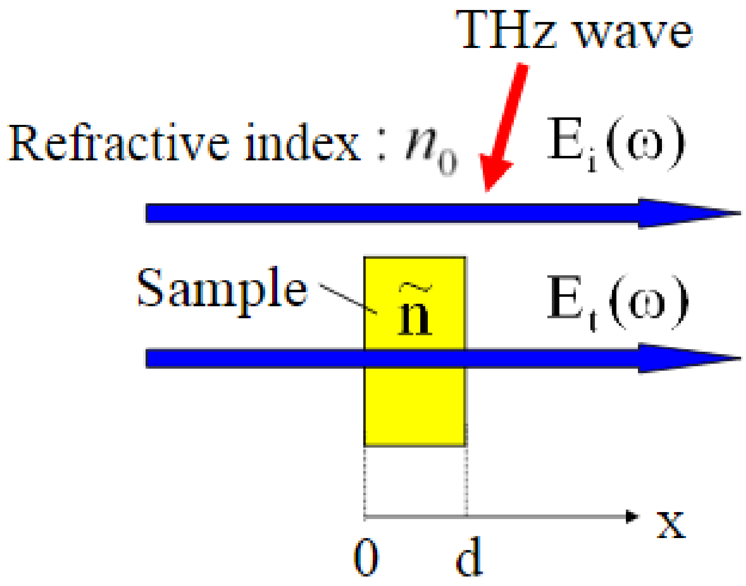
$$\tilde{E}(\omega) \equiv A(\omega)e^{-i\phi(\omega)} = \int dtE(t)e^{-i\omega t}.$$

Dispersion of optical properties

At x=d

$$E_i(\omega) = E_0 \exp\left\{ i\left(\frac{n_0 \omega d}{c} + \phi \right) \right\}$$

$$E_t(\omega) = E_0 \exp\left\{ i\left(\frac{\tilde{n}(\omega) \omega d}{c} + \phi \right) \right\}$$



$$T(\omega) = \left| \frac{E_t(\omega)}{E_i(\omega)} \right|^2 \qquad \Delta\phi(\omega) = \phi_t(\omega) - \phi_i(\omega)$$

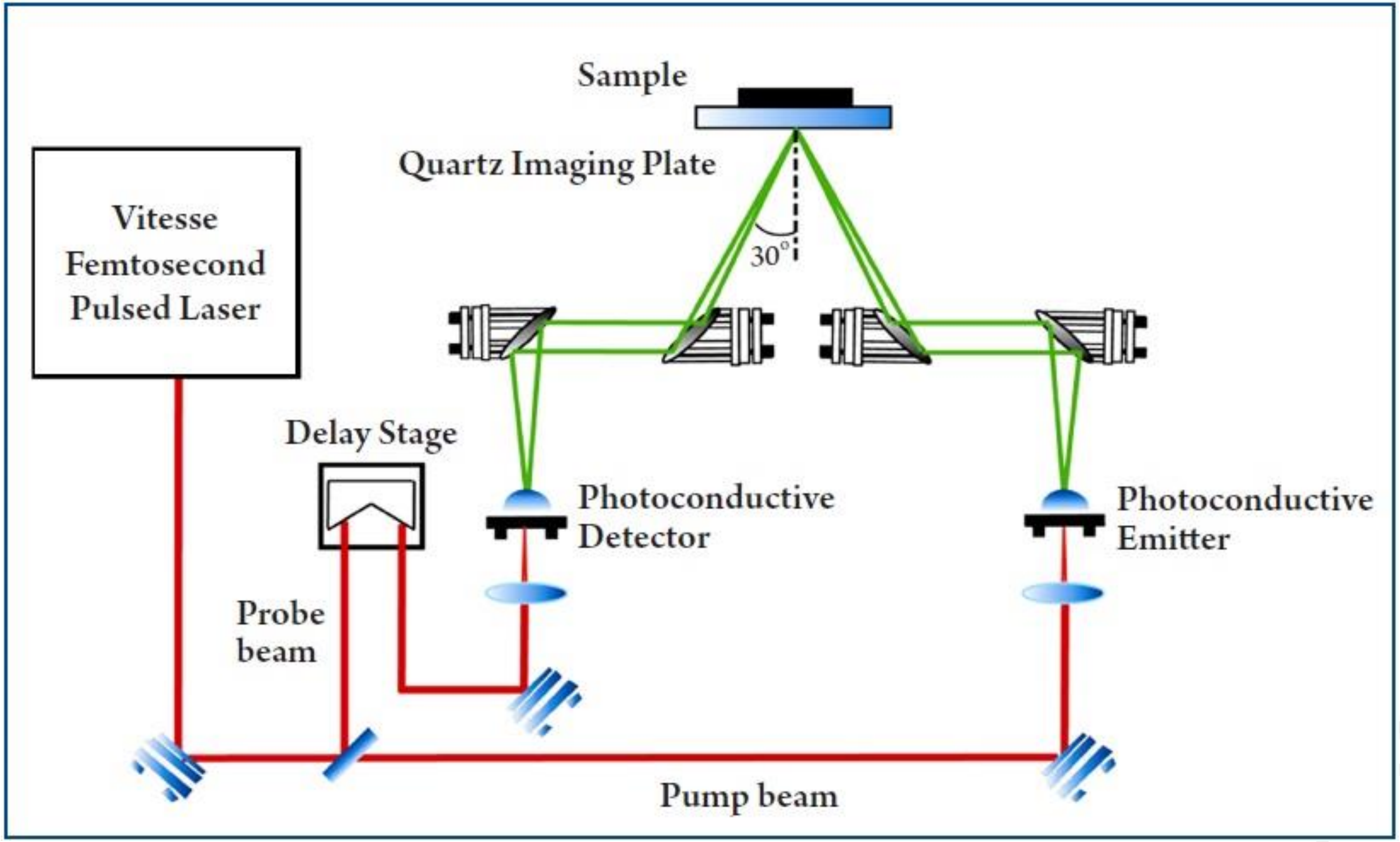
Refractive index: $n(\omega) = \frac{c}{\omega d} \Delta\phi(\omega) + n_0$ Extinction coefficient: $\kappa(\omega) = -\frac{c}{2\omega d} \ln T(\omega)$

Complex index of refraction : $\tilde{n}(\omega) = n(\omega) + i\kappa(\omega)$

Types of THz spectroscopy

- Reflection spectroscopy
- Transmission spectroscopy
- Absorption spectroscopy
- Emission spectroscopy
- Dielectric spectroscopy
- Relaxation spectroscopy
- «Optical pump-THz probe» spectroscopy
- Attenuated total reflectance spectroscopy
- Differential spectroscopy

THz Time-domain imaging



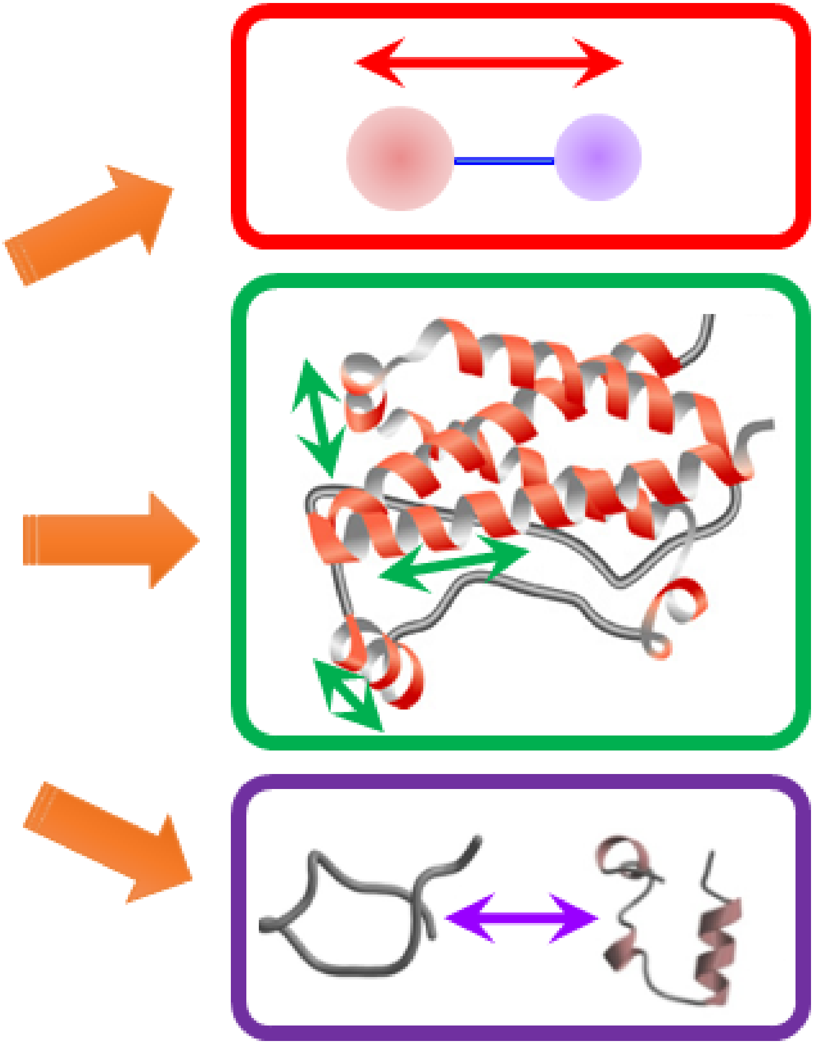
Yu, Calvin, et al. "The potential of terahertz imaging for cancer diagnosis: A review of investigations to date." *Quantitative imaging in medicine and surgery* 2.1 (2012): 33-45.

CW vs Time-domain imaging

	cw-THz wave imaging	Pulsed THz wave imaging
Cost	$50,000–$150,000	$200,000–$1,000,000
System complicity	Low	High
Weight	3 kg	10 kg
Speed	100,000 point/s	< 4,000 point/s
Data complicity	Low	High
Spectral information	No	Yes
Depth information	No	Yes
Refractive index	No	Yes

Spectral signatures of biomolecules

Motion	Time scale	Frequency range
Atomic vibration	sub-ps	Infrared wave ("chemical")
Collective motions	ps	THz wave ("elusive")
Protein folding	ns ~ ms	Microwave ("biological")



THz spectroscopy of small biomolecules

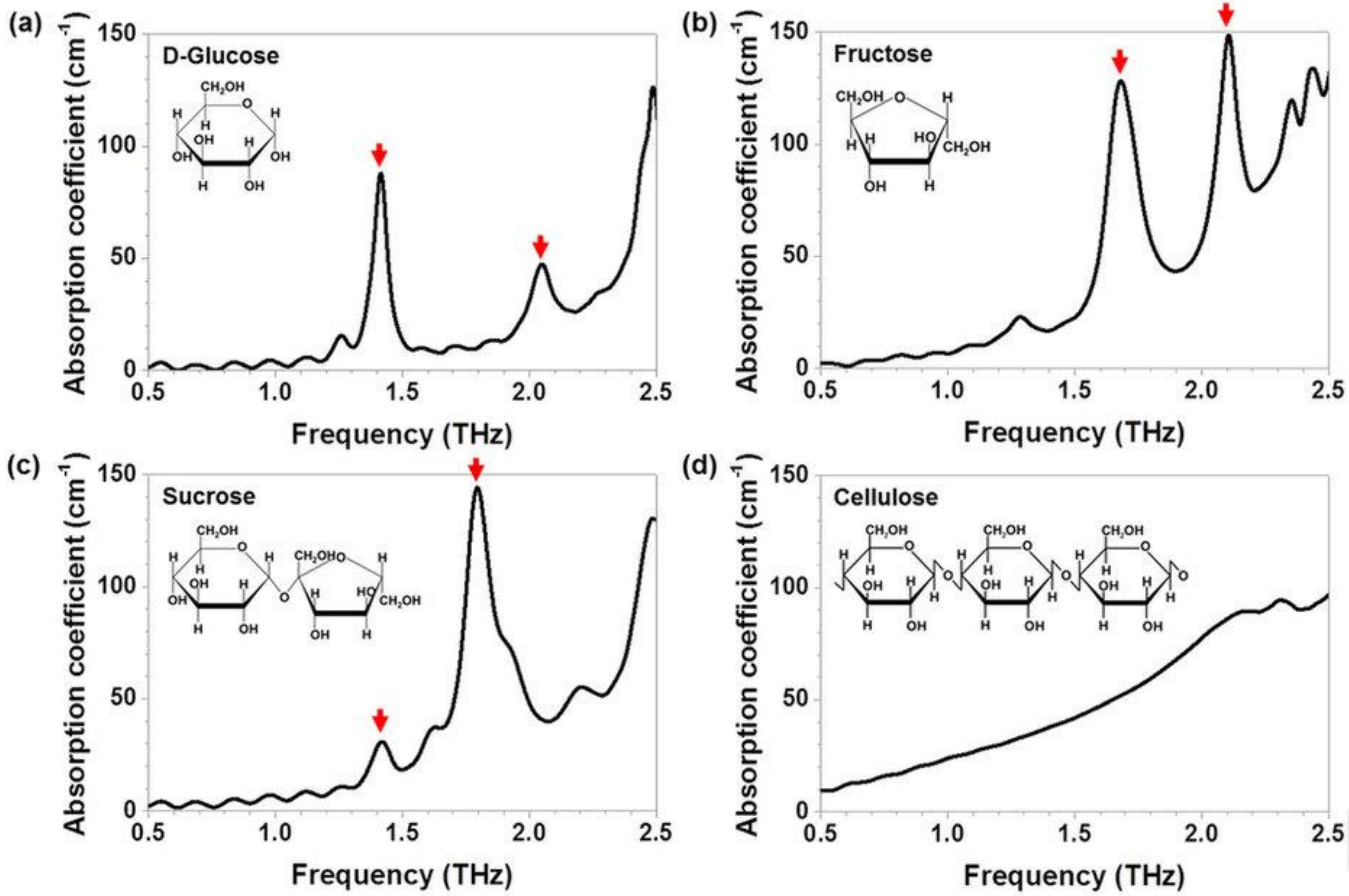
Small biological molecules: mononucleotides, fatty acids, monosaccharides, amino acids.

THz spectra of small molecules usually exhibit clearer spectral features due to less broadening and overlap. As THz waves are strongly absorbed by water and other polar liquids, THz spectroscopy requires samples to be solid-state or dissolved in nonpolar liquids (*gasoline, oil, etc.*).

Due to the interaction among atoms, vibration modes in biomolecules differ from the simple harmonic format. The spectra of the biomolecules also suffer from inhomogeneous broadening, causing the absorption features to be indistinguishable from each other. Measuring the spectrum at a low temperature minimizes spectral broadening and thus narrows absorption features

Methods: Transmission, reflection, absorption, ATR spectroscopy

THz spectra of small organic molecules



Lee, Dong-Kyu, "Highly sensitive and selective sugar detection by THz nanoantennas" *Scientific reports* 5 (2015).

THz spectroscopy of macro biomolecules

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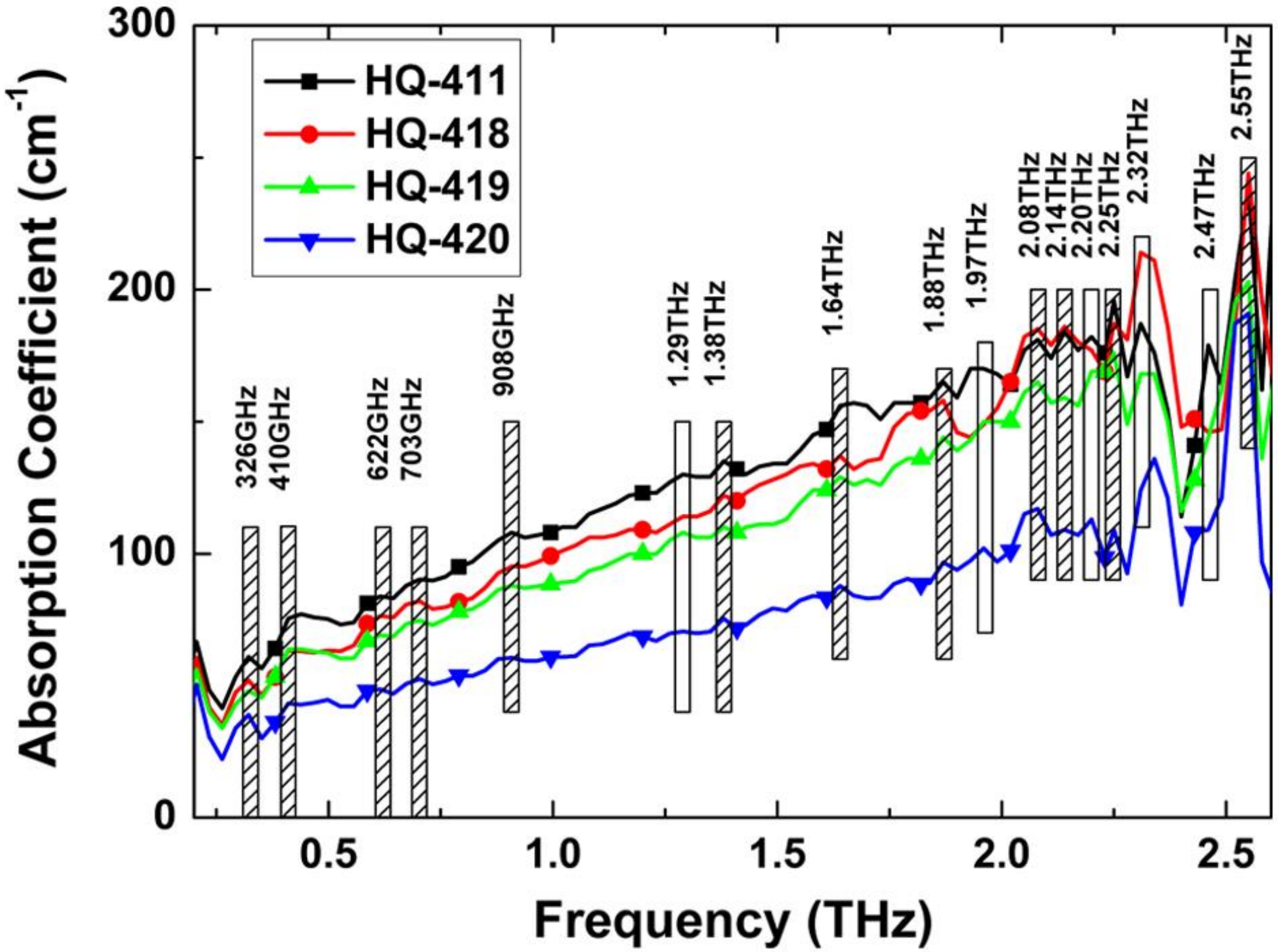
Biomolecules that contain even more monomers, such as proteins, polysaccharides, nucleic acids (DNA, RNA), lipids, usually **do not give clear spectral features** in THz band due to broadening and overlapping of spectral features. When THz wave interacts with a molecule, part of the wave can be transmitted, and **a phase change can be induced**. Different molecules, or the same molecules at different conformations or configurations, may present different absorption and refractive indexes. So, THz spectroscopy can be used to evaluate **aberration of the molecules**.

Moreover, the function and activity of a protein is determined not only by its molecular structure but also by **conformation and configuration** of the molecule. As proteins are extremely complex, physical structure and properties arise from interactions between different amino acids in the chain, even if they are not directly neighbors; when a protein is formed, it folds into a unique shape that determines its function. If a protein molecule is excited by far infrared light, the excitation changes its vibration structure and thus causes a **change in THz wave absorption**. The change of absorption recovers after a short interval referred to as **relaxation time**.

Methods: Transmission, absorption, ATR, optical pump-THz probe spectroscopy

THz absorption spectra of oligonucleotides with only single-base mutations



Tang, Mingjie, et al. "Terahertz spectroscopy of oligonucleotides in aqueous solutions." *Journal of biomedical optics* 20.9 (2015): 095009-095009.

THz spectroscopy of biological cells

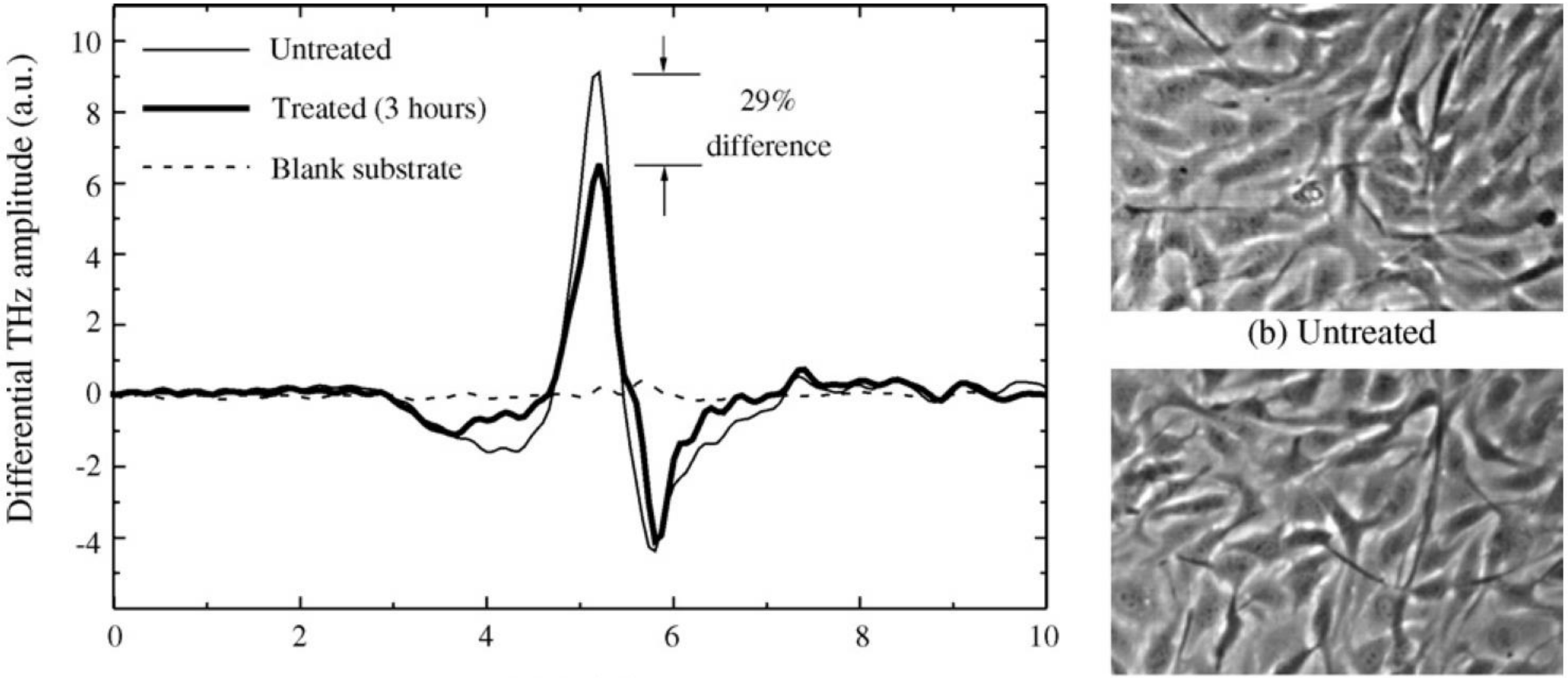
A cell is the fundamental unit of life, and it can individually play some functional roles.

Most human cells range in size from less than one micron to tens of microns. Since the size of a cell is much larger than a biomolecule, it does **not present a clear spectral feature** in the THz frequency band.

However, different categories of cells, or the same kinds of cells at different conditions may respond differently to THz waves. As a result, one can distinguish those cells via their **different THz responses**.

Methods:
Transmission, absorption, dielectric, differential spectroscopy

THz differential waveforms of bovine lung microvessel endothelial cells in response to vascular endothelial growth factor



(a)

(b) Untreated

(c) Treated for 3 hours

Liu, Hai-Bo, et al. "Sensing minute changes in biological cell monolayers with THz differential time-domain spectroscopy." *Biosensors and bioelectronics* 22.6 (2007): 1075-1080.

THz spectroscopy of biotissues

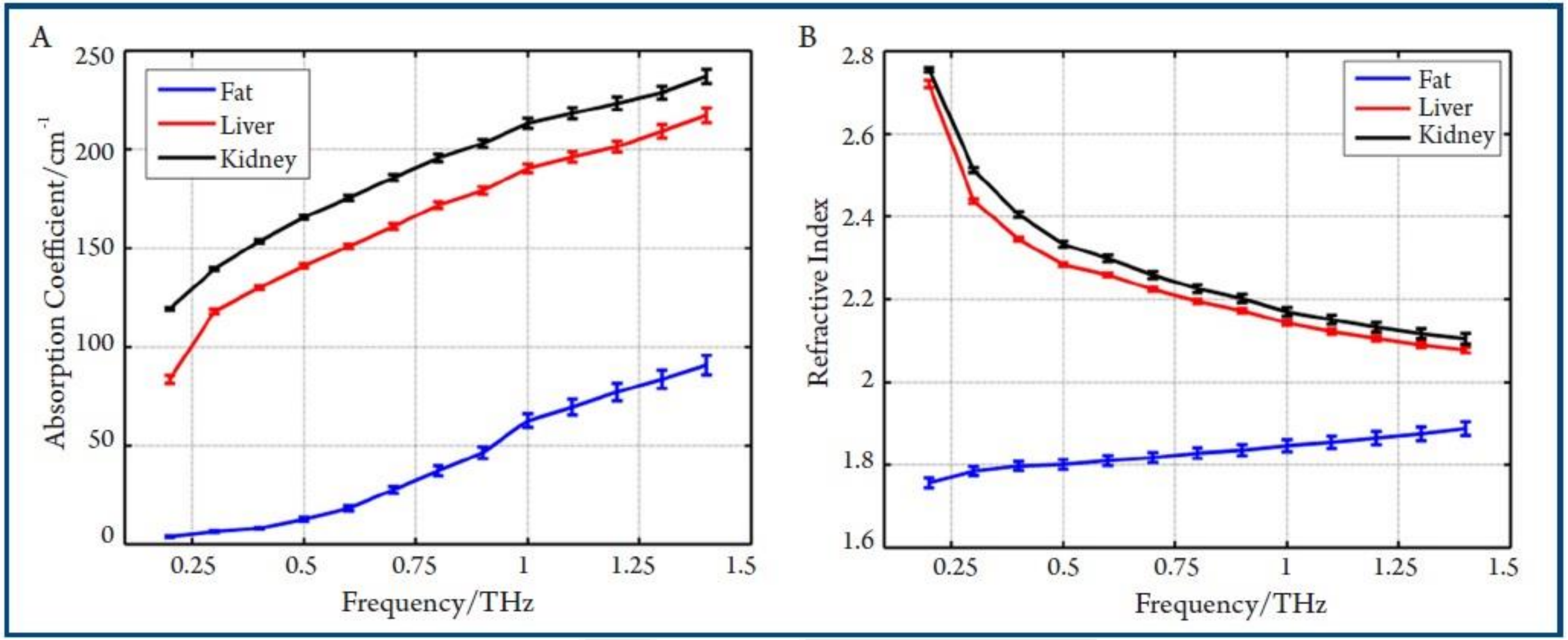
Tissues (skin, bone, muscle, fat, liver, kidney, tooth, etc.) are an ensemble of similar cells and form an intermediate stage between cells and organisms. The syndromes of most illnesses are present at the tissue level. As a result, the identification of sick tissues is very important in diagnosing diseases.

This makes it possible to use THz wave spectroscopy to identify cancerous tissues. The reason different tissues have different responses to THz waves is not yet known, however, a common understanding is that this may be due to **different water concentrations in different tissues.**

Methods:

Transmission, reflection, absorption, dielectric, ATR spectroscopy

Optical properties of biological tissues



Yu, Calvin, et al. "The potential of terahertz imaging for cancer diagnosis: A review of investigations to date." *Quantitative imaging in medicine and surgery* 2.1 (2012): 33-45.

THz imaging of biological objects

Due to the different THz spectra of different tissues, THz imaging can be used in medical diagnostics. However, the **two factors** should be noted:

- **penetration capability:** the capability of THz waves to penetrate through lots of daily items such as clothes or bandages. Therefore, THz waves can be used to investigate an illness or a wound concealed by those materials.
- **limited THz waves transmission:** the high absorption of THz waves by water in most tissues. Since most human tissues (such as muscle) are composed of water, THz waves can only penetrate into the human body a shallow distance, and cannot be used to inspect organisms inside the human body like an X-ray.

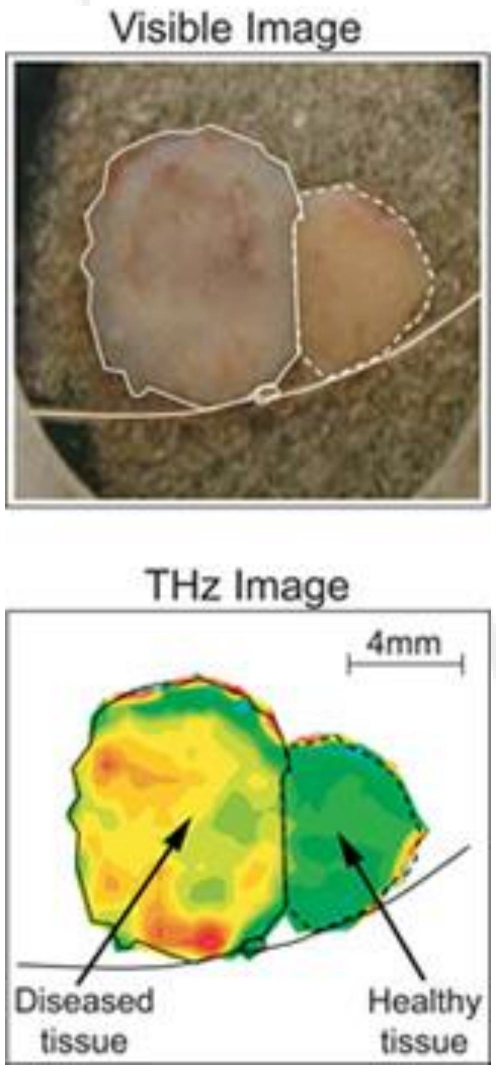
THz imaging in medical diagnostics is limited to **following conditions**:

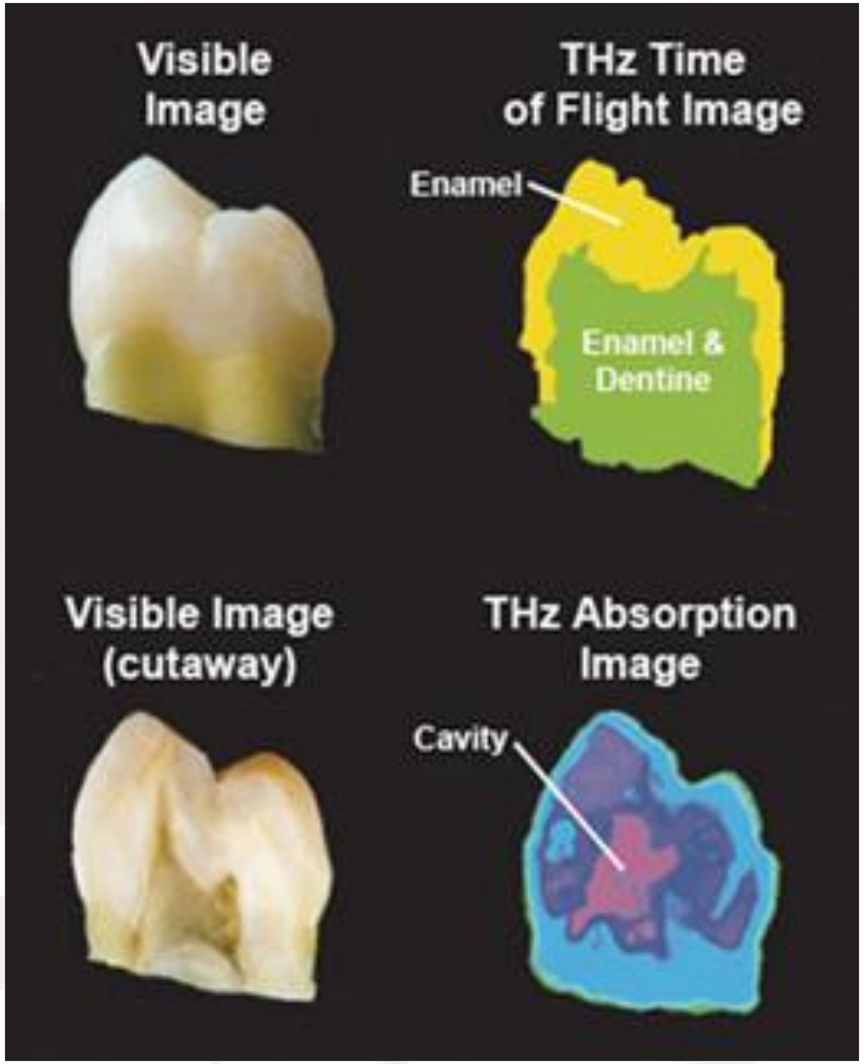
THz wave imaging can be used

- to diagnose skin diseases,
- to investigate slices of tissues,
- to inspect inside the human body via an endoscope.

Besides **breast tissue, bone and teeth** are other elements of the human body that have higher transmittance for THz waves.

Terahertz imaging of basal cell carcinoma and human tooth





Images courtesy TeraView Ltd.

Hydration of Molecules and Its Response

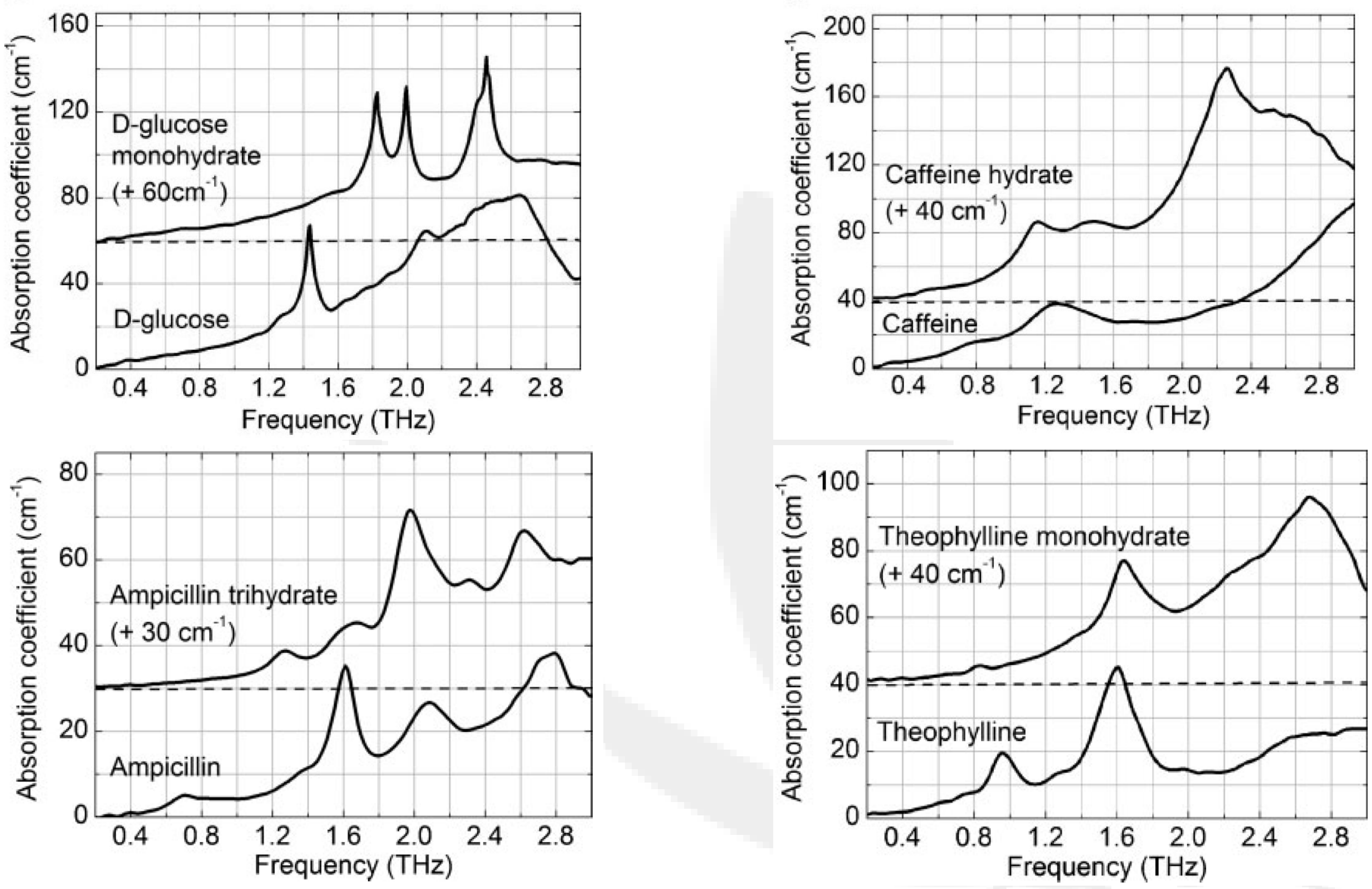
THz waves strongly interact with water, which is the essential material of all life. Most living things need to associate with water in order to remain active. The existence of water **reduces the dynamic range** of THz spectroscopy.

On the other hand, the high sensitivity of THz spectroscopy to water molecules can be employed to verify the **existence of water in biological samples** as well as to identify the formation of water molecules in the biosamples.

Hydration is a very common method by which water molecules exist in other materials. Hydration and dehydration of a material can dramatically change its properties, and therefore it is important to know the hydration condition of materials in applications such as quality control of pharmaceuticals.

Methods: Transmission, reflection, absorption, ATR spectroscopy

THz spectra of anhydrous and hydrate molecules



Liu, Hai-Bo, Yunqing Chen, and X-C. Zhang. "Characterization of anhydrous and hydrated pharmaceutical materials with THz time-domain spectroscopy." *Journal of pharmaceutical sciences* 96.4 (2007): 927-934.

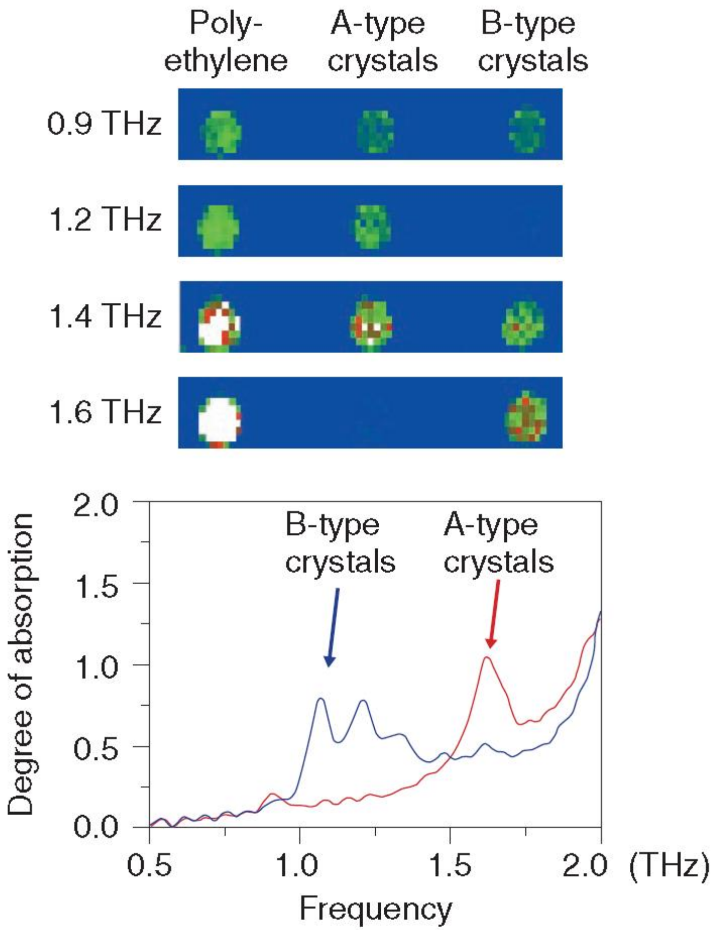
Quality Control of Pharmaceutical Products

THz spectroscopy can be used to identify **molecular compositions** if the compositions have spectral features in the THz band. THz technologies can be used in the **quality control of pharmaceutical products** to inspect if the drug meets the product specifications, such as concentration of effective composition, degradation level.

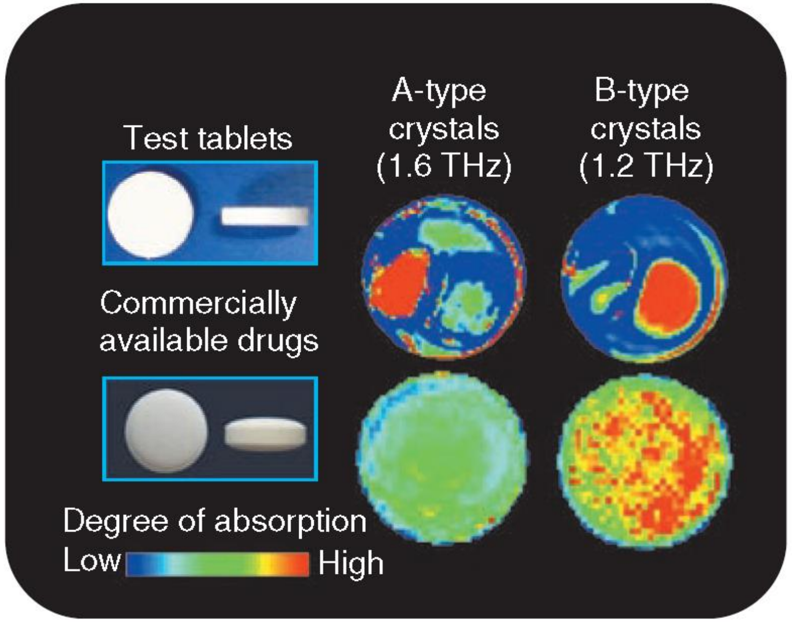
Most medicine tablets have a shell structure in order to protect the active agent and to control digestion of the tablets after being taken. The high quality of the shell helps the tablets to provide the optimized effect for treatment. One important quality control measure regarding these tablets is to make sure the shell structure is uniform and complete, forming layers in the tablet. THz time-of-flight imaging can be used to **map a 3D profile of shell** according to the reflection of THz pulses from different layers of the tablet.

Methods: Transmission, reflection, absorption, ATR spectroscopy, imaging

THz spectra and images of tablets



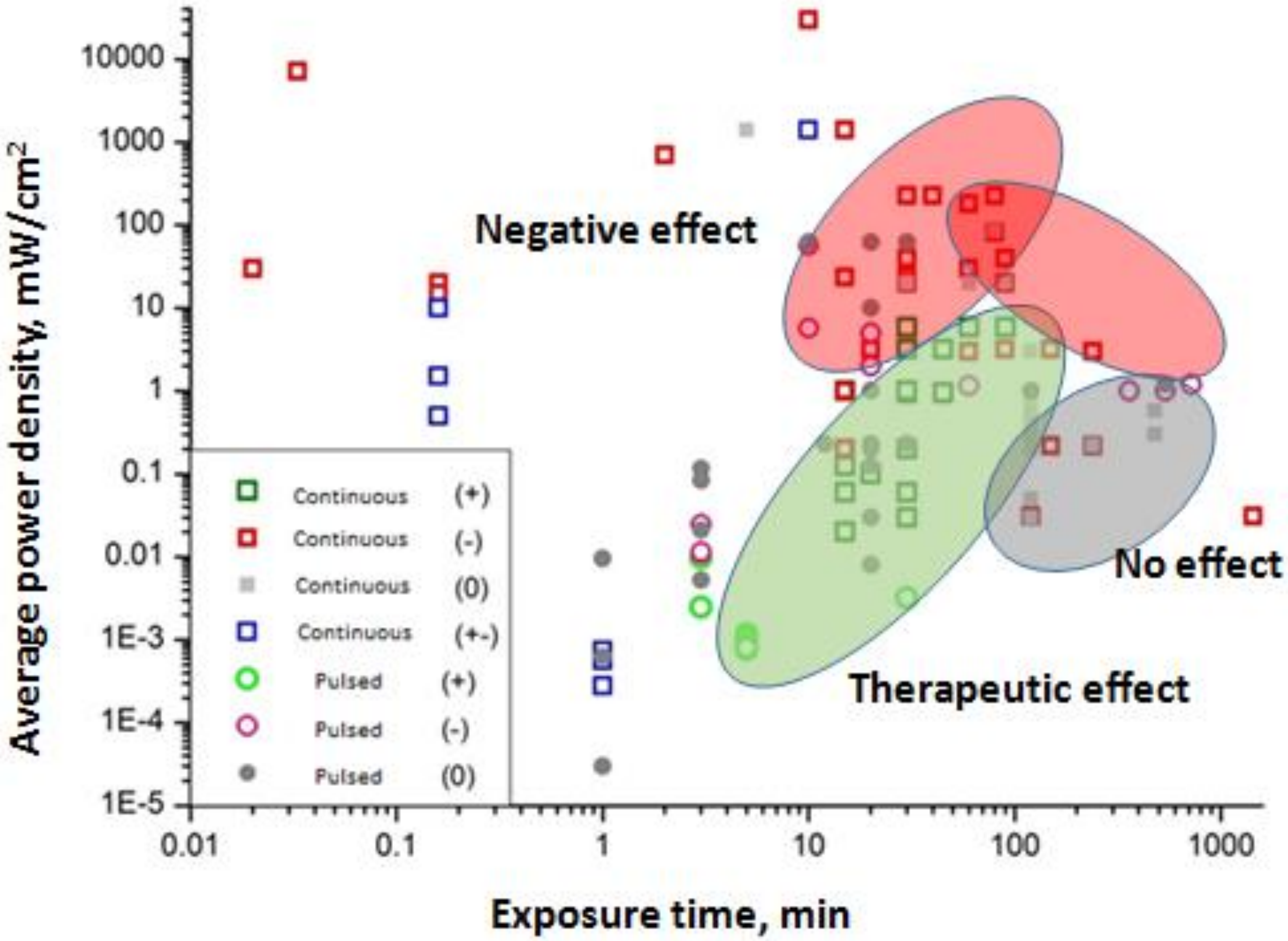
(a) Terahertz absorption spectra and transmittance images of a tablet of crystalline polymorphic famotidine.



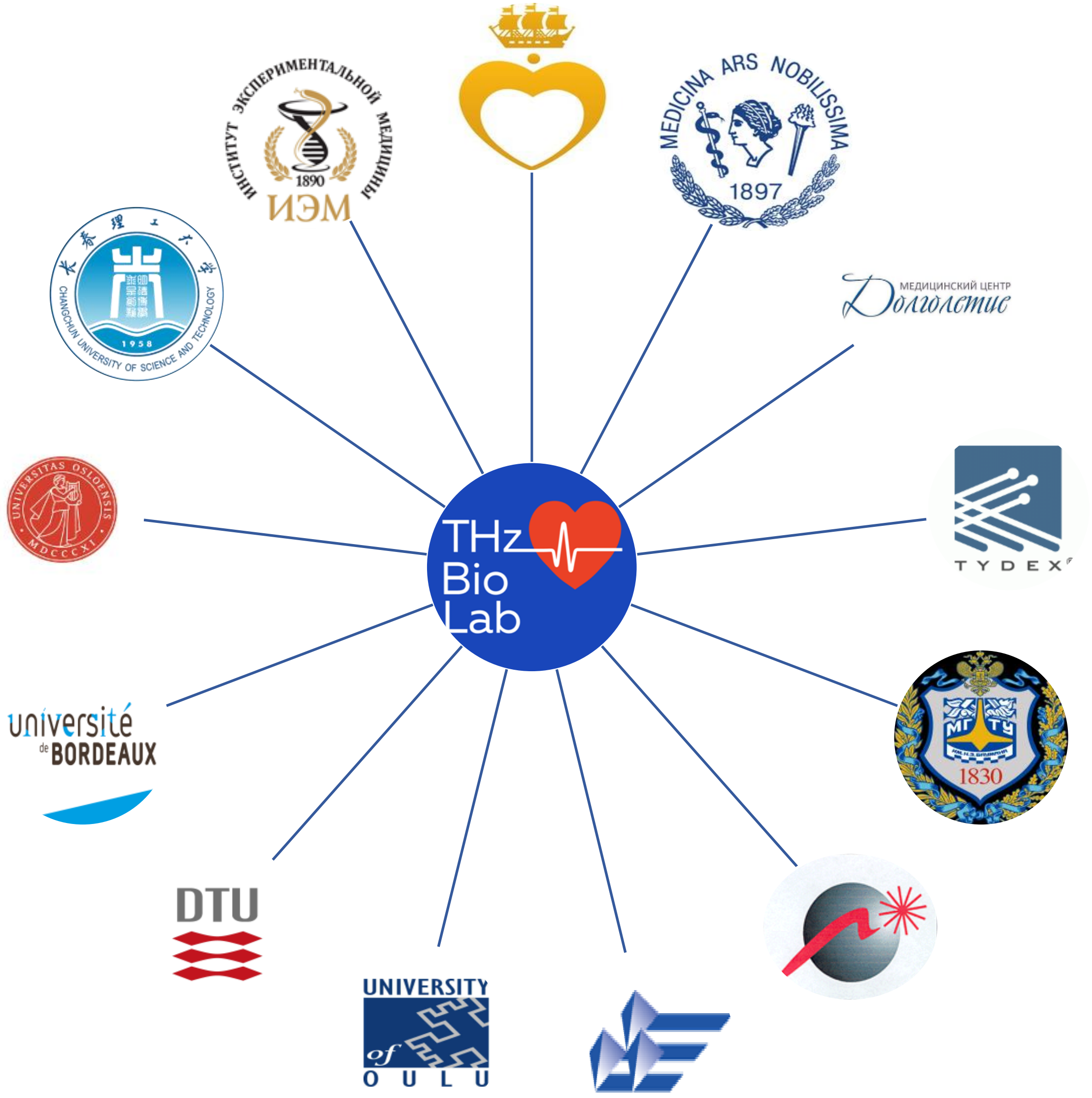
(b) Terahertz absorbance images of test and commercial tablets.

Ajito, Katsuhiro, Yuko Ueno, and Ho-Jin Song. "Visualization of pharmaceutical drug molecules by terahertz chemical imaging." *NTT technical Review* 10.2 (2012).

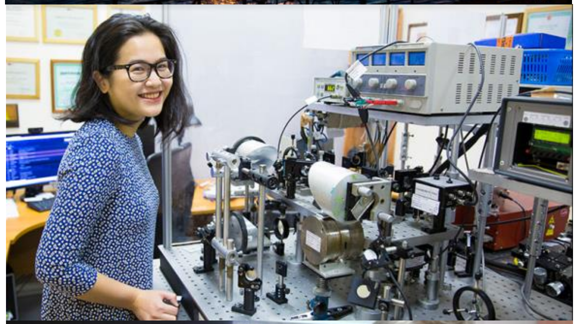
Safety of THz radiation



THz biomedicine laboratory
ITMO University (St Petersburg, Russia)

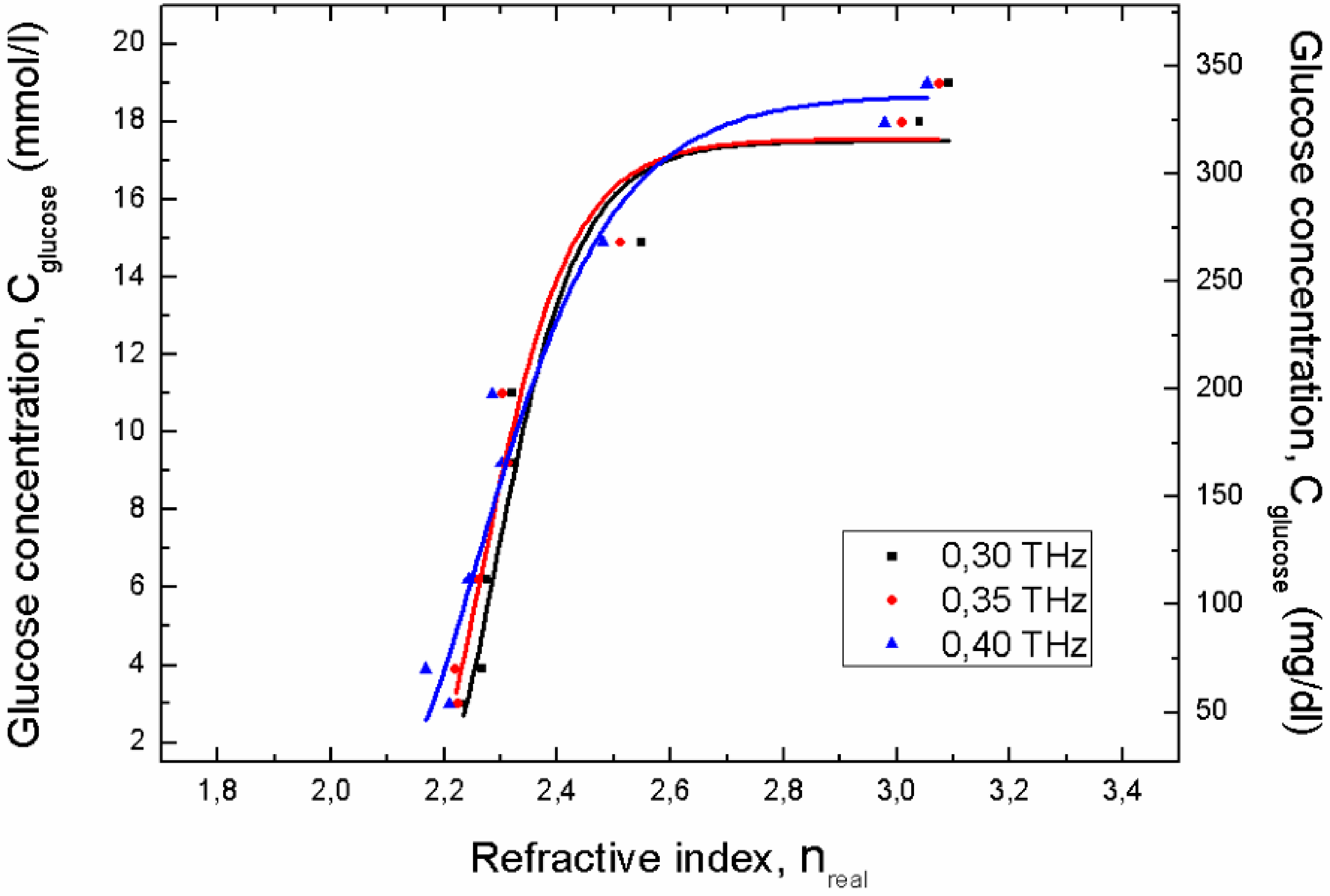


Laboratory staff : 60
Students : 30
PhD students: 6
Medical staff: 15
Research staff: 9

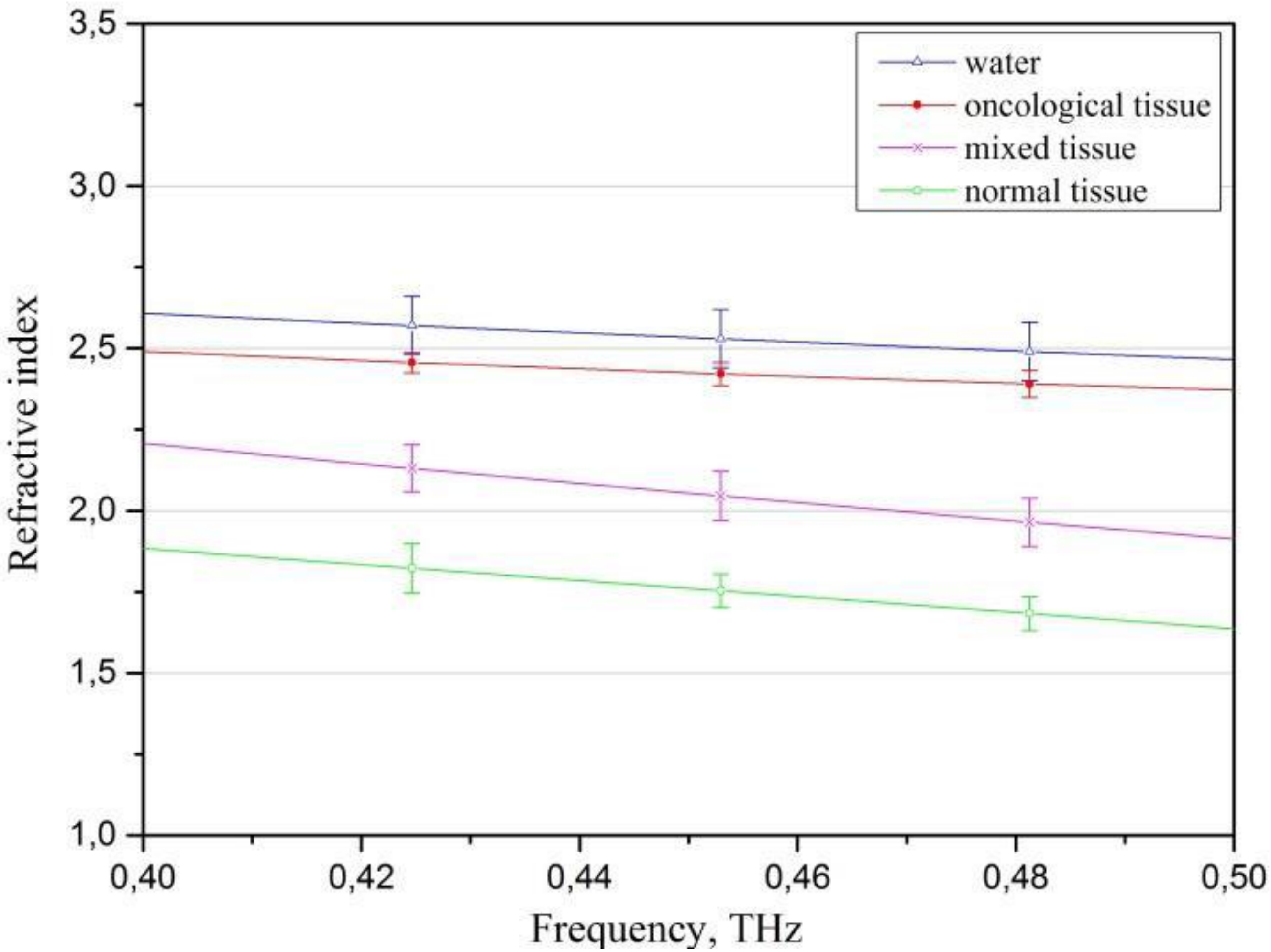


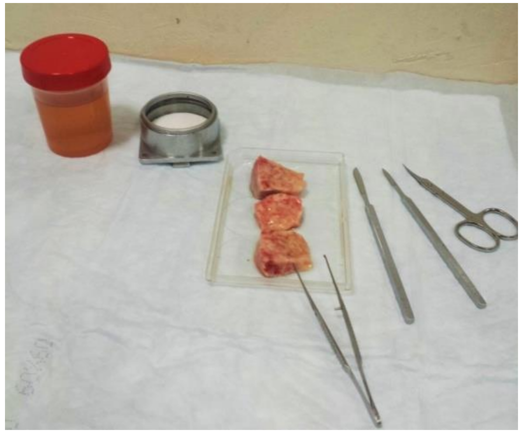

DIABETES
THz
Bio
Lab
THz

Diagnosis of glucose concentration in blood



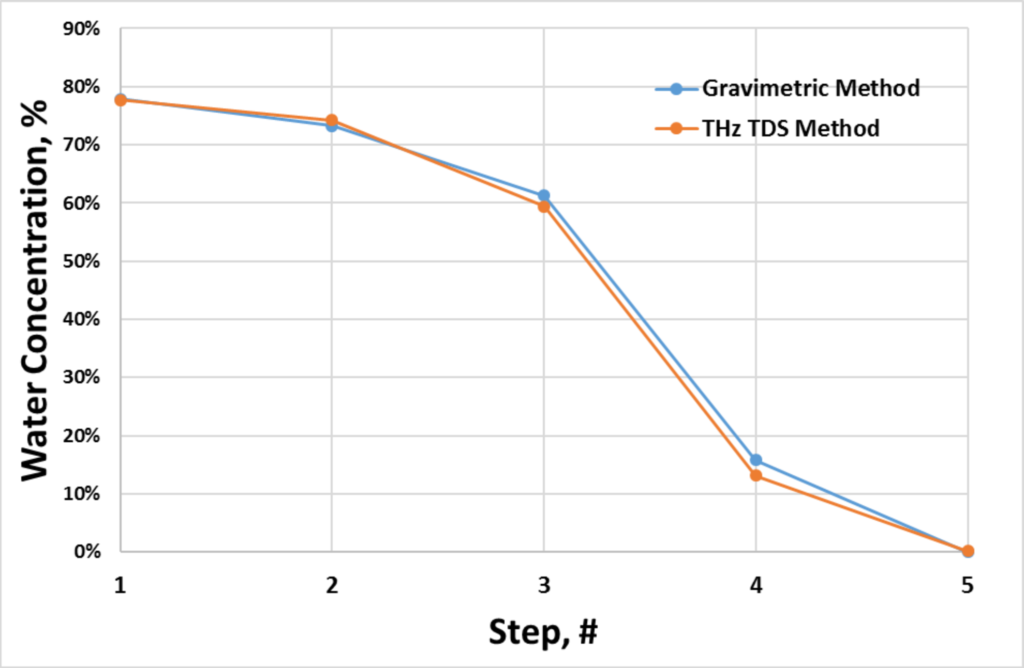
Medical diagnosis of gastric cancer



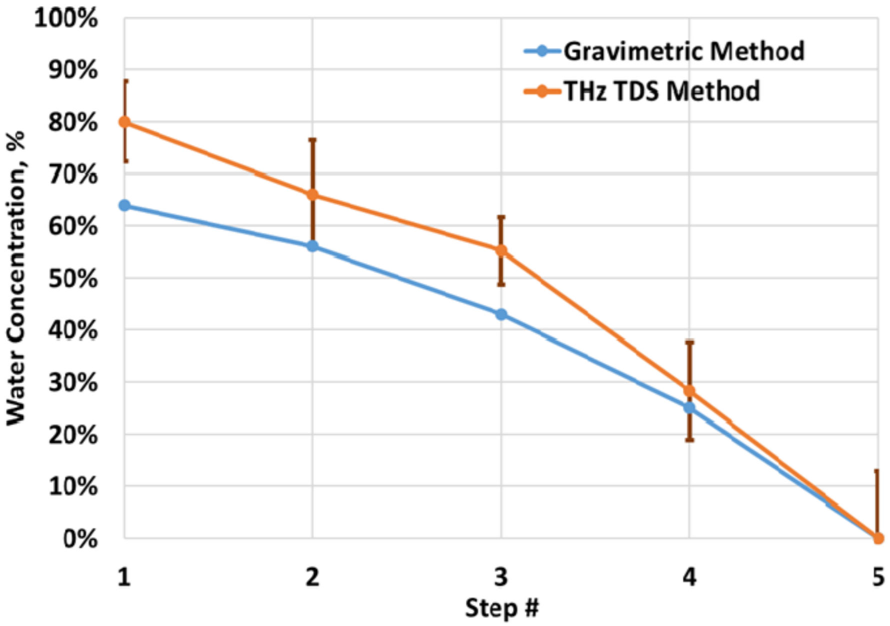


A.A. Goryachuk, et al., Biomedical Optics Express, 2017 (in press)

Determination of water concentration



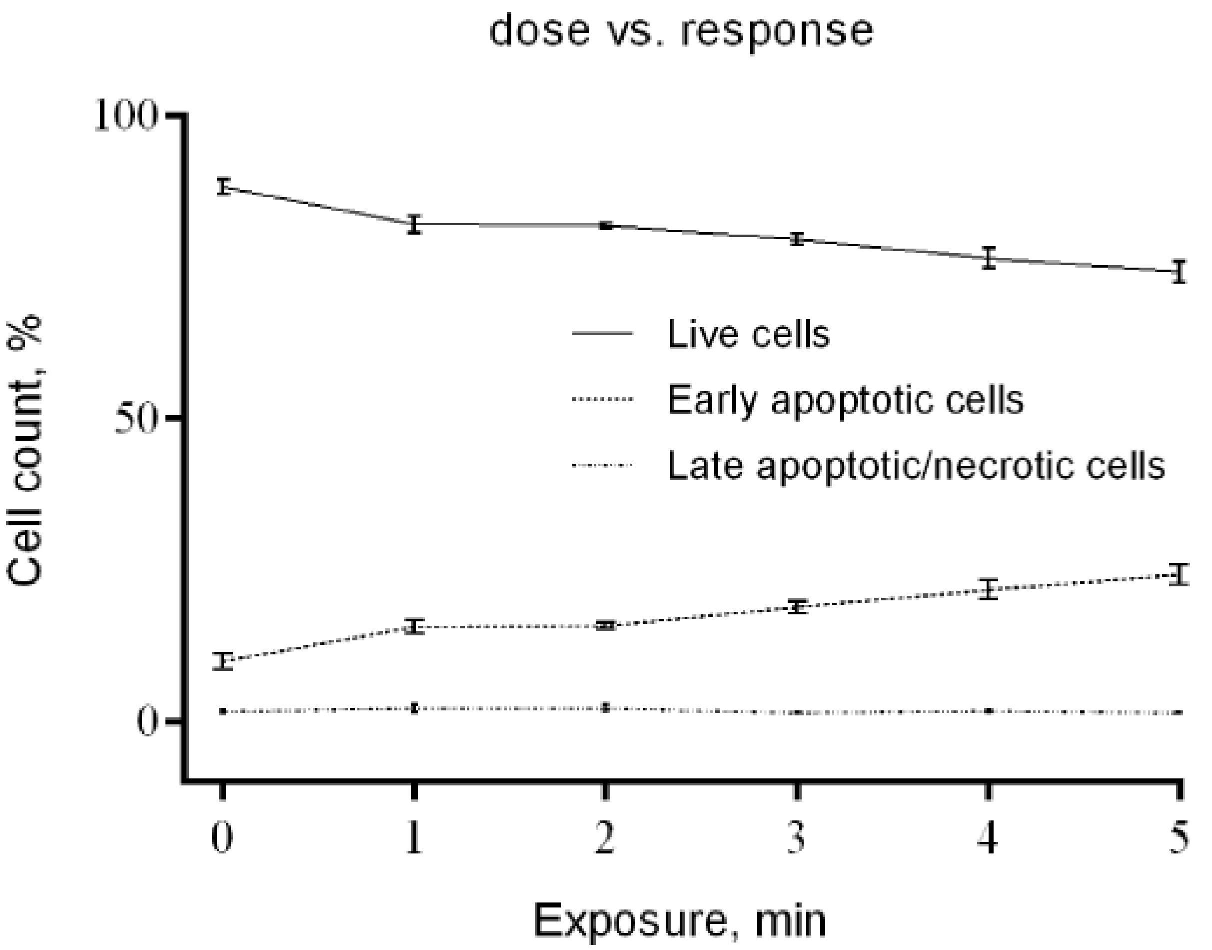
Transmission mode



Reflection mode

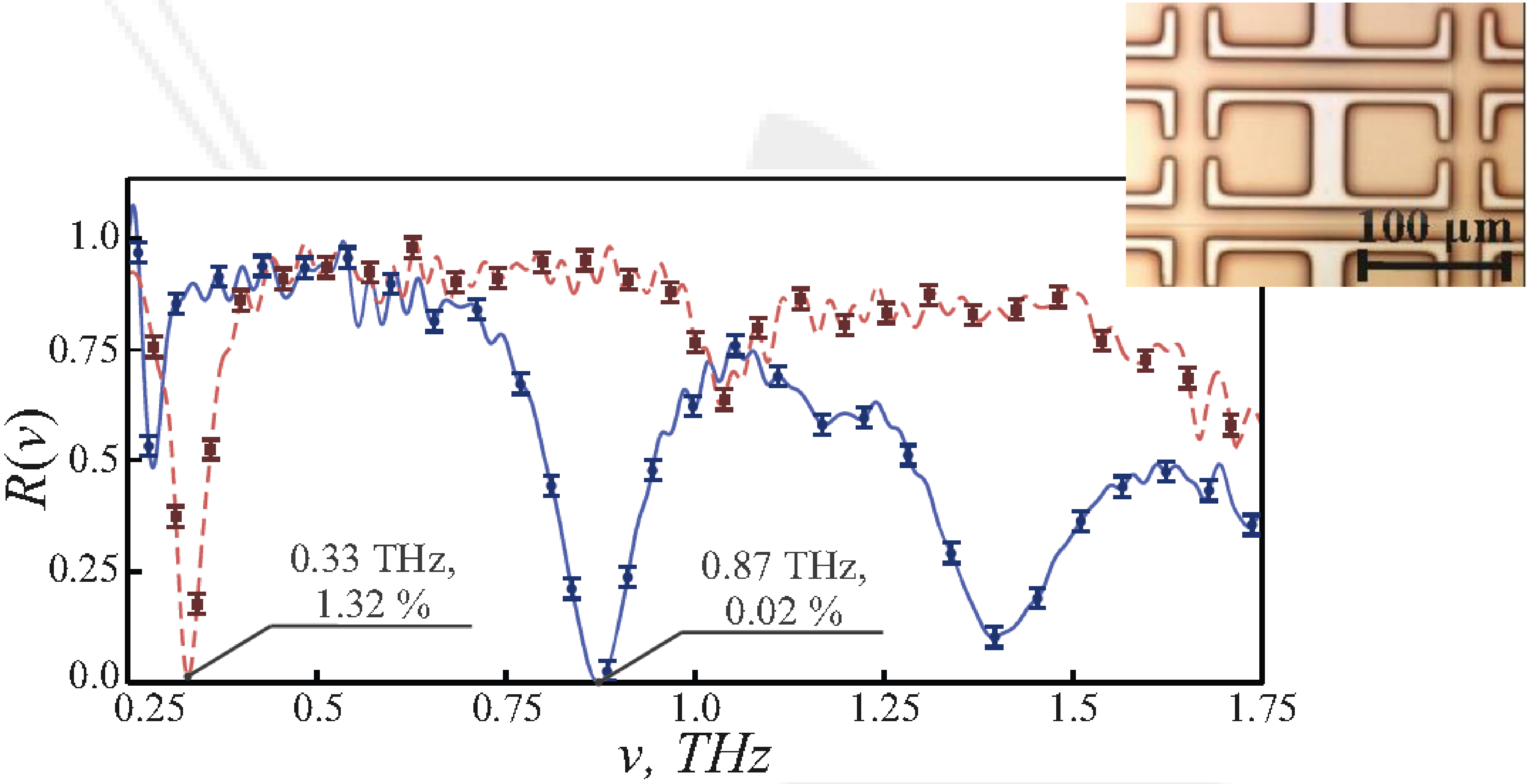
Assessment of Water Content in Biological Samples by Terahertz Time Domain Spectroscopy M. Borovkova; M. Khodzitsky; A. Bykov; I. Meglinski , European Conference on Biomedical Optics, 25-29 June, 2017

THz Radiation Influence on Rat Glial Cells



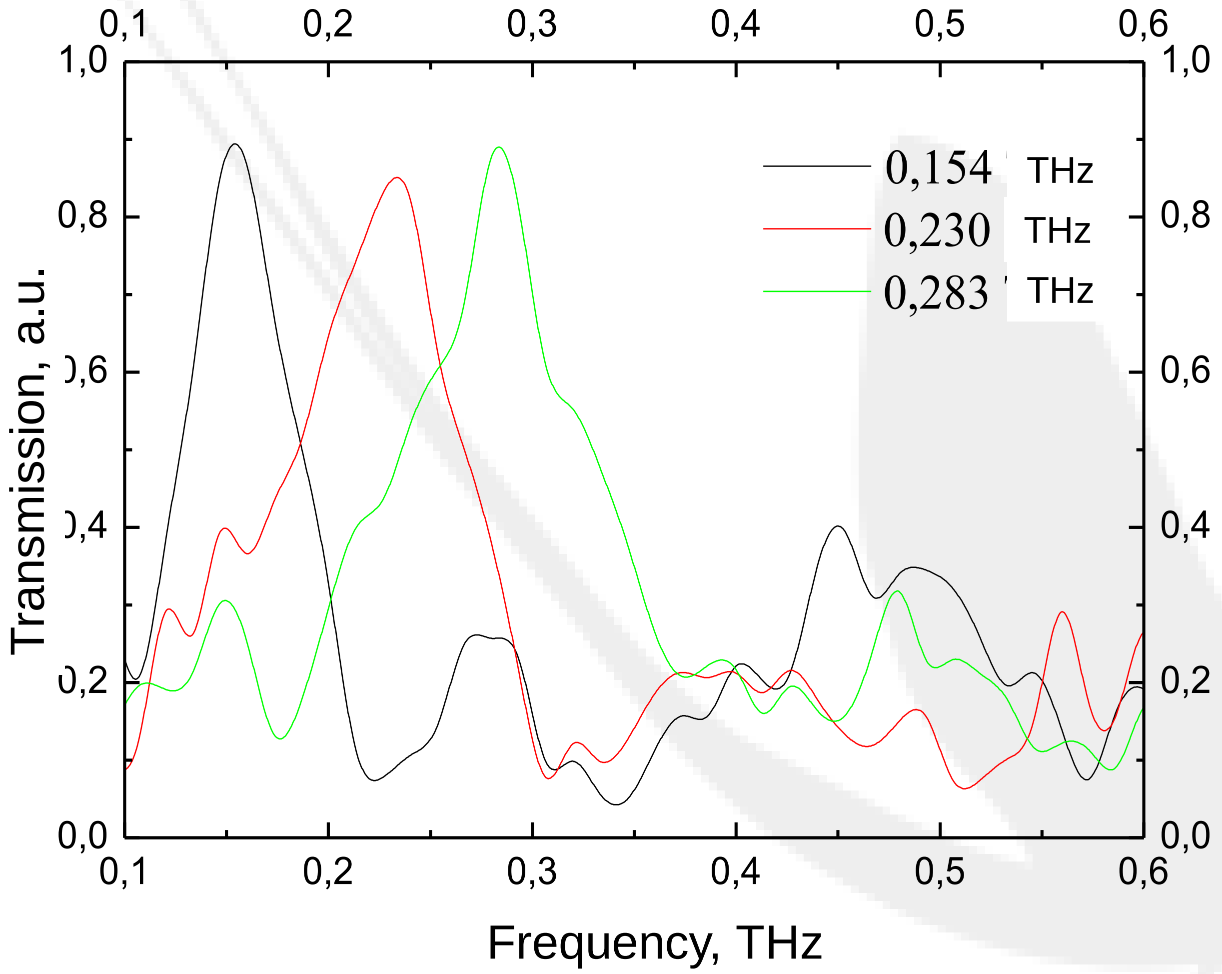
M.A. Borovkova, et al., Biomedical Optics Express, 2017

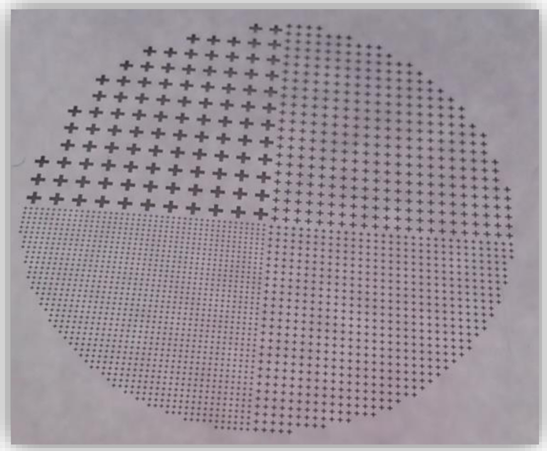
Development of ideal terahertz absorbers



D.A. Gommon, et al., IOP Conference Series: Physics, 2016

Development of tunable terahertz filters





V.Yu. Soboleva, et al., Journal of Optical Technology, 2017

Conclusion

Therefore THz spectroscopy and imaging are ideal tools for the examination of active biomedical samples for diagnosis of diseases, quality control of pharmaceutical products, etc. As biomedical applications are relatively new to the THz field, more effort is needed to bring THz technology to the point at which it can be used in real biomedical applications. Due to the complexity of working with biological samples, biological applications are considered a mid- to long-term goal of THz research.

Thank you!

Dr. Mikhail K. Khodzitsky

PhD student Tianmiao Zhang

Terahertz Biomedicine Laboratory,

ITMO University, Saint Petersburg, Russia

Phone: 7 905 202 24 86

E-mail: tmzhang91@gmail.com