Biomedical Applications of Terahertz Technology

Vincent Wallace

Terahertz and Optical Technology

THOT

http://www.physics.uwa.edu.au/research/terahertz

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THz Applications

non-destructive testing

semiconductor

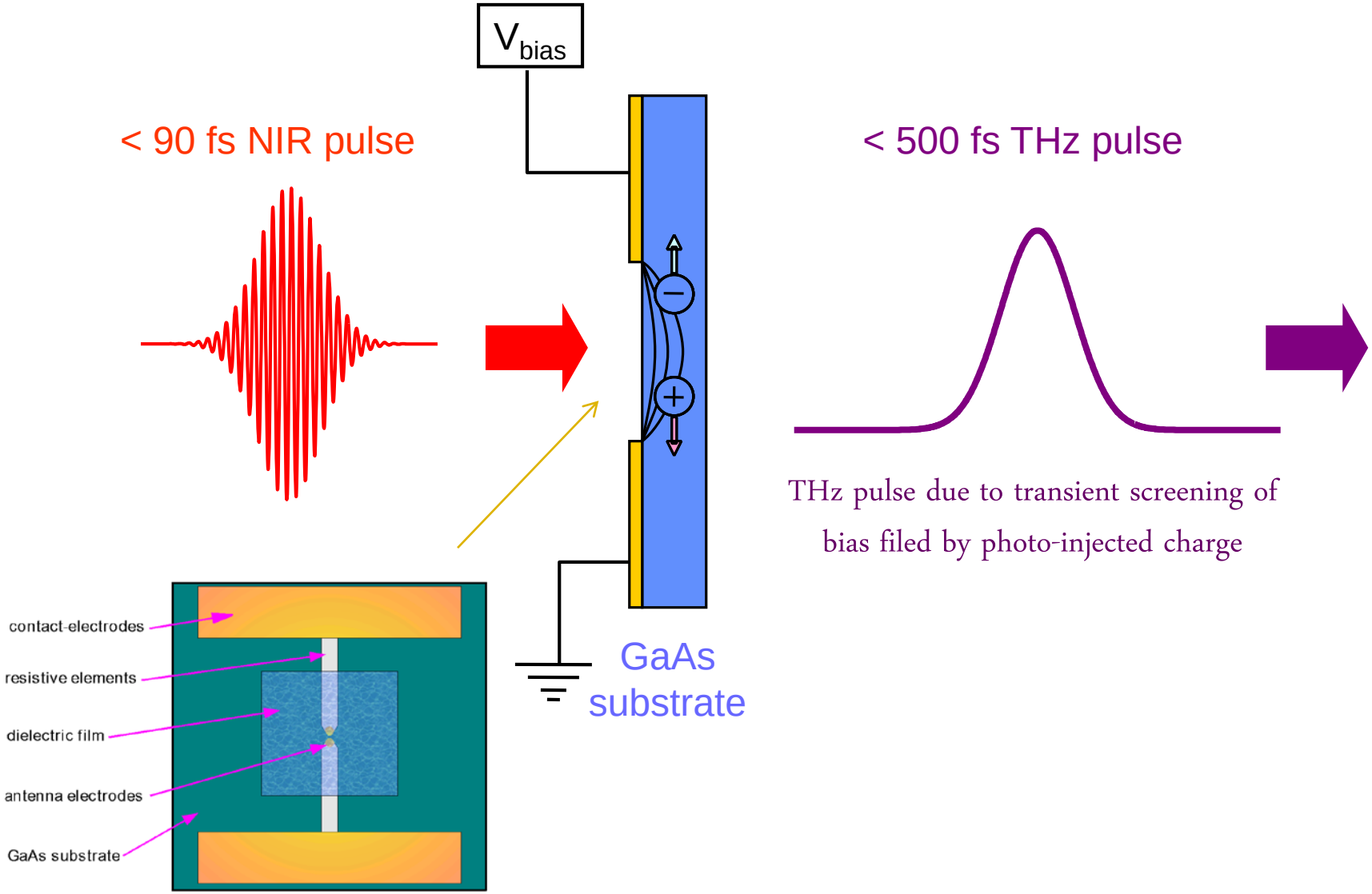
security and defence

pharmaceutical and analytical

medical

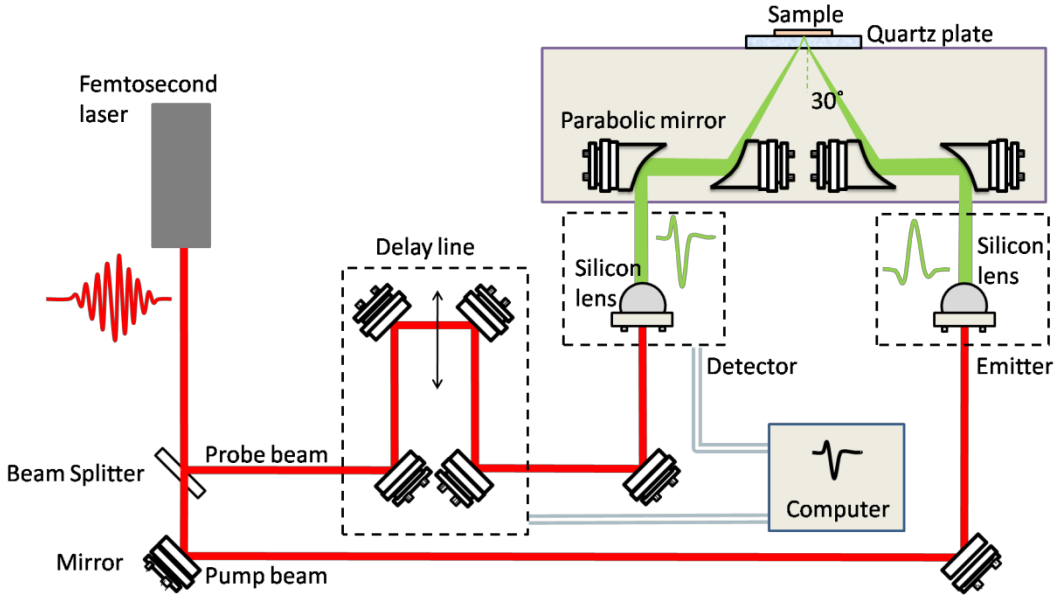
Terahertz time-domain technology

Laser-gated photoconductive antenna



THz pulse due to transient screening of bias filed by photo-injected charge

Terahertz Pulse Imaging (TPI™): System



- Photoconductive source and detector
- Reflection or Transmission mode

Terahertz Pulse Profile

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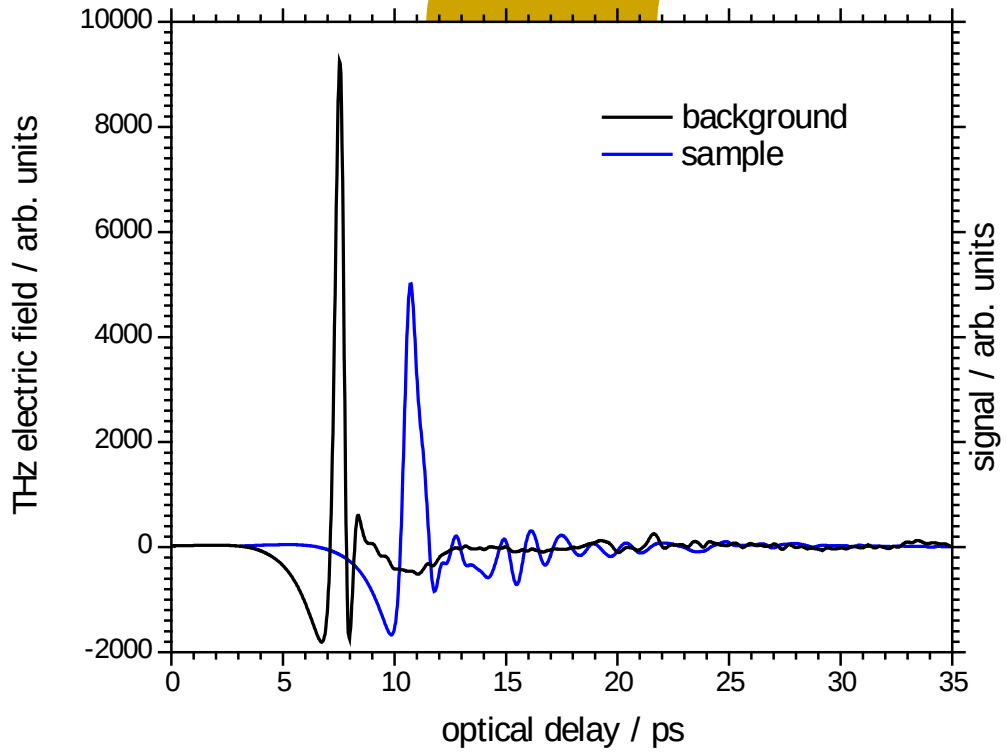
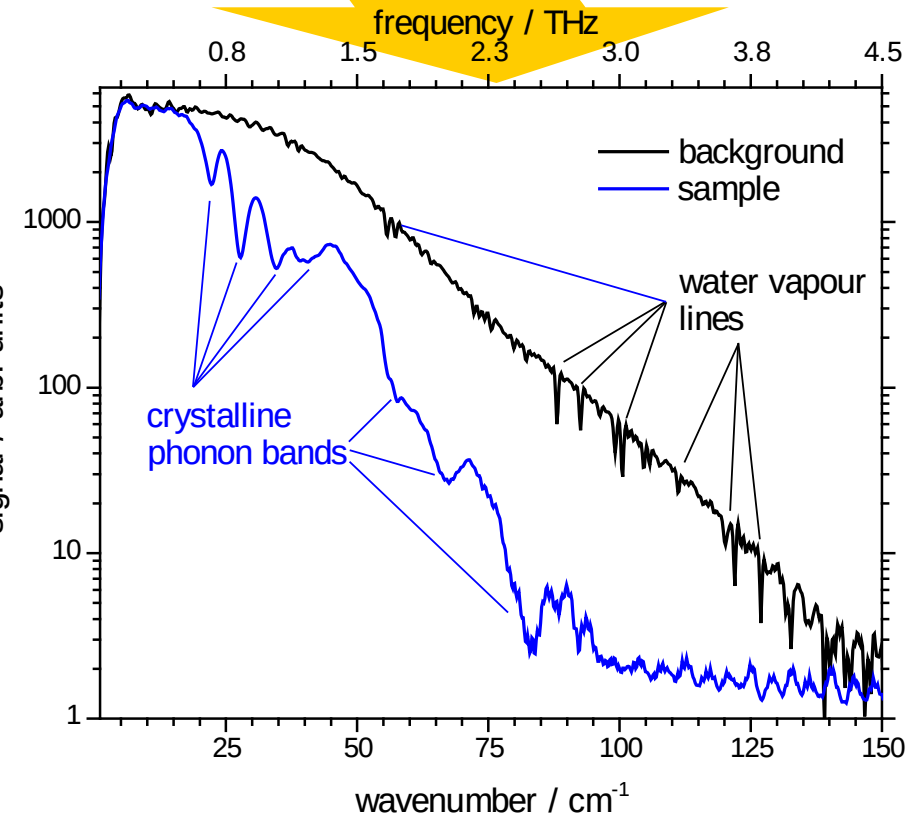
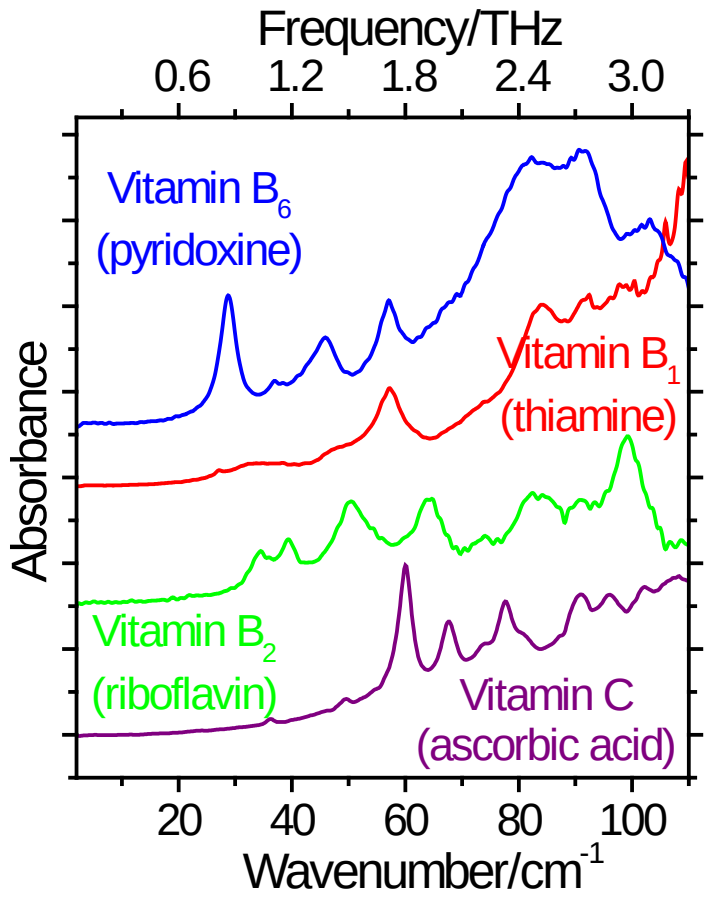
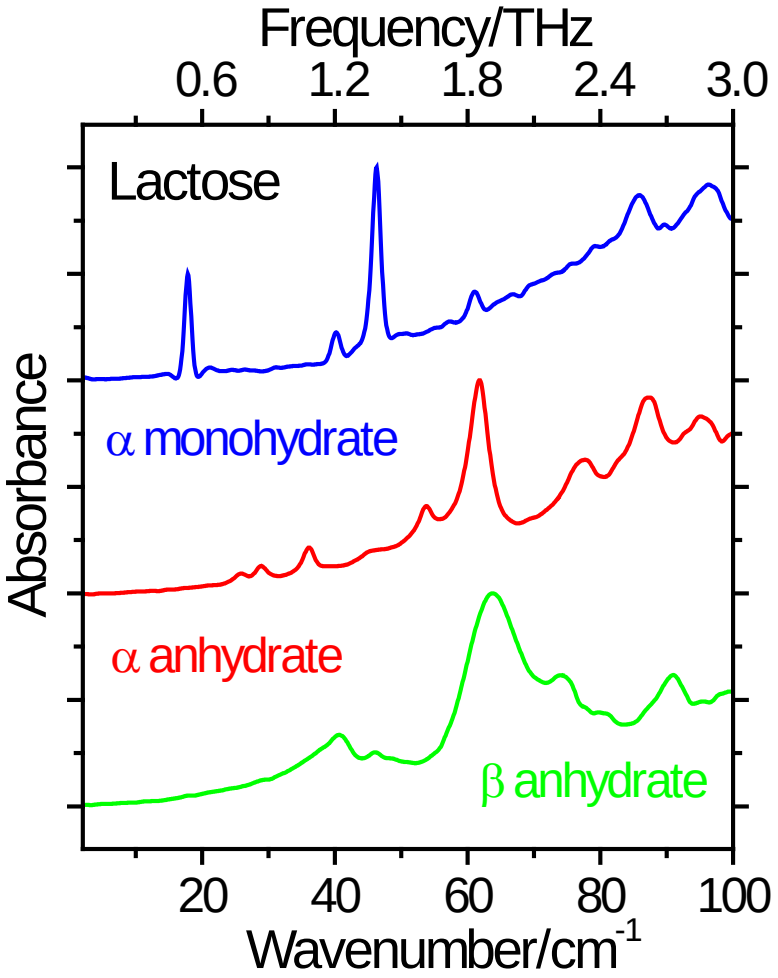
FFT





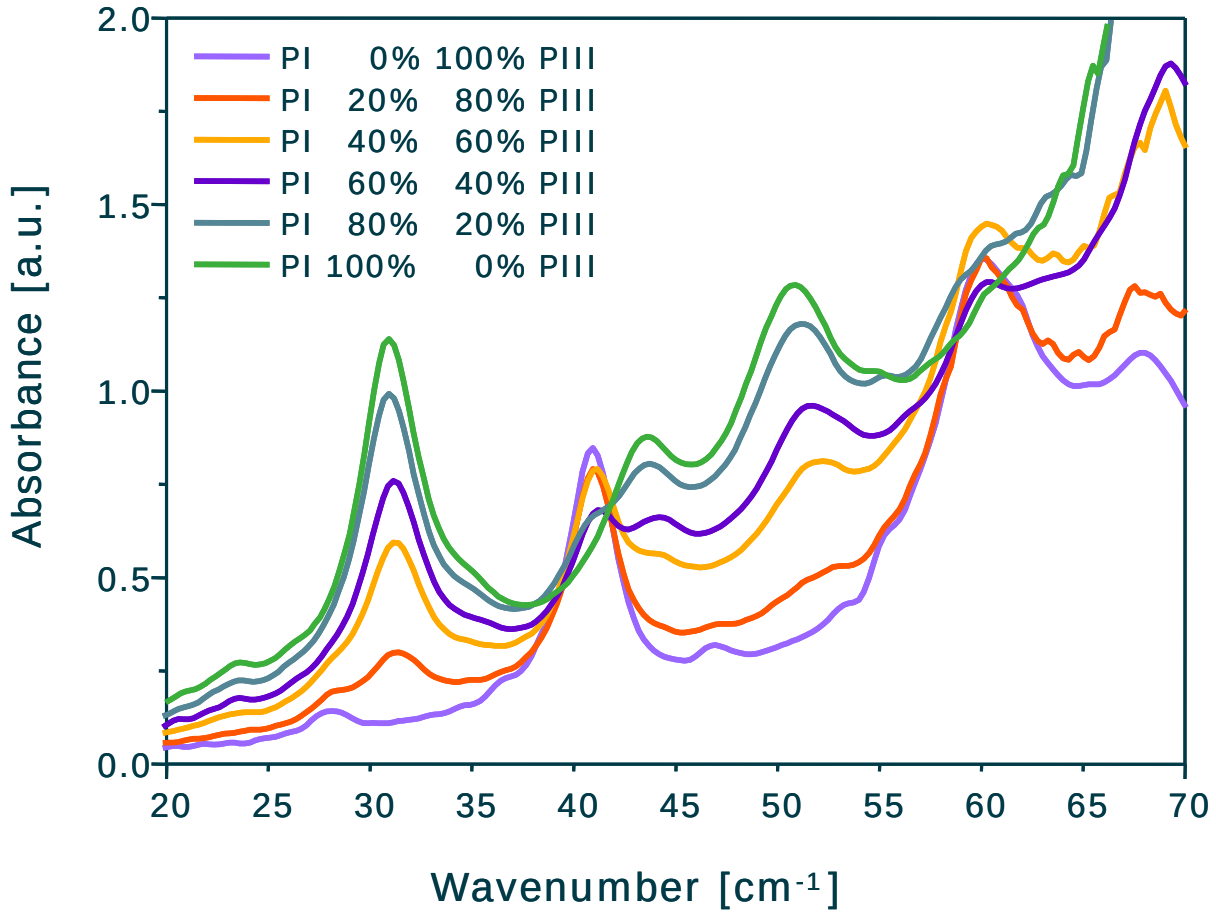
Terahertz pulsed spectroscopy
Characterizing materials in crystalline form





TPS Analysis of Polymorphs

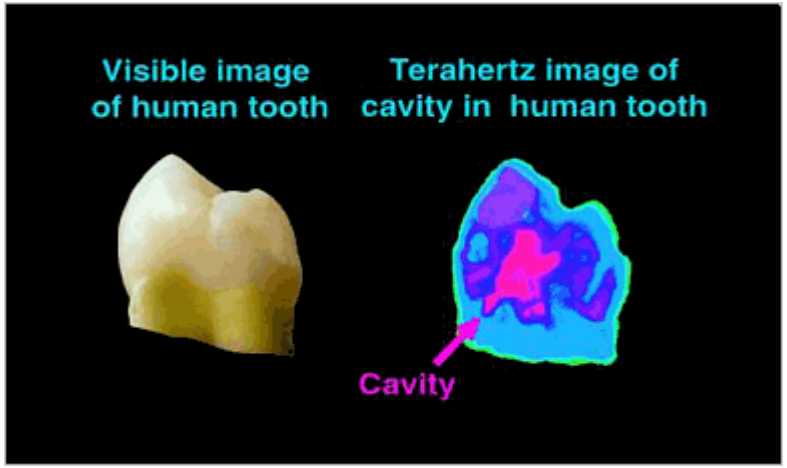
Carbamazepine Form III/I



Strachan, C.J., et al., *Using terahertz pulsed spectroscopy to quantify pharmaceutical polymorphism and crystallinity.* J. Pharm. Sci., 2005. **94**(4):837-846.

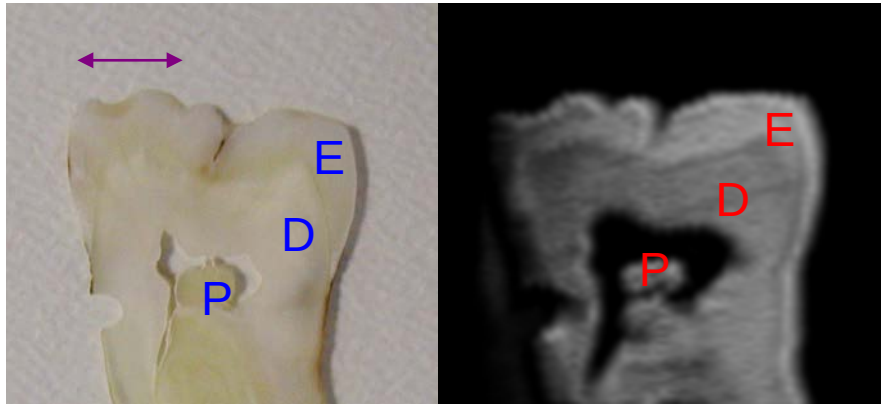
THz Imaging of disease (dental caries)

– Demineralisation of enamel can be detected using THz as it causes a change in refractive index



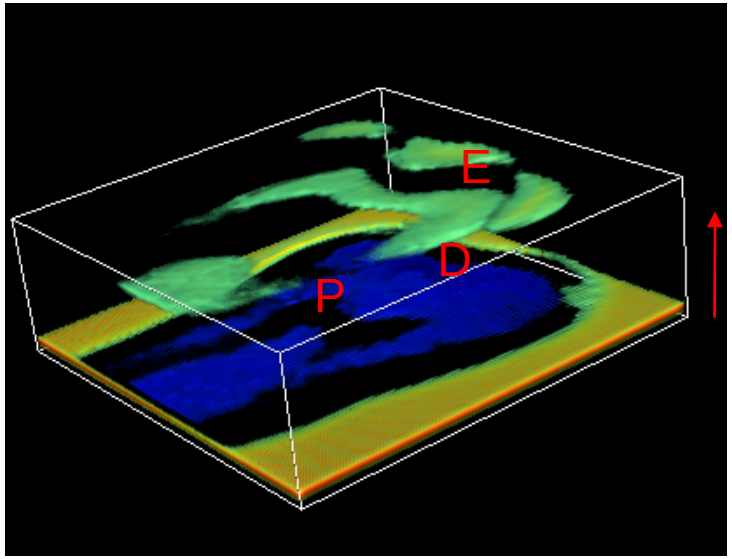
Crawley et al. Caries Research 37(5):352-359 (2003)

Visible image of transverse slice



P= Pulp; D= Dentine; E=Enamel

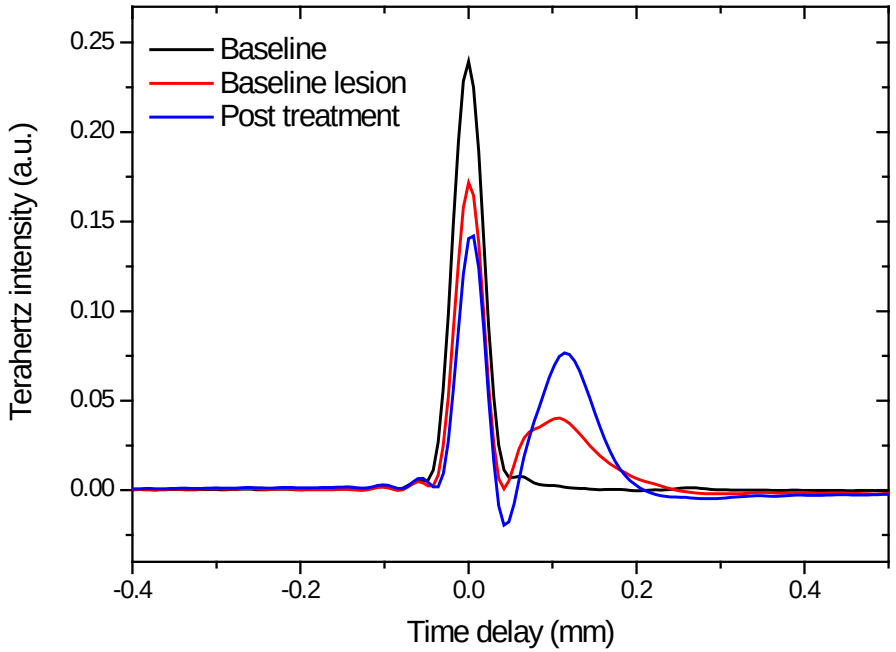
THz image, formed using refractive index profile

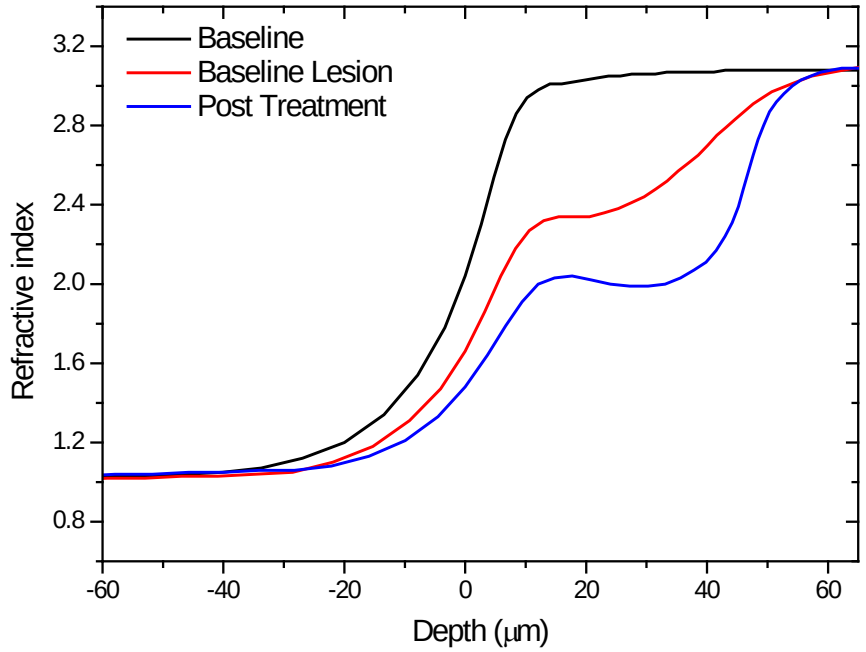


Quasi 3D image from time of flight data

Terahertz Enamel data

- The figures below show the change in THz response for the same sample at three stages of treatment.
- The refractive index profile is analogous to a transverse microradiography (TMR) mineral content profile





THz – non destructive ∴ can do repeat measurements of same sample
TMR - destructive

Terahertz as a Medical Imaging Modality

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- Pulsed THz radiation covers frequencies from 100 GHz to 4 THz

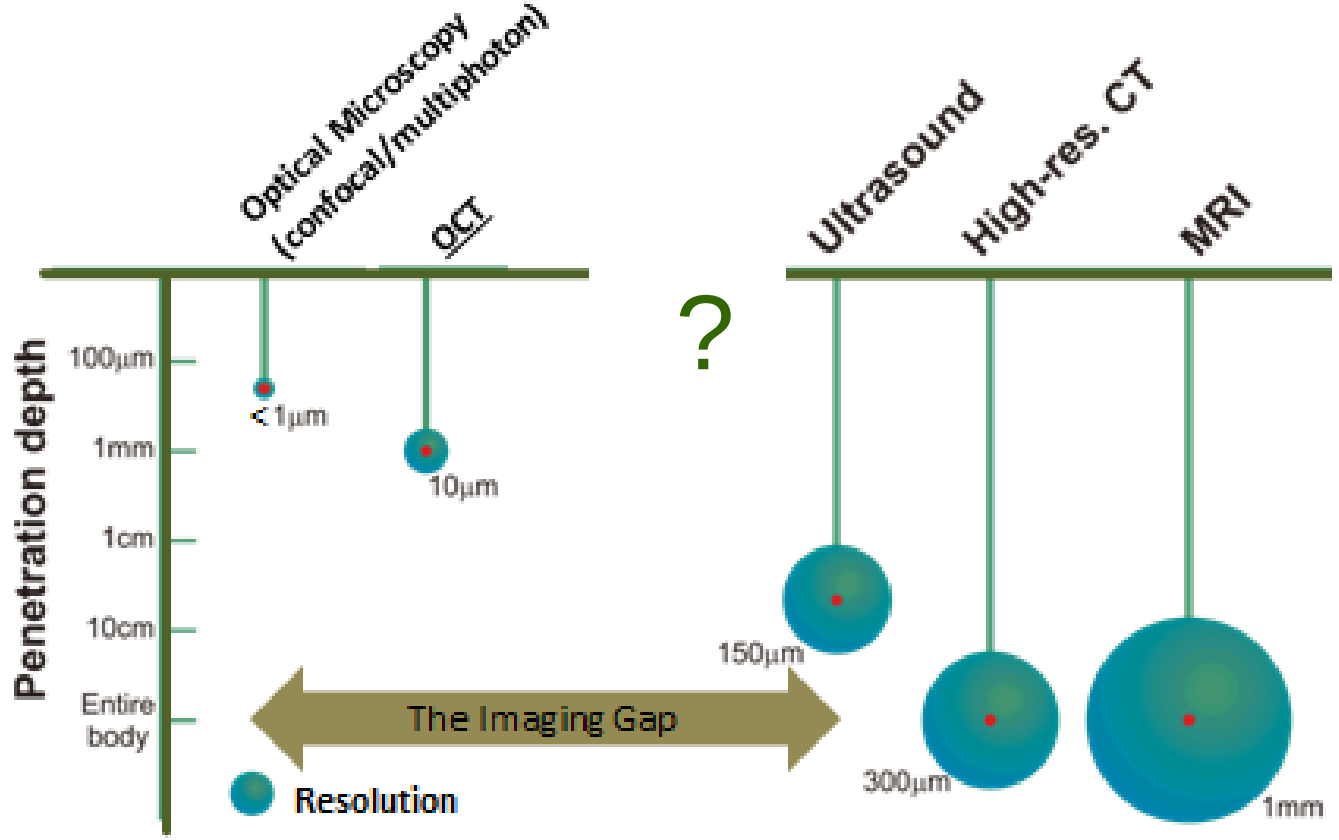
  Spectroscopic Information - diagnostics

- THz radiation is non-ionizing
- Less scatter than NIR/optical due to longer wavelength
- THz wavelengths short enough for sub-millimetre resolution

  Spatial resolution: 250μm laterally, 20μm axially

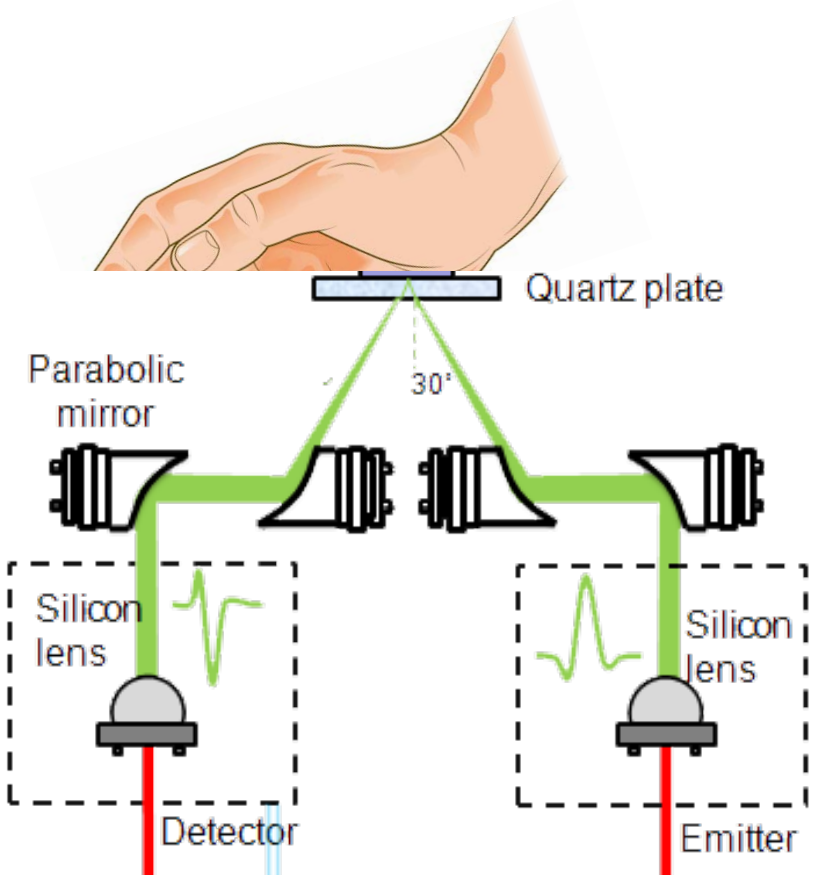
- Time-domain imaging allows for quasi 3D data collection

Problems in Medical Imaging

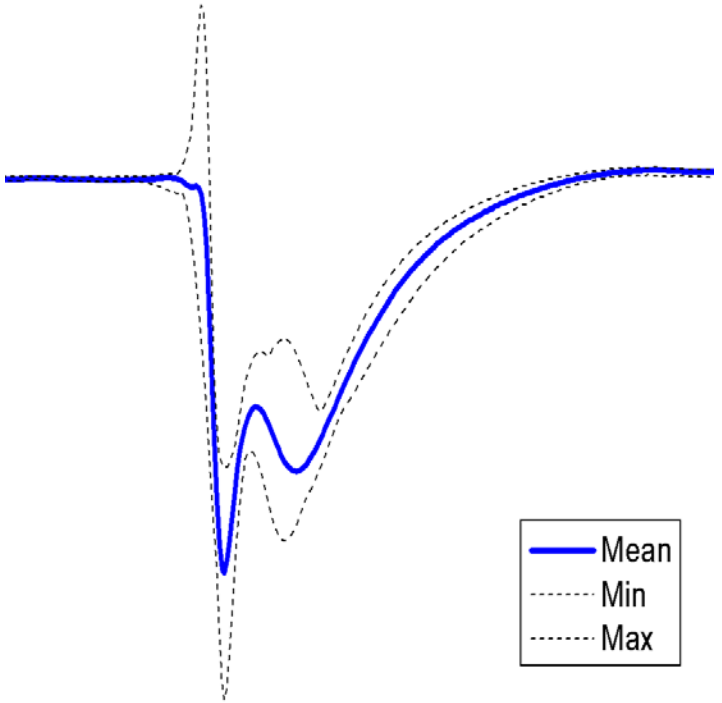


Skin Imaging

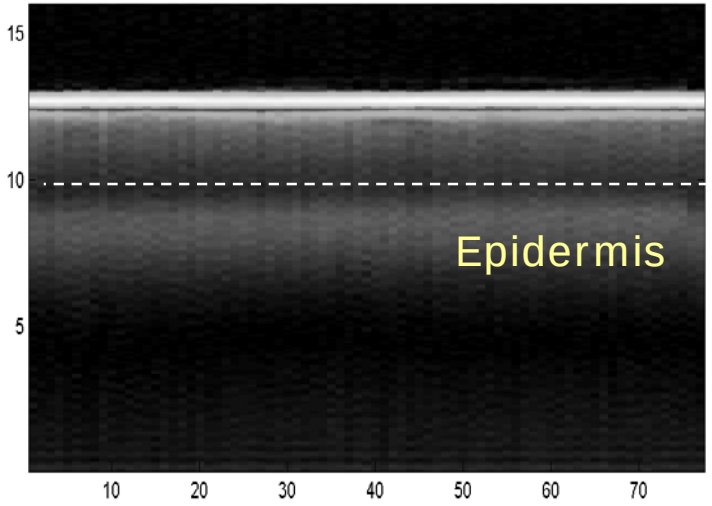
Skin study, Pickwell *et al*, Phys. Med. Biol. 49, 1595-1607 (2004)



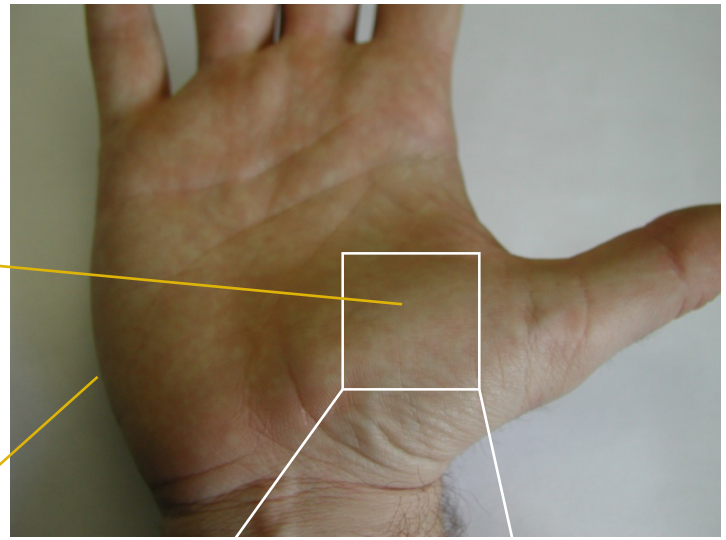
A THz point reflection (A-Scan)

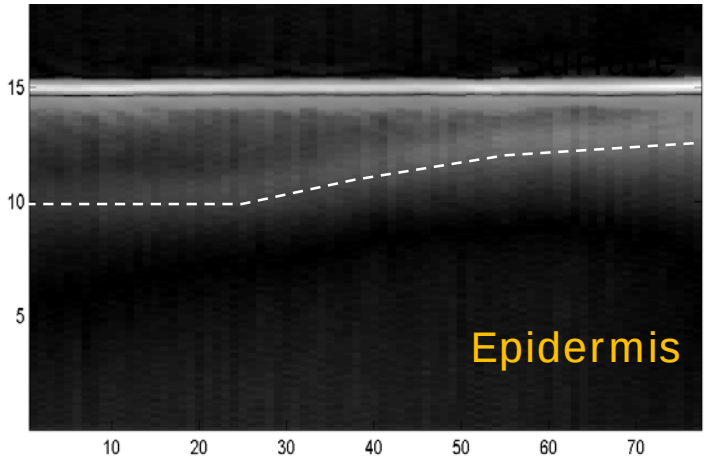


line-scan Images



Stratum corneum

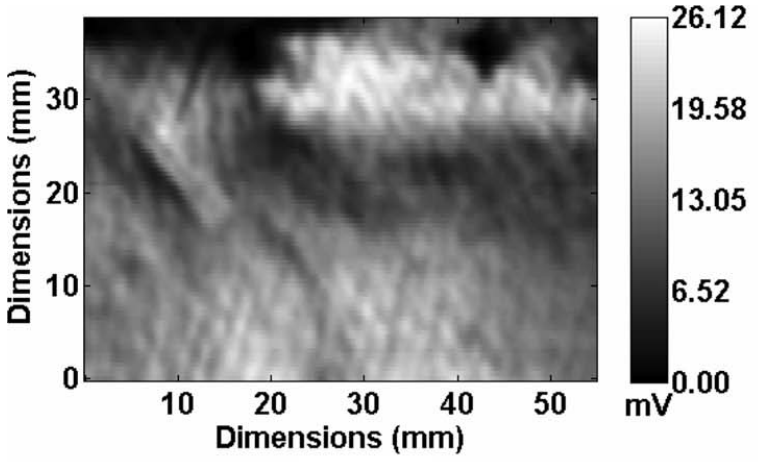


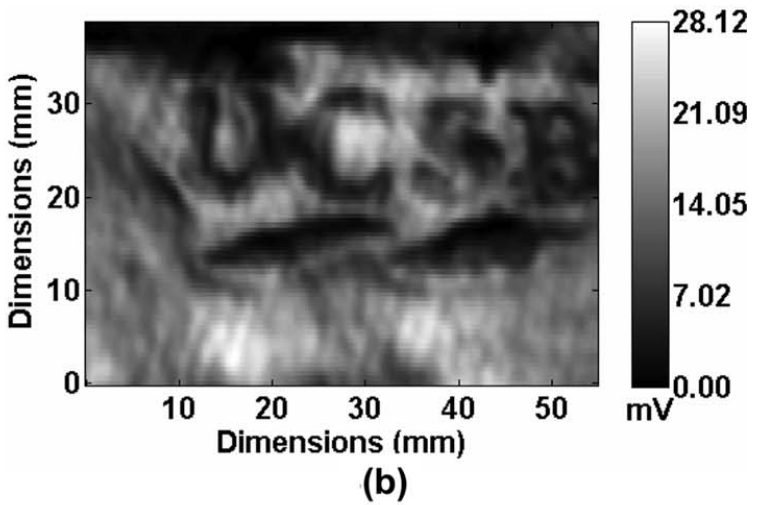


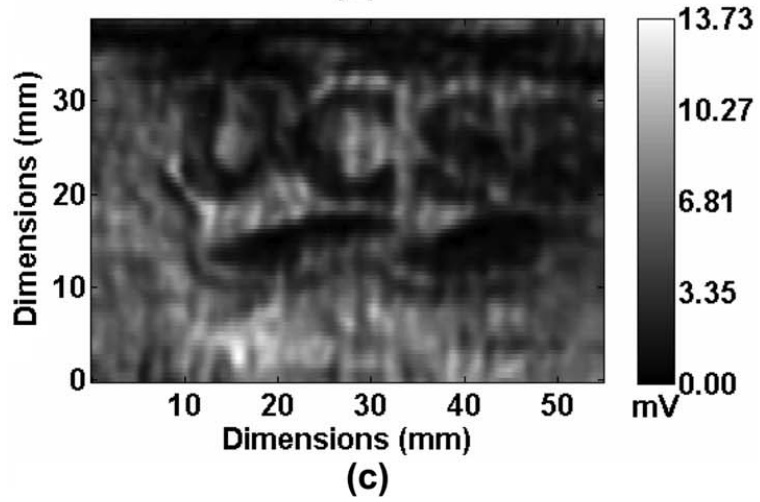
Stratum corneum

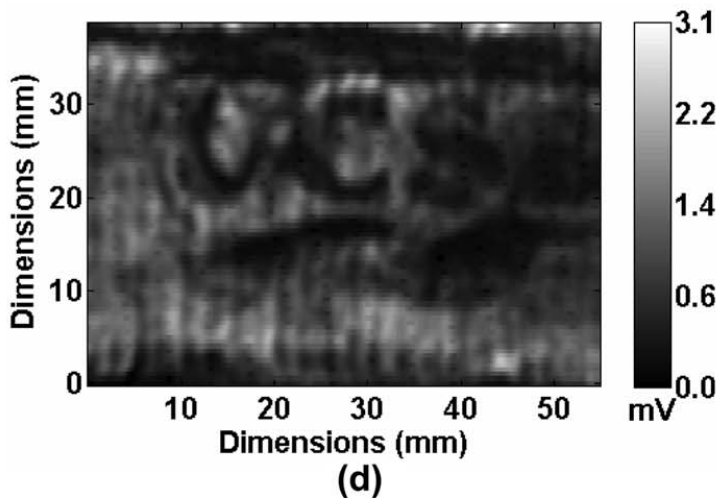
Applications
Skin conditions
Skin Hydration
Cosmetics Industry

Burns (Brown et al, 2008 OPT. LETT.)





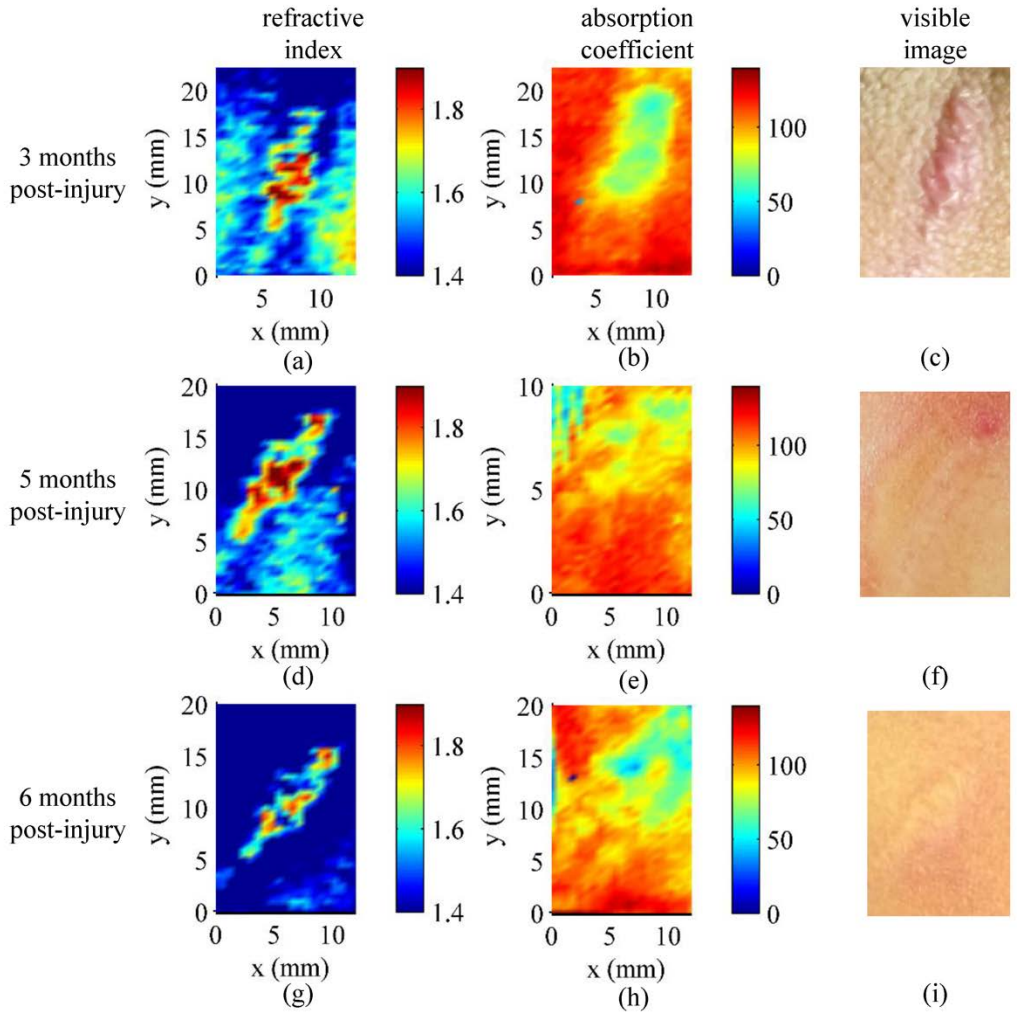




Recent results

Terahertz imaging of scarring process

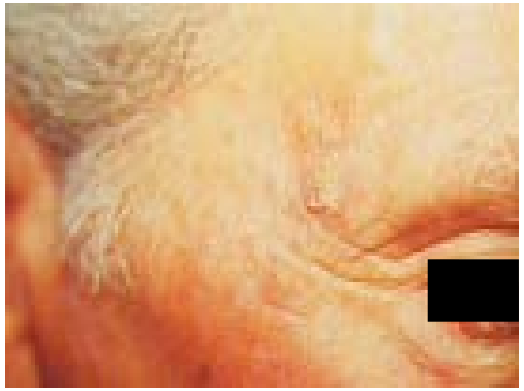
- Terahertz is used to image a scar at different time post-injury.
- The structural change during scar formation and developing can be detected by terahertz
- The scar which is almost invisible in the visible image still has a sharp contrast in the terahertz image



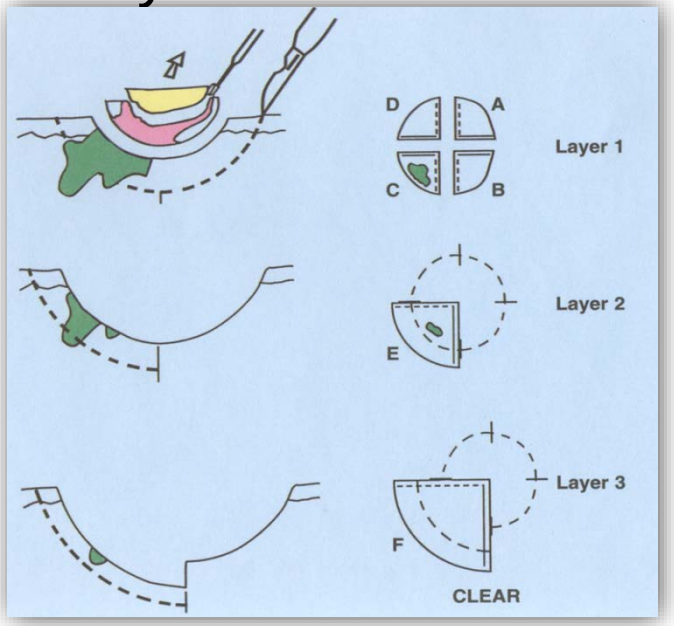
Paper in draft

Basal Cell Carcinoma (BCC)

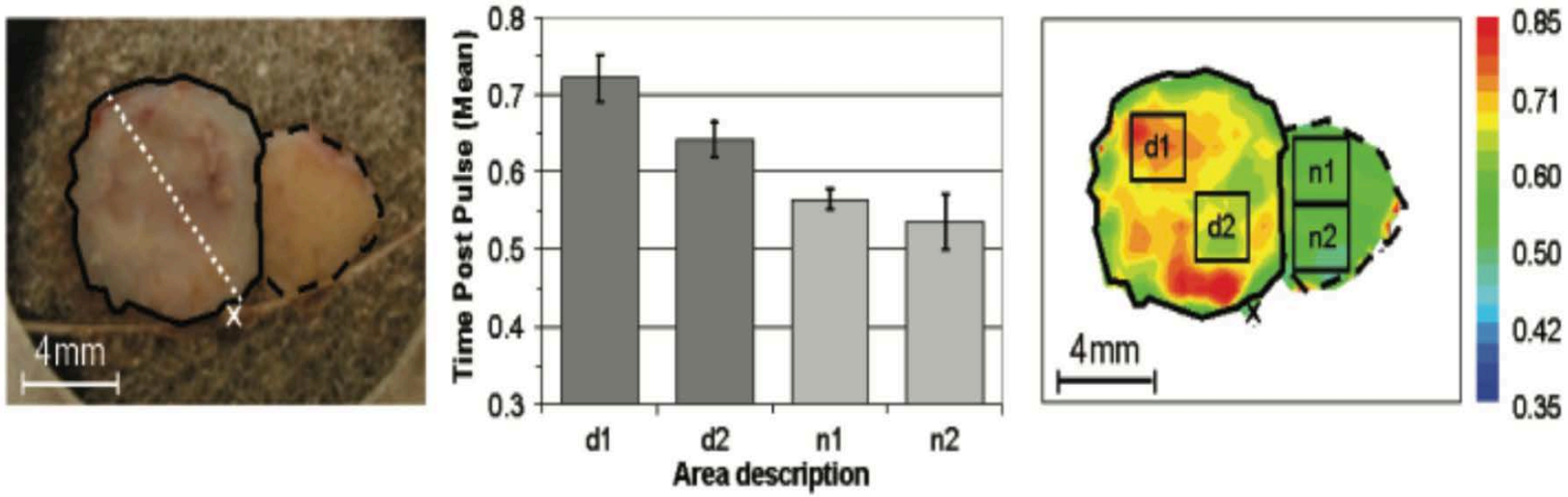
- Most common form of skin cancer
- >1 million annual incidence US
- 80% excised safely, 20% ill defined/large
- Mohs' surgery time consuming and costly
- Low mortality, High morbidity



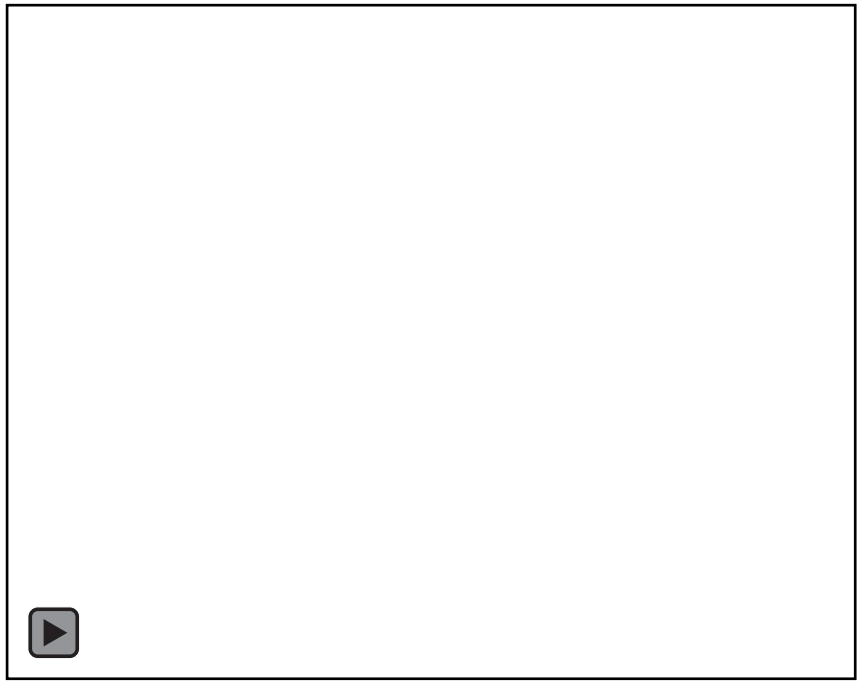
'Malignant Tumors of the Skin', ed. Chu and Edelson



Excised BCC


4mm
Time Post Pulse (Mean)
0.8
0.7
0.6
0.5
0.4
0.3
d1
d2
n1
n2
Area description
d1
d2
n1
n2
4mm
0.85
0.71
0.60
0.50
0.42
0.35

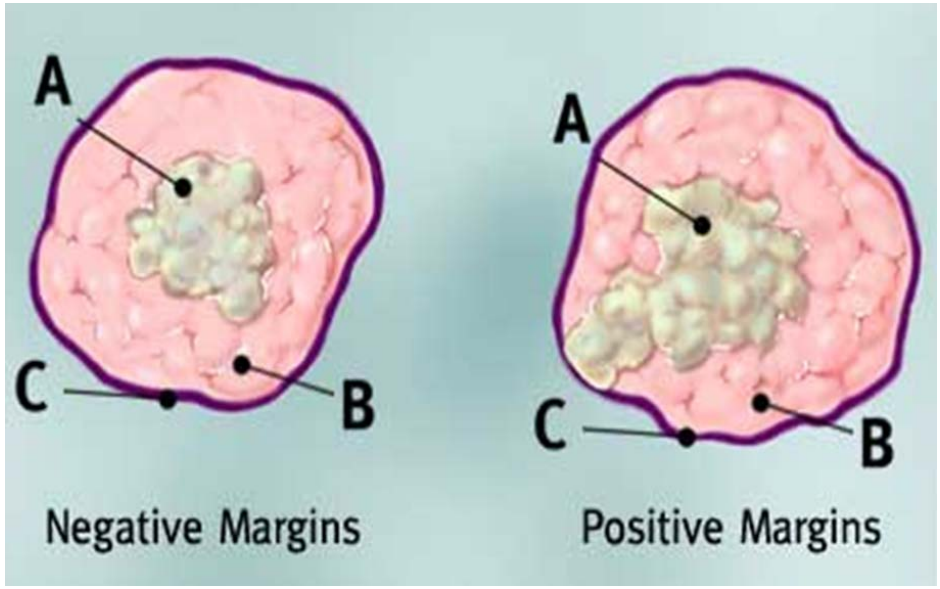
in vivo surface and depth information (BCC)



Clinical need – Breast Cancer Surgery

- Breast cancer is the commonest cancer in women in the western world
- Lifetime risk of 1 in 8
- Incidence is ever increasing

- Treatment is via surgery combined with radiotherapy/chemotherapy
- Problem is that **25-30%** of patients return for a second surgical procedure



THz Study: Tissue Sample Preparation and Pathology

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Surgery

↓

Sample marked for pathology

↓

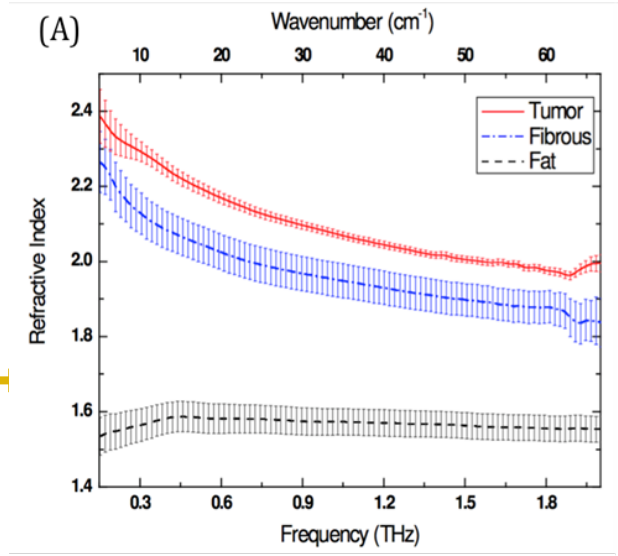
Tissue samples imaged with TPI1000 System

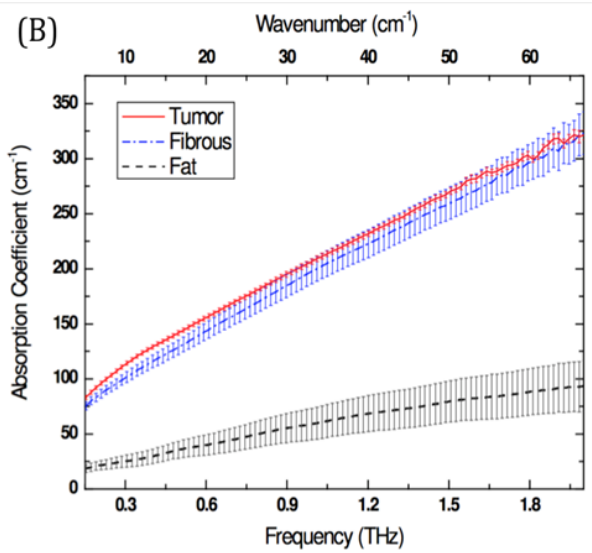
↓

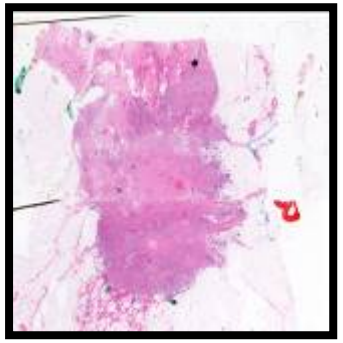
Formalin Fixed

↓

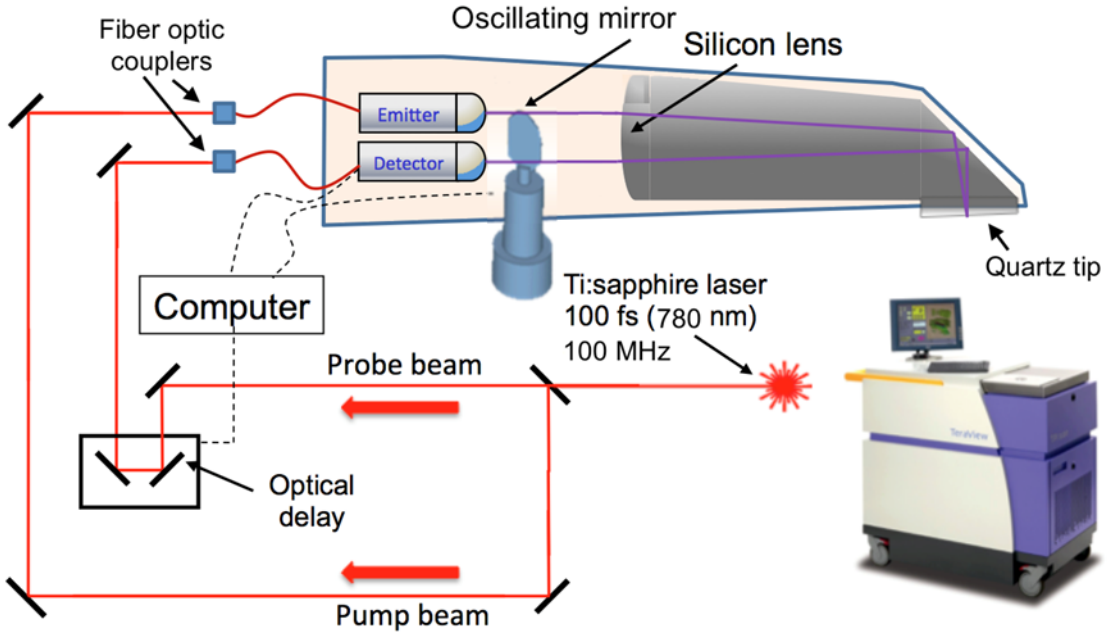
Histology

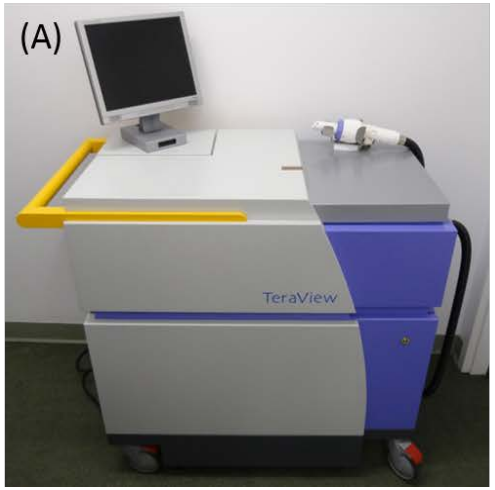


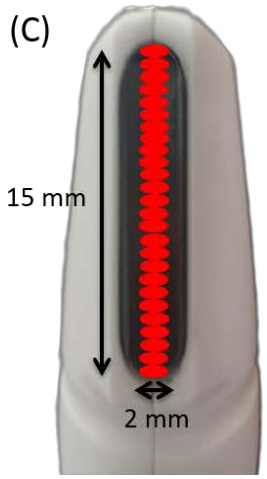




Handheld TPI probe (Teraview Ltd.)







Material and methods

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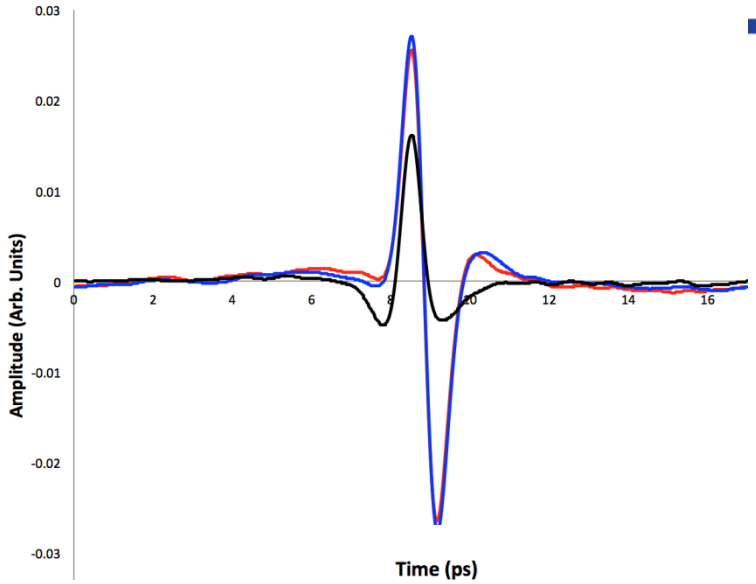
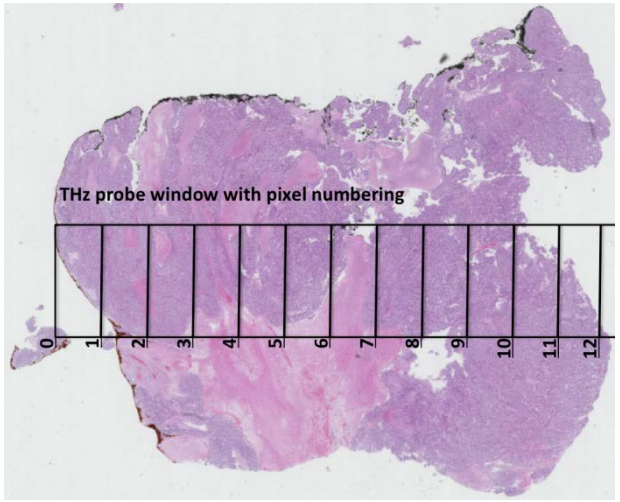
THz data acquisition



Detailed pathology



Per pixel area
- Tissue type (tumour, fibrous, adipose)
- Cell density (%)

Dataset

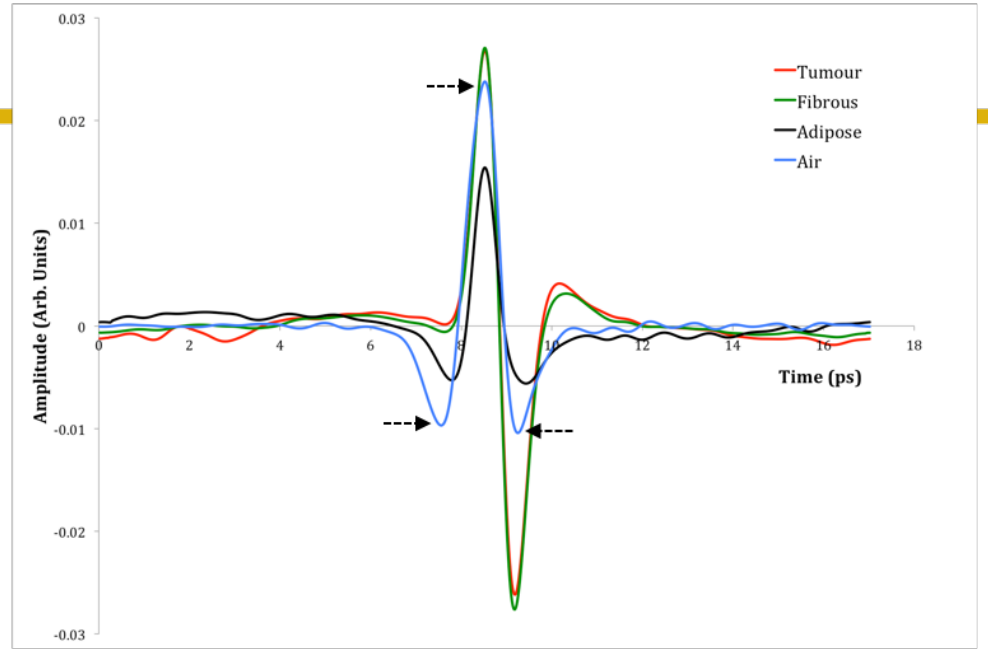
In total 126 samples from 106 patients were scanned

46 samples met the strict inclusion criteria required to accurately correlate THz to histopathology

Tissue type	No of samples	No of patients
Tumour	20	18
Invasive NST[1]	*16*	*15*
Invasive lobular	*2*	*2*
DCIS[2]	*2*	*2*
Fibrous	21	15
Adipose	5	5
Total	**46**	**32**

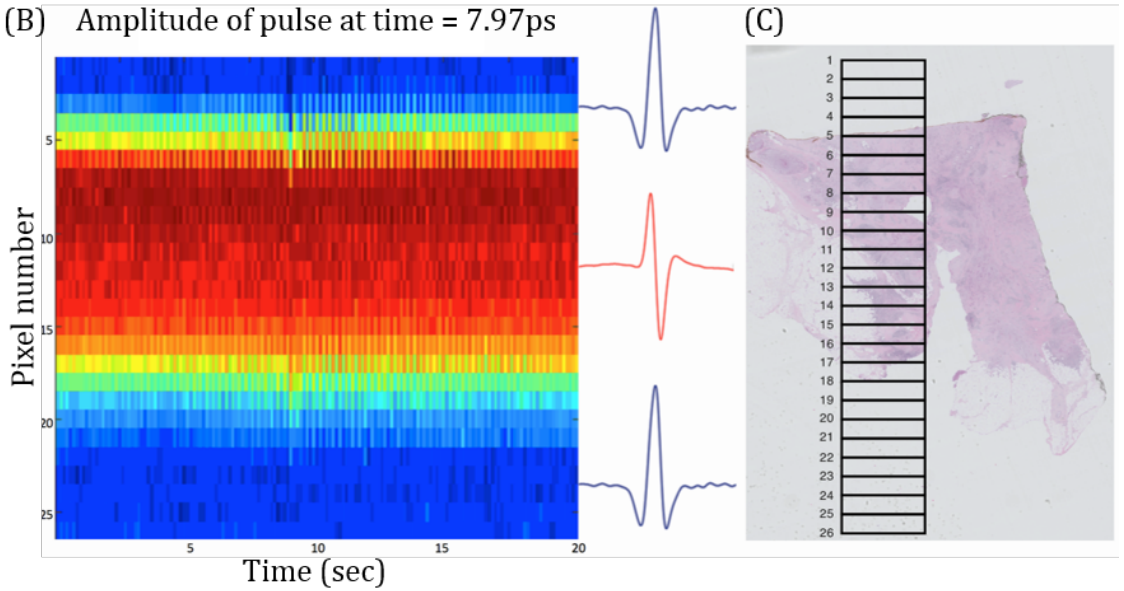
NST = no special type i.e. invasive ductal carcinoma
DCIS = ductal carcinoma in situ

(A)



(B) Amplitude of pulse at time = 7.97ps

(C)



Gaussian wavelet deconvolution for tissue classification

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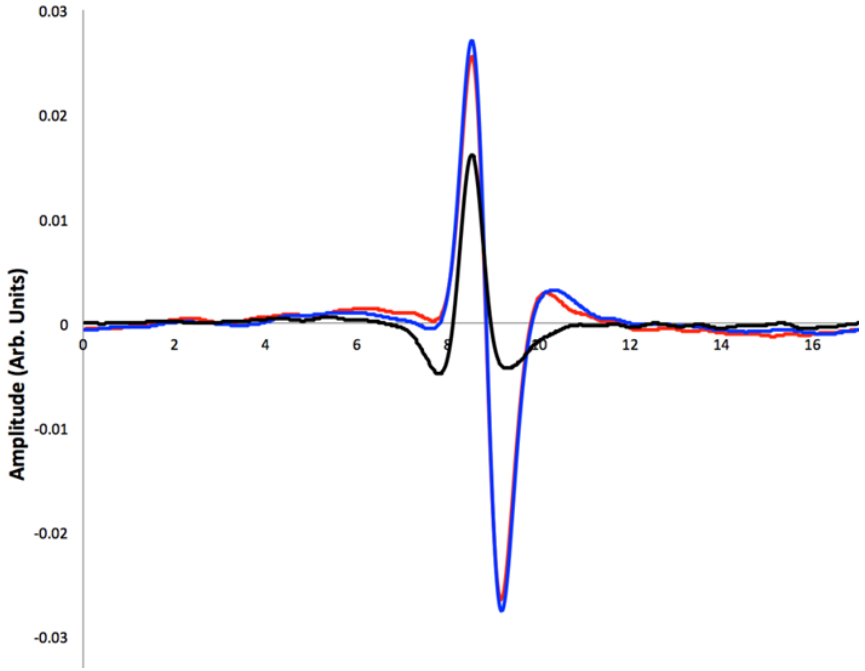
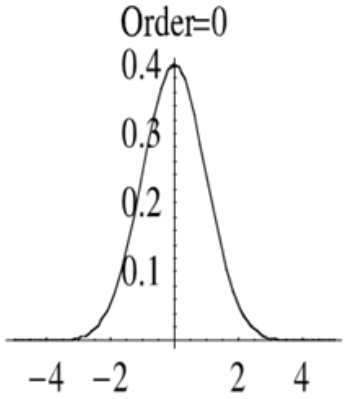
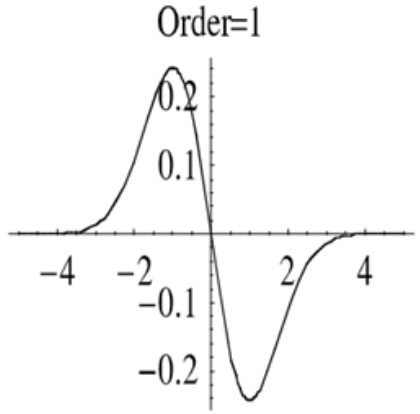
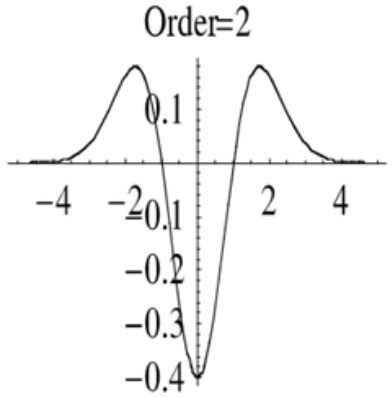
Collected data

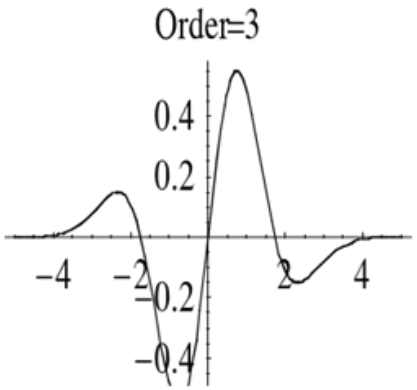


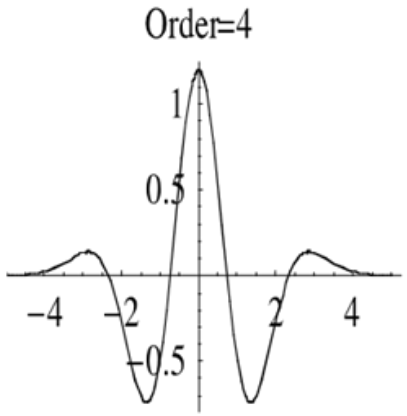
Gaussian Derivatives







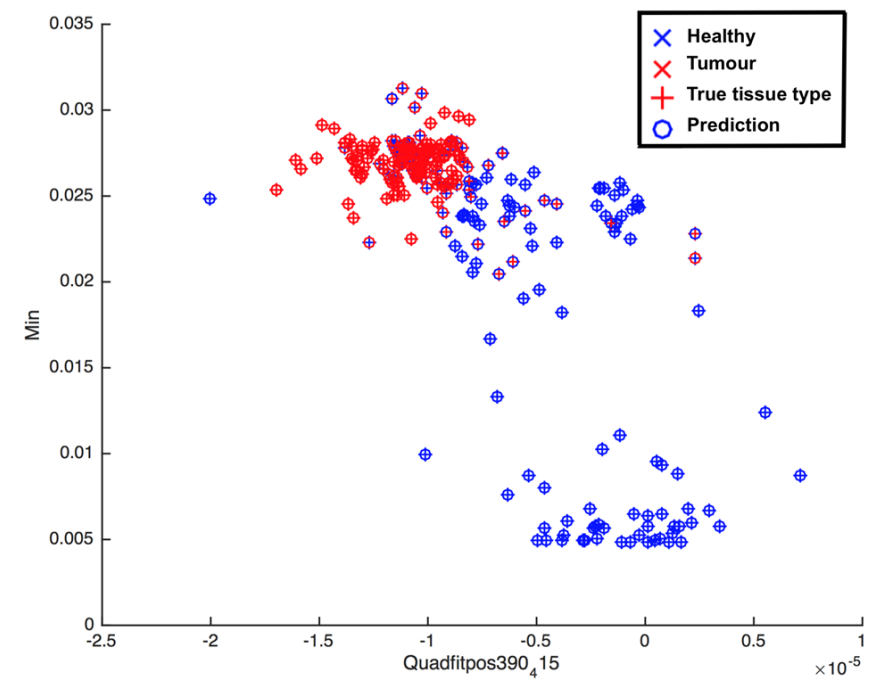




Results Bayesian Classification

(using wavelets – leave one out)

2D-cluster plots and classification plots



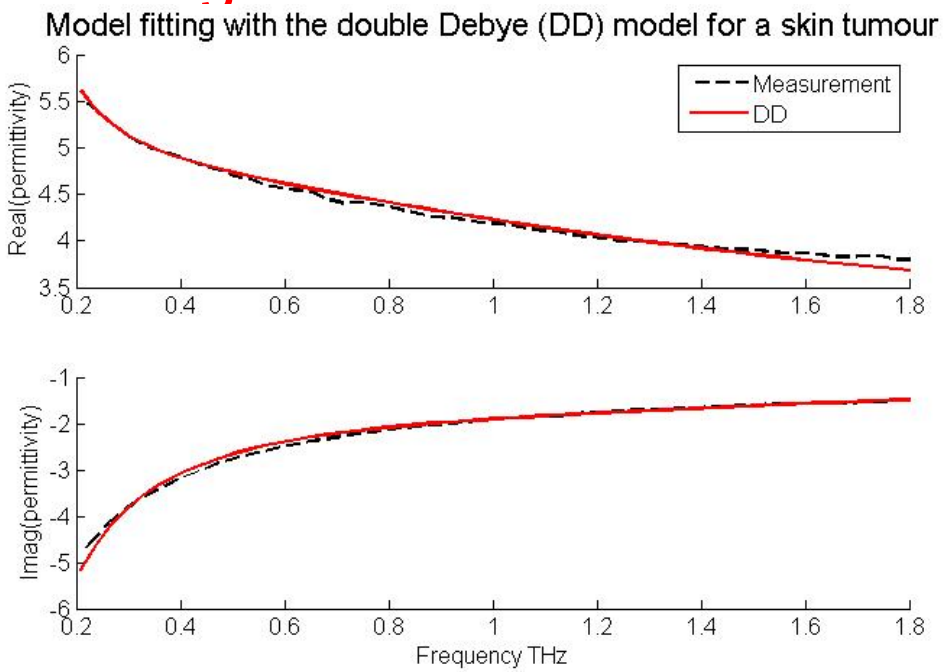
Sensitivity	**90.9%**
Specificity	**91.5%**
Positive predictive value	**71.4%**
Negative predictive value	**97.7%**

Opportunities for FEL THz beamline studies

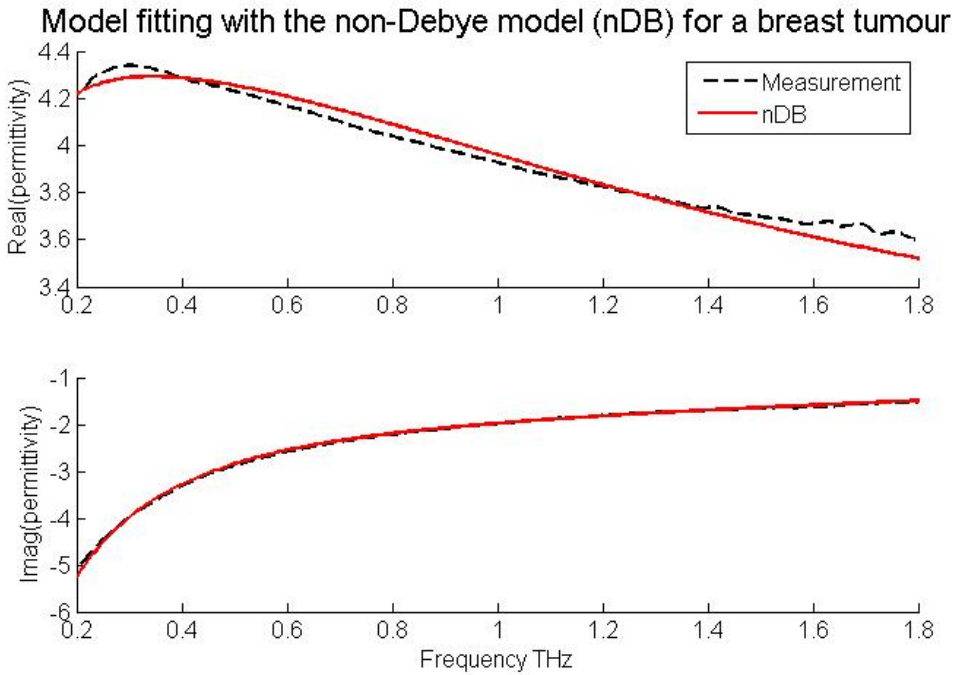
- Imaging of tissues/animals
- Effects of intense THz radiation on biological systems
- Threshold measurements
- Perturbation of biological processes
- Hydration studies
- Polarisation changes / vibrational circular dichroism

Thanks for listening

Modelling Skin and Breast Cancer Using Parameters of Dielectric Models



$$\mathrm{DD}: \tilde{\epsilon}(\omega) = \epsilon_\infty + \frac{\epsilon_s - \epsilon_2}{1 + j\omega\tau_1} + \frac{\epsilon_2 - \epsilon_\infty}{1 + j\omega\tau_2}$$



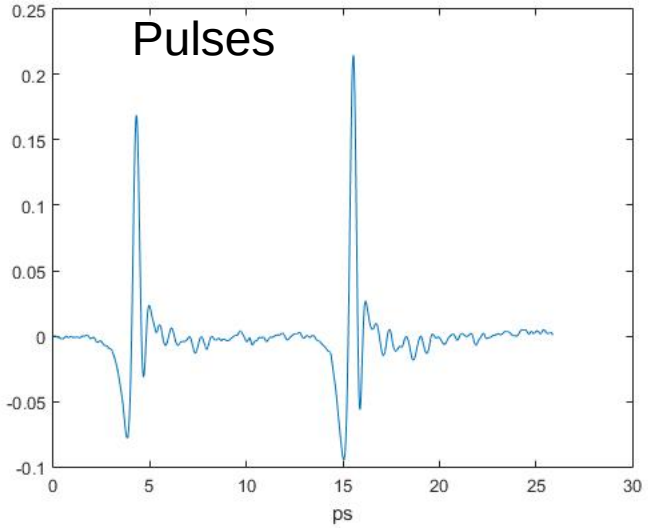
$$\mathrm{nDB}: \tilde{\epsilon}(\omega) = \epsilon_\infty + \frac{\omega\tau_1\Delta\epsilon_1 + \Delta\epsilon_2}{1 + (j\omega\tau_1)^\alpha} + \frac{\Delta\epsilon_3}{1 + j\omega\tau_2} + \frac{\sigma}{j\omega}$$

Recent Results:

- We previously have shown the double Debye model (DD) and the non-Debye model for breast tissue (nDB) are capable of describing complex permittivities of skin and breast tissue effectively.
- Optimisation methods have been developed to improve fitting the models.
- We have found that several parameters of DD and nDB have potential ability to discriminate skin and breast cancer.

Imaging Skin and Breast Cancer Using Parameters of Dielectric Models

THz Reflection Pulses



- Complex refractive Index
- Complex permittivity
- Parameters of the model nDB

Terahertz Image of Breast Tumour

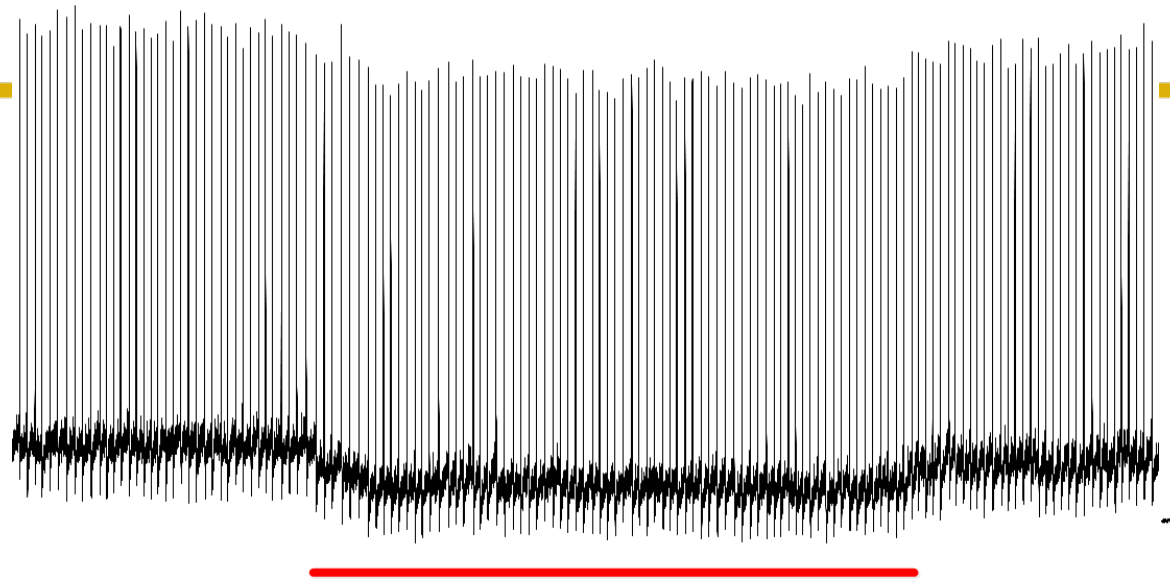
Goal:

- Correctly reconstruct refractive index and permittivity of breast tissue
- Extract parameters of the nDB for correctly mapping breast tumour margins

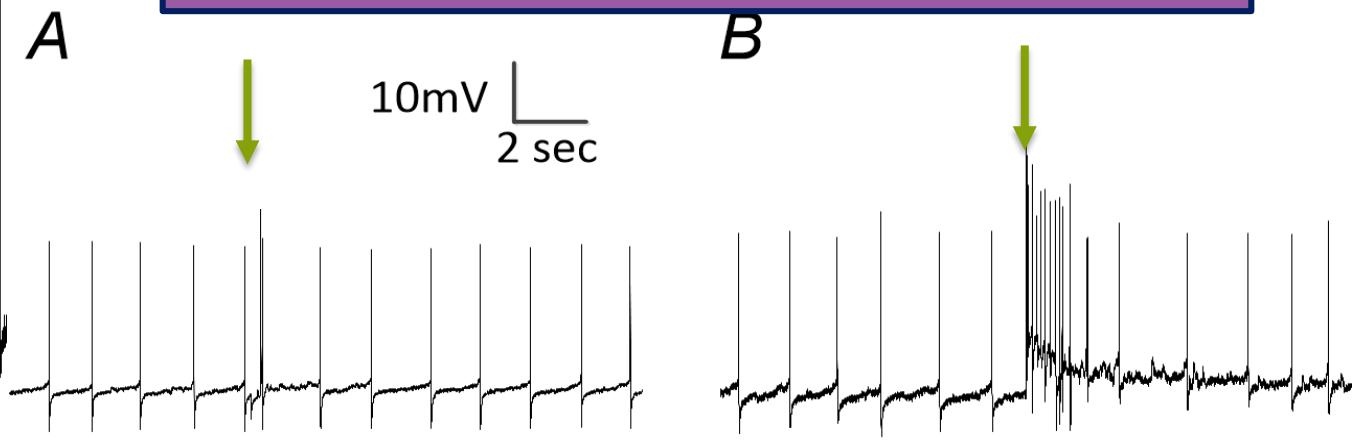
Methodology:

- Apply signal processing techniques to remove noise and align measured reflection pulses
- Develop a reflection model together with an appropriate optimisation algorithm to extract the nDB parameters

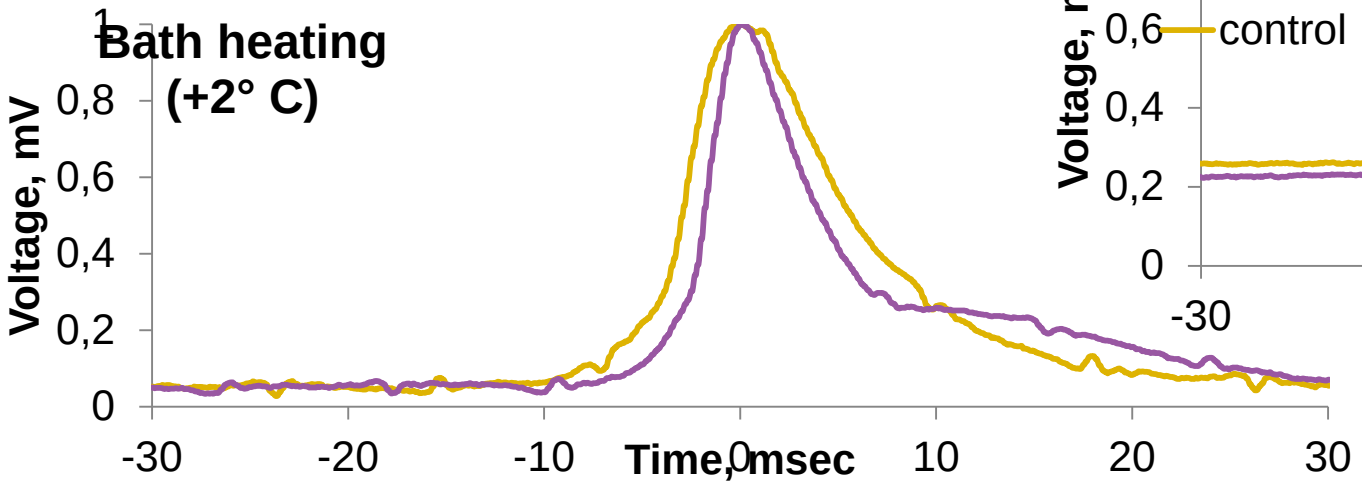
CW STIMULATION MODE (60 GHZ)

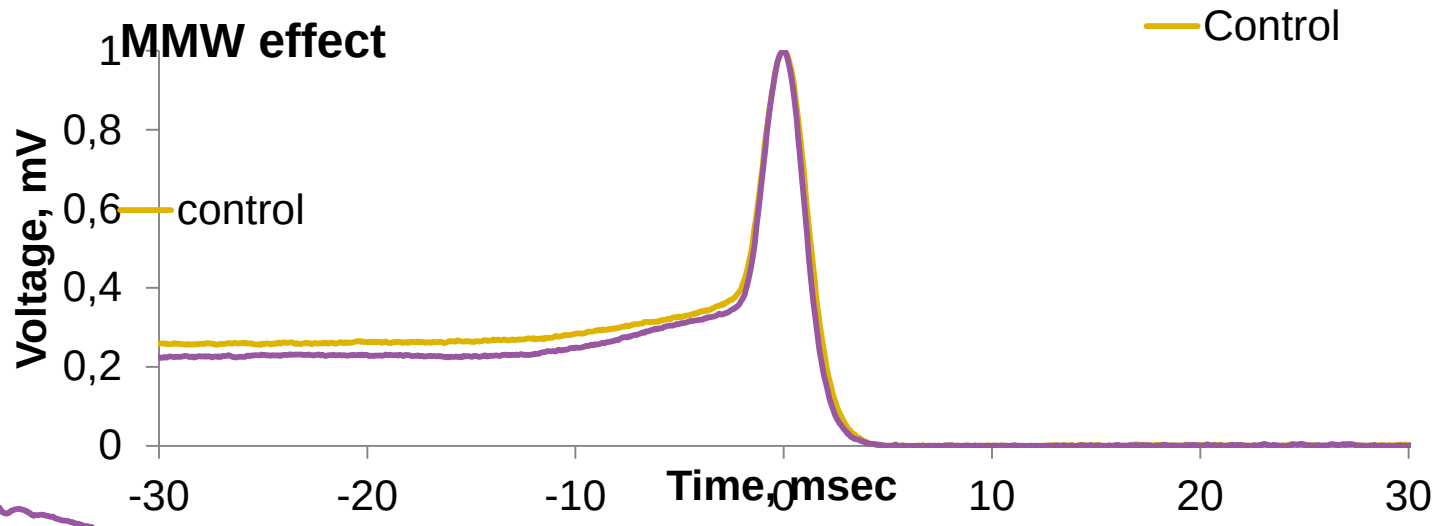


HIGH POWER PULSED STIMULATION MODE (nanosecond pulse)



MMW 3.6 mW/cm²

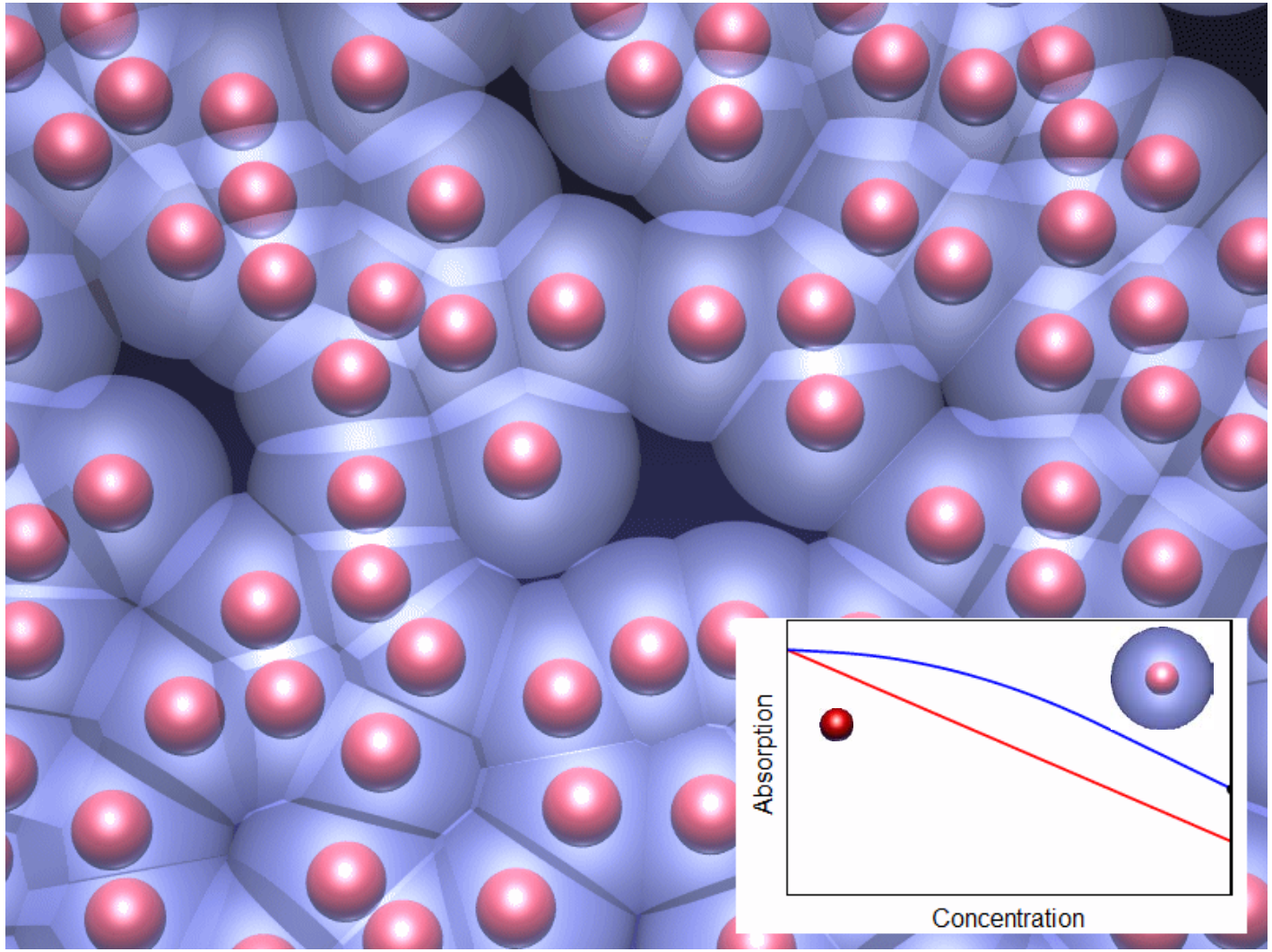




Neurostimulation with nanosecond pulsed electric fields: A combined electrophysiology and multiphoton imaging approach in intact ganglia Sergii Romanenko[1], Delia Arnaud-Cormos[1], Sylvia M. Bardet[1], Philippe Leveque[1] & Rodney P. O'Connor[1]

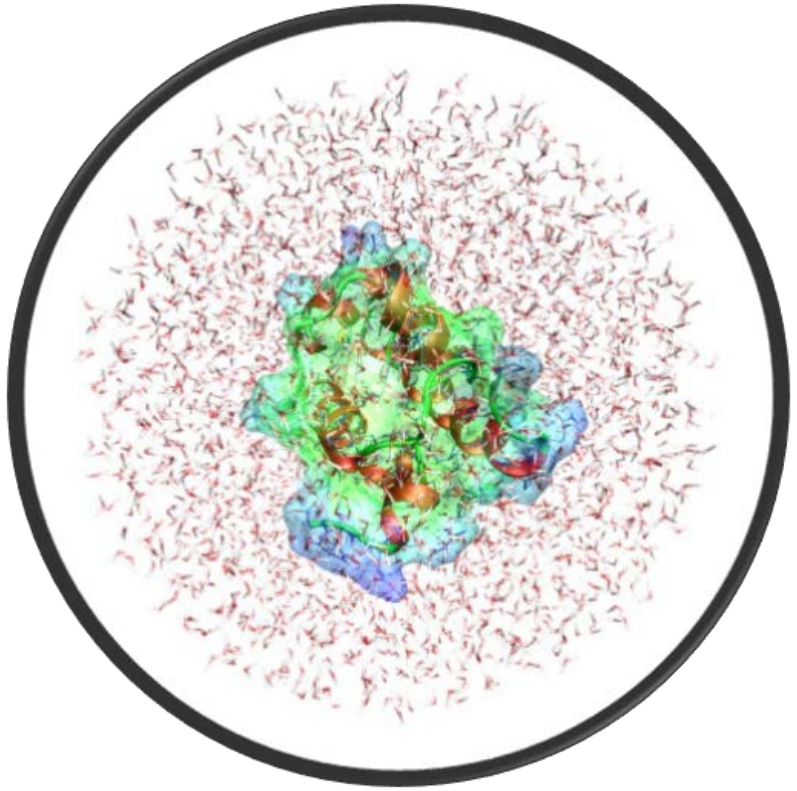
THz absorption of aqueous solutions

(M. Heyden, M. Havenith)



Biomolecular solutes

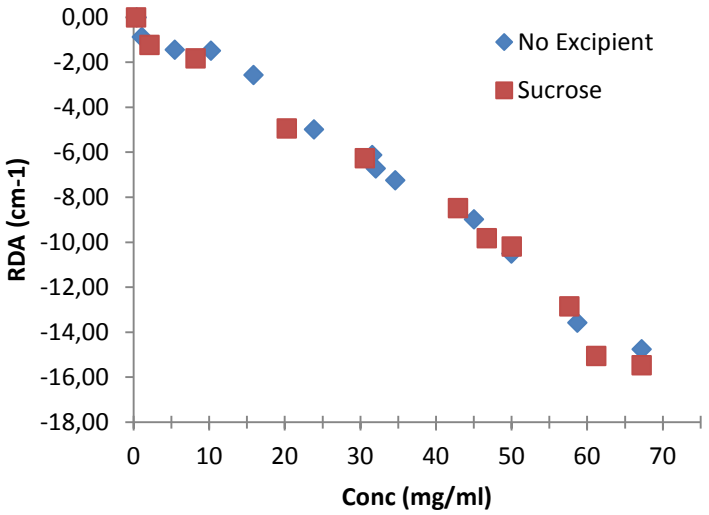
Proteins in Solution

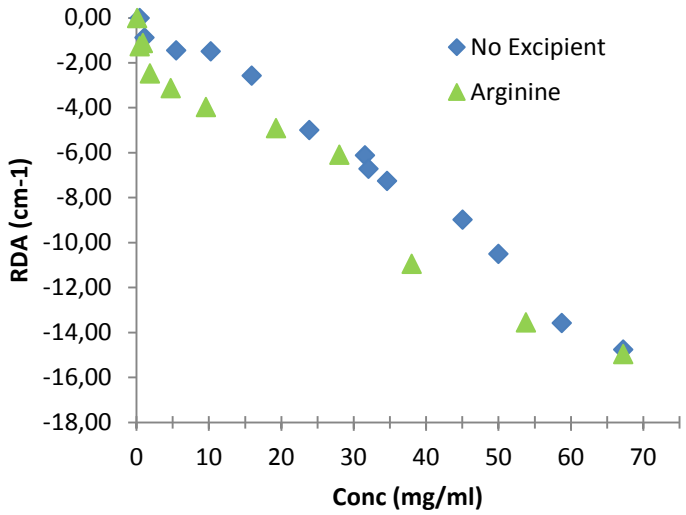


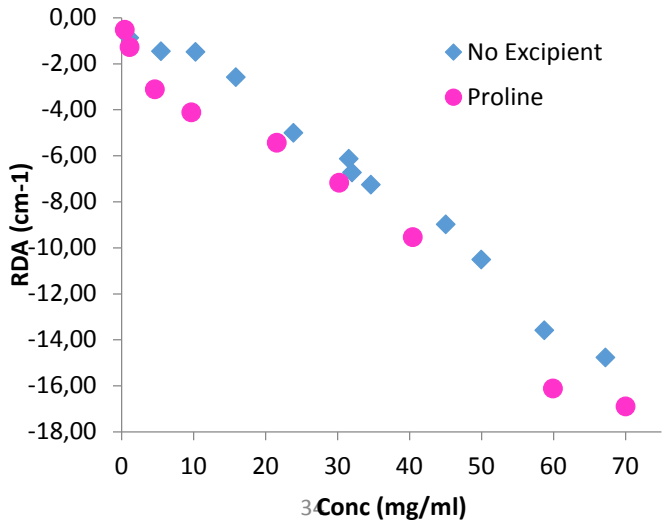
- Hydration/solvation shell shown to be 3 times larger than previous thought

Monoclonal Antibody: Study of Sucrose, Arginine and Proline

Relative difference in absorption (RDA)







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