“A new approach to the diagnosis of cervical, oesophageal and prostate cancer based on a combination of infrared and terahertz techniques.”

Peter Weightman

Physics Department, University of Liverpool.

Towards disease diagnosis through spectrochemical imaging of tissue architecture.

EPSRC: EP/K023349/1:

Critical Mass £ 3.2m

Collaborators

Universities of

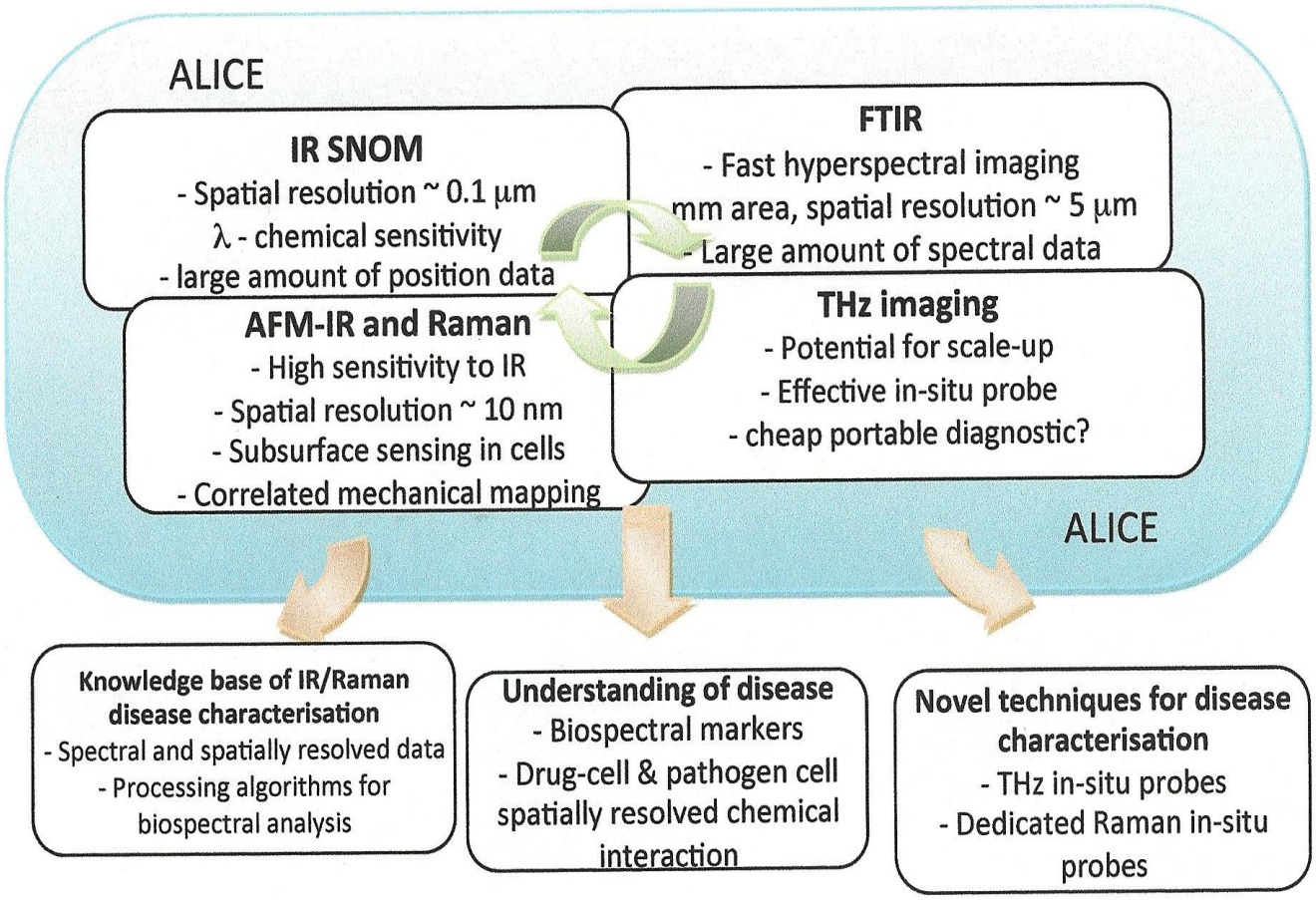
Cardiff, Lancaster

Liverpool, Manchester

Hospitals

Lancaster, Liverpool

Manchester



Objectives

1 **To advance the understanding of oesophageal, cervical and prostate cancers through the application of IR, Raman and THz techniques.**

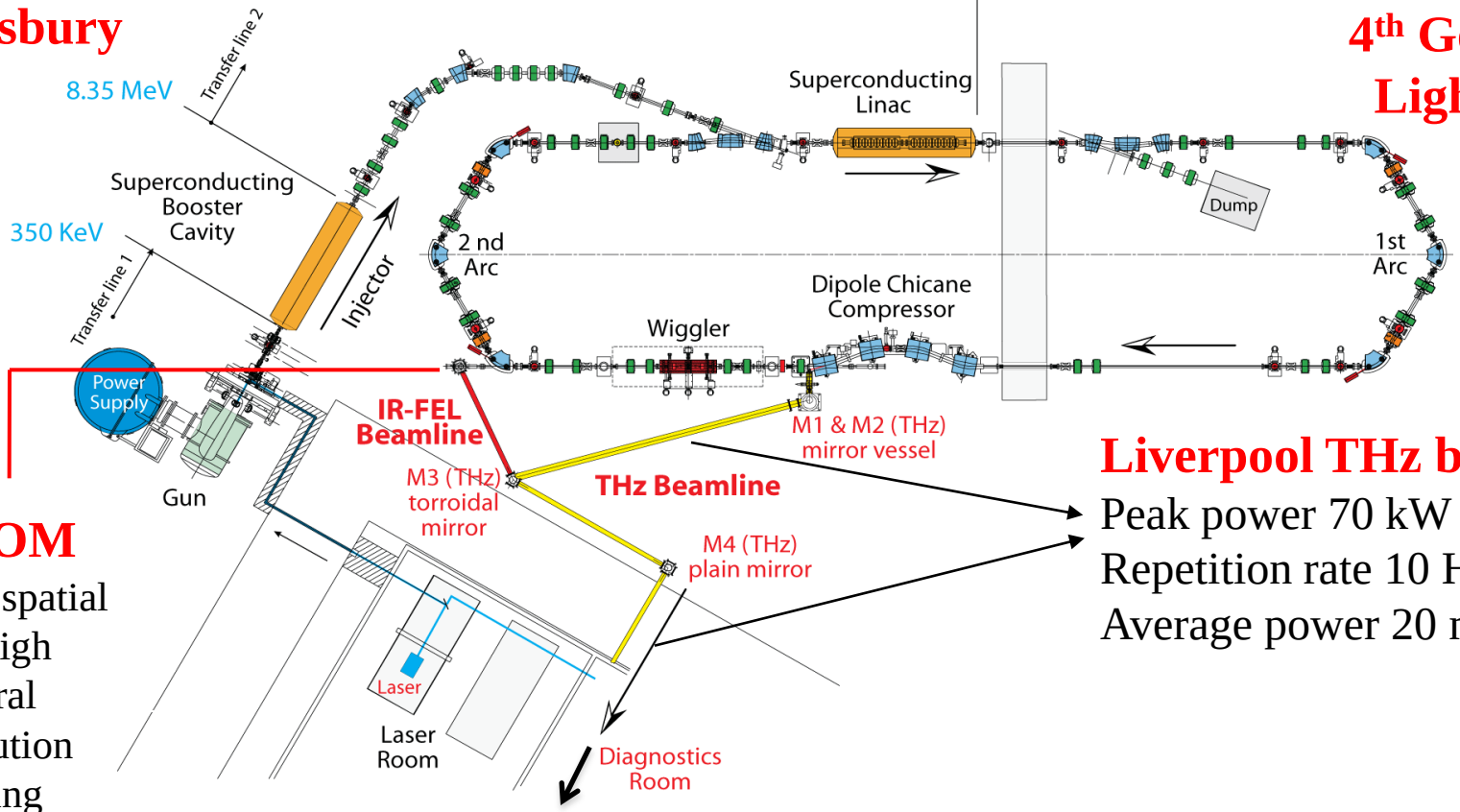
2 **To clarify the potential of IR, Raman and THz techniques for the characterisation of cancerous tissue since conventional approaches appear to have reached their limits..**

Some studies of breast cancer.

Energy Recovery Linear Accelerator / ALICE

Daresbury

4th Generation Light source



SNOM

High spatial and high spectral resolution imaging

Liverpool THz beamline

Peak power 70 kW in 0.8 psec
Repetition rate 10 Hz
Average power 20 mW

Tissue Culture Facility (cleared for research on cancerous tissue)

Potential of ALICE for cancer research

1 Infrared free electron laser and scanning near field microscope (SNOM)

Diagnosis of extracted tissue

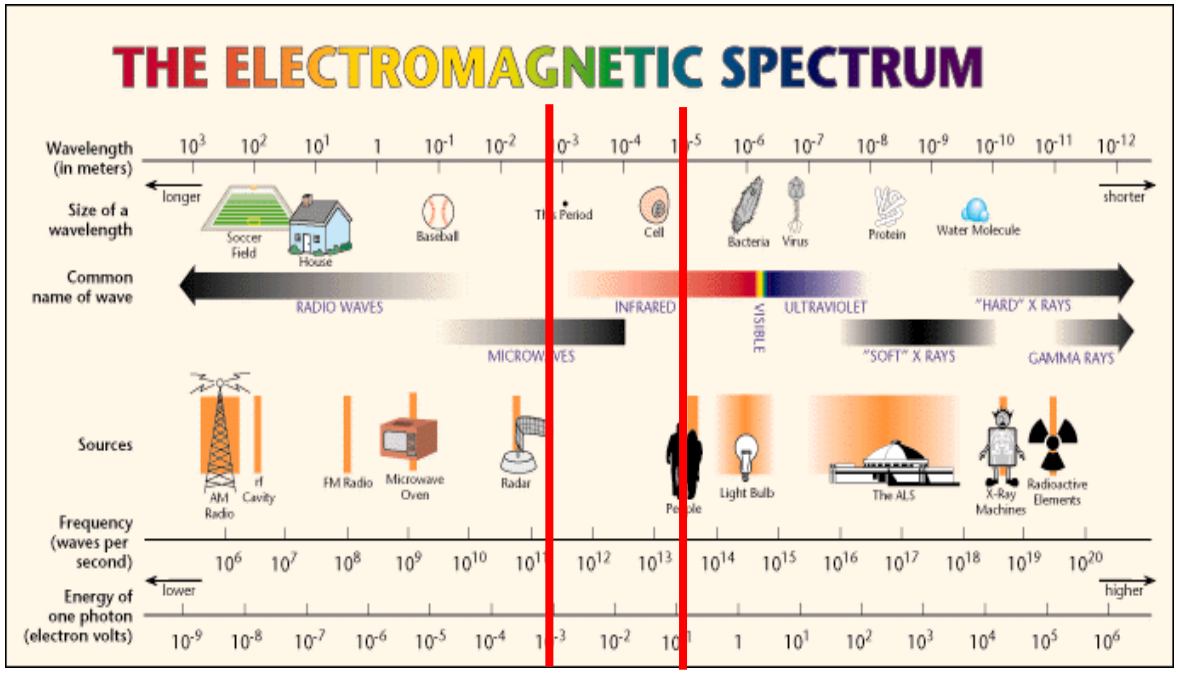
2 THz beamline and tissue culture facility

Development of portable diagnostic instruments,

A new therapy?

http://www.youtube.com/watch?v=d7Lbyuqor8A

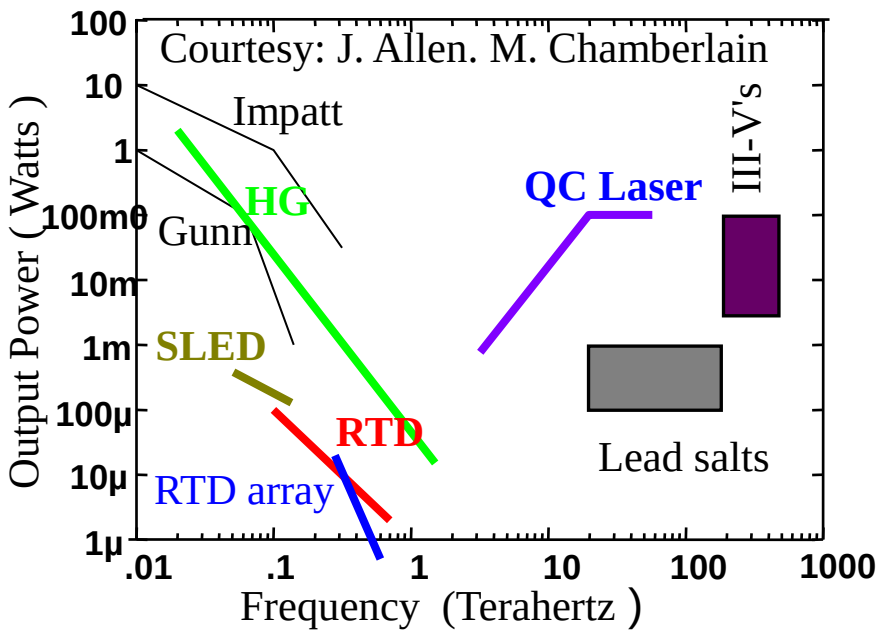
Terahertz radiation: Non ionising



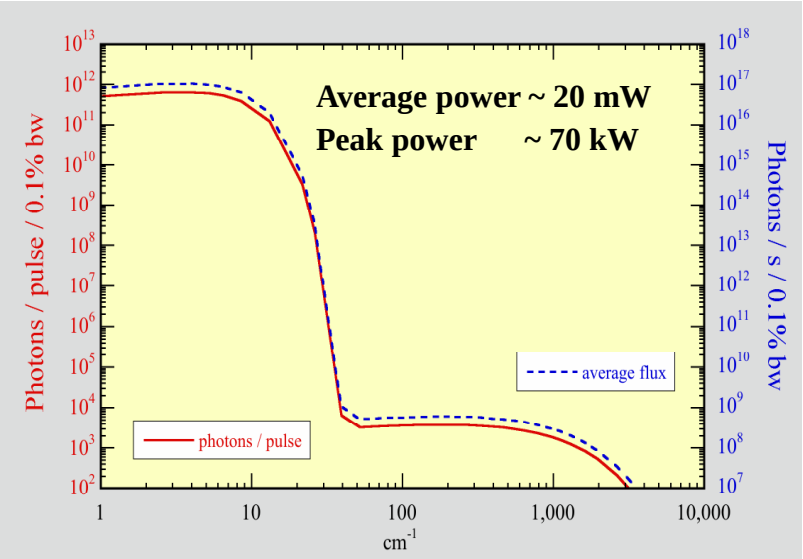
Laboratory instruments:

1 THz

~ 100 μwatts



ALICE Accelerator



Liverpool THz Beamline and TCF

Laboratory instruments

At 1 THz ~ 100 □ watts

Accelerators

Carr et. al. Nature 420 153 (2002)

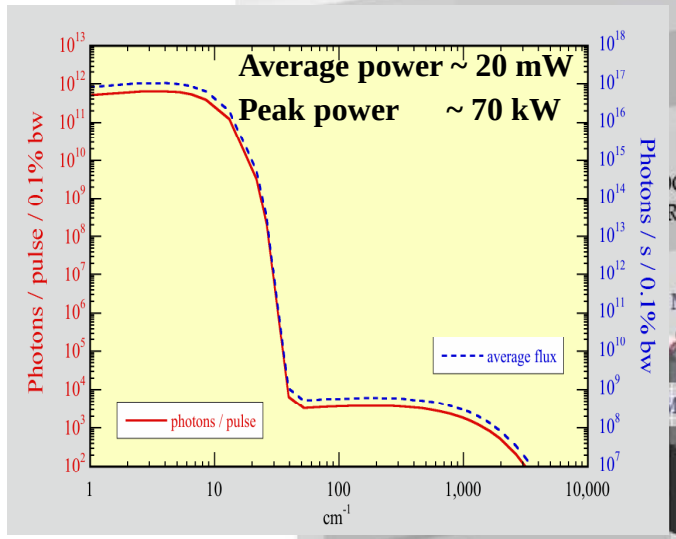
Short electron bunches

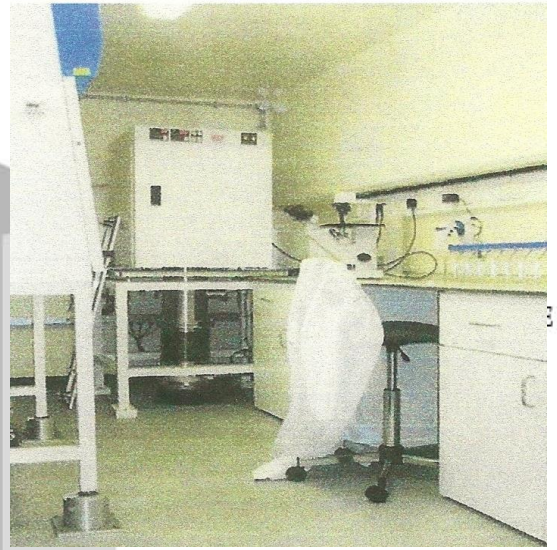
Bunch length < wavelength

Coherent emission

massive output power

ALICE





1st Floor Tissue Culture Facility

Lower level hutch for a variety of THz experiments

Significant funding and staff from physics dept.

THz Imaging: Medical Applications

A THz imaging system is being tested in Guys hospital to identify cancerous tissue

Existing instruments are low power - μW to mW (ALICE 10 kW)

Contrast mechanisms are not understood and diagnostic protocols crude

Need for research combining spectroscopy and microscopy at kW

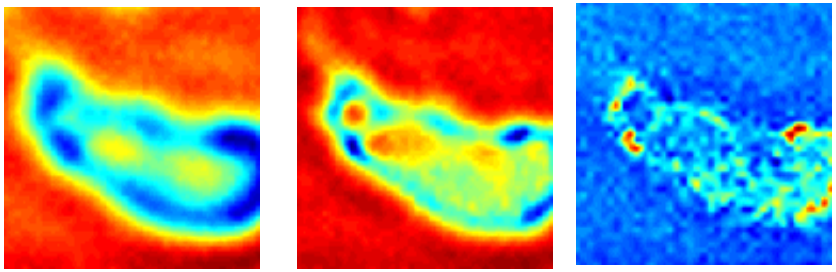
Does Malignancy have a THz signature?

Research could lead to development of low cost portable diagnostic equipment

Develop hand held THz probe to guide surgery.

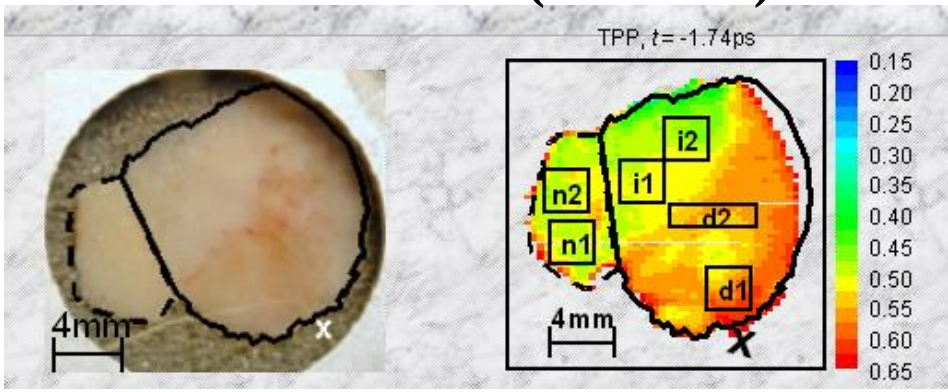
Melanoma (Martyn Chamberlain)

0.5 THz **1.0 THz** **2.0 THz**



Multiple frequency comparison

Basal cell carcinoma (Teraview)



visible

THz

malignancy in red

Detector development with Carole Tucker (Cardiff) and Yaochun Shen (Liverpool)

THz Experiments in Cell Tissue Culture Facility

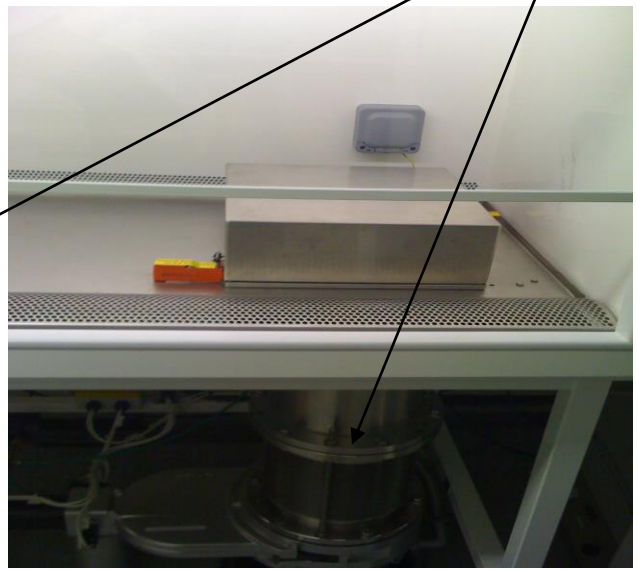
Does THz radiation have potential as a cancer therapy?

"Intense THz pulses cause H2AX phosphorylation and activate DNA damage response in human skin tissue." L. V. Titova et. al. Biomedical Optics Express 4 559-68 (2013)

"Intense THz down regulate genes associated with skin cancer and psoriasis: a new therapeutic avenue?" L. V. Titova et. al. Nature Scientific Reports 3 : 2363 (2013)

Stem cells in culture

CO_2 Incubator



Microbiological safety cabinet

Tissue culture facility with particulate free air conditioning.

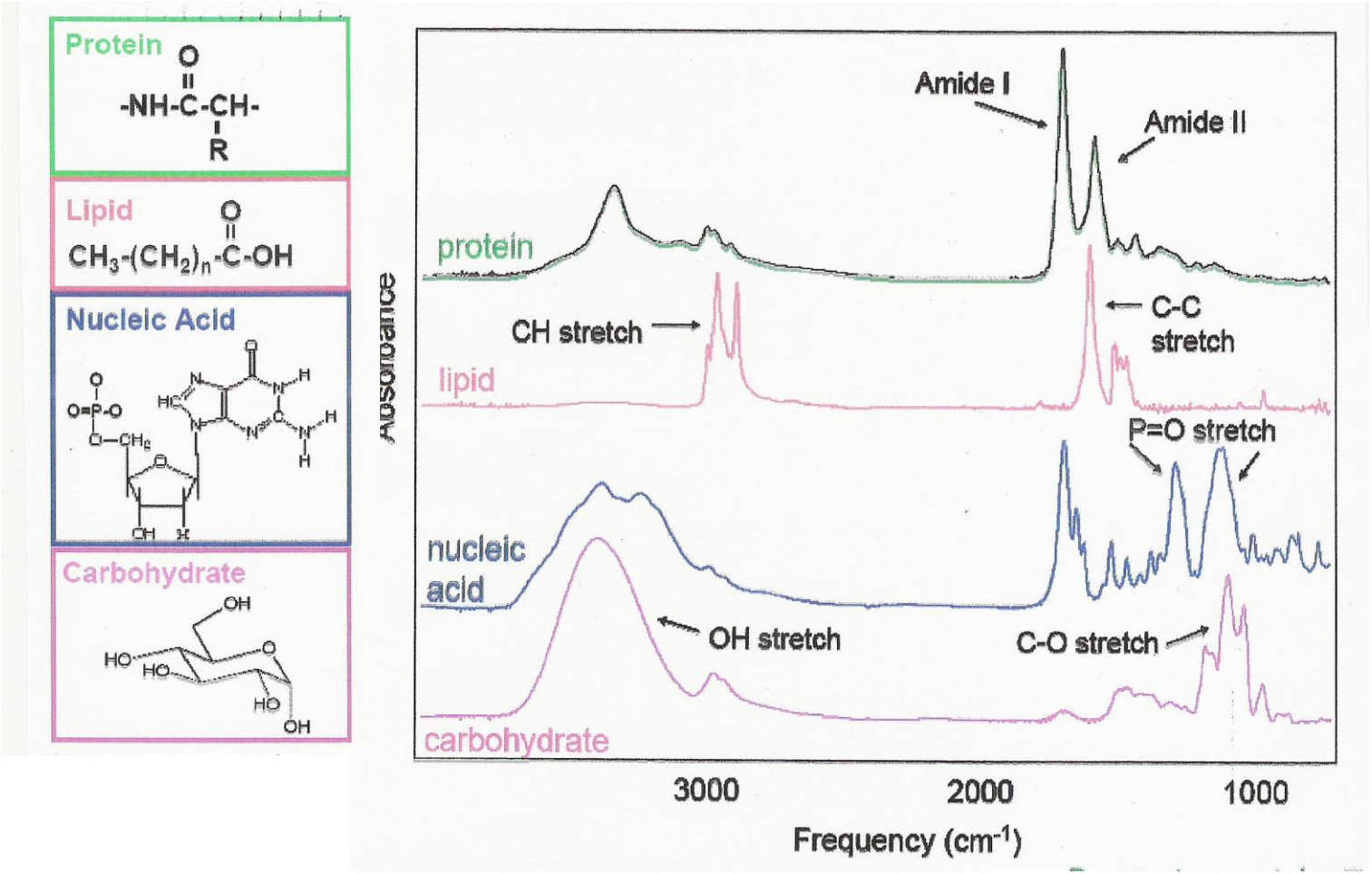
Application of the

SNOM on the IR FEL

to the study of oesophageal cancer.

Spectroscopy and microscopy in the infrared

Strength: Spectral fingerprints of molecules



Weakness: Long wavelengths Diffraction limited spatial resolution ~ □/2

Solution: Near field optics ----> SNOM ---> needs high intensity

Combine Spectroscopy and SNOM ---> needs very high intensity ---> IR FEL

Previous work: Infrared studies of oesophageal tissue

Fourier transform infrared (FTIR)

On laboratory instrument: spatial resolution ~ cms^2

On synchrotron, diffraction limited, spatial resolution ~ 5 μm

Conclusions: Cancer characterised by:-

DNA concentration ~ doubles and DNA spreads over larger areas

Protein concentration reduces by ~ 6%

High DNA : Glycoprotein ratio

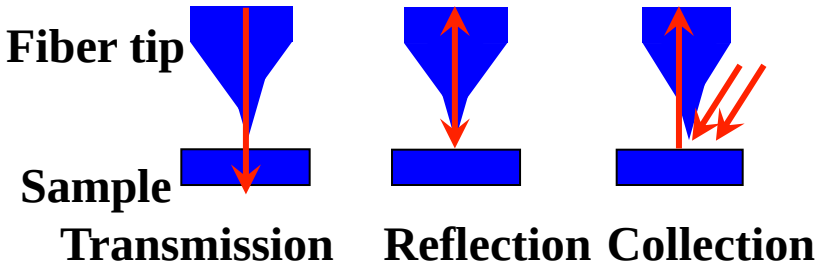
Current research

ALICE IR FEL+ SNOM spatial resolution ~ 0.1 μm

T.D. Wang et. al. PNAS 104 15864 (2007)

IR FEL + SNOM: Sub-cellular imaging of live cells

Scanning Near Field Microscopy (SNOM) in IR



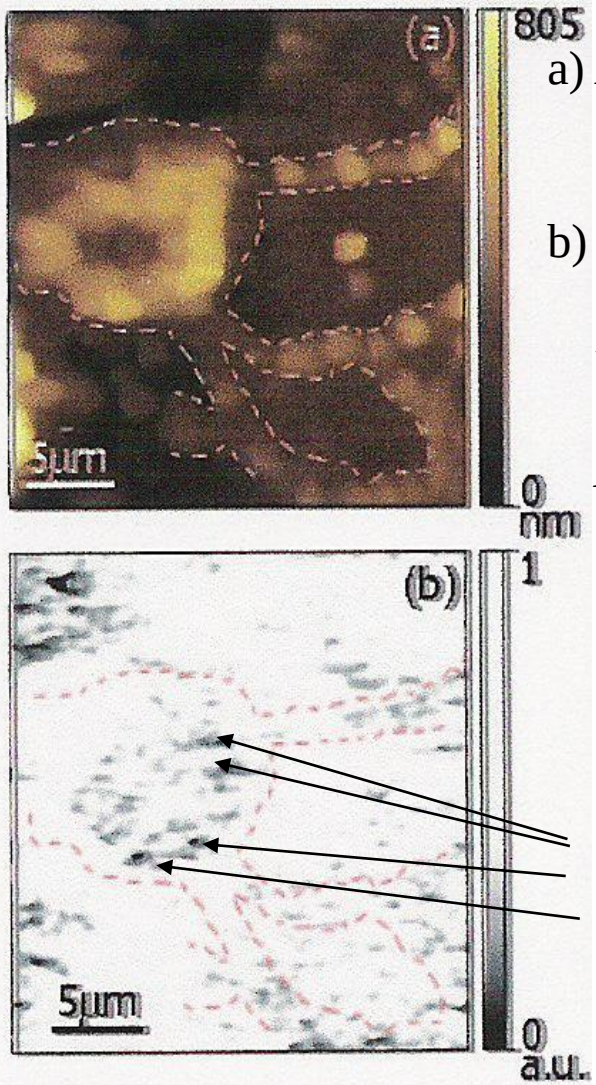
Spatial resolution beats diffraction limit, □/2
Spectral resolution to locate distribution of proteins, lipids and DNA (IR signatures)
Sub-cellular resolution of live cells

Combined spectral/spatial resolution
Key is intensity of source

	Resolution
Synchrotron (diffraction limited)	10 □m
Free Electron Laser (FEL)	0.1 □m

Challenges
slow, need good pulse to pulse stability

Eg. Detection of specific molecules in a cell



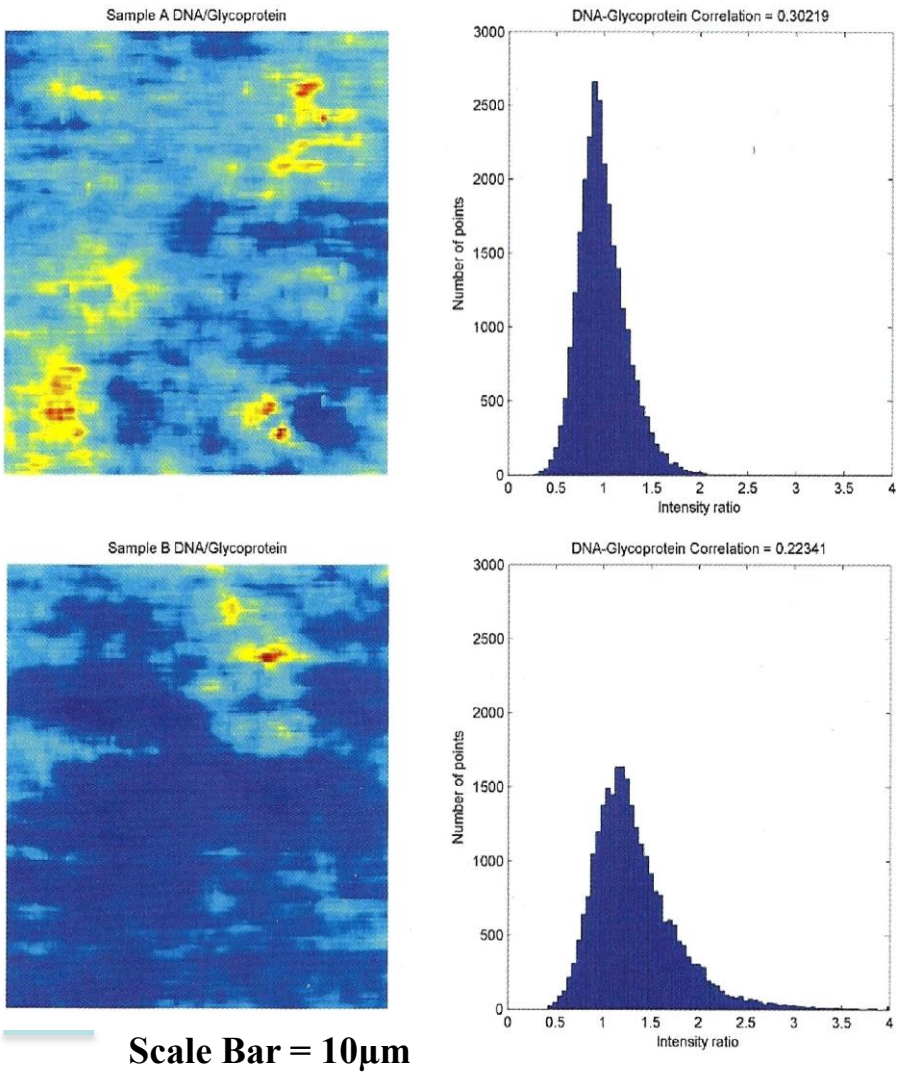
a) AFM Image of a neuron.

b) SNOM Image at 6.25 □m the absorption maximum of Alexa 488 fluorophore attached to GluR2 receptors on neurons

GluR2 receptors

Generosi et al, J. App. Phys. **104** 106102 (2008)

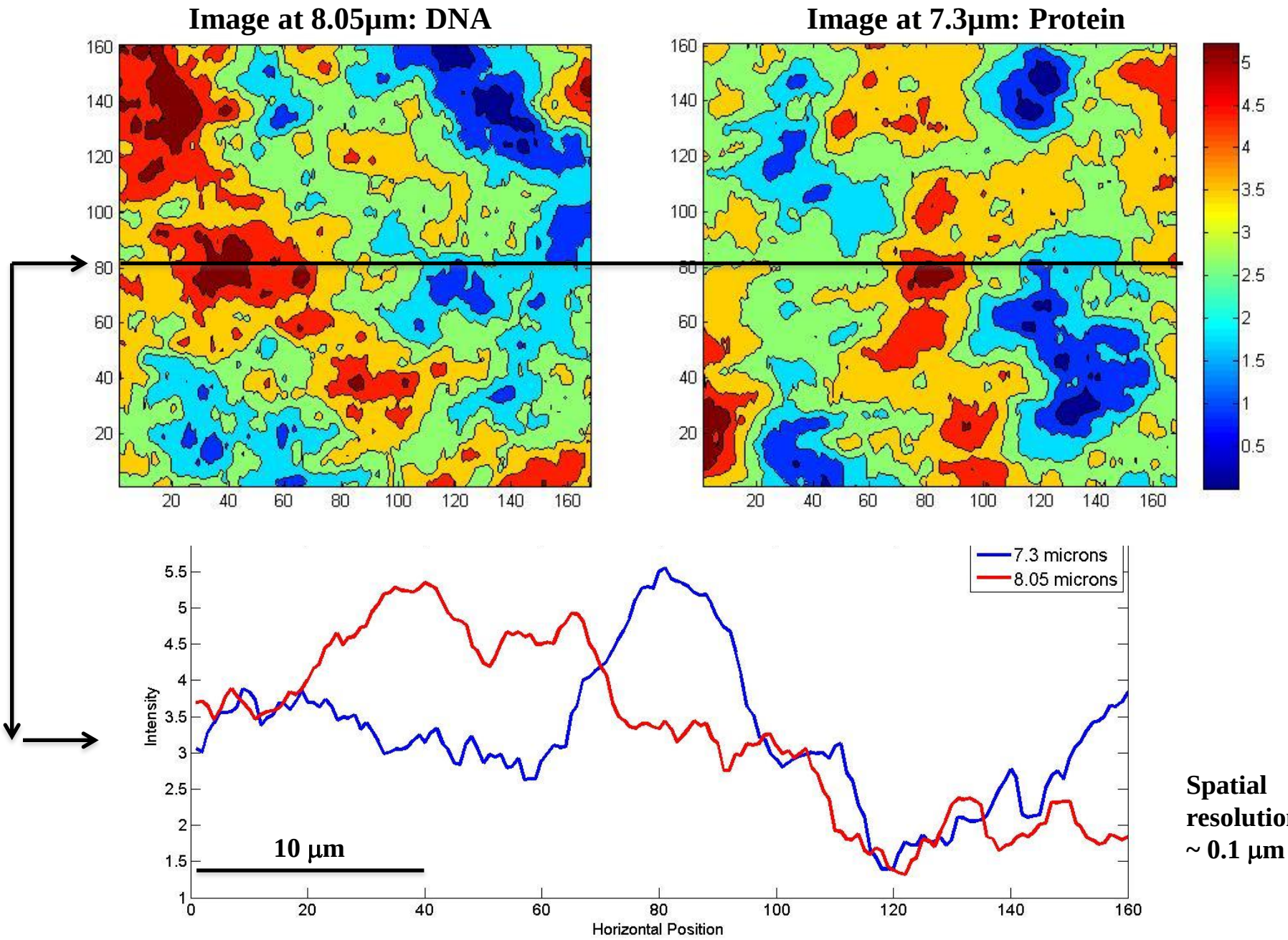
Imaging Processing: Pixel Intensity Comparisons



Preliminary analysis of the DNA: gylcoprotein ratio in cancerous (top image) and non-cancerous tissue (bottom image)

Analysis Andy Wolski

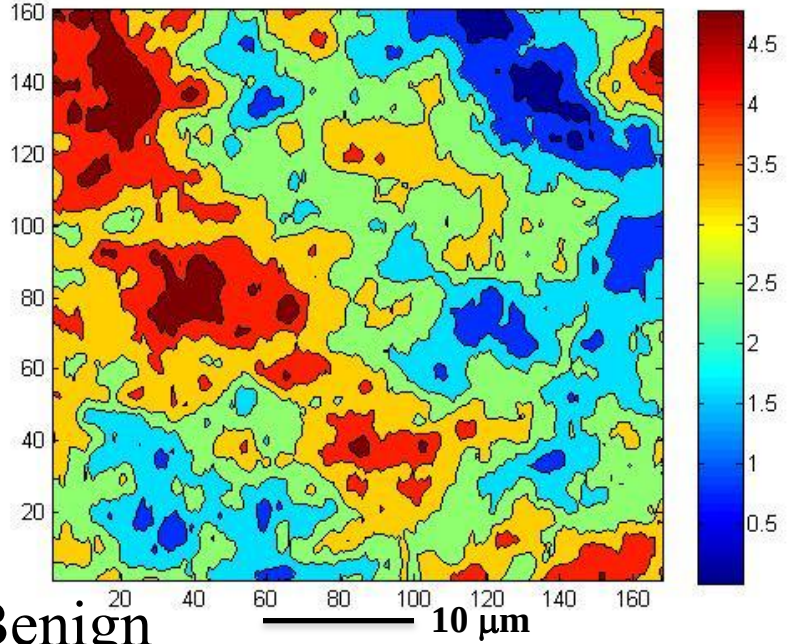
Analysis of Images obtained at 8.05 µm and 7.3 µm : Spatial correlations?

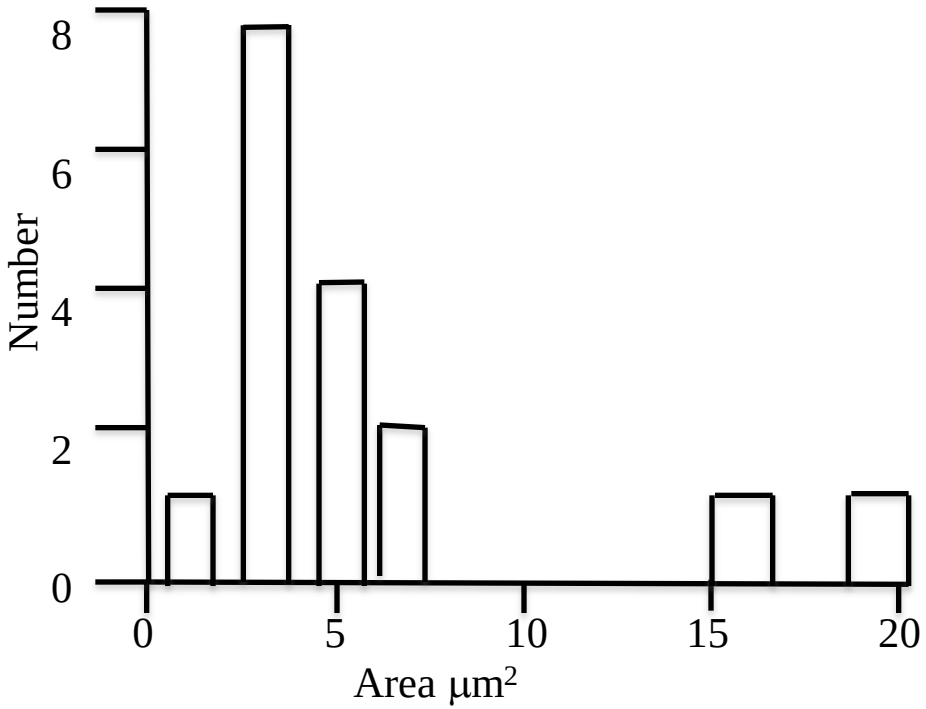


Spatial resolution ~ 0.1 µm

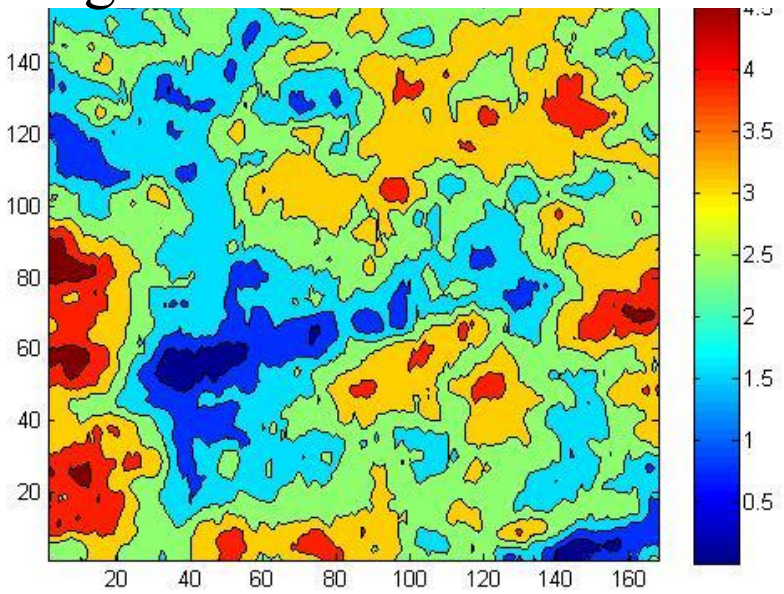
Analysis of Images obtained at 8.05 μm: Areas of most intense contours

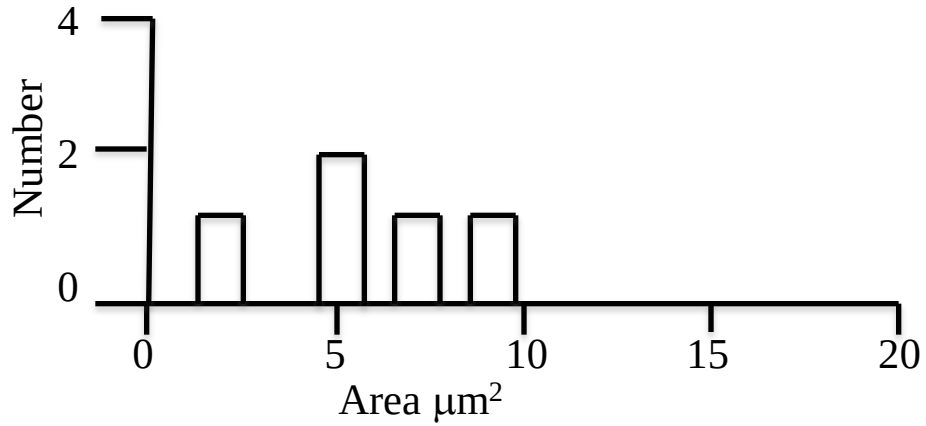
Cancer



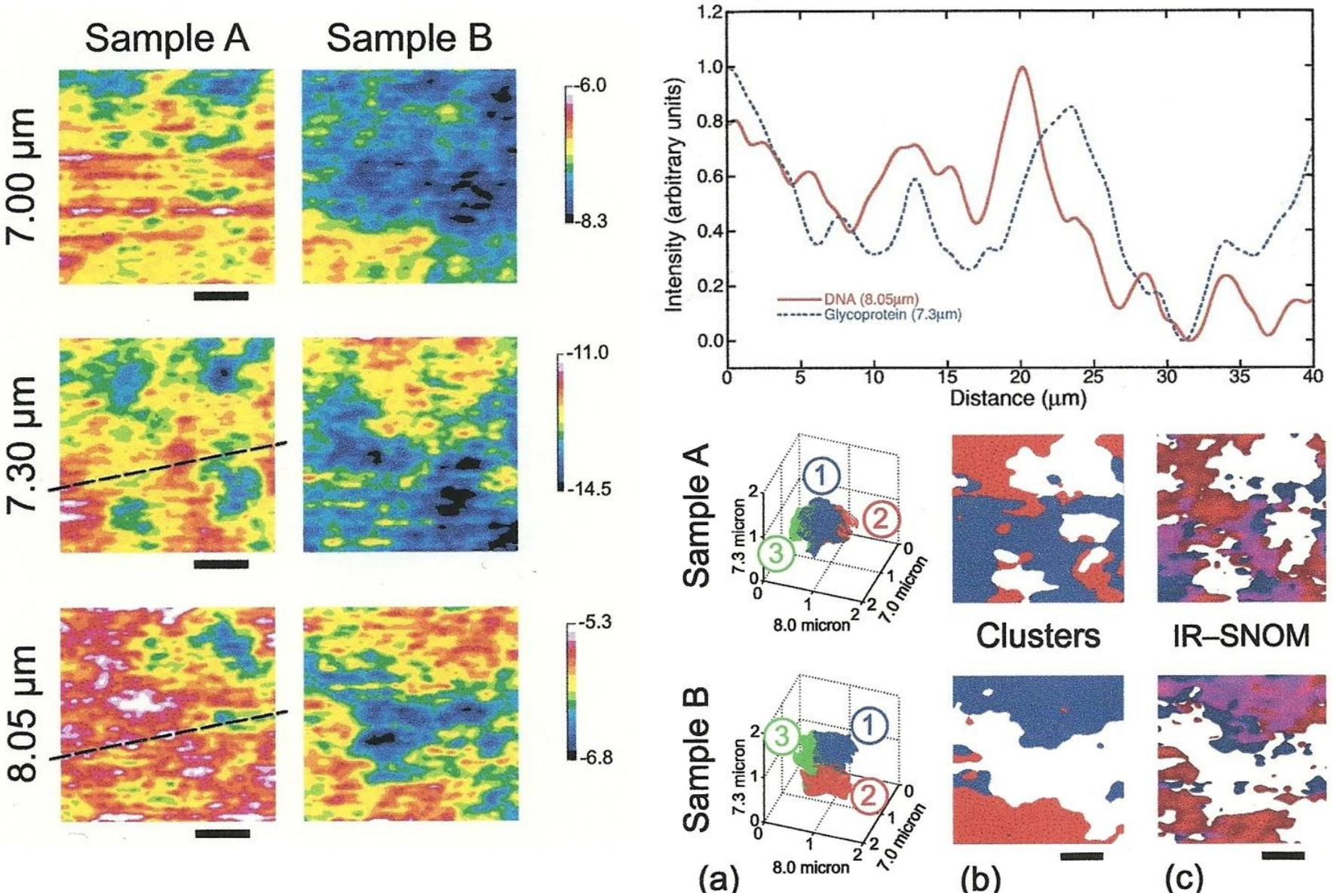


Benign





Oesophageal Adenocarcinoma: Subcellular characterisation

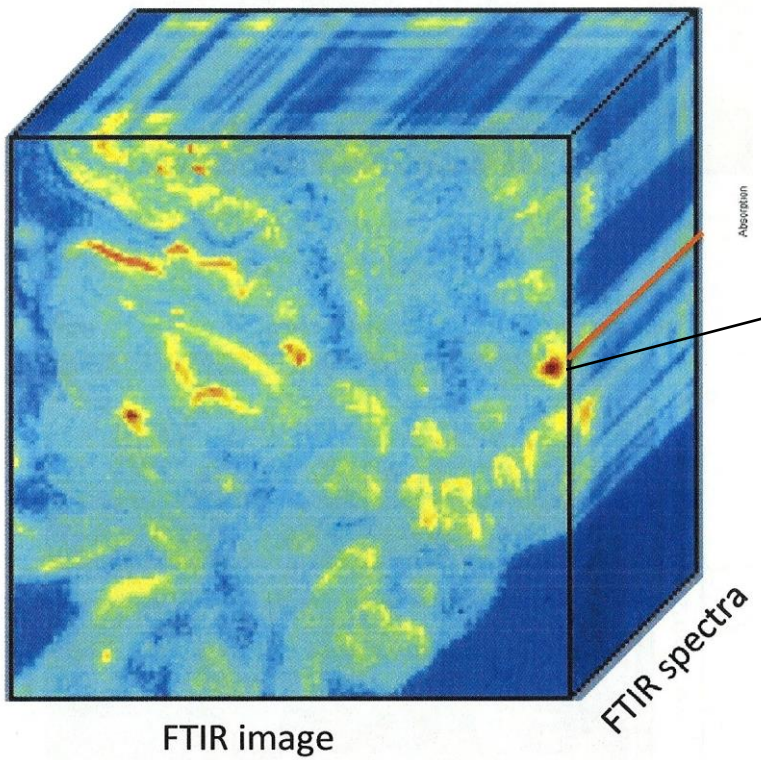


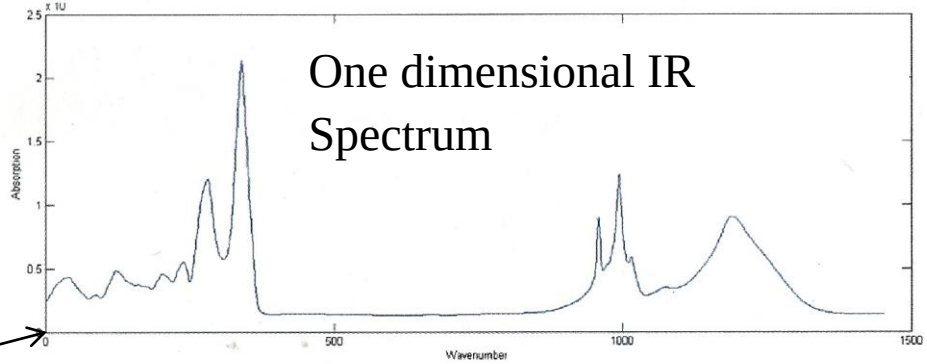
Near-field Optical Microscopy with an IR Free Electron Laser applied to Cancer Diagnosis. A.D. Smith et. al. Appl. Phys. Lett. **102** 053701 (2013)

Analysis of FTIR Imaging

of oesophageal cancer.

Oesophageal Adenocarcinoma: FTIR Spectral Imaging





Analysis

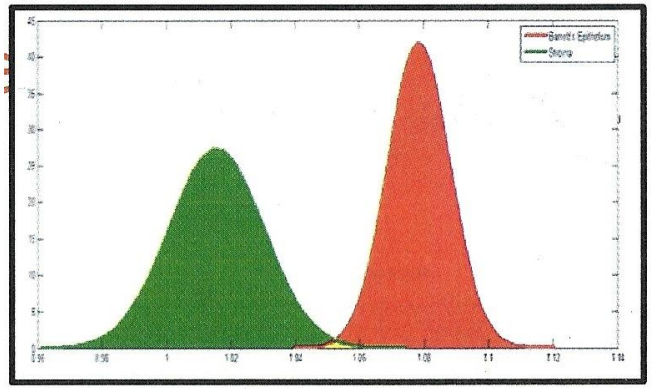
A many (n x n) pixel image at each λ

For any λ_i and λ_j create image in which value of each pixel
$I(\lambda_i,\lambda_j)$ = (pixel value in λ_i image) / (pixel value in λ_j image)

Make a histogram of this image
- Horizontal axis = pixel value = ratio
- Vertical axis = number of pixels with that pixel value

Histogram depends on tissue type and (λ_i,λ_j)

Using known tissue type and many (λ_i,λ_j)

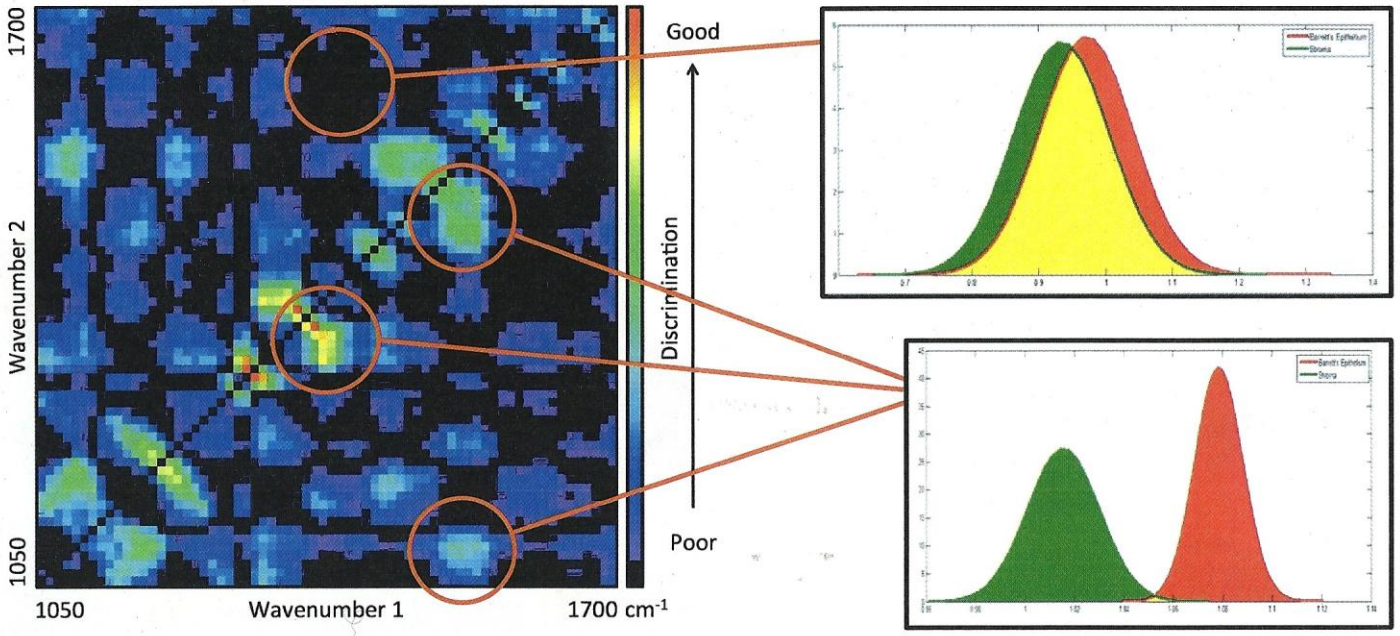


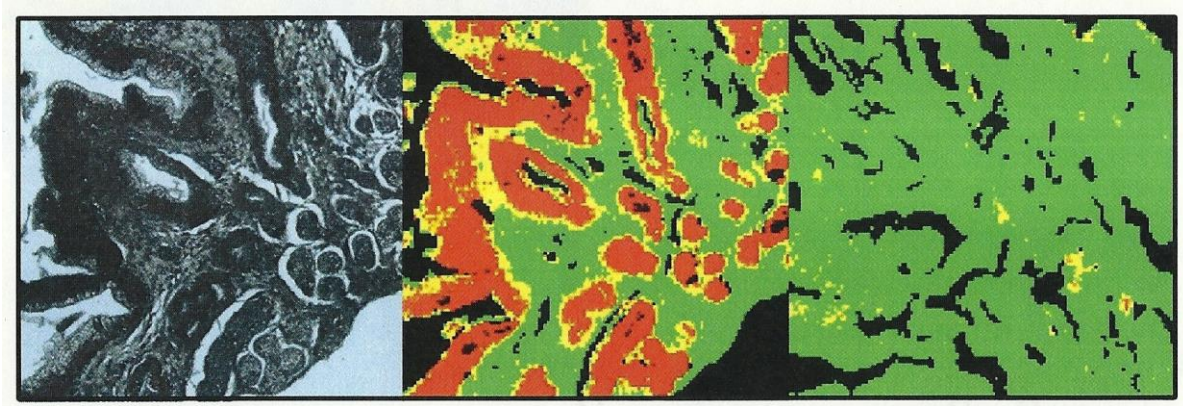
Benign Cancer

Tim Craig and James Ingham

Oesophageal Adenocarcinoma: FTIR Spectral Imaging

Guided Cluster Analysis





Tim Craig and James Ingham

Conclusions

1) Accelerator based sources of IR and THz have potential for cancer diagnosis.

Considerable more work needed on reproducibility and patient variability.

2) If successful need to develop cheap systems for use in hospitals.

£ 10m?

3) Maybe able to develop portable THz instruments for cancer diagnosis.

Endoscopes?

4) Intense THz radiation as a cancer therapy???

Very controversial but makes sense theoretically.

Needs a lot more research. ALICE accelerator: tissue facility ideal environment.

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