MId- to NEaR infrared spectroscopy for improVed medical diAgnostics

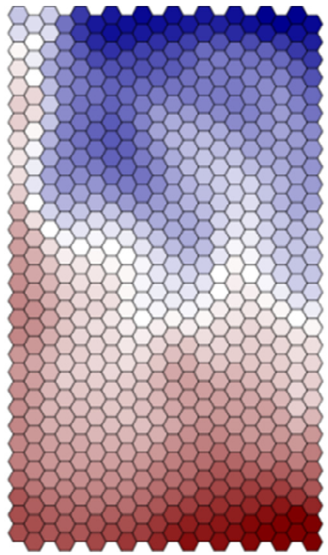
MINERVA

Project overview presentation

Motivation: to improve early cancer diagnosis

- **One in four Europeans will die from cancer**
  - Early diagnosis reduces mortality
    - Single most important factor
  - Identification whilst cancer is surgically curative

- **Early identification is very difficult**
  - Cancerous cells are very similar to healthy cells
  - Diagnosis becomes easier as the cancer develops



- **State-of-the-art diagnostic technique**
  - Microscopic examination of tissue sample
  - Notoriously difficult
    - Subjective judgement
  - High inconsistency rate
    - Even between expert pathologists.

Images courtesy of Gloucestershire Hospitals NHS Foundation Trust

Mid-IR spectroscopy: a new tool for pathologists

- **Mid-IR covers "fingerprint region" of the spectrum**
  - Spectral region studied in MINERVA: 1.5 µm to 12 µm
  - Allows identification of biomolecules
    - Fats, proteins, carbohydrates etc.
    - Type and distribution
  - Provides important new information for disease diagnosis

BUT

- **Spotting "cancer markers" is NOT sufficient**
  - Complex nature of biological samples
  - Inter-related distribution of species
  - Biochemical changes due to disease are difficult to detect
- **A more subtle technique is required**
  - Multivariate analysis.

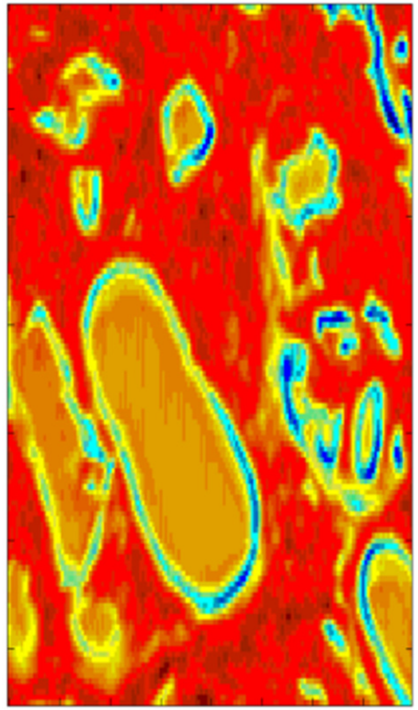
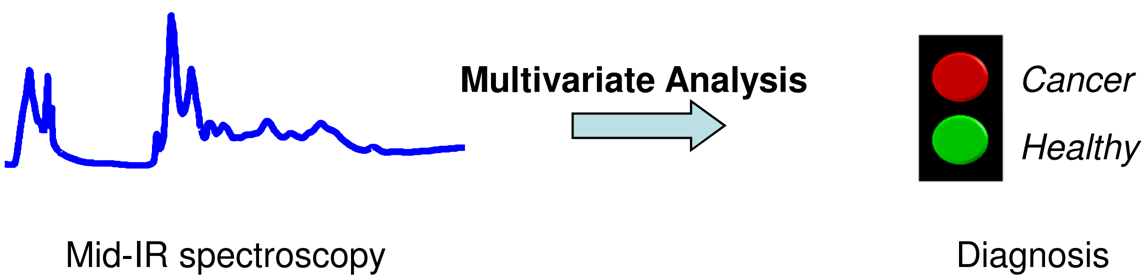


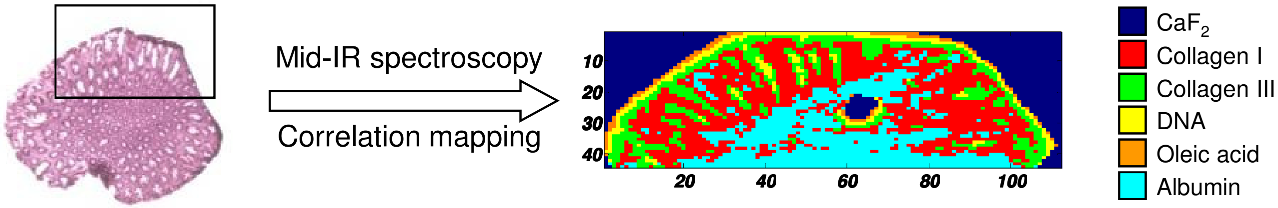
Image of prostate tissue using mid-IR. [Courtesy of University of Exeter.]



Multivariate analysis and correlation mapping

- **Multivariate analysis of mid-IR spectra**
  - Computer-based mathematical technique
  - Automated process

- **Correlation mapping**
  - A type of multivariate analysis
  - Identifies the location of different biochemicals in a sample
  - Enables visualisation of diseased regions or cells



Images courtesy of Gloucestershire Hospitals NHS Foundation Trust

- **MINERVA combines novel mid-IR spectroscopy and correlation mapping**
  - Could lead to a breakthrough diagnostic technology.

Innovation & challenges: photonic hardware

- **MINERVA is developing new photonic hardware**
  - Mid-IR glass fibres
  - Mid-IR components
    - Fused couplers
    - Acousto-optic modulators
      - Calomel crystals
  - Novel pump lasers
    - 2.9 µm and 4.5 µm
  - Ultra-long wavelength supercontinuum sources (SCSs)
    - 1.5-4.5 µm (ZBLAN)
    - 1.5-5.5 µm (InF_3)
    - 3-9 µm and 4-12 µm (chalcogenide)
  - Detectors
    - Using T2SL technology.

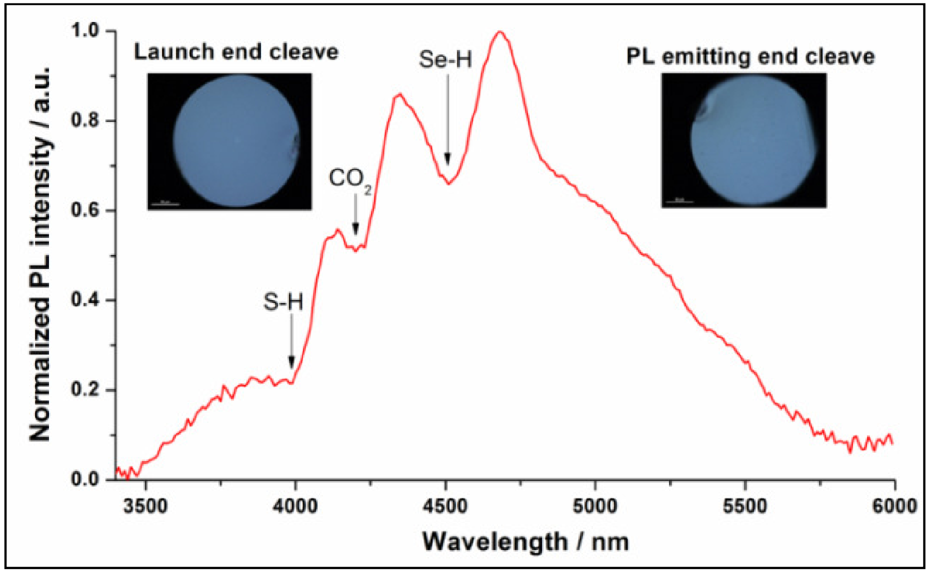
Innovation & challenges: bio-medical

- **MINERVA explores the mid-IR for medical applications**
  - Analysis of mid-IR interaction with tissue
    - Prepared samples
    - *In vitro* modelling
    - Future extension to *in vivo* testing
  - Develop multivariate diagnostic algorithms
  - Demonstrate spectral discrimination
    - Cell types
    - Pathology types
  - Data handling methodologies
    - Real-time read-out
    - User interface
  - Dissemination activities.

Mid-IR optical fibre 1: Fibres for pump lasers

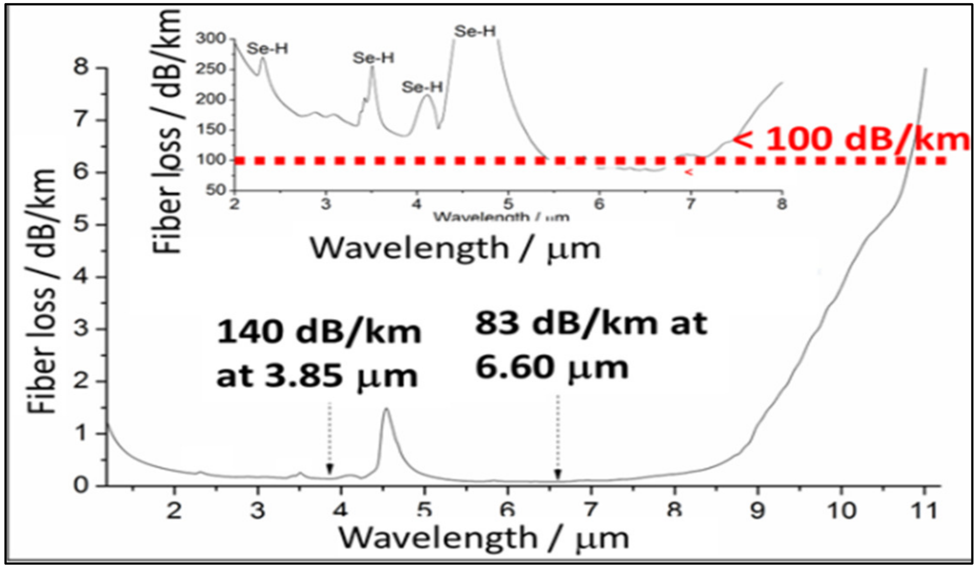
- **Chalcogenide glass low loss mid-IR optical fibre sources**
  - Ultra-high purity materials
  - Innovative processing
- Small-core Pr^{3+}-doped Ge-As-Ga-Se step-index fibre (SIF)
- Emission 3.5 - 6 µm and 7.8 ms lifetime
  - Maintained from parent bulk glass
  - Unaffected by SIF heat processing

Tang et al.
Mid-infrared photoluminescence in small-core fiber…
Optical Materials Express **5**, p. 870-886 (2015).



- Mid-IR fibres from Ge-As-Se extruded preforms
  - Record lowest loss: 83 dB km^{-1}
  - Record transmission distance: 52 m

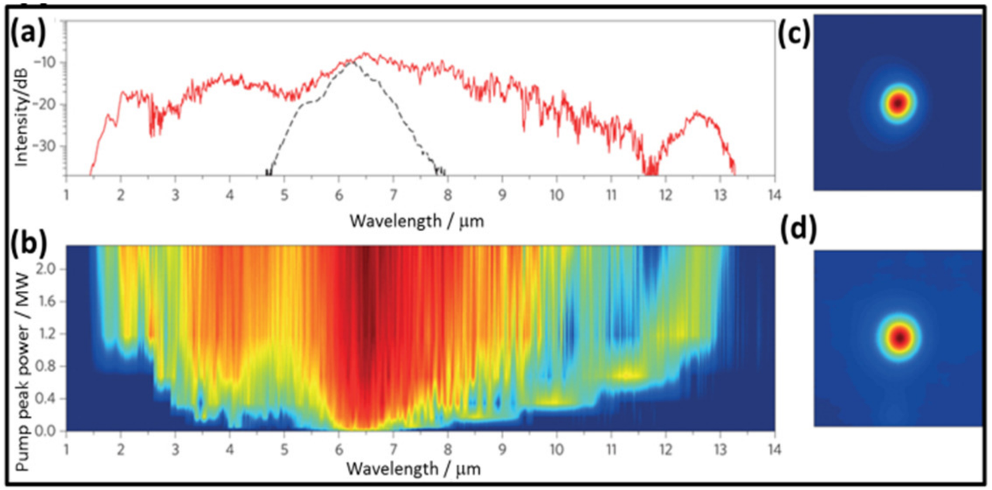
Tang et al.
Low loss Ge-As-Se chalcogenide glass fiber…
Optical Materials Express **5**, p. 1722-37 (2015).



Mid-IR optical fibre 2: fibres for supercontinuum

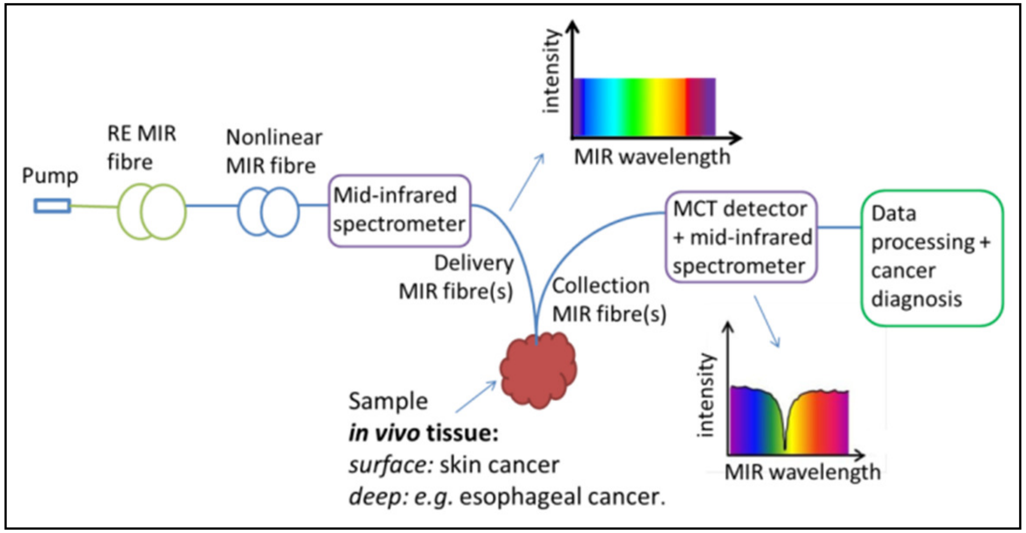
- Record numerical aperture (NA~1) fibre pumped at 6.3 µm
    - Record widest and longest wavelength supercontinuum source (SCS)
    - 1.4 to 13.3 µm

C.R. Petersen et al.
Mid-infrared supercontinuum covering the 1.4–13.3 µm…
Nature Photonics **8**, p. 830-834 (2014).



- Mid-IR spectral imaging of biological tissue ***in vivo***
    - *i.e.* **the mid-IR optical biopsy**
- Characteristic spectral sets acquired
    - Mid-IR SCS / tissue interaction
    - Molecular discrimination and early cancer diagnosis.

A.B. Seddon et al.
Mid-infrared Spectroscopy/Bioimaging: Moving toward MIR optical biopsy
Bio-Optics World Feb-2016

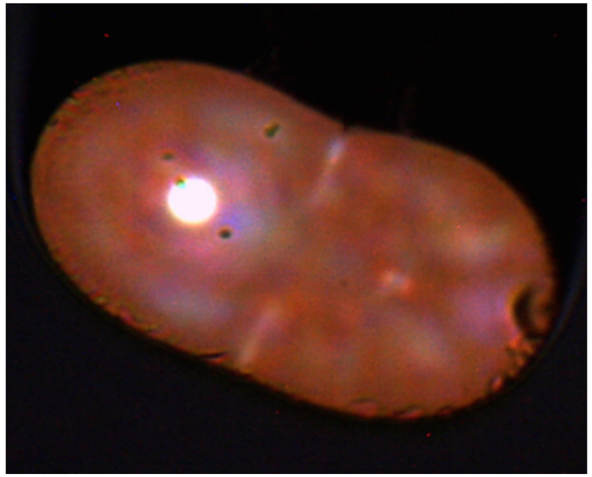


Passive components 1

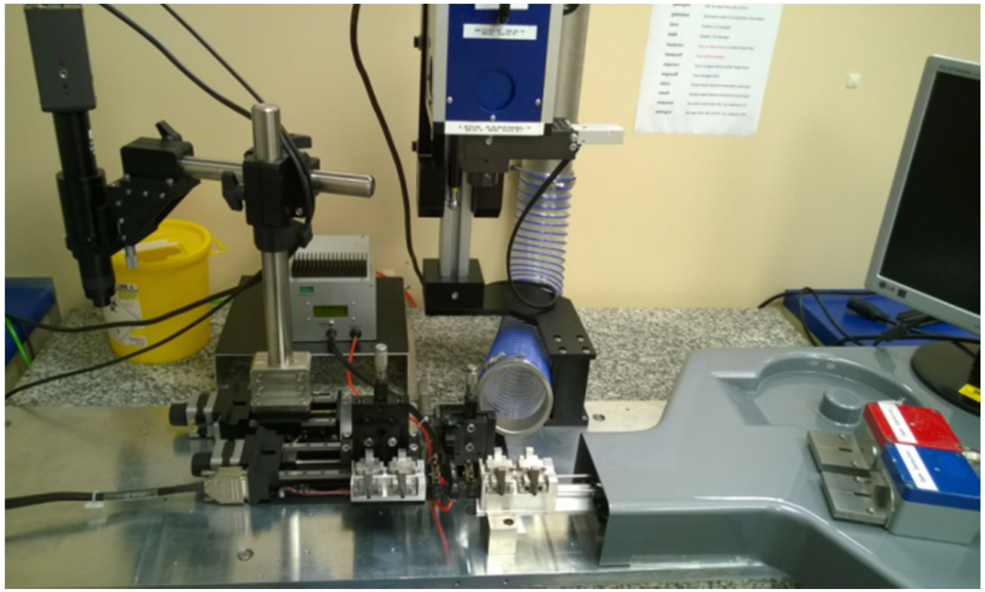
Gooch & Housego

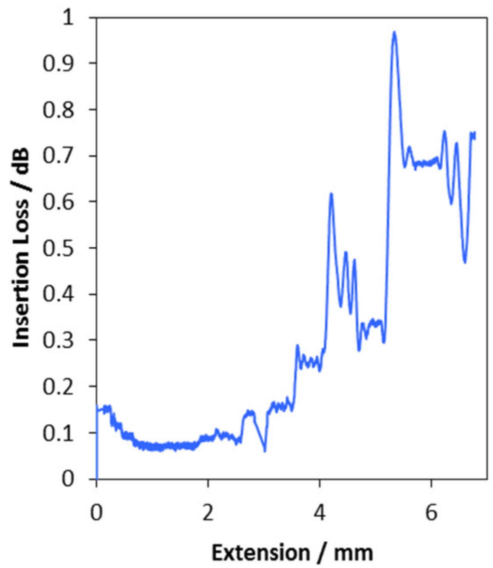
New fusion workstation for mid-IR fibres

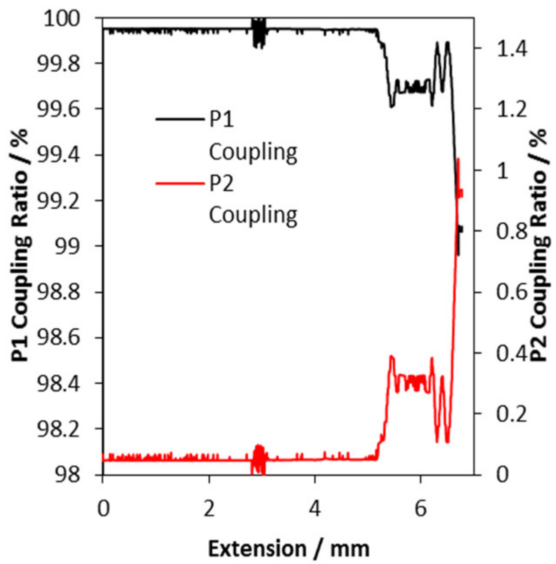
- Novel heating method for soft glass fibres
- Custom system built at G&H (Torquay)
- First ever single-mode ZBLAN/chalcogenide fused fibre couplers demonstrated



Gary Stevens et al.,
Mid-IR fused fiber couplers
Phot. West 2016: Proc. SPIE **9730**, 973007 (2016)







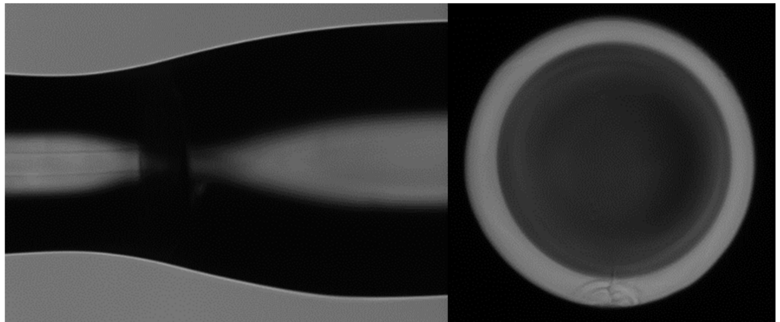
Passive components 2

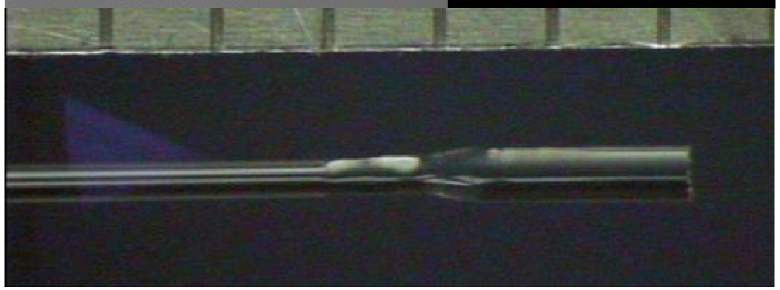
Developing fibre end protection methods

- Fibre end caps fabricated
  - ZBLAN & chalcogenide

Splicing technique development

- ZBLAN-to-ZBLAN
- ZBLAN-to-silica
- Silica-to-chalcogenide
- Chalcogenide-to-chalcogenide





Tapering techniques optimised

- Part of fused device fabrication
- SCG components

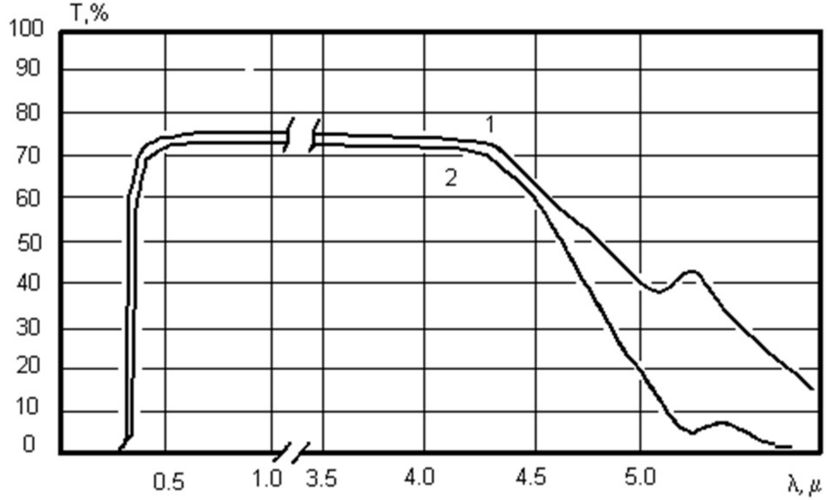
Packaging mid-IR fibres

- Stable mounting of soft glass structures

Acousto-Optic Devices (2-4 µm) 1: AO Q-Switch (AOQS)

Gooch & Housego

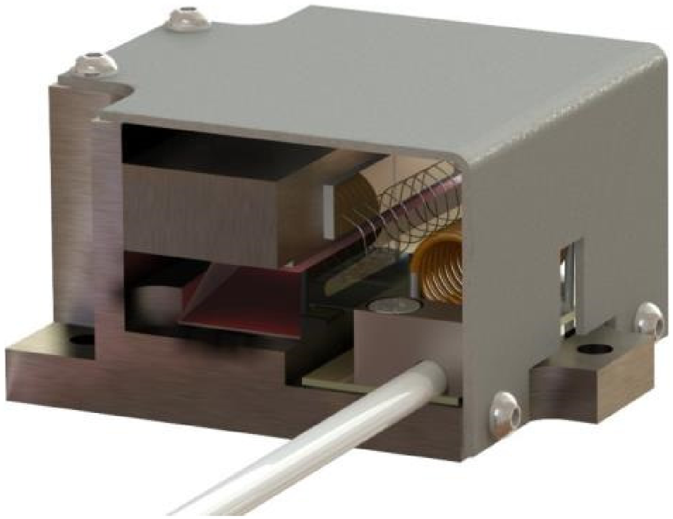
- The AOQS located inside the laser cavity “holds off” the onset of lasing
  - Energy is concentrated into a short pulse of very high intensity



TeO2 transmission, 20 mm thick sample
1 - O-polarization, 2 - E-polarization

- MINERVA purpose-built AOQS designed to operate at λ ~ 2·8 µm

- Host material and AR coatings need to withstand exceptionally high optical power density
  - Material of choice — Tellurium dioxide (TeO_2)
  - Damage threshold — >50 MW/cm^2
  - Optical polarisation — Random
  - Loss modulation — 80%

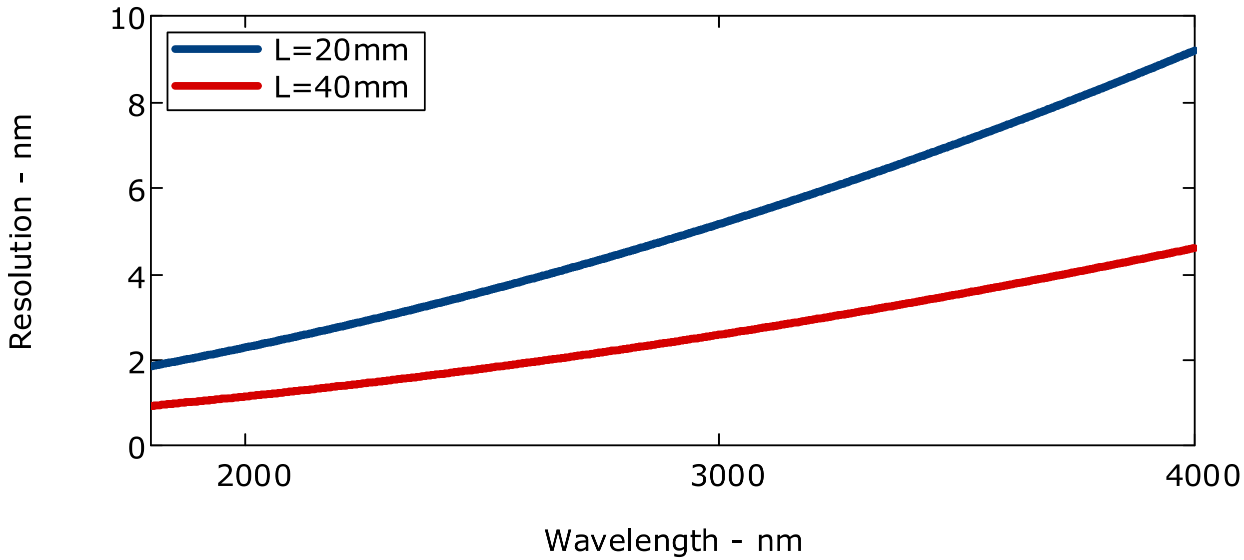


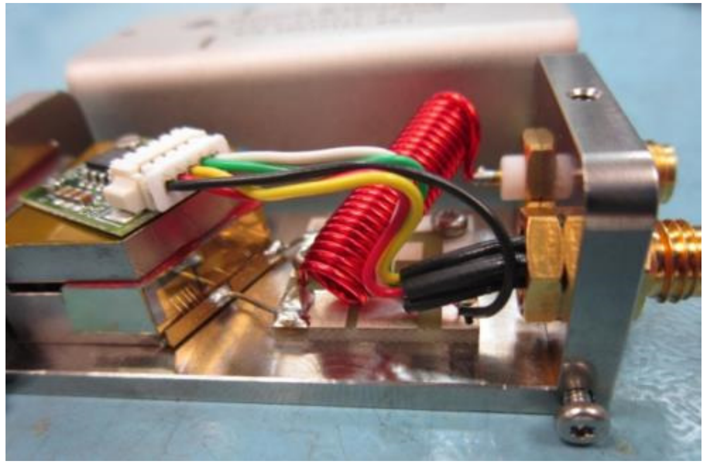
- Used to achieve ground-breaking performance for a 2·79 µm Q-switched Er:ZBLAN fibre laser

Acousto-Optic Devices (2-4 µm) 2: AO Tunable Filter (AOTF)

Gooch & Housego

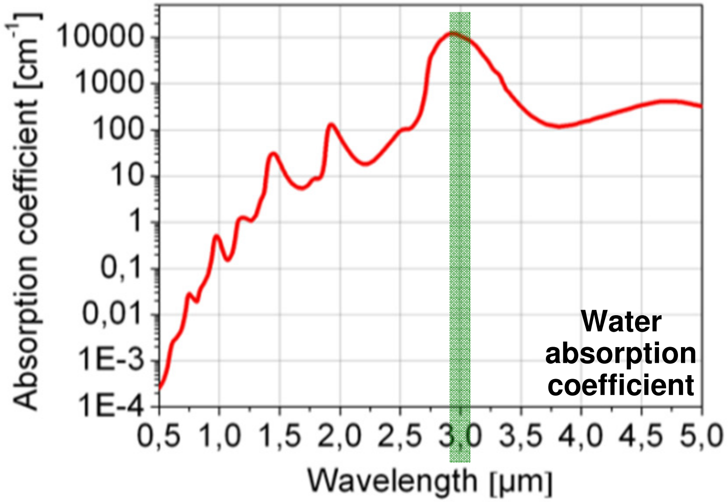
- An AOTF is a electronically controlled solid-state optical passband filter
- Two MINERVA designs of AOTF have been developed
- Objective: Filter & control a mid-IR (2-4 µm) SCS
  - Quasi-collinear slow shear AO interaction for low drive power in the mid-IR
  - 20 mm or 40 mm interaction length
    - 20 mm; $\delta\lambda$ ~ 5 nm @ 3 µm, <1 W RF power
    - 40 mm; $\delta\lambda$ ~ 2·5 nm @ 3 µm, <1 W RF power

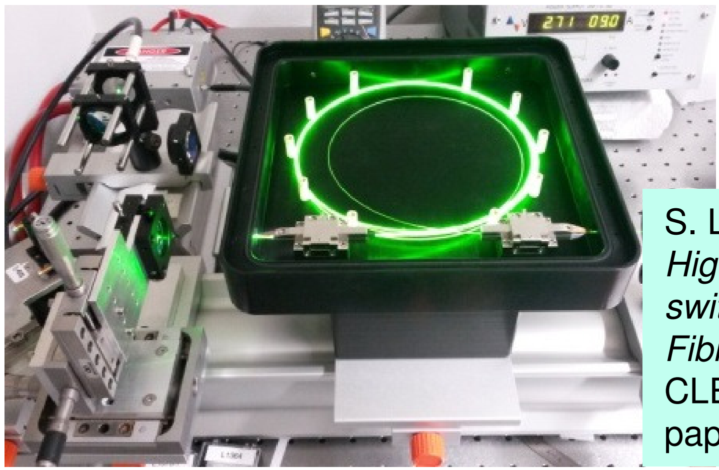




Pump lasers

- **2.9 µm Q-switched fibre laser**
  - MINERVA target: high power, high energy
  - Er:ZBLAN fibre laser
- Applications
  - "Stepping stone" pump source for SCG
  - High absorption by water makes it an excellent laser for surgical cutting
- World beating performance achieved!
  - Pulse energy: 560 µJ
  - Pulse duration: 53 ns@1 kHz
  - Peak power: 10.6 kW





S. Lamrini et al.
High-Energy Q-switched Er:ZBLAN Fibre Laser at 2.79 µm
CLEO Europe 2015 paper CJ-7.2

- **4.5 µm mode-locked fibre laser**
  - MINERVA target: world first demonstration!
  - Pr-doped chalcogenide ultrafast fibre laser
    - Ultra-pure MINERVA fibre from NOTT
    - 2 µm Tm-doped fibre pump laser
  - Applications
    - Pump source for long-λ (4-12 µm) SCG
    - Biomedical spectroscopy
    - Precision surgery
  - Work continues!!!

Fluoride glass SCSs (1.5 to 5.5 µm)

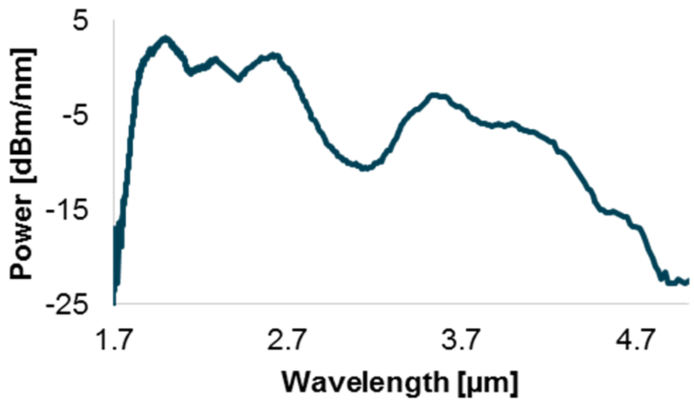
- **Extended the spectrum**
- Longest wavelength from a fibre-pumped ZBLAN-based SCS: 4.75 µm

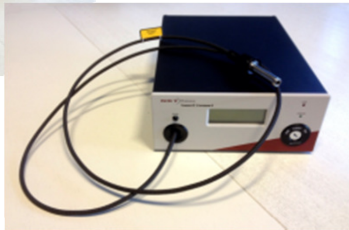
Peter Moselund et al., *Highly Stable, All-fiber, High Power ZBLAN Supercontinuum Source Reaching 4.75 µm...*
Advanced Solid State Lasers 2013 Postdeadline Papers (JTh5A)

- Highest power in the 3.5-4.7 µm atmospheric transmission band: 1.34 W

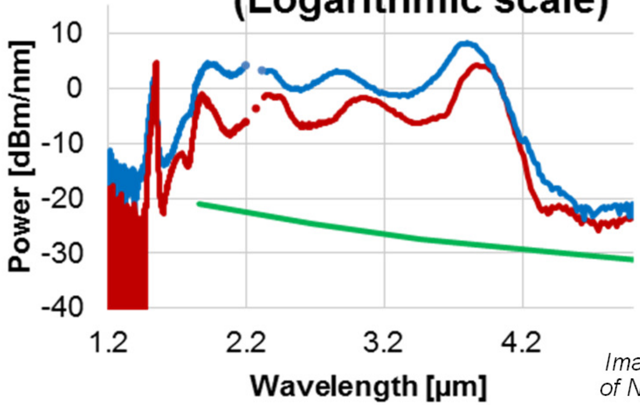
Peter M. Moselund et al., *All-fiber mid-IR supercontinuum: a powerful new tool for IR-spectroscopy*
Phot. West 2016: Proc. SPIE **9703**, 97030B (2016)

- **Improved reliability**
- MINERVA has taken mid-IR SCS from lab curiosity to product maturity
- >2000 h service free operation on multiple systems demonstrated
- NKT products coming soon!
- **Beat the synchrotrons!**
- MINERVA lab system is two orders of magnitude brighter than the IR beamline of a synchrotron! *(Publication in progress)*





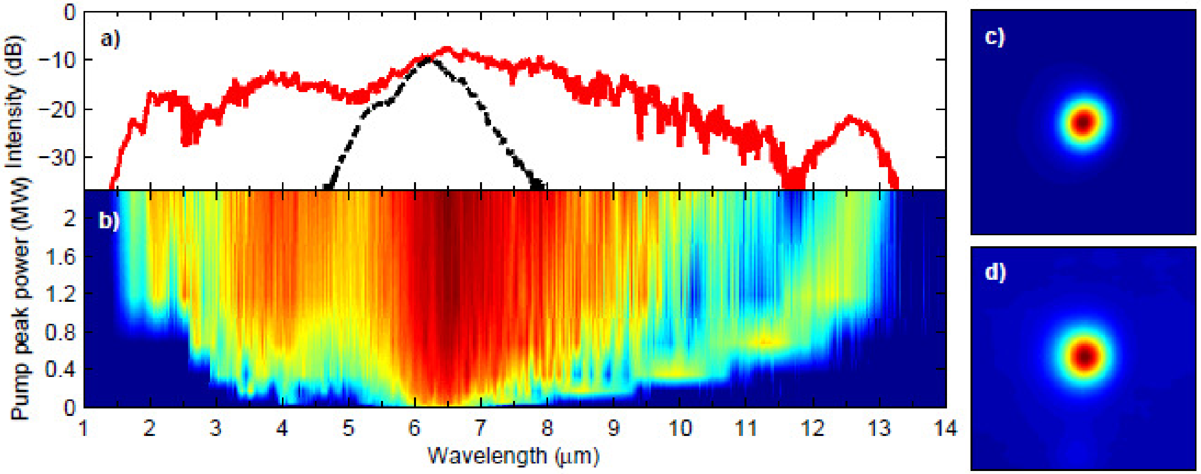
Comparison to Synchrotron (Logarithmic scale)



Images courtesy of NKT Photonics

Ultra-long wavelength SCSs 1

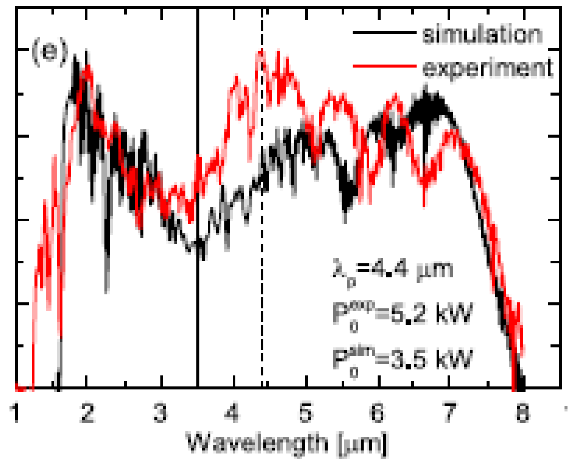
- **MINERVA has delivered world-beating mid-IR supercontinuum sources**
  - Initial modelling predicted SCG to very long wavelengths
    - State-of-the-art two-polarisation multimode modelling at DTU
    - These simulations have now been demonstated experimentally!
  - World record mid-IR bandwidth: from 1.4-13.3 µm



C.R. Petersen *et al.*
Mid-infrared supercontinuum covering the 1.4–13.3 µm molecular fingerprint region using ultra-high NA chalcogenide step-index fibre
Nature Photonics **8**, 830 (2014)

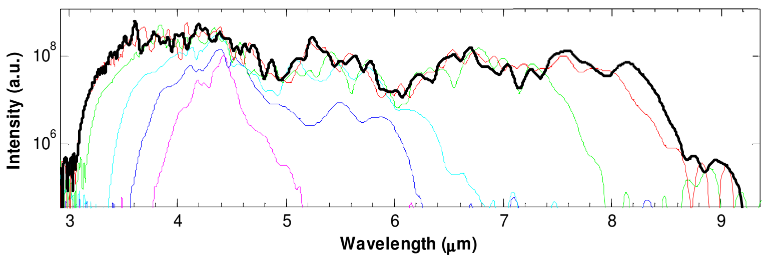
- World-record average power above 4.5 µm: 15.6 mW
  - Pump source: 4.4 µm 400 fs MHz OPA

U. Møller *et al.*
Multi-milliwatt mid-infrared supercontinuum generation in a suspended core chalcogenide fiber
Optics Express **23**, 3282 (2015)



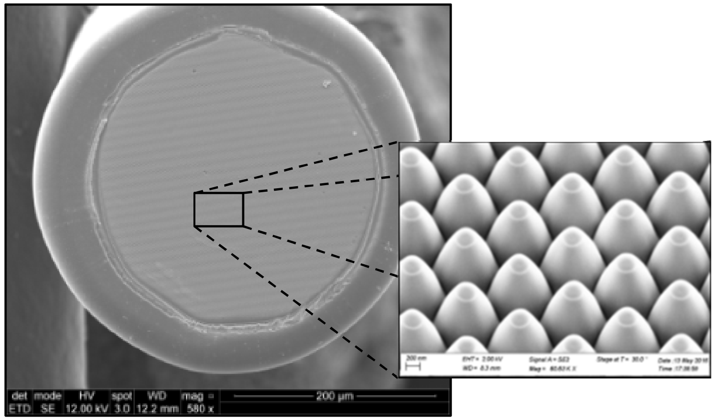
Ultra-long wavelength SCSs 2

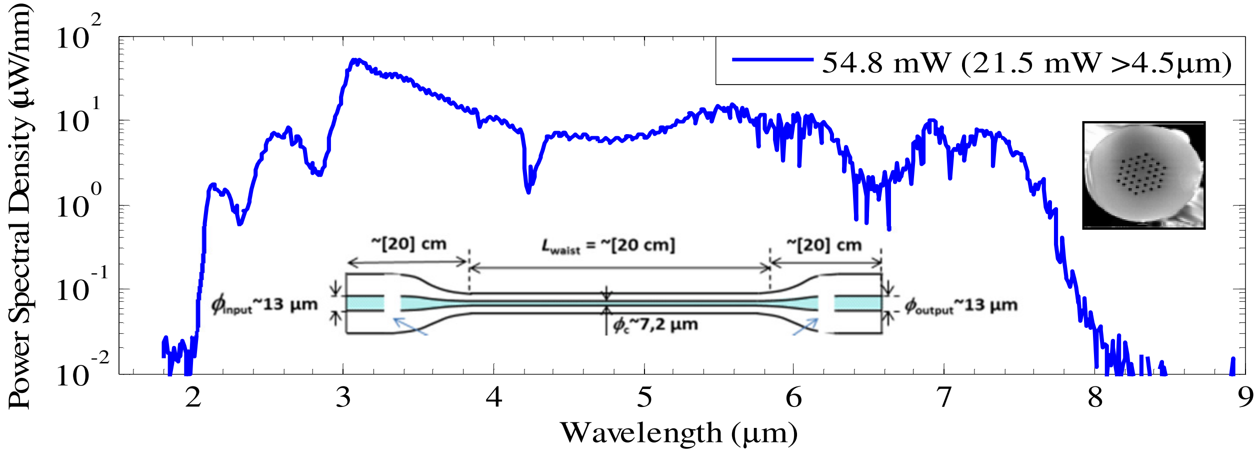
- **Focus on commercially relevant MHz mid-IR supercontinuum sources**
  - Portable with high average power out to *c.* 9-10 µm
  - 4.4 µm OPA or 4.4 µm cascaded supercontinuum pump
  - Nano-imprinted fibre
  - Fibre end-caps



- **MINERVA chalcogenide step index NOTT fibres**
  - Good power handling and broadband low loss

- **Custom-made MINERVA designed chalcogenide PCFs**
  - Taper from large core (good power handling) to small core (correct zero-dispersion)
  - Achieved SCG to 8.5 µm

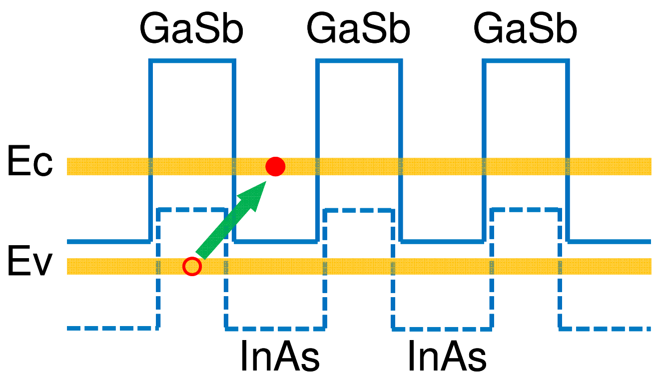




Detectors: Type-II super-lattice detectors (T2SL)

- **T2SL detector technology**
  - High quality, high performance, cooled photon detector
  - Thin layers of InAs and GaSb
    - Broken band type-II alignment
  - Broadband
    - Cut off wavelengths from 2 to 30 µm

Image using a 320×256 MWIR T2SL detector taken at 110 K [Courtesy of IRnova.]



Band alignment of InAs / GaSb and the forming of minibands.

- **A III/V-material**
  - Good manufacturability at low cost
  - Higher operating temperature than InSb
  - Lower cost than MCT.

Detectors: MINERVA developments

Image of the MINERVA IDCA [Courtesy of IRnova]

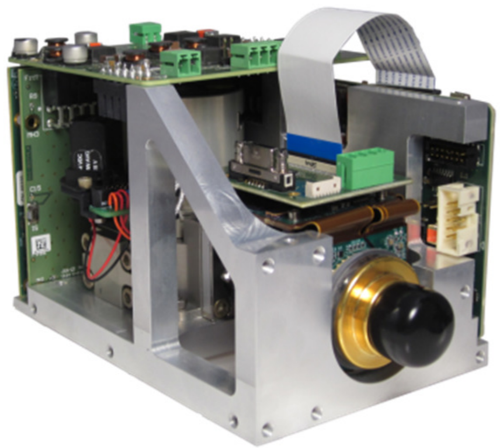


Image of the XCO camera platform which will integrate the MINERVA IDCA [Courtesy of Xenics]

- **MINERVA is pushing T2SL technology to its limits!**
- Development of detector in the mid-IR wavelength band
  - 2-5.5 µm detector
  - NETD*<20 mK @120 K and f/4
- IRnova Integrated Detector/Cooler Assembly (IDCA)
  - 1.3 Mpixel detector array on 12 µm pitch
  - Hybridised with Xenics designed read-out circuits
  - Integrated in a state-of-the-art module with Stirling cooler.
- New Xenics camera employing cooled T2SL technology based on IRnova's IDCA

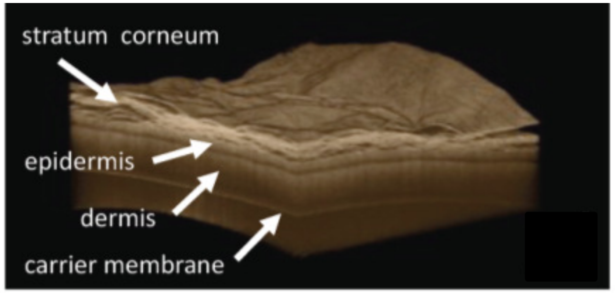
*Noise Equivalent Temperature Difference

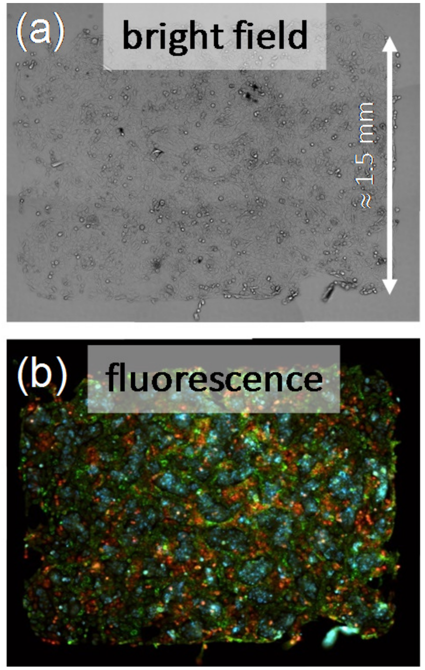
Demo: skin cancer identification

- **Mid-IR spectroscopy for fast screening of human body surfaces**
  - Rigid probe for human skin surface examination
  - Identification of altered cells and tissue lesions

- **MINERVA uses human skin equivalent models (HSE)**
  - 3D test standards grown in petri dishes
  - Generation of reference spectra of HSEs

- **Establishment and evaluation of test systems for skin cancer cell identification**
  - Acquisition of cell type specific mid-IR spectra
  - Analysis of mid-IR spectral changes induced by sample preparation
  - Correlation of mid-IR spectra with fluorescence labelled single cell standards

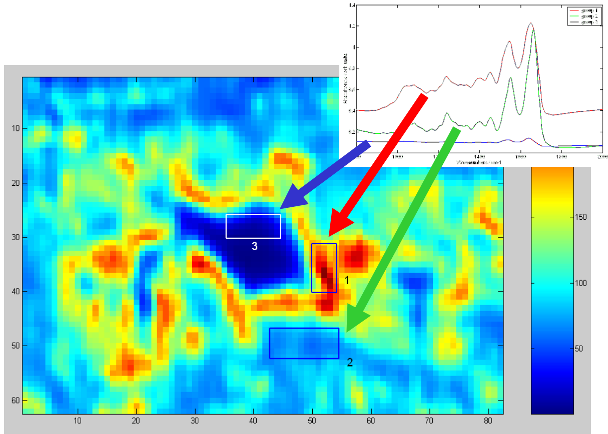


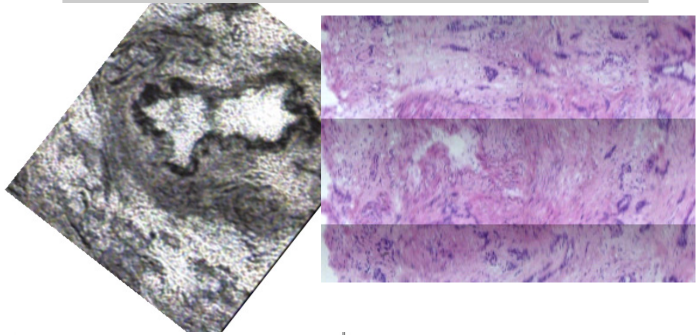


Upper image: Optical coherence tomography image of a MINERVA 3D human skin equivalent
Lower image: bright field (a) and fluorescence (b) microscopy images of a fluorescence labelled single cell standard (mixed cell culture including fibroblasts, keratinocytes and skin cancer cells) for verification of skin cancer cell identification. Different fluorescence colours indicate different cell types.[Courtesy of NKT and WWU]

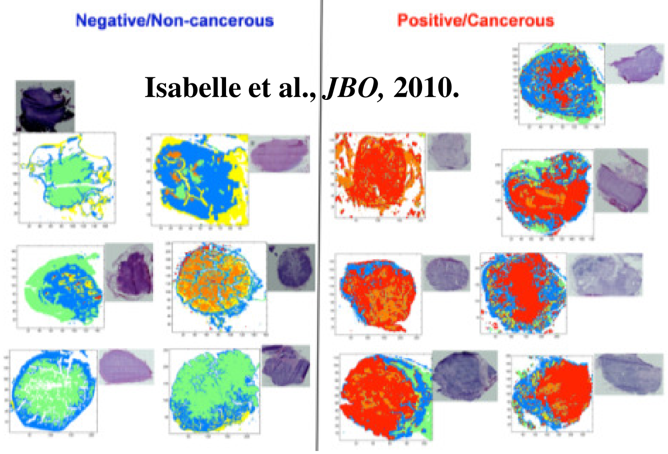
Demo: high volume screening

- **MINERVA will develop mid-IR micro-spectroscopy for rapid screening**
  - High intensity mid-IR microscope for rapid analysis of disease-specific chemical signatures
  - Discrimination of
    - Abnormal cells from cytological specimens
    - Abnormal cells and tissues from unstained tissue sections



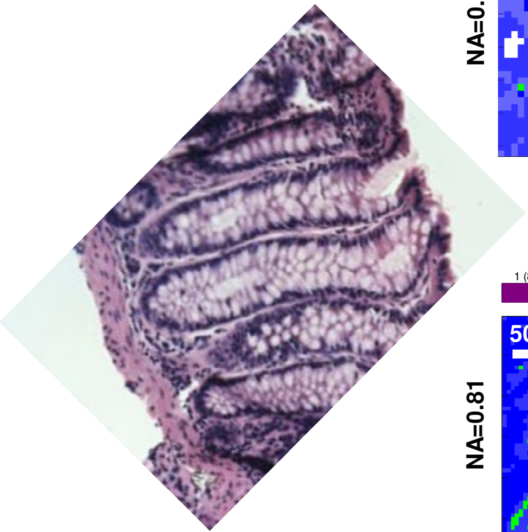


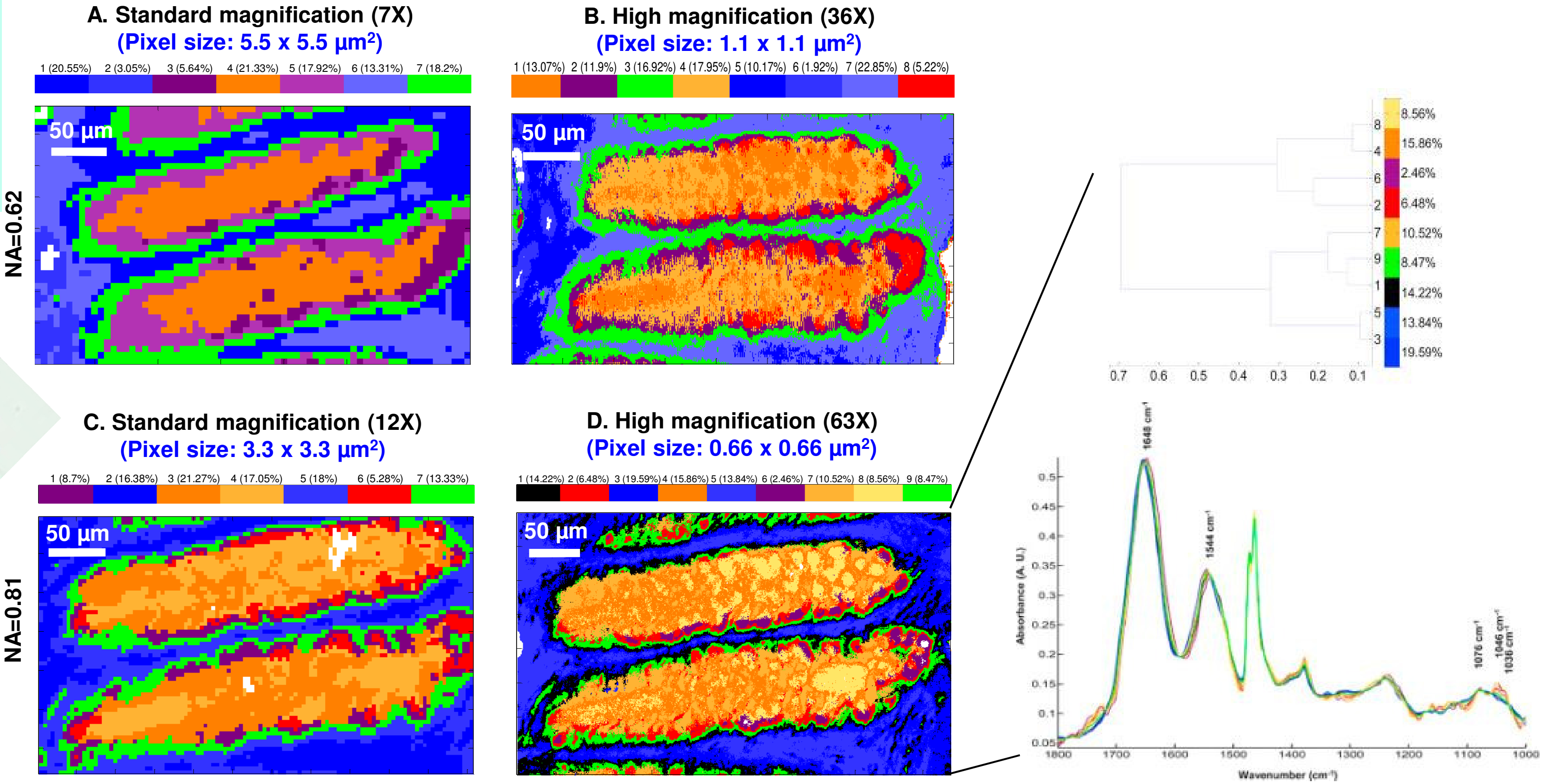
- **Evaluation of system for *ex vivo* human samples**
  - MINERVA will use human cells and tissues collected during routine clinical testing
  - Acquisition of mid-IR spectra from cells and tissues using globar mid-IR sources (hot SiC rod)
    - Comparison of performance with MINERVA supercontinuum sources
  - Analysis of spectral changes and correlation with gold standard histopathology / cytology.



Demo: High resolution benchtop imaging

J. Nallala, et al.,
Enhanced spectral histology in the colon using high-magnification benchtop FTIR imaging
Vib. Spec. (in press Nov-2016)



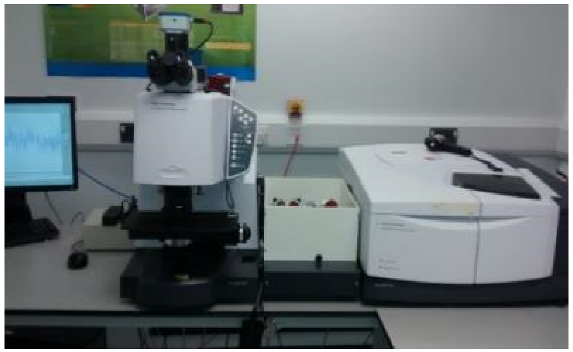


- Comparison of FTIR benchtop imaging using different NA objective lenses
  - Cluster analysis of normal colon tissue w.r.t. HE stained tissue
  - Right: cluster centroid spectra and dendrogram corresponding to Fig. D
  - Shows typical glycoprotein features corresponding to mucin
- NB Images obtained using Globar®-FTIR benchtop imaging
  - Work underway to compare with SCS-based discrete frequency imaging

Demo: High resolution imaging

- First application of mid-IR SCS-based rapid IR imaging on tissue samples of clinical origin
- Individual frequencies to be tested and compared with conventional sources
- Testing will include samples from outside the consortium
  - Do you have an interesting sample for mid-IR spectroscopic testing?!

Tunable Mid-IR supercontinuum source



Discrete Frequency Imaging

Optimal regions for model performance Variable Importance for Projection (VIP)

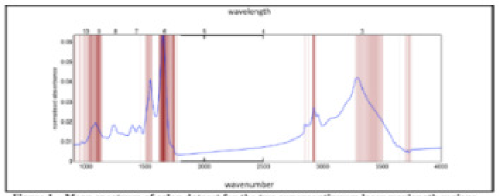


Figure 1 – Mean spectrum of colon dataset for the two supercontinuum laser wavelength regions combined. Shaded regions indicate those identified by VIP as significant.

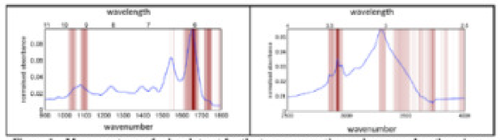
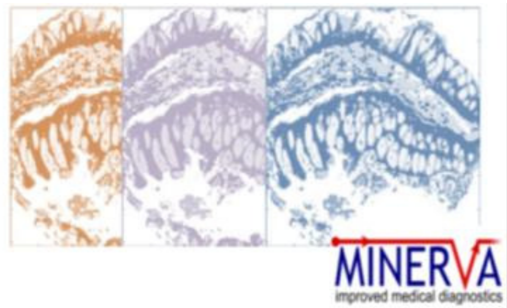


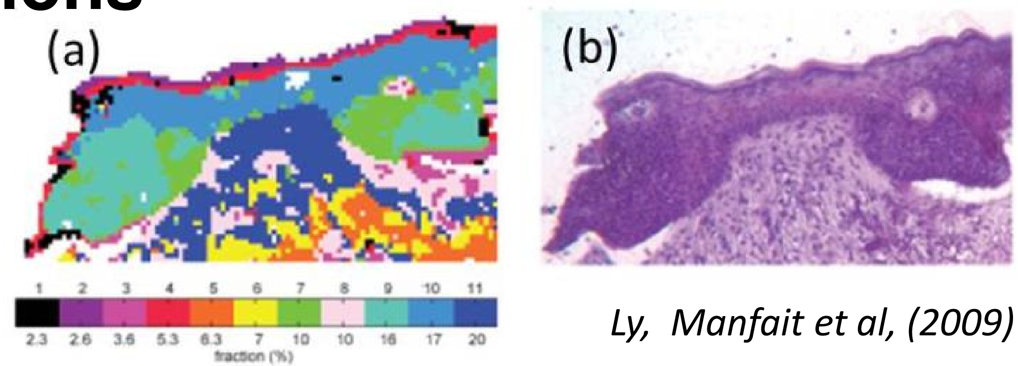
Figure 1 – Mean spectrum of colon dataset for the two supercontinuum laser wavelength regions. Shaded regions indicate those identified by VIP as significant.



Gavin Rhys Lloyd & Nicholas Stone
Method for Identification of Spectral Targets in Discrete Frequency Infrared Spectroscopy for Clinical Diagnostics
Appl Spectrosc. **69**, p. 1066 (2015)

MINERVA impact

- **MINERVA target applications**
  - Skin cancer detection
    - Rigid skin probe for use in hospitals and surgeries
    - MINERVA will only use skin models
  - Screening pathology
    - High throughput microscope-based screening
    - Hospital pathology labs
    - Cytological and histological
  - Impact: Fewer biopsies and improved survival rates
- **Potential spin-off applications**
  - Spectroscopy
  - LIDAR
  - Laser surgery
  - Sensing.



Ly, Manfait et al, (2009)

MINERVA Advisory Group

- MINERVA has established a group of interested parties to:
  - Guide MINERVA research
  - Develop new exploitation routes for mid-IR technology
  - Use and provide samples for the MINERVA imaging systems
  - Identify novel applications

- New members welcome!

- Target organisations:
  - End users (hospitals, medical practitioners)
  - Research organisations (bio-medical and photonic)
  - Universities
  - Industrial companies.

Project information

- **MINERVA is funded under the European Commission's Seventh Framework Programme**
  - Programme acronym FP7-ICT
  - http://cordis.europa.eu/fp7/ict/home_en.html

- Funding scheme : Large-scale integrating project - CP-IP
- Activity : ICT-8-3.5 - Core and disruptive photonic technologies
  - Project Reference 317803

- Project cost 10.6 M€
- Project funding 7.3 M€

- Start date 01-Nov-2012
- End date 31Jul-2017
- Duration 57 months.

Consortium

1	Gooch & Housego (UK) Ltd.	UK (Coordinator)
2	NKT Photonics A/S	DK
3	LISA Laser Products OHG	D
4	BBT-Materials Processing SRO	CZ
5	Xenics NV	B
6	IR Nova AB	S
7	University of Nottingham	UK
8	Technical University of Denmark	DK
9	Vivid Components Ltd.	D
10	Westfaelische Wilhelms-Universitaet Muenster	D
11	The University of Exeter	UK
12	Gloucestershire Hospitals NHS Foundation Trust	UK
13	Universidad Politecnica de Valencia	E

Contact

Thanks for your attention!

www.minerva-project.eu Project website

For further information, please contact:

jward@goochandhousego.com Technical

bruce@vividcomponents.co.uk Admin & Advisory Group