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.
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

- **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…*  

- **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…*  
**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...*  

- 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

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
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)

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

• MINERVA purpose-built AOQS designed to operate at $\lambda \sim 2.8$ 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)

- 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; δλ ~ 5 nm @ 3 µm, <1 W RF power
    - 40 mm; δλ ~ 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

- 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!!!

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

www.minerva-project.eu
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*

- **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)*
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 demonstrated experimentally!
  - World record mid-IR bandwidth: from 1.4-13.3 µm

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

**References**

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)

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

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

- 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

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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?!

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.

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

• 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

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Thanks for your attention!

www.minerva-project.eu  Project website

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