PROJECT FINAL REPORT

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Abbreviations

Some of the key abbreviations used in this report include:

AOTF	Acousto-Optic Tuneable Filter
CW	Continuous Wave
FTIR	Fourier Transform Infrared spectroscopy
IDCA	Integrated Dewar Cooler Assembly
LWIR	Electromagnetic radiation with wavelength 7.5-12 µm
MM	Multimode
MWIR	Electromagnetic radiation with wavelength 3-5.5 µm
NA	Numerical aperture
OPA	Optical Parametric Amplifier
PCF	Photonic Crystal Fibre
QE	Quantum Efficiency
RE	Rare Earth
ROIC	Read-Out Integrated Circuit
SC	Supercontinuum
SCS	Supercontinuum Source
SCG	Supercontinuum Generation
SIF	Step Index Fibre
SM	Single-mode
T2SL	Type II Superlattice
ZDW	Zero dispersion wavelength.

Executive summary

MINERVA (MId- to NEaR infrared spectroscopy for improVed medical diAgnostics; www.minerva-project.eu) was a project funded by the European Commission through its Seventh Framework Programme (FP7). It brought together thirteen partners from across Europe with the common objective of developing mid-infrared (mid-IR) technology based on super-continuum sources (SCSs) to improve the early diagnosis of cancer.

The MINERVA mid-IR range (1.5 to 12 µm) is rich in spectroscopic absorption peaks of biomolecules such as fats, proteins and carbohydrates. This region of the spectrum offers an exciting area for real-time molecular sensing, *e.g.* in medicine and healthcare, environment and energy (*e.g.* monitoring exhaust gases) and security (*e.g.* detection of narcotics or explosives). In particular this spectral region can be used to identify the presence of early cancer.

MINERVA has developed fibre, lasers and broadband sources, components, modulators and detectors to access this important part of the spectrum. In parallel it has identified analytical techniques using the new photonic hardware which in due course could help to improve early skin cancer diagnosis and the rapid automatic assessment of biopsy samples using a microscope. Bringing all these advances together, MINERVA has demonstrated the first supercontinuum-based mid-IR imaging microscope for biological tissues.

These advances include:

- Chalcogenide fibres for infrared transmission and supercontinuum generation
- Ultra-low loss Pr-doped fibre for mid-IR fibre lasers
- First ever SM ZBLAN fused fibre coupler
- Various AO tuneable filters (AOTFs) for the wavelength range 1.5 to 4.5 µm
- AO Q-switch suitable for 2.9 µm operation
- A novel multi-channel “smart driver” offering extremely flexible AOTF operation
- A new long-λ AOM based on Ge suitable for operation beyond 10 µm
- Largest reported single crystal calomel crystals (35 mm diameter)
- Highest peak power 2.9 µm laser (10.6 kW)
- Longest wavelength ZBLAN supercontinuum source
- Record long wavelength average power (24 mW>4.5 µm) and long wavelength supercontinuum bandwidth (1.4-13.3 µm)
- Broadest mid-IR SCG in a tapered chalcogenide PCF spanning 1-11.5 µm
- Advances in T2SL mid-IR based sensors (detectors and readout ICs)
- First evaluation of multivariate algorithms with high spatial resolution FTIR
- Human skin equivalent standardised models
- Segmentation and registration algorithms for identification of structures in microscope images
- Algorithms for identification and differentiation of tumour cells from normal skin cells
- High resolution mid-IR imaging microscope based on SCS in the 3-4.5 µm wavelength range
- Scanning modality microscope based on SCS in the 4-7.5 µm wavelength range

In addition to these scientific achievements, MINERVA has driven the introduction of new products including lasers, SCSs, acousto-optic modulators and drivers, crystal and related components and detectors for the mid-IR.

This document describes the substantial progress made during the project. Contact emails are given for each MINERVA topic, or see the website for more information (www.minerva-project.eu). Here there is a list of all the journal (almost forty) and conference papers (almost a hundred) published on the project results. This included a double dedicated session on MINERVA at Photonics West 2016, and a session is planned for Photonics Europe 2018 (22-26 Apr-2018; Strasbourg, France). The project concluded with a workshop in Munich at which the project results were presented to a large expert audience, and the slides are available from the website (http://minerva-project.eu/events/workshop-30-jun-2017).

Context and objectives

Context

In recent years it has become clear that mid-IR imaging spectroscopy has the potential to open a new chapter in bio-medical imaging and offers an effective tool for early cancer diagnosis and improved survival rates. Rather than a search for "cancer marker" absorption peaks, great progress has been made by analysing the entire bio-molecular mid-IR spectral signature using automated algorithms. However, the lack of suitable sources, detectors and components has restricted progress. MINERVA aimed to develop the underlying photonic hardware, and investigate the potential for the technology.

MINERVA has developed a new mid-IR technology platform on which entirely novel supercontinuum sources (*c.* 1000× brighter than thermal sources) covering a wide range of the mid-IR, with appropriate components and detectors, have been integrated into **the first reported supercontinuum-based mid-IR imaging systems.** This work has covered a wide range of photonic hardware development:

- Low loss chalcogenide fibres for fibre lasers, supercontinuum generation and delivery
- Fibre end caps, splicing and fusion technology for soft glass fibres
- Calomel crystal technology and novel designs for mid-IR AO modulators
- Flexible fast AO driver technology to enable high speed hyperspectral image acquisition
- Low cost T2SL FPA detectors with performance matching state-of-the-art devices
- 2.9 µm Er:ZBLAN and 4.5 µm Pr-doped chalcogenide fibre laser pumps
- Robust designs for a range of mid-IR SCG sources:
    - 1.5-4.5 µm from ZBLAN fibre
    - Longer wavelength (1.5-13 µm) sources based on chalcogenide fibre.

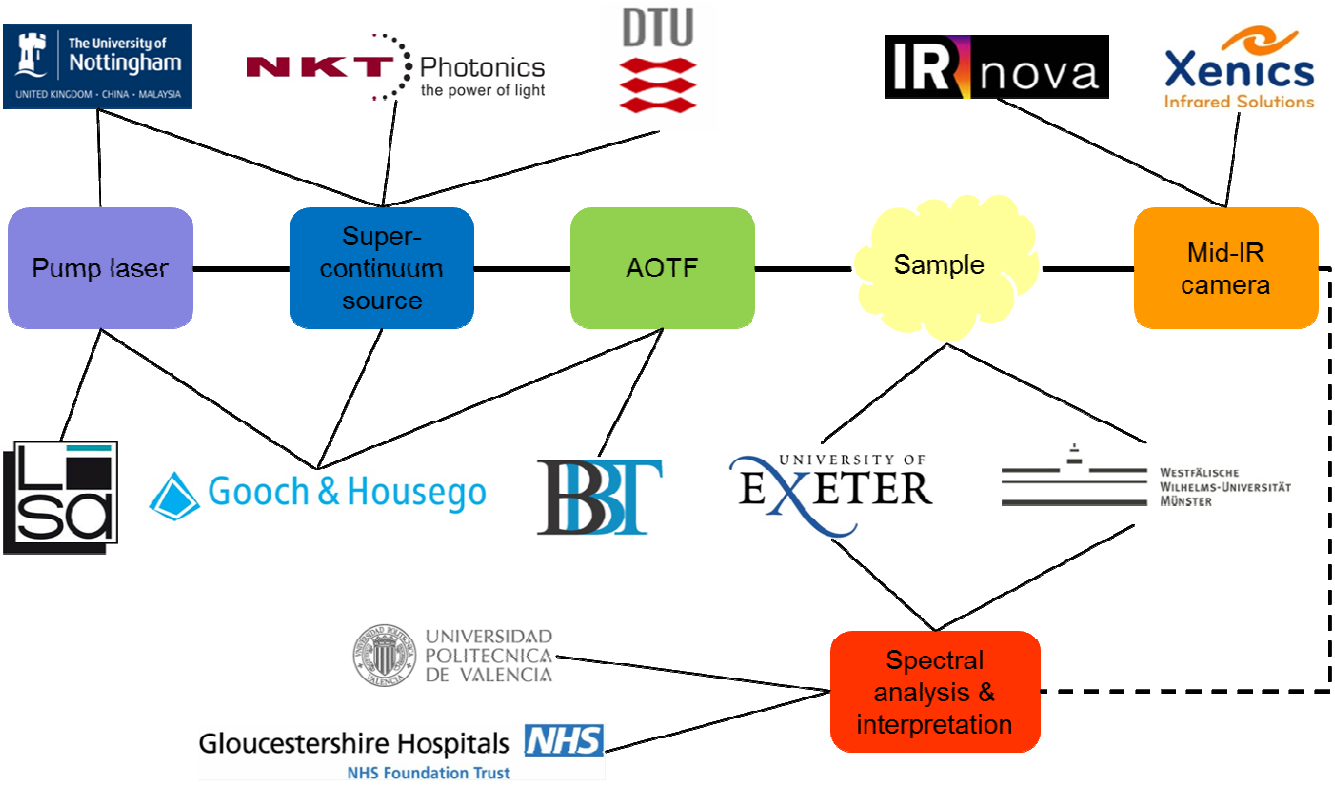

Figure 1: Schematic of the MINERVA workprogramme

The schematic above shows the overall system, and the contributions made by the MINERVA partners. The fibre, source, modulator and detector technology were integrated into a mid-IR imaging system, which offered high resolution multi-spectral images across the mid-IR with image acquisition times orders of magnitude faster than the state-of-the-art FTIR technology. These "image cubes" were studied by medical partners to begin the highly complex task of understanding how this new information could be used to improve medical diagnosis.

Two specific high impact applications were addressed:

- High volume pathology screening: *i.e.* automated microscope-based examination of samples
- *In vivo* remote, real-time skin surface examination: *i.e.* non-invasive investigation of suspected skin cancer.

At the start of the project there was a lack of practical sources and components for this spectral region, and so these mid-IR diagnostic techniques were restricted to laboratory demonstrations. MINERVA has developed fibre, lasers and broadband sources, components, modulators and detectors to access this important part of the spectrum. In parallel it has identified analytical techniques using the new photonic hardware which in due course could help to improve early skin cancer diagnosis and the rapid automatic assessment of biopsy samples using a microscope.

Objectives

The project activities fall into three inter-related areas: hardware development, software and analysis and the demonstration. The objectives in each of these areas were as follows.

1) Hardware development

Fibre development

University of Nottingham

- Development of new chalcogenide fibres based on ultra-low loss materials and fabrication techniques to provide robust fibre media for the supercontinuum sources:
    - Rare-earth-doped Pr-Ge-Ga-As-Se chalcogenide fibres for a 4.5 µm pump laser
    - Step-index As-Se/Ge-As-Se chalcogenide fibres for SCG from 4-12 µm source

Component development

Gooch and Housego (Torquay)

- Development of fibre components for delivery of IR radiation in the 2 to 12 µm wavelength range:
    - End cap components for preventing optical damage to fibre ends
    - SM fused chalcogenide fibre components
    - Process for connecting different fibre types (soft glass & silica) with low insertion loss

Gooch and Housego (UK)

- Acousto-optic mid-IR modulators
    - AOTFs for filtering and wavelength sweeping in spectroscopic measurements
    - AOQS for WP3 mid-IR pump lasers.

BBT

- Growth of the large (36 mm diameter) single crystal and pre-processing of calomel boules

2.9 µm and 4.5 µm pump fibre laser development

LISA Laser

- Develop pump sources for mid-IR SC sources in WP5
    - 2.9 µm high power (30 W CW) and high energy Q-switched Er:ZBLAN fibre laser
    - 4.5 µm mode-locked Pr-doped chalcogenide fibre laser

Fluoride fibre supercontinuum sources (1.5-4.5 µm)
NKT Photonics

- Develop portable fluoride fibre-based mid-IR supercontinuum sources from 1.5-5.5 µm:
    - Develop a powerful 15 W 2 µm MOPA pump source
    - Build on existing ZBLAN fibre technology to develop a 1.5-4.5 µm 5W average power SC source
    - Develop very low noise techniques for these SCSs (target 10% of existing noise levels).

Chalcogenide fibre supercontinuum sources (3-12 µm)
DTU Fotonik

- Modelling SCG in these new fibres for various fibre parameters: peak power and pump wavelength to determine optimum combinations of pump and fibre parameters
- Supercontinuum source build and test
    - 4-12 µm sources using novel fibre and pump combinations

Detectors
Xenics
IRnova

- Development of T2SL imaging detectors to cover the entire mid-IR bandwidth (3-12 µm):
    - 1-5 µm MWIR detectors
    - 5-12 µm LWIR detectors

2) Software and analysis

Screening pathology-process development
University Of Exeter
Gloucestershire Hospitals NHS Foundation Trust
Universitat Politecnica De Valencia

- To develop the clinical applications of mid-IR spectral histo-/cyto- logical screening and to identify the key system specifications for optimum performance:
- Measurement protocols
- Develop and optimise read-out and multivariate diagnostic algorithms
- Test performance of mid-IR spectral imaging for target applications

Skin cancer identification-process development
Westfälische Wilhelms-Universität Münster

- Development and testing of a human skin equivalent *in vitro* model for skin cancer detection:

➔ Characterization of 3D model systems for human skin
    - Protocols for 3D epidermal and skin cancer in vitro systems culture
    - Test for human epidermal marker proteins

➔ Evaluation of a mid-IR system for human skin analysis
➔ Generation of reference spectra of human skin equivalents
➔ Analysis of mid-IR depth information
    - Correlation of mid-IR spectra with confocal images of fluorescence labelled cells.

3) Demonstration

Led by Gooch and Housego (Torquay)

- Demonstration of the MINERVA technology to the wider bio-photonics community by fabricating a multi-functional portable unit
- Integration of MINERVA sources, components and detectors with protocols, procedures and software developed in the project in a flexible system which may be adapted for either:
    - High volume microscope-based cytological and histological spectral screening
    - Human skin surface examination with a rigid probe for skin cancer identification.

Dissemination and exploitation
In addition to this technical work there was a programme of dissemination activity

Led by Vivid Components

- Dissemination of project results to clinicians, industry, the public and investment communities
    - Conference presentations and peer-reviewed journal publications
    - Technology transfer workshop
    - Newsletters, public website and other dissemination material

The project has achieved success across all these target areas. It has set a number of records, re-defined the state-of-the-art and boosted mid-IR technology in Europe, with several important new products resulting directly from this research. This report will present the project results and provide contact information for those desiring further information.

Main project results

MINERVA was a high risk project which was based on some exciting theoretical work. Based on the potential for long wavelength mid-IR supercontinuum sources with reasonable power, it was planned to build an imaging system in the mid-IR which could offer a new tool for clinicians in the fight against cancer.

The ground-breaking theoretical basis for the project was published in 2014 (Opt. Exp. **22**, p. 19169) and described the huge potential of the MINERVA approach for long wavelength supercontinuum sources (SCSs). [This paper was selected as a "Research Highlight" (Nature Photonics **8**, p. 746; 2014).] This theoretical basis was subsequently verified experimentally by the MINERVA team (Nature Photonics **8**, p. 830 (2014)) using entirely novel MINERVA fibre and sources. This was the first SCS to reach beyond a wavelength of 13 µm. This landmark paper has now been cited over 300 times (including 60 citations in 2017) and forms the basis for research at groups based in Australia, Poland, China, Japan and the US.

This major advance underpinned a wide range of other innovations by the MINERVA consortium in the area of mid-IR technology. As planned, these novel SCSs were integrated with new components and fibres, advanced detectors and bespoke algorithms, to deliver novel high resolution mid-IR imaging systems.

The following are all scientific records or world firsts achieved by the project:

1) Highest NA in a mid-IR optical fibre
   - Optical Materials Express **4**, p. 1444 (Jul-2014)

2) Lowest loss arsenic selenide fibre (25 dB/km at 2.71 µm)
   - Optical Materials Express **5**, p. 1722-1737 (Aug-2015)

3) Longest transmission in germanium arsenic selenide fibre (52 m)
   - First time transmission of this kind has been achieved
   - Optical Materials Express **5**, p. 1722-1737 (Aug-2015)
   - Extended to 82 m Oct-2016 (paper in preparation)

4) Record photo-luminescent intensity and lifetime in Pr-doped fibre
   - Optics Express **22**, p. 21236 (Sep-2014)

5) Identification of a previously unknown absorption in Pr-doped glass due to [H-Se] at 4.54 µm
   - Presented at ICTON 2016 (Paper Th.B6.1)

6) First ever recorded fluorescence at 4-5 µm in a small core fibre
   - Optical Materials Express **5**, p. 870-886 (Apr-2015)

7) First ever mid-IR fibre dispersion characterisation system

8) First ever SM ZBLAN fused fibre coupler
   - Proc. SPIE **9730**, 973007 (Apr-2016)

9) Largest single crystal optical quality calomel crystal (28 mm diameter; later 36 mm)
   - Three crystallisers now commissioned for 36 mm crystals

10) Highest peak power 2.9 µm laser (8.3 kW and then 10.6 kW)
    - This exceeds the previous record by an order of magnitude

- Presented at CLEO Europe 2015 (Paper CJ-7.2)

11) Longest wavelength ZBLAN supercontinuum source (1.2 W; 4.75 µm)
    - Presented at Advanced Solid State Lasers 2013 (paper JTh5A)

12) Record average power (24 mW) and long wavelength supercontinuum generation (>13 µm)
    - Nature Photonics **8**, p. 830 (Sep-2014)

13) Broadest mid-IR SCG in a chalcogenide PCF spanning 1-11.5 µm
    - Optics Express **25**, p. 15336-15347 (Jun-2017)

14) First use of a cascaded supercontinuum source
    - Optics Express **24**, p. 749-758 (Jan-2016)

15) First evaluation of multivariate algorithms with high spatial resolution FTIR
    - Analyst **140**, p. 2215-2223 (Dec-2014)

16) Optimised electronic de-paraffinisation process
    - Analyst **140**, p. 2369-2375 (Feb-2015)

17) Unique high resolution mid-IR imaging system
    - Journal of Physics: Conference Series **619**, p. 012032 (Jun-2015)

18) First SCS-based mid-IR microscope
    - Paper in preparation

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Fibre development

University of Nottingham

Over the course of the MINERVA Project the University of Nottingham, UK, (NOTT) has developed successfully, and reported in the open literature for the first time in each case, three major new types of mid-infrared (mid-IR) transmitting chalcogenide glass optical fibres, as follows and as detailed below:

1) Lowest optical loss selenide chalcogenide glass optical fibre

Ultra-low loss Ge-As-Se fibre was successfully achieved through chemical processing; the lowest loss recorded was 83 dB/km at 6.6 µm wavelength, with transmission through 52 m of fibre. This was the first ultra-low optical loss Ge-As-Se reported in the open literature. This breakthrough in low optical loss Ge-As-Se chalcogenide glass optical fibre served three important purposes for the work at NOTT in MINERVA:

(a) Ge-As-Se chalcogenide glass optical fibre is an excellent passive conduit fibre for mid-IR radiation
(b) Ge-As-Se chalcogenide glass is the major part of the chalcogenide glass host for rare earth ion doping and achieving high glass quality
(c) Ge-As-Se chalcogenide glass is the cladding glass of the step index fibre used for the record-breaking wavelength span mid-IR SCS.

2) Longest excited state 10 ms lifetimes in small core rare earth chalcogenide glass fibre
In their background work, prior to MINERVA, the NOTT Group had studied the glass stability of rare earth ion doped selenide chalcogenide-glasses. Through this work, knowledge had been gained about the problems of surface and bulk glass devitrification on incorporating rare earth ion dopants in selenide chalcogenide glasses. During MINERVA this prior knowledge was applied to an intensive programme of fibre development work aimed at making rare earth ion doped selenide chalcogenide glass fibre of small core with long photo-luminescent (PL) lifetimes. This goal was successfully achieved and a new record reported in the public domain of long PL lifetimes (up to 10 ms) preserved in small core (10 µm diameter) selenide chalcogenide glass optical fibres for the first time. The significance of the long lifetimes of the doped in rare earth ions in the small core fibre achieved at NOTT is that this means that neither glass devitrification nor rare earth ion clustering occurred during the intricate thermal processing to achieve fibre. The overall aim during the MINERVA project was to make rare earth ion fibre lasers for operation >4 µm, based on rare earth ion doped chalcogenide glass small core fibre and the world-class results achieve at NOTT means that NOTT leads this field on the world-scene and has a good idea of the way forward and potential collaborators.

3) Widest-span mid-IR supercontinuum (SC) generation, in chalcogenide-glass optical fibre
Prior to the MINERVA project NOTT had already demonstrated that chalcogenide glasses with widely disparate refractive indices could be thermally co-processed. Also prior to MINERVA, Seddon of the NOTT team had published in the public domain the proposal that pumping chalcogenide glass step index fibre at the longer wavelengths 4-5 µm than published to that date should provide a supercontinuum to span the molecular 'fingerprint' spectral region for identifying molecular cell types associated with cancer. During the MINERVA project, the Group of Ole Bang at DTU, Denmark and NOTT made the record-breaking mid-MIR SCS: 1.4-13.3 µm wavelength, in selenide chalcogenide glass fibre, published in Nature Photonics [Nov-2014]. This paper was picked out as a Nature highlight in the News & Views section (Steinmeyer & Skibina, Nat. Photon. 2014) where it was stated that: "The demonstration of chalcogenide fiber-based supercontinuum sources that reach beyond a wavelength of ten micrometres is set to have a major impact on spectroscopy and molecular sensing."

➔ *For more information please contact: Angela Seddon Angela.Seddon@nottingham.ac.uk*

Mid-IR fibre component development
Gooch and Housego (Torquay)
Development of fibre components for delivery of mid-IR radiation in MINERVA leveraged extensively G&H's vast technological expertise in fibre optics. Close collaboration with project partners, LISA and NOTT led to several technological advancements in the field:

- End cap components for preventing optical damage to fibre ends
- SM fused chalcogenide fibre components
    - First ever SM ZBLAN fused fibre coupler; Proc. SPIE **9730**, 973007 (2016)
- Process for connecting different fibre types (soft glass & silica) with low insertion loss

Soft-glass end caps have been developed primarily for facet protection of the LISA demonstrator Er:ZBLAN fibre which has shown the world-record breaking performance in both pulse energy and peak power (see below). This successful demonstration highlights the high quality of MINERVA produced fibre components and the effectiveness of the approach in ruggedising the ZBLAN fibres.

Current processes for manufacturing of the single-mode fused fibre couplers revolves around unique properties of the mature silica technology. Soft glasses like ZBLAN present many different challenges due to very different thermal and mechanical properties. Building on the existing know–how and thanks to the concentrated effort delivered through MINERVA a step-like advance in the material processing was achieved leading to the world's first demonstration of single-mode fused couplers in ZBLAN fibre. Currently, the insertion losses of the devices are still larger than for the silica equivalents but given the adverse properties of the fibre material this remains to be a major breakthrough in component technology for mid-IR.

➔ *For more information please contact: Mark Farries* mfarries@goochandhousego.com

Mid-IR AO components

Gooch and Housego (UK)

G&H (UK) Ltd played a key part in the project, acting as the Technical Coordinator and developing active optical components. In order to build the MINERVA imaging systems, specialised acousto-optic (AO) components were developed for operation in the 2-4 µm region, some of which are now available as products.

- Various AO tuneable filters (AOTFs) for the wavelength range 1.5 to 4.5 µm
- AO Q-switch suitable for 2.9 µm operation
- A novel multi-channel "smart driver" offers extremely flexible operation of AOTFs
- A new long-λ AOM based on Ge suitable for operation beyond 10 µm.

An AO Q-Switch for operation at ~3 µm was built and incorporated by LISA Laser into an Er:ZBLAN fibre laser. With this system LISA demonstrated a pulse energy of 560 µJ at pulse rep-rate of 1 kHz and pulse width 69 ns, peak power was 10·6 kW. This was world record-breaking performance. This Q-switch design is now available as a commercial product.

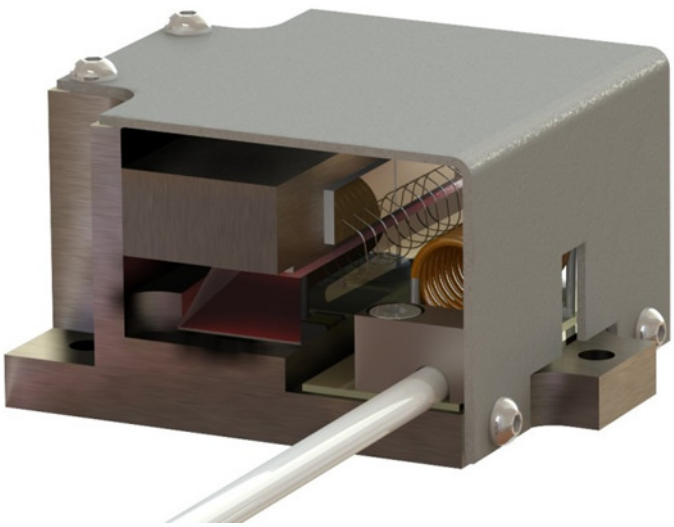

Figure 2: Q-switch for 3 µm operation: now available commercially from G&H (UK)

In parallel, two designs of AO tunable filters (AOTFs) covering the spectral range 2-4·5 µm were developed to operate with NKT's new generation of md-IR supercontinuum source. A narrow resolution AOTF had a resolving power ($R=\lambda/\Delta\lambda$) of 500, whilst an ultra-narrow resolution AOTF had R=1000. Both of these represented excellent performance for an AOTF in this wavelength range. These AOTFs, or their derivatives are now available commercially.

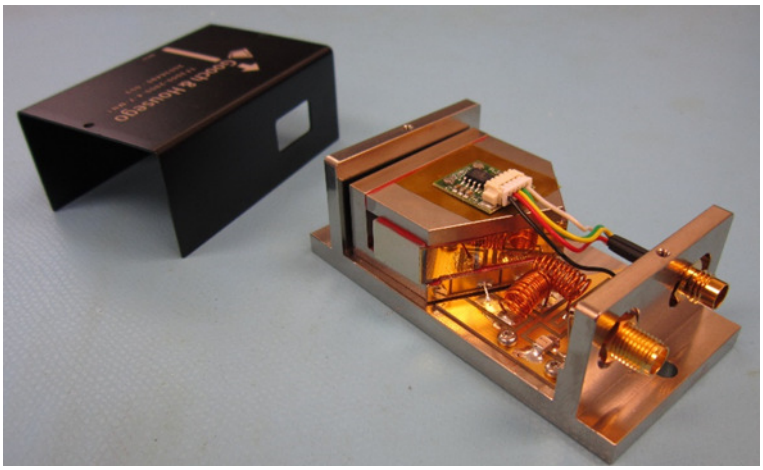

Figure 3: Ultra-narrow resolution AOTF: now available commercially from G&H (UK)

In order to better exploit the performance potential of the new AOTFs (*i.e.* very fast tuning with random access and adaptable performance) a multi-channel RF "smart-driver" along with the necessary interface software was developed. This is now being introduced as a commercial product.

In a bid to reduce the power consumption of AO devices at longer wavelengths (the drive power scales with λ^2), a series of experimental AOTFs with resonant acoustic structures was built. These effectively "recycled" the acoustic energy thus using it more efficiently. An advantage of approximately a factor of four was demonstrated providing a useful reduction in drive power. Innovations of this type are likely to be exploited in future products

Finally, a number of potential AO materials potentially suitable for operation in the long wave-IR (>4 µm) were evaluated. Although ultimately not exploited within the MINERVA project, this activity proved to be very useful in the optimisation of commercial AO devices for operation in the LWIR region.

➔ *For more information please contact: Jon Ward* jward@goochandhousego.com

Component development-Calomel crystals
BBT Materials Processing

Participation in the MINERVA project has been a significant step for BBT Materials Processing and its technological research and development activities. Through MINERVA, BBT has consolidated its position as the world leading producers of calomel, a material used for mid-IR components due to its excellent transmission at long wavelengths.

During the first half of the project, the first ever 35 mm diameter calomel single crystal of high optical quality was grown. After the manufacturing of six new crystallizers for the growing of large calomel boules, several further calomel ingots were grown and used for the processing of acousto-optic substrates for the LWIR AOTF filter tested by Gooch & Housego.

Figure 4: Calomel boule, diameter 35 mm (above)

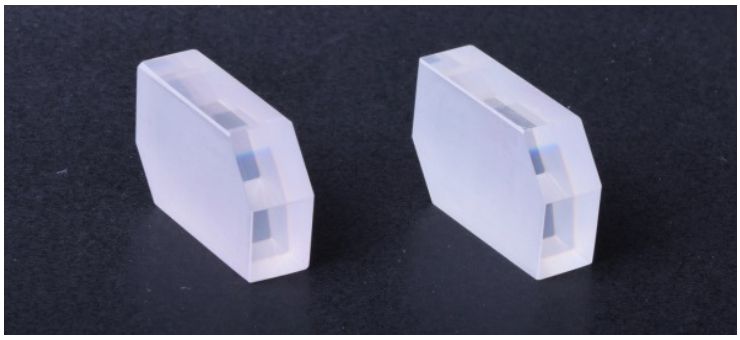

Figure 5: Calomel AOTF substrates (right)

The development and progress of the growing technology for large calomel boules has generated several spin-off market-oriented opportunities for the company. These products may increase a company revenue in the near future and create new job positions, once the product achieves a corresponding TRL for the market. One potential product is an IR calomel polarizer for MWIR and LWIR regions. A unique system of IR transparent, birefringent wedges made of calomel represents a brand new type of polarizer for the infrared optics market. These polarizers find application in the field of spectroscopy, astronomy, lasing, IR optical setups and other areas where a polarized mid-IR source is necessary.

Figure 6: Calomel IR polarizers

Another spin-off covers the development of new type of spectrometer based on calomel prisms. The extremely large birefringence of the material is used in a Fourier transform spectroscopy (FTIR) systems for detection of gases and liquids. The set-up can be used to demonstrate FTIR spectroscopy, as well as 2D-IR spectroscopy and can be extended to other spectroscopic modalities such as vibrational circular dichroism and step-scan FT spectroscopy.

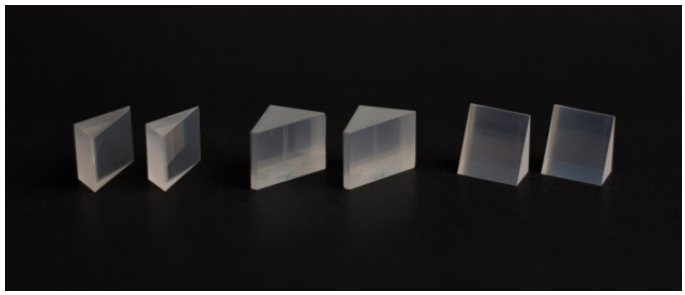

Figure 7: Calomel IR prisms

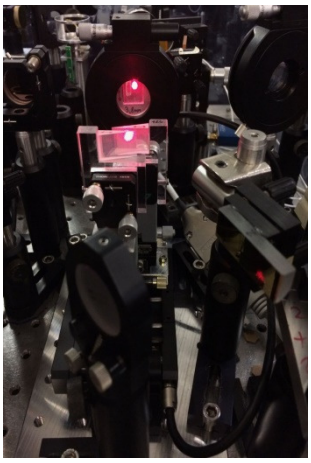

Figure 8: Calomel birefringent spectrometer breadboard setup

All these activities will require new two employees which will cover manufacturing and processing needs for these possible products. An essential condition for the market entry is a corresponding AR coating for all the calomel components, which is currently under development. BBT is currently looking for a suitable partner for a collaborative project on the anti-reflection coating development.

➔ *For more information please contact: Cestmir Barta; BBT*
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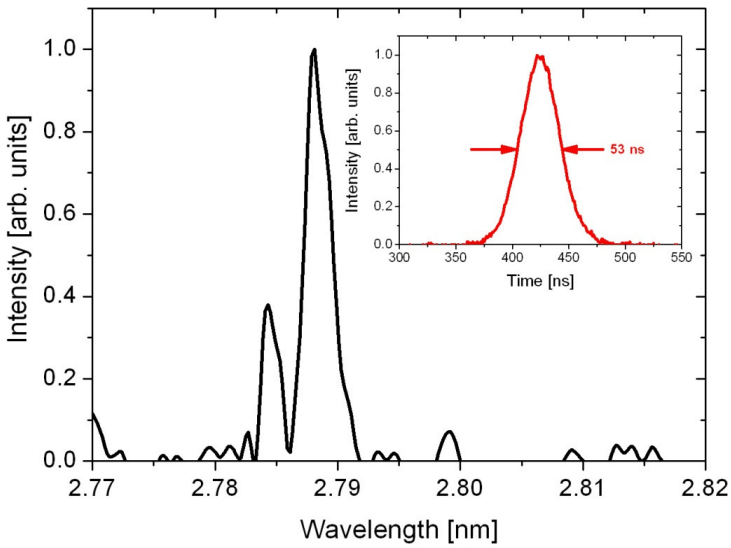
Pump lasers

LISA Laser

Within MINERVA LISA's key task was the development of novel mid-IR lasers in close collaboration with the partners NOTT and G&H. After several initial fundamental tests LISA demonstrated a high energy Er:ZBLAN fibre laser with unprecedented performance using components from G&H. The partners followed the approach of acousto-optic Q-switching an external cavity to exploit the full flexibility of the system. This effort led to world record values for both the pulse energy and peak power.

During the development work, LISA carried out experiments for the handling (stripping, cleaving, splicing) of soft glass fibres and worked on both high power and high energy laser operation with different resonator configurations. Coated focussing and collimating optics have been designed and manufactured for the laser studies. After the evaluation of the first tests (in CW operation) it was necessary for LISA's scientists and engineers to design a compact and robust cooled housing for the 2.9 µm laser.



The main components are the 976 nm diode-pumped Er:ZBLAN multimode fibre and a novel TeO_2-based acousto-optic modulator (AOM) fabricated by G&H. The results were presented at CLEO Europe 2015 (Paper CJ-7.2). The maximum pulse energy extracted from the laser oscillator was 560 µJ at a pulse repetition rate of 1 kHz. The corresponding minimum pulse duration was 53 ns corresponding to a maximum pulse peak power of 10.6 kW. The energy fluence at the output fibre end was calculated to be ~70 J/cm² at the maximum pulse energy level. These values exceed already published work by an order of magnitude and clearly demonstrate the potential for the practical use.

Figure 9: Laser spectrum at 2.79 µm and pulse duration (inset graph) of the Q-switched Er:ZBLAN fibre laser at room-temperature.

Publications from other groups show that the threshold for soft tissue cutting is *c.* 4.4 J/cm² (D. V. Chuchumishev *et al.* CLEO 2014, paper SM4P.7). The MINERVA system exceeds this value by a

factor of almost twenty. Therefore LISA was motivated to start with laser-tissue interaction experiments during the project duration in order to investigate the practical use. Promising results were achieved by hand-guided cutting of soft tissue. The most interesting result compared with LISA's commercially available medical lasers at 2 µm is significantly reduced collateral damage and lower carbonisation effects. LISA has discussed these results with clinical partners to identify potential applications and it appears to be promising tool for stapedotomy.

Work continues at LISA and products are expected in the near future.

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Fluoride fibre-based supercontinuum sources

NKT Photonics

The mid-IR region can give access to a wealth of information on the chemical composition of a sample. However, access to this information has until now been difficult because of the lack of bright broadband light sources in the mid-IR region. Until now the only broadband light source which could really satisfy this need was a mid-IR synchrotron beamline. However synchrotron beamlines are expensive, large and not at all portable (see

Figure ***11***); therefore they could only be applied to scientific research and proof of principle studies but not widespread applications. One of the goals of the MINERVA project was to develop a benchtop light source more than 1000× brighter than a "Globar" (the standard laboratory thermal source) to approach the performance of a synchrotron. At the beginning NKT Photonics had already demonstrated an initial prototype mid-IR supercontinuum source, but this proof-of-principle source relied on a rather unreliable and very expensive design. The first years of development was plagued by many breakdowns but through the improvements made in MINERVA it has been possible to develop a source which is much simpler, much more reliable and much easier to use.

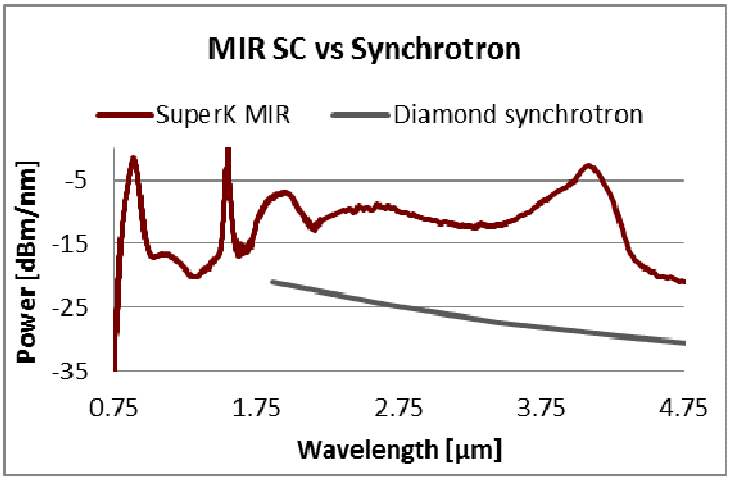

Figure 10: Graph showing NKT SCS output power compared with the Diamond synchrotron

Figure 11: Aerial photo of the Diamond Light Source (Didcot, UK).

In MINERVA NKT has developed zirconium fluoride (ZrF_4) glass fibre supercontinuum sources (SCSs) to cover the 1.5-4.5 µm spectrum. NKT expects that these new sources will be used in spectroscopic applications which were previously unobtainable or impractical. They will allow long range or high resolution measurements which were previously only possible with much more expensive and bulky instruments such as optical parametric oscillators (OPOs) or synchrotrons.

As these mid-IR SCSs become available and known in the field the MINERVA consortium expects the emergence of new markets. For example, an important spectroscopic application in the

petrochemical industry is to monitor single wavelengths in the 3-3.5 µm band in order to optimise the refining processes. Monitoring the whole spectrum simultaneously would allow a full real-time chemical analysis of the output chemicals.

As mentioned above, the first prototype sources had poor reliability and would usually only last 100-200 h. Since then NKT has taken this laboratory demonstration, reduced the noise level, improved the long-term stability, optimised the output spectrum shape and packaged the system in a robust housing. A maintenance-free lifetime of over two years of continuous 24-7 operation has been demonstrated, hugely exceeding the project targets.

NKT has also far surpassed the original goals regarding the brightness of the source by developing sources more than a million times brighter than typical Globar thermal sources and even an order of magnitude brighter than a synchrotron! It has shown the limits of zirconium fluoride based systems by setting a new record for the longest wavelength supercontinuum generated at 4.75 µm (presented at the conference on Advanced Solid State Lasers; Paris France Oct-2013).

However, the chemometric specialists in MINERVA found that the main region of interest was the 2.5-3.8 µm region so NKT devised new sources in which the main power in the output spectrum was shifted down to the main region of interest by altering the design of the nonlinear fibre. Recently at the Laser World of Photonics trade show in Munich in June 2017 a new product (SuperK MIR) was released based on the MINEVA developments so that all research groups can get access to this new innovative light source which is also already catching the eye of potential OEM system manufacturers.

Figure 12: MINERVA supercontinuum source development. Left: the prototype mid-IR supercontinuum source at the beginning of the project. Right: The SuperK MIR product launched at the end of the project.

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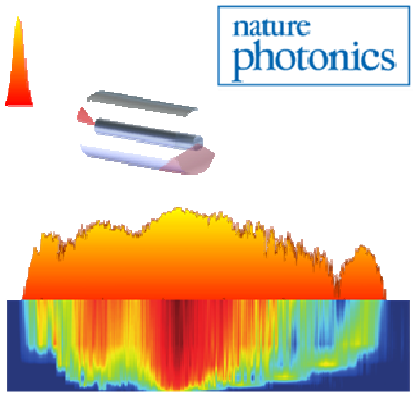
Chalcogenide fibre supercontinuum sources (3-12 µm)

DTU Fotonik

The MINERVA project originated largely as a result of some theoretical work at DTU which suggested that if fibres with certain characteristics could be manufactured, then there was the potential to fabricate sources which exhibit supercontinuum generation (SCG) to extremely long wavelengths. During the project these simulations have been confirmed experimentally (through new source designs and novel fibres), setting several records along the way. This work has established a new area of mid-IR supercontinuum source research which is being pursued by several groups around the world.

Prof. Bang's team at DTU Fotonik had the task of fibre modelling in MINERVA in close collaboration with the fibre manufacturing group at University of Nottingham. The DTU group also modelled dynamic SCG along the fibres using both measured material data and calculated fibre properties. This advanced modelling required extensive computational resources in order to accurately follow the rapid spectral broadening, which covers over four octaves (from 1 µm to 16 µm); made possible by the strong non-linearity of chalcogenide glasses and the extremely high numerical aperture (NA) of the Nottingham fibres.

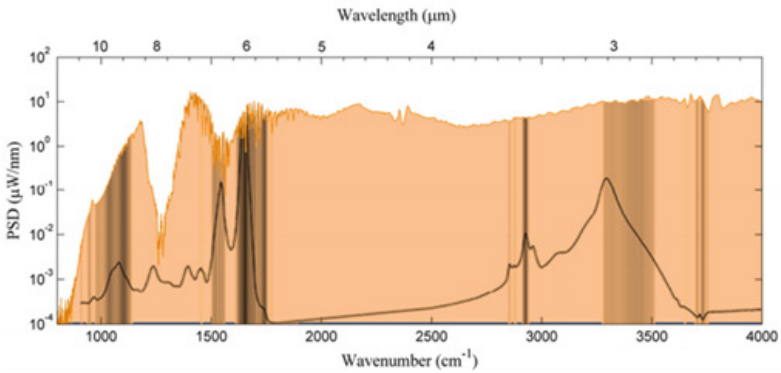


Record supercontinuum spanning 1.4-13.3 µm

The ground-breaking theoretical basis for the project proposed by DTU was published (Optics Express **22**, p. 19169-19182 (Aug-2014)) and highlighted the huge potential of the MINERVA approach This paper was selected as a "Research Highlight" by Nature Photonics in Oct-2014 (Nature Photonics **8**, p. 746 (Oct-2014) "Reaching the mid-infrared."). This theoretical basis was subsequently verified experimentally using MINERVA fibre and sources.

Figure 13: Schematic from the 2014 Nature Photonics paper showing the long wavelength SCG in an optical fibre.

The first experimental demonstration showing record long wavelength emission was a "hero experiment" using a fs pump source which was also published in Nature Photonics (Vol. **8**, p. 830 (Sep-2014)). This served to demonstrate the capability of the chalcogenide fibres fabricated by Nottingham University to cover the MINERVA target of *c.* 2-12 µm. It also served to validate the DTU simulations and numerical modelling that had led to the design of these fibres.



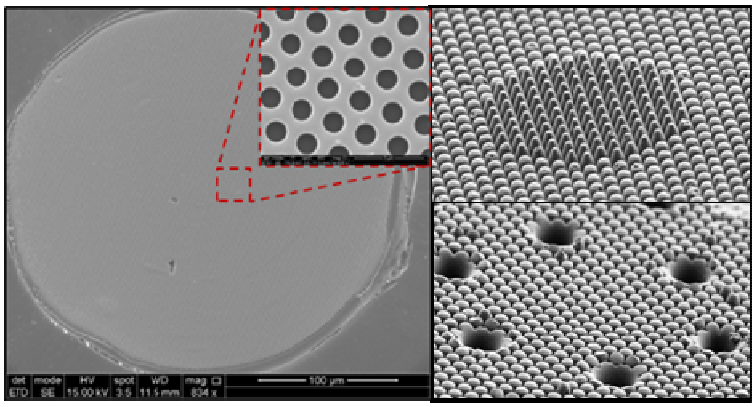
Record average power from 1-11.5 µm

In close collaboration with University of Rennes and French specialty-fibre manufacturer SelenOptics DTU demonstrated the highest average output power from a long wavelength mid-IR supercontinuum source with 35.4 mW from 1-11.5 µm and 57 mW from 1-8 µm (Opt. Express **25**, p. 15336 (2017)).

Figure 14: Schematic showing SCG from a tapered PCF with key absorption peaks of interest for MINERVA

Fibre end-face nanoimprinting improves transmission

Because of the very high refractive index of many materials used to transmit the mid-IR, the reflection at fibre facets is very large, resulting in high loss from each interface. Coatings are very difficult with these materials and this severely reduces the output power of the sources.



In collaboration with DTU Nanotech, DTU Fotonik has demonstrated an increased transmission of 9% per end face in large core multimode chalcogenide fibres, and up to 13% in bulk glass discs. In the most recent work the group has also demonstrated the feasibility of imprinting small core and photonic crystal fibres which is an exciting area which will continue to be pursued after the end of the MINERVA project.

Figure 15: Electron micro-graphs showing the nanoimprinted structures on the fibre ends, designed to reduce the back-reflections from the high index glass/air interface.

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Mid-IR imaging detectors

IRnova

IRnova's task was to develop and manufacture an imaging detector to become a part of the MINERVA demonstration instrument. This task was carried out together with IRnova's partner, Xenics, whose first task was to provide IRnova with a read-out integrated circuit (ROIC) and later to complement the integrated Dewar cooler assembly (IDCA) manufactured at IRnova with a mechanical frame and case, optics and electronics to make it a camera.

The specification requirements were formulated ambitiously. IRnova was to develop a focal plane array (FPA) based on the novel Type-2 Superlattice (T2SL) technology with high resolution, small pitch and wide bandwidth. T2SL technology potentially combines the performance of currently used HgCdTe technology with the stability, image quality, robustness and manufacturability of III-V technology.

At the start of the project IRnova produced detectors based on T2SL technology with the resolution of 320×256 pixels on a 30 µm pitch with a cut-off wavelength of 5 µm operating at 80-100 K. The challenge of the project was to push the technology to the edge and develop an FPA with a resolution of 1280×1024 on a 12 µm pitch with a cut-off wavelength of 12 µm operating at 100 K. Such a detector would without doubt set the state-of-the-art for the current IR-technology. Large arrays with a shorter cut-off wavelength (MWIR) based on this demanding pitch were also planned.

The development of an infrared detector requires firstly the theoretical band-gap engineering followed by epitaxial growth of the designed structure but also the development of semiconductor processes for such large arrays of small pixels. The hybridisation process, at which the photosensitive detector chip is bonded to the ROIC also needs substantial development and is a huge challenge in itself. An additional task was to design and construct a high vacuum Dewar vessel and develop the process of the FPA integration into it.

MWIR arrays

IRnova can now proudly report that the MWIR arrays were delivered and most of the project goals were successfully achieved. Several novel photosensitive structures were developed, grown and characterised. The innovation was to design a so-called "inverted structure" which greatly simplifies

the semiconductor process and allows for ~100% fill factor, *i.e.* no light is lost because of pixelisation. Optical response (Figure 1) is fair and can further be improved by applying anti-reflective coating.

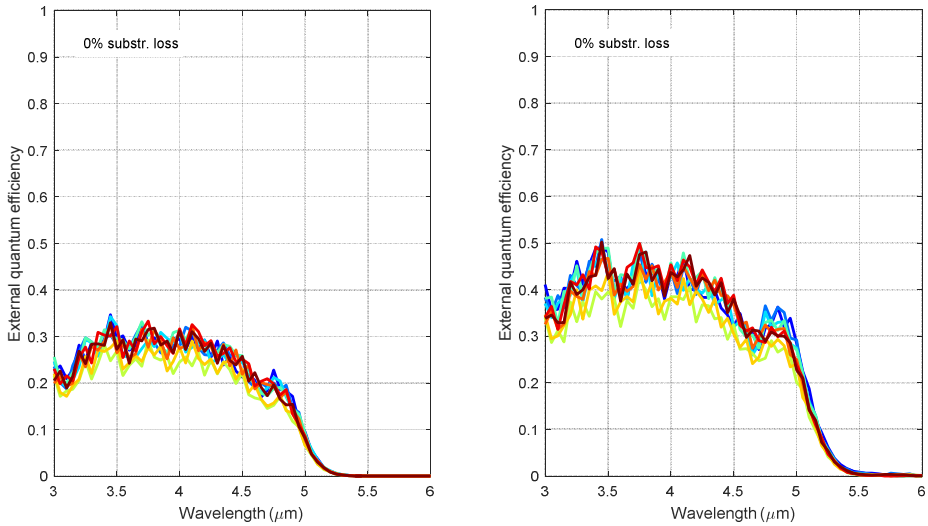

Figure 16: External conversion efficiency of the MWIR sample array (cut-off λ 5.3 µm) without anti-reflective coating at 80 K (left) and 120 K (right). The sample is part of a fully processed detector chip hybridised with a specially designed fan-out chip. (No ROIC was involved in the measurements.)

The grown structure was successfully processed into arrays and test FPAs were successfully hybridised.

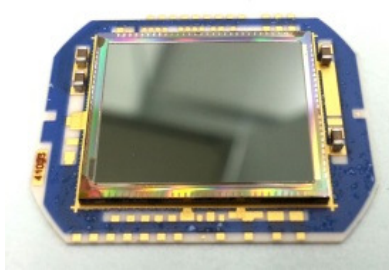

Figure 17: A photo of the newly hybridised FPA. The photosensitive detector chip is bonded to the read-out chip (ROIC) and the hybrid is mounted on specially designed ceramic carrier.

LWIR arrays

Unfortunately the target performance was not achieved on the structure with the cut-off wavelength at 12 µm. Materials for longer wavelengths are more demanding regarding the passivation and are more sensitive to the hybridisation process. However the developed material showed a good response and is very close to the state-of-the-art performance predicted by empirical Rule 07 (the industry-standard rule of thumb) for HgCdTe technology.

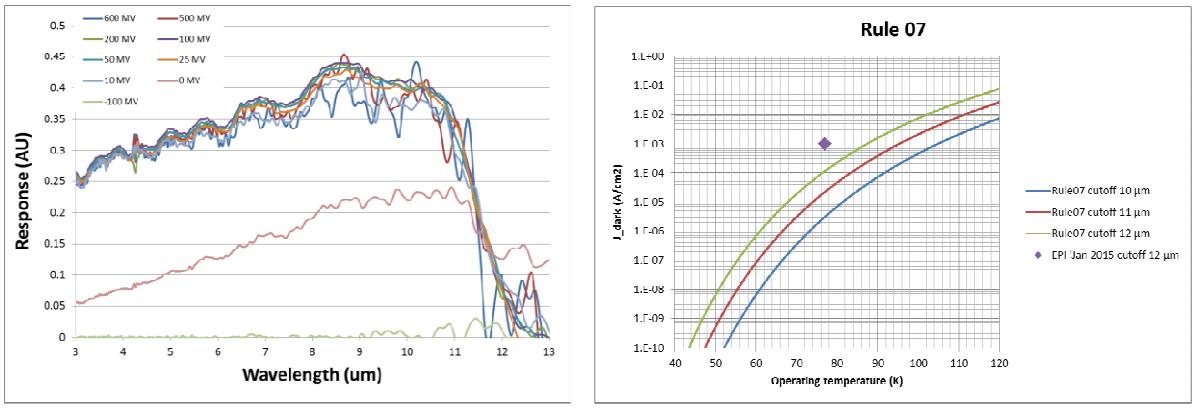

Figure 18: Optical response of the LWIR structure with cut-off wavelength 12 µm and its performance in terms of dark current vs. operating temperature according to Rule 07.

Despite this disappointing result, remarkable progress in the development of commercially available wide bandwidth high definition, high performance detectors with cut-off wavelengths up to 12 µm has been achieved through MINERVA. Innovations developed in the project have been and will continue to be used by IRnova for other products.

For example, the hybridisation and integration processes were applied to a new IRnova product employing an array of 640×512 pixels on 15 µm pitch both in the wavelength range of 3-5 µm and 8-12 µm. Figure 19 shows images taken with a demonstration camera equipped with a new product from IRnova – IRnova640LW, a detector with a resolution of 640×512 pixels on a 15 µm pitch (based on QWIP technology) with good sensitivity in the 8-12 µm range.

Figure 19: Images taken with a demonstration camera using new product from IRnova. The Irnova640LW is a detector with a resolution of 640×512 pixels on 15 µm pitch based on QWIP technology with good sensitivity in the 8-12 µm range. [Note the cool hair.]

Another new product, IRnova640MW, a detector with the same resolution and pitch but based on T2SL technology sensitive in the 3-5 µm range, has also been released and is being integrated in the IDCA at the time of writing.

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Camera development

Xenics

Working closely with IRnova, Xenics led the MINERVA work to improve mid-IR detection and develop high resolution cameras for this wavelength region based on T2SL. Apart from MINERVA applications, T2SL technology has exciting potential for gas detection of key greenhouse gases with absorption lines in the atmospheric transmission bands, such as methane and perhaps also sulphur hexafluoride (SF_6).

Compared with a traditional bulk material for the 3-5 µm range, such as InSb, T2SL requires less cooling and thus draws less power, which allows for longer cooler lifetime and consequently lower life-cycle cost. For the 8-12 µm range, the traditional alloy bulk material HgCdTe (or “MCT”) is difficult to fabricate with high yield, partly due to the extreme sensitivity of the bandgap to composition (particularly the HgTe: CdTe alloy ratio). Here T2SL materials have distinct advantages in fabrication.
As described in the previous section, in MINERVA IRnova has worked on improving the quantum efficiency (QE) of the detectors. This improves the signal-to-noise ratio and allows a reduced integration time for each image frame. Xenics has designed and manufactured a ROIC which

enables the use of an FPA with close to 100% fill factor and high QE. Megapixel arrays on 12 µm pitch (1280× 1024) with high yield and high QE were produced in an industrial environment for the MWIR domain.

Xenics' first task was to design and manufacture a ROIC suitable for integration with T2SL detectors and later to build a camera integrating the Dewar-cooler assembly (IDCA), manufactured by IRnova, with mechanics, optics and custom electronics.

The specification requirements were formulated extremely ambitiously. The challenge of the project was to develop a MWIR and LWIR FPA with the resolution of 1280×1024 on a 12 µm pitch. By the project start, Xenics had already experience with the design of a megapixel resolution ROIC, but this was on a larger pitch (17 µm) and chiefly for applications in the SWIR domain.

The design for the MINERVA ROIC turned out to be even more challenging than expected. Nevertheless, the measured yield at room temperature is very satisfactory for the first attempt.

- The pixel architecture is CMDI based: this pixel topology was favoured over the classic DI configuration because of its high injection efficiency at low input photo current
- The ROIC presents two or four analogue outputs for frame rates up to 100 Hz; an on-chip digital core contains the SPI configuration interface and a sequencer generating the protocol to control the analogue core.
- The ROIC also supports on-chip bias generation, completely configured through SPI interface.

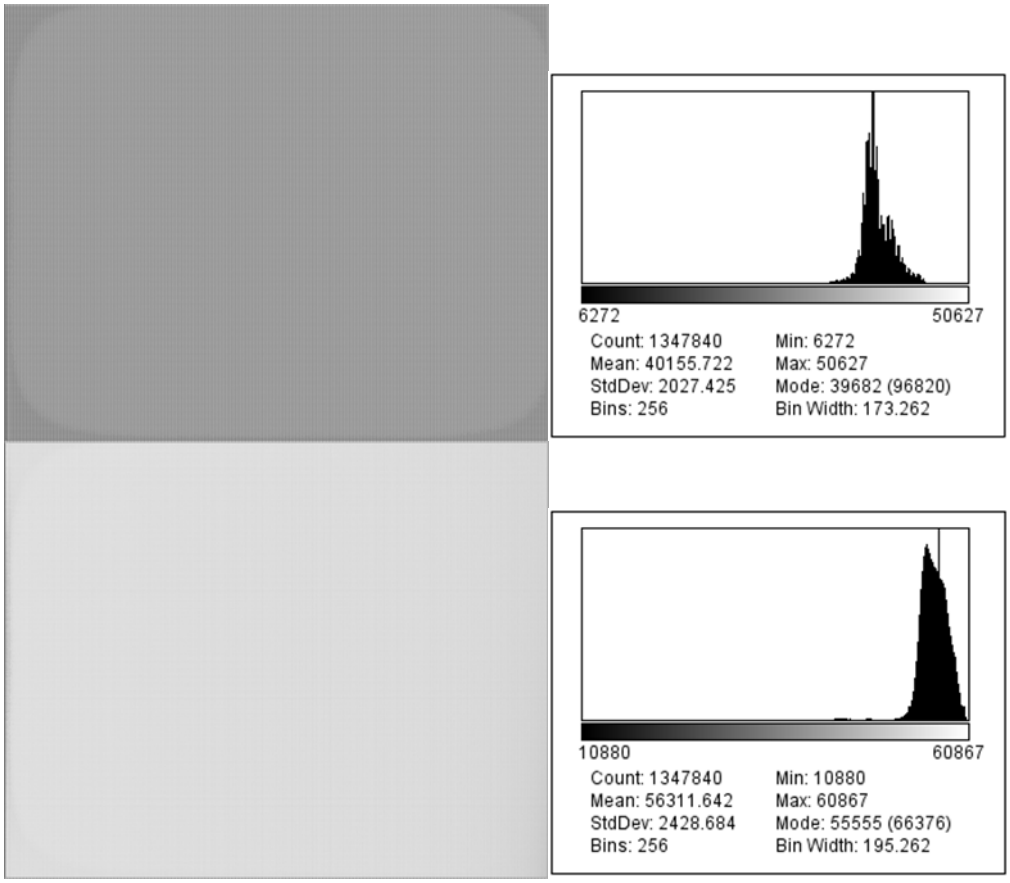

Figure 20: Image functionality tests and correspondingly generated histograms.

The second main task for Xenics was to design the camera to drive the IDCA provided by IRNova. The design of the camera includes both hardware and firmware:

- The hardware element consists of the proxy electronics needed to drive the ROIC and convert the signals emitted from it into a suitable format for further processing and presentation. Usually, proxy electronics consists of a driver, a pre-amplifier and an analogue to digital convertor (ADC). These elements are located on one or several boards.
- The firmware consists of the digital platform governing the operation of the camera module. In this case the design was particularly complicated due to the high level of flexibility required to integrate different types of detectors in the same camera module. In due course this will allow development to a family of related products to be introduced on the market.

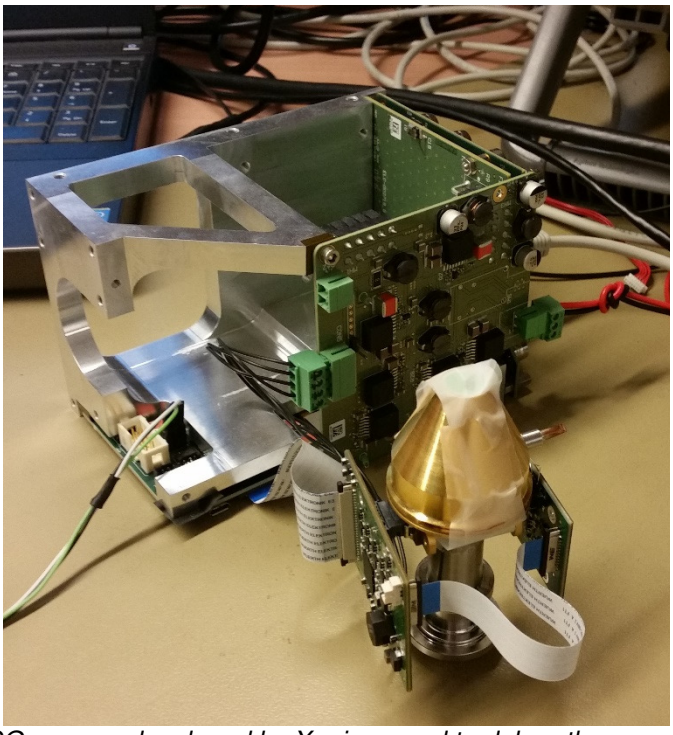

Figure 21: Photo of the XCO camera developed by Xenics, used to debug the proxy electronics with the mock-up IDCA without cooler.

Although not used in the final MINERVA demonstrator, the camera developments within MINERVA projects allowed Xenics to launch a new family of MWIR camera modules – XCO-640[1] – and high speed MWIR cameras – Tigris-640[2] – integrating different detectors. Moreover, the launch of Tigris-640-Thermography has been announced for Q1 2018.

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4) Software and analysis

Screening pathology-process development

This work was chiefly the result of the collaboration between University Of Exeter, Gloucestershire Hospitals NHS Foundation Trust and Universitat Politecnica De Valencia

Baseline studies

The first major MINERVA application is high volume pathology screening, led by Prof. Stone's team at the University of Exeter. By carefully analysing the mid-IR spectral information from microscope

[1] http://www.xenics.com/en/xco-640
[2] http://www.xenics.com/en/camera/tigris-640

images of patient samples, it is hoped that healthy tissue may be distinguished from diseased material by an automatic process. This analysis is a specialism of GHNT, whose main task was to provide supporting evidence for the MINERVA instrument specifications. This was achieved by analysing an existing dataset and applying pattern recognition techniques to discriminate between benign and cancerous samples from human colon tissue biopsies. Sensitivity and specificity of up 86-99% can be achieved with the existing dataset. Using this study as a baseline GHNT was able to assess the impact of various factors that will affect the quality and speed of the MINERVA instrument.

Multivariate pattern recognition algorithms
Reducing the number of data points per spectrum is one way to potentially speed up the system; measuring fewer wavenumbers means a faster total acquisition time. Multivariate pattern recognition algorithms were used to identify potential wavenumber targets for the MINERVA instrument. A further advance was the development of an optimised electronic de-paraffinisation process, which allows access to a wide range of existing samples. (Analyst **140**, p. 2369-2375 (Feb-2015).) A minimum acquisition time per spectrum means that the MINERVA instrument will be able to rapidly assess samples in a clinical timeframe. However, reducing acquisition time also increases the amount of noise. To determine what level of noise can be tolerated by the pattern recognition algorithms GHNT simulated the addition of noise to the baseline study until it was no longer able to discriminate between pathology groups. This allowed a minimum target SNR to be determined for the MINERVA instrument whilst maintaining an acceptable ability to discriminate between pathology types.

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Segmentation and registration of images
UPV, in close collaboration with the Exeter and GHNT, has applied different image processing techniques, such as segmentation and registration, to analyse histological samples of colorectal cancer. Based on these operations, the team worked towards the development of a fully automatic method to register different sections of tissue measured with two different microscopic modalities: H&E stained microscopic images and unstained FTIR micro-spectroscopy.

The group's main objectives in MINERVA were focused on segmentation and registration of different kinds of images: infrared spectral images (IR), white light, and those most used by clinicians at present, the haematoxylin and eosin stained images (H&E). The latter is the current "gold standard" used to distinguish between a healthy or pathological patient sample. The objective within MINERVA was to automatically segment regions of interest (healthy and pathological) in the H&E images and look for their features in the infrared spectrum. To achieve this goal the H&E image must be registered with the white light image (which is already registered with the infrared volume). So, the work is focused on two interactive steps: registration and segmentation.

Registration allows the matching of elements that clinicians considered important in the H&E images with the spectral images. A successful registration task would allow users to learn, and later identify, the areas from which diseased and healthy cells and patients can be distinguished. Segmentation concerns the accurate extraction of the cell contours. This would reduce the huge amount of data to be analysed looking for subtle biochemical changes ("cancer markers"). Once the contours have been identified, the regions must be classified as healthy or cancerous depending on subtle features including shape, texture and clustering. This is an extremely difficult task, but the use of the spectral information in the mid-IR should eventually aid clinicians to improve on the current gold standard.

This method, successfully applied to more than 100 different samples, allows the comparison of information obtained with the current gold standard in histopathology (H&E images) and with the promising analytical mid-IR micro-spectroscopy.

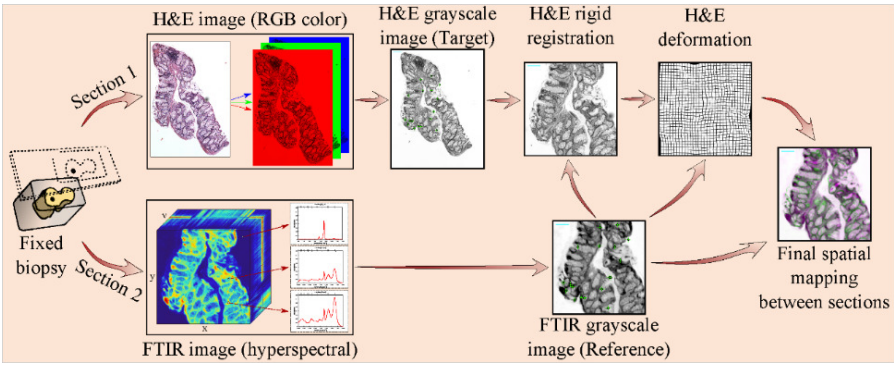

*Figure 22: Schematic showing the multimodal registration method developed by UPV. Further details can be found in: Peñaranda et al., "Multimodal registration of optical microscopic and infrared spectroscopic images from different tissue sections: An application to colon cancer", Digital Signal Processing, **68**, p. 1-15 (2017).*

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Developing a working protocol for large scale pathology screening

- Conventional FTIR spectral histopathology is used to diagnose cancerous tissues based on specific molecular/spectral fingerprints.
- Using extensive data classification algorithms, the most significant of these spectral frequencies are identified which are sufficient for diagnosis thereby reducing the amount of data required.
- A novel supercontinuum mid-IR light source; developed in MINERVA providing higher signal to noise, is tuned to the selected spectral frequencies for rapid diagnosis of cancer via discrete frequency imaging.

The main task in the final part of the project was to establish a working protocol for large scale pathology screening and diagnosis using mid-IR spectroscopy. Currently FTIR spectral histopathology, which combines IR spectroscopy and histopathology, the gold-standard for diagnosis, has the potential to be developed as a cancer diagnostic tool. However, some aspects of the current technology are limited, posing a challenge for the approach to be translated into a clinical set up, where precision, speed and cost effectiveness are significant factors. Current technology assembled in a benchtop system, employs a "Globar" light source and a focal plane array (FPA) detector which record an entire mid-IR spectrum (2-12 µm) in each pixel of a hyperspectral image. In order to deliver a diagnosis, all the frequencies of this spectrum need to be subjected to rigorous data mining algorithms that can require huge amount of processing time and data storage facilities. In addition, the light sources have a limited brightness limiting the use of high-resolution optics for detailed pathology screening.

To this end, an improved diagnostic workflow was established for large scale pathology screening and diagnosis to be able to adapt the novel mid-IR imaging technology being developed as part of MINERVA. To standardise the workflow, various tasks were carried out including substrate optimisation, sample preparation and instrumental parameters standardisation. A total of 100 formalin fixed paraffin embedded samples from four pathology groups (normal, adenomatous, hyperplastic and cancerous) were imaged in standard (5.5×5.5 μm^2 pixel resolution) and high-resolution (1.1×1.1 μm^2 pixel resolution) modalities using a benchtop set-up. The FTIR images were segmented into their constituent pathology groups based on the molecular information using several approaches (independent K-means clustering, common K-means clustering, digital pathology based image segmentation and registration). Classification algorithms were trained and validated independently on each of this approach to discriminate different pathologies.

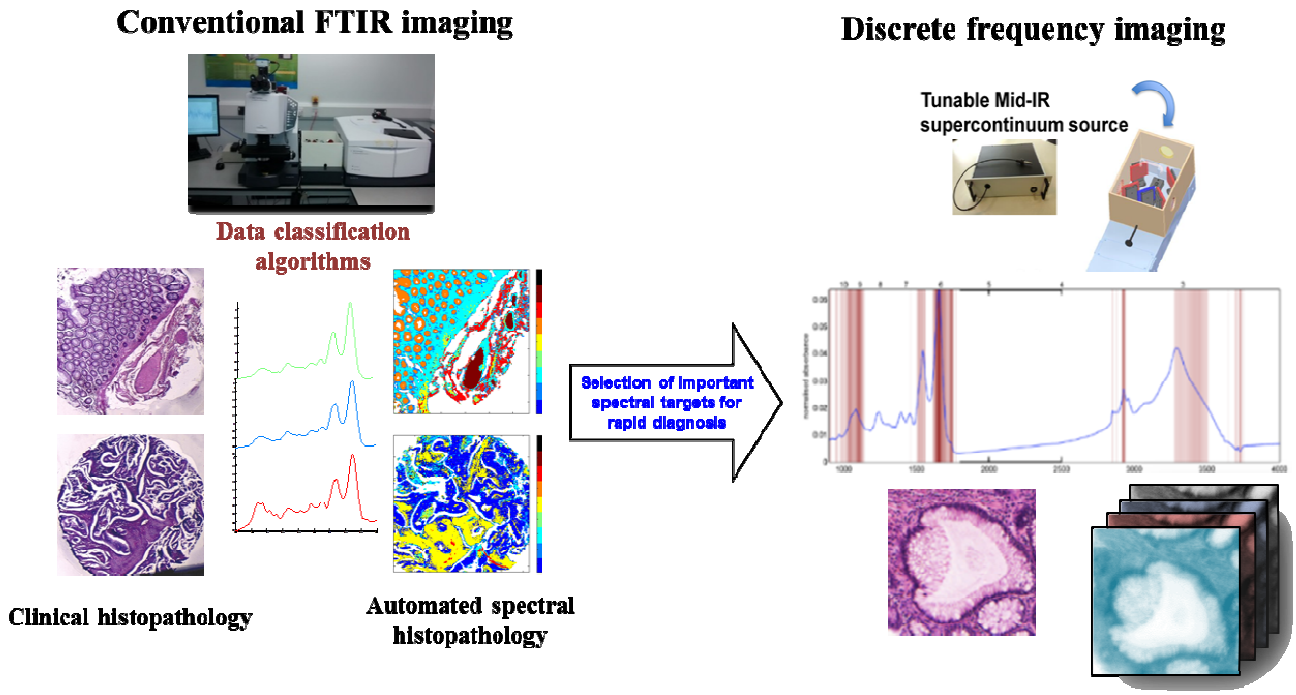

Figure 23: Schematic showing the process followed to simplify the algorithm and speed up the analysis of "data cubes". Conventional high resolution images were analysed to deduce the most important peaks for diagnosis. The rapidly tunable MINERVA source could then avoid many unnecessary wavelengths.

In order to establish a diagnostic work flow for the novel MINERVA technologies, key spectral signatures were identified, sufficient for delivering a diagnosis. This discrete frequency imaging work flow can be incorporated into the novel MINERVA technology using supercontinuum light source and megapixel detectors providing improved signal to noise, faster imaging capabilities, lesser data storage capacities for an overall rapid screening and diagnosis.

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Skin cancer identification-process development

Westfälische Wilhelms-Universität Münster (WWU)

The second major MINERVA application is to prototype a probe which will allow clinicians to non-invasively assess skin lesions for signs of cancer. This work is led by Prof. Schnekenburger at WWU Münster with UPV providing specialist input on image processing. Prof. Naranjo leads the image and signal processing group at UPV.

Through MINERVA the collaboration between WWU and UPV, with assistance from Exeter and GHNT, has led to some important results. WWU has developed standardised human skin equivalents (HSEs) which can be used to study skin lesions in a systematic way. These HSEs can include known numbers of cancer cells at specified depths, allowing for a highly versatile tool for study. Algorithms for identification and differentiation of tumour cells from normal skin cells were developed and characterized. Further single cell standards for extended systematic investigations of skin cancer cell identification by mid-IR spectroscopy were designed, prepared and documented. In addition scattering measurements were explored for depth selective mid-IR characterisation of HSEs.

Human skin equivalents

One project aim was the transfer of MINERVA technologies to skin cancer diagnostics including usage of mid-IR spectroscopy for fast screening of human body surfaces and identification of pathophysiologically altered cells and tissue lesions. This required cell and tissue standards for performance testing of novel optical components and systems, as well as for training of the subsequent advanced data analysis. Hence, the work of WWU in MINERVA focused on the establishment of standardized samples with spectral information of representative skin constituents as well as normal and tumorous skin cells. The complexity of the established samples increased as the technology progressed: from rather simple single-layered 2D samples with separated cell types, via 2D samples with mixed cells, to three-dimensional, collagen-embedded, separated cell layers, and finally to complex 3D human skin equivalents.

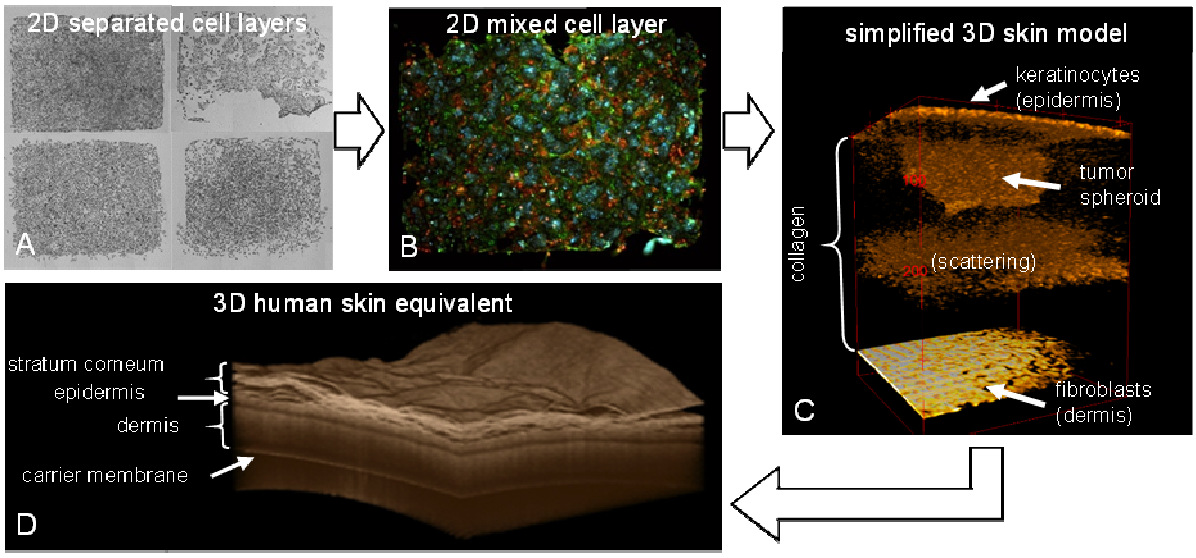

Figure 24: A) Bright-field image of a single-layered test standard with separated areas including different skin cell types on CaF_2 substrate. B) Fluorescence image of a mixture of fluorescence labelled cells grown in a single-layer on CaF_2 substrate. Cells of the same colour belong to the same skin cell/skin cancer cell type. C) Optical coherence tomography (OCT) 3D image of a tumour spheroid embedded in collagen with dermal fibroblasts at the sample bottom and epidermal keratinocytes at the top. D) OCT image of human skin equivalents with different layers including stratum corneum, epidermis and dermis.

Along with the design of the mid-IR test standards, procedures for sample preparation on mid-IR compatible substrates were developed and fluorescent markers were established to enable distinction of cells in mixed samples. During the development process, the structure of 3D samples was inspected in 2D by histology and in 3D by optical coherence tomography (OCT) in collaboration with the MINERVA partners at NKT. Moreover, the storage capabilities of the samples for long-term preservation of spectral properties was verified.

In order to identify suitable marker spectra of human skin, samples were analysed with mid-IR spectroscopy in collaboration with the partners GHNT and Exeter. The received spectral data were used as reference for technology performance testing and for the evaluation of novel algorithms for skin cancer cell recognition and classification developed by the MINERVA partner UPV.

➔ *For more information please contact: Juergen Schnekenburger schneke@uni-muenster.de*

Differentiation algorithms

UPV, with the help and supervision of Exeter and GHFT, was responsible for analysing hyperspectral FTIR images acquired from cell cultures of different types of skin cells including

melanoma, which were prepared by the University of Münster (WWU). This task required the application of different complex techniques, not only from the image processing field, but also from other analytical fields, such as multivariate analysis, machine learning and chemometrics. Special efforts were made to reduce unwanted variations in cell spectra not related with the cellular biochemistry that mislead the discrimination of malignant from benign skin cells. In particular, spectral pre-processing techniques based on the most advanced knowledge of the physicochemical phenomena involved in FTIR micro-spectroscopy were applied, which try to remove severe artefacts masked inside FTIR absorbance spectra, such as classical and resonant Mie scattering.

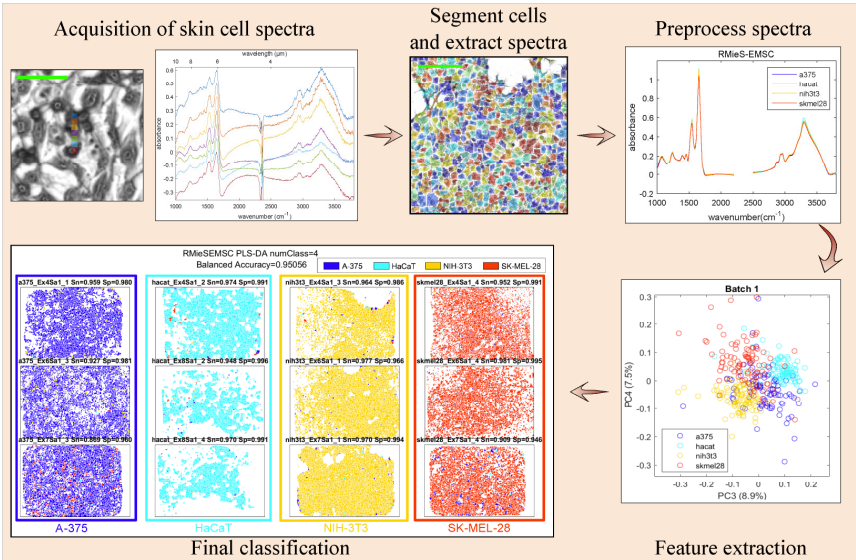

Figure 25: Illustration of the main tasks accomplished during the analysis of skin cell cultures. Further details can be found in: Peñaranda et al, "Multivariate classification of Fourier Transform Infrared hyperspectral images of skin cancer cells", EUSIPCO 2016, p. 1328-1332.

➔ *For more information please contact: Valery Naranjo vnaranjo@dcom.upv.es*

5) Demonstration

Led by Gooch and Housego (Torquay)

Fast hyper-spectral imaging

Typical measurements with state-of-the-art FTIR systems take several hours to build up spectral images with modest pixel counts. The aim in MINERVA was to reduce the time taken to collect data to a few seconds and at the same time to increase the spectral resolution and image pixel count.

The rapid cytological imaging system has been designed to operate over a wavelength range of 2-4.5 µm allowing for acquisition of 100 wavelength slices of 300k pixels each in only 2 s. While this wavelength region is of interest for diagnosing cancer and other medical conditions, far greater specificity can be obtained by extending the wavelength range into the fingerprint region (5.5-10 µm).

First demonstration of long-wavelength supercontinuum spectroscopic tissue imaging
Through the combined efforts of DTU, G&H, and University of Exeter, the MINERVA project achieved its objective of high resolution imaging using a supercontinuum-based system in the mid-IR. The team was able to demonstrate spectroscopic imaging of paraffinised colon tissue from 5.7-7.3 µm using the high-power mid-IR long wavelength supercontinuum source developed within MINERVA. In the MINERVA long-λ (4-7.5 µm) trials good images of cell samples were obtained. Cell nuclei could be well resolved and the image quality was comparable with those obtained by commercial FTIR instruments. These encouraging results highlight the viability of SCS-based imaging for mid-IR spectroscopic tissue differentiation.

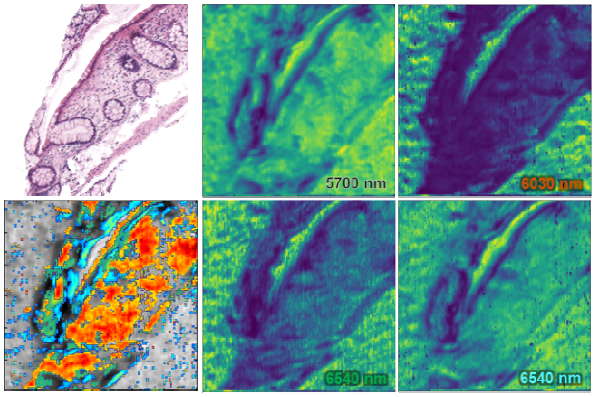

Figure 26: Top left) H&E stained image of the sample. Middle and right) Sample images at different mid-IR wavelengths. Bottom left) False coloured composite image showing main absorption features

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Potential impact

[There is much more information available from the project website (www.minerva-project.eu).]

Socio-economic impact and wider societal implications

MINERVA has developed an impressive array of hardware, software and expertise for use in the mid-IR. During the course of the project this region of the spectrum has grown in importance both from a scientific and increasingly from a commercial perspective. The socio-economic impact of this trend could have major consequences for society and commerce. Through contributing to the range and capabilities of mid-IR technology, MINERVA will assist in bringing some of these benefits to society at large. Some examples are briefly explored in the following section.

- *Materials processing:* Broadly speaking, 3 µm radiation may be used for the vast majority of material processing operations that may be carried out using traditional 1 µm radiation including CW, pulsed and short pulse regimes. The importance of eye-safe radiation in these high power industrial and commercial applications cannot be overstated. In addition, it offers certain other advantages over 1 µm radiation for several important materials. Many important transparent plastic materials, *e.g.* polyethylene and polyamides, do not significantly absorb radiation shorter than *c.* 1.7 µm. Consequently in order to machine or weld transparent plastic with 1 µm radiation, either absorptive pigments must be added, or absorbing intermediate layers are necessary, adding to cost and time. This is of particular importance for applications requiring FDA or CDRH approval for addition of each new substance to a process, *e.g.* medical device manufacturing, pharmaceuticals, food packaging *etc.*[3]. Using mid-IR lasers, *e.g.* the LISA 2.9 µm source, the emission wavelength may be tuned directly to the specific material absorption, to obtain optimal processing characteristics in a simpler process.

- *Environmental monitoring:* A large group of applications is based on the absorption of mid-IR radiation by certain substances. The 3-5 µm region is full of absorption bands for different substances with the common name "volatile organic compounds" (VOCs). In the 8-12 µm band there are also a number of substances which absorb IR radiation. One example of particular importance is sulphur hexafluoride (SF_6). This gas has absorption peak at 10.55 µm and is used in power engineering as a spark extinguisher, but it is 20,000 times more potent than carbon dioxide as a greenhouse gas. IRnova has products for detecting gases in both bands and MINERVA technology will improve these systems. Regions containing these gases may be clearly seen on the camera display. The principle of operation makes use of absorption-emission of the IR radiation by gas molecules for visualising leaks.

  Some of the Earth observation (from space) applications are also based on this principle. Others use the temperature difference of some regions compared with others. This includes not only gas emissions in urban and rural area, but also ice, vegetation, ocean currents *etc.* The wavelength range from 12-15 µm is of primary interest for these applications. IRnova has entered into development of a new project supported by ESA to develop T2SL detectors for these wavelengths, which is virtually a direct continuation of the development work performed within MINERVA.

- *Laser surgery:* Relatively low power (*c.* 100 W CW) commercial DPSSL devices at 2 µm exploiting the benefits for surgical cutting have been developed, such as the LISA Laser Revolix series. The LISA 2.9 µm source developed in MINERVA is also of great interest for surgical applications because its wavelength corresponds to a water absorption peak. The

[3] J. Neukum, "Innovation enriches high-power diode laser market" Optics and Laser Europe (October 2008).

strong absorption results in excellent haemostasis (*i.e.* prevention of bleeding) with minimal penetration; a strong vaporisation effect without risk of deep tissue damage. This would make such lasers ideal for a range of clinical applications including stapedotomy (an operation performed on the middle ear) and other delicate procedures. Further investigations at LISA are already underway.

- *Agriculture and food:* Recent advances, including those in MINERVA, in sources, detectors and components in the 2-12 µm region open the door to exploiting mid-IR spectroscopy for larger markets including agricultural applications. The potential for photonics in agriculture is well known, *e.g.* for detecting plant disease[4] [5] or identifying weeds[6] but extending the technology to the mid-IR opens an entirely new range of opportunities. The potential scope is huge: from microscopic examination at a cellular level (*e.g.* to measure photosynthetic activity), analysis of cuttings or samples or even whole individual plant or animal specimens (to identify early stages of disease or presence of pathogens) to measurement of areas of crops (*e.g.* spectroscopic analysis of the reflected sunlight for precision evaluations of fruit ripeness or irrigation requirements). In due course the broadband supercontinuum sources developed in MINERVA, with their unprecedented bandwidths (exceeding 2-12 µm) covering the whole fingerprint region of the spectrum, could be commercialised and combined with detection systems and machine learning algorithms. A range of new mid-IR spectroscopic integrated systems could be offered for precision agriculture.

- *Mid-IR cameras:* MINERVA included work in the so-called thermal infrared region (3-12 µm). A key benefit of using this wavelength range is its passive nature. No external sources of radiation are required; all objects emit radiation because of their temperature. There are two sub-bands within this range, 3-5 µm and 8-12 µm, which coincide with atmospheric transparent "windows." In addition, the peak of thermal emission at ambient temperature (~300 K) is around 9 µm. All this makes the mid-IR very useful for imaging. Aside from military applications, it is extremely useful for security and surveillance of large areas (harbours, airport runways, border regions *etc.*), where typical distances are of the order of several kilometres and where uncooled detectors perform rather poorly. Another important application is search and rescue, since a person in the open sea can be detected from a helicopter at distances of several kilometres.

  Until recently the field of thermal imaging has been restricted in industry and other civilian applications due to high cost and the physical footprint and weight of the camera systems. Applications mostly involved stationary cameras or those carried on large vehicles. Both these issues were addressed in MINERVA. IRnova focused on the development of more affordable detectors with smaller detector size or better resolution and better performance. Xenics is also using MINERVA technology to reduce the size and cost of its products.

  Smaller detector size matters since the camera requires smaller optics and hence has reduced size and weight. (Furthermore, the price of the optics increases dramatically with diameter.) Better performance includes conversion efficiency, which allows shorter integration time and thus higher frame rate, but also operating temperature. Higher operating temperature, achieved thanks to the development of T2SL technology in MINERVA, allows a reduction in the dimensions of the cooler, improves its service time and reduces battery drain (*i.e.* extends battery life). Together with higher sensitivity with good signal-to-noise

[4] Anne-Katrin Mahlein, "Plant Disease Detection by Imaging Sensors – Parallels and Specific Demands for Precision Agriculture and Plant Phenotyping," Plant Disease **100**, p. 241-251 (2016).

[5] A-K Mahlein *et al.*, „Hyperspectral imaging for small-scale analysis of symptoms caused by different sugar beet diseases," Plant Methods, **8**, p. 3 (2012).

[6] Longchamps *et al.*, "Discrimination of corn, grasses and dicot weeds by their UV-induced fluorescence spectral signature," Precision Agriculture, **11**, p. 181-197 (2010).

ratio, all these factors are already opening access to new applications, including hand-held devices. It is too early to give details, but IRnova has already shipped the first samples to customers.

Finally, it is noted that T2SL is expected to have a lower environmental footprint than existing technology, as it employs less hazardous materials. Also, yield is higher and device lifetime is expected to be longer. Altogether, the final impact should be noticeably lower than that of *e.g.* MCT technology. However, a full life cycle analysis of T2SL products and comparison with competing technologies is still to be performed.

- *Bio-medical mid-IR imaging:* MINERVA had two primary applications: high volume pathology screening and human skin surface examination. It has certainly shown that there is great potential for the former. The latter proved more difficult than expected due to the properties of skin and its interaction with the mid-IR. Attenuated total reflection (ATR) approaches have shown promise. This is a subject of ongoing research at WWU.

  However, it is clear that the mid-IR is playing an increasingly important role in diagnostics. Systems based on quantum cascade lasers (QCLs), *e.g.* the US-based Daylight Solutions Spero systems have shown excellent results. FTIR systems offer extremely high resolution images in the mid-IR which have been very useful in some of the MINERVA analysis and algorithm development. Diagnostics based on Raman spectroscopy in the mid-IR have continued to show impressive results throughout the duration of the MINERVA project. The team at Exeter has already used these techniques, *e.g.* to identify calcifications in breast tissue.

  The table below shows one view of the pros and cons for these and other real-time imaging technologies. The results from MINERVA suggest that with further work, European SCS-based systems could offer the same or better resolution images than the state-of-the-art, at lower cost and with much faster acquisition times.

Technology	**Objective**	**Speed**	**Cost**	**Reduce biopsies?**	**Info type**
MINERVA (*in vivo*)	++	++	TBC	+	Biochem./ biomolec.
MINERVA (*ex vivo*)	++	++	TBC	-	Biochem./ biomolec.
Digital chromoendoscopy	-	-	+/-		Structure
Fluorescence	-	+	+/-	+	Structure
Multimodal	-	+		+	Structure
Optical coherence tomography (OCT)	-	+	-	-	Structure
Biomarker targeted endoscopy (needs stain)	+	-	TBC	+	Specific molecular
Confocal (needs stain)	-	-	-	+	Structure
Elastic Scattering Reflectance	-	+/-	TBC	+	Structure
Raman	++	+/-	TBC	++	Biochem./ biomolec.

If you have any questions or require more information, please get in touch!

Main dissemination activities

MINERVA has had a very active programme of dissemination activity. More info can be found on the project website www.minerva-project.eu. These activities include:

- Almost one hundred papers and posters at sixty international conferences
- 37 peer-reviewed journal papers
- Eight newsletters
- Project presentation
- Project video
- Project workshop (30-Jun-2017)

Exploitation of results

MINERVA was a sophisticated and complex project with many different areas of expertise. In a nutshell it developed hardware and software for the mid-IR which culminated in the demonstration of the first ever supercontinuum-based mid-IR imaging system. In parallel it has developed clinical algorithms and understanding of how this new spectroscopic information might be used by clinicians to assist in the diagnosis of early cancer.

The hardware has already led to a number of new products and more are in the pipeline. Several important new relationships have been forged or strengthened through the project, and each of the individual partners has benefited in its own way, as outlined in the following summary.

Exploitation by industrial partners

1 G&H

MINERVA has been a positive project for G&H. Important relationships with collaborating companies and organisations have been formed or strengthened.

In the field of acousto-optics (a key technology for G&H) its close collaboration with other consortium members (especially NKT & LISA) has led to the development and launch of key AO products for the mid-IR region (2-4·5µm), including AO tunable filters and Q-Switches. New techniques, for example “resonant acoustic” were explored to maximise the potential of the available AO materials. In addition, AO media for the long wavelength IR (up to about 11 µm) were investigated and compared.

In the field of fibre-optics, another key technological area for G&H, critical mass of know-how established within the project led to the first demonstrations of mid-IR fibre fused components placing the G&H at the forefront of the technical development in the emerging market with significant potential for growth.

The design and development of the MINERVA systems has introduced a range of new skills into the company; skills that will be valuable as G&H seeks to increase its systems capabilities.

MINERVA has led to specific new products in the field of acousto-optics and fibre-optics:

- Ultra-narrow Resolution AO Tunable Filter (AOTF) – Developed specifically for the new generation mid-IR supercontinuum being developed by NKT, and meeting NKT’s desired

goal of as narrow band as is practicable. This was the AOTF deployed with the "MINERVA Lite" system, and the equivalent device has subsequently been sold to third-parties outside of the MINERVA project.

- Narrow Resolution AO Tunable Filter (AOTF) – Designed to be more user-friendly than the Ultra-Narrow resolution AOTF, which required a collimated diffraction-limited beam of 5 mm diameter to achieve its performance potential.
- Resonant AOTF – An AOTF with a resonant acoustic structure that effectively recycles the acoustic energy thus improving the AO conversion efficiency (*i.e.* lower drive power). This is particularly important when operating in the IR since the drive power is proportional to λ^2.
- AOTF Smart Driver – A new generation of RF drivers better able to capitalise on the flexibility and adaptability of an AOTF has been developed. In particular the mode of control and the implementation of a GUI was developed under MINERVA. The driver system is now being launched as a G&H product.
- Soft Glass Fibre End Caps – These components are used for protection of the soft glass fibre ends and reduction of facet reflection in high index fibres, increasing the fibre reliability and power handling capability. They are expected to accelerate the market acceptance of the mid-IR fibre fused components and facilitate further mid-IR fibre product development.
- Soft Glass Fibre Fused Couplers- Mid-IR fused couplers are expected to form a backbone of mid-IR optical signal delivery and manipulation allowing for cost-effective and compact mid-IR instrumentation.
- A scientist/engineer working full-time on the development of the MINERVA systems will continue at G&H in a permanent position after the completion of the project.

2 NKT

MIINERVA has been a very positive project for NKT. The development of the 2-5.5 µm supercontinuum sources which NKT was responsible for has allowed NKT to go from basic proof of principle mid-IR systems at the beginning of the project to the launch of the most advanced and reliable mid-IR supercontinuum system on the market at the end of the project.

The 2-5.5 µm SCS which has been developed will allow NKT to enter a completely new market which has previously been starved of high brightness light sources and where the arrival of mid-IR SCSs can herald a revolution in new applications. The advances created in MINERVA not only allows NKT to become one of the market leaders in this new field but has also served as a spearhead for the entire field as NKT has set new records for the power levels and wavelengths accessible by this type of source. Even more important in a field where poor reliability was the norm and few manufacturers could show proven source run-times of more than a few hours NKT has been able to prove the true potential of the technology by demonstrating that with proper engineering systems can run 24-7 for years and thus be applied not only in scientific experiments but also in general industrial process monitoring or medical diagnostic systems.

The main technical advances with commercial potential that has resulted from the MINERVA project are:

- A low power low repetition rate, more compact and lower cost but higher noise SCS source: This was developed early in the project and used for test and development. This design will remain as a possible option to be adopted for suitable OEM applications which can live its drawbacks in return for smaller cost and size.
- A high power, high repetition rate, low noise mid-IR SCS. The development of improved prototypes in the MINERVA project were subsequently further developed into the newly launched mid-IR SCS product from NKT.

- Mid-IR SCS filtered with AOTF: The collaboration between NKT and G&H has demonstrated that a mid-IR SCSs can be filtered using an AOTF to produce a very flexible and compact tuneable light source in the mid-IR. Both the mid-IR SCS and the mid-IR AOTF will continue to be commercially available after the end of the project.
- The developments started in MINERVA will continue in ongoing development projects (*e.g.* FLAIR and MidTech in H2020) further developing the mid-IR SCS as well as manufacturing the current version of the system.

3 LISA

The MINERVA project pushed LISA's interest and capabilities in mid-IR lasers significantly forward. At the beginning of the project LISA had experience and knowledge about bulk crystals emitting in the 3 µm wavelength range. These lasers were based on flashlamp pumped Er-doped garnet crystals. Within MINERVA LISA learned about Er-doped ZBLAN fibre lasers and started to work with this novel technology. The results achieved within MINERVA led to the demonstration of the world's most powerful Er-doped ZBLAN fibre laser regarding both pulse energy and pulse peak power. These results were achieved with the novel TeO_2 Q-switch developed by G&H.

This 2.9 µm laser is being developed as a stand-alone product for surgical applications.

4 BBT

MINERVA has been an extremely important and highly beneficial project for BBT. During the project BBT has established relationships with a key laser manufacture (LISA) and several important players in optics and acousto-optics (G&H *etc.*). In addition to direct (planned) results, *i.e.* large calomel single crystal boules and AOTF substrates, there are also several follow-up and/or related results that are very promising and a route to new projects and opportunities has opened.

First, BBT plans to focus its commercialization efforts to infrared polarization optics *e.g.* IR polarisers, waveplates, scramblers, substrates for FTIR spectrometers, laser isolators *etc.* After completion of the development phase this will be extended to AOTF products *e.g.* for hyperspectral IR cameras.

Achieved results:

- Calomel single crystal boules of diameter up to 35 mm
- Oriented and polished calomel single crystal cuts made of the calomel crystal boules: sections, plates, prisms, substrates, AOTF blanks *etc.*). BBT is currently preparing the necessary measures for introducing some of them as standard products.
- Publication of the paper (Optics Express **23**, p. 21509 (2015); impact factor 3.488) has boosted the company's visibility and reputation.

5 XENICS

Thanks to MINERVA Xenics has consolidated its position in the market for MWIR cameras. The most important results from the project can be summarized as follows:

- Xenics has enlarged its portfolio with a 1.3 Megapixel ROIC on 12 µm pitch:
    - The pixel topology is characterized by high injection efficiency at low input photocurrent
    - It is capable of running up to 200 fps
- Xenics has launched a family of new camera modules – XCO-640 – based on hardware and firmware design developed within the project, but integrating different detectors
- Xenics is developing the next generation of cooled MWIR cameras including thermography based on the XCO-640
    - Release is expected by Q1 2018.

6 IRNOVA

MINERVA has been a major success for IRnova. During the course of the project, the company has achieved a number of valuable benefits for its technological development and strengthening its position in the market. They can be summarized as follows:

- IRnova has received a powerful boost in the development of T2SL technology:
    - Several designs of the photosensitive epi-layer have been tested
- Extensive experience in design of IDCA and the integration process has been acquired at IRnova which is now used in current products and will be used in future product development.
- IRnova has launched a new product based on T2SL technology (IRnova640MW) which employs an FPA with 640×512 pixels on 15 µm pitch.
- The hybridisation technique and the packaging solution developed for IRnova640MW allowed IRnova to launch another product, IRnova640LW. (NB This product is based on QWIP technology rather than T2SL).

Exploitation by academic partners

7 NOTT

Ongoing research

MINERVA has fundamentally changed the reputation of the University of Nottingham on the world scene. Nottingham has published game-changing papers on ultra-low loss chalcogenide-glass fibres, rare earth doped small core chalcogenide glass fibres with long photo-luminescent lifetimes and also fibres capable of very broadband supercontinuum generation in the mid-IR to cover the molecular ‘fingerprint’ region for new types of molecular sensing with potential in early cancer diagnosis.

Seddon, the MINERVA PI, has received many invitations for invited talks and also offers of ongoing collaborations worldwide. Since the end of the MINERVA project Nottingham has won ongoing funding from the UK Engineering and Physical Research Council, Innovate UK, for an extruder-build and Nottingham. Nottingham has also awarded an Honorary Professorship to a Senior member of the Gooch and Housego team, collaborators in MINERVA, in order to consolidate this fruitful relationship. The equipment improvement and expertise and knowledge gained during MINERVA is helping to attract all of these assets to Nottingham.

8 DTU

MINERVA has had a significant impact on the supercontinuum research activities at DTU Fotonik, which has resulted in a number of record publications including the first demonstration of mid-IR cascading above 5 µm[7], record long-wavelength average power from a fibre[8], and record bandwidth from a fibre, which was published in Nature Photonics[9]. These results have drawn the attention of many within the photonics community, which has resulted in a number of invited talks (CLEO, Photonics West) and research collaborations outside of MINERVA. All of this has helped put DTU in the absolute lead of long wavelength supercontinuum development, and it will continue to advance the field of long wavelength sources in collaboration with its research partners. It is important to emphasize the critical role of the MINERVA partners in the success of our research, namely NOTT for providing high quality fibres, NKT for providing high quality pump systems, and G&H for enabling the first demonstration of tissue imaging using long wavelength supercontinuum.

10 WWU

The Biomedical Technology Center of the University Hospital Münster (WWU) is a specialised unit for the targeted development of biomedical samples for technology development and for the development and testing of prototypes for medical diagnostics. It holds a variety of specialised equipment for label-free optical cell and tissue analysis including modular optical technologies as digital holographic microscopy and holographic tomography; an optical cell stretcher, optical coherence tomography, infrared spectroscopy and flow cytometry. The technologies of the Center are offered within the Medical Faculty Münster but also as a commercial service to researchers and companies from outside.

The Center's own optical technology development has a focus on digital holographic imaging, which is combined with other label-free optical technologies such as flow cytometry or mid-IR. It has developed a variety of biomedical applications including digital pathology, cytotoxicity screening, drug development and fast blood analysis for disease screening. These applications will be protected by WWU patents and will be commercialised in a spin-out from the Biomedical Technology Center. The Center has also set-up its own software platform for device control and image analysis. WWU has developed prototypes close to market, which are now presented to major companies for marketing.

WWU includes the development of standardised cell and tissue samples and mid-IR spectroscopy in various research projects and students education. A national project developing a combined digital holographic imaging, mid-IR and flow cytometry device for the detection of micro-plastic particles in water is based on the MINERVA mid-IR experience. This project will continue for the next two years and foster WWU's mid-IR research. The projects instruments include a supercontinuum laser source from the MINERVA partner NKT. WWU will therefore continue the research and application of MINERVA components. Moreover, WWU is also partner of the new H20220 project GALAHAD, which assembles experienced partners from MINERVA for another optical research topic, optical coherence tomography (OCT). WWU will contribute the experience in biological sample standardisation and data generation from biomedical cells and tissues to GALAHAD.

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[7] C. R. Petersen, P. M. Moselund, C. Petersen, U. Møller, and O. Bang, "Spectral-temporal composition matters when cascading supercontinua into the mid-infrared," Opt. Express **24**, p. 749 (2016).

[8] C. R. Petersen, R. D. Engelsholm, C. Markos, L. Brilland, C. Caillaud, J. Trolès, and O. Bang, "Increased mid-infrared supercontinuum bandwidth and average power by tapering large-mode-area chalcogenide photonic crystal fibers," Opt. Express **25**, p. 15336 (2017).

[9] C. R. Petersen, U. Møller, I. Kubat, B. Zhou, S. Dupont, J. Ramsay, T. Benson, S. Sujecki, N. Abdel-Moneim, Z. Tang, D. Furniss, A. Seddon, and O. Bang, "Mid-infrared supercontinuum covering the 1.4–13.3 µm molecular fingerprint region using ultra-high NA chalcogenide step-index fibre," Nat. Photonics **8**, p. 830-834 (2014).

Within the WWU Biomedical Technology Center's new department for label-free optical imaging of cells and tissues, it will offer its optical technology range to research partners from the University Hospital Münster and associated research institutions. The partners will bring in a broad variety of medical and research applications for mid-IR spectroscopy of cells and tissues and for combined imaging using mid-IR and other label-free optical technologies. The Center's own research interest is the combination of mid-IR spectroscopy and OCT since this would allow the identification of a cell or tissue structure by a specific chemical composition using mid-IR and the localization and depth imaging of the structure by OCT.

The WWU Biomedical Technology Center has a strong funding by direct industry collaborations. It provides specifically targeted biological tests to new devices or biomedical models from cells to animal testing for preclinical drug development. Within these business activities it will include the MINERVA experience in cell and tissue standardisation and skin sample testing in its assay portfolio. Future industry contracts or national or European funded projects may use this technology.

11 EXETER

The MINERVA project has fundamentally improved Exeter's internal know-how. The journal and conference papers have enhanced the reputation of the group and significantly expanded knowledge in the field. The high magnification tissue measurements (with Globar sources) have broken new ground. The demonstration of electronic de-paraffinisation using this high magnification data is a useful technique which can be applied in other areas. The improved sample handling and spectroscopic imaging protocols will be useful in ongoing research. Furthermore the methodologies to optimise pathology training and validation of machine learning classification models, including IR image analysis steps and segmentation and registration of H&E images, will be extremely valuable for future work.

Exeter's standing in the field has been enhanced, including a Marie Curie grant in this area. Several new proposals have been made based on this reputation and background. The group now has greater capability and has taken on more Ph.D.s in this area looking at using the IR for diagnostics in the oesophagus and breast cancer.

12 GNHT

The software and algorithms developed as part of the MINERVA project and other ongoing research mean that there is the potential for a software package that can be used alongside innovations by other groups (such as spectrometers, probes *etc.*). All of the software and algorithms developed by GHNT for MINERVA will enhance future research and raise its research profile. GHNT has expanded its expertise in the use of High Performance Computing (HPC) and the handling of large datasets. As a MINERVA partner GHNT has been included as authors on a number of journal articles and had the opportunity to present at international conferences that otherwise would not have been possible. GHNT developed strong collaborations with other MINERVA partners for ongoing research and strengthened internal links with clinicians and researchers. Furthermore, participation in MINERVA also strengthened GHNT's inclusion in another EU funded project (GALAHAD).

Many funding bodies now require open access as much as possible. GHNT is considering ways to allow open access to its databases of spectroscopic images by other research group (*e.g.* using the Zenodo platform). This will aid further research in general but will also allow GHNT to assess interest in the field and seek out potential collaborators for future research. Open access will also raise the profile of the trust by generating citations for its research.

13 UPVLC

UPVLC is among the universities with the highest capability of technological transfer in Spain. The Service of Promotion and Support to Research, Innovation and Transfer (I2T) together with the institute IDEAS-UPV are in charge of advising on the creation of spin-off enterprises at UPVLC. IDEAS-UPV is the facilitator and manager of any entrepreneurship born at UPV. The mission of IDEAS-UPV is to promote and develop the entrepreneurial culture, stimulate and raise awareness in the university community of the creation and support of innovative enterprises in the Community of Valencia. IDEAS-UPV is also responsible for informing and advising the university community about the process of creating companies at UPVLC within the framework of the "Regulation on Enterprises Creation from the Activity of University Research at Polytechnic University of Valencia".

The image and signal analysis techniques developed in MINERVA can be adapted to other technologies more used nowadays in pathological diagnosis. Therefore, the future commercialization and spin-off potential is promising.

The MINERVA project has given rise to several master theses and the Ph.D. thesis entitled "Application of artificial vision algorithms to images of microscopy and spectroscopy for the improvement of cancer diagnosis" by Francisco Peñaranda, which will be defended in the months soon after project completion. To date UPVLC members have published (as first author) one journal paper, one book chapter and have attended four international and one national congress in support of the MINERVA project. The project has also promoted the mobility of researchers between universities. In particular, one researcher from UPVLC visited the University of Exeter for three months.

Thanks to the research knowledge acquired in MINERVA, several courses of UPVLC's degrees related with biomedical engineering and taught by Prof. Naranjo have included new techniques, capabilities and practical examples developed within the project.

The MINERVA project has fostered the introduction of UPVLC's researchers in the medical field of pathological diagnosis, which presents a high potential for technical development. The techniques and algorithms developed within MINERVA for supporting histopathological diagnosis are being adapted successfully in other related projects and collaborations. In particular, Prof. Naranjo coordinates a national project in collaboration with Universidad de Granada and Hospital Clinico de Valencia, which started in 2016 and will end in 2019. In that project, a total of fifteen researchers are trying to develop new algorithms to analyse histopathological images with the aim of improving the diagnosis of prostate cancer. This application is more aligned with the current diagnosis technologies and the future potential for exploiting the adapted results from MINERVA is very promising.

In addition, thanks to the MINERVA Project; UPVLC is now collaborating with some partners from MINERVA in another European project within the Horizon 2020 Programme. In the GALAHAD project, UPVLC is fusing the background learnt in MINERVA with its previous experience in developing algorithms to improve the diagnosis of eye diseases.

Finally, the exploitable results of the project have been registered in the UPVLC platform "CARTA" which records the capabilities, software results and patents of UPVLC and aims to publicise them to potential clients and investors.