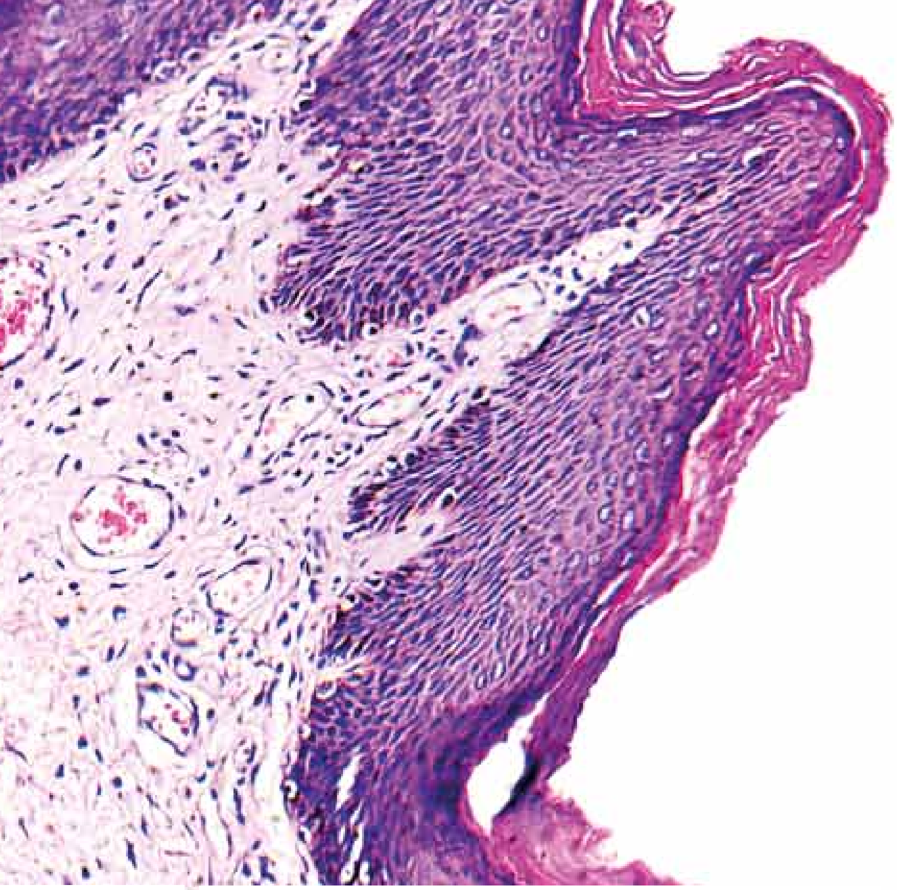

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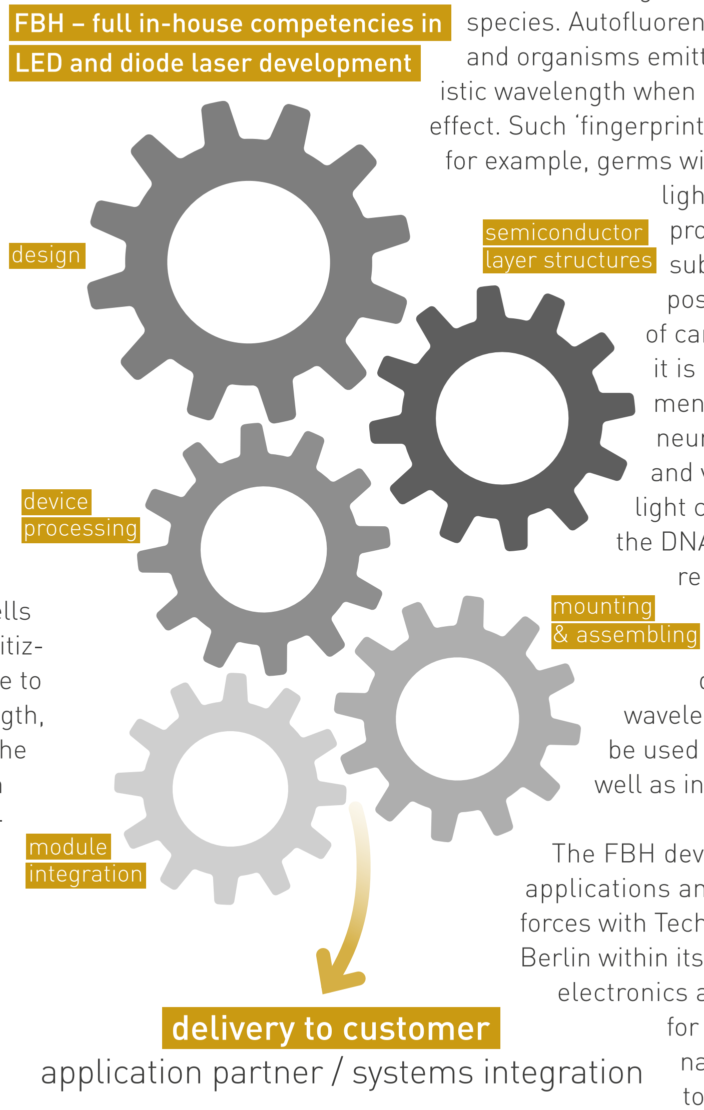
Photonics for Medicine & Life Sciences

- tailored semiconductor light sources – diode lasers & UV LEDs
- handheld probe – bringing Raman spectroscopy out of the lab
- looking into the hearts of living cells
- therapy with targeted light

Best choice – semiconductor light sources for medical therapy and life sciences

Light has a great effect on the physical and mental health of living creatures since it controls important biological processes – from metabolism, appetite, and wellbeing to the hibernation of animals. Accordingly, light is used in many ways for medical therapy and in life sciences. Such applications usually require light with well-defined properties, which is ideally provided by semiconductor light sources. They are not only robust and small-sized, but their emission wavelengths and radiation characteristics can be tuned by the design of the semiconductor layer structure. The Ferdinand-Braun-Institut is involved in various activities targeting to improve as well as to open up novel applications for diode laser and LED technology.



Diode lasers – non-invasive examination, treatment, and diagnostics

The FBH develops and realizes diode lasers in a great variety of designs and packages. FBH lasers are used, for example, in photodynamic therapy (PDT). Here, cancer cells are enriched with a photosensitizing agent activated by exposure to light of a very specific wavelength, which is therefore crucial for the success of the treatment. With this approach, a targeted non-invasive or minimally invasive manipulation is possible. Diode lasers are key devices not only for treatment but also in diagnostics. This includes measurements based on Raman spectroscopy where the weak Raman lines are often obscured by fluorescence and ambient light. The FBH has developed particularly capable two-wavelength diode lasers enabling shifted excitation Raman difference measurements (SERDS). SERDS allows to separate the Raman lines from perturbing light, thus leading to an even greater sensitivity. Wavelength-stabilized, tunable, and dual-wavelength lasers are also well applicable for the measurement of molecular absorption lines in the atmosphere, e.g., to quantify water vapor concentrations and for high-resolution spectroscopy. Since diode lasers are very compact and reliable they open up mobile applications, enabling in situ measurements that deliver instant results without detour via the laboratory. This makes them a highly attractive option for replacing bulky solid-state and gas lasers in many application fields.

UV LEDs – widely applicable, from disinfection and germ detection to plant growth

Exposure to ultraviolet (UV) light causes multifaceted reactions on organic substances and living species. Autofluorenscence, i.e. substances and organisms emitting light of a characteristic wavelength when excited by UV light is one effect. Such 'fingerprints' can be used to detect, for example, germs with high sensitivity. UV light also triggers plants to produce health-promoting substances that are supposed to reduce the risk of cancer. In phototherapy it is used to treat impairments of the skin such as neurodermatitis, psoriasis, and vitiligo. Moreover, UV-C light can irreparably damage the DNA and thus suppress the reproduction of microorganisms when applied in sufficiently large doses and with the right wavelength. This feature may be used in water disinfection as well as in food production.

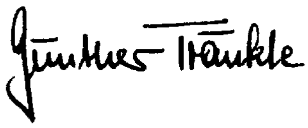
The FBH develops UV LEDs for such applications and additionally joined forces with Technische Universität (TU) Berlin within its Joint Lab GaN Optoelectronics and within 'Advanced UV for Life', an interdisciplinary consortium aiming to open up new markets and expanding existing ones for UV LED technology. LEDs score with freely adjustable wavelengths, low heat radiation, and the option to switch and dim the intensity. Even short pulses down to few ten nanoseconds are possible. Due to their small dimensions, FBH's LEDs can be integrated into radiation modules with a great variety of shapes and designs – several functional models have already been successfully realized by the Prototype Engineering Lab at the institute. These units can be operated at low DC voltage, making it even possible to use batteries or solar cells.

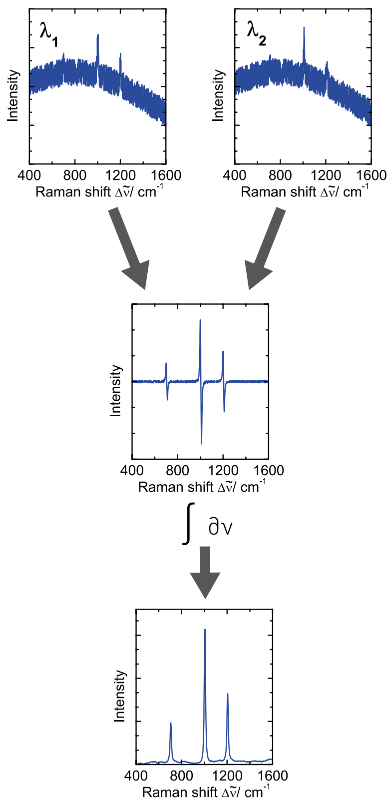
Editorial

Medical technology and life sciences have developed into the photonics market with the highest turnover for manufacturers of optical components and systems worldwide. According to the latest survey of the branch association SPECTARIS, 17 % of the global market revenues are generated by optical medical technology, which is therefore one of the centerpieces of German photonics. Our research project situation and increasing requests from industry in this field confirm this positive trend. Activities within the Zwanzig20 consortium 'Advanced UV for Life', managed by the FBH and funded by the German Ministry of Education and Technology with up to 45 million Euros until 2019, additionally underline the relevance.

In our current frequent issue we have compiled a selection of current developments utilized in optical medical technology and life sciences. I wish you an inspiring reading!

Yours sincerely,
Günther Tränkle





SERDS – how to separate Raman signals from disturbing background interferences

Shifted excitation Raman difference spectroscopy (SERDS) is a powerful and easy-to-use spectroscopic technique to separate wanted Raman signals from unwanted disturbing background signals such as fluorescence or ambient light. To achieve this, an excitation light source with two individually controllable emission lines with slightly shifted wavelengths at λ_1 and λ_2 is necessary. Their spectral distance should be selected close to the spectral width of the Raman signals under study – about 10 cm^{-1} for solids and liquids.

Samples are then successively excited with both laser lines. This way, the Raman signals are shifted by the amount of the spectral distance between both emission lines, whereas the background signals remain unchanged. After the measurement, the two measured Raman spectra are subtracted and generate a SERDS spectrum, thus clearly separating Raman signals from background interference. Such SERDS spectrum is similar to a derivative-like signal, subsequent integration leads to a Raman spectrum in a conventional form.

Making R&D results utilizable – prototype engineering at FBH, enabling

- rapid transfer into market-oriented products, processes, and services
- demonstrators for customized applications:
  - integration of research modules and components in portable stand-alone devices
  - miniaturization of laboratory set-up into easy-to-use models
  - practical prototypes integrating power supply, sensors, control unit, and laboratory electronics

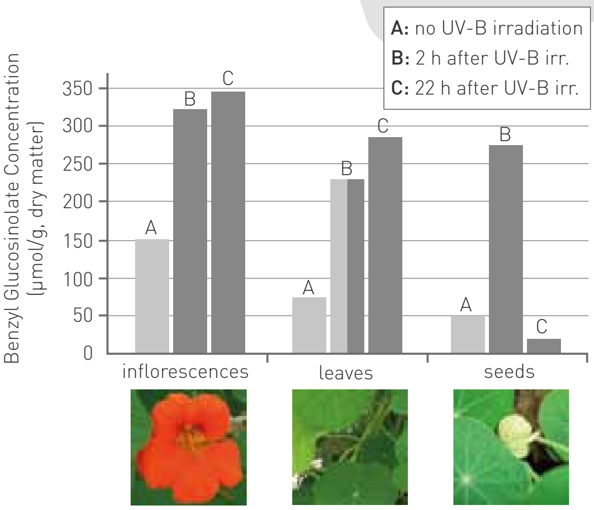
www.fbh-berlin.com/prototype-engineering

A perfect match – tailored UV LEDs for health and nutrition

They are small and robust, and their emission wavelength can be easily adjusted to achieve the maximum effect. Additionally, they offer low heat development, thus preventing undesired effects from heat load – on the used equipment as well as the target to be analyzed or treated. This makes UV light-emitting diodes (LEDs) optimally suited for a wide range of medical and biological applications involving sensing, treating, and disinfection. The FBH has been comprehensively exploring and developing UV LEDs for many years, from the material to easy-to-use radiation modules.

UV-A LEDs to deliver faster germ detection results

Microbiological contaminations in sensitive areas such as production lines in pharmaceutical and food industries are an imminent danger. Germany alone counts about 200,000 cases of food poisoning every year. Moreover, thousands of tons of food have to be destroyed annually due to contamination. Current test procedures for microbiological contamination only provide reliable results after hours or even days, whereas methods using autofluorescence could deliver prompt results. This technique is explored within the interdisciplinary 'Advanced UV for Life' consortium: by Silicann Systems and the Hans Knöll Institute using application-specific LEDs emitting at 340 nm developed by the FBH.



Effect of short-term UV-B irradiation (dose 0.27 kJ) on benzyl glucosinolate concentration in different organs of Tropaeolum majus. Different colors mark relevant statistical differences within the respective organ, identical colors indicate statistical irrelevance.

UV-B LEDs to trigger health-promoting substances in plants

A high consumption of fruits, vegetables, and herbs is known to lower the risk of both cancer and heart diseases due to the protective effect of certain substances provided by plants – secondary plant metabolites. UV-B radiation can affect the concentration and composition of these desired substances produced in plants. FBH has designed and fabricated a radiation module using its recently developed UV LEDs emitting at a wavelength of 307 nm. This unit is being used by IGZ – Leibniz Institute of Vegetable and Ornamental Crops to study the impact of the UV-B wavelength on crops like broccoli, kale, and nasturtium.

UV-C LEDs to disinfect water

The load of microorganisms in water can be reduced by UV-light irradiation in the wavelength range of 260 – 280 nm. As a result, chemicals like chlorine and bleach are dispensable. Current UV-C LEDs are a proper choice for applications requiring small amounts of liquids to be disinfected. The carrier fluid in a flow cytometric cell sorter, for example, has to be kept germ-free for a long time and must not heat up during sterilization. FBH has successfully implemented a compact UV-LED module emitting at 280 nm at Deutsches Rheuma-Forschungszentrum, thus extending service intervals.

Next steps to improve UV-LED performance

FBH currently focuses on the development of UV LEDs emitting around 310 nm and 265 nm, respectively. Their typical output power of about 1 mW when driven at 20 mA serves the needs of the applications described. However, future applications like the disinfection of large amounts of drinking water require power and efficiency numbers which are at least one order of magnitude higher than the current values. Degradation rates of the UV LEDs also need to be reduced to allow for stable operation over 100,000 hours. The FBH is thus addressing technological improvements on all levels of LED chip development, involving defect reduction by patterned substrates as well as enhanced light extraction with optimized designs.

Module for plant lighting – UV light-emitting diodes stimulate health-promoting secondary metabolites in plants

Bringing SERDS out of the lab – compact handheld probe for real-world Raman investigations

Raman spectroscopy is a powerful and established tool to analyze organic and inorganic materials and substances. To accomplish on-site measurements thus delivering prompt results, portable Raman sensors for in situ analysis became increasingly important in recent years. Mobile devices open up application fields such as point-of-care diagnostics, food inspection, and detection of harmful substances. Due to their small dimensions and low power consumption, wavelength-stabilized diode lasers are ideally suited as excitation light sources to realize compact and robust sensors.

However, outdoor applications bring along additional challenges. Fluorescence originating from, e.g., biological samples and ambient light could mask the weak Raman signals and hence complicate identification, especially for unknown substances. Shifted excitation Raman difference spectroscopy (SERDS) is a capable and easy-to-use spectroscopic technique to overcome these drawbacks. This way, Raman signals can be clearly separated from disturbing background interference. For SERDS, an excitation light source with two individually controllable emission lines is necessary. The FBH has already demonstrated suitable monolithic dual-wavelength diode lasers emitting at 785 nm and 671 nm, respectively.

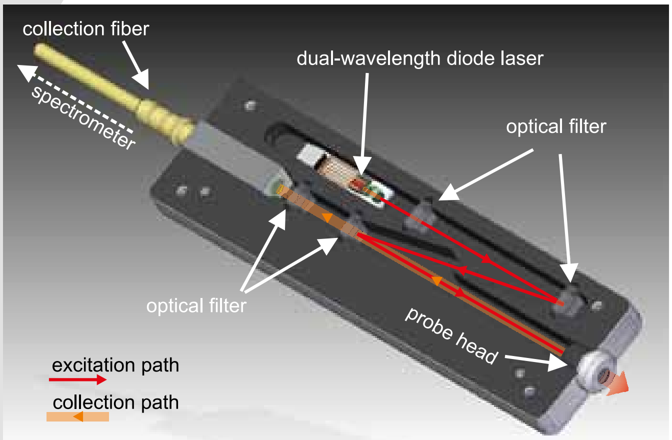
Handheld SERDS probe

Now, the FBH implemented such a 785 nm diode laser into an in-house developed handheld probe. Inside, micro-optics and optical filters are used to direct the laser light and the Raman photons in a 180°-backscattering geometry. An integrated optical fiber finally transfers the Raman signals to a spectrometer for analysis. The light-weight probe is milled from aluminum with dimensions as small as 120 mm x 28 mm x 12 mm, comparable to a highlighter. Experimental results demonstrate the suitability of the handheld probe for Raman spectroscopy and enable outdoor SERDS investigations for real-world applications. First measurements with the handheld device have just been successfully conducted in an on-site agricultural field testing; the results are currently being assessed.

Technical key figures and test results

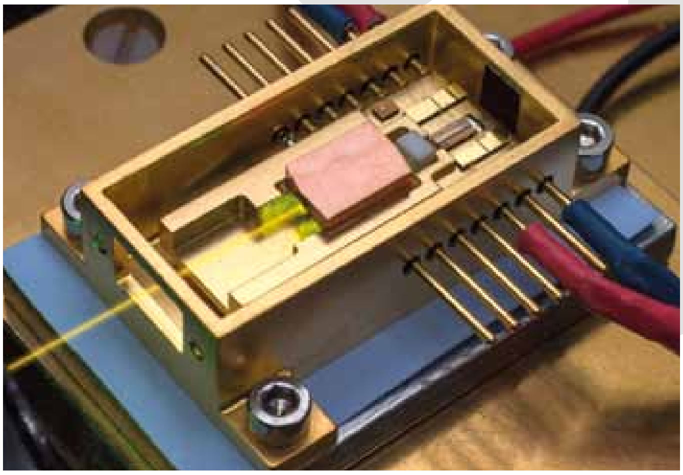
The diode laser provides an excitation power up to 120 mW at sample with a total power consumption of less than 0.6 W. Two separate controllable emission lines show a spectral width ≤ 11 pm (≤ 0.2 cm^{-1}) and a spectral distance of 0.62 nm (10 cm^{-1}), which is well suited for SERDS. Raman experiments were carried out using the SERDS probe and polystyrene (PS) as test sample. For these experiments, the excitation power was set to 50 mW, and a single Raman spectrum was measured with 0.2 s integration time.

The strong Raman line at 999 cm^{-1} shows a net intensity of 14,500 counts with a signal-to-background noise of S/σ_B = 580 and a signal-to-noise ratio of SNR = 115, close to the shot noise limit. Beside this, stability tests were performed using 365 successively measured Raman spectra of PS with 0.2 s exposure time and a step size of 10 s. Here, a stable center position of the Raman line at 999 cm^{-1} within a spectral window of 0.1 cm^{-1} was achieved, and the Raman intensity showed a peak-to-peak variation less than ± 2 %. A quartz glass window protects the inner parts of the SERDS probe from a sample, and Raman signals from the quartz glass show only minor interferences.



Handheld probe with dual-wavelength diode laser for in situ SERDS measurements

Looking into the hearts of living cells



Compact yellow-emitting diode laser module for novel medical and biological sensing applications

For a long time, optical spectroscopy was restricted to watching living cells only from the outside. However, by 'labeling' selected proteins with special self-fluorescent molecules or fluorophores, their paths can be tracked within the cell itself. Individual proteins and their interaction can now be observed with techniques like Fluorescence Lifetime Microscopy (FLIM) and Fluorescence Lifetime Correlation Spectroscopy (FLCS). The new observation capabilities open up prospects in drug development, e.g., for cancer treatment by blocking selected chemical reaction of proteins.

Light sources emitting in the visible yellow and red spectral range are particularly interesting in this regard as fluorophores here are more stable. Unlabeled cells also show less autofluorescence compared to the blue spectral region. Excitation of different fluorophores in the yellow region requires different narrow-band lasers – for example a 560 nm laser exciting Atto565 or mCherry, whose emission can be distinguished from other fluorophores like Atto532 and mOrange stimulated with a 532 nm laser. This way, the different fluorescence and fluorescence decay reveal the mechanisms inside of living cells.

The FBH is currently developing diode laser sources at 560 nm suitable for such spectroscopy applications. Unlike commercial low-cost 532 nm laser sources, 560 nm sources are still under research. Activities at FBH focus on second harmonic generation (SHG) of high-power laser diodes emitting near 1120 nm as direct semiconductor lasers at 560 nm are not readily available to date. These infrared-emitting laser diodes are specially designed to operate in short-pulse mode below 200 ps to observe fluorescence decay times with repetition rates up to 40 MHz. This fast pulse operation combined with output powers up to the watt range and nearly diffraction-limited beams allows an efficient SHG to 560 nm in small-sized modules. 100 mW laser radiation has already been demonstrated with them in continuous-wave (cw) operation.

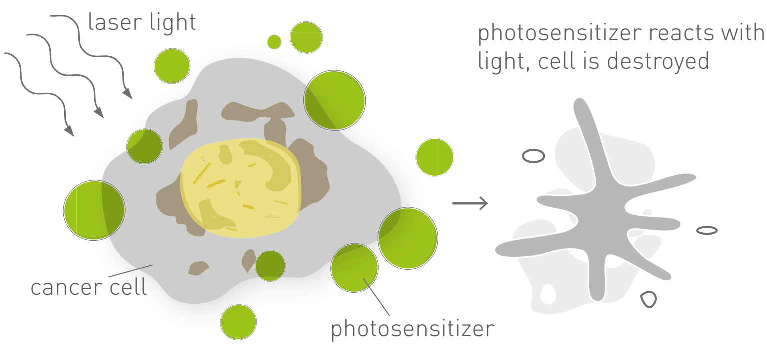
Therapy with targeted light

Treating diseases with light is known for some years. To be effective, light with well-defined wavelengths is required, which is ideally provided by light emitting diodes (LEDs) and diode lasers.

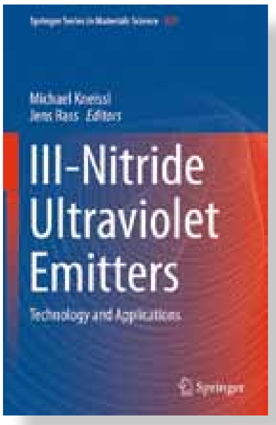
Psoriasis and vitiligo, for example, have a global prevalence of about 2 %, and their treatment costs more than one billion Euros per year only in Germany. Phototherapy using narrow band UV-B light is an established therapy option for these skin diseases. However, currently available UV light sources such as discharge lamps and excimer lasers are either bulky, expensive, or require high voltages for operation. UV-B LEDs overcome these drawbacks and even allow for a targeted therapy limited to the affected areas, thus protecting healthy skin. Their emission can additionally be tailored to the spectrally most effective wavelengths – which is 310 nm for phototherapy. FBH und TU Berlin developed the appropriate UV LEDs that meet the specifications for medical equipment delivering 5 mW output power with lifetimes beyond 3,000 hours.

Targeted medical treatment is also possible with diode lasers. Photodynamic therapy, for example, uses a light-sensitive drug (photosensitizer) that accumulates in cancer cells. After illumination with laser light of a specific wavelength, reactive oxygen is generated, thus damaging bad tissue and destroying cancer cells. Photosensitizers are especially known in the red spectral region between 635 nm and 740 nm. In the last years, the FBH developed highly reliable devices with adapted beam quality for this medical treatment. These include 650 nm diode lasers with a maximal output power of about 3 W and a reliable operation of more than 20,000 h at 1.2 W.

How photodynamic therapy works



Product in focus



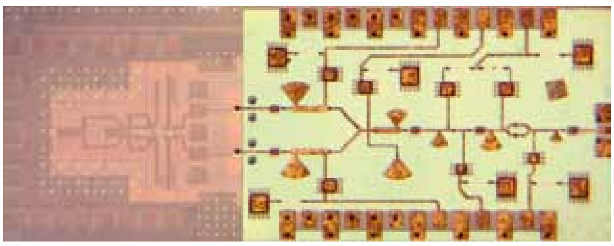
Out now – overview on III-nitride ultraviolet emitters

This newly published book, which is edited by two FBH colleagues, gives a comprehensive in-depth look into the state-of-the-art of semiconductor UV emitters, about their technology and applications. ISBN 978-3-319-24100-5

Advances in MMIC for terahertz signal generation

Signal generation at frequencies above 100 GHz represents a technical challenge, which is addressed by FBH due to the strong demand for such signal sources. FBH has established two novel technologies: a transferred-substrate (TS) InP-DHBT process and SciFab, a heterointegrated InP-on-BiCMOS process. Both are available to external customers. FBH has advanced the state-of-the-art using both processes and demonstrated a number of interesting microwave monolithic integrated circuit (MMIC) signal sources, exhibiting record bandwidth and/or signal power levels. In particular, FBH has realized a broadband doubler in TS InP-DHBT technology covering the full G-band between 140 – 220 GHz with an output power of > 5 dBm across the band. Power amplifiers have also been improved in terms of output power > 20 dBm, thermal limitation, and power-added efficiency of > 20 %. Moreover, FBH has realized a 180 GHz frequency doubler with > 10 dBm output power and more than 20 GHz bandwidth.

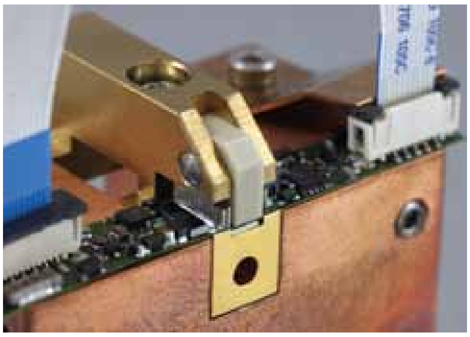
Using the SciFab process, FBH has increased the output power of a signal source based on a VCO in BiCMOS and a doubler in InP technology to reach 7 dBm signal power at 164 GHz with tuning range limited only by the VCO. It has also realized a signal source at 330 GHz using the same VCO and a quadrupler with -12 dBm output power and 30 dB harmonic rejection.



Heterointegrated mm-wave source operating at 164 GHz. The SiGe-BiCMOS voltage-controlled oscillator with 82 GHz center frequency (left) drives an InP-DHBT frequency doubler and power amplifier (right) through a differential RF transition

High-power laser drivers for nanosecond pulses

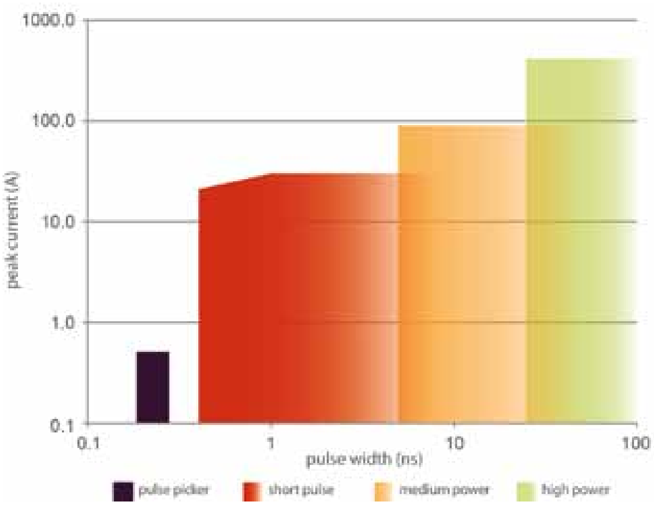
Lasers generating short optical pulses with high peak power and pulse widths in the range from 10 ps to 100 ns are key components for a broad range of applications. These include LiDAR imaging as well as fluorescence spectroscopy and micromachining systems. In addition to the power and pulse width specs, high repetition rates, good beam quality, and high energy efficiency are required.



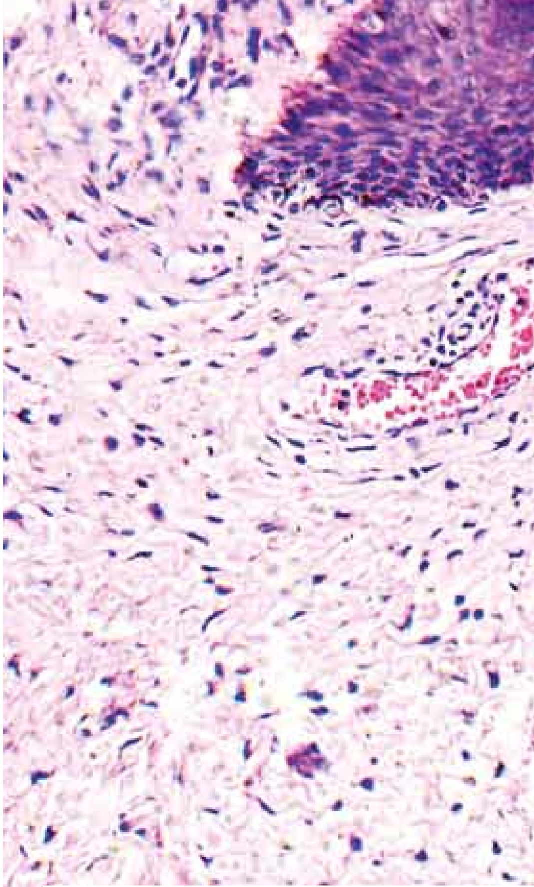
High power laser module with integrated GaN driver optimized for short pulses

Gain switching of the laser diode, i.e., switching on and off the injected current, offers a simple, cost-effective, and power-efficient possibility to generate optical pulses with widths down to at least 0.5 ns. However, to reach optical powers in the high watt range, electrical pulses with current amplitudes beyond 10 A must be handled. The main challenges in realizing such drivers are twofold: (i) to have fast-switching transistors with the appropriate current capabilities and (ii) to drive the short current pulses through the board and laser parasitics into the internal diode.

FBH's combined expertise in both laser diodes and high-speed power electronics forms the ideal setting for developing short-pulse laser components. Its modules with integrated GaN-based drivers offer unprecedented performance in terms of current and pulse width, from 430 A at 25 ns to 30 A at 0.4 ns.



Performance characteristics of integrated GaN driver for FBH pulsed laser modules



The Ferdinand-Braun-Institut, Leibniz-Institut fuer Hoechstfrequenztechnik (FBH) researches electronic and optical components, modules and systems based on compound semiconductors.

These devices are key enablers that address the needs of today's society in fields like communications, energy, health, and mobility. Specifically, FBH develops light sources from the visible to the ultra-violet spectral range: high-power diode lasers with excellent beam quality, UV light sources, and hybrid laser modules. Applications range from medical technology, high-precision metrology and sensors to optical communications in space. In the field of microwaves, FBH develops high-efficiency multi-functional power amplifiers and millimeter wave frontends targeting energy-efficient mobile communications as well as car safety systems. In addition, the institute fabricates laser drivers and compact atmospheric microwave plasma sources operating with economic low-voltage drivers for use in a variety of applications.

The FBH is a competence center for III-V compound semiconductors and has a strong international reputation. FBH competence covers the full range of capabilities, from design to fabrication to device characterization.

In close cooperation with industry, its research results lead to cutting-edge products. The institute also successfully turns innovative product ideas into spin-off companies. Thus, working in strategic partnerships with industry, FBH assures German technological excellence in microwave and optoelectronic research.

The Ferdinand-Braun-Institut develops high-value products and services for its partners in the research community and industry which are tailored precisely to fit individual needs. With its Prototype Engineering Lab, the institute additionally created an active interface between science and economy. By means of functionally-efficient models and prototypes it turns excellent research results even faster into market-oriented products, processes, and services. The institute thus offers its international customer base complete solutions and know-how as a one-stop agency – from design to ready-to-ship modules to industrial-suited prototypes.

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