Biophotonic sensors with integrated Si_3N_4-organic hybrid (SiNOH) lasers for point-of-care diagnostics

Presented by Davin Birdi

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https://rdcu.be/cU81e

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Abstract
Early and efficient disease diagnosis with low-cost point-of-care devices is gaining importance for personalized medicine and public health protection. Within this context, waveguide-(WG)-based optical biosensors on the silicon-nitride (Si_3N_4) platform represent a particularly promising option, offering highly sensitive detection of indicative biomarkers in multiplexed sensor arrays operated by light in the visible-wavelength range. However, while passive Si_3N_4-based photonic circuits lend themselves to highly scalable mass production, the integration of low-cost light sources remains a challenge. In this paper, we demonstrate optical biosensors that combine Si_3N_4 sensor circuits with hybrid on-chip organic lasers. These Si_3N_4-organic hybrid (SiNOH) lasers rely on a dye-doped cladding material that are deposited on top of a passive WG and that are optically pumped by an external light source. Fabrication of the devices is simple: The underlying Si_3N_4 WGs are structured in a single lithography step, and the organic gain medium is subsequently applied by dispensing, spin-coating, or ink-jet printing processes. A highly parallel read-out of the optical sensor signals is accomplished with a simple camera. In our proof-of-concept experiment, we demonstrate the viability of the approach by detecting different concentrations of fibrinogen in phosphate-buffered saline solutions with a sensor-length (L-)related sensitivity of $S/L = 0.16$ rad nM^{-1} mm^{-1}. To our knowledge, this is the first demonstration of an integrated optical circuit driven by a co-integrated low-cost organic light source. We expect that the versatility of the device concept, the simple operation principle, and the compatibility with cost-efficient mass production will make the concept a highly attractive option for applications in biophotonics and point-of-care diagnostics.

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Overview:

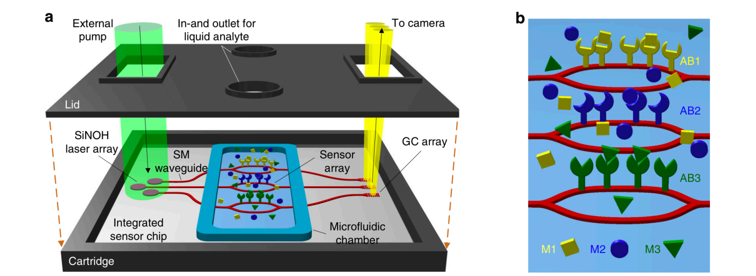

Fig. 1 Concept of the Si_3N_4-based biosensor with co-integrated lasers. a The Si_3N_4 chip combines a SiNOH laser array with an array of sensors, illustrated as Mach-Zehnder interferometers (MZI), and is placed in a cartridge (black) containing windows for optical pumping and read-out. The sensor comprises a microfluidic chamber with an in- and outlet for the liquid analyte solution, which is formed by the chip surface, the cartridge lid, and an elastic seal (blue) between the chip surface and lid acting as the chamber sidewalls. The integrated SiNOH lasers are pumped by an external light source with a large pump spot size such that high-precision alignment is not needed. The light originating from the sensor output is radiated from the chip to a read-out camera by grating couplers. **b** Simplified schematic of the MZI-based sensor. Each MZI contains one sensing and one reference arm. The sensing arms are functionalized with individual antibodies AB1, AB2, and AB3 that bind specific target molecules M1, M2, and M3, respectively, to the WG surfaces

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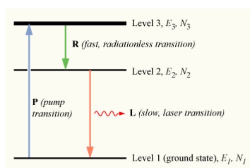
Organic Laser Pumping

"The SiNOH lasers are pumped from the top by a frequency-doubled Nd:YLF pulsed laser (CL523, CrystaLaser) at a wavelength of 523 nm, a pulse duration of 20 ns, and a repetition rate of 20 Hz,"



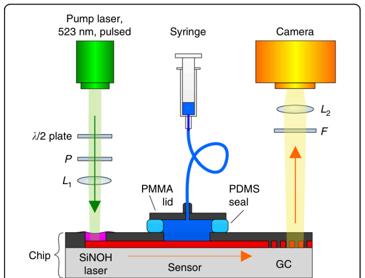


Fig. 5 Schematic of the experimental setup. The SiNOH laser is

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Previous Work:

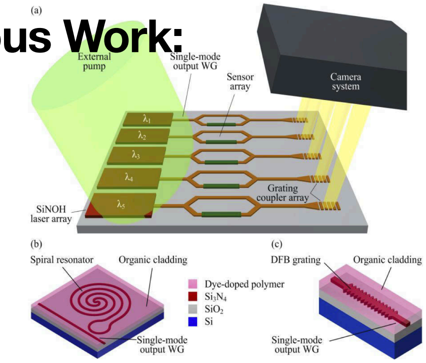

Fig. 1. Basic concept of integrated Si_3N_4-organic hybrid (SiNOH) lasers. (a) SiNOH lasers feeding an array of waveguide-based sensors. The lasers are optically pumped from the top by an external light source illuminating an extended spot, without any need for high-precision mechanical alignment. Laser light is emitted directly into the Si_3N_4 single-mode WG and can hence be efficiently coupled to an array of on-chip sensors, here illustrated as Mach-Zehnder interferometers. The light from the sensor output is radiated to the top by grating couplers and captured by a camera. (b) SiNOH laser with spiral-shaped resonator. The active WG consists of a Si_3N_4 core with a dye-doped organic cladding as a gain medium. An appropriate resonator design in combination with a suitable gain medium allows to realize various emission wavelengths $\lambda_{1...n}$ on the same chip. The ring resonator is coiled up into a double spiral and coupled evanescently to a single-mode output WG. (c) SiNOH laser with distributed-feedback (DFB) resonator, formed by a strip WG with periodic sidewall corrugations.

Daria Kohler, Isabel Allegro, Sentayehu Fetene Wondimu, Lothar Hahn, Wolfgang Freude, and Christian Koos, "Lasing in Si3N4-organic hybrid (SiNOH) waveguides," Opt. Express 28, 5085-5104 (2020)

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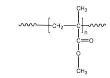
Organic Laser Composition:

Chemical Structure of the poly (methyl methacrylate):



The cladding window of the SiNOH laser (magenta) is filled with dye-doped PMMA acting as an organic gain material.

PMMA is acrylic!!

recorded spectral range of 10 nm. The peak power of the emitted laser pulse is on the order of 100 mW, which is twice as high as that of previously demonstrated SiNOH lasers[20]. This improvement was achieved by using open-spiral cavities, which do not require a large S-turn at the centre and thus provide a better overlap with the pump

5.1 Dye doped polymers

Organic dyes embedded into a host matrix provide broadband gain to amplify light for lasing applications[25]. The population inversion is achieved with pulsed optical excitation. In our work, we employ the organic dye 2-(4-(bis(4-(*tert*-butyl)phenyl)amino)benzylidene)malononitrile (PMN) embedded into a poly(methyl methacrylate) (PMMA) host polymer as gain material[26]. The doping level of small-molecular dyes is limited by a quenching process originating from the interaction between individual dye molecules[27]. The optimal concentration to achieve highest gain for the selected dye-doped polymer is 5 wt%. The organic dye PMN efficiently absorbs at the emission wavelength of a 450 nm blue high-power laser diode. The use of a laser diode as an optical pump source offers a compact low-cost alternative to bulky and expensive laser systems.

Rainer Hainberger, Paul Muellner, Moritz Eggeling, Alejandro Maese-Novo, Stefan Nevlacsil, Jörg Schotter, Florian Vogelbacher, Jochen Kraft, Martin Sagmeister, Xue Zhou, Jinhua Huang, Mingzhu Li, Ke-Jian Jiang, Yanlin Song, Dana Seyringer, Elisabet Rank, Wolfgang Drexler, "CMOS-compatible silicon nitride waveguide photonic building blocks and their application for optical coherence tomography and other sensing applications," Proc. SPIE 11283, Integrated Optics: Devices, Materials, and Technologies XXIV, 112830P (25 February 2020); doi: 10.1117/12.2543585

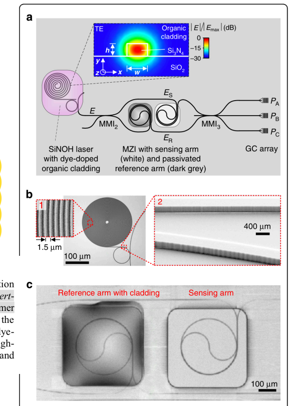


Fig. 2 Fabricated demonstrator chip, combining a SiNOH laser with an MZI-based biosensor. a The SiNOH laser cavity is an open-

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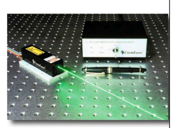
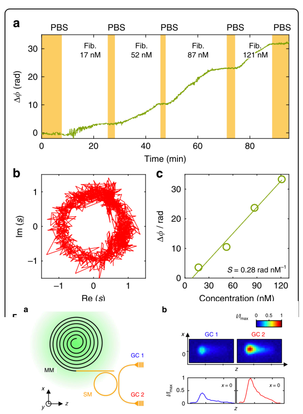
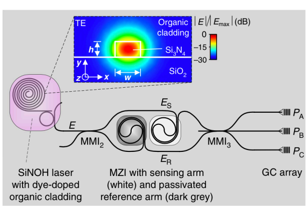
Experiment:

Fibrinogen

For the proof-of-concept demonstration, we detected the adsorption of fibrinogen onto the surface of the Si3N4 WG







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What is Fibrinogen?

Context for previous slide:

- "In our **proof-of-concept experiment,** we demonstrate the viability of the approach by **detecting different concentrations of fibrinogen** in **phosphate-buffered saline solutions** with a sensor-length (*L*-)-related sensitivity of *S*/*L*=0.16rad nM−1 mm−1."
- Fibrinogen is one of 13 coagulation factors responsible for normal blood clotting.
- When you start to bleed, your body initiates a process called the coagulation cascade, or clotting cascade. This process causes coagulation factors to combine and produce a clot that'll stop the bleeding.
- If you don't have enough fibrinogen or if the cascade isn't working normally, clots will have difficulty forming. This can cause excessive bleeding.

How is testing usually done (CDC Government Lab. Procedure Manual):

- Requires blood to be collected in 3.2% trisodium citrate at 9:1 blood:coagulant ratio
- Centrifuge at 3500rpm for 7 minutes
- Use STA Compact Analyzer

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Discussion:

- Proven that it can be done and there is room for improvement
- Leaving the rest for private industry?

Discussion

Our proof-of-concept experiment demonstrates the viability of optical biosensors driven by co-integrated SiNOH lasers as highly scalable low-cost light sources, which can be adapted to a wide range of emission wavelengths by varying the gain material. Nevertheless, the concept leaves much room for further improvement for highly sensitive detection in point-of-care diagnostics. A short discussion of these aspects is provided in the following sections.

Towards compact portable sensor systems for point-of-care applications

An essential part of the sensor system that requires further elaboration for technically viable point-of-care operation is the pump source. Our current demonstration relies on a bulky benchtop-type Nd:YLF laser, emitting pulses with an energy of 500 nJ at a rather low repetition rate of 20 Hz. The pulse length amounts to 20 ns, leading to a low duty cycle of 4×10^{-7} and an accordingly low average output power, which requires a long integration interval of 2 s for the read-out camera. In a point-of-care system, this bulky solid-state laser may be replaced by a compact high-power laser diode, emitting at 520 nm with a CW output power of, e.g. 900 mW[36,37]. Under pulsed operation, these diodes could provide pump-pulse energies typically ranging from 120 to 130 nJ, which is still above the lasing threshold from 30 to 40 nJ of the current devices. Moreover, the repetition rates can be greatly increased to, e.g. to 1 kHz, such that the system could be

seconds[38] between subsequent pulses. It should also be noted that the design of the laser cavity and the pumping scheme could be further optimized, thereby offering even higher output powers and lower thresholds, which might eventually be compatible with pump-power levels offered by light-emitting diodes (LEDs). On the receiver side, signal read-out and data analysis may rely on compact highly sensitive cameras for visible wavelengths and on compact powerful processors, both of which are readily available on the market.

How is this helpful to us:

- On-chip easy to manufacture (scale) lasers

  Comparison to Photonic Wire Bonding lasers to chip, can this be a more effective method to scale many lasers on one chip/wafer?

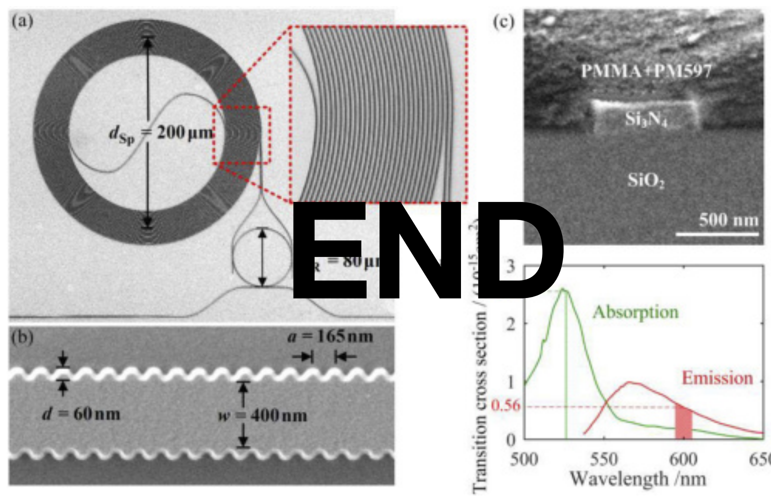
- Grating Coupler to camera interface:

  Images are continuously recorded at an exposure time of T = 2 s. The intensity radiated by each GC is detected by summing the grey-scale values of a 30 × 40-pixel area around the corresponding intensity maximum of the camera.

The "On a Boat Idea:"

LiDAR explained: What this laser tech can do for your new iPhone

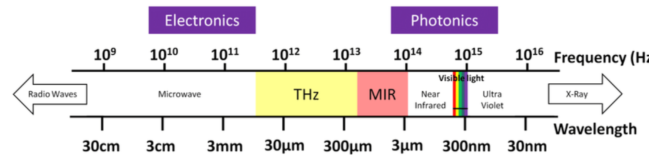
Some of the new iPhones have laser sensors built in, but what does that actually mean for you?



END

Background: Si_3N_4

Bio-Photonics:



Chen, Yuk Nga. (2015). Antenna Coupled Quantum Infrared Detectors.

"In bio-photonic applications, the visible (VIS, λ=400, ..., 700 nm) and short-wavelength near-infrared (NIR, λ=700, …, 1100 nm) spectral ranges are of particular interest[3], offering a low absorption[4] and hence permitting large interaction lengths of the guided light with analytes in mostly aqueous solutions[5,6]"

Silicon Photonics: silicon nitride versus silicon-on-insulator

Roel Baets[1,2], Ananth Z. Subramanian[1,2], Stéphane Clemmen[1,2], Bart Kuyken[1,2], Peter Bienstman[1,2], Nicolas Le Thomas[1,2], Günther Roelkens[1,2], Dries Van Thourhout[1,2], Philippe Helin[3], Simone Severi[3]

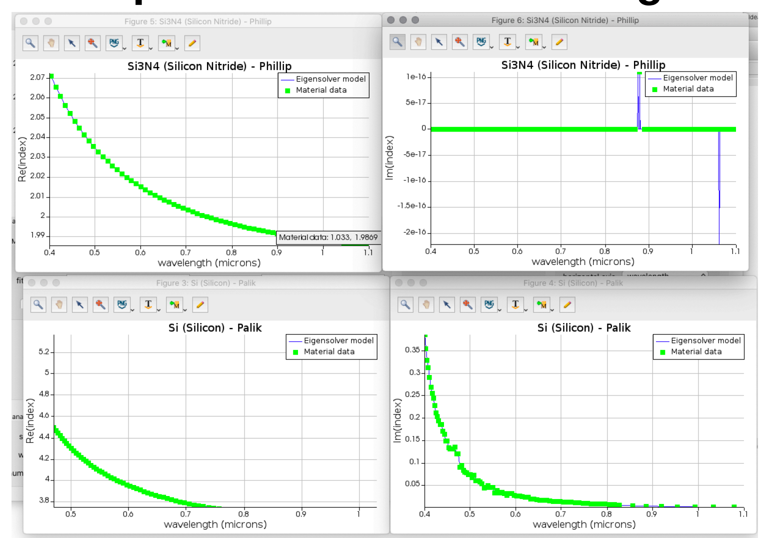
1: Ghent University – imec, Dept. of Information Technology, Photonics Research Group, Sint-Pietersnieuwstraat 41, B-9000 Gent, Belgium
2: Ghent University, Center for Nano- and Biophotonics (NB-Photonics), B-9000 Ghent, Belgium
3: imec, Kapeldreef 75, B-3001 Leuven, Belgium

PIN or APD detectors with the silicon waveguides. With this approach detectors operating at data speeds beyond 40 Gb/s have been demonstrated. The integration of light sources is typically done with hybrid approaches today but at the research level rapid progress is being made to integrate III-V-based sources by means of wafer-scale processes in the CMOS-fab.

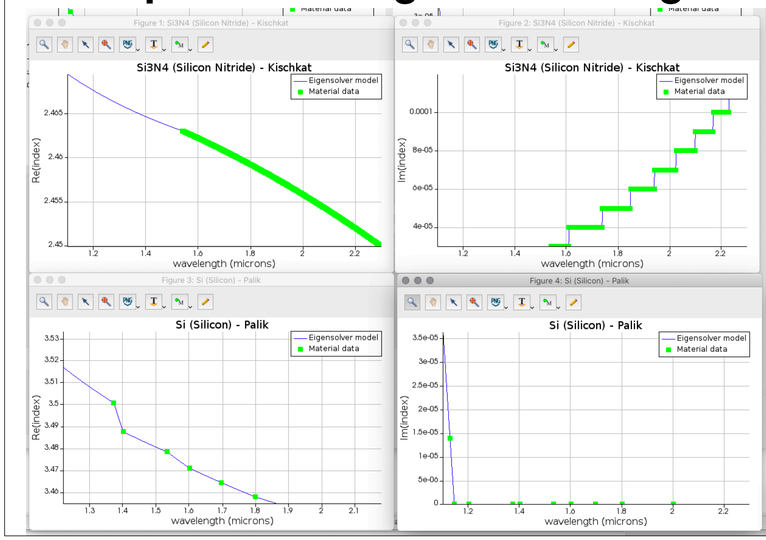
Transparency range: SOI-based waveguides have low absorption losses in the wavelength range from 1.1 µm (band edge of silicon) to about 3.7 µm (onset of mid-IR absorption of silica). For applications requiring shorter wavelengths (e.g. data communication at 850 nm, sensors operating in the therapeutic window etc.) SOI is not an option. Since SiN is transparent throughout most of the visible range – down to at least 500 nm – it is a viable candidate to implement "silicon photonics" at wavelengths below 1.1 µm [6]. This has led to demonstrations of spectroscopic functions [7-8], Raman spectroscopy-on-chip functions [9-11] and integration with colloidal quantum dots emitting in the visible [12].

Side Note (III-V Materials - Wikipedia): For example, gallium arsenide (GaAs) has six times higher electron mobility than silicon, which allows faster operation; wider band gap, which allows operation of power devices at higher temperatures, and gives lower thermal noise to low power devices at room temperature; its direct band gap gives it more favourable optoelectronic properties than the indirect band gap of silicon; it can be alloyed to ternary and quaternary compositions, with adjustable band gap width, allowing light emission at chosen wavelengths, which makes possible matching to the wavelengths most efficiently transmitted through optical fibers. GaAs can be also grown in a semi-insulating form, which is suitable as a lattice-matching insulating substrate for GaAs devices. Conversely, silicon is robust, cheap, and easy to process, whereas GaAs is brittle and expensive, and insulation layers can not be created by just growing an oxide layer; GaAs is therefore used only where silicon is not sufficient.[2]

Comparison at lower Wavelengths



Comparison at Higher Wavelengths



Background: KIT

Who are the (some) authors:

Daria Kohler

Research Assistant since 2014 with KIT in the Institute of Photonics and Quantum Electronics (IPQ) at the Karlsruhe Institute of Technology (KIT) as part of the Integrated Optical Sensors on the Si3N4-Organic Hybrid (SiNOH) Platform

Taken from the KIT IPQ Team Website

He is a professor at Karlsruhe Institute of Technology (KIT) since 2010, where he is affiliated with the Institute of Photonics and Quantum Electronics (IPQ) and the Institute of Microstructure Technology (IMT). His research focusses on integrated photonics and the associated applications in high-speed optical communications, optical signal processing, biophotonics, as well as optical sensing and metrology.

Taken from Vanguard Photonics Website