BIOSENSORS AND MEDICAL

Contents

EXECUTIVE SUMMARY

The IPSR-I Biosensors and medical addresses integrated electronic-photonic technology applications for sensors and other products needed by the healthcare industry for health diagnostics and monitoring, as well as control of air, water and food safety and quality. Together these sciences and technologies often are addressed as Biophotonics.

There are a number of sensor applications that could be met with integrated photonic technology, but there are also competing technologies, such as MEMs, that could meet some current and future application needs. This PEG addresses biosensors and medical needs, but not the technology solutions that are addressed in the Sensors chapter of this roadmap. The objective of this chapter is to identify markets that might be early adopters of integrated photonic systems technology.

The motivations for electronic-photonic integration include: (1) utilization of the existing complementary metal oxide semiconductor (CMOS) manufacturing investment to produce low-cost analog or digital components and (2) to increase the functionality and performance by augmenting electronics solutions with photonic technologies. These enabling technologies include:

- Heterogeneous packaging (Through-Silicon Vias (TSV) for stacked chips and silicon interposers),
- System in Package (SiP) and Package on Package (PoP)),
- Integrated photonics systems,
- Lower loss interconnects (low-loss laminates in printed circuit boards and packages), and
- More efficient power conversion (wide band-gap material).

This chapter focuses on enumerating the trends during the next decade that integrated electronics-photonics technology must meet to satisfy the biosensor and medical market needs. These trends particularly focus on:

- Packaging technology,
- PCB and connector technology and costs, and
- Testing and assembly/joining technologies

INTRODUCTION

Healthcare is the maintenance or improvement of health via the prevention, diagnosis, and treatment of disease, illness, injury, and other physical and mental impairments in human beings. Professional providers or practitioners deliver healthcare in allied health professions, physicians, physician associates, dentistry, midwifery, nursing, medicine, optometry, audiology, pharmacy, psychology, and other health professions. Healthcare is regarded as an important determinant in promoting the general physical and mental health and well-being of people around the world. An example of this was the worldwide eradication of smallpox in 1980, declared by the WHO as the first disease in human history to be completely eliminated by deliberate healthcare interventions. It is also a huge market for sensors.

In the last 20 years, both Europe and the United States have had to face a continuous aging population, as well as economic issues linked to sustainably unbalanced healthcare systems. Also, the reemergence of epidemics, highlighted by the devastating impact which the Covid-19 pandemic is now having on economy and society, speaks to the increasing need for a treatment-oriented system, the health organization system moves towards a diagnostic- and prevention-oriented one.

In the food sector, a growing demand arises for safer, healthier, and higher quality food to battle increasing risks of epizootic diseases and food related disorders, threats in sustainable agricultural and fish production. The role of food and food production on health and climate change puts pressure on methods for quality and process control, as well as rapid microbiological methods to monitor the whole production system. Several of these issues have in common a strong need to study real-time evolution of living organisms or part of them such as tissues, organs, cells, proteins, and DNA.

Electronic-photonic integration is becoming increasingly important for photonic sensor applications, including biophotonics. The benefits of using integrated photonics are:

- Reduced size, weight, and power (SWaP),
- Improved performance,
- Reduced number of optical and/or electrical interfaces,
- Realization of new functionalities, and
- Reduced cost for volume manufacturing.

The enabling technologies for integrated photonic sensors include:

- Heterogeneous packaging (Through-Silicon Vias (TSV) for stacked chips and silicon interposers),
- System in Package (SiP) and Package on Package (PoP),
- Integrated photonics systems,
- Lower loss interconnect (low-loss laminates in printed circuit boards and packages), and
- More efficient power conversion (wide band-gap materials).

MARKET POTENTIAL

OVERVIEW

Pharmaceuticals and other medical devices are the leading high technology exports of Europe and the United States. Therefore, healthcare offers a huge market for biophotonics. According to industry and market classifications, such as the Global Industry Classification Standard and the Industry Classification Benchmark, healthcare includes many categories of medical equipment, instruments and services as well as biotechnology, diagnostic laboratories and substances, and drug manufacturing and delivery. Healthcare contributes to a significant part of a country's economy. In 2011, the healthcare industry consumed an average of 9.3 percent of the GDP or US$ 3322 per capita across the 34 members of OECD countries. The US (17.7%, or US$ 8508), The Netherlands (11.9%, 5099), France (11.6%, 4118), Germany (11.3%, 4495), Canada (11.2%, 5669), and Switzerland (11%, 5634) were the top spenders. These percentages have only increased over the past decade and are likely to explode due to the Covid-19 pandemic.

This chapter focuses on the trends, opportunities and challenges for healthcare and photonics in explicating trends for the next decade that integrated electronics-photonics technology must address for the Biophotonics Market. These trends include:

- Packaging technology,
- Miniaturization
- PCB and connector technology and costs, and

- Testing and assembly/joining technologies.

BIOPHOTONIC SENSORS

The foci of this roadmap on photonic sensors are (1) photonic chip-scale, (2) systems-level devices for the detection of chemical and biological targets, and (3) physical and environmental sensing systems. This section, in an effort to define the needs and not the solutions, does not include the sensors required for Internet of Things (IoT), dealt with in a section by itself. It does include sensing applications that might be better addressed by alternative sensing technologies that embrace an integrated photonics component or sub-system.

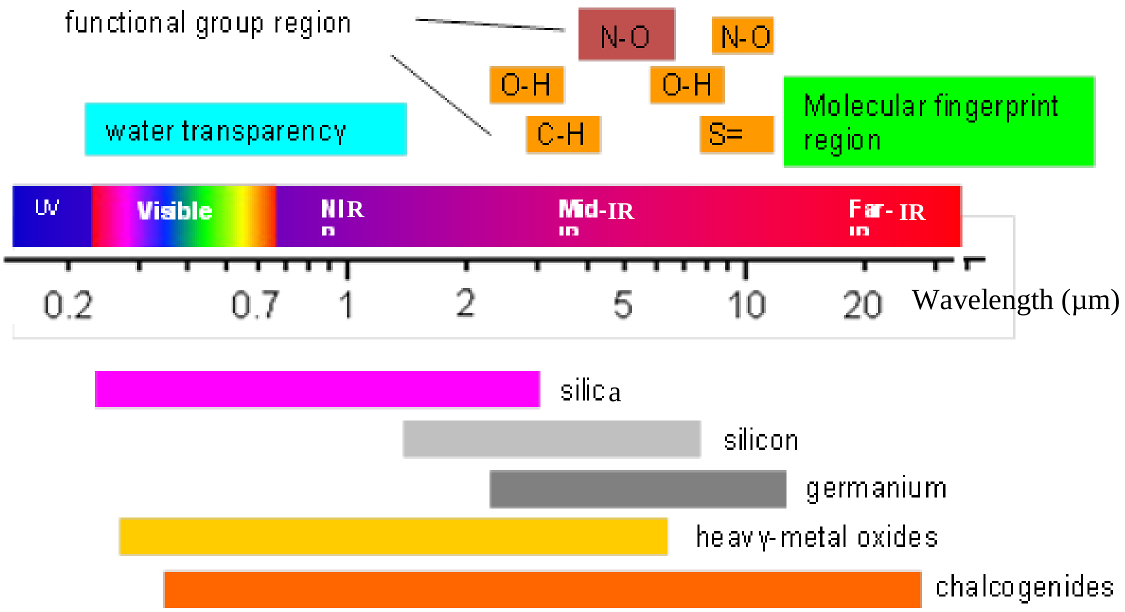


Figure 1. CMOS-compatible materials for photonic sensors

During past decades light sources and photo detectors have been developed to cover a wide range of wavelengths from ultraviolet (UV) to visible to infrared (IR). Similarly, new photonic elements able to transduce a sensing event have been developed, and others have been re-purposed from the telecom industry, thereby providing a highly diverse set of sensing mechanisms. These advancements open a new set of sensor applications. Figure 1 compares some of the most well-explored materials for this application space.~~ 2020~~.

With the number of innovations taking place in the technology of photonic sensors, the market is expected to grow significantly at a considerable compound annual growth rate. The demand for products that use photonic sensors is rising. According to a recent market research reports published by Technavio (http://www.technavio.com/)[1] the medical sensors market pre-Covid-19 is estimated to grow at a CAGR of 9% between 2019 and 2023 and is expected to reach USD 18 Billion by 2023. The key drivers for this growth are the increasing prevalence of chronic diseases, a rising demand for medical sensors in a home care settingand an increasing adoption of medical sensor technology. An increasing number of applications

---

[1] "Global Medical Sensors Market 2019-2023" published by Technavio (www.technavio.com)

in the industrial sector (including food, air, and water quality monitoring) are also major drivers for the photonic sensors market.

Most of the drivers under the photonic sensors are based on unique properties such as distributed sensing, ability to multiplex and immunity to EMI. The restraining factor for the quick adoption of a photonic sensors market has been the historically high cost and lack of standards, ultimately resulting in lack of awareness and adaptability by the customer. Also, the biophotonics sensor market is quite segregated and fragmented, with long R&D and New Product Introduciton (NPI) cycles and high certification barriers, leading to high a significant business risk in the commercial market. Consumer applications such as wearables and smartphones are driving the development of identification application. As an entry point, the consumer market is very attractive as it can drive very large volumes depending on user case adoption, cost, and technical maturity. The smartphone industry has revolutionized the sensor industry as mobile applications today add ever more sensors. Biophotonic gas sensors could be the next to be integrated in smart phones and/or wearables.

APPLICATIONS

PHOTONIC GAS SENSORS

Rapid growth in photonic gas sensors is expected because of the global concern over air quality for both environmental monitoring and public safety. Covid-19 fatality is thought to increase at high levels of air pollution. It is expected that many of these biophotonic sensors will be used in (Industrial) Internet of Things applications. Yole Développement’s Gas Sensor report estimates that the total gas sensor market currently is growing, driven by Heating, Ventilation Air Conditioning (HVAC) and future consumer applications. It was worth $560M in 2014 and will reach almost $920M in 2021, at 7.3% CAGR. An upside market of almost $65M in 2021 is possible if gas sensors are adopted widely in consumers products.

There are plenty of gas sensor applications, each with its own technical requirements, such as the gases to be measured, sensitivity and selectivity, response time, lifetime and power consumption. Each application also has its own business requirements including regulations, target price, maturity of the market, and competition.

There are six main market segments:

1. Consumer: Gas sensors embedded in consumer products including home devices, wearable electronics and mobile phones;
2. HVAC: Gas sensors used for indoor/in-cabin air quality monitoring;
3. Transport: Gas sensors used for exhaust gas measurement or in engine control for heavy duty vehicles;
4. Medical: Gas sensors used for breath analysis in ventilation and point of care;
5. Defense and Industrial Safety; and
6. Environment: Gas sensors used to monitor air quality and pollution peaks.

Gas sensing technology is a complex field with nine different sensing approaches. In general, the right selection for gas-sensing technology depends upon price, form factor, power consumption, sensitivity, and response time. According to Yole “optical technologies (one of the nine approaches) have the highest accuracy and longest lifetime but are not widely used in the transport market because the environment is tough and cost pressure is high. They are largely used in HVAC, especially Non Dispersive Infrared sensors (NDIR). Further integration will open the way to portable systems for industrial applications.

Optical technologies such as NDIR, Fourier Transform Infrared (FTIR), chemiluminescence, and micro chromatography are very accurate, but bulky and costly with high power consumption in some cases. NDIR is an optical technology that can achieve very low power consumption when photodiodes are used with LEDs.”

BREATH ANALYSIS BY TRACE GAS MONITORING[2]

About the technology

Exhaled breath is an attractive tool for monitoring the metabolic status or disease of a person, since it is non-invasive and fast. Humans exhale hundreds of gases, including inorganic compounds (e.g., ammonia, nitric oxide, hydrogen sulfide) and volatile organic compounds (VOCs), arising from their normal body metabolism. Breath analysis in clinical settings is beneficial and reveals new insights regarding the origins, pathways, and pathophysiological roles of breath components. Endogenous emissions reflect the changes in the internal metabolism when illness occurs.

Photonic based sensing can meet the demand for a continuously increasing need for hand-held, miniaturized devices that are affordable, accurate and user-friendly and provide a good specificity and selectivity, with a real-time response. Depending on the spectroscopic method and light source, it can provide real-time (breath-cycle resolved) detection of one or more volatile compounds.

The most common optical method used for exhaled breath analysis is molecular absorption spectroscopy. The analysis is based on measuring either fundamental (mid-IR, 3-10 μm), or first overtone (near-IR, 1-2 μm) rotational-vibrational transitions or, in exceptional cases, electronic transitions in the visible/UV wavelength range.

The number of analytes that can be detected depends on the wavelength coverage of the light source. Current standard implementations of optical breath instrumentation use lasers with narrow tune ability, which limits the number of analytes to a few per instrument. Such lasers include DFB diode lasers (0.7-3 μm) and VCSELs in the visible and near–infrared spectral range, as well as DFB interband cascade lasers (ICLs) (3-6 μm) and quantum-cascade lasers (QCLs) (3-14 μm) in the mid-infrared. These lasers allow mode-hope free wavelength tuning in a narrow wavelength range (1-5 cm^{-1}).

For extended multispecies detection, two (or several) narrowband lasers can be combined. Wider tunable lasers are ECDLs and external-cavity QCLs (EC-QCLs), where the laser is mounted in an optical cavity with wavelength selective device, which provides a narrow line width and broadband wavelength tuning range. Wider coverage is obtained with infrared optical frequency combs (OFCs) or super continuum light sources. OFCs combine the advantages of narrow line width, continuous wave lasers with the broad wavelength coverage. This feature makes OFC an ideal source for sensitive, broadband and yet high-resolution spectroscopy. Their potential in simultaneous detection of different biomarkers in human breath has been demonstrated. They are able to detect molecules with broad absorption features and at the same time discriminate and characterize the interfering species, yielding a selective multispecies detection advantage.

Real-time breath analysis is conflicting with the need for high sensitivities. Many breath biomarkers are present at low parts per billion levels (or below). Thus, to attain the needed sensitivity, a long absorption path length is needed (multi-pass cells, high-finesse optical cavities).

---

[2] Contributions from: Radboud University, the Netherlands; University of Helsinki, Finland; Umeå University, Sweden; University of Oxford, UK; Grenoble University Hospital, France; Johns Hopkins University, USA; Imperial College London, UK; Semmelweis University, Hungary

In optical cavities absorption path lengths can reach hundreds of meters up to a few kilometers, depending on the reflectivity of the mirror coating. In the mid-infrared wavelength region, the mirror reflectivity is less advanced, but is compensated by the stronger absorption line strengths of the molecular transitions.

Breath biomarkers

Without path length enhancement, laser spectroscopy can detect only the most abundant breath species: carbon dioxide (CO_2), water vapor (H_2O) and oxygen (O_2). Real-time laser spectroscopic measurements can yield important physiological and medical information of the main respiratory gases within a breath cycle. A significant example is the determination of oxygen consumption (VO_2) on a breath-by-breath basis.

Real-time breath gas analysis with sub-second time scale is also achieved for another abundant specie: carbon monoxide (CO). This molecule is identified as a cellular signal molecule and its main endogenous sources are systemic and induced heme breakdown. In addition, the molecule is a potential biomarker for oxidative stress and respiratory diseases. Laser-based CO detection offers much better sensitivity, precision and time resolution than traditional electrochemical CO sensors.

One of the most appealing and hence studied molecules for medical applications is nitric oxide (NO). NO is an indicator of airway inflammation in humans, a signaling molecule and a physiological messenger in mammalian cells, involved in various bio-chemical pathways. Exhaled NO (eNO) is a useful biomarker in the diagnostics of asthma and other respiratory diseases.

Real-time signatures of the surgical response triggered by oxidative stress can be observed by measuring the production of small hydrocarbons such as ethane, pentane, and ethylene that can be measured in a clinical setting. In the exhaled breath of cystic fibrosis (CF) patients, hydrogen cyanide (HCN) is detected as a result of bacterial infection. Current diagnostic techniques lack sensitivity (cough swab), are very invasive and commonly miss early infections, especially in young children. As such, HCN detection in exhaled breath has an excellent potential, because the $^{13}CO_2/CO_2$ ratio from human breath is used for identification of *Helicobacter pylori* infection, liver malfunction, and excessive growth of bacteria in the body. The detection of carbon disulfide (CS_2) to indicate cirrhosis and a potential non-invasive marker of respiratory bacterial colonization in cystic fibrosis NH_3 detection as product of protein metabolism relevant for a number of disease states and human physiology.

Potential of spectroscopic breath analysis

The US Food and Drug Administration has included a number of optical-based breath tests, most of the FDA approved tests are single-species tests. Recent advances in nanotechnologies, optoelectronics and photonics integration reinforce the demand for compactness and miniaturization of the devices. Optical detection is virtually maintenance free and can operate continuously for long periods of time. The strength of optical detection lies in its specificity, sensitivity, reliability and quantization, in real-time, resolving individual breath cycles without the need for frequent calibration.

However, laser-based spectroscopy is mainly a sensor technology, focusing on a single identified molecule. In the exploratory/discovery phase of a disease via breath sampling, a single compound is not sufficient. Only a few optical studies have carefully addressed the untargeted analysis of medium-to-high molecular weight species that absorb over a broad wavelength range. Demonstration experiments have been conducted using super continuum lasers and optical frequency combs, but practical routine implementations lie still in the future.

The technology of lasers has advanced considerably in the past few years and more wavelengths are available for gas sensing and applications outside the laboratory. Furthermore, new avenues have been opened for the design of compact instruments:

Optical methods do not require ionizing radiation (unlike CT and PET), expensive scanners and reagents (unlike Helium and Xenon-MRI). They are simply to conduct and can be undertaken in any standard lung-function testing laboratory.

For detection of light molecular compounds, such as C_2H_4 or NH_3, optical methods are much more sensitive compared to mass spectrometry.

The fast development of OFCs and super continuum sources, promise substantial improvements for broad band spectrometry in the near future, making them highly interesting for biomedical applications.

Concerning analytical capabilities, optical methods need to be improved. Broadband photonic sources need a robust algorithm that can discriminate between multiple absorbing molecules using their specific spectroscopic features.

WEARABLE SENSORS

There will be more than three billion sensors in wearable technology devices by 2025, with more than 30% being emergent sensor types according to "*Wearable Sensors 2015-2025: Market Forecasts, Technologies, Players*" a report from IDTechEx.[3] They forecast a $70 billion market by 2025 The report gives detailed coverage of the 15 most prominent sensor types in wearable technology today, including inertial measurement units (comprising combinations of accelerometers, gyroscopes, magnetometer, and barometers), optical sensors (including optical heart rate monitoring, and wearable cameras), wearable electrodes, chemical sensors, flexible stretch, pressure, and impact sensors, temperature sensors, microphones, and other emerging wearable sensors.

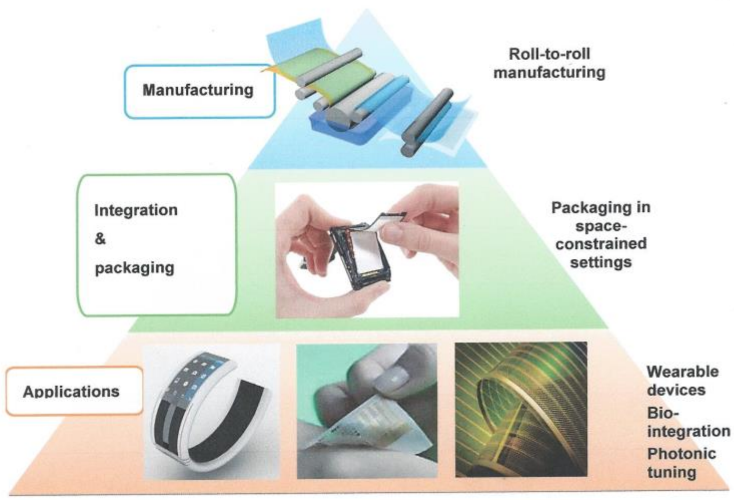


Figure 2. The future of the photonics wearable sensor market depends upon flexible photonics

Many of the most prominent wearable technology trends are tied closely to the properties and limitations of sensor systems. Sensors are the most diverse component type in wearable devices, and they also enable the key functions that will go into wearable devices and make them wearable. Advances with wearable sensors are a vital driver for the future of wearable technology and the Internet of Things (IoT). Their incorporation alongside new energy harvesting and storage techniques, efficient power management systems, and low power systems together with form factors that will be increasingly flexible, fashionable, and invisible will drive the wearable technology market to $70bn by 2025.

---

[3] "Wearable Sensors 2015-2025: Market Forecasts, Technologies, Players" a report from IDTechEx

Many of the functions in health care and health monitoring are preferably implemented in devices attached to the person to be monitored. Figure 2 illustrates how wearable photonic sensors will take advantage of flexible photonics technology currently being developed by manufacturing innovation institutes (MII) (America Makes).

Figure 3 illustrates IDTechEx's forecast of the types of sensors technologies that will be used by the wearable market in the near future. It shows that optical sensors may capture a significant portion of the market.

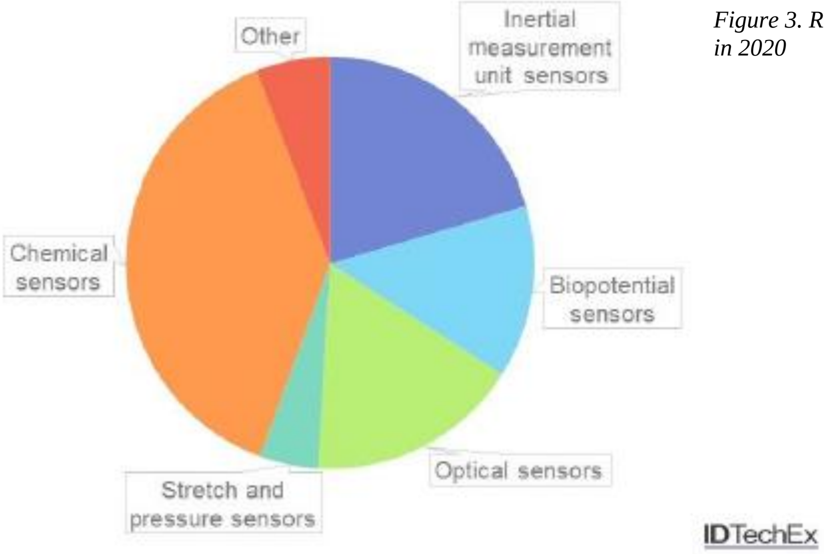


Figure 3. Relative market sizes by wearable sensor type in 2020

However, other market research studies come to significantly different conclusions on the market segmentation for wearable sensors. One can conclude in general that there is great uncertainty and risk in determining exactly whtat "the next big thing" in wearable sensors will be.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT is a real-time non-invasive imaging technique with depth range in biological tissues of between 0.01 mm and 3 mm and axial resolution of several microns. The principle of OCT is shown in Figure 5.

Depth resolution (axial resolution, δz) is in the order of microns and related to the configuration and coherence length of the light source, which is inversely proportional to the spectral width (Δλ) of the source and the index of refraction (n) of the material. A significant spectral width (~ 50 – 100 nm) is required to obtain the depth information (by Fourier transformation).

Lateral resolution is determined by the spot size obtained by the optics in the light path of the sample.
Penetration depth, or imaging depth is inversely proportional to the spectral resolution of the spectrometer, nm per pixel, (or the spectral linewidth Δλ of the laser in the case of a swept source system). Furthermore, the imaging depth is determined by the absorption and scattering properties of the tissue.

The contrast is based on the different (back-)scattering properties of the tissue under study (Figure 6). To identify (diseased) tissue, the morphology of the image should be validated against medical databases and/or histology. Additional information can be obtained by quantitative analysis of the scattering behaviour. More accurate identification can be obtained by combining OCT with spectral information (e.g. Raman-scattering, fluorescence or photon absorption).

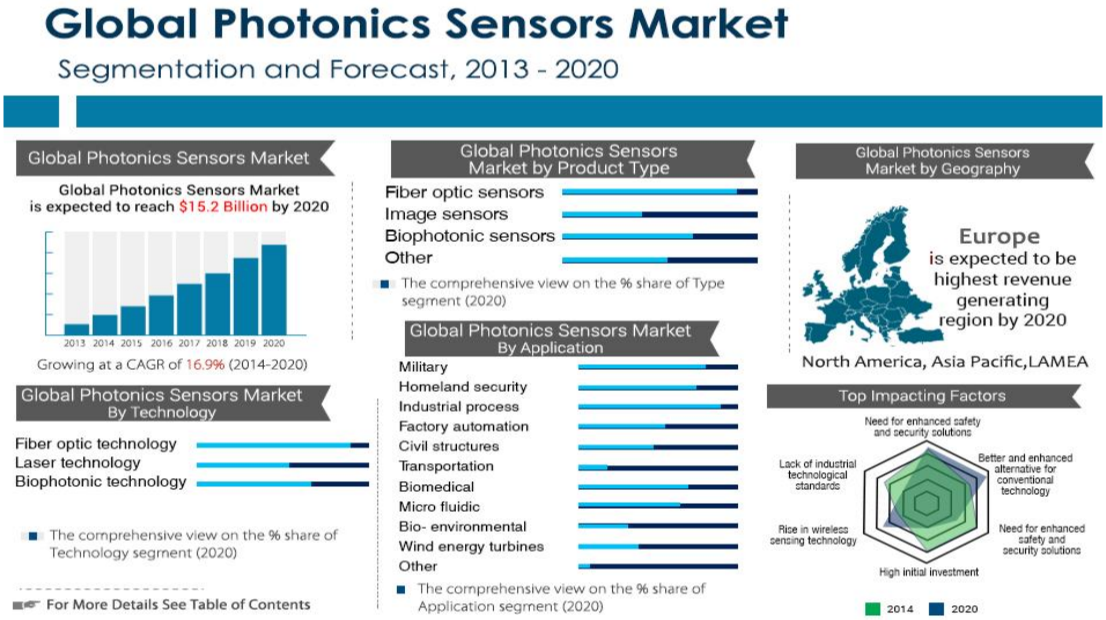


Figure 4. Allied Research projection of the Global Sensors Market in 2020

Please note that shorter wavelengths (VIS and NIR) are beneficial for improved contrast and higher axial and lateral resolutions, whereas larger wavelengths (1000-1500 nm) have the advantage that the imaging depth is larger because of the lower absorption and scattering properties of the tissue at these wavelengths.

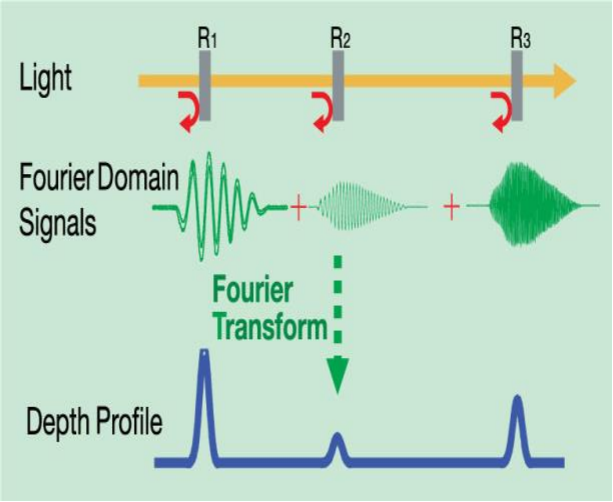


Figure 5. . Working principle of Optical Coherence Tomography (OCT)

An overview of the working range of OCT and of alternative imaging techniques is shown in Figure 7.

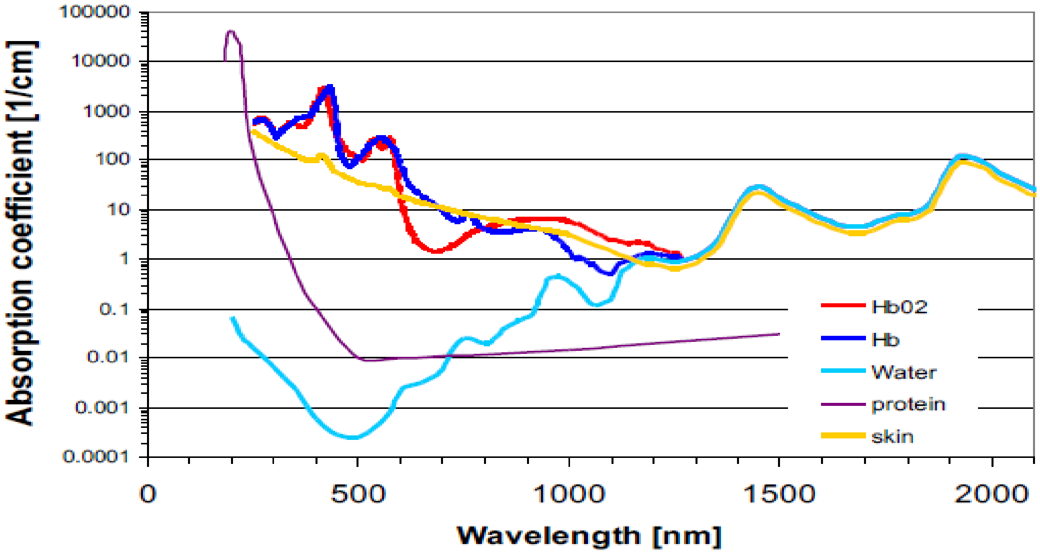
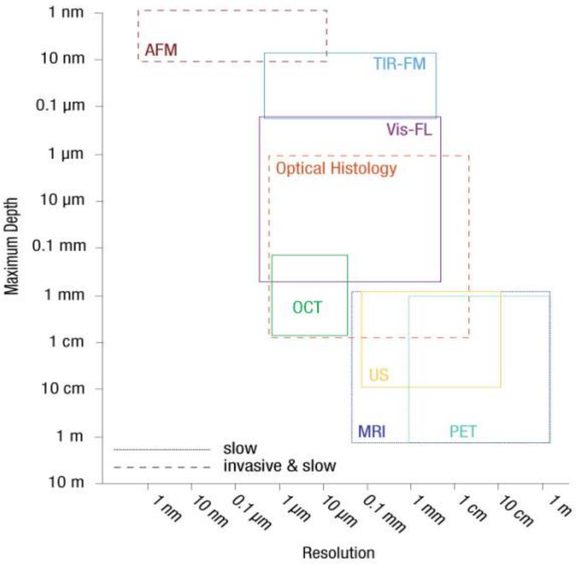


Figure 6. Absorption of light for different tissue constituents

Present and future implementations of OCT

Several companies (e.g. Bioptigen, Santec, Thorlabs, Wasatch Photonics) offer OCT systems that are useful for research. Those systems have typically center wavelengths of 800, 950, 1050, 1300 and 1550 nm, and resolutions in the order of 5 micron. For instance, Thorlabs offers a customized OCT benchtop system with 6.0 µm axial resolution in air with 2.9 mm imaging depth (930 nm Center Wavelength) or 3.0 µm axial resolution in air with 1.9 mm Imaging Depth (900 nm Center Wavelength).



Axial imaging resolution δz is given by coherence length l_c (1/bandwidth $\Delta\lambda$) of the light source;

$$\delta z = l_c = \frac{2 ln2}{\pi\, n} \frac{\lambda^2}{\Delta\lambda}$$

imaging depth depends on the spectral resolution of spectrograph or instantaneous bandwidth of the swept source.

$$z_{max} = \frac{\lambda^2}{4n\,\delta\lambda}$$

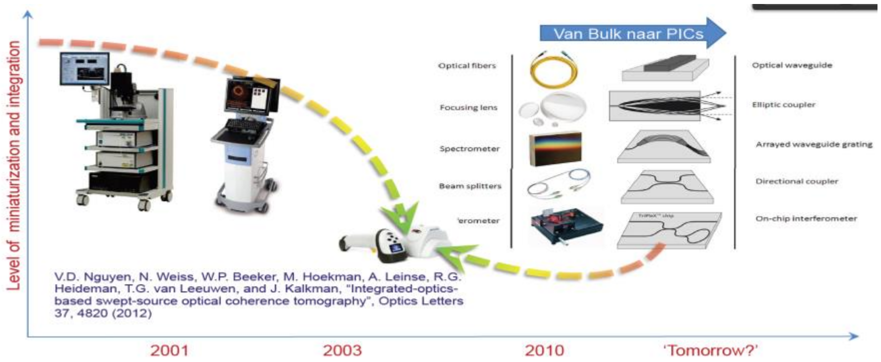
n is the index of refraction, λ is the center wavelength of the spectrum

Figure 7. OCT and competing imaging techniques. This figure is not fully correct. Optical histology has a maximum depth of 10 micron (slice thickness) with a resolution typically between 1-5 micron. OCT should range from 10 micron till 3 mm in depth.

Those systems are mostly based on bulk optical components and cost 60-120 k$. Edmund Optics introduced a relatively cheap (12 k$) OCT system that is partly based on integrated photonics components.
For clinical applications (e.g. in cardiology, dermatology, gastroenterology, gynecology, oncology, ophthalmology, pulmonology, urology) specialized systems are available (e.g. Carl Zeiss Meditec, St. Jude Medical, Heidelberg Engineering, Optovue, Topcon Medical Systems, Volcano Corporation, Michelson Diagnostics).

Figure 8. Benchtop OCT system (courtesy Thorlabs)

Increasing the index contrast will decrease the bending curvature and thus decrease footprint of the chip and AWG. Increased gain band width will increase probing depth range. Using low-power actuation for sweeping the source will thermally stabilize. Input coupling optimization of the fiber through tapering on the chip can confine the optical signal in large contrast, low-footprint chip with reduced coupling loss. Small linewidth laser (or swept source towards 100 Hz) or high-resolution AWG (<0.2 nm per exit pixel) will enable large probing depth combined with use of larger pixel array.



V.D. Nguyen, N. Weiss, W.P. Beeker, M. Hoekman, A. Leinse, R.G. Heideman, T.G. van Leeuwen, and J. Kalkman, "Integrated-optics-based swept-source optical coherence tomography", Optics Letters 37, 4820 (2012)

Figure 9. Development of OCT equipment from (large) tabletop formfactors to a handheld device using integrated photonics

The exact specifications of future devices are dependent on the application and the technology which is used (swept sources or spectral domain OCT). A brief overview is given in the table below. Currenly established is a 200 mm^2 chip size (including external laser source). Bare-die integration would be beneficial.

OCT	[unit]	5 years	5-10 years	10-15 years
Annual revenue	[$/year]	x	X	x
Cost price	[$/unit]	x	X	x
Energy consumption	[W]	~20W	~10W	~5W
Wavelength range	[nm]	850, 950, 1050, 1300 and 1550	VIS, 850, 950, 1050, 1300 and 1550	VIS, 850, 950, 1050, 1300 and 1550
Reliability	[%]	99	99.9	99.99
Footprint	[mm²]	200	100	10
Output power	[W]	0.01	0.01	0.01
Life cycle	[years]	3	3	3
Bandwidth	[nm]	50, 65, 90, 110 and 150 nm respectively	40, 50, 65, 90, 110 and 150 nm respectively	40, 50, 65, 90, 110 and 150 nm respectively
Sweep time	[micro-seconds]	~30	~30	~30
Speed	[m/s]			

POINT-OF-CARE DIAGNOSTICS

Point-of-Care (PoC) diagnostics concerns medical tests to diagnose a patient's condition without the need for time-consuming tests in dedicated laboratories. PoC covers testing at home, bed-side testing in hospital emergency rooms and critical care clinics, chair-side testing in a dental care setting and testing at the General Practitioners (GP) office. It is beneficial for the patient, who has a quick diagnosis and early start of targeted treatment, and who can therefore recover more quickly. In turn, quicker recovery saves costs on hospital occupation, pharmaceuticals and professionals. Finally, the PoC diagnostic test itself can be low-cost. Consequently, not only individual patients benefit, but also society as a whole. This is particularly apparent with the testing needs for the Covid-19 pandemic.

Current (non-photonic) technologies

Current diagnostic tests are mostly done in specialized labs, to which the GP sends blood, saliva or urine samples for analysis. The most common test is the Enzyme-Linked Immuno Sorbent Assay (ELISA) test: a patient's sample is adsorbed onto a surface and exposed to antibodies which bind only to the specific biomarkers that are targeted in the test. If these biomarkers are present in the sample, the antibodies will bind and remain on the surface, otherwise they will be flushed away. The ELISA test is a so-called 'labelled' test, meaning that the antibodies are labelled with a discriminating molecule. This molecule is an enzyme that, for subsequent detection, converts a substrate in a coloured product. The rate of colour change is dependent on biomarker concentration. Alternatively, fluorescent labels can be used. By examining the fluorescence of the sample, the amount of binding can be established, providing a measure for the biomarker concentration in the sample. Drawback of this technique are required analysis time and costs.

Electrochemistry is the second most used detection method for current commercial tests. It is based on the movement of electrons in redox reactions, detected when a potential is applied between two electrodes. The most familiar electrochemical biosensor is the blood glucose sensor.

PHOTONICS TECHNOLOGIES FOR POINT-OF-CARE DIAGNOSTICS

SURFACE PLASMON RESONANCES (SPR)

Surface Plasmon Resonances (SPR) uses the evanescent field (i.e. the small fraction of the light which penetrates outside an optical waveguide) for detection of surface-bound molecules. SPR is quite complex in terms of handling and read-out system (compared to photonic devices (see below), making the technology difficult to scale to multi-analyte tests, and sensor chips are expensive.

Application example: Early Detection of Prostate Cancer

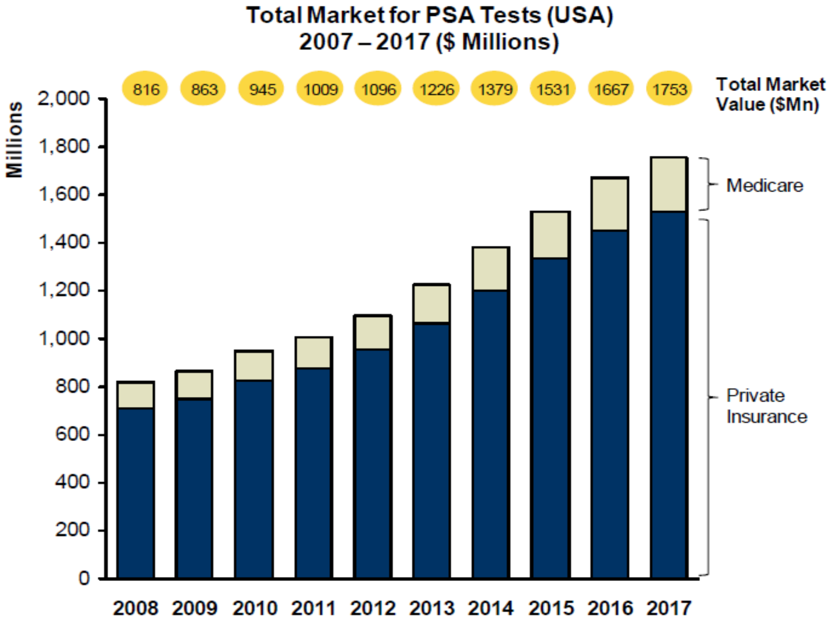


Figure 13. Market for prostate cancer screen tests (done via testing for Prostate Specific Antigen [PSA]).

With an aging population, there is a growing need for more testing for medical conditions such as prostate cancer. Prostate cancer has very high survival rates if the cancer is caught and treated early, so screening is very important. Figure 13 shows the development of this market in the past decade, a trend which is expected to continue.

The current method of screening for prostate cancer involves taking a blood sample and sending it to an external lab to test for the concentration of Prostate Specific Antigen (PSA). At high concentrations (an “abnormal result”), PSA is a possible indicator of prostate cancer, and then patients undergo further testing. The current lab method of sensing the concentration of PSA in the blood is an Enzyme Linked Immuno-Sorbent Assay (ELISA) method that has a limit of detection of 0.01 ng/mL; however, it takes several days for the lab to perform the test and send the results back to the doctor and patient. If the result is abnormal, the doctor and patient then have to spend more time discussing the results and next steps during another scheduled doctor’s visit. The extra handling and administrative work that comes from getting results back from an external lab also increases the risk of errors, which can result in malpractice lawsuits for doctors. Instead, integrated photonic sensors provide the promise of nearly instantaneous results from a single drop of blood taken and processed right in the doctor’s office.

This faster turnaround time would potentially allow doctors and patients to immediately discuss the next steps in care, making the visit more efficient and simplifying the process for everyone involved. The lower risks of administrative errors also reduce the number of malpractice lawsuits experienced by doctors, and since the testing is done in their office instead of offsite, doctors can capture the revenue stream from insurance reimbursements, further adding to the economic incentive for adopting integrated photonic sensors. Of course, a challenge for the area is that this scenario also requires changes to the standard doctor's office patient flow and to the reimbursement model, and thus it will be necessary for the improvement in patient outcomes for point-of-care photonic bio-sensors to be quantifiable and tested.

INTEGRATED PHOTONIC DEVICES

Several integrated photonic devices have been shown to be effectively applied towards the sensing of biomarkers: interferometers (especially the highly sensitive Mach-Zehnder and bi-modal waveguide types), ring resonators and photonic crystals.[5] The working principle can be illustrated for instance by the case of the ring resonators (Figure 11, left). In a ring resonator, light is coupled into and out of a waveguide which forms a closed circle. An optical signal coupled into the ring can circulate along the waveguide. At each roundtrip, a fraction of the light (in the order of 10%) is directed to the exit waveguide. If an integer number N of wavelengths fit in the ring, input light interferes constructively with the light in the ring, and the output power is high. If an $(N + ½)$ times a wavelength fit in the ring, the opposite holds. Consequently, as a function of wavelength, sharp resonances are observed (Figure 11, right). The ring resonator is coated with similar antibodies as in the ELISA test. A small fraction of the light (the so-called evanescent field) penetrates outside the waveguide and interacts with biomarkers that may bind to the surface, causing a wavelength shift of the resonance pattern. This shift can be determined accurately, and from this the biomarker concentration can be calculated.

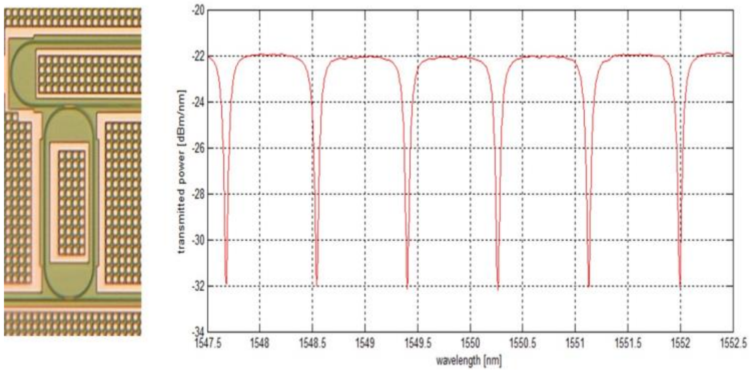


Figure 11. ring resonator: photograph of device with input and output

Ring resonators, interferometers and photonic crystals form essentially an optical sensor which detects changes in the refractive index near the surface. Details of the other device types and their sensitivity comparison can be found in literature (ref. [5] for instance.)

The bio-chemical selectivity and sensitivity are obtained from the antibodies. Many rings can be multiplexed on a single sensor chip, each ring being coated with a particular antibody. The surface functionalization is a key step to success and should be localized to the waveguide for maximum sensitivity. Microfluidic systems are front and center to bringing the biomarkers to the waveguide surface, also when pre-processing of sample fluids needs to be done. A microfluidic system (so called lab-on-a-chip) are

---

[5] A.F. Gavela, D.G. García, J.C. Ramirez and L. M. Lechuga, Sensors 2016, 16, 285; doi:10.3390

ideally suited for this. Micro-fluidics and photonics are a perfect match and integrating the two can be done at wafer level.

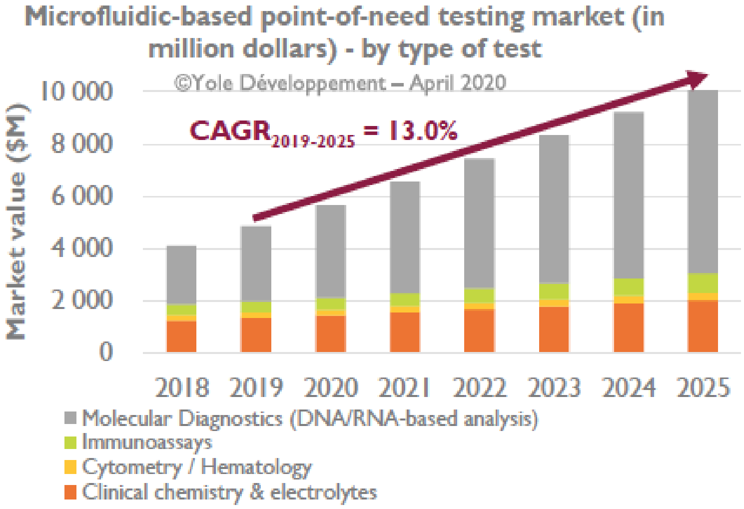


Fig.12 Microfluidic-based Point-of-Need testing market – (Yole Dèveloppement April 2020, www.yole.fr)

Fluorescence-based as well as label-free Point-of-Care tests based on integrated photonic devices technologies are appearing more and more in the market (see Figure 12), for instance through the company Genalyte. The challenges to market introduction include pharmaceutical business models that need to change, costs, and clinical validation, involving all entities including health authorities, diagnostic companies, and pharmaceutical companies. The Covid-19 pandemic may prove to effectively lower this barrier.

Integrated photonic devices are also expected to play an important role in personalized medicine. Personalized medicine is an emerging field that promises radical changes in healthcare. It refers to the tailoring of medical treatments to each patients' individual needs and characteristics. Personalized diagnostic tests such as Alere-CD4 monitoring already exist and will spread in the near future.

TECHNOLOGY AND BUILDING BLOCKS OF POINT-OF-CARE DIAGNOSTIC DEVICES

Waveguides

For a ring resonator-based biosensor as an example, waveguides are the basic building block. Key parameters of the waveguides are:

<u>Low loss</u>: low-loss waveguides enable high-Q resonators.
<u>Bending radius</u>: integration of many sensors requires biosensors to be small. Moreover, small sensors help to reduce the sample volume required. In some architectures, a large Free Spectral Range is required, demanding small rings, and therefore small bending radii. SOI for instance allows relatively low bending radii, compared to other material systems.

Operating wavelength: biosensors can be made using standardized waveguide platforms for 1550 nm; however, using waveguides that are transparent at 850 nm are beneficial because the system components (sources, detectors) have lower costs.
Backscatter: back-scattered light gives rise to fano resonances and resonance splitting. Generally, this is not desired or must be accurately controlled.
Slot waveguides: the slot waveguide is a strategy to enhance the sensitivity. It requires high-end device processing.
Exposed waveguides: The sensitivity of the refractive index w.r.t. ambient index must be as high as possible and must be uniform across a wafer.
Reference waveguides: temperature reference devices must be impermeable to ambient.
Temperature dependence: ideally the sensor is temperature independent.
Polarization: the sensitivity to ambient index is polarization dependent.

Optical interfaces

The sensor chip should have an optical input and output. Permanent fiber connection is expensive, cost reduction and high robustness is obtained either with a temporary free-space coupling, or by flip-chip mounting of detectors and VCSELs. Flip chip components add to the cost of the single-use biosensor. Key parameters are:
Coupling efficiency: high efficiency enables operation at lower power, and reduced self-heating. It also improves signal-to-noise ratio, and facilitates large-scale multiplexing.
Bandwidth: the optical bandwidth must be sufficient for appropriate measurement.
Polarization: it can be advantageous if the optical coupler acts as a polarization filter to make sure that only one polarization state is applied to the sensor.

Composite building blocks: directional couplers / MMIs

Couplers between ring and bus waveguides are required to make a ring resonator. Key parameters are:
Split ratio: asymmetric split ratios are typically required to make high-Q resonators
Insertion loss: the coupler induces only minimal extra losses to maintain high Q.

Composite building blocks: ring resonators

The ring resonators are composed of ring waveguides and directional couplers. Key parameters are:
Free Spectral Range (FSR): free design parameter
Full Width Half Max (FWHM): small FWHM generally gives higher sensitivity, though signal processing can also provide good sensitivity at relatively large FWHM.
On/Off ratio: a large on-off ratio is good for accurate determination of resonance wavelengths.
Sensitivity (nm/RIU): determined by the waveguide geometry.
Absolute wavelength: in some architectures, the absolute wavelength must be controlled to provide an absolute rather than relative measurement.
Area: a small sensor area is advantageous for low sample volumes, and for integration of many sensors on a small chip. Small chip size in turn is advantageous to reduce costs.

Bio sensitive surfaces

Functional coating

- Selectivity: bind only specific biomarkers.
- Non-specific binding: other biomarkers do not provide a false signal.
- Lifetime: the coating can be stored over a long period of time before use.
- Localization: ideally, the functional coating is only in the immediate vicinity of the ring resonator so that scarce biomarkers do not bind outside the evanescent field.

  - Minimum size: the coating must be applied in small areas so that a small sample volume is sufficient to do a measurement.

Multiplexing

  - Number of sensors: multiple sensors (and reference sensors) can be multiplexed in series or in parallel. This puts demands on data processing (series) or the number of input / output ports (parallel).
  - Cross talk: the response of one sensor should not affect the reading of other sensors, within to-be-specified limits.

Microfluidics

  - Application specific: may contain different elements, number of inputs, etc.
  - Assembly: ideally on wafer scale to reduce costs

System aspects

With a set of biosensors on a chip, the biosensor system is not complete. It also involves (automated) handling of sensors and software for data processing, control and calibration. It needs to be integrated in an easy-to-use unit satisfying all relevant governmental regulations. It will have key performance specifications such as size (handheld?), level of multiplexing (multiple sensors on one chip), analysis time, sensitivity, selectivity, limit of detection and required sample volume. Specifications may differ from bio assay to assay.

A key parameter is the price: COG of the read-out unit, price of a biosensor chip, and price of a chip with functional coating. That ultimately determines the price of a single test.

Future developments

Today's technology can provide high-quality ring resonators: the optics is sufficiently mature for commercialization, as proven by for instance Genalyte. Further improvements in the domain of integrated optics are outlined below. Additional technology challenges are in the domain of the biochemistry and (localized) application of coatings to chips, and in advanced micro fluidics.

Improved sensitivity (regular milestone)

Specify: bulk sensitivity to be increased to 500 nm/RIU. This must result from optimized waveguide geometries, polarization, slot waveguides or smart sensor designs.
Measurable results: bulk sensitivity is objectively measurable.
Acceptable: with 100 nm/RIU already viable systems can be built. Increasing sensitivity will open applications involving smaller target molecules or lower concentrations.
Realistic: 200 nm/RIU should certainly be achievable.
Time: 100 nm/RIU (now) 200 nm/RIU (5 years), 500 nm/RIU (15 years).
Alternative: the wavelength shift is obtained at higher accuracy. This also increases sensitivity to noise, drift, temperature, vibrations, etc.

Absolute wavelength (desirable milestone)

Specify: the resonance wavelength of a ring resonator is known by fabrication.
Measurable results: absolute accuracy corresponds with required sensitivity
Acceptable: pre-calibration is the general way around, but this does not fit all applications
Realistic: possibly, it requires a photo-induced process step
Time: result obtained in 10 years
Alternative: pre-calibration of the chip under measurement conditions.

Bend radius (desirable milestone)

Specify: at 850 nm wavelengths, the bending radius of a waveguide is in the order of 100 um. This must be reduced to enable reduced sample volume, higher degree of multiplexing, and lower cost at a given chip price per area. Increased bend radius should not compromise sensitivity. It requires better process control to reliably make thicker layers at low stress, and to enable more aggressive designs that will fail in case of large process variations.
Measurable results: more sensors at smaller chip area
Acceptable: 50 um radius
Realistic: small compromise on sensitivity may be acceptable.
Time: 100 um (today), 50 um (2 years), 40 um (5 years), 25 um (10 years)
Alternative: if visible wavelength bend radii cannot be reduced, over-all system specs may be only achievable on SOI, accepting the higher costs of lasers and detectors for 1550 nm.

Chip cost and volume (critical milestone)

Specify: chip price drops to < 0.05 EUR / unit at 1000,000 chips / year
Measurable results: negotiable.
Acceptable: 0.5 EUR / mm2 may be acceptable. Chip price should not exceed 25% of the price of the complete (disposable) test cartridge.
Realistic: 0.5 EUR / mm2 is a realistic number.
Time: 0.5 EUR / mm2 in 2 years, 0.1 EUR/mm2 in 5 years, 0.05 EUR/mm2 in 10 years.
Alternative: if the chip real estate remains costly, more effort should be put into reducing chip area for a give number of sensors.

Efficient couplers to fiber (regular milestone)

Specify: coupling efficiency in/out of the chip must be improved to have better SNR and therefore better accuracy, and to enable vast multiplexing.
Measurable results: over-all chip transmission.
Acceptable: 3 dB/interface. Current numbers are 5 dB/interface for non-optimized SOI, and this enables realization of simple sensor systems. Improvement beyond that is certainly needed.
Realistic: 2 dB/interface. Overlays in SOI, and spot size converters in dielectrics, should enable this.
Time: 5 dB/interface (today), 3 dB/interface (2 years), 2 dB/interface (5 years). The timing of this is rather fast, as it is realistic and highly beneficial.
Alternative: use more laser power, improved electronics and signal processing, slower measurements.

Multiplexing (regular milestone)

Specify: Number of individually addressable sensors per mm2 increases to 400, to allow detection of more biomarkers in smaller sample volumes.
Measurable results: more individually addressable sensors per mm2.
Acceptable: 5 sensors / mm2 may be acceptable.
Realistic: 400-sensors/ mm2 is a realistic number.
Time: 5 sensors / mm2 in 2 years, 50 sensors / mm2 in 5 years, 400 sensors / mm2 in 10 years.
Alternative: Higher sensitivity would allow dilution of the sample to increase sample volume and still be able to detect the (lower) biomarker concentrations.

Photonic bio sensors	[Unit]	5 years	5-10 years	10-15 years
Annual revenue	[$/year]	2,4M	6M	12M
Cost price	[$/unit]	0.65	0.12	0.07
Energy consumption	[W]	n.a.	n.a.	n.a.
Wavelength range	[nm]	850 / 1550	850 / 1550	850 / 1550
Reliability	[%]	99	99.9	99.99
Footprint	[mm²]	1	0.5	0.25
Output power	[W]	n.a.	n.a.	n.a.
Life cycle	[Years]	Single-use	Single-use	Single-use
Bandwidth	[Bps]	n.a.	n.a.	n.a.
Swap time	[Seconds]	30	2	1
Speed	[M/s]	n.a.	n.a.	n.a.

MINIMALLY INVASIVE INSTRUMENTS

The advance of various medical technologies has enabled minimally invasive surgical procedures. Surgery by definition is invasive and many operations requiring incisions of some size are referred to as open surgery. Incisions made can sometimes leave large wounds that are painful and take a long time to heal. Minimally invasive surgery encompasses surgical techniques that limit the size of incisions needed and so lessen wound healing time, associated pain and risk of infection. So, minimally invasive instruments support the goal to have less operative trauma, other complications and adverse effects. The typical operation time is longer but hospitalization time is shorter. Usually special medical equipment may be used, such as fiber optic cables and special surgical instruments handled via tubes inserted into the body through small openings in its surface[4].

In principle minimally invasive instruments are mechanically limited and to be treated as flexible instruments. Correct functional behavior can be improved by adding specific sensing capabilities that provide a haptic feedback to the operative, i.e. surgeons. This is of particular use in those situations where sight and sensorics are limited, either due to the accessibility and/or Electomagnetic Interference (EMI) restrictions, i.e. in MRI environments. With the advantages of optical fibers being made of glass that is insensitive to EMI, chemically inert, small, of low weight and allowing distributed sensing in a single wire, fiber optic sensing is ideal for many applications.

Shape sensing and haptic feedback are widely adaptable means to remotely add a sense of direction and applied forces to instrument operation by appropriate operatives. An example of such a product is the OptiGrip, a co-development commissioned by EFI[5]. It is the world's first optical haptic feedback grasper,

---

[4] Wikipedia contributors. "Minimally invasive procedures." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia, 30 Sep. 2017. Web. 15 Jan. 2018.

[5] Fiber optic sensing based on integrated photonics, a key enabling technology platform for medical applications, T. van Leest[1], R. Evenblij[1], A. de Leth[2], P. Kat[3], M.P.H. Vleugels[4], 1) Technobis Fibre Technologies, Technobis Group, Alkmaar, The

as well as the first OEM product with an ASPIC-based system. State-of-the-art optic sensors are used to measure the amount of force exerted with the grasper tips and coupled back to the Grip with adjustable feedback strength, thus allowing a tremendous improvement of the sense of feel the operator has of its actions during surgery.

For example, it allows to distinguish between different types of tissue, even feel artery pulsation and benefits from the shortness of the training process for specialists.

In general, the statement is that minimally invasive interventional techniques reduce the costs of the health care system and help societies to cope with the increasing difficulty to provide care at acceptable standards. The type of interventional techniques most needed, yet least provided, are those procedures with which one can access deeper structures in the human body with minimal damage to healthy tissue. Current technical limitations in navigating instruments of minimal dimensions make that in the majority of all interventions the traditional open approach is still used.

As an example, steerable MRI compatible robotic instruments with precise force sensing for accurate tissue characterization and dexterous navigation in percutaneous interventions were developed, where biocompatible fiber sensors were applied to provide a means to monitor deflection and shape of a percutaneous needle apparatus for biopsies procedures. Shape sensing would add real-time directional sense during operation that typically only would be provided through (slow) MRI and CT monitoring.

OTHER HEALTHCARE APPLICATIONS

Optical Coherence Tomography, Point-of-Care testing and minimally invasive instruments are just three areas where PIC technologies will have a significant impact on diagnosis and therapy in Healthcare. Other applications include cytometry, oximetry and with longer time horizons DNA/RNA sequencing and potentially also the introduction of PIC to optogenetics. In that field, the addressing of large functional ensembles of neurons, i.e., "brain circuits" is achieved by electro-optically stimulating neural circuits with very high spatiotemporal precision.

CRITICAL (INFRASTRUCTURE) ISSUES

TECHNOLOGY NEEDS

BANDWIDTH

Interconnect bandwidth demand is growing quickly. Silicon photonics is expected to become available in a broader range of applications because of (1) the cost advantages of silicon processing and (2) packaging to create increased density of interconnections.

Netherlands, thijs.vanleest@technobis.com, 2) Technobis Mechatronics, Technobis Group, Alkmaar, The Netherlands, 3) Technobis Group, Alkmaar, The Netherlands, 4) Endoscopic Force-reflecting Instruments B.V., The Netherlands.

POWER

The challenge of electrical power defines the limits of how components are integrated; that is, the number of cores on a processor chip, the interconnect density, the speed trade-offs associated with different signaling options, and the advantages of optical vs. electrical.

ENVIRONMENT

Most sensing applications are in uncontrolled environments. Encountering corrosive environments is more frequent, and the electronics-photonics must be able to withstand those elements. Temperature extremes and moisture protection are also necessary in uncontrolled environments. Biophotonics includes the focus on control of air, water and food safety and quality.

LATENCY

Latency is not critical in most sensing applications.

MINIATURIZATION

Miniaturization is a major trend in every industry sector, and Healthcare is no exception. Until now, healthcare technologies have often been bulky, expensive systems that are installed in hospitals and life science labs (the CT scanner, MRI, etc.). Today, more compact and affordable systems are available at the doctor's office (Point of Care). The next step will be small devices available at a patient's home (Home Care), or anywhere for that matter (glucometer, oxymeter, electro-cardiograms on smartphones, etc.).

TECHNOLOGY CHALLENGES

The new technologies that are becoming available must meet the challenges identified in the previous sections: bandwidth, power, thermal, and environmental. Key new processor packaging technologies being developed will impact the technology that can be leveraged. With the increase in mobile electronics, a new set of technology becomes available, but at a much different scale of size and bandwidth than needed for other markets.

The packaging and component technologies that will be developed and integrated into applications will be those that develop acceptable cost and risk of adoption. Thus, the packaging for integrated silicon photonic components must utilize as much common technology as possible from the technology developed during the next decade for conventional electronic packaging. This utilization of electronic packaging technology is illustrated in Figure 17.

The following seven paragraphs discuss six packaging technology challenges. The first five challenges address electronic packaging; the last three address challenges for integrated silicon photonic packaging.

TSV

Through Silicon Vias (TSV) are enabling 2.5D silicon interposers and 3D chip stacking providing high-density interconnect and therefore, high bandwidth capability between components. Also, glass interposers may be a factor for some applications with Through Glass Vias (TGV) providing advanced connectivity. Memory modules have already been introduced with TSVs and their applications will continue to expand. The introduction of TSV has lagged behind expectations due to yield and cost issues that need to be addressed.

ADVANCED PACKAGING -SIP AND POP

A critical issue in electronic-photonic systems is the selection of packaging technology. The choice may differ by application, and several different technologies may be used in a single application. Currently the packaging and manufacturing approaches used for system integration include:

- Wire-bonding of side-by-side chips,
- Flip-chip integration,
- Wafer-scale 3D integration, and
- Monolithic integration.

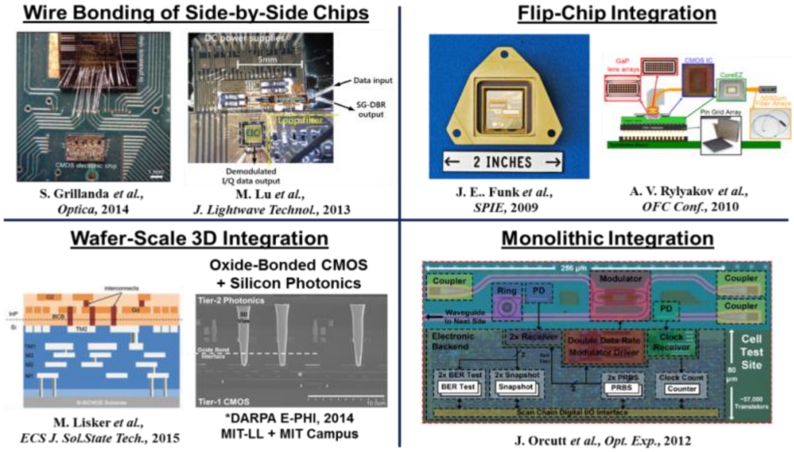


Figure 17. Packaging and manufacturing approaches used for system integration,

Systems in Package and Package on Package technologies provide the capability of optimizing cost and function in a package. Integrating voltage regulation and silicon photonics with processor chips or bridge chips will increase. Mobile systems are where the current growth driver in this technology segment originates. Integrated Photonic applications will adopt these advanced package technologies that enable high-bandwidth interconnect in the existing power envelope.

LOW-LOSS DIELECTRICS FOR PACKAGES

Reduced dielectric loss materials are used increasingly for high-speed electrical channels, and the demand for those materials will increase as speeds above 50 GB/s/channel are adopted. However, low-loss electrical channels also require attention is given to processing and the design of all the elements of packages and printed circuit boards. The copper roughness, via stubs, antipad size and shape, and internal via and PTH design are all as important as the loss characteristics of the dielectric material. Coreless packages and thin laminates for improved via and PTH design will reduce discontinuities significantly for high-speed channels.

The footprint design at the electrical connector will require special design to avoid becoming the bandwidth-limiting factor in a package to board, backplane, or cable interconnection. This footprint design includes:

- Via, or PTH diameter,
- Length and stub,
- Antipode size and shape, and
- Routing escapes from the vias, or PTH, and land sizes.

Reference plane gaps, holes, and interconnection to PTHs that create return path discontinuities are part of the channel design.

EFFICIENT POWER DISTRIBUTION

To address these technology challenges efficiently, the power efficiency must also continue to improve. The channel shielding requirements demand a greater number of layers and vias for the high-speed channel. Improving the power efficiency demands lower impedance power distribution for lower I^2R loss and lower inductance for faster regulation. This shielding requirement creates a trend towards more metal and placing regulation closer to the loads competing with the short reach signaling and increased signal shielding. These trends also leverage the advanced packaging concepts of TSV, SiP and PoP described above to contribute to the economic driver to adopt this technology.

OPTICAL INTERCONNECTS

Optical interconnects will be used more broadly. Integrating optical devices into packaging to reduce trace length and power demand for high-bandwidth interfaces will require advanced heterogeneous packaging that leverages SiP and PoP technology components for increasing integration at the package level. Low-cost single-mode optical connectors will be needed to support pluggable electro-optical modules.

CONCLUSIONS

The quickly increasing number of interconnected devices is driving photonic technology and the resultant growth of data bandwidth between those devices. Meeting the demands of increased data bandwidth, processing and storage must be done under the constraints of capped available power for most applications. The attributes that are important are data bandwidth, power efficiency, and the environmental conditions in which the systems operate. Addressing these challenges will require:

- Advanced integration using stacking with vias,
- Advanced packaging integration built on the System-in-Package and Package-on-Package technologies (already in production use in mobile computing),
- Integrated photonics to enable the integration of dense optical systems,
- High-bandwidth connectors,
- Low-loss materials and design features to maximize the reach of electrical interconnect, and
- Power regulation integration to improve efficiency.

The increased performance that these enabling technologies will provide must be priced below the cost of existing technology for their adoption by the industry.

CONTRIBUTORS

Bob Pfahl, IPSR/iNEMI-Editor

Ben Miller: University of Rochester

Anu Agarwal: MIT

Nick Usechak: U.S. Airforce Research Center

Thierry Robin, Tematys

Paul van Dijk, LioniX

Ton van Leeuwen, Academic Medical Center Amsterdam

Rolf Evenbleij, Technobis

Frans Harren, Radbout University Nijmegen

Peter Harmsma, TNO

Fair use disclaimer: this report contains images from different public sources and is a compilation of the opinion of many experts in the field for the advancement of photonics, the use of which has not always been explicitly authorized by the copyright owner. We are making such material available in our efforts to advance understanding of integrated photonics through the research conducted by the contributors of this report. We believe this constitutes a fair use of any such copyrighted material as provided for in section 107 of the US Copyright Law. In accordance with Title 17 U.S.C. Section 107, the material in this report is distributed without profit to those who have expressed a prior interest in receiving the included information for research and educational purposes.