# Technology prognosis of Biophotonics (imaging, diagnostics, monitoring)

## Introduction: Biophotonics technologies and markets

Biophotonics is a multidisciplinary interplay between light and living matter, which harnesses light-based technologies in medicine, life sciences and related fields. The main advantages of biophotonics over the traditional clinical technologies are non-invasiveness and reduced time of diagnostic procedures (making them more patient-friendly) as well as more focused and precise therapeutic and surgical procedures (resulting in higher success rate). The biophotonic market is currently in its nascent stage, with augmenting scientific research observing evolution in technology and offering a vast variety of applications.

Biophotonic technologies have received growing attention in the recent years, with diagnostics and monitoring paving path for new optical technologies. Exhaustive research and investments have resulted in the development of laser fluorescent, confocal and two-photon microscopes that provide images of molecules and tissues at exceptional resolution, contributing toward unprecedented diagnostics. Laser photodynamic therapy (PDT) is a new promising technology to combat cancer; recently is has switched to more cost-efficient light-emitting diode (LED) irradiation technology. A novel photosensitizing fluorescent protein called KR (Killer Red), which has the potential in gene therapy has been identified, and a novel therapeutic strategy called PhotoGene Therapy (PGT) for pathologic angiogenesis was proposed. Optogenetic techniques open the way to trigger brain functioning by photoexcitation with blue and yellow light. They are just a few examples illustrating the enormous potential and accelerated demand in the photonic technologies for healthcare. Besides, a number of non-medical applications of biophotonic technologies are expected to offer several growth avenues over the next few years. In figures, the global biophotonics market is expected to reach USD 59.9 billion by 2022 from USD 36.8 billion in 2016, at annual growth rate of ~ 10.2% [1].

However, the market is retrained so far by the slow adoption rate due to the low acceptance from end users, cost benefit inefficiency, and lack of skilled professionals. Due to the potential of utilizing optical technique to comprehend the functioning of cells under surveillance, without damaging the integrity of the same, biophotonics is projected to witness a more significant growth during the forecast period of 2017-2022. Some of the factors driving the Biophotonics market are:

- Growing geriatric population
- Increasing use of biophotonics in cell and tissue diagnostics
- Emergence of nanotechnology in biophotonics
- Developments in optical and opto-acoustic tomography
- Market penetration in non-medical sector

The market for biophotonics is segmented, based on application (e.g. diagnostics, therapeutics, monitoring), technology (e.g. surface imaging, inside imaging, see-through imaging, optical microscopy, spectro-molecular, biosensors, medical lasers), and geography. North America currently holds the largest share in the market thanks to the increased investment in R&D activities, but also due to the rising prevalence of cancer. While Europe follows North America, the Middle East & Africa and Asia-Pacific regions are expected to witness rapid growth and contribute to the biophotonics market revenues over the coming years.

This technology prognosis is prepared based on results of the expert panel discussion "Biophotonics technology trends" carried out during the 2nd International Conference "Biophotonics Riga – 2017" which was organized with support of the SOPHIS programme on 27-29 August, 2017 in Riga [2].

## 1. Future trends in tissue imaging

A part of this project was devoted to development of new technologies for non-contact skin macro-imaging. Generally, also other tissues can be specifically macro-imaged if they are freely accessible to the imaging sensors/cameras, for instance surgically excised ex-vivo tissue samples (e.g. breast tumours) or internal in-vivo tissues (e.g. brain) during open surgeries. The identified main general trends in tissue macro-imaging are outlined below.

### 1.1. Hyperspectral and multispectral imaging

Collecting a number of narrowband spectral images in hyperspectral (overlapping bands) or multispectral (non-overlapping bands) modalities after processing provide x-y images of molecular compounds on the tissue surface and/or sub-surface, so far unused unique diagnostic information. Both imaging modalities certainly will be further developed in coming years and also combined with other imaging techniques (e.g. fluorescent imaging, OCT) for multiplexed imaging in translational research and for clinical applications. Standardized tissue phantoms for imaging will be created and validated to set "golden standards" for clinical use. Hyperspectral digital tissue microscopes for stereology analysis will be further developed, as well. Mobile camera-supplied devices like smartphones will be equipped with handy spectral illumination add-ons to ensure wider applications of hyper/multi-spectral imaging for personalized medicine and home-based healthcare. To reduce the image acquisition time, single-snapshot spectral imaging technologies will be further developed.

### 1.2. Fluorescence imaging

Fluorescence imaging is a powerful tool for real time feedback of therapy and surgery procedures, especially in brain surgery and endoscopy. Set of tissue autofluorescence imaging parameters (intensity, lifetime, photobleaching rate, etc.) provides useful information on tumour chemical composition and its margins, so this technique for sure will be further developed in future. Sensitized fluorescence (i.e. with fluorescing additives) imaging is and will be widely used for photodynamic therapy feedback; the recent trend is use of up-converting nanoparticles as fluorescing agents to provide deeper penetration in tissues by NIR excitation (e.g. with 980 nm). A novel optical treatment modality – nano-theranostics is and will be developing rapidly.

### 1.3. Polarization imaging

Tissue imaging with polarization sensitivity is another emerging area of biophotonics. Analysis of Mueller matrix has shown ability to detect cancerous regions in tissue ex-vivo samples, and intensive research is going on to transfer this technology for in-vivo applications. A new research field – twisted light polarimetry and imaging – is being developed currently.

### 1.4. Photoplethysmography imaging

Photoplethysmography imaging (PPGI), one of research directions in this project, has gained global attention during the recent years. Rapid improvement of temporal and spatial characteristics of consumer and professional cameras has opened new possibilities for remote detection of nearly real-time images of human skin blood perfusion and arterial pulsation parameters (e.g. pulse rate, amplitude) with high resolution at considerable distances, up to hundreds of meters. This exciting biophotonic technique finds applications not only in healthcare (distant heart rate and respiratory rate measurements, anaesthesiology control, etc.) but also in security systems, forensics and other non-medical areas. Big companies like PHILIPS develop a series of PPGI-based consumer products that will be widely used in near future.

The identified future trends related to the above-regarded imaging instrument designs are: reduced size/weight, enhanced resolution, cable-free (battery powered), mobile platform or smartphone based, non-contact, fast – preferably real time or snapshot imaging.

## 2. Future trends in optical clinical diagnostics

### 2.1. New principles of operation

Currently the most popular optical techniques for clinical use are spectrometry for blood and tissue fluid analysis and microscopy for tissue sample cellular analysis. Novel imaging technologies are entering the field (see above), as well as several principally new techniques. One of those is optical clearing of tissues – application of specific liquids that reduce scattering and make the superficial layers of tissue more transparent, so increasing the light penetration depth and enhancing the quality of deep tissue images. A revolutionary idea to be implemented in future is tissue laser principle for diagnostics under opto-acoustic interactions. Twisted light tissue polarimetry is a promising future technology, as well.

### 2.2. Combined data collection

To increase specificity and sensitivity of optical diagnostics, several optical techniques are to be combined for faster implementation of biophotonics in healthcare. As example, laboratory tests and primary clinical trials have confirmed efficiency of combined reflectance, fluorescence and Raman spectroscopy for skin cancer diagnostics. Another efficient combination under development is ultrasound + light, enabling to visualize under-skin vascular networks with very high resolution. Studies of numerous other combinations are going on and certainly will result with new clinical technologies in future.

### 2.3. Improved user's friendliness

Probably the main advantage of optical technologies in diagnostics is non-invasiveness, in many cases also non-contact procedures, which certainly are more patient-friendly than the routine clinical methods. On the other hand, biophotonic technologies have to be user friendly also for doctors, nurses and other medical personnel. This determines some future trends in biophotonic instrumentation for clinical applications. First, informative touch-screens will be widely used. Second, the device outputs will provide clinical diagnostic criteria compared to their critical values instead of the directly measured physical parameters or specific (e.g. spectral) images. Third, the devices will be portable – pocket sized and wireless. If internal processors will not be able to provide all calculations, the initial measured data will be transmitted to external server or computer and the results returned to the device via *bluetooth* or *wi-fi* network. Besides doctors and other medical personnel, more and more biophotonic devices are targeted for personal use (e.g. smartphone add-ons and applications), so user's friendly designs should be ensured in this case, as well. First of all it relates to customer level smartphone devices for diagnostics – 6.3 billion smartphones are estimated to be in operation worldwide by year 2021.

Generally, the main future trend for biophotonics in diagnostics is transfer from pre-clinical studies to routine clinical applications. As many pre-clinical trials are running now, we can expect a number of certified optical clinical diagnostic technologies in a near future.

## 3. Future trends in optical in-vivo monitoring

### 3.1. Real time cerebral blood flow monitoring

Cerebral stroke and brain traumas are between the most fatal human health disorders, mainly caused by uncontrolled blood leakage in brain. In spite of highly developed brain surgery technique, real time blood flow monitoring remains an unsolved issue and as a challenge for biophotonics. Laser Doppler flowmetry and laser speckle techniques, as well as PPG sensors can detect only the upper vascular networks. For deeper brain blood flow monitoring opto-acoustic methods may be helpful and will be increasingly developed in the coming years. Also photon time-of-flight (TOF) technologies may appear useful for this clinical application.

### 3.2. Camera-based health monitoring

Due to the aging population worldwide, home self-monitoring is becoming an increasingly important component of general healthcare. Camera-based health monitoring technologies represent another future trend of biophotonics. PPGI and similar techniques are well-adapted for continuous real-time monitoring of cardiovascular (CV) and tissue viability parameters – heart rate, arrhythmia, blood perfusion, etc. The monitoring cameras may be installed stationary, e.g. in bedrooms to control CV parameters during the sleep, or, thanks to their tiny dimensions, directly fixed at specific locations of interest on the body. One possible application for that is continuous monitoring of spectral and spatial changes in healing wounds or suspicious skin lesions. Deep learning databases are under intensive development currently; they will provide threshold values for many human health parameters to be monitored in the nearest future.

## References


[1] Global Biophotonics Market – Growth, Trends & Forecast (2017 - 2022). https://www.mordorintelligence.com/industry-reports/biophotonics-market?gclid=Cj0KCQiAg4jSBRCsARIsAB9ooavKn01497jnfCzOghh5iG7IiRKSCJr53xEZ7Pcm9i5U3pQHP8hIRO0aAmojEALw_wcB

[2] www.lu.lv/bpr17