Asian Journal of Physics
Vol. 33, Nos 3 & 4 (2024) 287-306
Available on: www.asianjournalofphysics.com

Medical diagnostics using gas in scattering media absorption spectroscopy GASMAS

Katarina Svanberg[1,2] and Sune Svanberg[3,2]

[1]*Division of Oncology, Department of Clinical Sciences, Lund University Hospital, SE-221 85 Lund, Sweden*

[2]*Lund Laser Center, Lund University, P.O. Box 118, SE-221 00 Lund, Sweden*

[3]*Department of Physics, Lund University, P.O. Box 118, SE-221 00 Lund, Sweden*

Dedicated to Professor Anna Consortini for her significant contributions and pioneering works in the field of atmospheric turbulence and her continuous commitment to promote optics at global level

Lasers, optical spectroscopy and imaging techniques provide many powerful approaches to fast, accurate and minimally invasive medical diagnostics. While most frequently broad-band spectroscopic techniques are used for tissue characterization, a new class of methods instead utilize narrow-band lasers for the monitoring of free gas *in situ* in the human body. The gas in scattering media absorption spectroscopy (GASMAS) technique relies on the fact that the absorptive imprints of free gases are typically 10,000 times narrower than those due to the tissue surrounding gas-filled vacuoles and cavities. Multiple scattering enhances the optical pathlength through the gas, but leaves absolute concentration assessments as a challenge. The GASMAS technique has many applications in food and fruit monitoring, as well as in studies of construction materials and pharmaceutical preparations. However, the present review will focus on emerging diagnostic techniques for common sinus and middle-ear infections (sinusitis and otitis), for surveillance of lungs, in particular for premature infants, and for studies of necrotizing bone structures.

Doi: 10.54955/AJP.33.3-4.2024.287-306

Keywords: Biophotonics, Optics, Gas spectroscopy, Medical diagnostics, GASMAS technique.

1 Introduction

Scattering, fluctuations and turbulence are very common physical phenomena encountered in optics, and frequently carry a negative connotation. Certainly, image blurring and impaired visibility are unwanted effects. The phenomena are of statistic nature and numerous efforts have been invested in describing them and also in searching remedies. The field of atmospheric light propagation has been the subject of much research (see, e.g., [1-3]). Biological tissues exhibit both scattering and absorption of light. The field of biophotonics deals with medical and biological applications of light, which is most commonly generated by lasers or light-emitting diodes (LEDs). Recent reviews of this rapidly expanding field include Refs [4-7], while also the numerous applications to other fields are covered, e.g., in [8]. Basic laser-tissue interaction mechanisms are discussed, e.g., in [9], and are in operation in diagnostic as well as therapeutic contexts. Many of these applications depend strongly on the choice of interaction wavelength, as, e.g., in photodynamic therapy (See, e.g., [10]).

Biophotonic studies most frequently concern tissue, which is condensed matter with comparatively broad spectroscopic fingerprints - seldom sharper than 10 nm. In contrast, free gas exhibits sharp absorption lines, typically 10,000 times more narrow. This calls for the use of narrow-linewidth lasers as biomedical light sources, in a similar way as when probing free gases, e.g., pollutants in the atmosphere [11,12].

Corresponding authors
e mail: sune.svanberg@fysik.lth.se (Sune Svanberg); *katarina.svanberg@med.lu.se* (Katarina Svanberg)

Free-gas monitoring in connection with biophotonics investigations basically has two different aspects. The first one concerns breath analysis, which is performed extra-corporally. Here, the monitoring is performed in a gas cell, which is filled with the sample of interest [13-15]. A high sensitivity is needed, since the concentration of gases, which are specific to certain diseases, are low.

The second type of free gas monitoring in biophotonics is a more recent one, where the studies are performed *in situ* in living tissue, such as paranasal sinuses, the middle ear, lungs and intestines, as well as certain bone structures. Here, the gas is present in cavities and pores imbedded in frequently massively scattering tissue. Then two main problems have to be handled. Firstly, the optical pathlength for light passing through gas becomes undefined, meaning that the Beer-Lambert law ([8], p 181), which is normally used for gas concentration assessment, is not directly applicable. Secondly, massive scattering and absorption in the surrounding host tissue cause very strong light attenuation. This is the case even when using a light wavelength falling in the so called "tissue optical window" – 700 - 300 nm – where the absorption is comparatively low. Still, very little light reaches the detector, and the fractional absorption imprint from the interrogated gas is also very small. Therefore, signals are frequently noisy and require sensitive detection electronics.

A new variety of spectroscopy for monitoring free gas was developed to overcome these problems: Gas in scattering media absorption spectroscopy (GASMAS) [16,17]. It emerged by combining experience from the environmental monitoring field, where sharp absorption lines in a non-scattering environment are detected, and the field of biophotonics, where broad-band absorptive features are studied in a heavily scattering scenario [18-20]. As pointed out, scattering normally causes a lot of problems, but in the context of GASMAS it also brings along some benefits – the pathlength through gas is increased by the massive multiple scattering, which enhances the fractional absorptive imprint.

Our paper is organized as follows. A brief medical background to medical diagnostics in general and *in-situ* gas monitoring in the human body in particular is provided in the next section. Then, the basics of the GASMAS technique, and how to overcome specific associated problems encountered in scattering media, are presented in Sect 3. Non-medical applications of the technique, e.g., in material sciences, food sciences and the pharmaceutical field are also briefly described for completeness. Four following sections then discuss applications to the human sinus cavities, studies towards the monitoring of middle-ear infection, lung monitoring for new-born children with potential extension to adults, and the study of bone decay. Conclusions and an outlook for the future are finally presented.

2 Medical background and the need for fast and non-invasive detection, monitoring and characterisation of tissue

2.1 General background

Therapy decisions in medicine are based on specific procedures to detect and specify the disease present. Even with an immense development in the medical field there are still a certain number of unmet needs to be solved in the health care sector. These include early detection of a disease as well as development of more individualized medical therapy. According to statistical estimates, the incidence of malignant tumor cases is expected to be doubled by 2040. Another prediction is that there will be 35 million new cancer cases by 2050, which is a 77% increase from the sitution today [21,22]. An explanation for this situation is the aging population. As a matter of fact, age is the paramount risk factor for developing malignant tumors. Nine out of ten cancers are diagnosed in people above the age of 45 years [23,24].

This fact calls for actions within the medical health care sector. Large surgical procedures may need to be exchanged for more non-invasive modalities with retained efficacy and less side-effects. The development of robotic surgery is one such trend [25], but there are also other ways of treating tumors embedded in the body, e.g., with interstitally delivered laser light, a true minimally invasive technique [26,27].

Along with the increasing number of malignancies, another situation has to be in focus for attention: the alarming and rapidly growing antibiotic resistance of bacteria, which seems to threaten the whole World. The World Health Organization even warns that we may enter a situation similar to the pre-antibiotic era facing an also increasing incidence of infectious diseases [28].

These clinical situations are examples, where it would be of great value to develop complementary non-invasive laser/light based spectroscopy methods for more precise detection and classification of the problem. Potentially attractive features of optical techniques include non-intrusiveness and real-time presentation of findings with high percentage numbers for sensitivity and specificity [29,30].

A lot of translational research efforts in biophotonics have been pursued, and some important additions have been brought all the way from the laboratory to the clinic. The true success story is the development of optical coherence tomography (OCT), both from the aspect of improved care of patients with retinal problems, and from a commercial point of view. OCT has really revolutionized some diagnostic procedures in ophtalmology. Every patient with retinal problems arriving to the ophtalmologist´s office normally has an OCT procedure performed [31,32].

We will give some background facts in various fields, pertinent to biophotonics, including early cancer detection, and some common infectious diseases. Furthermore, we will discuss some critical aspects in neonatology, related to the fact that 10% of all babies these days are born preterm and therefore need special therapy [33]. Some aspects of osteoarthritis will also be elucidated, taking into account that more than 25% of the population is affected by early onset from the age of 45 years [34]. All these various clinical situations will be related to possible biophotonics solutions resulting in an improved situation for the health sector and better care benefitting the patients.

2.2 Early tumor detection

The available arsenal of modalities for tumor detection includes ionizing-radiation-based techniques, such as computed tomography (CT) scintigraphy (SPECT) and positron emission tomography (PET), but also ultrasound imaging and magnetic resonance imaging (MRI). Although very advanced, the conventional diagnostic techniques fail to detect very early tumor growth when the malignant lesion is only a few cell layers thick, and long before symptoms of a malignancy are recognized. Taking into account that the prognosis for the patients is clearly related to early diagnosis, the incitament to develop techniques for early detection is clear [35]. Complete response rates reach above 90% for many malignant tumors if discovered at an early stage.

Hollow organs are investigated using endoscopic procedures in combination with biopsies to collect tissue samples for histopathological investigation. The challenge is to find the areas of interest, the early onset of cancer, which might be invisible, and therefore "blind" biopsy is performed with a certain risk to miss the targets due to their subtle features [36]. One clinical example where a biophotonics technique has been developed and to a certain degree is routinely used is in urology, where dramatically improved possibilities for early tumor detection for *in situ* bladder cancer are now available. By using laser-induced fluorescence imaging, non-visible tumor, earlier easy to miss, can be detected with high specificity and sensitivity in real-time. This means that not only the papillary tumors are identified by endoscopy, but also the non-visible carcinoma *in situ* lesions, which have a potential to grow right through the mucosa and develop a life-threatening disease within a short time span [37,38]. The versatility of this technique is quite clear and the potential for other clinical applications is obvious.

2.3 Infectious diseases and antibiotic resistance

A general trend for infectious diseases is an increasing incidence worldwide. This is due to many factors, out of which one is the climate change [39]. This increasing incidence of infections in combination with the alarming increase of multi-drug resistance among pathogenic bacteria constitutes a true challenge to the whole World [40,41,28]. The situation has to a certain degree been ascribed to the misuse of the medication and the unavailability of newer antibiotics [42]. In 2019, 1.27 million deaths were directly attributed to drug-resistant infections globally. By 2050, up to 10 million deaths are predicted to occur annually for the same reason [43,44].

The World Health Organization (WHO) points out the fact that the antibiotic resistance may hamper the possibility to treat some very widespread and serious diseases. This is the case for tuberculosis, for which first- and second-line antibiotics show a failing effect and a third line is not available.

The agents causing infectious diseases are investigated by Polymerase Chain Reaction (PCR) or Petri-dish bacterial growth, often with an antibiotics response study [45]. In such a way, the efficacy of the antibiotics is classified in relation to the bacteria. The majority of antibiotics were developed during the period 1960-1980, and after that large pharmaceutical companies have departed from research and development on innovative antibacterial drugs. The development of new classical antibiotics has decreased substantially. This is particularly the case in the US, but the trend is the same in Europe [46]. This fact is mainly due to economical aspects, since the health trend, supported by the health organizations, is to use as little antibiotics as possible to as few patients as possible.

An estimation reveals that more than half of the use of antibiotics in human medicine is unnecessary, as virus and not bacteria [47] cause the infections. The over-prescription of antibiotics can be illustrated by taking the examples from some common diseases, such as sinusitis and middle-ear infection. It is well known that a substantial part of the sinus infection cases reverts to health only with anticongestion- and pain-relieving medication [48]. With the anticongestion sprays, the connecting channels from the sinus cavities open up and the enclosed fluid can be released. Comparative studies of patients with acute sinusitis have been performed. The patients were randomly given antibiotics or not. The consensus was that antibiotics should be reserved only for carefully selected patients with a higher probability for developing severe bacterial disease, and not as a standard action to the entire non-selected group of patients.

Another common infectious disease is acute middle ear infection (*Acute Otitis Media, AOM*) in small children. Approximately 80% of all children will go through *AOM* infection before school age [49-51].

The disease appears in young individuals due to the anatomical structure of the channel, the *Eustachian tube* connecting the middle ear with the nose. This tube is in small children horizontal, which results in a slow release of the infectious fluid into the nasopharynx. Due to a stagnation of the fluid behind the tympanic membrane, the eardrum, which separates the middle from the outer ear, is overfilled with blood and becomes swollen due to the release from inflammatory cells. This causes the patients an intense pain. The standard diagnostic procedure is performed with an otoscope, but the investigation does not give any precise guidance for therapy. Usually, the standard result is a prescription of antibiotics, which in certain cases, particularly if the child is below one year of age, might be correct, but for children above that age most often the decision should rather be watchful waiting for a natural healing. Unfortunately, this recommendation is not followed and a true over-prescription results.

As the examples above show, there is certainly a true need for more precise diagnostics to guide in the therapy decision. In the case of sinusitis, one such possibility might be to use GASMAS to probe the oxygen content in the sinuses. If the concentration of oxygen is substantial and the channels between the sinus and the nasopharynx are open no antibiotics should be prescribed. In the case of *AOM*, one possibility is to use a combination of reflectance spectroscopy in order to objectively get a measure of the redness of the eardrum, and GASMAS to assess the oxygen concentration behind the tympanic membrane. A better guidance for the therapy outcome should be possible with such monitoring,

2.4 Neonatology

An increasing percentage of babies (approximately 10% worldwide) are born preterm and the majority suffers from deficient respiratory ability due to non fully developed lungs [33]. The lack of continous

24-hour bed-side surveillance of the lung function, and systems for identifying serious events, such as a punctured (*pneumothorax*) or collapsed (*atelectasis*) lung, indicates a true need for innovative actions in neonatology for improving the care and alert the personal for immediate actions.

Since the lungs are the last organs to be fully developed during the pregnancy, the preterm babies suffer from impaired breathing. The main problem concerns the alveoli, the small hollow structures at the end of the bronchioles. When fully developed the alveoli have an inner lining covered with a surface-active complex of phospholipids and proteins, the surfactant, which is produced in the lungs from week 26, and increases week by week [52]. The main function of the surfactant is to prevent the alveoli to collapse and fall together at the end-expiration. With insufficient surfactant, the result is a deficiency in keeping the volume of the alveoli, and the amount of inhaled air decreases. This means that the oxygen distribution to the blood stream from the liquid-air interface in the alveoli is limited, resulting in a too low saturation which affects all organs, and particularly much the brain.

Due to the insufficient lung development, the preterm infants have an increased risk to develop Acute Respiratory Distress Syndrome (ARDS) [53,54]. This syndrome is associated with fluid formation in the alveoli, which in turn breaks down the surfactant and prevents full air filling. ARDS, if not treated at an early stage, may lead to lung scaring and eventually to a stiff lung with breathing problems later in life [55].

A very critical situation for these vulnerable patients is if the whole or part of the lung collapses. This is called atelektasis and leads to reduced or absent gas exchange. If the lung alveoli cannot keep the volume, and an atelektasis happens, a serious following event may occur with a puncture (pneumothorax) of the lung. This is a very critical situation for the small infant and should immediately be observed. With no alarm system in place such events may not be observed instantly causing delayed action.

The therapy delivered to the small pre-term babies consists of the administration of artificial surfactant and continuous positive airway pressure support in an effort to keep the alveoli open and air filled. The conventional follow-up of the therapy is repeated X-ray-based imaging of the lungs, and blood-gas laboratory tests. The gas analysis only gives a global measure of the status and only indirectly tells about the lung function. The ionizing-radiation-based CT has a potential risk for the infant later in life and should be used with obvious precautions. It is quite clear that all efforts should be taken to avoid ionizing radiation to the small babies, in particular knowing that the risk of developing a malignancy later in life is 10-15 times higher than for non-exposed babies [56,57].

Continous photonics-based bed-side lung monitoring of the free oxygen has a true potential to add diagnostic strength in the surveillance of the status, and thus avoiding detrimental X-ray exposure. With an alarm function in the surveillance system, the critical events described can immediately be detected for fast actions.

With GASMAS there is a possibility to develop equipment, which could provide 24-hour surveillance of the lung function and also spatially resolve the lung lobes to more in detail follow the status. Such a system can also provide instantaneous evaluation of the effectiveness of a given medical intervention. The system might be referred to as an “optical stethoscope”.

Another complication for the preterm infants is the *necrotizing enterocolitis* (NEC), an acute inflammatory condition, where part of the intestine becomes necrotic with a risk of perforation [58]. The incidence ranges from 1-8% of all cases in preterm delivery. As NEC is a condition accompanied by strong gas release, it makes it a true candidate for GASMAS-based monitoring.

The handling of patients with severe Covid 19, the disease that has threatened the whole World, would probably have been improved with an interactive possibility to adjust the ventilator providing oxygenation of the lungs [59]. The challenge to take lung monitoring for small infants further to be used for older children and even adults is addressed in an ongoing research activity at our department.

2.5 Bone necrosis due to inadequate blood supply caused by fracture or medication

Bone decay relates to deficient or disrupted blood supply via the arterial vessel system in the bone membrane (the *periosteum*). A location, where this is of particular interest is the hip joint. Necrosis of the femoral caput in the hip joint (ONFH; osteonecrosis of the femoral head) is a late-state result of disrupted blood supply to the bone structure. The most common reason is a traumatic fracture [60]. However, also non-traumatic bone necrosis (NONFH) hits a certain number of mostly young patients and is particularly devastating if it occurs in the hip joint with the *caput femuri* affected [61-63]. The etiology is partly unknown, but there is a certain connection to steroid medication as well as to smoking and abuse of alcohol. This variety of ONFH is more common in China and Japan than in Europe or the US [64].

Early diagnosis of NONFH is difficult, since there is currently no standard diagnostic procedure that can reveal an early onset of the disease. Therefore, most patients with NONFH show substantial necrosis already at the time of diagnosis.

The developing of ONFH involves crack formation in the caput structure covered with the bone membrane. The necrotizing process is connected with the formation of gas, which builds up pores in the caput. With a situation, where no specific diagnostic methods are available, it would certainly be very valuable to develop a modality for identification of the process. Then the patient could benefit from an early intervention that may reverse the process or prolong the time before surgical intervention is necessitated by heavy pain [65]. GASMAS seems to be an ideal modality as it relies on gas monitoring in an enclosed organ, in this case the caput. Adopted for minimal-invasive arthroscopic investigation, with or without addition of laser-Doppler techniques for assessing the blood flow, it could really add diagnostic strength in the handling of this devastating disease affecting mainly young people.

3 Fundamentals of gas in scattering media absorption spectroscopy (GASMAS)

Porous materials are common, and occur as man-made structures or naturally occurring substances. Enclosures of gas are incorporated in the solid matrix material. Examples of common porous materials are wood, ceramics, polystyrene foam, pharmaceutical preparations, and food stuffs, including fruits. Pore sizes would vary widely and frequently reach the micro- or even nanometer scale. At interfaces, where there is a step change in the index of refraction, light transmitted into the medium will scatter. Multiple scattering will occur if pores are abundant and will result in a random walk of the photons. Light propagation at all is clearly only possible if the bulk material is reasonably transparent to light of the wavelength employed, and the material will then appear translucent. On a much larger scale, a similar situation occurs in atmospheric optics, where the light encounters scattering aerosol particles. Such situations can be probed by lidar (light detection and ranging) techniques [11,12]. If particles are abundant (like in clouds or in fog), multiple scattering occurs, and light will only propagate diffusely and visibility is lost. In the DIAL (differential absorption lidar) approach, minor polluting gas constituents can be monitored using a tuneable laser, which can sense the spectral imprint of the gas in the light, which is backscattered by mostly particulates (see, e.g., [66]). Contrary to the DIAL case, the gas inside the scattering pores within the bulk material is instead sensed in GASMAS. The strong difference in response to wavelength variation is critically utilized in both cases. The Mie scattering particles as well as the partly absorbing bulk material does not exhibit any sharp structures, which in contrast is the case for the free gas, with imprints typically 10,000 times sharper. Figure 1a shows the (large-scale) multiple scattering lidar case (scattering particles in air) and (b) the (small-scale) GASMAS case, with scattering pores in a bulk material, respectively. Figure 1c shows the GASMAS transillumination case, where the detector is placed on the back side of the sample. Diffuse scattering through gas clearly also occurs if we have a larger cavity imbedded in a scattering surrounding, such as human tissue (Fig 1d). Finally, detected light levels when a constant-power freely propagation laser is scanned is shown in the lower left part of the figure, while the transmission spectrum of light traversing the scattering sample is shown to the lower right. Very sharp gas absorption imprints (typically 10^{-3} nm or few GHz broad) are observed superimposed on the slowly varying bulk material absorption spectrum.

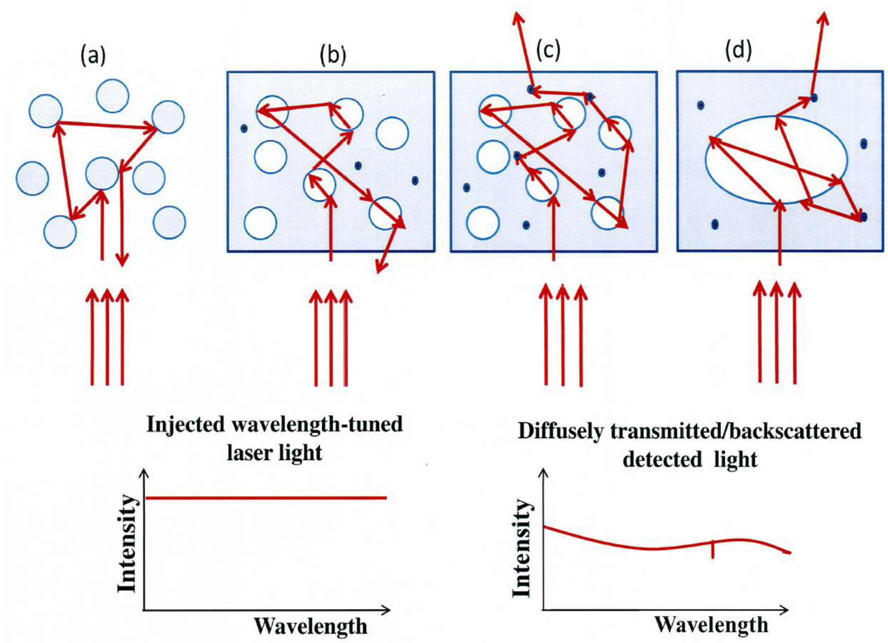

Fig 1. Principles of GASMAS. (a) The multiple-scattering lidar case, with aerosol particles in air causing scattering and the gas surrounding the particles being probed; (b) the GASMAS case, where gas-filled pores in the bulk material cause scattering, and absorption when light enters the pore; back-scattering geometry; (c) the same as case (b), but now the signal is observed in transillumination (transmission); (d) the GASMAS case with a single, large gas-filled cavity, surrounded by scattering material. The lower left part of the figure shows the constant laser output power as a function of wavelength. The lower right part shows the recorded absorption spectrum after the light has passed the sample – a broad spectral distribution due to the slow frequency response of the bulk, condensed-matter material, and a super-imposed very sharp spectral imprint due to light passage through free gas (from [67]).

Since light emerges diffusely from the sample and thus cannot be focussed to a small area it is necessary to use a large-area photodiode or a photomultiplier tube, placed in close contact with the sample to accomplish the detection. A tuneable semiconductor laser is frequently the most suitable laser source for GASMAS studies. Output powers could vary between few mW up to the W level, the latter levels now being achieved by using a tapered amplifier to boost the oscillator output. The radiation is fiber-optically brought to the patient or sample. This has the double purpose of flexibility and preventing influence of external gas absorptive imprints, which is particularly important, since the gases of interest are mostly molecular oxygen, water vapour and sometimes carbon dioxide. Corresponding absorption wavelengths occur around 760, 935 and 2,050 nm, respectively. We note that the first two wavelengths fall in the tissue optical window, which is clearly of paramount importance in biomedical applications. The relevant molecular transitions are mostly week or even partly "forbidden", and the distance through gas will always be quite small. Further, the over-all emerging light from the sample might be attenuated by a factor of a million compared to the injected light level. Thus, it is obvious that very sensitive and noise-reducing detection techniques are needed. Analogue, or more recently, digital lock-in (frequency- and phase-sensitive) techniques are thus employed. The diode laser is repetitively scanned through a selected rotational-vibrational line by a current ramp. Superimposed a fast sinusodial current is applied to "tag" by wave-length modulation the signal of interest, which is then detected as a first- or second-harmonic signal, mimicking the first or second derivative of the recorded intensity.

Practical implementations of the GASMAS technique are discussed, e.g., in [68-70]. Two individual laser sources can be modulated at different frequencies, and their outputs be merged into the same transmission fibre. Then, a common detector can receive the individually tagged signals for convenient simultaneous dual-gas monitoring. A frequently encountered problem in diode laser spectroscopy is the occurrence of interference fringes, which can mask weak true absorption features. Techniques for eliminating fringes are described, e.g., in [71].

According to the well-known Beer-Lambert law, the absorptive imprint in light passing a gas is determined by the product of the gas concentration and the optical pathlength (see, e.g., [8]). GASMAS studies, in which it is important to determine the true concentration of a studied gas, e.g., molecular oxygen, then encounter the problem that we have an undefined pathlength due to the multiple scattering with a distribution of short and long pathlengths through gas. The result of a GASMAS measurement can then be given as the equivalent path-length L_{eq} in a reference gas, e.g., ambient air, which would cause the same fractional absorptive imprint as recorded through the sample. A real concentration determination would clearly require a measurement of the average pathlength through the gas-containing pores only. For the interesting case of molecular oxygen concentration determination this can, for "wet" samples, be achieved by simultaneously measuring the signal from water vapour in the pores. For saturated water vapor (100% relative humidity) the concentration is only determined by the temperature through the Arden-Buck relationship [72]. Here, the relevant effective pathlength is directly obtained, since the concentration is known. By adopting this pathlength also for the oxygen measurement, its concentration would be readily obtained. While absolutely true only if the interrogation wavelengths for both gases would be very close, the actual wavelength differences induce some changes in the behaviour of light in the bulk surrounding matrix. The general pathlength determination issue for GASMAS applications is discussed in [73], where also an independent method is presented, which allows gas concentrations to be determined without any knowledge of pathlength. The detailed absorption line shape, which depends on the collision partners and their concentrations, is then analyzed [74].

The present paper deals with the medical diagnostics possibilities of GASMAS, but we will here briefly mention some other areas of application. Initial studies with the technique were actually performed on porous building materials, such as polystyrene foam and wood [16,68,75-77]. Wood, which has a highly anisotropic structure, was also studied regarding its technically very important drying processes [78]. Ceramics are frequently translucent and have been much studied also as constituting an alignment-free "multi-pass cell", achieved by the massive multiple scattering [79,80]. The apparent pathlength can then be hundreds of times larger than the physical size of the sample. Further, pore-size assessment in nano-porous materials, as based on the modification of the measured lineshapes due to frequent wall collisions has been studied [16,81-84]. Pharmaceutical tablets are frequently quite translucent, and it is of special interest to study their porosity, which is related to their controlled release of active substances [85-88].

The GASMAS technique has an interesting application in non-intrusive measurements on food packages and food-stuffs [89-93, www.gasporox.com], which are frequently subjected to modified atmosphere packaging (MAP) [94,95]. Hen eggs could be characterized for age and with regard to being fertilized or not [96,97]. Fruits constitute an important part of any diet. Being strongly porous they are suitable for studies of gas contents and gas exchange [98-102]. Spectroscopic measurements can also be useful in assessments of maturation and ripening processes [101,103].

After this presentation of the fundamentals of the GASMAS technique and its non-medical applications, we will now turn to the some emerging applications related to human sinus cavity monitoring, middle-ear infection diagnostics, lung monitoring, and assessment of the health status of bone structures. Certain aspects of GASMAS studies on human subjects were earlier reviewed in [17,67].

4 Monitoring of paranasal sinus cavities

The maxillary and the frontal sinuses are the most easily accessible sinus cavities for optical probing. In addition, the porous mastoideus bone, located behind the outer ear, can be assessed without problems. Our first frontal sinus study was performed in backscattering geometry and showed that it is possible to observe a faint signature due to oxygen [104]. Better signals are obtained by separating injection and detection localizations more. Thus, light can fiber-optically be transmitted from the upper part of the orbita while the detector is located on the forehead. The maxillary sinuses can be probed from the outside in a similar way. Propagating the light from the inside of the mouth cavity and detecting the emerging scattered light on the cheek bone, results in a considerably stronger gas signal. Good understanding of signal conditions is obtained by pursuing Monte-Carlo simulations of photon propagation through sinuses and surrounding tissue [105].

Subsequent studies allowed signal optimization [106,69,70] and utilization of oxygen signal normalization on simultaneously monitored water vapour signals. Encouraged by the results, a clinical trial on 40 patients with sinus problems, and referred for CT scanning, was conducted and showed good agreement between GASMAS data and the CT results [107]. Subsequent studies showed that the GASMAS signals also show good stability and reproducibility over time for healthy subjects [108,109]. Studies on the mastoideus structure also gave encouraging results [110].

The ventilation of sinuses is a very important aspect in characterizing potential medical problems. If the channels connecting to the nasal cavity are open, the situation is favourable. GASMAS provides a very interesting and valuable objective means of characterizing ventilation. Then the oxygen signal from a cavity is observed for some short time period, after which pure nitrogen is flushed through a nostril of the patient, who is breathing normally through the mouth. When channels are open, the oxygen signal is reduced because of the displacement of oxygen by nitrogen. On stopping the nitrogen flow, the oxygen signal is recovered. This is illustrated in Fig 2. We note that the application of decongestion spray does not change conditions for a healthy volunteer. On the contrary, a rhinitis volunteer shows an initial lower oxygen level due to partial filling with liquid, and no influence of nitrogen flow is seen, since the channels are blocked. The application of spray will cause an opening of the channels and a corresponding subsequent response to nitrogen flushing [109].

5 Diagnostics of middle-ear infection

As mentioned, middle ear infection (*otitis media*) is a very common disease, which frequently is “treated” with anti-biotics, also when caused by virii and not by responding bacteria. The misuse strongly contributes to the wide-spread increase in antibiotics resistance. The eardrum is frequently inspected by an otoscope. We have been working towards the development of a powerful new type of otoscope, which would allow GASMAS monitoring of gas behind the ear-drum and spectrocscopic characterization of the drum redness by observing the reflection spectrum, while still allowing the normal visual or video inspection. Such an instrument is illustrated in Fig 3, and was applied in measurements on simple middle-ear phantoms as indicated. Nitrogen flushing of the instrument interior, but also of the phantom itself, showed clear response to oxygen gas displacement by nitrogen. Measurements were also performed on a more realistic phantom based on a fish bladder [111,112].

Hopefully, a combination of reflectance and GASMAS data can provide a substantially improved diagnostics of the common disease. Clearly, extensive verifying measurements of patients are needed for the verification.

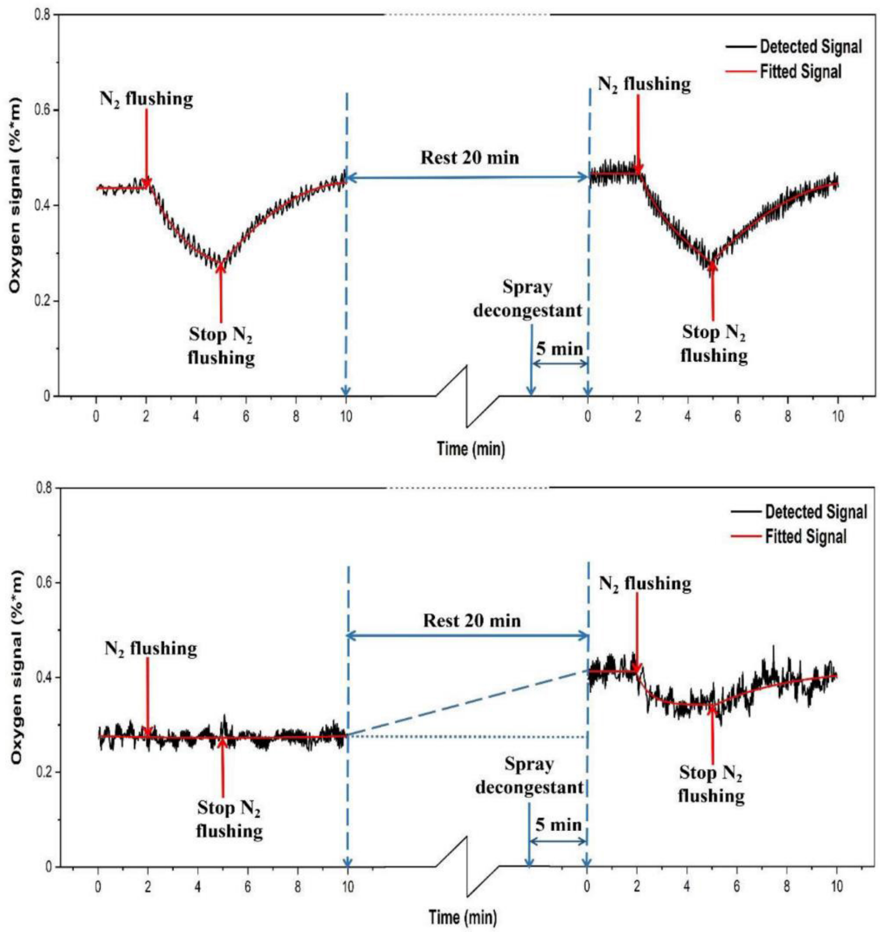

Fig 2. The measured O_2 signal from the left frontal sinus of a healthy, and a rhinitis volunteer (top and bottom panels, respectively). The dynamics of gas exchange, in the absence and presence of the administration of decongestant spray, are shown. In particular, the opening up of the channel by spray is clearly demonstrated for the rhinitis volunteer (From [109]).

6 Monitoring of lungs

In a similar way as for the applications just discussed, our work aiming at improved lung diagnostics, in particular for neonatal children, started with phantom studies [113]. Fresh boar lung tissue, which was placed between slabs of gelatine was prepared to serve as a phantom, mimicking the human situation. The lungs were flushed with air or pure nitrogen, and oxygen and water vapour GASMAS signals were monitored. While good oxygen signals were observed for air filling, no signal was observed during nitrogen flushing. Water vapour signals were un-affected as expected. Based on these results, a pilot study on three healthy new-born infants was performed, with equipment as shown in Fig 4 [114], and encouraging results were obtained.

Subsequent studies on a larger number of new-born healthy children show good oxygen and water vapour signals from the lungs [115]. The work was accompanied by measurement on phantoms to find out optimum placements of the light distribution- and detection probes [116-120]. Clinical studies on a larger number of small children are in planning [121, (www.neolamedical.com)].

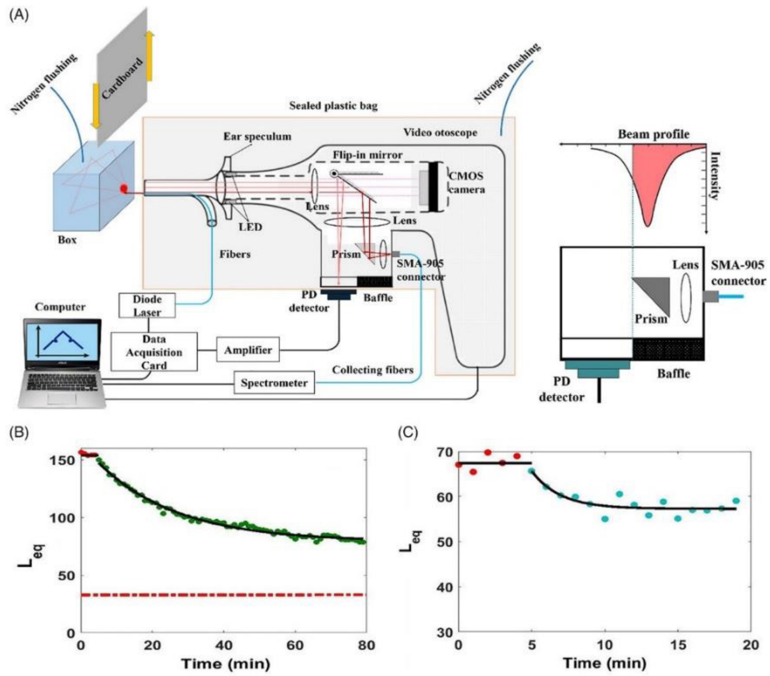

Fig 3. (A) Experimental otoscope set-up with GASMAS and reflection spectroscopy recording provisions, as well as direct visualization. Measurement on a middle-ear phantom are illustrated. An imaging system to allow effective blocking of the strong back-scattering from the eardrum, while more efficiently collecting the diffusely emerging signal-carrying light is in place. The blocking baffle arrangement in front of the detector and the prism arrangement for capturing the eardrum reflectance spectrum are specially emphasized. (B) Reduction of the water vapor signal when the otoscope interior is flushed with dry nitrogen gas. (C) Further water vapor signal reduction when the middle-ear phantom is flushed with dry nitrogen is observed, demonstrating that signal from behind the "drum" was observed (from [112]).

In order to extend lung monitoring to larger children, or even adults, exploratory work is being pursued [122]. A novel way to increase the available light level for the much more attenuating tissue in adults is being introduced, where the laser light is instead injected into the lung tissue from a probe positioned in the endotracheal tube used in anesthesia procedures [123,118]. Then light only has to travel one way through the tissue. Promising results have been obtained in a study on pigs [124]. In the scaling up, it is important to increase the available laser light intensity, which can be made by using a tapered semiconductor amplifier. Such a unit can boost the primary tuneable diode laser output level from typically 10 mW to the W level. Exploratory work with such equipment on porcine lungs *in vitro* is now being pursued, as illustrated in Fig 5 [125].

7 Monitoring of bone structures

Exploratory *in-vitro* studies of free gas in decaying bone structures were performed, with a focus on the caput of the femural bone. The rational was that decay of organic material gives rise to gas generation. The gas formed in small pockets inside the material would certainly not be the easily accessible oxygen, but rather methane and other gases with absorption lines outside the tissue optical window. However, a gas-filled void in a "wet" material would always be subject to water vapor at 100 % relative humidity. Thus, water vapor could readily be used in the search for the presence of such pores. We performed two studies on caputs, which were obtained from standard hip revision orthopedic operations, that were performed due to pressing medical needs [126,127]. Such samples might be expected to contain gas-filled pores due to inadequate blood supply and an ongoing decay process. For comparison, we studied a number of caput samples, which were obtained

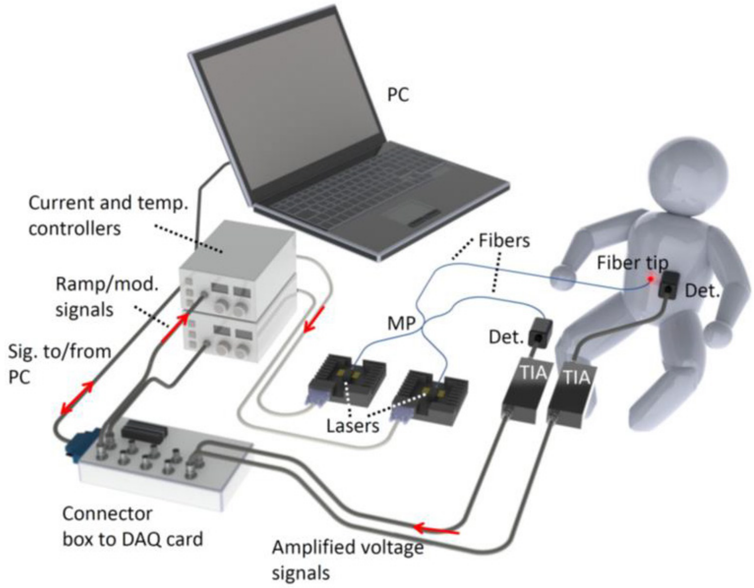

Fig 4. Simultaneous monitoring of oxygen and water vapor signals in GASMAS studies on small children. Two diode lasers are employed to generate the necessary wavelengths. By using two different modulation frequencies for the two lasers, effective "tagging" was achieved for the laser outputs, which were transmitted through a joint fiber. Then, a single detector could be used in the measurements and the signals could be separated using lock-in techniques (from [114]).

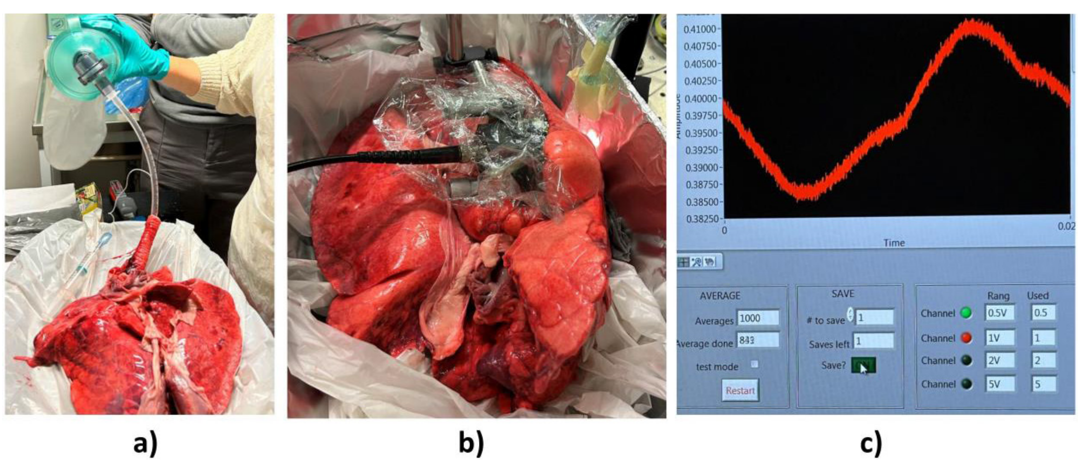

Fig 5. Photos from exploratory studies of GASMAS measurements on porcine lungs. (a) Lungs from a newly slaughtered pig, being ventilated by a Ruben artificial mechanical breathing unit (AMBU), which is connected to air, oxygen or nitrogen gas supplies. (b) Measurements through a lobe of a pig lung, with light injection through a diffusing probe and penetrating photons detected by a solid-state detector. (c) Absorptive imprints of oxygen gas shown in transmitted light as the tapered amplifier laser radiation is scanned through the transition (from [125]).

from operations following accidents for otherwise healthy patients. Such samples could be expected to exhibit little bone pores. Results are shown in Fig 6, and illustrate that our assumption was fully warranted. Measurements on tibial condyle bones, extracted from the tibia in knee revision surgical procedures motivated by arthrosis degeneration, showed only very minor gas signals [128]. The conclusion is that the GASMAS technique, applied using arthroscopic techniques on patients could give valuable objective information on the status of hips, while not being useful for knee patients.

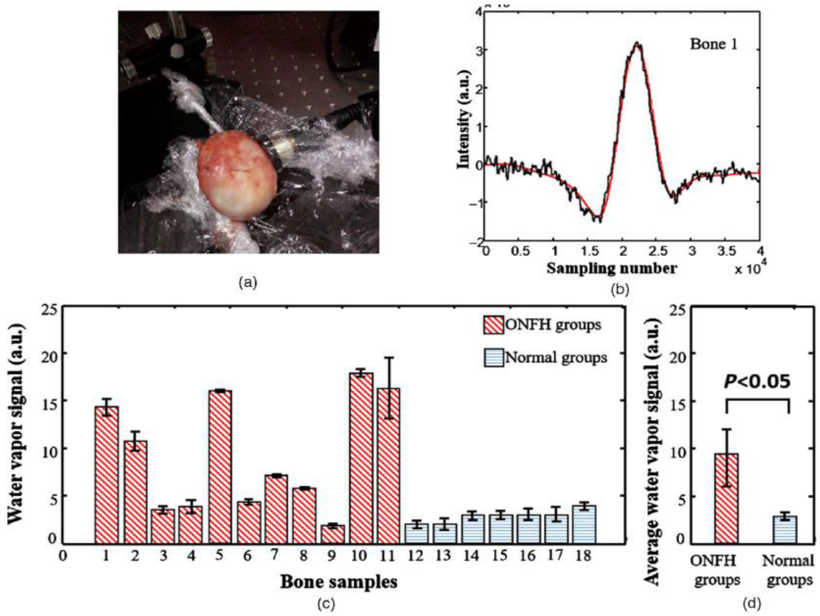

Fig 6. The experimental setup for GASMAS measurements and the results for 18 femoral heads, studied *in vitro*. (a) GASMAS measurement arrangement with transmission probe and detector, (b) water vapor signal (second derivative of the absorption imprint) from one of the samples, and (c) data for all 18 samples. ONFH (osteonecrosis of the femoral head) samples are indicated in red, whereas normal femoral head samples are indicated in blue. The mean values and SD of the two groups are shown in (d) with a p value < 0.05 (from [127]).

8 Conclusions and outlook

We have described how free gas in cavities and porous structures in the human body can be studied using narrow-band laser spectroscopy. The strongly scattering organic tissue poses certain challenges for gas in scattering media absorption spectroscopy, GASMAS, which requires special methods for gas concentrations determinations. The field differs significantly from most other areas of biophotonics, where normally broad spectroscoplic structures in organic matter are studied. Diagnostic methods are being developed for sinusitis and otitis, and might have an important role in fighting over-prescription of antibiotics with related development of bacterial resistance. Lung monitoring for new-borns is important, and prospects for the extension of the techniques to older children or even adults exist. We have also discussed how bone necrosis can be detected using the GASMAS technique.

While gas monitoring in human tissue is in an early stage of development, it shows considerable promise for improved medical diagnostics. With further development and miniaturization of the technique, it may play an important role in future health-care systems. Non-medical applications are numerous and were also briefly mentioned in the present review.

Image blurring is a common feature when linear light propagation is perturbed. Adaptive optics can provide a remedy to atmospheric turbulence [129]. Human tissue is strongly scattering and causes heavy loss of image contrast for deeper lying structures. Different approaches using wave-front engineering have been developed to overcome this problem [130]. Limited spatial resolution certainly pertains to GASMAS [105]. Improved gas imaging might be obtained by using wave-front engineering approaches also in the GASMAS context. Here, the sharp gas imaging demonstrated in MRI using spin-polarized inert gases can provide inspiration [131].

The development of the GASMAS technique resulted from the combination of experience from the environmental monitoring and biophotonics fields, and was mediated by close interaction between physicians and physicists.

Dedication

This contribution is dedicated to Prof Anna Consortini, a great scientist in atmospheric optics, an effective motor in organizing research to enhance international collaboration, and a strong advocate in sharing with scientists in less favoured regions. The authors greatly appreciate the friendship and interactions with Anna through the years!

Acknowledgements

The authors gratefully acknowledge the stimulating collaboration with and great contributions by a large number of colleagues and graduate students in the quest to apply the Gas in scattering media absorption spectroscopy to biomedicine during more than 20 years. Our work was supported by many funding agencies, to which we are very grateful.

References

1. Consortini A, Ronchi L, Stefanutti L, Investigation of atmospheric turbulence by narrow laser beams, *Appl Opt,* 9(1970)2543–2547.
2. Consortini A, Laser and Turbulence: How our atmospheric propagation researches started and where they arrived, in *Imaging and Applied Optics 2019,* OSA Technical Digest (Optica Publishing Group, 2019), paper PTh2D.1.
3. Wyngaard J C, Turbulence in the atmosphere, (Cambridge University Press), 2010.
4. Popp J, Tuchin V V, Chiou A, Heinemann S H, (eds), Handbook of Biophotonics, Volumes 1-3, (Wiley-VCH), 2011.
5. Boas D A, Pitris C, Ramanujam N, Handbook of Biomedical Optics, (CRC Press), 2011.
6. Jelinkova H (ed), Lasers for Medical Application, (Woodhead Publishing), 2013.
7. Dimish U S, Olivo M, (eds), Frontiers in Biophotonics for Translational Medicine, (Springer, Singapore), 2015.
8. Svanberg S, Atomic and Molecular Spectroscopy - Basic Aspects and Practical Applications, 5th edn, (Springer-Nature, Heidelberg), 2022.
9. Svanberg S, Laser spectroscopy in medical diagnostics, Chap 10 in [6], pp 286.
10. Svanberg K, Bendsoe N, Photodynamic therapy for human malignancies with superficial and interstitial illumination, Chap 25 in [6], pp 760.
11. McManamon P F, Lidar technologies and systems, (SPIE, Bellingham), 2019.
12. Svanberg S, LIDAR, Chap. 13.3 in Träger F, (ed), Springer Handbook of Lasers and Optics, *2nd edn*, (Springer, Heidelberg), 2012, p 1146.
13. McCurdy M R, Bakhirkin Y, Wysocki G, Lewicki R, Tittel F K, Recent advances of laser-spectroscopy-based techniques for applications in breath analysis, *J Breath Res*, 1(2007)014001/1-12; 10.1088/1752-7155/1/1/014001.
14. Wang C, Sahay P, Breath analysis using laser spectroscopic techniques: Breath biomarkers, spectral fingerprints, and detection limits, *Sensors,* 9(2009)8230–8262.

15. Lin Y, Manalili D, Khodabakhsh A, Cristescu S M, Real-Time Measurement of CH_4 in human breath using a compact CH_4/CO_2 sensor, *Sensors*, 24(2024)1077; doi.org/10.3390/s24041077.
16. Sjöholm M, Somesfalean G, Alnis J, Andersson-Engels S, Svanberg S, Analysis of gas dispersed in scattering solids and liquids, *Opt Lett*, 26(2001)16–18.
17. Svanberg S, Gas in scattering media absorption spectroscopy – from basic studies to medical applications, *Laser Photonics Rev*, 7(2013)779; doi.org/10.1002/lpor.201200073.
18. Andersson M, Grönlund R, Persson L, Sjöholm M, Svanberg K, Svanberg S, Laser spectroscopy of gas in scattering media at scales ranging from kilometers to millimeters, *Laser Physics,* 17(2007)893.
19. Svanberg S, Analysis of trapped gas – Gas in scattering media absorption spectroscopy, *Laser Phys*, 20(2010)68–77.
20. Svanberg S, Gas in scattering media absorption spectroscopy, in Sigrist M (ed), *Encyclopedia of Analytical Chemistry,* doi. 10.1002/9780470027318.a9325.pub2 (John Wiley & Sons), 2019.
21. United Nations Global News on Human Health, https://news.un.org/en/story/2023/10/1141952.
22. https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services.
23. https://www.webmd.com/cancer/cancer-incidence-age.
24. DePinho R, The age of cancer, *Nature,* 408(2000)248–254.
25. Diana M, Marescaux J, Robotic surgery, *British J Surg*, 102(2015)e15–e28; doi.org/10.1002/bjs.9711.
26. Shafirstein G. Bellnier D, Oakley E, Hamilton S, Potasek M, Beeson K, Parilov E, Interstitial photodynamic therapy — A focused review, *Cancers,* 9(2017)12; doi.org/10.3390/cancers9020012.
27. Komolibus K, Fisher C, Swartling J, Svanberg S, Svanberg K, Andersson-Engels S. Perspectives on interstitial photodynamic therapy for malignant tumors. *J Biomed Opt,* 26(2021)070604; doi. 10.1117/1.JBO.26.7.070604.
28. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (2023), doi.org/10.3390/antibiotics11081079.
29. Svanberg S, Tissue diagnostics using lasers, in *Lasers in Medicine*, Chap 6, Waynant R W (ed), (CRC Press, Boca Raton), 2002, pp 135–169.
30. Andersson-Engels S, Svanberg K, Svanberg S, Fluorescence imaging in medical diagnostics, Chap 10 in [4], pp 265–305.
31. Pircher M, Zawadzki R J, Review of adaptive optics OCT (AO-OCT): Principles and applications for retinal imaging, *Biomed Opt Express*, *8*(2017)2536–2562.
32. Drexler W, Fujimoto J G (eds), Optical Coherence Tomography: Technology and Applications, (Springer), 2008.
33. Walani S R, Global burden of preterm birth, *Int J Gynecol Obstet*, 150(2020)31–33.
34. Eustice C, Centers for Disease Control and Prevention (CDC), The connection between age and arthritis, 2023, https://www.verywellhealth.com/age-and-arthritis-189653.
35. Crosby D, Bhatia S, Brindle K M, Coussens L M, Dive C, Emberton M, Balasubramanian S, Early detection of cancer, *Science*, 375(2022)6586; doi. 10.1126/science.aay90.
36. Di Pietro M, Canto M I, Fitzgerald R C, Endoscopic management of early adenocarcinoma and squamous cell carcinoma of the esophagus: screening, diagnosis, and therapy, *Gastroenterology,* 154(2018)421–436.
37. D'Hallewin M A, Bezdetnaya L, Guillemin F, Fluorescence detection of bladder cancer: a review. *European Urology*, 42(2002)417–425.
38. Zaak D, Karl A, Knüchel R, Stepp H, Hartmann A, Reich O, Stief C, Diagnosis of urothelial carcinoma of the bladder using fluorescence endoscopy, *BJU International*, 96(2005)217–222.
39. Dennis S, Fisher D, Climate change and infectious diseases: The next 50 years, *Ann Acad Med Singap,* 47(2018)401–404.
40. Aslam B, Wang W, Arshad I, Khurshid M, Muzammil S, Rasool M H, Nisar M A, Alvi R F, Aslam M A, Qamar M U, Salamat M K F, Baloch Z, Antibiotic resistance: a rundown of a global crisis, *Infect Drug Resist* Oct 10(2018)111645–1658.
41. Urban-Chmiel R, Marek A, Stępień-Pyśniak D, Wieczorek K, Dec M, Nowaczek A, Osek J, Antibiotic resistance in bacteria — A review, *Antibiotics*, 11(2022)1079; doi. org/10.3390/antibiotics11081079.

42. Butler M S, Henderson I R, Capon R J, Blaskovich M A T, Antibiotics in the clinical pipeline as of December 2022, *J Antibiot* (Tokyo), 76(2023)431–473.
43. Liyanarachi K V, Solligård E, Mohus R M, Åsvold B O, Rogne T, Damås J K, Incidence, recurring admissions and mortality of severe bacterial infections and sepsis over a 22-year period in the population-based HUNT study, PLoS One, 17(2022)e0271263; doi: 10.1371/journal.pone.0271263.
44. Jones K E, Patel N G, Levy M A, Storeygard A, Balk D, Gittleman J L, Daszak P, Global trends in emerging infectious diseases, *Nature*, 451(2008)990–993.
45. Li H, Bai R, Zhao Z, Tao L, Ma M, Ji Z, Jian M, Ding Z, Dai X, Bao F, Liu A, Application of droplet digital PCR to detect the pathogens of infectious diseases, *Biosci Rep,* 38(2018)BSR20181170; doi:https://doi.org/10.1042/BSR20181170.
46. Madden J, Outterson K, Trends in the global antibiotics market, *Nat Rev Drug Discov,* 3(2023)174. doi: 10.1038/d41573-023-00029-5.
47. Wise R B, Antimicrobial resistance priorities for action, *J Antimicrob Chemother*, 49(2002)585–586.
48. Falagas M E, Giannopoulou K P, Vardakas K Z, Dimopoulos G, Karageorgopoulos D E, Comparison of antibiotics with placebo for treatment of acute sinusitis: A meta-analysis of randomised controlled trials, *The Lancet Infectious Diseases*, 8(2008)543–552.
49. Mukara K B, Lilford R J, Tucci D L, Waiswa P, Prevalence of middle ear infections and associated risk factors in children under 5 years in Gasabo District of Kigali City, Rwanda, *Int J Pediatr,* (2017)4280583; doi. 10.1155/2017/4280583.
50. https://www.nhsinform.scot/illnesses-and-conditions/ears-nose-and-throat/middle-ear-infection-otitis-media/
51. Venekamp R P, Sanders S L, Glasziou P P, Del Mar C B, Rovers M M, Antibiotics for acute otitis media in children, *Cochrane Database Syst Rev,* 6(2015),CD000219. doi: 10.1002/14651858.CD000219.pub4. Update in: Cochrane Database *Syst Rev*. 11(2023)CD000219; doi.org/10.1002/14651858.CD000219.pub.
52. Bernhard W, Lung surfactant: Function and composition in the context of development and respiratory physiology. *Ann Anat,* 208(2016)146–150.
53. Matthay M A, Zemans R L, Zimmerman G A, Arabi Y M, Beitler J R. Mercat,A, Calfee C S, Acute respiratory distress syndrome, *Nature Reviews Disease Primers*, *5*(2019)18; doi.org/10.1038/s41572-019-0069-0.
54. Kommawar A, Borkar R, Vagha J, Lakhkar B, Meshram R, Taksande A, Study of respiratory distress in newborn. *International Journal of Contemporary Pediatrics* 4(2017)490–494.
55. Mart M F, Ware L B, The long-lasting effects of the acute respiratory distress syndrome. *Expert Review of Respiratory Medicine* 14(2020)577–586.
56. Slattery M M, Morrison J, Preterm delivery, *Lancet*, 360(2002)1489–1497.
57. Goldenberg R L, Culhane J F, Iams J D, Romero R, Epidemiology and causes of preterm birth, *Lancet* 371(2008)75–84.
58. Jin Y T, Duan Y, Deng X K, Lin J, Prevention of necrotizing enterocolitis in premature infants – An updated review, *World J Clin Pediatr*, 8(2019)23–32.
59. Phua J, Weng L, Ling L, Egi M, Lim C M, Divatia J V, Shrestha B R, Arabi Y M, Ng J, Gomersall C D, Nishimura M, Koh Y, Du B, Asian Critical Care Clinical Trials Group. Intensive care management of corona virus disease 2019 (COVID-19): Challenges and recommendations, *Lancet Respir Med*, 5(2020)506–517. Erratum in: *Lancet Respir Med*, 5(2020)e42.
60. Ehlinger M, Moser T, Adam P, Bierry G, Gangi A, de Mathelin M, Bonnomet F, Early prediction of femoral head avascular necrosis following neck fracture. *Orthopaedics & Traumatology: Surgery & Research*, 97(2011)79–88.
61. Seamon J, Keller T, Saleh J, Cui Q, The pathogenesis of nontraumatic osteonecrosis. *Arthritis*, (2012)601763, doi: 10.1155/2012/601763.
62. Lee M S, Hsieh P H, Shih C H, Wang C J, Non-traumatic osteonecrosis of the femoral head - from clinical to bench, *Chang Gung Med J*, 33(2010)351–360.
63. Mont M A, Hungerford D S, Non-traumatic avascular necrosis of the femoral head. *JBJS*, 77(1995)459–474.

64. Zhao D W, Yu M, Hu K, Wang W, Yang L, Wang B J, Gao X H, Guo Y M, Xu Y Q, Wei Y S, Tian S M, Yang F, Wang N, Huang S B, Xie H, Wei X W, Jiang H S, Zang Y Q, Ai J, Chen Y L, Lei G H, Li Y J, Tian G, Li Z S, Cao Y, Ma L, Prevalence of nontraumatic osteonecrosis of the femoral head and its associated risk factors in the Chinese population: Results from a nationally representative survey. *Chin Med J,* 128(2015)2843–2850.
65. Liu N, Zheng C, Wang Q, Huang Z, Treatment of non-traumatic avascular necrosis of the femoral head, *Exp Ther Med*, 23(2022)321; doi: 10.3892/etm.2022.11250.
66. Zhao G Y, Zhang W X, Duan Z, Lian M, Hou N B, Li Y Y, Zhu S M, Svanberg S, Mercury as a geophysical tracer gas - Emissions from the Emperor Qin tomb in Xi´an studied by laser radar, *Sci Rep*, 10(2020)10414; doi.org/10.1038/s41598-020-67305-x.
67. Svanberg K, Svanberg S, Monitoring of free gas in-situ for medical diagnostics using laser spectroscopic techniques, in [7], pp 307–321.
68. Somesfalean G, Sjöholm M, Alnis J, af Klinteberg C, Andersson-Engels S, Svanberg S, Concentration measurement of gas imbedded in scattering media employing time and spatially resolved techniques, *Appl Opt*, 41(2002)3538–3544.
69. Persson L, Lewander M, Andersson M, Svanberg K, Svanberg S, Simultaneous detection of molecular oxygen and water vapor in the tissue optical window using tunable diode laser spectroscopy, *Appl Opt*, 47(2008)2028–2034.
70. Lewander M, Guan Z G, Svanberg K, Svanberg S, Svensson T, Clinical system for non-invasive in situ monitoring of gases in the human paranasal sinuses, *Opt Express*, 13(2009)10849–10863.
71. Persson L, Andersson M, Andersson F, Svanberg S, Approach to optical interference fringe reduction in diode-laser-based absorption spectroscopy, *Appl Phys B*, 87(2007)523–530.
72. Buck A L, New equations for computing vapor pressure and enhancement factor, *J Appl Meteorol*, 20(1996)1527–1532.
73. Mei L, Somesfalean G, Svanberg S, Pathlength determination for gas in scattering media absorption spectroscopy, *Sensors*, 14(2014)3871–3890.
74. Lundin P, Mei L, Andersson-Engels S, Svanberg S, Laser spectroscopic gas concentration measurements in situations with unknown optical path length enabled by absorption line shape analysis, *Appl Phys Lett*, 103(2013)034105; doi.org/10.1063/1.4813860.
75. Alnis J, Anderson B, Sjöholm M, Somesfalean G, Svanberg S, Laser spectroscopy on free molecular oxygen dispersed in wood materials, *Appl Phys B*, 77(2003)691–695.
76. Karlsson M, Lundin P, Cocola L, Somesfalean G, Svanberg S, Bargigia I, D´Andrea C, Nevin A, Farina A, Pifferi A, Cubeddu R, Orlandi M, Non-invasive optical diagnosis of gases in wood, *Shipwrecks 2011*, (ed) Ek M, ISBN 978-91-7501-142-4, (Vasa Museum, Stockhom 2011), p 176.
77. Bargigia I, Nevin A, Farina A, Pifferi A, D'Andrea C, Karlsson M, Lundin P, Somesfalean G, Svanberg S, Diffuse optical techniques applied to wood characterization, *J Near Infrared Spectrosc*, 21(2013)259–268.
78. Andersson M, Persson L, Sjöholm M, Svanberg S, Spectroscopic studies of wood-drying processes, *Opt Express*, 14(2006)3641–3653.
79. Svensson T, Adolfsson E, Lewander M, Xu C T, Svanberg S, Disordered, strongly scattering porous materials as miniature multi-pass gas cells, *Phys Rev Lett*, 107(2011)143901; doi.org/10.1103/PhysRevLett.107.143901.
80. Lou X T, Xu C T, Svanberg S, Somesfalean G, Multi-mode diode laser correlation spectroscopy using gas-filled porous materials for pathlength enhancement, *Appl Phys B*, 109(2012)453–460.
81. Svensson T, Shen Z, Laser spectroscopy of gas confined in nanoporous materials, *Appl Phys Lett*, 96(2010)021107; doi.org/10.1063/1.3292210.
82. Svensson T, Lewander M, Svanberg S, Laser absorption spectroscopy of water vapor confined in nanoporous alumina: Wall collision line broadening and gas diffusion dynamics, *Opt Express*, 18(2010)16460–16473.
83. Xu C T, Lewander M, Andersson-Engels S, Adolfsson E, Svensson T, Svanberg S, Wall collision line broadening at reduced pressures: Towards non-destructive characterization of nanoporous materials, *Phys Rev A*, 84(2011)042705; doi.org/10.1103/PhysRevA.84.042705.

84. Svensson T, Adolfsson E, Burresi M, Savo R, Xu C T, Wiersma D S, Svanberg S, Pore size assessment by high-resolution laser spectroscopy of wall collision line broadening of confined gases: Experiments of strongly scattering nanoporous zirconia ceramics with fine-tuned pore sizes, *Appl Phys B*, 110(2013)147–154.
85. Svensson T, Persson L, Andersson M, Svanberg S, Andersson-Engels S, Johansson J, Folestad S, Noninvasive characterization of pharmaceutical solids by diode laser oxygen spectroscopy, *Appl Spectrosc*, 61(2007)784; doi.org/10.1366/000370207781393.
86. Svensson T, Andersson M, Rippe L, Svanberg S, Andersson-Engels S, Johansson J, Folestad S, VCSEL-based oxygen spectroscopy for structural analysis of pharmaceutical solids, *Appl Phys B*, 90(2008)345–354.
87. Svensson T, Alerstam E, Johansson J, Andersson-Engels S, Optical porosimetry and investigations of the porosity experienced by light interacting with porous media, *Opt Lett*, 35(2010)1740–1742.
88. Johansson J, Sparén A, Wikström H, Tajarobi P, Koch R, Lundin P, Långberg A, Sebesta M, Lewander Xu M, Optical porosimetry by gas in scattering media absorption spectroscopy (GASMAS) applied to roller compaction ribbons, *Int J Pharm*, 592(2021)120056; doi.org/10.1016/j.ijpharm.2020.120056.
89. Lewander M, Guan Z G, Persson L, Olsson A, Svanberg S, Food monitoring based on diode laser gas spectroscopy, *Appl Phys B*, 93(2008)619–625.
90. Lundin P, Cocola L, Olsson A, Svanberg S, Non-intrusive headspace gas measurements by laser spectroscopy — Performance validated by an intrusive reference sensor, *J Food Eng*, 111(2012)612–617.
91. Lewander M, Svensson T, Svanberg S, Olsson A, Non intrusive measurements of food and packaging quality, *Packaging Technology and Science,* 24(2011)271–280.
92. Zhang H, Lin H Y, Li T Q, Duan Z, Svanberg K, Svanberg S, Non-invasive optical detection of oxygen content in food packages using Gas in Scattering Media Absorption Spectroscopy, *Acta Optica Sinica,* 36(2016)90230005; doi.10.3788/AOS201636.0230005.
93. Li T Q, Lin H Y, Zhang H, Svanberg K, Svanberg S, Application of tunable diode laser spectroscopy in assessment of food quality, *Appl Spectrosc*, 71(2017)929–938.
94. Church I J, Parsons A L, Modied atmosphere packaging technology - A review, *J Sci Food Agri,* 67(1995)143–152.
95. Phillips C A, Review: Modified atmosphere packaging and its effects on the microbiological quality and safety of produce, *International J Food Sci & Techn*, 31(1996)463–479.
96. Li W S, Lin H Y, Zhang H, Svanberg K, Svanberg S, Detection of free oxygen and water vapor in fertilized and unfertilized eggs by diode laser spectroscopy – Exploration of diagnostics possibilities, *J Biophotonics,* 11(2018) e201700154; doi 10.1002/jbio.201700154.
97. Li Y, Li W S, Hu L N, Svanberg K, Svanberg S, Non-intrusive Studies of Gas Contents and Gas Diffusion in Hen Eggs, *Biomed Opt Express*, 10(2018)83–91.
98. Persson L, Anderson B, Andersson M, Sjöholm M, Svanberg S, Studies of gas exchange in fruits using laser spectroscopic techniques, Proc Fruitic 05, Information and Technology for Sustainable Fruit and Vegetable Production, 543-552, Montpellier, (September 2005).
99. Persson L, Gao H, Sjöholm M, Svanberg S, Diode laser absorption spectroscopy for studies of gas exchange in fruits, *Opt Lasers Eng*, 44(2006)687–698.
100. Tylewicz U, Lundin P, Cocola L, Rocculi P, Svanberg S, Dejmek P, Gómez Galindo F, Gas in scattering media absorption spectroscopy (GASMAS) detected persistent vacuum in apple tissue after vacuum impregnation, *Food Biophysics*, 7(2012)28-34.
101. Zhang H, Huang J, Li T Q, Wu X X, Svanberg S, Svanberg K, Studies for tropical fruit ripening using three different spectroscopic techniques, *J Biomed Opt*, 19(2014)067001; doi.org/10.1117/1.JBO.19.6.067001.
102. Huang J, Zhang H, Lin H Y, Li T Q, Mei L, Svanberg K, Svanberg S, Gas exchange in fruits related to skin condition and fruit ripening, *J Biomed Opt,* 21(2016)127007, doi: 10.1117/1.JBO.21.12.127007.
103. Lin X B, Zhang H, Hu L N, Zhao G Y, Svanberg S, Svanberg K, Ripening of avocado fruits studied by spectroscopic techniques, *J Biophotonics*,13(2020)e202000076; doi.org/10.102.jbio.202000076.
104. Persson L, Svanberg K, Svanberg S, On the potential for human sinus cavity diagnostics using diode laser gas spectroscopy*, Appl Phys B*, 82(2006)313–317.

105. Persson L, Kristensson E, Simonsson L, Svanberg S, Monte Carlo simulations of optical human sinusitis diagnostics, *J Biomed Opt*, 12(2007)054002; doi.org.10.1117/12.779088.
106. Persson L, Andersson M, Cassel-Engquist M, Svanberg K, Svanberg S, Gas monitoring in human sinuses using tunable diode laser spectroscopy, *J Biomed Optics*, 12(2007)054001; doi.org.10.1117/1.2777189.
107. Lewander M, Lindberg S, Svensson T, Siemund R, Svanberg K, Svanberg S, Clinical study assessing information on the maxillary and frontal sinuses using diode laser gas spectroscopy, *Rhinology*, 50(2011)26; doi.org.10.4193/Rhino.10.231.
108. Huang J, Zhang H, Li T Q, H Y Lin, Svanberg K, Svanberg S, Assessment of human sinus cavity air volume using tunable diode laser spectroscopy, with application to sinusitis diagnostics, *J Biophotonics*, 8(2015)985; doi.org/10.1002/jbio.201500110.
109. Zhang H, Han N, Lin Y Y, Huang J W, Svanberg S, Svanberg K, Gas monitoring in human frontal sinuses – Stability considerations and gas exchange studies, *Sensors*, 21(2021)4413; doi.org/10.3390/s21134413.
110. Lindberg S, Lewander M, Svensson T, Siemund R, Svanberg K, Svanberg S, Method for studying gas composition in the human mastoid cavity by use of laser spectroscopy, *Annals of Otology, Rhinology & Laryngology*, 121(2012)217–223.
111. Zhang H, Huang J, Li T Q, Svanberg S, Svanberg K, Optical detection of middle ear infection using spectroscopic techniques - Phantom experiments, *J Biomed Opt*, 20(2015)057001; doi 10.1117/1.JBO.20.5.057001.
112. Hu L N, Li W S, Lin H Y, Li Y, Zhang H, Svanberg K, Svanberg S, Towards an optical diagnostic system for otitis media using a combination of otoscopy and spectroscopy, *J Biophotonics*, 12(2019) e201800305; doi.org/10.1002/jbio.201800305.
113. Lewander M, Bruzelius A, Svanberg S, Svanberg K, Fellman V, Non-intrusive gas monitoring in neonatal lungs using diode laser spectroscopy: Feasibility study, *J Biomed Opt,* 16(2011)127002; doi.org/10.1117/1.3663211.
114. Lundin P, Svanberg E K, Cocola L, Lewander Xu M, Somesfalean G, Andersson-Engels S, Jahr J, Fellman V, Svanberg K, Svanberg S, Non-invasive monitoring of gas in the lungs and intestines of newborn infants using diode lasers: Feasibility study, *J Biomed Opt*, 18(2013)127005; doi.org/10.1117/1.JBO.18.12.127005.
115. Svanberg E K, Lundin P, Larsson M, Åkesson J, Svanberg K, Svanberg S, Andersson-Engels S, Fellman V, Diode laser spectroscopy for noninvasive monitoring of oxygen in the lungs of newborn infants, *Pediatric Research*, 79(2016)621–628.
116. Liao P, Larsson J, Svanberg, E K, Lundin P, Swartling J, Lewander Xu M, Bood J, Andersson-Engels S, Computer simulation analysis of source-detector position for percutaneously measured O_2-gas signal in a three-dimensional preterm infant lung, *J Biophotonics*, 11(2018)e201800023; doi.org/10.1002/jbio.201800023.
117. Larsson J, Liao P, Lundin P, Svanberg E K, Swartling J, Lewander Xu M, Bood J, Andersson-Engels, S, Development of a 3-dimensional tissue lung phantom of a preterm infant for optical measurements of oxygen—Laser-detector position considerations, *J Biophotonics*, 11(2018)e201700097; doi. https://doi.org/10.1002/jbio.201700097.
118. Larsson J, Leander D, Lewander Xu M, Fellman V, Bood J, Svanberg E K, Comparison of dermal vs internal light administration in human lungs using the TDLAS-GASMAS technique—Phantom studies, *J Biophotonics*, 12(2019) e201800350; doi. org/10.1002/jbio.201800350.
119. Pacheco A, Jayet B, Svanberg E K, Dehghani H, Dempsey E, Andersson-Engels S, Numerical investigation of the influence of the source and detector position for optical measurement of lung volume and oxygen content in preterm infants, *J Biophotonics*, 15(2022)e202200041; doi.org/10.1002/jbio.202200041.
120. Pacheco A, Matias J, Grygoryev K, Hansson M, Bergsten S, Andersson-Engels S, Laser absorption spectroscopy measurements of different pulmonary oxygen gas concentrations in transmittance and remittance geometry: phantom study, *J Biomed Opt*, 28(2023)115003; doi.org/10.1117/1.JBO.28.11.115003.
121. Panaviene J, Pacheco A, Schwarz Ch E, Grygoryev K, Andersson-Engels S, Dempsey E M, Gas in scattering media absorption spectroscopy as a potential tool in neonatal respiratory care, *Pediatric Research*, 92(2022)1240–1246.
122. Lin Y Y, Lundin P, Svanberg E K, Svanberg K, Svanberg S, Sahlberg A-L, Gas in Scattering Media Absorption Spectroscopy on small and large scales – Towards the extension of lung spectroscopic monitoring to adults, *Translational Biophotonics*, (2021); doi. 10.1002/tbio.202100003.

123. Svanberg S, Svanberg E K, Larsson M, System and method for laser based internal analysis of gas in a body of a human, US Patent 11,744,467 (2023).
124. Svanberg E K, Larsson J, Rasmussen M, Larsson M, Leander D, Bergsten S, Bood J, Greisen G, Fellman V, Changes in pulmonary oxygen content are detectable with laser absorption spectroscopy: proof of concept in newborn piglets, *Pediatric Research*, 89(2021)823–829.
125. Palme H, Lin Y Y, Svanberg E K, Bergsten S, Svanberg K, Svanberg S, Sahlberg A-L, (Work in progress), 2024.
126. Lin H Y, Li W S, Zhang H, Chen P, He W, Svanberg S, Svanberg K, Diagnostics of femoral head status in humans using laser spectroscopy – *In vitro* studies, *J Biophotonics*, 10(2016)1356-1364; doi.10.1002/jbio.201600229.
127. Chen D L, Li W S, He W, Zhang H, Zhang Q W, Lin H Y, Svanberg S, Svanberg K, Chen P, Laser-based gas absorption spectroscopy in decaying hip bone: Water vapor as a predictor of osteonecrosis, *J Biomed Opt*, 24(2019)065001; doi.org/10.1117/1.JBO.24.6.065001.
128. Chen P, Li W S, Lin H Y, Chen D L, Li Y, Svanberg K, Svanberg S, Assessment of free gas in the tibial condyle bone of the human knee by diode laser spectroscopy with possible application to arthrosis diagnostics, *IEEE J Sel Top Quant Electr*, 25(2018)1–4; doi.org/10.1109/JSTQE.2018.2871610.
129. Hampson K M, Turcotte R, Miller D T, Kurokawa K, Males J R, Ji N, Booth M J, Adaptive optics for high-resolution imaging, *Nat Rev Methods Primers*, 1(2021)68; doi.org/10.1038/s43586-021-00066-7.
130. Gigan S, Katz O, Aguiar H B De, Andresen E R, Aubry A, Bertolotti J, Bossy E, Bouchet D, Roadmap on wavefront shaping and deep imaging in complex media, *J Phys Photonics*, 4(2022)042501; doi.org/10.1088/2515-7647/ac76f9.
131. Roos J E, McAdams H P, Kaushik S S, Driehuys B, Hyperpolarized gas MR imaging: Technique and applications, *Magn Reson Imaging Clin N Am*, 23(2015)217–229; doi.org/10.1016/j.mric.2015.01.003.

[*Received*: 25.02.2024; *accepted*: 01.03.2024]

Katarina Svanberg is an M D and a Ph D, and has been working as a clinical doctor as well as an adjoined professor in Oncology at Lund University, Sweden. Further, she served as a distinguished professor, part-time for 10 years, at South China Normal University, Guangzhou. She has been director and later chairperson of the board for the Lund Medical Laser Centre. During a period of more than ten years she was on the board of the International Society of Optics and Photonics (SPIE), including in its presidential chain for four years and also serving as the president of the society. She received the US National Institute of Health (NIH) Award for Translational Efforts to take optical techniques from the lab bench to the patients. Among other prizes, she was also the recipient of the SPIE Gold Medal. Her main research interests are within the field of laser applications in medicine.

Sune Svanberg obtained his Ph D from University of Gothenburg, Sweden in 1972. He is since 1980 a professor of Physics at Lund University, Lund, Sweden - presently with emeritus status. During 30 years he was head of the Atomic Physics Division, and during 20 years founding director of the Lund Laser Centre. During 2011-2021, he was also a part-time distinguished professor at South China Normal University, Guangzhou. He holds 9 honorary doctor/professor appointments, is a member of 6 scientific academies, a fellow of 5 learned societies, and received numerous national and international awards. He is a recipient of the Chinese Friendship Award, and is an honorary citizen of Guangzhou. He served on many boards and committees, including a 10-year membership of the Nobel Committee for Physics of the Royal Swedish Academy of Sciences. Based on a long career in basic atomic spectroscopy and high-power laser/matter interactions, his current research interests focus on laser spectroscopic applications to the environmental, ecological and biomedical fields.


Happy days with Anna Consortini in Ostiglia and in Ferrara!