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New directions for optical breast imaging and sensing: Multimodal cancer imaging and lactation research

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Abstract

We provide an overview of optical methods used in breast imaging and monitoring. We discuss limitations and opportunities, and present new directions where biomedical optics can play a role in breast health.

One direction regards steps to bring the promise of photoacoustic breast imaging to fruition. We argue that a hybrid approach, combining photoacoustics with ultrasound imaging, is important for comprehensive evaluation of breast lesions. Such an approach combined with multi-parameter quantitation can provide the necessary breakthrough in breast cancer management.

Another direction involves the application of existing optical modalities for the breast to an entirely new application area: human lactation research. Whereas breastfeeding plays a crucial role in public health, many breastfeeding problems are not well understood and breastfeeding rates need to be improved. We describe how current optical imaging and sensing modalities can play a role in obtaining fundamental knowledge into the origin and treatment of breastfeeding problems.

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Introduction

Optical methods have the advantages of using non-ionizing energy, not requiring painful breast compression, being fast and inexpensive, and being capable of extracting functional and molecular information from tissue. This latter capability is due to the ease with which multiple wavelengths of light can be used to probe tissue. In combination with quantitative algorithms, this allows extracting hemoglobin (Hb) concentration, Hb oxygen saturation, as well as concentrations of water and lipid content, and tissue scattering. Several of these parameters are known to be changed in breast disease, and are expected to be different in the various phases of breast development.

In addition to the well-known optical methods, a technique gaining much attention is photoacoustic (PA) imaging [1]. As the name suggests, pulsed light is used to excite ultrasound waves in tissue where optical absorption has taken place. The ultrasound waves travel to the boundary, with little scattering, where they can be detected using ultrasound detectors. The distribution of optical absorption in tissue can be mapped by using the ultrasound signals measured at multiple locations,. By this, for example, blood vessels can be visualized with high resolution.

In this article, we summarize the current knowledge of the use of optical methods on the breast, and discuss fruitful new directions. It is not our intention to review the existing literature, for which we refer to existing extensive work [2–8].

The human breast in health and disease: The knowns, the unknowns, and the challenges

Throughout the female lifespan, the human breast undergoes a sequence of developmental stages. Early breast formation starts *in utero*, followed by maturation during puberty under the influence of hormonal regulation [9]. We discuss the breast developmental stages in the human adult breast, and challenges and opportunities for biomedical optics technical solutions. In simplified chronological order, these stages include menstruation, pregnancy and lactation, and (post)menopause.

Menstruation

Changes in breast composition

An average menstrual cycle of 28 days can be described by a proliferative phase (day 3–7), a follicular phase (day 2–8), a luteal phase (day 15–20), a secretory phase (day 21–27) and a menstrual phase (day 28–2). During the follicular phase, lobules are relatively small and metabolic activity is low. Lobule size and metabolic activity increase during the luteal phase and secretory phase. The secretory phase is also associated with fluid accumulation and venous congestion. These processes are reverted during the menstrual phase [10].

Challenges for optical breast tumor visualization

Several optical techniques have been developed and applied for studies on the breast, most often for potential roles in breast cancer management, due to the capacity to extract pathophysiological signatures of tissues [1,11] The enhanced vascularization and changes in local blood oxygen saturation associated with cancer, as well as altered water and lipid concentrations in the affected tissues can be detected using optical methods. Since optical techniques use non-ionizing energy and their imaging performance is relatively unaffected in the presence of glandular tissues, they have a role to play in the imaging of pre-menopausal subjects. In this subject population, x-ray imaging is not preferred due to its poor sensitivity in breasts with high content of glandular tissue—the so-called radiodense breast. Further, glandular tissue is vulnerable to ionizing radiation and exposure to x-rays is not recommended.

PA breast imaging is attractive for conducting studies in various aspects of breast health due to its ability to visualize angiogenesis-driven optical absorption changes in breast tumors, with submillimeter resolution as deep as 40 mm in breast tissue, and capability of real-time imaging [8]. Recently, the method is taking flight with a handheld implementation receiving approval from the US Food and Drug Administration (FDA) for a role in diagnosis of breast cancer [12]. Such a handheld device is built around a linear ultrasound array by providing pulsed laser light for PA excitation using an appropriate light delivery arrangement. There are also three-dimensional PA computed tomography (CT) embodiments where the breast is pendant in an imaging bowl with a hemispherical array of ultrasound detectors and appropriate light delivery mechanisms [8]. By computed tomography (CT) we mean that images are formed by reconstruction from multiple projections (acquisitions) around the breast.

It is interesting to note that in dynamic-contrast enhanced (DCE)-MRI, enhancement of normal parenchymal tissue, the so-called background parenchymal enhancement (BPE), often interferes with the imaging of breast lesions [13]. BPE is influenced by hormonal fluctuations in the menstrual cycle, and MR imaging requires to be timed usually in week two of the menstrual cycle. Considering that optical methods are highly sensitive to subtle physiological changes in the breast, like MRI, it can be expected that the phase of the menstrual cycle has an influence on PA measurement results. A handful of studies have been conducted [14,15] using purely optical methods but also using PA imaging [16] However a complete understanding of the changes and their influence has not yet been elucidated, and consensus is currently absent on timing of measurements.

We believe that this is an interesting area to continue to investigate where the most important questions from an operational point of view would be: does the healthy breast exhibit different qualitative and quantitative features at different phases of the menstrual cycle? If so, can we relate these changes to healthy breast physiology? Do these changes have an influence on lesion visualization, and would it be imperative to have a specific timing for an optical scan of the breast?

Pregnancy and lactation

Changes in breast composition

During pregnancy, the breasts undergo a transformation to fulfill their main biological function: lactation. On a macroscopic scale, the most important changes in breast composition include i) an increase in the amount of glandular tissue to synthesize milk, and ii) an increase in vascularization to secure adequate nutrient supply for milk synthesis. During lactation, breast composition is highly dynamic due to continuous changes in milk content. Hemodynamics can change dramatically upon active milk ejection by the breast during a breastfeed, due to regulation of this process by the vasodilating hormone oxytocin [17−19]. After lactation, the breasts undergo a reversed process, referred to as post-lactational involution. The involution process is associated with a decrease in breast volume, a decrease in the glandular to adipose tissue ratio and vascular regression [20].

Challenges for optical breast tumor visualization

While pregnancy-associated breast cancer is not common, breast tumor visualization in the pregnant and lactating breast poses major challenges for any imaging modality, due to enhanced breast volume, breast density, blood content and dynamically changing milk content. This results often in diagnosis at a later stage where tumor burden is higher. Breast imaging during this life stage of a woman may be an opportunity for application of optical methods. To the best of our knowledge, no studies have been documented yet on optical breast tumor visualization during pregnancy and lactation. It is expected that optical imaging depth will be markedly reduced compared to the non-pregnant, non-lactating breast.

Challenges from the perspective of infant nutrition and maternal health

Breastfeeding offers many short-term and long-term health benefits for both mothers and infants [21,22]. Breastfed infants have a reduced risk of life-threatening infections, diarrhoea, obesity and several non-communicable diseases in later life, while mothers themselves benefit from a reduced risk of breast, and ovarian cancer. Nevertheless, many mothers who desire to breastfeed, feel discouraged along the way by factors of both biomedical (e.g. inadequate milk supply, pain) and psychosocial (e.g. fatigue) nature [23]. In 2019, only 41% of infants worldwide were exclusively breastfed in the first six months of life [24]. According to the Global Nutrition Targets of the World Health Organisation (WHO) and the United Nations Children's Fund (UNICEF) [24], this number should be improved to 70% by 2030.

Better breastfeeding support on a medical and societal level is essential for reaching the Global Nutrition targets [21,22,24]. This includes a crucial role for the imaging and diagnostics field: currently, only a limited number of objective methods are available to investigate and support lactation [25]. As a consequence, many breastfeeding problems are not well understood, or misdiagnosed. These problems include (the perception of) insufficient milk supply and lactation pathologies like nipple trauma, mastitis and Raynaud's phenomenon. Many of these breastfeeding problems are associated with inconclusive evidence and unanswered questions regarding breast tissue composition, metabolic activity, milk removal, and hemodynamics during lactation. A major challenge includes the development of dedicated methods to quantify these physiological parameters, in order to obtain fundamental insight into lactation physiology and facilitate an early diagnosis of breastfeeding problems. Only when this challenge is solved, can better treatment and prevention strategies be developed.

(Post) menopause

Changes in breast composition

During menopause, a decrease in estrogen levels triggers a change in breast tissue composition, which includes a reduction in glandular tissue content. As a consequence, the overall breast size reduces. The (post) menopausal period is associated with an increased risk for the development of both benign and malignant breast lesions [9]. The median age for breast cancer diagnosis varies per world region but is approximately 60 years in the USA and EU, and 50 years in China [26]

Challenges for optical breast tumor visualization

Despite advances, current imaging modalities for breast cancer all suffer from shortcomings. Most importantly, there are overlaps between features of malignancies and benign abnormalities and often also healthy tissues, leading to false-positives and false-negatives.

The presence of hemoglobin, with its strong optical absorption, in the enhanced blood vessel network associated with tumor growth, can betray the presence of the carcinoma to light. Further, it is thought that the oxygen saturation (SO_2) in malignant tissues is lower than in benign tissues. This calls for multi-spectral imaging and quantitative reconstruction algorithms to extract a measure of SO_2 to perform discrimination. Diffuse optical imaging has been employed in several studies in visualizing breast cancer. However, despite much promise the method is yet to see clinical translation. Here, PA imaging is highly promising, since it provides high resolution deep inside tissue, predominantly because it does not detect light, but rather ultrasound which undergoes three orders of magnitude lower scattering than light.

New directions for optical breast imaging and sensing

Optical breast tumor visualization

The ideal sought-after PA imaging system is one that is a hybrid of PA and ultrasound (PA-US) computed tomography for 3D full-view of the breast. Such an imager theoretically possesses the ability to extract four imaging contrasts from tissue. First, in the PA mode of this imager, hemoglobin (Hb) absorption from tumor vascularization would be visualized. Second, utilizing spectral differences in absorption of Hb and oxyhemoglobin (HbO_2) tissue oxygen saturation (SO_2) would be extracted. From the US mode, the imager would recover a measure of the elastic properties of the tissue in the form of ultrasound reflectivity contrast well known to demonstrate tumor morphology [27] and sound speed contrast, which is known to be increased in malignancies [28]. This integrated information would allow for a highly comprehensive and quantitative evaluation of the tissue under inspection. While such a system does not exist, a first prototype has been developed in the form of the highly sophisticated PAMMOTH imager [29] that can extract the first three of the four possible imaging contrasts from tissue. Studies are ongoing to establish the imaging performance of the prototype on phantoms and then further on human subjects.

With the ideal sought-after system, quantitative PA imaging will enable to image functional information in the form of vascular patterns and oxygen status, and the US mode will enable imaging of morphology. The technique will have potential to lead to a comprehensive assessment of the lesion in diagnosis. Such a system will also have the potential to improve screening, if it were engineered in subsequent versions to be high throughput, simple to operate for staff, inexpensive and with a low burden to the subject. However, it is good to keep in mind that breast screening is one of the most controversial medical procedures, and any other new technique will be highly scrutinized at multiple levels.

A niche role for the method could be in monitoring of neoadjuvant chemotherapy (NAC) in breast cancer. The predominant goals of this approach are to: 1) reduce tumor size enabling breast-conserving surgery; 2) treat possible future metastatic disease, even if undetectable in pre-operative staging; and 3) tailor future chemotherapeutic decisions.

It is known that effective chemotherapy reduces tumor vascularity and microvascular permeability at early stages. This will be manifested as an overall decrease in blood vessel density, with changes in oxyhemoglobin reflecting diminished vascular supply and tumor tissue oxygen consumption [30,31]. This could be an important application area for hybrid PA-US imaging.

Human lactation research and support

So far, optical breast imaging and sensing have been fully devoted to breast cancer visualization due to its noninvasive, safe and pain free advantages above other imaging modalities. Here, we discuss that these virtues are not limited to breast cancer research alone, and may play a crucial and pioneering role in advancing human lactation research.

On a macroscopic scale, the process of milk synthesis and secretion is expected to depend primarily on mammary blood (i.e. nutrient) supply, glandular tissue content and activity, and active milk ejection by the breast. As lactating breast physiology is highly dynamic, simultaneous quantification of all parameters of interest is favorable. Spectroscopic optical breast imaging techniques operating in the near-infrared wavelength range may potentially reveal new insights into all of these parameters simultaneously [32]. From years of breast cancer research, it is known that many of these techniques can accurately quantify water, lipid and oxy/deoxy-hemoglobin concentrations in breast tissue. In favor of lactation research, water and lipid concentrations relate to the glandular and adipose tissue content of the breast [31] and oxy/deoxy-hemoglobin concentrations relate to mammary blood content and metabolic activity [17,18]. Recently, we demonstrated that diffuse optical spectroscopic imaging (DOSI) is indeed effective in evaluating the changes in breast tissue composition during post-lactational involution [20]. As human milk can be optically modeled as a mixture of water and lipid [33], dynamic changes in these parameters may potentially also provide new insights into milk secretion and displacement inside the lactating breast. Besides spectroscopic optical breast imaging, other optical imaging and sensing modalities can reveal additional important insights into the lactating breast. For instance, laser Doppler flowmetry can be used to explore hemodynamics inside the microcirculation of the skin. This technique can potentially predict the occurrence and duration of the milk ejection reflex during a breastfeed [19], which is crucial for effective milk transfer to the infant.

Besides lactating breast physiology, optical methods also offer unique possibilities to analyze human milk itself. Human milk composition is highly variable between mothers, over the course of lactation, and even within a single breastfeed. Adequate quantification of milk composition is important in premature infant feeding for estimating total nutritional intake [34], but also to answer important questions on, for example, the influence of maternal diet on milk composition and infant development [35]. As biochemical methods that estimate milk composition are labor-intensive, alternative methods based on near-infrared and mid-infrared spectroscopy have been recently adapted from dairy industry to human milk applications [36]. Other optical methods have only been marginally explored for the purpose of milk composition analysis, but recent advances in elastic light scattering methods [33,37] and Raman spectroscopy [38–43] also show high potential for accessible and nondestructive human milk analysis.

Potential hurdles in the optical approach

Light penetration in tissue is limited, due to multiple scattering and absorption. However, when the breast is in a pendant position, it is accessible from all sides for light. A multitude of light injection points coupled with a hemispherical detection geometry around the breast allows an optimal penetration of light that has seen blood vessel networks being visualized up to 50 mm deep [44,45]. This could enable full-breast imaging in all but very large breasts. Alternatively, breast flattening through a supine measurement position can be advantageous in diffuse optical imaging studies of the breast [20,31].

Imaging of SO_2 is one of the promises in PA imaging. The high resolution of PA imaging, in contrast to that of diffuse optical methods, is essential for imaging of the microvascular SO_2, which provides insights into local changes in metabolism known to be dysregulated in cancer. Yet to achieve accurate estimation of SO_2 using the *in vivo* spectral signatures of Hb and HbO_2, is one of the crucial challenges in the field. The difficulty arises due to the unknown spatial distribution of light fluence inside the breast, which also changes with wavelength. Various approaches are being investigated to estimate the light fluence, often using light propagation models, and less often using experimental measurements.

For lactation science in particular, the limited temporal resolution of most optical breast imaging techniques may pose additional challenges. Sufficient temporal resolution ($\sim$10 Hz sampling rate) is required to resolve the most important dynamic nuances in lactation physiology, which include the milk ejection reflex, heart rate and infant suckling behavior. Whereas current diffuse optical imaging studies are limited to ∼0.3 Hz sampling rate [32], recent technological advances demonstrate that this limitation can be overcome [46].

Perspectives and outlook

In this article, we have introduced two promising new directions for optical breast imaging and sensing: hybrid PA-US and lactation science. The proposal for hybrid PA-US 3D imaging promises the ability to perform a comprehensive evaluation of a suspect breast, which can lead to a role within the breast cancer management paradigm. With several major technological advances being made and with more expected in the near-future, clinical studies using state-of-the-art systems will have priority. We believe that we may be at the cusp of clinical breakthroughs using hybrid PA-US 3D systems in the coming decade.

With respect to lactation science, the coming period will be a highly exciting time to work in this field with myriad opportunities. Our current biophotonics toolkit offers an extraordinary range of optical imaging and sensing methods that can play a unique role in the development of noninvasive, accessible methods to investigate both the lactating breast and the composition of human milk. Considering the global importance of breastfeeding and the relatively nascent stage of this new application field, we would like to emphasize that urgent action is needed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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