Recent Developments in Instrumentation of Functional Near-Infrared Spectroscopy Systems

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Abstract: In the last three decades, the development and steady improvement of various optical technologies at the near-infrared region of the electromagnetic spectrum has inspired a large number of scientists around the world to design and develop functional near-infrared spectroscopy (fNIRS) systems for various medical applications. This has been driven further by the availability of new sources and detectors that support very compact and wearable system designs. In this article, we review fNIRS systems from the instrumentation point of view, discussing the associated challenges and state-of-the-art approaches. In the beginning, the fundamentals of fNIRS systems as well as light-tissue interaction at NIR are briefly introduced. After that, we present the basics of NIR systems instrumentation. Next, the recent development of continuous-wave, frequency-domain, and time-domain fNIRS systems are discussed. Finally, we provide a summary of these three modalities and an outlook into the future of fNIRS technology.

Keywords: NIRS technology; spectroscopy; imaging; bioinstrumentation; near-infrared

1. Introduction

The invention of near-infrared spectroscopy (NIRS) enabled many investigations and development in various scientific fields ranging from pure research laboratory experiments to robust industrial procedures for different purposes [1,2]. More interestingly, numerous biomedical studies have been carried out using NIRS systems [3–5]. Among many applications, medical diagnostics, such as functional neuroimaging, cancer diagnosis, rehabilitation, and neurology, have been a drive for numerous investigations and development [3–6]. Starting in the 1990s, a new chapter of NIRS has spawned numerous efforts to develop functional NIRS (fNIRS) systems for different applications [2,7–10]. These efforts followed naturally from the understanding that fNIRS allows functions that are not available by using other techniques. fNIR imaging (fNIRI) and spectroscopy were just some primary examples. More specifically, cerebral blood flow (CBF) and cerebral blood volume (CBV) are indirectly connected with mental activity. Neural activity increases the cerebral metabolic rate of oxygen which consumes glucose and oxygen and releases vasoactive neurotransmitters which lead to vasodilation of arterioles and finally leads to a local increase in CBF and CBV [11]. Therefore, fNIRS is considered one of the main emerging neuroimaging techniques. This allows physicians to view activity within the human brain without the need for quite complicated invasive neurosurgery. The potential of such techniques has been reviewed in several recent papers [6,12–15].

Studying light-tissue interaction at any frequency band is a quite complicated and interesting task at the same time, because the materials of the biological tissues are multilayered, multicomponent, and optically inhomogeneous. It includes reflection, refraction, absorption, and multiple scattering of photons in the tissue as shown in Figure 1. The fact that the absorption by water molecules is lower than oxyhemoglobin and deoxyhemoglobin in the light wavelength range between 650 and
1000 nm enables us to easily estimate the concentration of oxyhemoglobin and deoxyhemoglobin. Nevertheless, strong scattering of light is a characteristic feature of tissue in which near-infrared light propagates in all directions and diffusely illuminates the tissue volume instead of following a narrow path. The absorption and scattering effects at NIR will be discussed in more detail in Section 2.

![Illustration of light signal propagation](image)

**Figure 1.** Illustration of the light signal propagation via a biological tissue after it has been partially absorbed and scattered.

In 1993, a NIRS measurement was performed by Hoshi and Tamura [16] by combining five single-channel NIRS instruments. Since then, NIRS instrumentation has been continuously developing and has established its place as a functional brain imaging modality in research use. For instance, a system with 96 sources, 64 detectors, and 3072 measurement channels was recently built [17]. Depending on the area of interest, a number of emitters and detectors are used and separated by a distance of few-to-several centimeters. The acquired raw data is then processed and analyzed using a computer. The estimation of the oxygen saturation of the probed tissue can be evaluated by evaluating the ratio of red-light intensity to the near-infrared light intensity that was re-emitted from the tissue. Therefore, the fraction of oxyhemoglobin measured, for example, at a spot on the brain reflects the local activity at that spot. Furthermore, this method uses a quite low fluence of non-ionizing light radiation. Interestingly, the light wavelengths used have a penetration depth of few centimeters within tissues. Increasing the source–detector separation distance provides a better penetration depth (higher depth sensitivity profile), however, fewer photons will reach the detectors, which results in a low signal-to-noise ratio (SNR). Clearly, there is a trade-off between the light penetration depth and the SNR. A source–detector separation of 3 cm is a reasonable compromise between depth sensitivity and SNR in the brain studies of adults population [18,19] while a source–detector separation of 2 to 2.5 cm is reasonable for the brain of infants population [20,21].

fNIRS instrumentations continually improve, facilitated in part by the availability of compact semiconductor optical photodiodes at the wavelength of interest. Nowadays, commercially compact and wearable systems are also accessible for imaging and spectroscopy. Even with such advancements, fNIRS systems continue to be a subject of practical developments to make them wearable and as compact as possible. The pros and cons of fNIRS have been reviewed in a number of articles [10,22,23]. Ref. [23] specifically discusses the main features of the commercially available fNIRS systems. fNIRS technology is experimentally flexible, silent, and can be easily integrated with positron emission tomography (PET), functional magnetic resonance imaging (fMRI), or electroencephalography (EEG). Nevertheless, fNIRS systems have two main limitations, namely a low spatial resolution of about 1 cm and its ability to get the hemodynamic response at the outer cortex only [23].

Over the last few decades, fNIRS systems have been designed by utilizing different NIRS techniques. These techniques can be categorized into three main types: (i) continuous wave (CW) by measuring the light attenuation using a constant tissue illumination; (ii) frequency-domain (FD) by utilizing the phase delay and attenuation of detected light; and (iii) time-domain (TD) by measuring the shape of short pulses after propagation through tissues. The signal acquired by these techniques is then post-processed using signal processing algorithms. Accordingly, various systems and techniques...
have been the subject of many informative articles and reviews. Table 1 represents a brief list of those review papers that focused on the fNIRS systems and their applications.

<table>
<thead>
<tr>
<th>Technique</th>
<th>Main Discussed Topics</th>
<th>Year</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CW-fNIRS</strong></td>
<td>fNIRS major events 1977–2011</td>
<td>2012</td>
<td>[1]</td>
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<tr>
<td></td>
<td>Simple point and multi-channel CW fNIRS</td>
<td></td>
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<td></td>
<td>Main fields of fNIRS applications</td>
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<tr>
<td></td>
<td>Technological design aspects (Sources and detectors)</td>
<td>2014</td>
<td>[24]</td>
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<tr>
<td></td>
<td>Analysis of fNIRI signals</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Characteristics of key fNIRS and Diffuse Optical Tomography (DOT) technologies</td>
<td>2017</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>fNIRS Most relevant references</td>
<td>2019</td>
<td>[13]</td>
</tr>
<tr>
<td><strong>FD-fNIRS</strong></td>
<td>Fundamental instrumentation design of FD-NIRS</td>
<td>1998</td>
<td>[26]</td>
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<tr>
<td></td>
<td>Solving the forward model for light propagation in tissue</td>
<td>2010</td>
<td>[27]</td>
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<tr>
<td></td>
<td>Developments in reconstruction methods</td>
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<td></td>
<td>A tutorial of the development of Diffuse optical imaging and its applications.</td>
<td>2012</td>
<td>[28]</td>
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<tr>
<td></td>
<td>DOT image reconstruction instrumentation and its clinical applications</td>
<td>2016</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>Basics of FD-NIRS and its application to functional brain studies</td>
<td>2020</td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Recent advances in acquisition and processing speed for several Diffuse Optical Imaging (DOI) modalities.</td>
<td>2020</td>
<td>[32]</td>
</tr>
<tr>
<td><strong>TD-fNIRS</strong></td>
<td>Basic features of the TD approach and diffuse optics</td>
<td>2016</td>
<td>[33]</td>
</tr>
<tr>
<td></td>
<td>Theoretical background, instruments, advanced theories and methods</td>
<td>2019</td>
<td>[14]</td>
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<tr>
<td></td>
<td>Brain monitoring clinical applications</td>
<td>2019</td>
<td>[15]</td>
</tr>
<tr>
<td></td>
<td>Time-gated detection modality</td>
<td>2020</td>
<td>[13]</td>
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However, most of the reviews have been focusing on the differences among these three techniques and their applications rather than the instrumentation of such systems. Therefore, the main goal of this paper is to remedy this gap by examining the main differences and similarities between the CW, TD, and FD techniques in building the fNIRS system from an instrumentation point of view. The manuscript is organized as follows: First, the light-tissue interaction at NIR represented by the effects relevant to fNIRS namely the absorption and scattering, and the basics of NIR instrumentation are presented in Section 2. In Sections 3–5, we discuss CW, FD, and TD fNIRS recently developed instrumentations. Section 6 then presents a comparison across these three modalities and finally, the paper is summarized in Section 7.

### 2. Near-Infrared Systems Instrumentation

As for any optical system at visible or NIR light ranges, instrumentation of NIRS system consists of an (i) emitter device to illuminate a small area of tissue with light at two or more wavelengths, namely red and infrared range, and (ii) a detector device to measure the back-scattered light emerging from the tissue, and (iii) a diffraction grating to enable differentiation and recording the intensity of different wavelengths [24]. Practically, several sources and detectors (that are called optodes) are required and the collective effect is measured.

In order to choose the optimal wavelengths for sources, the effects relevant to fNIRS such as absorption and scattering need to be carefully considered. At NIR wavelengths, the atoms or molecules absorb a part of the light energy. The absorption level is determined based on the molecular composition...
of tissue, the wavelength of the emitted light, and the thickness of the tissue. Within the NIR window, molecules such as water and lipids are minimal absorbers compared to the iron-containing hemoglobin present within the blood. In this wavelength window, deoxyhemoglobin (Hb) and oxyhemoglobin (HbO₂) absorb light strongly. Figure 2 illustrates these absorption properties of the deoxyhemoglobin (Hb) and oxyhemoglobin (HbO₂) as well as the so-called “diagnostic/therapeutic window” where water absorption is at its minimum. Thus, light in this optical window can penetrate deeper in tissue [34–36].

![Figure 2. The light absorption of the deoxyhemoglobin (Hb) and oxyhemoglobin (HbO₂) of biological tissue (re-drawn from the data taken from Ref. [37]). In the diagnostic window, the absorption level between Hb and HbO₂ is notable, and water absorption is at its minimum.](image)

Unlike the absorption, a scattering interaction occurs when light strikes a particle and changes direction. Numerous factors, such as wavelength, particle size, and refractive index of tissue, contribute to the prevalence of scattering. There are two general types of scattering: elastic and inelastic. With elastic scattering, no energy is lost; the light simply changes direction. With inelastic scattering, some energy is lost from the incident light during the interaction, which would mean altered frequency and wavelength. The scattering considered here is the former. Similar to absorption, the intensity of light measured by the detector at a distance in the medium is less than the original intensity of light incident on the tissue described by Beer-Lambert law. For the adult head, due to scattering and absorption, only about one in 10⁹ photons that enter the tissue will actually reach the position of a detector located on the surface a few centimeters away from the source. Both absorption and scattering reduce the signal and in actual tissues, they both are present simultaneously [34].

Considering the above effects of light-tissue interaction at NIR, there are a variety of NIR sources currently exist. The incandescent light bulb has often been used in the past while light-emitting diodes (LEDs) are increasingly becoming the main sources in use due to its reliability, low power consumption and its long lifetimes [1,7,13]. At the NIR spectrum range, LEDs are available at different emission wavelengths with output power in the range of mW. Commonly available wavelengths are 660 nm, 670 nm 700 nm, 850 nm, 870 nm and 940 nm. The spectral half-width of LEDs in the 600 nm region is around 20 nm and the widths increase in longer-wavelength materials to around 40 nm for LEDs in the 900 nm region. Nevertheless, wavelength-scanned lasers and frequency combs are used whenever high precision spectroscopy is required [38]. Laser diodes have the advantages of small size, low energy consumption and high output coherent light with output power in the range of mW. At the NIR spectrum range, the GaAs/AlGaAs material (850 nm) and vertical-cavity surface-emitting laser (VCSEL) [39], which range from 750–980 nm, are commonly used.

For typical fNIRS optode separation distances, the intensity of light that penetrates the head and reaches the detector is very small—on the order of only a few mW to pW [40], which is an
extremely small value. Therefore, high-sensitivity detectors are crucial in this case. Hence, the choice of detectors includes light-sensitive diodes, photomultiplier tubes (PMTs), semiconductor-based pin, and charge-coupled device (CCD) cameras [41–43] as well as avalanche photodiodes (APDs) [44]. More recently, silicon photomultipliers (SiPMs) have been intensively utilized for fNIRS applications as well [41,44,45]. SiPMs feature major advantages in terms of sensitivity, gain, and speed to acquire the signal [46]. Moreover, they provide a much higher responsivity, three or more orders of magnitude larger than PDs or APDs [41]. The choice of the photodetection devices depends mainly on the intended application and the source emitted wavelengths. For instance, the silicon-based pin is a good choice in the case of the shorter end of the NIR spectrum (400 nm to 1000 nm). In contrast, Germanium and InGaAs based pin photodiodes are suitable for the long-range of the NIR. More specifically, the wavelength of the Germanium pin photodiodes range is from 800 nm to 1600 nm while it is from 1100 nm to 1700 nm for the InGaAs ones. Nevertheless, the responsivity for the silicon-based pin peaks in the range between 800 nm and 900 nm. For silicon and Germanium Avalanche Photodiodes (APD) types, silicon APD has a higher and wider gain (20–400) with minimum dark noise (0.1–1 nA) in comparison to Germanium APD, which has a gain range (50–200) with a dark noise range from 50–500 nA. This makes silicon-based pin a common choice for many fNIRS systems [47,48].

The question that arises here is how many sources and detectors should be used and even more importantly where to locate them. In a recent paper [49], the translation of regions of interest (ROI) to the placement of optodes on a measuring cap has been thoroughly investigated as shown in Figure 3. The authors presented a toolbox in this paper to simplify selecting the right fNIRS optode positions on the scalp. It is based on the overlapping between the simulated photon transport from optodes positioned in 130 positions on the cap and the regions of interest within the brain.

Figure 3. fNIRS cap layout with corresponding color-coded channels. Reproduced from reference [49].

Figure 4 shows a simplistic example of a montage of one source (in orange color) and a total of eight detectors. Hence, we can have up to eight channels to be measured. In case we have more than one source, we need to consider the optical coupling between the light sources and detectors. Actually, it is one of the most important factors affecting the quality of data. The poor coupling may lead to several types of errors in the measurement. These include motion artifacts caused by contact pressure variation, sliding of the probe along the skin, and light leaks. Motion artifacts can lead to signals that are partly or wholly useless. Light leaks may lead to a signal that looks normal but has a lower physiological contrast-to-noise ratio than a signal not affected by a light leakage [50]. Hence, such systems should be checked before taking any measurements against the dark noise.
The main property of NIR devices is the maximum possible number of channels. Conventionally, a channel is defined as a possible path between an emitter and a detector. Therefore, the maximum possible number of channels for 8 emitters and 8 detectors system is $8 \times 8 = 64$ channels. Practically, it is unlikely that the detectors receive a measurable signal from distant emitters, for instance on the other side of an adult head. Hence, detectors are placed within 3–4 cm distance from the corresponding emitters. Depending on the optodes arrangement, a total number of 20–25 channels can be valid using systems with eight emitters and eight detectors [24]. One of the important parameters to consider is the movement artifact due to the mechanical instability of the optodes on the subject. Various designs of optode holders that keep the optodes securely in place and retain a stable contact and pressure against the skin have been proposed [13,25,51]. More importantly, lightweight and comfortable enough caps have been developed to allow some movement for the subject [52].

Several types of systems are currently available for fNIRS measurement techniques: continuous-wave, frequency domain, and time domain. Theoretical light penetration depths and sensitivity profiles are extremely similar for a CW system, a 200 MHz modulated FD system, and a 500 ps pulsed TD system [13]. However, the light signals from FD and TD systems can typically penetrate deeper into the brain than CW systems. Besides, it is feasible with both FD and TD systems to differentiate between the brain and extra-cerebral tissue in superficial regions. Some review papers have already compared these techniques [53,54]. Nevertheless, our paper is concerned with the recent advances of various instrumentation elements of these three systems that have been proposed in the last few years.

### 3. Continuous Wave fNIRS Instrumentation

The simplest form of tissue spectroscopy methods is the continuous wave technique. It is based on the steady light illumination of tissue and the detection of the transmitted light intensity through the tissue as depicted in Figure 5. In turn, it gives an idea about the relative light attenuation without differentiating the impacts of scattering and absorption. The strongest absorbers present in the blood are the hemoglobin molecules. Hence, valuable information is accessible such as relative changes in blood volume and oxygenation can be obtained. Hence, the relative concentration level can be evaluated with high reliability and contrast from the background. So, it is not a surprise to know that it is currently the most widely used fNIRS technique. The CW technique is very useful as it is very sensitive. Moreover, the sampling rate of less than a second is doable. Furthermore, CW systems can be made to be quite affordable for spectroscopy and imaging as well. In CW systems, the source emits light at the same intensity and the changes in the intensity are measured then by a detector. The light penetration depth increases as the source-detector separation increases, but the measured intensity is less, which leads to a low SNR as illustrated in Figure 5.

![Figure 4. Eight channels montage with one source and eight detectors.](image_url)
fNIRS systems can be miniaturized quite easily by employing commercially available light sources and detectors. However, achieving wearable fNIRS systems is quite challenging for the fact that high requirements for signal quality and system reliability are required. Most fNIRS systems employ two wavelengths where laser diodes are used as emitters and PMTs or APDs are used as detectors. Figure 6 depicts a block diagram of such a multiwavelength system [55]. Digital gain control is used to equalize all the channels over a 20 dB range. Next, a multiplexer can be used to sample one wavelength at a time. Then, to avoid aliasing at 250 samples/s, the storage capacitor is oversampled by an analog-to-digital converter (ADC) and this gives a temporal resolution of oxygenation measurement of >0.3 s. A modified Beer-Lambert principle is used here and it should be noted that the scattering is considered both homogenous and fixed [24,53,56].

Utilizing all eight sources during data collection provides a sampling frequency of 6.25 Hz when the sources are lit sequentially (standard mode). It can be increased by reducing the number of sources used during data collection. Employing only half of the eight sources, for example, results in a sampling frequency of 10.42 Hz—an increase of more than 4 Hz. Detectors are connected to the main unit by optical fibers. Optical fibers consist of a core for transmitting light and a covering to both keep internal light from escaping and external light from entering.

A multiwavelength approach has also been considered via selecting optimum wavelengths over the complete NIR spectrum to find the concentration changes [57]. Although development is being...
made on devices and methods using this fNIRS multi-spectral approach, they have two drawbacks [58].
It features an increased computational complexity. Moreover, there is a need to reduce the incident
power as light with a multiwavelength has higher total power than light with a limited number of
wavelengths. Instead, one can sample at the two optimal wavelengths as many times as possible in
order to achieve a higher SNR.

In a pioneering work that started in 2015, Von Lühmann et al. suggested a wireless fNIRS for
mobile neuroergonomics and Brain-Computer Interface (BCI) Applications [59]. The system uses
Time-Division Multiplexing (TDM) of the fNIRS channels. Interestingly, they aimed to have such
a system as an open-source instrument. The suggested module offers four dual-wavelength fNIRS
channels using 750 and 850 nm with a quite broad emission of 30 to 35 nm. The incoherence and
uncollimated characteristics of these sources allow for (i) a stronger strength used for tissue examination,
(ii) the optodes to be in direct contact with the scalp as a result of almost no heating of the tissue, and it
is (iii) no harm for the eyes. When using TDM, various factors have to be taken into accounts such as
inter-channel crosstalk, heating, and battery consumption. More importantly, the SNR is restricted by
the width of the used time frames. Figure 7 shows this open-source fNIRS system.

![Figure 7. Complete system with (a) single 4 channel fNIRS module and (b) Bluetooth module. Reproduced from reference [59].]

Following that, the original system has been significantly improved and called the ninjaNIRS
as shown in Figure 8 [60]. The new system has a very small footprint, scalable that supports up to
128 optodes. They are basically the core of this variable system. The optode itself digitizes the system,
the signal and therefore the interface is a purely digital bus. It has a Field Programmable Gate Arrays
(FPGA) onboard, at the side of the multi-wavelength led and photodetector. The long-term goal of
this study has been to build a high-density fNIRS-EEG-Eye-tracking system that has a long interval to
continuously monitor brain activity in real-time during movement, social interaction, and perception
whilst being portable, miniaturized, lightweight and wearable.
Another very interesting scheme has been proposed in 2017 by Wyser et al. to achieve a wearable and modular fNIRS system with four wavelengths \[40\] as shown in Figure 9. The scheme features three main characteristics: (i) the ability to measure short-separation (SS) and long-separation (LS) channels, (ii) four wavelengths can be utilized, and (iii) modular optode design that can be put on different brain regions. High modularity is obtained via a miniaturized hardware design of optode modules. It is worth mentioning here that sources and detectors can be individually connected to a central unit. For many fNIRS applications, in particular BCIs, the ability to measure the SS and LS channels can help to detect the desired signal and compensate for unwanted signals. Also, to achieve more robust estimates of concentration changes, four wavelengths are included.

![Figure 8. ninjaNIRS optodes and controller. Reproduced from reference [60].](image)

Figure 9. A compact fNIRS instrument. (a) The PCB next to a 10-cent euro coin. (b) Picture of the fNIRS system with two optode modules. (c) Conceptual sketch illustrating the arrangement of the system. Reproduced from reference [40].

The following aspects have been carefully considered during the design process of this system and are summarized in Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Required</th>
<th>Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal quality (SNR)</td>
<td>40–60 dB 60 dB</td>
<td>64 dB</td>
</tr>
<tr>
<td>Sampling frequency</td>
<td>Above 6 Hz</td>
<td>NS source; ND detector</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 Hz/[NS × (1 + 0.06 × ND)]</td>
</tr>
<tr>
<td>Safety</td>
<td>Temperature should not exceed 42 °C</td>
<td>≤41 °C</td>
</tr>
<tr>
<td></td>
<td>Optical power below 10 mW</td>
<td>1 mW</td>
</tr>
<tr>
<td>Usability</td>
<td>Small weight</td>
<td>Graphical user interface</td>
</tr>
<tr>
<td>Modularity</td>
<td>The number of channels is scalable</td>
<td></td>
</tr>
</tbody>
</table>
The third wearable CW-fNIRS system has been suggested by Chiarelli et al. [61]. It is based on silicon photomultiplier detectors and lock-in amplification with fiber-less and multi-channels. Due to the use of optical fibers in the fNIRS system, mechanical constraints will start being a problem to fNIRS due to the difficulty of stabilizing the optodes onto the scalp to get the required coupling. In fact, to avoid the use of optical fibers, the solution that was proposed in this study is by having direct contact between the sources and detectors from one side and the skin from the other side. The detectors on the scalp will not be allowed to be located as sensitive detectors, such as PMTs, are used. Since PMTs are delicate, bulky, and operate at high voltages, they become impractical in real-life operations. Recently, a solution was employed for fNIRS by using solid-state detectors such as single-photon avalanche diode (SPADs) that feature high sensitivity, although this will make the detector area very small, which is not a favorable solution. In fact, using photodiodes for light detection leads to low sensitivity and a dynamic range of the wearable CW-fNIRS systems.

As illustrated in the block diagram in Figure 10, the designed fNIRS system, named DigiLock consisted of three boards and an FPGA unit. All the necessary components for signal filtering and two sigma-delta converters (TI ADS1298) were used on the ADC board. The LED board implemented 32 time-multiplexed outputs for 16 dual-wavelength LEDs and an adjustable current source. The SiPM board contains an adjustable DC-DC converter for the SiPMs bias generation. Interestingly, during the multiplexing cycle, each combination of LED current source and SiPM bias could be dynamically adjusted for optimal signal acquisition. A single-board computer built around the Xilinx Zynq 7Z020 all programmable system-on-chip (SoC) was based on the FPGA board (MYIR Z-turn). Other useful peripherals were added to the board such as RAM, flash memory, USB, Ethernet, and temperature sensor. Using a tailored hardware description language (HDL) program, all the essential parts needed to execute the lock-in algorithm were implemented within the FPGA. The FPGA handled the elaboration chain implied by the lock-in algorithm and time-sharing synchronization among the LEDs and the ADCs after reading the data from the ADC converters. Employing and using the algorithm, SiPM bias, and automated calibration of each LED current were implemented.

![Figure 10. Block diagram of the DigiLock system. Reproduced from reference [61].](image)

The fourth system is a modular, fiberless, and features a flexible-circuit-based wearable fNIRS as shown in Figure 11a,b [62]. It is called Advanced Optical Brain Imaging (AOBI) system. In order
to facilitate efficient tessellation, it was designed as a diamond-like shape to cover a surface such as the head surface. This system can be used for quite long time periods with high flexibility of coverage. A single AOBI module has one long-separation channel of 30 mm, four channels with medium-separation of 21.4 mm, and a one-short separation channel of 8 mm.

Figure 11c shows a configuration of three flexible AOBI modules placed over an optical phantom. It results in 54 dual-wavelength channels, 26 of which are below the 40 mm separation used in fNIRS systems. The sampling frequency of all 54 dual-wavelength channels is 33.3 Hz, while a single AOBI module samples at 100 Hz. An SNR of more than 50 dB has been achieved in all intra-module channels, while inter-module channels show an SNR of more than 40 dB up to a 52 mm SD separation.

Thus, this system has features tailored towards full-head coverage and was made following a fibreless, wearable, and modular approach. The flexible-circuit configuration enables the modules to conform and bend to help in enhancing optode-scalp coupling. Moreover, the diamond module shape is well-situated to cover head surfaces. Hence, the main present constraints of the bulky systems with fiber optics can be replaced by much smaller and lighter electrical connections. In the near future, these wearable and low-cost systems will considerably help in acquiring high-density fNIRS measurements. For the preprocessing of the collected fNIRS signals and the filtration of the different types of noise signals (instrumental noise, experimental error, and physiological noise), we refer the reader to Refs. [63–65] for more information in this regard. For advanced postprocessing, feature extractions and classification techniques, the reader is referred to Refs. [66–68].

4. Frequency-Domain fNIRS Instrumentation

Continuous Wave modality is useful to measure light intensity attenuation. However, there are mainly two limitations to the use of CW fNIRS instruments. First, the CW instruments rely on the modified Beer-Lambert principle which assumes a constant scattering degree from all sites of light. The other limitation is the assumption to estimate the light traveled distance, the differential path length (L), where this mode contains no direct information about the time of flight. Hence, it is very difficult to separate the absorption from scattering in a heterogeneous medium using CW systems. Frequency Domain (FD) instruments are the evolution of the CW NIRS instruments. Thirty years ago, FD modality has been recognized as an alternative technique to measure the absorption and scattering coefficients.

In the 1990s, the work was about developing the theory and building some prototypes [26,69–73]. Nevertheless, those developments led to what is now the only available commercially FD based instrument by ISS (Table 3). Since 2000, the main works focused on the applications mainly in the area of breast and brain imaging and validating these applications in large clinical studies [74–79].

In FD fNIRS system, NIR light is modulated at a particular radio frequency (RF) usually in the range of a few hundred MHz. The selection of these frequencies is based on the distinct sizes and depths of the imaged object [76]. A high modulation frequency is suitable, for example, for imaging...
small breast lesions near the surface, while a low modulation frequency is suitable for imaging deeper
and larger lesions as illustrated in Figure 12. Ideally, however, all modulation frequencies should be
used to obtain the most accurate optical image reconstruction of the imaged object. On the other hand,
acquiring NIR measurements with all modulation frequencies is unfavorable in the clinical setting
to avoid patient motion. Therefore, one modulation frequency is usually selected for clinical studies
based on the depth of the targeted area.

![Diagram](image_url)

**Figure 12.** Schematic representation of NIR light penetration for both low and high modulation
frequency. The figure illustrates two detected signals successively along with the possible photon paths
“banana shape” in different layers with various absorption coefficient and reduced scattering coefficient.

As photon propagates into deeper tissue, its phase shift measurements quantify the degree of the
scattered photon in tissue, therefore, tissue scattering parameter is no longer assumed. Both the phase
and the amplitude intensity of the attenuated NIRS light can be extracted from the measurements
of the FD system. Figure 13 illustrates the principle of dual-phase lock detection [80]. Primarily, the
system consists of two mixers, two low-pass filters, and $90^\circ$ phase-shifter. The first mixer mixes the
signal and the reference, where the first lowpass filter ensures the output is a DC signal, $S_1 = 0.5 A \cos(\phi)$. In the same manner, the $90^\circ$ shifted reference signal is mixed with the original signal where
the second lowpass filter ensures the output is a DC signal, $S_2 = 0.5 A \sin(\phi)$. From $S_1$ and $S_2$, the
amplitude-phase unit extracts both the amplitude and phase based on:

$$A = 2 \sqrt{S_1^2 + S_2^2} \tag{1}$$

$$\phi = \arctan \frac{S_2}{S_1} \tag{2}$$

If the NIR probe consists of “$N$” number wavelengths sources, “$S$” number of sources, and “$D$”
number of detectors, and since both the amplitude and phase at each source-detector pair can be
extracted, the resulting total number of measurements for each set of measurements has a total of
$M = 2 \times (N \times S \times D$). As stated earlier, when NIR light penetrates inside the human tissue, scattering
of NIR light within human tissue dominates the absorption of the light propagation in such tissue.
This imposes a significant challenge to FD-NIRS optical tomography with regard to its spatial resolution
and localization accuracy. In fact, the spatial resolution of the optical tomography is limited by the
signal-to-noise ratio in the order of 20% of the imaging depth [80].
For breast imaging applications and to overcome the spatial resolution challenge, several groups have studied the co-registration of FD-NIRS optical tomography with other high-resolution imaging modalities such as MRI, ultrasound, and mammography [81–84]. In this approach, high spatial resolution images are used to guide the optical functional imaging with high localization accuracy. One research group has investigated the co-registration of mammographic x-ray images and optical breast imaging. The functional information provided by FD-NIRS optical tomography and the anatomical information provided by mammography imaging offers information that neither mammography nor optical imaging is enough single-handedly [83].

Once the optical scanning is completed, the optical probe shown in Figure 14a is removed to allow the breast to be compressed for the mammography scanning. The pressure pain associated with mammography scanning is the main disadvantage of this approach. Alternatively, the MRI-guided optical imaging has been investigated to image adipose and fibroglandular breast tissue by another group [82]. In this approach, the optical probe is a circular geometry consists of six laser diodes emit light at two wavelengths 660 and 850 nm modulated at 100 MHz as presented in Figure 14c. For each source illumination, measurements are collected from 15 locations with photomultiplier tube (PMT) detectors. Unlike the mammography and optical breast imaging approach, the MRI and NIR data are acquired simultaneously. The bulk size and the high cost of MRI systems are real challenges for this technique.

![Figure 13. Block diagram of a conventional dual-phase lock detection system.](image)

![Figure 14. Co-registration of FD-NIRS optical tomography with (a) mammography (Reproduced from reference [83]); (b) ultrasound (Reproduced from reference [84]); and (c) with MRI for breast imaging [82]; Copyright (2006) National Academy of Sciences, U.S.A.](image)
The ultrasound (US)-guided optical imaging approach was also investigated [76,84]. In this approach, the co-registration of the B-scan ultrasound images are utilized to improve the localization of breast tumor, while the optical imaging provides optical absorption information of the tumor vasculature. In the flat surface optical probe geometry illustrated in Figure 14b, the probe consists of 9 source locations and 14 PMT detectors. The NIR light is emitted by four laser diodes of wavelengths 730, 785, 808, and 830 nm modulated at 140 MHz. The B-scan ultrasound probe is located at the center of the optical probe, where it is surrounded by NIR sources and detectors. The ultrasound is considered safe for the patients, its cost is relatively low, and it is a movable system. Figure 14 depicts the three different approaches aimed for breast imaging.

In the last five years, there has been renewed interest in improving the fNIRS technology itself leading to new advantages associated with FD and potentially new applications. Roblyer and his team have recently developed an ultrafast frequency-domain diffuse optics system with a deep neural network (DNN) processing method to measure the optical properties [86]. The DNN is used to replace the time-consuming Levenberg–Marquardt iterative algorithm which was adopted to fit the calibrated amplitude and phase measurements to an analytical forward model. In contrast to the iterative algorithm, the DNN is 3–5 orders of magnitude faster to estimate the optical properties of measured tissue. Therefore, the developed system combined with DNN enables a robust tissue oxygenation monitoring system that can be able to acquire, process, and display absolute concentrations of hemoglobin at an adequate rate to catch the cardiac cycle at the higher speed [86].

In an effort to maximize the penetration depth, Sassaroli et al. has shown that with combinations of sources and detectors using a dual-slope method, phase information can provide deeper sensitivity [87,88]. In this theoretical work, the authors have presented a dual-slope (gradients versus source-detectors separations) method with a requirement of at least two sources and two detectors arranged symmetrically. In comparison to the conventional single-slope method, the dual-slope method has achieved maximal depth sensitivity for all three data types in FD-NIRS (DC, AC, and phase).

In their recent work, Doulgerakis et al. has systematically studied the reconstructed image quality when phase shift measurements incorporated from an FD high-density measurement system [89]. It has been shown that phase information provides not only deeper information sensitivity but also higher effective resolutions than the CW method [89]. This could be potentially very important for fNIRS, where gaining a distance as little as 1 mm or 2 mm means one can reach deeper in the cortex. Both works, by Sassaroli et al. [87] and Doulgerakis et al. [89], showed experimentally that FD systems appear to be sensitive to deeper optical layers. There are different approaches for image reconstruction to recover the optical properties from the FD-NIRS measurements. For instance, a two-step image reconstruction approach was investigated in Refs. [90–92]. Moreover, different regularization techniques such as Tikhonov regularization and Levenberg Marquardt regularization were also studied and the reader is referred to Refs. [93–95] for more information about that.

5. Time-Domain fNIRS Instrumentation

In time-domain fNIRS systems, the tissue is irradiated with picosecond short pulses. At the detector side, detectors that feature very fast responses have to be used in order to record the amplitude of the light pulse as it leaves the tissue as shown in Figure 15. Typically, the received signal is smeared out compared with the original signal as a result of the randomly distributed lengths of photons interacting with different diffusive layers of the tissue and induce various scattering events and form the distribution of time-of-flight (DTOF) of the received photons. Hence, the absorption and scattering properties of the tissue can be assessed using the pulse peak and its time, area, and width. By integrating the temporal profiles, the intensity can be obtained.
Figure 15. Mechanism of TD NIRS showing the incident light short pulse and two detected signals successively along with the possible photon paths “banana shape” in different layers with various absorption coefficient and reduced scattering coefficient.

Next, the modified Beer-Lambert law can be used to evaluate the absorption variations. Moreover, the mean optical path lengths are calculated from the center of gravity of the temporal profile [96]. The computations of the mean path length and absorption variations are model-independent. Hence, the values of scattering and absorption coefficients ($\mu_s$ and $\mu_a$) can be obtained using the nonlinear least-squares method after applying the diffusion equation in reflectance mode into all observed temporal profiles [97]. In turn, absolute concentration levels can be obtained using this technique, which enables time-resolved measurements with any given source-detector distance that in principle can go down to zero. The intracerebral and extracerebral absorption variations are determined then from moments (integral, mean time of flight and variance) of DTOFs [98].

One of the early fNIRS-TD systems is from Hamamatsu Photonics KK, Hamamatsu, Japan [99]. It utilizes three-wavelength with a generated light pulse width of 100 ps, a peak power of 60 mW, an average power of 30 μW, and a pulse rate of 5 MHz as depicted in Figure 16. On the detection side, a PMT was used in photon-counting mode. The received signals are then processed by a TRS circuit. It consists mainly of a time-to-amplitude converter, an ADC, and a histogram memory. Optical fibers are used to illuminate the tissues and to collect the diffuse light accordingly. Two transmitters and two detectors are used and hence two spots can be illuminated at the same time.

Figure 16. Photograph and schematic diagram of a time-resolved spectroscopy system. Reproduced from reference [14].
There have been some other attempts from academia to build TD-fNIRS systems to assess intracerebral and extracerebral absorption changes as shown in Figure 17 [100]. Indocyanine green (ICG) bolus tracking was utilized for the clinical assessment of brain perfusion at the bedside. Time-correlated single-photon counting (TCSPC) electronics [45] scheme has been utilized for this purpose. A supercontinuum light was generated by fiber lasers with 40 MHz repetition frequency for in-vivo measurements and 80 MHz for in phantom studies. Optical fibers (length = 2 m, NA = 0.22, diameter 400 µm) with used to deliver light to the surface of the phantoms or tissue. A low power level of 20 mW was used. A power density of no more than 2 mW/mm² was used at the surface of the skin. A fiber bundle (length 1.5 m, NA = 0.22) was utilized to transfer the photons to the detection system. For in-vivo measurements, the source-detector separation was r = 3 cm and for phantom studies, it was r = 1, 2, 3, and 4 cm. A detector module PML equipped with polychromator (NA = 0.135 and uses 77,414 diffraction grating) and 16-channel PML. Additional losses of photons in the photodetection system were due to the discrepancy between numerical apertures of the detection bundles (0.22) and polychromator (0.135). Nevertheless, lower NA of the using fiber bundles would cause photons losses at the tissue side. Absorption modifications were evaluated from the mean time of flight and variance of its distributions of photons and analyzing the changes in the total number of the received photons measured at 16 wavelengths from the range of 650–850 nm, which replaces earlier technique of measuring at multiple distances with different separations. Phantom, as well as in-vivo measurements, have been carried out for validation.

![Figure 17. The setup for multiwavelength time-resolved diffuse reflectance measurements. Reprinted with permission from [100] © The Optical Society.](image)

The results of phantom and in-vivo measurements indicated that the optical signal detected at r = 3 cm has a proper quality to assess blood flow in the brain cortex with high precision. The main advantage of this design that it requires a single source-detector separation. A modified algorithm based on the DTOFs acquisition for the single source-detector pair was utilized in this study. The algorithm is based on the assessment of changes of moments of the DTOF’s measured at all the wavelengths.
More recently, another TD-fNIRS was built based on four-wave mixing (FWM) laser and fast-gated single-photon avalanche diode and as shown in Figure 18. The laser source was FWM laser delivering light at two wavelengths, namely 710 and 820 nm. The temporal duration of about 25 ps FWHM with a repetition rate of 40 MHz. A variable optical attenuator was used to attenuate the light beam and then a collimator was used to collimate the light into a 400 µm fiber. The sample was then illuminated with the collimated beams. The diffused light was detected using two 1 mm core fibers (NA of 0.37). The separation between the source and the detector was 0.5 or 3 cm. In order to evaluate the concentration of HbO2 and Hb hemoglobin in the in vivo measurements, a filter centered at 710 or 820 nm was utilized to distinguish the two wavelengths. Time-gated detectors (FG-SPAD) modules were used. Another synchronization signal was taken from the laser and split into two parts. The first part was used to feed the FG-SPAD modules in order to trigger the detector. A “stop” signal for both acquiring boards was facilitated by the second part that was fed to the time-correlated single-photon counting (TCSPC) circuit. Accordingly, the “start” signal for the TCSPC was delivered by each FG-SPAD module.

Figure 18. Setup schematics for the in vivo experiment. Reproduced from reference [101].

Phantoms as well as in vivo testing were used for the system characterization. Using the fast-gating technique with a small inter-fiber distance allowed a great increase of the early photons when the space between the source and the detector was reduced. This was a big advantage compared with a non-gated detector as this peak of “early photons” would cause a saturation of the dynamic range, thus decreasing the capability to discriminate a perturbation in depth. This study showed that the gating scheme can enhance the contrast-to-noise-ratio and contrast for the detection of absorption perturbation, irrespective of source-detector distance.

6. CW, FD and TD Comparison and Commercial Systems

FD systems operate by emitting light continuously from a source. That light varies as a sinusoid in intensity with frequencies on the order of megahertz. Detectors measure both the reduction in intensity and the phase shift of the light after it passes through tissue. Combining this information allows a direct measure of absorption and scattering coefficients by assuming that HbO2 and Hb are the only absorbers that contribute significantly, which eliminates the necessity to define a pathlength for the light. The two main advantages of FD systems are high temporal resolution and absolute quantification of HbO2 and Hb concentrations. Disadvantages include a relatively large amount of noise within scattering measurements as well as greater complexity and, therefore, cost more than some other NIRS systems. Unlike FD systems, TD systems emit light in short, picosecond-order bursts–or impulses– rather than continuously. These short impulses are broadened to a few nanoseconds, as well
as reduced in amplitude, upon transversing biological tissue and the resultant signal is known as either the temporal point spread function (TPSF) or the distribution time-of-flight (DTOF). The broadening of the initial impulse is a consequence of the highly scattering biological tissue; not every photon will follow the same path between source and detector.

By determining the photon’s time of flight, path-length can be directly calculated using the speed of light. Like FD systems, TD systems are also able to determine absorption and scattering coefficients. However, TD systems have an even greater overall cost than FD systems. They also require relatively long acquisition times to obtain a reasonable SNR and possess somewhat large dimensions with the need for physical stabilization. An advantage of TD systems over others, though, is the potential for greater spatial resolution as Torricelli and colleagues demonstrated with zero-separation measurements. Similar to FD systems, the light sources of CW systems emit light continuously, as their name implies. Depending upon the specific hardware, the emitted light intensity either has a constant amplitude or varies sinusoidally with frequencies at or below tens of kilohertz. Combining the detected signal intensities with estimates of the differential path-length factor (DPF) allows for calculation–via the MBLL–of relative hemoglobin concentration changes. Primary advantages of CW systems over others include their simplicity, smaller size, and low cost. Hence, CW systems provide the best SNR at sampling frequencies above 1 Hz as well as the potential for the highest sampling rate. However, they also have several disadvantages. CW systems cannot determine absolute quantities of HbO₂ and Hb [24] and cannot distinguish between absorption and scattering. It limits the accuracy as the overall scattering coefficients of the investigated tissues is subject-dependent. Therefore, a single point CW-NIRS only provides variations of hemoglobin concentration. However, measurement of the light attenuation at a number of source/detector separations enables us to estimate the absolute µa of the tissue by fitting the measured spatially resolved light attenuation to the solution of the diffusion equation [102]. Last, any change in optode position or amount of pressure against the scalp could significantly alter detected intensities. Finally, Table 3 gives an overview of the commercially available fNIRS systems. Most of those systems are based on the CW technique. Nevertheless, those systems differ when it comes to the number of sources and their types, detectors, and their types, number of channels, the used wavelengths, and sampling rate.
<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>S</th>
<th>D</th>
<th>C</th>
<th>Source Type</th>
<th>Detector Type</th>
<th>A (nm)</th>
<th>Sampling Rate (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous Wave Systems</strong></td>
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<tr>
<td>Artinis [103]</td>
<td>Brite</td>
<td>10 or 11</td>
<td>7 or 8or8×</td>
<td>Up to 54</td>
<td>LED</td>
<td>Photodiodes</td>
<td>760, 850</td>
<td>50 or 100</td>
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<tr>
<td></td>
<td>OxyMon</td>
<td>/</td>
<td>/</td>
<td>Up to 108</td>
<td>Laser</td>
<td>APD</td>
<td>765, 855</td>
<td>50-250</td>
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<td></td>
<td>OctaMon</td>
<td>/</td>
<td>/</td>
<td>8</td>
<td>LED</td>
<td>Photodiode</td>
<td>765, 855</td>
<td>50</td>
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<tr>
<td></td>
<td>PortaLite</td>
<td>/</td>
<td>/</td>
<td>1 or 3</td>
<td>LED</td>
<td>Photodiode</td>
<td>765, 855</td>
<td>50</td>
</tr>
<tr>
<td>Biopac [104]</td>
<td>NIR100</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>LED</td>
<td>Photodiode</td>
<td>730, 850</td>
<td>2</td>
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<tr>
<td></td>
<td>fNIR2000M Series</td>
<td>/</td>
<td>/</td>
<td>Up to 18</td>
<td>LED</td>
<td>Silicon photodiode</td>
<td>730, 850</td>
<td>5 or 10</td>
</tr>
<tr>
<td>Cowerlabs [105]</td>
<td>NTS fNIRS system</td>
<td>6 or 8 or 16</td>
<td>6 or 8 or 16</td>
<td>/</td>
<td>Laser</td>
<td>APD</td>
<td>780, 850</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>LUMO</td>
<td>4</td>
<td>4</td>
<td>/</td>
<td>APD</td>
<td>/</td>
<td></td>
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<tr>
<td>Hamamatsu [106]</td>
<td>NIRO-200NX</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>LED</td>
<td>Photodiode</td>
<td>735, 810, 850</td>
<td></td>
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<tr>
<td>Hitachi [107]</td>
<td>ETG-4100</td>
<td>18</td>
<td>16</td>
<td>up to 52</td>
<td>Laser</td>
<td>APD</td>
<td>695, 830</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>ETG-4000</td>
<td>18</td>
<td>16</td>
<td>up to 52</td>
<td>Laser</td>
<td>APD</td>
<td>695, 830</td>
<td>10</td>
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<td></td>
<td>ETG-7100</td>
<td>/</td>
<td>/</td>
<td>up to 120</td>
<td>Laser</td>
<td>APD</td>
<td>695, 830</td>
<td>10</td>
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<td>NIRX [108]</td>
<td>NIRScout</td>
<td>8-64 (single) or 16-128 (tandem)</td>
<td>4-32 (single) or 8-64 (tandem)</td>
<td>2048</td>
<td>LED or Laser</td>
<td>SP or APD</td>
<td>Laser (2 or 4 λ, 685, 780, 808 and 830 nm) or LED (2 λ, 760 nm and 830 nm)</td>
<td>2.5 Hz-42.5 Hz (up to 100 Hz for NIRScoutX and NIRScoutX+)</td>
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<td>NIRSport 2</td>
<td>8-64</td>
<td>8-64</td>
<td>40-60</td>
<td>LED</td>
<td>SP or APD</td>
<td>760, 850</td>
<td>70-240</td>
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<tr>
<td></td>
<td>OBELAB [109]</td>
<td>NIRSIT</td>
<td>24</td>
<td>32</td>
<td>up to 204</td>
<td>laser</td>
<td>/</td>
<td>780, 850</td>
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<tr>
<td>Rogue Research [110]</td>
<td>Brainsight NIRS</td>
<td>4-16 (24 is possible)</td>
<td>8-32</td>
<td>Up to 72</td>
<td>Laser</td>
<td>SP or APD</td>
<td>705, 830</td>
<td>Up to 50</td>
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<tr>
<td>Soterix medical [113]</td>
<td>NIRSIT</td>
<td>24</td>
<td>32</td>
<td>up to 204</td>
<td>Laser</td>
<td>/</td>
<td>780, 850</td>
<td>/</td>
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<tr>
<td>Shimadzu [112]</td>
<td>LABNIRS</td>
<td>/</td>
<td>/</td>
<td>up to 142</td>
<td>Laser</td>
<td>PT</td>
<td>780, 805, 820</td>
<td>/</td>
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<td><strong>Frequency Domain Systems</strong></td>
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<tr>
<td>S: Source/D: detector/C: channel; PMT: Photomultiplier tube; APD: avalanche photodiodes; SiPM: Silicon Photomultipliers.</td>
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7. Conclusions and Future Perspective

In this paper, we have discussed the recently developed fNIRS systems from an instrumentation point of view. More specifically, the main features, differences, and similarities between the three different modalities (CW, FD, and TD) in building fNIRS systems have been reviewed and discussed. It is evident that the FD modality provides more information than the CW counterpart. Thus, better quantification of optical properties of tissue and higher depth sensitivity are possible advantages of the FD technique. However, the complexity of the FD systems and their relatively high cost are clear disadvantages. The recent renewed interest in improving FD fNIRS technology has improved the FD technique to be faster with better resolution and could provide higher sensitivity for imaging deeper tissues. This will pave the way for many potential applications. TD-NIRS systems, on the other hand, have not been as popular as CW-NIRS systems due to their complexity. Nevertheless, we have reviewed a few recent publications that reported TD systems and carried out measurements using phantoms and in-vivo of hemoglobin concentration. Interestingly, with only one channel, it is possible to estimate the optical properties of the tissue from the evaluation of the distribution of the time of flight of photons. Unlike the TD and FD systems, the compact and the simplicity of building CW systems notably allowed this modality to be commercially available for numerous applications. The current development in size and sensitivity of the semiconductor optical detectors will further allow the development of high-density fNIRS systems. With that, more channels could be used for measurements, which ultimately will enhance the quantification of optical properties of tissues.

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