2

State of the Technology

In this chapter, the current state of the technology will be reviewed, beginning with a brief overview of NIRS history. Afterwards, the current understanding of NIRS signals and physiology will be summed up, followed by an overview of methods for tissue interrogation as well as theoretical and mathematical models. Then, the literature on NIRS technology will be reviewed, aiming to extract the most critical aspects for a new and next-level design. Finally, current fields of application for fNIRS instruments in research and medicine will be briefly discussed.

2.1 Brief Overview of History

The use of continuous light for the non-invasive investigation of human tissue by transmitting it through parts of the body is a method known for at least a century. While W. C. Röntgen discovered the non-visible spectral range of electromagnetic waves, today known as X-rays, and its benefits for medical diagnosis in 1895, other scientists used transillumination with visible light as an aid in the diagnosis of breast tumors [22] or diseases of the testis [23].
Along with the research on transillumination for anatomical insights, discoveries in the fields of spectroscopy and oximetry laid the foundations of modern physiological diagnosis: Mathematical work on the absorption of light in probes by Lambert (Switzerland) in 1760 and its extension to the Beer-Lambert Law by Beer (Germany) in 1852 [24] provided a description of the absorption of light in homogeneous media. Further research focused on the spectroscopic retrieval of physical and chemical information about the blood and especially hemoglobin in tissue. The works on oxy-hemoglobin spectra (Hoppe-Seyler 1862), hemoglobin as oxygen carrier in blood (Stokes 1864), spectral changes of light penetrating tissue (Vierordt 1876) and others led to the field of medical oximetry: An optical technique for invasive and non-invasive measurement of blood oxygenation. In 1894, Hüfner was the first to conduct spectroscopic in vitro determination of the absolute and relative amounts of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR). In 1938, Matthes and Gross performed the first non-invasive clinical absorption measurements for spectroscopic HbO and HbR concentration determination in the ear [25–27]. Further research, e.g. on the optical absorption spectra of HbO and HbR, and the application of the Beer-Lambert Law by Horecker in 1943 led to the first commercial oximeter. In 1970, Hewlett-Packard introduced the first device for clinical oxygen saturation derivation using 8 wavelengths in the ear [28]. Soon after, in 1974, Aoyagi proposed the new approach of pulse-oximetry, which is widely used nowadays [29].

While non-invasive clinical (pulse-)oximetry focused on the global oxygen saturation of the body's arterial blood measured in the ear or in the fingertips, Jöbsis pioneered the field of non-invasive optical methods in 1977 by no longer considering the skull - and bones in general - to be a natural border for light. By using near-infrared light, he proved the feasibility of non-invasive local spectroscopy of cortical tissue oxygenation through the intact skull [1] and is therefore considered to be the initiator of modern functional Near-Infrared Spectroscopy (fNIRS).
Following his publications, research in the late 1980s and in the 1990s mostly aimed to enhance the understanding of the physiology of the signal, NIRS instrumentation and mathematical concepts. This was accompanied by a general growth in development and use of optical instruments for biomedical applications driven by a growing understanding of fundamental optical processes applied to biological materials and the emergence of new optical technologies [30]. In 1988, Delpy provided a modification of the Beer-Lambert Law (BLL) by taking light scattering into account [2]. This so-called "Modified Beer-Lambert Law"' (MBLL) permitted the calculation of relative oxygenation levels from the measured NIRS signal. Several fNIRS instruments were then built with the goal to enhance instrumentation and find ways to obtain absolute values [3–6]. In 1993, four research groups independently demonstrated the feasibility of non-invasive brain activity investigation using fNIRS [7–10], followed by an increase of publications using NIRS technology for brain activity studies. From the 2000s until today, the next major step was to increase the number of optodes and lead to the design of imaging instruments for brain activity mapping from topographic information: functional Near-Infrared Imaging (fNIRI). Today, instruments are introduced that combine fNIRS with EEG [15].

2.2 NIRS Principle and Signals

Functional Near-Infrared Spectroscopy is a diffuse optical method for the measurement of local oxygen-dependent metabolism. fNIRS, Diffuse Optical Tomography (DOT) and Near-Infrared Imaging (NIRI) are all based on the same concept [13]:
Near-Infrared (NIR) light is emitted into the head at one specific position and undergoes random scattering and absorption processes in the tissue attenuating it by 7-9 orders of magnitude. A fraction propagates through the tissue on a banana-shaped path back to the surface where it is then detected by a NIR-sensitive photodetector (see fig. 2.1).

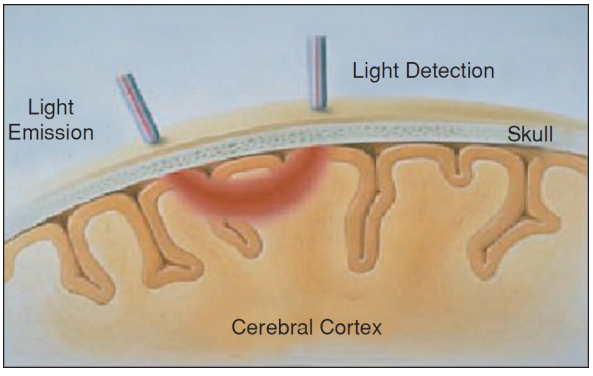

Figure 2.1: Principle of NIRS, fig. taken from [14].

As most parts of the tissue, largely water, are relatively transparent to light in the NIR range, the emitted light can penetrate the cranium and reach sufficient depth [31]. This characteristic optical range of approx. $600 - 900\,nm$ in which tissue is relatively transparent to light is often referred to as *optical window* in literature (see fig. 2.2). While absorption and scattering by components of the tissue (e.g. collagen, proteins, fat ...) remain fairly constant, some chromophores such as oxy-hemoglobin (HbO), deoxy-hemoglobin (HbR) and cytochrome oxidase are strong absorbers for NIR light with their concentrations changing with metabolism and blood flow.

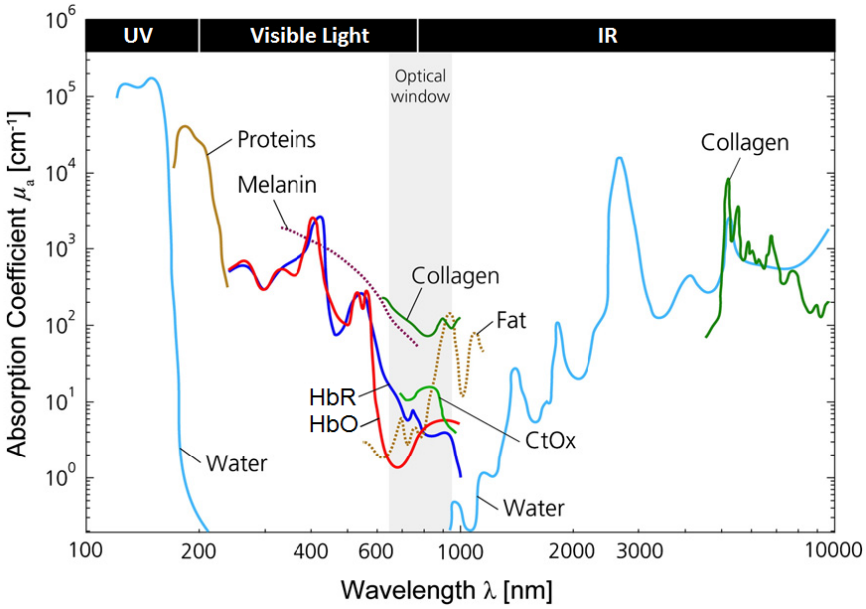

Figure 2.2: Optical window for NIR light, fig. taken from [11].

If two different wavelengths are chosen so that absorption by HbR and HbO is maximal, changes in concentrations of the two chromophores result in measurable attenuation changes that can be quantified, e.g. with the Modified Beer-Lambert Law (see next section). This oxygen-dependent optical absorption is also key to (pulse) oximetry. However, there are certain differences between the two methods:

- Pulse oximetry only monitors changes in the optical density of tissue during pulse intervals, calculating arterial hemoglobin oxygen saturation
- fNIRS measures tissue oxygenation and local hemoglobin oxygen saturation through a cross section of tissue volume including capillaries, arterioles and venules and is referred to as next generation of tissue oxygenation monitors [32].

Some works also use cytochrome oxidase (cytochrome aa3) as a chromophore for the indication of intracellular oxidative processes with cytochrome aa3 being the terminal enzyme of the intracellular respiratory chain [30]. Since this approach is done rarely, it will not be taken into further account in this work.

The interaction between local oxygenation changes measured with fNIRS and electrical brain activity are still subject to research. However, a correlation between local blood oxygenation and neuronal activation (*hemodynamic response*) exists. Three main factors

affecting local HbR and HbO concentrations in the brain were identified by Wolf et al. [33]:

- local cerebral metabolic rate of oxygenation (CMRO2),
- regional cerebral blood flow (rCBF) and
- cerebral blood volume (CBV).

These factors generally occur at the same time during neuronal activation and are summarized as *neurovascular coupling*. During local brain activation, an increase in rCBF disproportional to the increase in oxygen metabolism results in a focal hyperoxygenation [34]. This is reflected in a decrease in HbR concentration accompanied by an increase in HbO concentration of typically 2-3-fold magnitude and thus results in an increase of total hemoglobin [35].
This hemodynamic signal can usually be observed with a latency of approx. 5-8 seconds after the begin of a stimulus/task [18] and is called *slow response* (see fig. 2.3). Focal decrease in HbO along with an increase in HbR is consequently interpreted as deactivation.

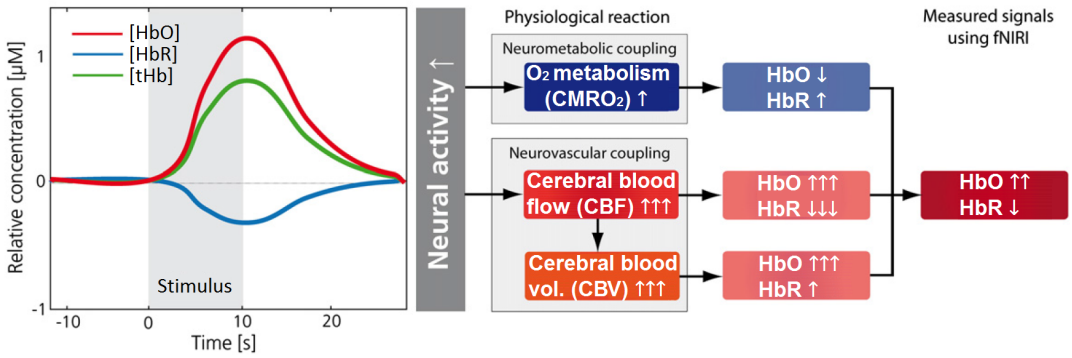

Figure 2.3: Typical NIRS response. HbO: oxy-hemoglobin, HbR: deoxy-hemoglobin, tHB: total hemoglobin, fig. taken from [11].

Since in the *slow response* the oxy-Hb-change is usually larger, it is preferred to the change of deoxy-Hb as a single indicator of brain activity changes. Obrig et al. criticized this, arguing that the decrease in deoxy-Hb is more valid as parameter because of its high negative correlation with the fMRI BOLD signal [35]. This correlation was investigated by several work groups and confirms the theoretical ideas about the nature of the BOLD response ([36], for further references see [12]) but was found to be highly variable between subjects [36].
Another *fast response* signal (latencies in the order of milliseconds) was documented and named Event Related Optical Signal (EROS) [33, 37]. It is thought to appear due to changes in scattering properties of the neuronal membranes during firing. Several research groups suggest that the EROS may correlate with evoked potentials commonly used in EEG [18, 20].
While in the optical NIRS signal the slow response is represented with about 1-2% changes in the signal's DC amplitude [20, 38], the fast response is much smaller and is represented with only 0,05% change in light intensity, requiring averaging techniques with several hundred to a thousand trials [18].

Non-stationary fNIRS signals based on HbO and HbR concentration changes are a combination of several components on which Scholkmann et al. gave a résumé [11]. They consist of:

- Evoked neurovascular coupling by a stimulus or task
- Non-evoked (spontaneous) neurovascular coupling
- Physiological/systemic interference: Evoked and non-evoked processes that are not included by neurovascular coupling.

The following table 2.1 gives a brief overview of the classification of the main components present in fNIRS signals:

		Cerebral	**Extracerebral**
Evoked	**Neuronal**	**Functional brain activity (neurovascular coupling)**: Directly related to functional brain activity. Small changes in relation to the overall variability of the fNIRS signals.	
	Systemic	**Systemic activity type 1**: Changes in blood pressure, $PaCO_2$, CBF / CBV. Strongest parameter affecting CBF/CBV: $PaCO_2$ - Hypocapnia (leads to decrease), hypercapnia (leads to increase)	**Systemic activity type 2**: Changes in blood pressure, skin blood flow/volume
Non-ev.	**Neuronal**	**Spontaneous brain activity (neurovascular coupling)**: Non-evoked, can be used to assess the "resting state functional connectivity" of the brain.	
	Systemic	**Systemic activity type 3**: Heart rate, respiration, Mayer waves, very low frequency oscillations. Hemodynamics or vasomotion associated with spontaneous hemodynamic oscillations - not stimulus evoked.	**Systemic activity type 4**: Heart rate, respiration, Mayer waves, very low frequency oscillations.

Table 2.1: Classification of main components present in fNIRS signals, based on [11].

Systemic activities type 3 and 4 are mostly periodic artifacts in the signal such as

- Heartbeat with $\approx 1 - 2\,Hz$
- Respiration with $\approx 0.3 - 0.1\,Hz$
- Mayer waves with $\approx 0.1\,Hz$

Mayer waves are spontaneous low-frequency blood pressure variations with resulting oscillations in both vascular and metabolic responses [39]. Their origins are not fully understood to this day.
To remove these artifacts or separate the signal components, several approaches were proposed. Univariate Methods: Band-pass and low-pass filtering to remove non-evoked components such as heartbeat and respiration (cut-off frequency of e.g. $0.2\,Hz$) and conventional averaging of fNIRS signals that are time-locked to the trials are commonly used. Further approaches are Hilbert spectral analysis / eigenvalue decomposition [40],

adaptive filtering techniques [41], Wiener filtering, discrete wavelet filtering [17], sliding window motion artifact rejection [42] and least squares regression (for more references see [11] and [12]).
Other approaches use multivariate methods such as several fNIRS signals from different source detector distances to identify and reduce the effects from extracerebral tissue such as scalp and skull.

2.3 NIRS Interrogation Approaches

There are three different functional Near-Infrared Spectroscopy interrogation techniques, each of which having their advantages and disadvantages:

- Continuous Wave NIRS (CW NIRS)
- Frequency Domain NIRS (FD NIRS) and
- Time Domain NIRS (TD NIRS).

In the following, all three techniques will be briefly described.

2.3.1 Continuous Wave NIRS

In the CW method (see fig. 2.4) continuous, slowly (kHz) chopped or modulated light at constant amplitude I_0 is used to transilluminate the tissue. The attenuation of the amplitude over time and the relative absorption are measured and evaluated.

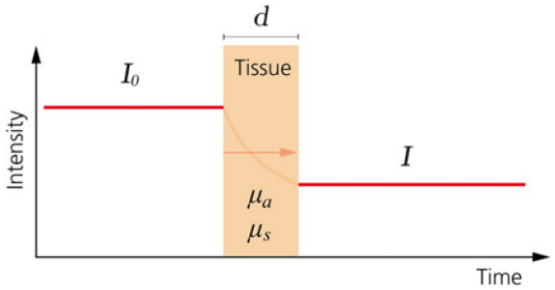

Figure 2.4: Continous Wave NIRS principle, fig. taken from [11].

Due to slow or no modulation of the light, its time changing component (e.g. phase shifts) cannot be resolved in this method. Consequently, it is not possible to differentiate between light scattering μ_s and absorption μ_a effects. Thus, only relative concentration changes of the chromophores based on a baseline can be determined.
The advantages of the method are nevertheless big: The technology is relatively low-cost, it can be integrated and miniaturized, it is lightweight and also works with mobile applications using wireless technology.

2.3.2 Frequency Domain NIRS

In the FD method (see fig. 2.5), first suggested by Gratton [43], light is intensity-modulated at radio frequencies in the range of several $10 - 100\,MHz$ and then sent

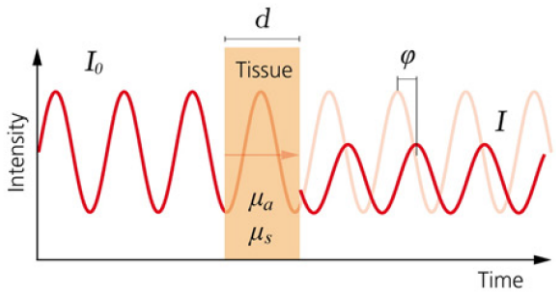

Figure 2.5: Frequency Domain NIRS principle, fig. taken from [11].

through the tissue. Photomultiplier tubes or fast photodiodes detect the signal, which now shows attenuation as well as a phase shift ϕ with respect to the incident signal. The measurement of ϕ allows the calculation of the optical path length and thereby differentiation between scattering and absorption effects. Thus, absolute chromophore concentrations can be determined. This method provides a higher SNR and is generally faster and less expensive than TD-systems [12] and uses narrower bandwidth. On the other hand, costs, complexity and volume of the instruments are considerably higher than in CW systems.

2.3.3 Time Division NIRS

TD methods (see fig. 2.6) introduce short picosecond pulses of light, which are broadened (scattering) and attenuated by the various tissue layers such as skin, skull, cerebrospinal fluid and brain [13]. The temporal point spread function of the photons leaving the tissue is then used for the determination of changes in attenuation and the optical path length.

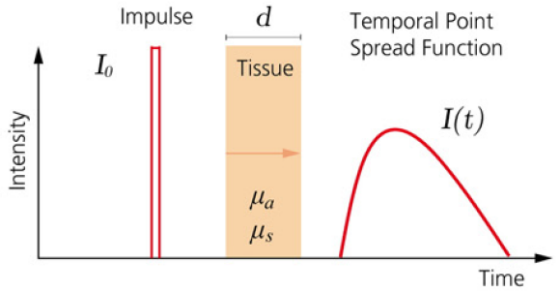

Figure 2.6: Time Domain NIRS principle, fig. taken from [11]

While TD systems can detect ballistic and diffusely scattered photons, they are expensive, require significant averaging times to improve SNR [44] and are often large and not directly suited to clinical monitoring [30].

Since quantification of absolute values is not as important in neuroscience as to detect brain activity changes with statistic significance, up to today most fNIRS and fNIRI systems in research as well as those commercially available on the market are based on Continuous Wave technology [11]. With respect to scope, expenses and mobility, this work focuses on the design of a CW system for neuroscience and BCI research.