Progress of near-infrared spectroscopy and topography for brain and muscle clinical applications

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Abstract. This review celebrates the 30th anniversary of the first *in vivo* near-infrared (NIR) spectroscopy (NIRS) publication, which was authored by Professor Frans Jöbsis. At first, NIRS was utilized to experimentally and clinically investigate cerebral oxygenation. Later it was applied to study muscle oxidative metabolism. Since 1993, the discovery that the functional activation of the human cerebral cortex can be explored by NIRS has added a new dimension to the research. To obtain simultaneous multiple and localized information, a further major step forward was achieved by introducing NIR imaging (NIRI) and tomography. This review reports on the progress of the NIRS and NIRI instrumentation for brain and muscle clinical applications 30 years after the discovery of *in vivo* NIRS. The review summarizes the measurable parameters in relation to the different techniques, the main characteristics of the prototypes under development, and the present commercially available NIRS and NIRI instrumentation. Moreover, it discusses strengths and limitations and gives an outlook into the "bright" future. [DOI: 10.1117/1.2804899]

Keywords: brain; muscle; near-infrared spectroscopy; near-infrared imaging; oximetry; tissue oxygenation.

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1 Introduction

This review celebrates the 30th anniversary of the first *in vivo* near-infrared (NIR) spectroscopy (NIRS) publication,[1] which was authored by Frans Jöbsis, who described his discoveries in two papers published in the *Journal of Biomedical Optics* 22 years after his original publication.[2,3]

Starting with the pioneering work of Jöbsis, noninvasive NIRS was first utilized to investigate cerebral oxygenation experimentally and clinically and, later on, muscle oxidative metabolism. In addition, since 1993, multichannel NIRS instruments have been largely applied to investigate the functional activation of the human cerebral cortex in adults[4–7] and later in newborns.[8] A number of recent detailed reviews describing the principles, the limitations, and the applications of NIRS have appeared in the literature.[9–18] The same is true for reviews describing the applications of NIRS on cerebral oxygenation monitoring in newborns and adults.[19–29]

The most recently available NIRS technology for monitoring cerebral oxygenation can contribute to the identification of deficits in cerebral oxygenation. Monitoring such deficits supports certain forms of therapy in reversing cerebral oxygenation issues and thereby preventing long-term neurological sequelae. Recently, it has been demonstrated that quantitative thresholds for cerebral oxygenation led to the identification of cerebral ischemia in the adult brain and thus increased the scope of clinical use of NIRS.[29] A number of recent detailed reviews describe the use of NIRS and NIRS imaging (NIRI) for human brain mapping[15,30–36] and muscle exercise pathophysiology.[37–43]

This review reports on the progress of the NIRS and NIRI instrumentation for brain and muscle clinical applications, 30 years after the discovery of *in vivo* NIRS. The review summarizes the measurable parameters in relation to the different NIRS techniques, the main characteristics of the prototypes under development, and the present commercially available NIRS and NIRI instrumentation. Moreover, a discussion on the strengths and limitations of NIRS and/or NIRI and an outlook into the "bright" future are reported.

2 Methods

Papers were retrieved by the authors through different strategies. First, a search on the two databases MEDLINE and INSPEC was performed using the keywords: "near infrared," "near infrared oximetry," "cerebral oximetry," "muscle oxygenation," "optical imaging," and/or "instrument." The references were screened and the full texts of relevant publications were retrieved. Next, the references of reviews were hand searched. The research was restricted to literature on the NIRS and/or NIRI instrumentation suitable for human muscle and brain measurements published or made available up to February 2007. Breast imaging instrumentation was not included, because its progress has recently been reviewed.[44–46]

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In addition, three-dimensional tomography was excluded, because it is covered by another paper in honor of Professor F. F. Jöbsis. The very recent proceedings of conferences organized by the following societies: Optical Society of America, The International Society of Optical Engineering (SPIE), Organization of Human Brain Mapping, American College of Sports Medicine, and the Polish Academy of Sciences were also consulted. Research groups known to be active in the field were contacted for gathering further information. The Web sites of the commercial systems were searched and visited for exploring the specifications of the instruments. After collecting all the documentation, a consensus was made by all authors to properly select material eligible for inclusion in this review. The material was sorted according to the type of NIRS and NIRI instrumentation and the parameters measured. Tables were generated to report the origin and properties of each instrument and all the measurable parameters.

3 Results

NIR from the 650- to 950-nm wavelength penetrates tissue relatively deeply. In this region of wavelength, chromophores such as oxyhemoglobin (O_2Hb in micromolar concentration), deoxyhemoglobin (HHb in micromolar concentration), cytochrome oxidase, water, lipids, and indocyanine green absorb light. Thus their concentration can in principle be measured by NIRS and NIRI. However, besides the light absorption, the strong light scattering of tissue in the NIR has to be taken into consideration. To quantify the measurements, theoretical models describing light transportation in tissue have been developed.[47] Because a general mathematical approach is not feasible, all the mathematical models rely on assumptions and approximations to simplify matters.[47] It is important to ensure that these assumptions are fulfilled, when applying NIRS and NIRI.

The most widely used approximations are the differential pathlength factor (DPF) method[48–50] and the diffusion approximation.[47,51–53] The DPF method is a relatively simple model that enables us to quantify changes in chromophore concentration. Absolute values cannot be obtained directly by the DPF method. Only changes in light attenuation are measured, and it is assumed that these changes reflect changes in the chromophore concentration. If geometrical or structural changes occur, they will be misinterpreted as changes in the chromophore concentration, which, for instance, might occur during motion artifacts. In addition, the DPF method assumes that the tissue and the change in chromophore concentration are homogeneous. To obtain quantitative values, the DPF, which accounts for the increased pathlength due to light scattering, has to be measured or taken from the literature.[54–59]

The diffusion approximation of the Boltzmann transport equation is another widely used mathematical model. The diffusion approximation has analytical solutions under the following assumptions: (1) tissue is homogeneous, (2) scattering is much larger than absorption, and (3) the tissue has a specific geometry—infinite, semi-infinite, slab, or two-layered.[47] To obtain correct values, it is again vital to observe these boundary conditions. The DPF method is in agreement with the diffusion approximation. The diffusion approximation can be used to measure absolute values of the absorption and scattering coefficients of tissue and from the absorption coefficient, absolute values of the chromophore concentration can be calculated. Generally, this requires measuring light intensity and the time of flight (i.e., the time the light takes to pass through the tissue).

Several techniques to physically carry out the measurements have been described and applied. Table 1 summarizes the different types of instruments and indicates key features, advantages, and disadvantages. The parameters that can be measured are outlined in Table 2.

Most of the parameters are based on the measurement of O_2Hb and HHb. In addition, NIRS's measurement of the changes in the redox state of oxidized cytochrome *c* oxidase (ΔoxCCO), as first proposed by Jöbsis,[1] has the potential to provide a unique method for monitoring changes of intracellular O_2 delivery.[9,60] Although much work has been done on the refinement of NIRS hardware and algorithms (utilized to deconvolute the light absorption signal), recent years have seen a vivid discussion in the literature on the possibility of measuring ΔoxCCO by NIRS. To improve the accuracy of the measurement of this NIRS parameter, most of the recent animal[61,62] and human[63,64] NIRS studies have been performed using a broadband approach with a continuous white light spectrum.

Continuous wave (CW) means that only changes in the light intensity are measured. Usually at least two different wavelengths are multiplexed to obtain spectral information. The ambient light level is also measured and subtracted by the NIRS instrument. CW can easily be used for imaging by using many source-detector pairs, which are distributed on the tissue of interest.[15,65–70] This method only allows the continuous quantification of relative values (except for absolute values of venous oxygen saturation[71,72]) and usually relies on the DPF method. Another disadvantage is represented by the fact that it is relatively sensitive to motion artifacts. The advantages are that CW is inexpensive and can be miniaturized to the extent of a wireless instrument,[73] even for imaging (Fig. 1). In addition, in many situations (e.g., studies of functional activity of the brain or intervention studies for testing reactions on drugs or changes in treatment[15,32,74]) relative values are sufficient (Fig. 2).

Spatially resolved spectroscopy (SRS) is also called multidistance spectroscopy and is based on light intensity being measured at several different source-detector distances.[75,76] One problem of NIRS and/or NIRI is that the light coupling between the optodes and the tissue is unknown, difficult to measure, and sensitive to changes on the tissue surface over time. SRS techniques assume that the coupling is the same for the different source-detector distances and, by measuring the intensity as a function of the distance, determine a parameter that is independent of the coupling.[76] This allows the determination of ratios of O_2Hb to total hemoglobin ($O_2Hb+HHb$) and thus tissue oxygen saturation. The application of cerebral NIRS in adults has been hampered by concerns over contamination from extracerebral tissues. Using SRS,[77] the brain was identified as the anatomic source of the signal on adult patients undergoing carotid endarterectomy. A change in brain oxygen saturation was predominantly associated with internal carotid artery clamping. The reason is that using a SRS approach, the superficial layers of tissue affect all the light bundles similarly and therefore their influence cancels out.

Table 1 Near-infrared spectroscopy and imaging instrumentation: Characteristics and main parameters directly measured.

	Single-Distance CW Photometers			1 or 2 Channels Oximeters				Imagers		
Parameters measured and instrument characteristics	Discrete wavelengths	Broadband second derivative	DWS	SRS CW	PMS MD	PMS MF	TRS	CW	PMS	TRS
[O_2Hb], [HHb], [tHb]	yes, changes[a]	yes, absolute value	no	yes, changes[a]	yes, absolute value	yes, absolute value	yes, absolute value	yes, changes[a]	yes, absolute value	yes, absolute value
Blood flow measurement	no	no	yes, relative	no	no	no	no	no	no	no
Scattering and absorption coefficient and pathlength measurement	no	yes, pathlength	no	no	yes	yes	yes	no	yes	yes
Tissue O_2Hb saturation measurement (SO_2,%)	no	yes	no	yes	yes	yes	yes	no	yes	yes
Penetration depth with a 4-cm source-detector separation	low	low	low	low, but deep for SO_2	deep	low	low	low	deep	low
Sampling rate (Hz)	≤100	1	≥5	≤6	≤100	≤1	≤6	≤100	≤50	1
Spatial resolution (cm)	n.a.	n.a.	feasible	n.a.	n.a.	n.a.	n.a.	≤1	≤1	≤1
Instrument size	very small	medium	medium	small	small	medium	medium	some bulky, some small	bulky	bulky
Instrument stabilization	n.r.	n.r.	required.	n.r.	n.r.	n.r.	required	n.r.	n.r.	required
Transportability	easy	easy	feasible	easy	easy	easy	easy	some easy, some feasible	feasible	feasible
Instrument cost	low	moderate	high	moderate	moderate	high	high	some low, some high	very high	very high
Caution for eye exposure to coherent sources	n.r.	n.r.	required	n.r.	n.r.	n.r.	required	depends on instrument	required	required
Stable optical contact	critical	critical	critical	not critical	not critical	critical	not critical	critical	not critical	not critical
Precise anatomical localization	no	no	no	no	no	no	no	scarce	scarce	scarce
Telemetry	available	n.a.	n.a.	available	difficult	difficult	difficult	available	difficult	not easy
Discrimination between cerebral and extracerebral tissue (scalp, skull, CSF)	n.a.	n.a.	feasible	n.a.	feasible	n.a.	feasible	n.a.	feasible	feasible
Possibility to measure deep brain structures	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns	feasible on newborns

[a]When the differential pathlength factor (DPF) is included to calculate the tissue pathlength [=DPF×(source-detector separation)].
CSF=cerebrospinal fluid, CW=continuous wave, DWS=diffusing-wave spectroscopy or diffuse correlation spectroscopy, HHb=deoxyhemoglobin, MD=multidistance geometry, MF=multifrequency measurement, n.a.=not available, n.r.=not required, O_2Hb=oxyhemoglobin, PMS=phase modulation spectroscopy, SRS=spatially resolved spectroscopy, tHb=O_2Hb+HHb, TRS=time resolved spectroscopy.

Table 2 Parameters measured directly and indirectly by near-infrared spectroscopy and imaging instrumentation.

Parameter	Units	Modality	Applicability (during muscle exercise)	Author [reference]
ΔO_2Hb, ΔHHb, ΔtHb,				Delpy 1997[129]
$\Delta oxCCO$,	a.u., $\mu M \times cm$, μM	D	Yes	Tisdall 2007[64]
OI				Grassi 1999[130]
		D (by SRS)	Yes	Matcher 1995,[75] De Blasi 1993,1994,[104,105] Quaresima 2002,[131] Cuccia 2005[80]
Tissue O_2 saturation	%	D (by PMS)	Yes	Fantini 1995[76]
		D (by TRS)	Yes	Oda 1996[132]
		D (by calibration)	Yes	Benni 2005[133]
		Second differential	No	Matcher 1994, Cooper 1996[58,134]
Muscle SvO_2	%	I (by VOM)	No	Yoxall 1997[135]
		D	No	Franceschini 2002[136]
Muscle tHb	μM	D (by PMS)	Yes	Franceschini 1997[126]
	a.u.	D (by DWS)	No	Durduran 2003[95]
Muscle BF	mL/100 mL/min	I (by VOM)	No	De Blasi 1994[105]
		I (by ICG)	Yes	Boushel 2000[137]
Muscle Hb flow	μM/min	I (by VOM)	No	Wolf 2003[106]
Muscle VO_2	mL/100 g/min	I (by VOM)	No	De Blasi 1993, 1994[104,105]
		I (by AOM)		
Muscle recovery time	s	D	No	Chance 1992[138]
Muscle compliance	mL/L/mmHg	I	No	Binzoni 2000[139]
Cerebral SvO_2	%	I (by VOM)	No	Yoxall 1995[140]
		D	No	Wolf 1997[72]
Cerebral tHb	μM	D (by PMS)	Yes	Choi 2004[78]
		I (by O_2 swing)	No	Wolf 2002[141]
		I (by O_2 swing)	No	Wyatt 1990,[101] Wolf 2002[141]
Cerebral BV	mL/100 mL	SRS and second differential	No	Leung 2006[142]
		I (by ICG)	No	Hopton 1999[143]
	a.u.	D (by DWS)	No	Durduran 2004,[96] Li 2005[94]
Cerebral BF	mL/100 mL/min	I (by O_2 swing)	No	Edwards 1988[100]
		I (by ICG)		Roberts 1993,[144] Keller 2000[145]
Cerebral VO_2	mL/100 g/min	Combination cerebral SvO_2 and BF	No	Elwell 2005[146]

Δ=Relative changes from arbitrary baseline, AOM=arterial occlusion Method, a.u.=arbitrary units, BF=blood flow, BV=blood volume, DWS=diffusing-wave spectroscopy, D=directly, I=indirectly, ICG=indocyanine green, OI=oxygenation index (ΔO_2Hb-ΔHHb), oxCCO=cytochrome c oxidase redox state, PMS=phase modulation spectroscopy, SRS=spatially resolved spectroscopy, SvO_2=venous O_2 saturation, tHb=O_2Hb+HHb, TRS=time resolved spectroscopy, VO_2=oxygen consumption, VOM= venous occlusion method.

Fig. 1 Wireless imaging instrument attached to a newborn infant's head. The squares (blue) represent the detector locations, while the circles (red) depict source locations, each equipped with light emitting diodes at two wavelengths (730 and 830 nm). The electronics to the right includes a Bluetooth device for wireless transmission, drivers for the light emitting diodes, filters, analog-to-digital converters, a microprocessor, and a power supply based on a battery. The instrument weighs as little as 40 g, has a sample rate of 100 Hz, and the battery lasts for approximately 3 h. The wireless technology is comfortable to wear, easy to apply, and enables measurements in moving subjects and everyday situations. (Color online only.)

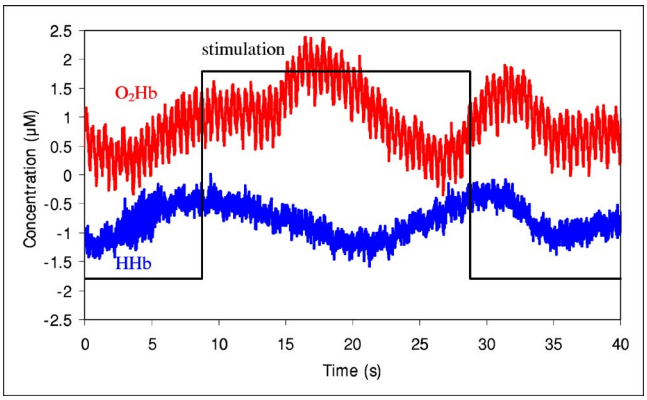

Fig. 2 A sample of a functional NIRs measurement with a 100-Hz sampling rate in a healthy neonate. The upper trace (red) depicts O_2Hb, and the lower trace (blue) HHb and the straight line (black) depict the duration of the visual stimulation. A number of physiological phenomena can be observed: (1) The arterial pulsations are visible in the O_2Hb tracing. The pulsations can be used to calculate the heart rate and arterial oxygen saturation. (2) Approximately every 10 s, there are fluctuations in the blood circulation (the so-called slow vasomotion). These changes are particularly evident in the O_2Hb tracing. (3) The O_2Hb increases and the HHb decreases during the stimulation. This corresponds to a typical functional cortical activation. Although the slow vasomotion partially masks the activation, the measurement can be repeated several times and thus the functional activation can be revealed statistically. (Color online only.)

Only deeper tissue layers have an effect on the values.[78,79] Using a single source-detector distance, however, the influence of the superficial tissues on the signals is relatively large. It depends on the source-detector separation. It can be minimized using large separations and a correction for an extracranial sample volume or both.[9]

The enhanced type of SRS, called spatial frequency domain measurements,[80] projects several bar patterns of different distances between bright bars and dark bars on the tissue. This type of imaging is able to determine absolute values.

Time resolved spectroscopy (TRS), also known as time domain spectroscopy,[49,81–85] is a technique that measures the time of flight in addition to the light intensity. It does so by emitting a short (~100 ps) pulse of light into the tissue and measuring the time point spread function of the light after it passes through the tissue. Due to the scattering process, the pulse will broaden and, due to absorption, the intensity will be reduced. The result of such a measurement is a histogram of the number of photons on the *y* axis and their arrival times on the *x* axis. The histogram also contains information about the depth of the photonic path, because photons that arrive later have a higher probability to have traveled deeper. The absorption and the reduced scattering coefficients are calculated from the histogram and the absorption coefficients are utilized to calculate the absolute values of the chromophores concentration. This technique is also used for three-dimensional imaging and tomography.[14,85,86] Thus, from the physicist's point of view, TRS is an excellent method because it yields a lot of information relatively rapidly and with a high dynamic range. However, it requires sophisticated instrumentation that is so far commercially unavailable. Because the instrumentation usually operates in photon counting mode, it is highly sensitive and can penetrate relatively large tissues (e.g., the head of a neonate). However, due to the low number of photons, TRS measurements are also characterized by a relatively high level of noise. From a clinical point of view, the disadvantages are represented by the physical size of the instrumentation, the use of glass fibers, and the photomultiplier tubes (i.e., the danger of destroying these detectors by excess ambient light). In the near future, technological advances in this field, in particular the miniaturization and reduction in cost of the instrumentation, will promote this technology.

Phase modulation spectroscopy (PMS) is also called intensity modulated or frequency domain spectroscopy. This technique is in principle equivalent to TRS except that it operates in the Fourier domain. This means that the light sources are intensity modulated at radio frequencies (50 MHz to 1 GHz). After passing through the tissue, the mean intensity (DC), amplitude (AC), and phase of the emerging wave are measured. The phase contains information about the time of flight. To obtain the same information as TRS, PMS requires scanning through all frequencies from 50 MHz to 1 GHz.[76,87–92] The result is a Fourier transform of the time point spread function of TRS. Only a few instruments are operated in scanning mode (also called multifrequency mode)[89–92] because the time resolution is relatively low. Most of the instruments are single frequency instruments and use a multidistance or SRS geometry.[76,87,88] It has been shown that the latter type of instrument is technically much simpler than TRS and provides measurements with a good signal-to-noise ratio and a high time resolution. In addition, unlike TRS instruments, SRS instruments can deal with a higher number of photons at the detector and thus with a higher signal-to-noise ratio. From a clinical point of view, the advantages are represented by the easier transportability and the commercial availability. How-

ever, compared to TRS, if only one frequency is used, PMS provides less information about the tissue. In addition, from a clinical point of view, the disadvantages are represented by the use of the glass fibers and the sensitivity of the photomultiplier tubes to excess light. In the near future, this technology might profit from technological advances and developments in the mobile communications industry, which lead to the miniaturization, optimization, and dramatic reduction in cost of crucial components such as synthesizers or demodulators.

Broadband imaging, or second differential spectroscopy,[89–93] means that white light is used instead of discrete wavelengths and, at the detection site, a spectrometer measures the whole range of wavelengths. The advantage is that a whole spectrum is available, which allows the discrimination of chromophores within the tissue with higher accuracy and less crosstalk. Using the second differential, even absolute values can be obtained if a certain water concentration can be assumed.[58] One disadvantage of second differential spectroscopy is that taking the derivative magnifies the noise level and thus measurements have a lower signal-to-noise ratio. Some groups also use a combination of broadband and PMS to be absolutely quantitative.[92] The disadvantage is that to utilize all wavelengths, the power of the light source needs to be higher and tissue warming may be a dangerous consequence.

Diffusing-wave spectroscopy (DWS), also called diffuse correlation spectroscopy, allows using lasers with a long coherence length and the speckle pattern that is created in the tissue.[94–98] Speckles, a pattern of bright and dark spots, are a result of the interference of light. This interference occurs when light with large coherence length (laser light) is going through the tissue by different paths, which may lead to constructive or destructive interference. Because in a tissue there is also movement, mainly of the blood, this interference pattern changes in time. The autocorrelation of the speckle pattern contains information about the blood flow. This technique is related to laser Doppler flowmetry, which measures superficial blood flow and is not included in this review. DWS is the fruit of a relatively recent development and the technology is relatively expensive. In the future, efforts for understanding the factors that affect the autocorrelation must be made to completely quantify blood flow.

NIRI, also called diffuse optical imaging (DOI) or topography, reconstructs two-dimensional images of the chromophore concentrations in tissue. The term "diffuse" in DOI refers to the fact that the theory is based on the diffusion approximation. This type of instrumentation operates usually in reflection mode. The resolution of the images achieved today is on the order of 1 cm.

Table 3 includes the main commercially available instruments, and Table 4 provides an overview of the most important recent noncommercial prototypes.

4 Discussion

Table 3 shows that quite a number of oximeters and imagers are commercially available. The presence of three big Japanese companies developing such devices underlines the consistent efforts made by this country in the field of NIRS and NIRI development. Unfortunately, so far, very few instruments have the approval of the American Food and Drug Administration. Therefore, their distribution has been limited to Japan and/or the European Community. Considering the high cost and the restricted clinical applications of the imagers, more oximeters than imagers have been sold particularly for monitoring adult brain oxygenation during heart surgery. It is not possible to report the exact number of the oximeters sold because the companies do not release such figures. However, it is possible to estimate that more than 2000 clinical oximeters are presently operating for different clinical applications.

The development of instrumentation and methodology has been proceeding in steps. At first, only CW instruments with one channel were available. These instruments allowed measurement of relative values only (i.e., changes in chromophore concentration). They provided useful information in many instances, particularly in intervention studies in which, for instance, the safety of drugs was tested (e.g., Ref. 99) or functional brain activity was investigated. In brain studies, absolute values of hemoglobin concentration or blood flow can be obtained using changes in oxygenation.[100–103] In muscle studies, the combination of relative concentration changes with a venous or arterial occlusion provides absolute quantitation of the oxygenation and blood flow.[104–106] In a second step, instrumentation based on spatially resolved or time resolved (TRS or PMS) methods led to the measurement of absolute values of concentration.[76] This considerable evolution enhanced the value of the NIRS measurements, because it allowed the comparison of concentration and oxygen saturation values among patients without any interventions. This paves the way for monitoring patients during treatment (e.g., in intensive care). In a third step, the use of multichannel instruments enhanced the scope of the measurements from single locations to two or three dimensions. This was another big step, because the single location measurements usually assumed that the values at a given location were representative for the whole area or organ. Imaging studies however showed that (1) this assumption is not true and (2) there may be considerable local variability in volume and/or flow and oxygenation.[106–109]

This leaves us with new problems that have to be solved to enhance NIRI advancement, for example, the placement of multiple channels, the handling of large amounts of data, and the algorithms for reconstructing images. However, NIRS and/or NIRI instrument development can be considered constant as witnessed, for instance, by the fact that every 2 to 3 years new models have been replacing the previous ones, particularly as far as oximeters are concerned. Usually, the new models are characterized by lower dimensions, weight, and cost, as well as improved data presentation, software, and precision. In addition, new techniques have been proposed and are under evaluation for improving the quantitation of oximeters (Table 4).

A large effort refers to the development of imaging instrumentation and image reconstruction algorithms. The main problem of imaging relies on the existence of the strong scattering of light in the NIR range and the very low number of light bundles. Most of the commercial imagers are based on CW light sources and are still very bulky and expensive (Table 3). The fact that several prototypes have been developed by industries and academic institutions using TRS and PMS approaches could suggest that these techniques would be utilized by the next generation of commercial clinical imagers

Table 3 Main commercial near-infrared clinical instrumentation.

Instrument		Technique	Number of channels	Company	Web site
Photometers	BOM-L1 TR	Single-distance CW	1	Omegawave, Japan	www.omegawave.co.jp
	HEO-200[a,b]	Single-distance CW	1	OMRON, Japan	n.a.
	Micro-RunMan[a]	Single-distance CW	1	NIM, Inc., USA	n.a.
	OXYMON MkIII	Single-distance CW	1 to 96	Artinis, The Netherlands	www.artinis.com
Oximeters	FORE-SIGHT[c]	Multidistance	1	Casmed, USA	www.casmed.com
	INVOS 5100C[c]	Multidistance	2 or 4	Somanetics, USA	www.somanetics.com
	InSpectra 325[c]	Multidistance	1	Hutchinson, USA	www.htbiomeasurement.com
	NIMO	Multidistance	1	NIROX, Italy	www.nirox.it
	NIRO-100	Multidistance	2	Hamamatsu, Japan	www.hamamatsu.com
	NIRO-200	Multidistance	2	Hamamatsu, Japan	www.hamamatsu.com
	O2C	Broadband	2	LEA, Germany	www.lea.de
	ODISsey[d]	Multidistance	2	Vioptix, Inc., USA	www.vioptix.com
	OM-220	Multidistance	2	Shimadzu, Japan	www.med.shimadzu.co.jp
	OxiplexTS	Multidistance PMS	1 or 2	ISS, USA	www.iss.com
	TRS-20	Multidistance TRS	2	Hamamatsu, Japan	www.hamamatsu.com
Imagers	Dynot	CW	up to 32	NIRx, USA	www.nirx.net
	ETG-4000[c]	CW	44	Hitachi, Japan	www.hitachimed.com
	ETG-7000[c]	CW	72	Hitachi, Japan	www.hitachimed.com
	Imagent	PMS	up to 128	ISS, USA	www.iss.com
	LED IMAGER	CW	16	NIM, Inc., USA	n.a.
	nScan D1200	CW	16 to 32	Arquatis, Switzerland	www.arquatis.com
	nScan W1200	Wireless CW	16	Arquatis, Switzerland	www.arquatis.com
	NIRO-200	CW	8	Hamamatsu, Japan	www.hamamatsu.com
	NIRS 4/58	CW	4 or 58	TechEn, Inc, USA	www.nirsoptix.com
	OMM-2001	CW	42	Shimadzu, Japan	www.med.shimadzu.co.jp
	OMM-3000	CW	64	Shimadzu, Japan	www.med.shimadzu.co.jp

[a]Wearable instrument.
[b]No longer commercially available.
[c]USA Food and Drug Administration's approval.
[d]30-min battery backup.
CW=continuous wave, n.a.=not available, PMS=phase modulation spectroscopy, SRS=spatially resolved spectroscopy, TRS=time resolved spectroscopy.

(Table 4). But why are there so many different instruments? One reason is that, unlike the other well-established imaging modalities such as magnetic resonance imaging (MRI) or computerized tomography (CT), the setup of NIRS and/or NIRI is highly dependent on the application performed and the tissue measured. Thus, each of the instruments optimizes a certain aspect. For example in neonatology, it is less important to utilize high sensitivity detectors, because neonatal tissue is relatively transparent, and neonatal measurements require soft and flexible probes to prevent lesions of the sensitive skin. An instrument, which optimally incorporates all the physical aspects of the technique (such as highly sensitive detectors) and therefore is capable of providing all the measurable parameters, might be impractical for any kind of

Table 4 Main recently developed near-infrared prototypes.

Name of the instrument or town of the university		Technique	Number of channels	University or firm	Author [reference]
Oximeters	Irvine	Broadband PMS	1	Irvine Univ., USA	Pham 2000,[147] Lee 2006[148]
	Keele	PMS	1	Keele Univ., UK	Alford 2000[149]
	Koblenz	Broadband SRS	1	Koblenz Univ., Germany	Geraskin 2005[150]
	NeoBrain	CW	8	Helsinki Univ., Finland	Nissila 2002[151]
	Philadelphia	Multidistance SRS	1	NIM, Inc., USA	Nelson 2006[152]
	IRIS-3	CW	1	INFM, Italy	Giardini[153]
	TSNIR-3	Multidistance SRS	1	Tsinghua Univ., China	Teng 2006[154]
	Zurich	PMS	1	Univ. Hospital Zurich, Switzerland	Brown 2004[155]
Imagers	Arlington	CW	64	Univ. of Texas, Arlington, USA	Kashyap 2007[156]
	Berlin	CW	22	Charité, Germany	Boden 2007[157]
	London	CW	20	Univ. College London, UK	Everdell 2005[158]
	NIROXCOPE 201	CW	16	BoğaziÇi Univ., Turkey	Akin, 2006[159]
	Nanjing	CW	16	Southeast Univ., China	Li 2005[160]
	New York	CW	var.	Columbia Univ., USA	Schmitz 2002[161]
	Philadelphia	CW	16	Drexel Univ., USA	Leon-Carrion 2006[162]
	St. Louis	CW	300	Washington Univ., USA	Culver 2006[163]
	Zurich[a]	CW	16	Univ. Hospital Zurich, Switzerland	Mühlemann 2006[73]
	Berlin	TRS	16	Physikalisch Technische Bundesaustalt, Germany	Liebert 2006[82]
	Boston	TRS	32	Harvard Univ., USA	Selb 2006[164]
	Hamamatsu	TRS	16	Hamamatsu, Japan	Ueda 2005[165]
	Milan	TRS	16	Politecnico of Milan, Italy	Contini 2006[166]
	Monstir	TRS	32	Univ. College London, UK	Schmidt 2000[167]
	Strasbourg	TRS	8	Strasbourg Univ., France	Montcel 2004[168]
	Warsaw	TRS	16	Academy of Sciences, Poland	Liebert 2005[169]
	Helsinki	PMS	16	Helsinki Univ., Finland	Nissila 2005[170]
	Seoul	PMS	16	Yonsei Univ., South Korea	Ho 2007[171]
	Hokkaido	SRS	64	Hokkaido Univ., Japan	Kek 2006[172]
	Irvine	SRS	CCD	Irvine Univ., USA	Cuccia 2005[80]

[a]Wearable instrument.
CCD=charge coupled device, the instrument uses a noncontact camera; CW=continuous wave; PMS=phase modulation spectroscopy; SRS=spatially resolved spectroscopy; TRS=time resolved spectroscopy; Univ.=university; var.=variable.

clinical application because, for instance, the detector is too sensitive to excess light and could therefore be easily destroyed.

The possibility to map the whole cerebral cortex convinced many cognitive neuroscience research groups to utilize NIRI instrumentation for human brain mapping studies. In this framework, sophisticated data processing methods have recently been investigated and applied to the analysis of NIRI data. Principal component analysis has been utilized for analyzing the spatial and spectral features of diffuse reflectance

data from brain tissue[110] and for suppressing systemic physiological contributions to the evoked hemoglobin-related signals.[111] Independent component analysis[112] and the continuous wavelet transform[113] have been proposed to detect activated cortical areas, whereas lagged covariance methods have been proposed to explore functional brain connectivity from event-related optical signals.[114] In the attempt to characterize the contributions of systemic parameters, such as the heart rate and the mean arterial blood pressure to the low-frequency oscillations in cerebral oxygenation,[115] researchers applied information transfer analysis. The recent and quickly growing emphasis placed on data processing procedures for NIRI data shows the importance that the NIRI field is attributing to the development of powerful and reliable data analysis tools. However, no standardized approach for NIRI data analysis has been established yet, laying further emphasis on the development of standard data processing schemes to elevate NIRI into a well-established human cortical imaging modality.[116]

One measured but not widely explored variable is the light scattering, which is related to tissue structure, cell membranes, and mitochondria. Unfortunately scattering and scattering changes are often disregarded when the focus is on the absorption. One example showing the potential value of scattering changes is their association with the neuronal activity.[117] The latter leads to small changes in light scattering at the neuronal level. Because the changes are small, they are difficult to detect. Although several groups report the detection of such changes,[118–122] there are some controversies.[123] New algorithms able to better separate the other physiological signals from the scattering changes might help to resolve this issue. Light scattering has also been investigated in NIR mammography for breast cancer detection.[124]

The progress of NIRS and/or NIRI is not as rapid as expected and hoped for.[22,125] There are several reasons for this. In fact, NIRS and NIRI have many pitfalls and limitations. Some typical examples can be summarized as follows. (1) For correct measurements, it is necessary to precisely know the assumptions in the physical models and to make sure that they are fulfilled (e.g., the boundary conditions assumed in the algorithms have to correspond to the geometry of the tissue under investigation). (2) An incorrect attachment of the sensor might lead to light piping and consequently large errors. (3) Heterogeneous tissue cannot be measured if the physical model assumes a homogenous tissue. (4) The different NIRS and NIRI approaches show a different degree of susceptibility to movement artifacts, single distance measurements are highly sensitive while multidistance geometries are relatively inert.[126] Often these pitfalls lead to errors that in turn are wrongly used to disqualify NIRS and/or NIRI results. A strong interdisciplinary collaboration between clinicians and scientists could facilitate the correct use of NIRS and NIRI. Another explanation for the slow progress is that there is not a unique ideal NIRS and NIRI instrument. Instead, different instruments could be optimal for a given clinical application. Another problem is that the clinical studies for understanding the meaning of a new parameter (such as tissue oxygen saturation), for establishing its normal values, and for determining limits requiring therapeutic or corrective actions (e.g., the administration of oxygen) call for time-consuming, extensive, and very expensive clinical studies.

There is considerable technical progress that, leading to a higher precision of the measurements and resolution of the images, could partly overcome the limitations of the technique. Also from the clinical perspectives there is considerable progress in view of the first clinical applications entering routine.[21,22,25–28,127] It can be predicted that the evolution of this progress will consist of an increasing variety of clinical applications in which NIRS and/or NIRI will become established techniques in hospitals.

5 Conclusion

Thirty years after NIRS's discovery, NIRS and NIRI are currently at a stage of transition from basic clinical research to an adjuvant in clinical applications. On average, two to three papers per day about the clinical applications of NIRS and NIRI are reported on MEDLINE and "Current Contents Connect" (Thomson Scientific, USA). In addition, several technical papers are published in journals not included in MEDLINE. In the next 5 years, additional efforts are expected in technology developments, commercialization, and clinical validation of oximetry and imager instrumentation. In particular, oximeters are expected to become capable of measuring absolute values, and this will give a consistent contribution for the expansion of their clinical applications. Multimodality imaging systems will be developed to integrate NIRI with various other well-established brain imaging techniques such as MRI and positron emission tomography.[128] Structural information of brain tissue that is obtained from conventional imaging tools, such as CT, MRI, and ultrasound, will provide highly useful coregistration and guidance that will ultimately improve the accuracy of NIRI image reconstruction. Because NIRS and/or NIRI have an inherently high contrast, technological and computational advances will enable image reconstruction with higher spatial resolution and sensitivity. NIRI techniques show a tremendous potential for noninvasive brain imaging by providing functional and metabolic maps of the activated brain cortex. The complementary information provided by changes in O_2Hb and HHb; the coregistration with electroencephalography and systemic parameters such as the heart rate, blood pressure, and respiratory rate; and the development of dedicated data processing algorithms are critically important for the analysis and interpretation of NIRI data.

In summary, although NIRS and NIRI have been growing slowly but constantly, NIRS and NIRI are on the verge of entering clinical everyday applications and have already brought many valuable insights in clinical research. There are good prospects that NIRS and/or NIRI will light up in the future, shed light on many physiological issues, and brighten the perspectives of many illnesses.

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