



Neonatal NIRS monitoring: recommendations for data capture and review of analytics

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Abstract

Brain injury is one of the most consequential problems facing neonates, with many preterm and term infants at risk for cerebral hypoxia and ischemia. To develop effective neuroprotective strategies, the mechanistic basis for brain injury must be understood. The fragile state of neonates presents unique research challenges; invasive measures of cerebral blood flow and oxygenation assessment exceed tolerable risk profiles. Near-infrared spectroscopy (NIRS) can safely and non-invasively estimate cerebral oxygenation, a correlate of cerebral perfusion, offering insight into brain injury-related mechanisms. Unfortunately, lack of standardization in device application, recording methods, and error/artifact correction have left the field fractured. In this article, we provide a framework for neonatal NIRS research. Our goal is to provide a rational basis for NIRS data capture and processing that may result in better comparability between studies. It is also intended to serve as a primer for new NIRS researchers and assist with investigation initiation.

Introduction

Brain injury is an important and consequential problem faced by many infants in the neonatal intensive care unit (NICU). Understanding injury mechanisms and developing tools for early intervention to enhance neuroprotection are high priorities. Near-infrared spectroscopy (NIRS) is a promising technology that allows noninvasive assessment of cerebral oxygenation on a bedside monitor [1, 2]. It has been widely adopted over the past two decades for research and is now increasingly being deployed for clinical use [3–5].

However, the use of NIRS to monitor regional tissue oxygenation in neonates remains a widely fractured field. This is likely a consequence of absent standards and coordination of the various stages of NIRS monitoring,

including data capture, processing, and methods for assessing oxygenation, oxygen extraction, and autoregulation. For autoregulation specifically, there have been numerous studies with concordant findings, but significant differences in approach make comparing trials a daunting task [6–10].

In this manuscript, we provide an overview of NIRS monitoring in the neonate, approaches for capturing data from commonly used devices, data handling methods, and techniques to assess NIRS-based cerebral autoregulation. These guidelines are intended for use in the neonatal population and cover a broad range of equipment and software. We conclude with a set of recommended practices, with the aim of providing a foundation for future neonatal NIRS practices.

Equipment

NIRS fundamentals

NIRS is a non-invasive technique for measuring the percentage of saturated hemoglobin in a target tissue. It relies on two physical principles: differential absorption of near-infrared light and the modified Beer–Lambert law [11]. NIRS devices utilize light in the near-infrared band (700–900 nm), to which skin, bone, and connective tissue are mostly transparent [12, 13]. As NIR light diffuses into

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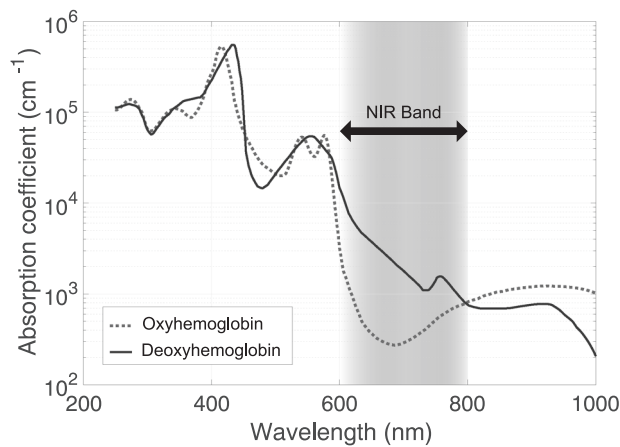


Fig. 1 Absorption coefficients of oxy- and deoxyhemoglobin in the infrared and near-infrared spectrum. Note the marked difference at ~700 nm, a difference leveraged in NIRS monitoring.

the tissue, it interacts with hemoglobin in four different ways: absorption, reflection, scattering, and transmission [13]. Although transmitted and absorbed light are lost and not returned to the sensor, a portion of the source light is reflected back to the sensor, and a smaller portion is scattered by motion, generally, blood flowing through arteries. Over the time frame of a typical NIRS recording, the underlying structure of the monitored tissue remains constant, therefore reflection, transmission, and scattering are assumed to be constant as well.

Thus, the only variable optical factor is absorption, which changes based on the degree of oxygen saturation. The absorption spectra of oxy- and deoxyhemoglobin in the near-infrared band are different, with greater absorption by deoxyhemoglobin (Fig. 1). Light of at least two different wavelengths (above and below 810 nm) is applied to tissues of interest, and the relative concentration of oxygenated and deoxygenated hemoglobin is estimated using the modified Beer–Lambert law, thus providing an index of tissue oxygenation [14]. Experimental NIRS systems utilize other optical properties and wavelengths of light as detailed below.

Unlike pulse oximetry, NIRS measurements are not pulse-synchronized and thus not limited to arterial hemoglobin sources. Instead, the light interrogates arterial, venous, and capillary beds, providing a regionalized composite measure. Given that only ~30% of blood is intraarterial at any given time in most tissues, NIRS monitoring provides an approximate 30/70 arterial/venous-weighted estimate of oxygen saturation [15, 16] which closely parallels jugular venous oxygen saturation [17].

Commercial NIRS monitors

A range of commercially available NIRS monitors with neonatal indications is listed in Table 1. Although all NIRS

Table 1 Commercially available NIRS devices with neonatal indications.

Device Name	Manufacturer	Regulatory approval ^a
BabyLux	BabyLux Project	Pre-market testing, investigational use only
EGOS-600	Tsinghua University	China
FORE-SIGHT Elite	Edwards	USA, EU, Japan
INVOS 5100c	Medtronic	USA, EU, Japan
MetaOx	ISS	Pre-market testing, investigational use only
NIRO 200NX	Hamamatsu Photonics	USA, EU, Japan
O3	Masimo	USA
OxyPrem 1.4	OxyPrem	EU
SenSmart X-100	Nonin	USA, EU, Japan

^aUSA approval indicates 510(k) clearance by FDA, China approval indicates CFDA clearance, EU approval indicates CE marking, Japan approval indicates certification from PMDA.

monitors operate under the fundamentals described previously, each contains proprietary signal-processing algorithms. While this systematic difference in measured saturation precludes comparison of absolute measurements, head-to-head comparison (NIRO vs. INVOS [18, 19], Nonin vs. ForeSight [20], INVOS vs. ForeSight [21]) of competing devices demonstrates the generally strong correlation between devices, supporting the notion that, despite proprietary differences, they are largely equivalent. Further, recent publications by Kleiser using a blood-lipid phantom have mathematically modeled the differences between devices, allowing for precise correction of measurements between devices [22–24].

Research monitors

Although there is some variation in emitter-detector difference and wavelength selection, all commercial NIRS devices use a single probe to detect regional oxygenation. Several different research optical devices are currently in development which greatly extend this technology into new avenues and may provide valuable additional information beyond regional tissue oxygenation.

One such technique is diffuse correlation spectroscopy (DCS). While currently available commercial NIRS devices utilize only differences in light absorption between oxyhemoglobin and deoxyhemoglobin, DCS also detects the scattering of light from moving red blood cells, enabling measurement of cerebral blood flow in addition to saturation [25]. DCS systems have been validated for neonates in a number of studies [26, 27], including infants with

congenital heart disease [28]. In a recent publication, the prototype BabyLux commercial DCS system was detailed [29].

Another technology, functional NIRS (fNIRS) or the more advanced derivative diffuse optical tomography (DOT), utilizes 10–20 or more individual optical channels embedded in “caps” with fixed optode positions. By synchronized capture of all channels, the system reconstructs three-dimensional cerebral oxygenation patterns across large regions of the cerebral cortex [30]. In this manner, changes in regional oxygenation in the setting of injury or response to stimuli can reveal metabolically connected networks, similar to functional MRI [31, 32]. In neonates, DOT has been used to classify the hemodynamic response during seizures [33] and for the detection of intraventricular hemorrhage [34].

Finally, broadband NIRS is a relatively new technique that has recently been applied to neonates. Unlike conventional NIRS which utilizes 3–5 fixed wavelengths of light, broadband NIRS utilizes more than 100 frequencies of light to characterize cytochrome-c-oxidase (CCO), the terminal electron acceptor in the electron transport chain [35]. Changes in the oxidation state of CCO can be detected using broadband NIRS and are thought to be more reflective of brain metabolism than oxy-/deoxyhemoglobin concentration [36]. Given the small concentration of CCO in the brain and confounding by competing for absorption by hemoglobin, CCO measurement has only recently become practical. Broadband NIRS has been demonstrated in piglet models of HIE [37] as well as pilot studies of human neonates with HIE [35, 38].

Probes

The majority of commercial NIRS monitors have specific pediatric or neonatal-sized sensors available. Beyond physical size differences from the adult probes, pediatric and neonatal probes also have shorter distances between the emitting light source and the detectors, altering the depth of penetration to provide greater sensitivity to signals transmitted through the thinner skull of an infant [39]. Differences in tissue saturation values between adult, pediatric, and neonatal sensors may range between 10% and 14% [20]. In addition, reference values for cerebral oxygenation measures in preterm infants have been based on studies using small adult sensors [40, 41], with the limited investigation into the optimal adjustment required for neonatal sensors [20].

The selection of a NIRS device is an institutional decision beyond the scope of this report. Key factors to consider include: device and sensor costs, availability of adhesive and non-adhesive probes (particularly important for preterm infants), availability of single-use or reusable probes, ease

of cleaning for infection control, regional regulatory approval (allowing research and clinical use on the same devices), and compatibility with existing monitoring hardware. A non-exhaustive search of prospective cerebral oxygenation studies reveals that the bulk of neonatal NIRS research has been conducted with the INVOS (Medtronic, Minneapolis, MN, USA), NIRO (Hamamatsu Photonics, Hamamatsu City, Shizuoka, Japan), and ForeSight (Edwards Lifesciences, Irvine, CA, USA) devices.

Data capture options

Commercially available NIRS devices are primarily intended for clinical use with a focus on trend monitoring and not long-term analysis. As such, recording data is a secondary consideration that requires additional planning, infrastructure, and costs. Key fundamentals of data capture platforms include (a) synchronized capture of comprehensive vital signs, (b) accurate time/date information, and (c) protection against data loss. Potential data capture approaches, including advantages and disadvantages, are presented as follows. Regardless of the method used, data should be captured at the highest possible sampling rate [42].

Local device

The simplest approach to capturing NIRS data is a direct download from NIRS devices. Several manufacturers provide a USB interface for this purpose, including the Hamamatsu, INVOS, and ForeSight devices. While this approach is the most straightforward, it has several drawbacks. First, data can only be downloaded after a monitoring session is complete. Power interruption or accidental deletion from the device can result in data loss, and the limited memory capacity on each device may result in data files being overwritten if not routinely downloaded. Second, this approach only permits the capture of NIRS data; other vital signs are not included in the file. Thus, data captured in this manner needs to be externally harmonized with other vital sign information. Finally, the time stamp for this NIRS data originates from the NIRS device clock, which is frequently not adjusted for daylight savings time or maybe reset in the case of power loss.

Central-hub and central-server data capture

To coordinate the synchronized capture of physiologic signals from multiple sources, a central computer is needed to receive the data and store it in a single, aggregated file. The typical “central-hub” strategy utilizes a laptop computer at the patient’s bedside which is physically connected to the NIRS monitor, the patient monitor, the ventilator, or a

host of other devices. This approach is advantageous in that the computer provides the timing data, so only one clock must be checked before starting the recording and the software writes the data directly to disk so that if there is a power interruption, previously recorded data is not lost. Some software packages also include integrated analytic tools, providing a low-resistance path for new investigators. The most significant disadvantage to the “central-hub” model is that generally requires the additional purchase of hardware (laptops, computer cabling) or software and may impose restrictions with limited device compatibility.

A variation on this method for data capture is the “central-server” model, where individual monitoring devices connect over a network to a centrally located server. The approach shares the same advantage of synchronized timing and adds the advantage of mostly automated capture, requiring minimal input from users to start and stop the recording and no need for a laptop at each patient’s bedside. The significant disadvantage is that it is the most complex solution, from an infrastructure standpoint, often requiring significant capital expense.

Software packages from NIRS manufacturers, as well as third-party software and hardware vendors, are listed in Table 2. Examples of INVOS and ForeSight capture configurations are shown in Fig. 2.

Recommendations for data capture

To analyze cerebrovascular hemodynamic data, important steps must be taken in the organization and format of captured data. Standardized data formatting will allow for easy exchange in multi-center collaborative efforts, the development of improved analytic tools, and the elimination of unnecessary conversion work. Three data storage principles are important to consider—open data format, consistent time stamping, and synchronization.

Open format

As previously noted, some software/hardware combinations result in files in a proprietary format. This is disadvantageous for several reasons. First, technological advances will eventually render most formats obsolete, requiring maintaining legacy systems and/or conversion tools to allow continued use of files originating in these systems. Second, proprietary formats may prevent sharing with other investigators lacking the same platform. Third, corruption of data files may result in data lossless manageable than using nonproprietary systems.

In contrast, open file formats, notably comma-separated value (CSV), are not proprietary or platform-specific and can be accessed using a wide range of tools. Processing

tools to summarize data and validate data integrity can be more widely applied with open formats. In addition, CSV files are also tolerant of corruption; although there will be data loss in the corrupted region of the file, the remainder of the file is usually accessible. However, CSV is not a particularly efficient format, resulting in significantly larger files than other formats. However, given the low relative costs of file storage, this has become less of a concern.

Timestamping

Accurate time stamping is essential for quantitative analysis of NIRS signals. There are several approaches to recording time data that may apply in different scenarios. The most ideal approach records to date and time information in an unambiguous fashion. One approach is to utilize the format published by the International Organization for Standards like ISO 8601 [43] which represents dates as YYYY-MM-DD where *yyyy* is a four-digit year, *mm* is the two-digit month, and *dd* is the two-digit date. ISO 8601 also includes a standard format for time representation, hh:mm:ss, where *hh* represents hours on a 24-h clock, *mm* is minutes, and *ss* is seconds.

An alternative approach is to use Unix timestamps, which is a system for describing time as the number of seconds which have elapsed since the “Unix epoch,” 00:00:00 Jan 1, 1970, UTC, accounting for leap seconds [44]. As a decimal value, Unix time-stamp data is easy to utilize for date/time manipulations as it is an integer value such as 1584316920. A distinct disadvantage of Unix time is the loss of daylight saving or time zone information, as all time is referenced to UTC, the successor to Greenwich Mean Time, and is not adjusted for daylight saving. Careful attention must be paid when comparing local time events (such as time of birth, medication administration, etc.) to data recorded in Unix time to ensure the correct offset is applied for locale and DST.

A consistent approach to time stamps should be an achievable priority for the NIRS research community.

Safety and privacy

Digital recordings offer significant convenience and are easily transferred between investigators facilitating collaborative research. This ease of use is also the source of potential safety and privacy concerns. Physiologic recordings are patient medical records and are subject to privacy laws such as HIPAA, PIPEDA, and GDPR. To maintain compliance with these regulations, all recordings should be de-identified, encrypted, and stored in locations with access controls (requiring a login that can be audited) and not on USB flash drives or external hard drives [45].

Table 2 Commercially available data capture platforms.

Name	Manufacturer	Data export format	Type of data capture	Other features and notes
VitalSync	Medtronic	CSV	Hub	<ul style="list-style-type: none"> •Can also be used as a clinical tool and features some “early warning” algorithms •Works with INVOS monitors
FS DAQ	Edwards	CSV	Hub	<ul style="list-style-type: none"> •Works with ForeSight monitors
SenSmart Data Management	Nonin	CSV	NIRS only	<ul style="list-style-type: none"> •Works with Nonin X-100 monitors •No synchronization with other monitors
OxyPrem	OxyPrem	CSV, XLS	NIRS only	<ul style="list-style-type: none"> •Works with OxyPrem 1.4 monitor •Indirect capture via webpage interface, requires internet access •No synchronization with other monitors
ixTrend	ixitos	CSV	Hub or server	<ul style="list-style-type: none"> •Captures all data from the patient monitor, requires Philips patient monitor •Compatible with multiple brands of NIRS monitors (via IntelliBridge module) •NIRS monitor must be connected to patient monitors to be added to the data stream
BedMaster EX	Excel Medical	Proprietary ^a	Server	<ul style="list-style-type: none"> •Captures all data from the patient monitor, compatible with GE and Philips patient monitors •Compatible with multiple brands of NIRS monitors •NIRS monitor must be connected to the patient monitor or separately to BedMaster server to be included in the data stream
Data Warehouse Connect	Philips	HL7	Server	<ul style="list-style-type: none"> •Captures all data from the patient monitor, requires Philips monitor •Compatible with multiple brands of NIRS monitors (via IntelliBridge module)
ICM+	Cambridge Enterprise	HDF5, CSV	Hub	<ul style="list-style-type: none"> •NIRS monitor must be connected to patient monitors to be added to the data stream •Captures all data from the patient monitor, works with Philips and GE monitors •Compatible with many NIRS monitors •Can interface with other ICU monitors (intracranial pressure, EEG, etc.) •Has many built-in analytic tools, especially for autoregulation
SignalBase	University of Utrecht	Proprietary	Hub	<ul style="list-style-type: none"> •Integrated platform to capture patient data, amplitude-integrated EEG, and NIRS (INVOS) signals •Includes visualization and autoregulation analytic tools
CNS Monitor	Moberg ICU Solutions	Proprietary ^a	Hub	<ul style="list-style-type: none"> •Conventional EEG monitor •Built-in compatibility with more than 30 different patient monitors include NIRS and patient monitors

^aFiles can be converted to other formats via conversion tools available upon request from the manufacturer.

Fig. 2 Examples of two different device configurations. On the left, an INVOS 5100c is integrated with a Moberg CNS monitor. On the right, a ForeSight Elite is integrated with a laptop computer. Both setups utilize portable rolling stands, allowing easy movement between patients.



For files that are shared with other investigators, researchers may wish to remove identifiable dates and times. One approach is to shift the date or time by a fixed amount of time. Alternatively, the time column could be recalculated, for example as the number of seconds since the start of the recording or the number of seconds since birth [46]. However, once recalculated, it is no longer possible to cross-reference time information with external events (such as the initiation of a medication or a known clinical event). In addition, serial time numbers should be recorded in actual units of time (i.e., seconds) so that the sampling rate can be ascertained by others.

Synchronization

Cerebral oximetry measures alone are not sufficient to calculate cerebrovascular autoregulatory function. At least one other source of information (e.g., arterial blood pressure, heart rate, or pulse oximetry) must be used. These other data streams can be used for autoregulatory assessment in addition to error detection and/or correction. However, synchronized recording of these multiple signals is essential for this process to work correctly.

As noted earlier, there are two ways to address this challenge. One approach is to synchronize all monitoring signals into a central monitoring device and sample data directly from the central device. The use of IntelliBridge modules to connect peripheral monitors to a Philips patient monitor is an example of this approach. Alternatively, a bedside computer (or networked server) could serve as the hub for multiple devices. Each device will need to have a

physical connection (via serial or network cable) to the hub computer. The Medtronic VitalSync and CAS/Edwards FS DAQ software packages are examples of this approach. A third, significantly less ideal option can be used when separate recording systems are used for each device. In this scenario, a “time mark” can be entered as an annotation in the recording stream. After the recording is complete, each individual file can be combined into a composite file, aligned by the “time mark” point. For this approach to work, it requires the user to press a button on two or more devices at exactly the same time and also requires each device clock to be precisely synchronized.

Approaches to error correction

Physiologic data collected in the NICU is contaminated with signal noise and artifacts. The challenge for researchers is to deploy artifact or error correction tools that reduce the impact of these outliers without accidentally removing valid data or creating significant gaps. Although some methods for cerebrovascular modeling tolerate some degree of missing data, large gaps remain problematic. Artifacts can be divided into three distinct categories: missing values, out of range values, and motion artifact.

Missing values

Missing data is most often caused when a sensor has been disconnected from a patient or the device has been placed in standby mode. For analytic purposes, missing values should

Table 3 Common approaches to data interpolation.

Name	Summary of approach
Nearest neighbor	Assuming the value of the next-nearest sample
Mean analysis	Taking the mean value of the sample before and after the missing data point
Linear interpolation	Using the slope of a best-fit line to predict missing values, assuming a linear relationship
Cubic interpolation	Fitting short length “splines” over regions shaped using third-degree polynomials
Spline interpolation	Similar to cubic interpolation though uses short-length splines, as opposed to polynomial functions, to model missing data in a piece-wise fashion

not be replaced with zeros, as this numerical value will alter statistical calculations (such as mean or standard deviation) or frequency-domain analysis. Missing values should instead be replaced with a “not a number” (NaN) representation. This approach prevents inadvertent mathematic skewing of results.

Out of range values

Although most values captured during recording will fall within expected normal ranges, some measurements will be outliers. Outlier values can be defined as point outliers, values that are so far outside the normal range that it is clear they are erroneous (e.g., heart rate of 475 bpm), and contextual outliers, which may be of nominally acceptable value but out of place when considering measurements obtained before and after that point [47]. The first type of outlier is considered an “out of range” value which should be removed from the recording. The second type of outlier is the result of motion artifact and will be discussed separately.

When removing out of range values, determination of upper and lower limits should be made a priori utilizing gestational age-appropriate values. While truly normative values are not well established in preterm neonates, existing retrospective data should be sufficient for blood pressure [48–50] and heart rate [51]. Point outliers represent error conditions and depart significantly from normal values and a simple screening for values two or three standard deviations from the mean is likely sufficient to exclude them without removing true patient data.

One commonly encountered scenario is exceedingly high or low values for arterial blood pressure, which occur when the line is being accessed for sampling or during infusions. Another common scenario is the generation of error codes, typically significantly out of range values reported by a monitor when a sensor has encountered an error (usually when the sensor is off the patient). Finally, some NIRS monitors have fixed ranges. For example, the INVOS 5100c does not report oxygen saturations below 15%. It is important that clinicians and researchers be aware of specific patient- and monitor-specific circumstances to determine whether out of range data represent a physiologic

disturbance vs. a monitoring error. In the latter case, these values can be readily identified as outliers in the recording and can be programmatically removed by replacement of all non-physiologic values with *NaN*.

Motion artifact

NIRS signals are prone to changes from baseline when patients move, an unavoidable reality in the neonatal population. Sudden signal changes can be recognized as contextual outliers but are more difficult to remove programmatically as the values may still remain within normative ranges. Analysis, therefore, must include methods for detecting and removing motion artifacts. NIRS probes with accelerometer-based movement detection sensors have been described in previous publications [52, 53], but this technology is not yet commercially available.

Fortunately, movement artifacts can also be determined using characteristic changes in the signal. A number of different approaches have been used in prior research including principal component analysis [54, 55], wavelet analysis [56], Kalman filtering [57], sliding window averaging [58], statistical inference [59], non-parametric threshold detection [60], or a combination of multiple approaches [61]. The systematic comparison of the different techniques suggests that the wavelet approach results in the greatest reduction in error, although these comparisons did not include all techniques nor are they neonate-specific [62–64]. Regardless of the method, all reports indicate that motion artifact correction is an essential component of data processing.

Interpolation

Interpolation methods refer to “best guesses” about missing values using nearby valid data. Common approaches to vital sign interpolation include nearest-neighbor [65], linear interpolation [66], and spline interpolation [67] (Table 3). The accuracy of these methods to estimate missing data is directly related to the length of missing data and the complexity of the approach used. The systematic comparison of interpolation methods suggests that spline interpolation provides the largest reduction in mean-square error [63, 68].

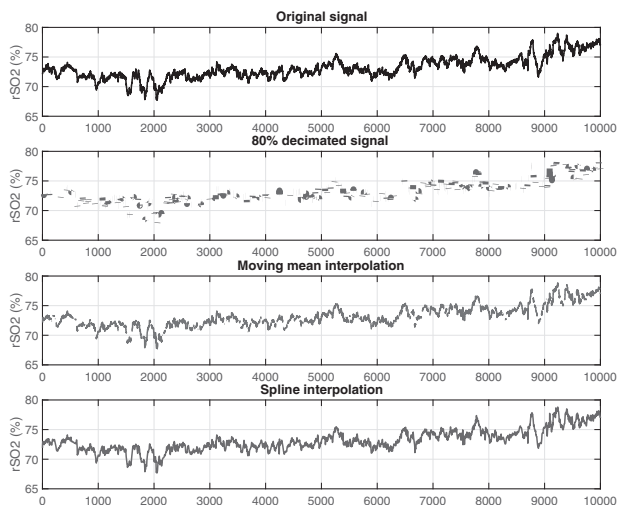


Fig. 3 The result of two different interpolation methods. First, 80% of the original signal is randomly removed. Moving mean and spline interpolation approaches are applied; note the significantly more continuous results of spline interpolation.

An example of the output of several approaches to interpolation is shown in Fig. 3.

There is considerable debate about the validity of using interpolation or imputation to fill in gaps caused by missing data [69, 70]. Although these techniques may permit the analysis of otherwise unusable data, this approach results in the mixing of synthetically generated data with real measurements and care must be taken to avoid the introduction of error. Missing data are common in longitudinal analysis and interpolation or imputation is an accepted approach [71]. The success of interpolation techniques is dependent on many factors including the predictability of the signal, the sampling rate, and the length of the missing segment [72]. Large segments of missing data present a difficult challenge that, even with sophisticated techniques, affects many domains of quantitative analysis [73]. Importantly, an empiric study of tolerance to missingness has not been conducted and remains an important unanswered question.

Some researchers have chosen to take a strict approach to missing data, excluding all segments with missing values. This approach does avoid the need for interpolation, but significant exclusion of underlying data may also introduce bias. The percent of missing data during the monitoring period should be reported in these cases. When interpolation is used, it is prudent to additionally report on the same data set without interpolative methods as a form of quality assurance.

Approaches to cerebral autoregulation

Cerebral autoregulation is the mechanism that modulates blood flow to the brain. This complex mechanism is responsible for fine adjustment of blood flow to match

delivered oxygen to metabolic demand in the setting of fluctuations induced by changes in cardiac output, carbon dioxide, and physical positioning (e.g., supine vs. upright). Significant evidence exists that autoregulatory function is altered by the degree of prematurity [7] and severity of illness for preterm infants [9] and the degree of brain injury for term infants with HIE [74, 75]. The primary challenge of autoregulation research is the difficulty in direct measurement. Though methods do exist to assess autoregulatory capacity, they are either impractical or unsafe for use in neonates owing to the need for intracranial pressure monitoring, ionizing radiation, and/or radioisotopes.

Far more feasible is the mathematical modeling of the autoregulatory function using known inputs (heart rate, arterial blood pressure) and known outputs (cerebral blood flow—either directly using DCS or indirectly by conventional NIRS oximetry, previously validated as a reliable proxy measurement) [2, 76]. Success in this line of investigation arises from careful planning; the analytic approach informs the data capture strategy as much as the capture approach drives analytics. There is no standard methodology for the characterization of cerebral autoregulation in neonates and several different approaches have been developed.

Time correlation

The simplest and most straightforward approach is to correlate mean arterial blood pressure (MABP) and NIRS measurements. When cerebral autoregulation is intact, there should be a minimal or negative correlation, indicating active autoregulation. To reduce the impact of the non-linear relationship between cerebral blood flow and autoregulation [77], correlations should be calculated over short time windows, most commonly in 20-min segments. Inherent in this approach is the need for a pre-defined threshold beyond which autoregulation is considered impaired. The number of segments with a correlation greater than 0.5 can be summed, and the cumulative number of these “pressure passive” time periods has been linked with adverse outcomes [6].

Time correlation is relatively robust to small segments of missing data. As the typical 20-min window contains 300–600 measurements (depending on sampling rate), the degree of correlation can still be ascertained if some data are missing. However, as the number of missing data increases, per-window estimates become less accurate. An example of this approach is shown in Fig. 4A.

Cerebrovascular reactivity

A variation of the standard time-correlation approach, a method measuring cerebrovascular reactivity can be used to identify the “optimal blood pressure.” This approach was

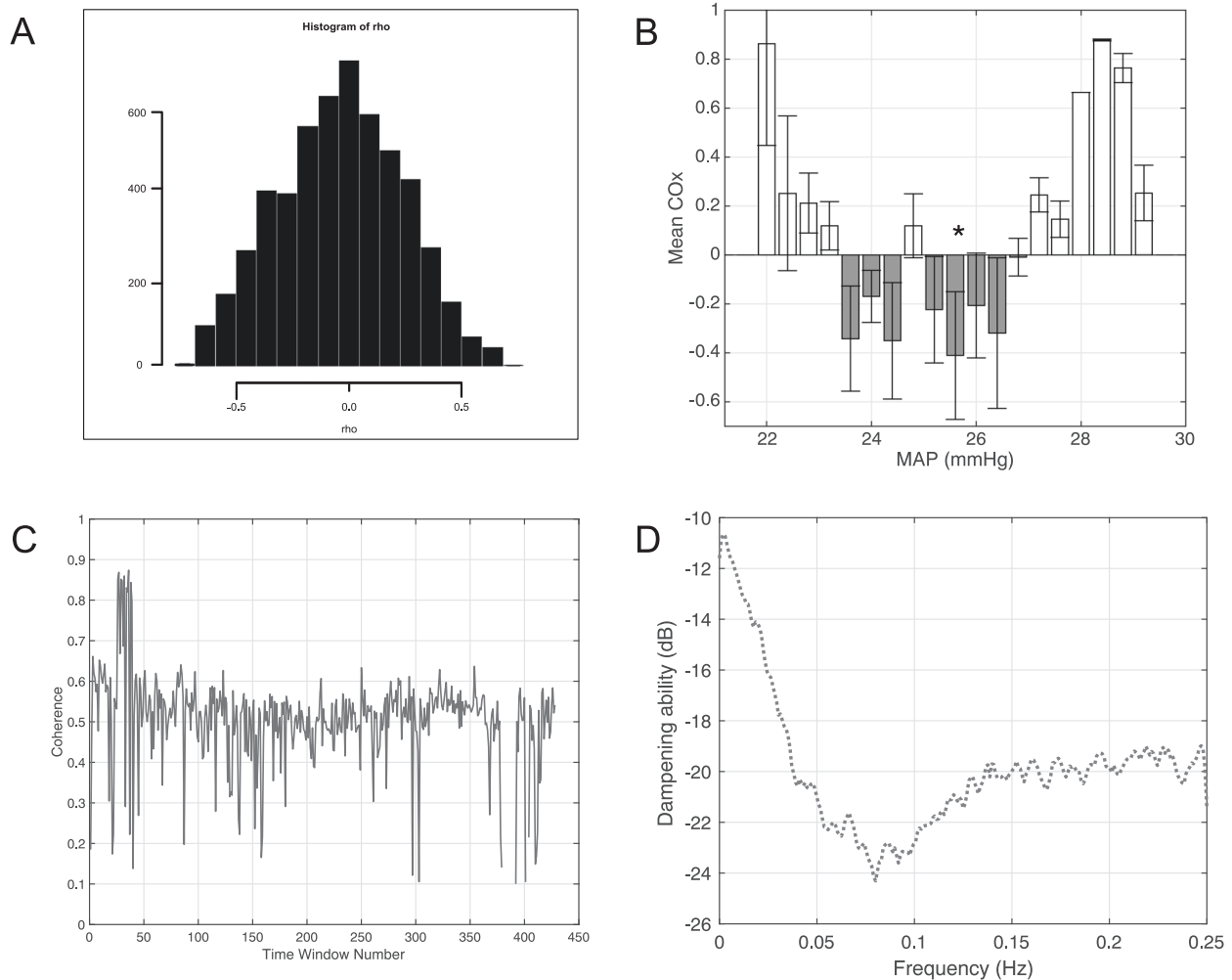


Fig. 4 Autoregulation methods. Example plots of four different methods for quantifying autoregulatory function including time correlation (A), cerebrovascular reactivity (B), coherence (C), and transfer function analysis (D).

initially developed using transcranial Doppler ultrasound [78, 79] but has been more recently adapted to the neonatal population using NIRS [8, 80–85]. In this approach, cerebral NIRS and MABP values are captured simultaneously and the correlation between the two is calculated over 5-min overlapping windows. The value of the correlation (termed COx) and the average MABP during the 5-min window are recorded and organized into “bins” of 1–2 mmHg. In this way, the average COx or correlation at each blood pressure can be assessed. Using this approach, one would expect a plot of mean COx by MABP to resemble a parabola, with increasingly positive values at the two ends representing failing autoregulation at BP extremes. In this approach, the “optimal” MABP is defined as the MABP with the lowest mean COx [84].

Cerebrovascular reactivity is quite robust in the presence of missing data owing to shorter time windows (5 min) which can accommodate gaps in the data. Furthermore, in the final stage of calculations, the correlation values in each

blood pressure “bin” are averaged across the entire recording. Sufficiently long recordings will have adequate data for a representative sample. An example of this approach is shown in Fig. 4B.

Frequency correlation

A related technique examines the correlation between oscillations of different frequencies in MABP and NIRS. Complex physiologic signals can be thought of as numerous interposed sine waves. The power spectrum, or the strength of oscillations in discrete frequency bands, can be mathematically determined using a technique called the Fourier transform and is performed rapidly using modern computers [86]. As in the time-domain analysis, these oscillations should be dampened by cerebrovascular autoregulation. Strong oscillations in cerebral blood flow (using NIRS as a proxy estimate), at the same frequencies as systemic blood flow, indicate failed autoregulation.

As with the time-domain approach, the recording can be partitioned into blocks of 20 min in which the *coherence* can be measured. Coherence is a measure of correlation but at a specific frequency or band of frequencies. Unlike a correlation coefficient, values range between 0 and 1, with 1 representing perfect coherence. As with the time-domain technique, coherence requires an agreed-upon threshold, beyond which autoregulation is judged to be impaired. Thresholds for significance have ranged from 0.384 [75] to 0.77 [9] in studies of preterm infants [9, 10, 87, 88] and term infants with hypoxic-ischemic encephalopathy [74, 75].

Calculation of the power spectrum is conventionally performed with Welch's method and requires continuous, uninterrupted data. Even a single missing point results in an error. The use of data windows allows for the calculation of coherence around missing time points by dropping those windows with missing data. Alternative methods have been developed to determine the power spectrum in the setting of missing data, but require special implementation [89, 90]. An example of coherence calculated over the length of a recording is shown in Fig. 4C.

Transfer function

An alternative frequency-domain approach models autoregulation as a “black box” that filters out blood pressure oscillations at specific frequencies. Autoregulation should serve as a high-pass filter [91] which filters out low-frequency (<0.20 Hz) oscillations in blood pressure, but not fast (high-frequency) changes which are likely needed to respond to rapid changes in cerebral metabolism.

In this method, the simultaneously collected MABP and NIRS values are partitioned into 20-min windows. A well-functioning autoregulatory system, operating as a high-pass filter, should provide significantly stronger dampening at lower frequencies (Fig. 4D). As with cerebrovascular reactivity, this approach was initially developed [92] using Doppler ultrasound measurement of cerebral blood flow before the later transition to NIRS technology [7, 93]. As transfer function analysis operates in the frequency domain, it shares the same vulnerability to missing data as frequency correlation. The use of interpolation and data windows are effective compensatory mechanisms.

Wavelet coherence

The wavelet coherence approach to autoregulation can be conceptualized as an alternative to frequency correlation while also incorporating the element of time, ultimately providing a hybrid of time and frequency correlation. Rather than decomposing a complex waveform into a series of sine waves of varying frequency and amplitude, wavelet

transformation breaks this signal into small “wavelets” or brief bursts limited in time and frequency. Hundreds of possible wavelet shapes can be scaled to match the underlying signal. By taking the wavelet transformation of a signal's autocorrelation function, the wavelet power spectrum can be obtained and is analogous to the power spectrum obtained through Fourier analysis. Coherence and transfer function analysis can be performed using the wavelet transformation of the NIRS and blood pressure signals. The strength of coherence or transfer function gain can then be visualized across frequencies and time and has been implemented using conventional and broadband NIRS in several studies of infants with HIE [94–96]. As with other approaches utilizing the frequency domain, wavelet analysis is not robust to missing data. The same set of tools used in other approaches (windowed data, interpolation) are equally useful in this approach.

Challenges to autoregulation methods

All the described methods quantify cerebral autoregulatory function. A significant challenge in the literature is the lack of simultaneous comparison of different methodologies to the same patient population to compare performance characteristics. What limited data exist in adult and animal populations suggest a general equivalence between compared approaches [97–99]. There are a number of known challenges with the described approaches [100]. Time correlation, frequency correlation, and cerebrovascular reactivity use thresholds to calculate autoregulatory function and a correlation greater than 0.5 is most used to identify periods of impaired autoregulation. Although recent efforts have been made to derive the ideal threshold based on statistical calculations [9, 75] the optimal value, if it exists remains elusive [101]. Regardless of the numeric value of the threshold, the mere existence of a threshold implies modeling of autoregulation as a binary function—either on or off. While this is mathematically simpler, it is likely an incomplete picture of the underlying biology.

Transfer function and wavelet coherence approach overcome this problem by less reliance on thresholds, instead of providing a continuous scale output. While this is advantageous, implementation of these approaches requires significantly greater technical expertise and the resulting measurement is conceptually more complex, providing a barrier to future clinical adoption.

Conclusion

NIRS is a valuable tool for estimating cerebral oxygenation and for modeling cerebral autoregulation. The availability of specific neonatal probes and the non-invasive nature of

Table 4 Neonatal NIRS data capture recommendations.

Category	Recommendation
Capture technique	Synchronized external capture (e.g., VitalSync)
Sampling rate	Highest possible
Data format	Comma-separated values (CSV)
Timestamp	dd-mmm-yyyy HH:MM:ss
Error correction	Replacement of missing or non-physiologic values with blank or <i>NaN</i>
Interpolation of missing data	No interpolation or spline interpolation

commercial NIRS devices make them particularly well suited for use in both term and preterm neonates. When properly implemented, it offers the potential to assess mechanisms underlying brain injury in this population and allows the informed design of novel neuroprotective strategies.

In Table 4, we have listed our recommendations. Although there is no governing organization to issue standards in this field, it is our hope that these recommendations provide a starting point for future neonatal NIRS research. Using a common framework to record, process, and analyze data will allow published results to be readily compared and facilitate future collaborations.

In addition to the harmonization of data capture, additional questions remain. In the data processing context, more research is needed to truly define the best method for handling missing or erroneous data. An active investigation is also needed to identify the best method for quantifying autoregulation in neonates at risk for brain injury. Choice of analytic methods should be driven by the objectives of the study and the nature of the captured data. A large, comparative study of the different approaches is required to fully evaluate the superiority (or equivalence) of any given method. Finally, there is a significant promise on the horizon for emerging NIRS technologies that will offer the ability to examine cerebral oxygenation and blood flow using novel approaches.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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