Intracranial Sensors for Continuous Monitoring of Neurophysiology

Nan Jiang,* Sergey Flyax, Wolfgang Kurz, Martin Jakobi, Savas Tasoglu, Alexander W. Koch, Ali K. Yetisen*

Dr. N. Jiang,
West China School of Basic Medical Sciences & Forensic Medicine, Sichuan University, Chengdu 610041, China
Email: jiangnansophia@scu.edu.cn

S. Flyax, W. Kurz, Dr. M. Jakobi, Prof. A. W. Koch, Dr. A. K. Yetisen
Institute for Measurement Systems and Sensor Technology, Technical University Munich, Munich, Germany

Dr. S. Tasoglu
Department of Mechanical Engineering and KUTTAM, Koc University, Turkey

Dr. A. K. Yetisen
Department of Chemical Engineering, Imperial College London, London
Email: a.yetisen@imperial.ac.uk

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Abstract: Monitoring physiological parameters in brain is important to identify early signs of secondary brain injuries. A variety of different intracranial sensors enable continuous monitoring of important brain parameters in clinical applications. However, many of the clinically approved and established technologies show drawbacks in zero-drift properties, accuracy and magnet resonance imaging (MRI) compatibility. This review gives a comparative overview of the established technologies and provides an outlook on fiber-optic sensors with potential use in future intracranial monitoring applications. Neurophysiological parameters recorded by bioelectrical signals include intracranial pressure (ICP), brain temperature, brain tissue oxygenation, cerebral blood flow, and cerebral metabolism. The comparison of ICP sensors revealed that piezoresistive strain gauge sensors provide the highest accuracy and the smallest zero-drift in clinical catheters. Fiber-optic pressure sensors show a potential to be used in future intracranial applications. Thermistors and thermocouples prove to be reliable for temperature measurement in intracranial catheters, but have limited MRI compatibility. Fiber-optic sensors show potential to be used in future intracranial catheters for temperature and oxygen measurement, as they provide higher accuracy and a better response time. Microdialysis catheters, in combination with new automated electrochemical and optical analyzers, provide the possibility of routine metabolism monitoring in clinics.
1. Monitoring in Neurocritical Care

Brain injuries, including traumatic brain injuries (TBI), are one of the major causes of death and disability in the modern world. A cross-sectional analysis in Europe from 2012 revealed a hospital discharge rate of nearly 300 per 100,000 due to TBI and a mortality rate of about 12 per 100,000 in the analyzed countries.\(^1\) Further the study showed that of injury-caused deaths, 37% were caused by TBI.\(^1\) Other studies show an even higher incidence and mortality rate in less developed countries.\(^2\) Clinical outcomes depend not only on the severity of the primary insult but also on the handling of secondary brain injuries (SBI), which can occur minutes, hours, and even days after the primary injury.\(^3\) Monitoring of physiological parameters in the human brain is an important technique to identify early signs of SBI.\(^4\) Irreversible injuries from hypertension, hypoxia, hemorrhage, and ischemia can occur in brain-injured patients due to the healing processes in the brain that follow the primary insult and lead to higher mortality risk.\(^5\) An early diagnosis and treatment of processes leading to these injuries is crucial for the patients outcome.\(^6\)

As it is very challenging to directly recognize SBI in comatose patients, monitoring of different parameters is useful.\(^7\) Over the years, various sensing technologies were developed for the continuous monitoring of the most significant parameters with limited emphasis on minimization of invasive interference of such technologies. In contrast to periodic monitoring, continuous sensing technologies provide a sustained value and have the advantage of an earlier diagnosis of pathophysiologies. Even though implantation of a sensor increases the infection risk, invasive techniques have established themselves for patients with serious injuries, as they have been proved to be a more accurate way to measure biomarkers inside the brain. However, many of the established sensors do not fulfill all desired requirements as they have drawbacks in zero-drift properties, accuracy, and MRI compatibility. Increasing the long-term accuracy of the sensors as well as reducing the size would improve the diagnostic usefulness of the sensors and minimize the infection risk. MRI compatibility is a factor of growing importance, as MRI screening becomes a more routine procedure for patients with TBI. This review paper gives a comparative overview of the available monitoring technologies in neurocritical care, presenting the established sensors, their technical specifications and recorded evaluations, and introduces new promising fiber-optic sensing approaches. Prior to the review of measuring techniques, different neurocritical parameters are introduced. An overview of the parameters, which are significant for clinical SBI diagnosis, is shown in Table 1.

1.1 Intracranial pressure (ICP) monitoring
ICP is an important parameter in monitoring patients with brain injury, as it plays an essential role in brain physiology itself and is also an indicator for different other pathophysiologies, which can cause SBI.\[^{8}\] The Monro-Kellie hypothesis states that the sum of volumes of brain tissue, cerebrospinal fluid (CSF), and blood in the cranium is constant. Thus, an increase in one of the components will lead to an increase in pressure or to a reduction in one of the other components.\[^{9}\] Consequently, an increase in ICP is an indicator for hematoma, edema, herniation, and hemorrhage. Due to the auto regulative mechanisms in the cranium, a change in ICP will also have an influence on the cerebral perfusion pressure (CPP) in the brain. The relation between ICP and CPP is given by $\text{CPP} = \text{MAP} - \text{ICP}$, where MAP is the mean arterial pressure. A rise in ICP will be compensated by a reduction of CPP, which may lead to insufficient blood supply if the CPP falls under a threshold of 50 mmHg. Monitoring of ICP and CPP will help to identify a homeostatic dysfunction of the brain.\[^{10}\] Several studies show that immediate management of elevated ICP through surgical intervention or medication will lead to a significant influence on the patients healing process.\[^{11}\]

1.2 Brain temperature monitoring

The brain temperature ($T_{\text{bt}}$) is an important neurophysiological parameter, which may vary slightly due to different physiological and pathophysiological conditions. In general, brain temperature depends on the metabolic activity of a brain region and the CBF. Small and short fluctuations occur under normal physiologic conditions, which stimulate neuronal metabolism or increase the CBF (e.g., emotions or physical activity). However, an increase in temperature occurs also in the injured brain due to different cellular healing responses, which might, inter alia, indicate an inflammatory response to an infection.\[^{12}\] However, solely monitoring of brain temperature using invasive approaches is occasionally in humans. Usually, head trauma can cause up to 3 degrees celsius higher brain temperature compared with the body temperature. A higher temperature can cause neuronal injury from severe ischemic stroke. Hence, monitoring of the brain temperature can provide important additional information in the therapy for patients with severe ischemic stroke.\[^{13}\]

1.3 Brain tissue oxygenation

Brain tissue oxygenation is measured as the partial pressure of oxygen ($P_O^2$) and is referred to as brain tissue partial oxygen pressure ($P_{bt}O^2$). Sufficient oxygenation is significant for aerobic cell metabolism, which makes up the major energy generation process in neurons. Brain tissue oxygenation is controlled by the CBF and the cerebral
arteriovenous oxygen tension difference. The detection of hypoxia implies not only insufficient oxygen supply but also indicates a risk for ischemia. Insufficient or excess oxygen supply causes cerebral hypoxia/ischemia and deleteriation of brain diseases. Therefore, monitoring of brain oxygenation could assess the balance between cerebral oxygen level and supply for treatment after ischemia.

1.4 Cerebral blood flow monitoring

Brain functions strictly depended on metabolites in the brain, and they are regulated by brain perfusion at the constant flow rate. Cerebral blood flow (CBF) defines the volume of arterial blood delivered to a unit mass of brain tissue per unit of time. Adequate blood perfusion is essential for the cells’ energy metabolism. Insufficient blood perfusion in the brain tissue ultimately results in cell death. Brain injury or stroke may severely affect regulatory process. Direct CBF monitoring can help vasospasm in subarachnoid hemorrhage (SAH) and thus prevent ischemic stroke through an early risk detection.

1.5 Cerebral metabolism monitoring

The cerebral metabolism is highly dependent on a sufficient supply of oxygen and energy substrates through CBF. Monitoring of different substrate levels that are involved in the metabolic process provides an insight into the metabolic activity and thus helps to detect ischemia and hypoxia. To identify a metabolic disturbance due to ischemia or hypoxia, the levels of ions, glucose, lactate, pyruvate, and glycerol are of interest. If the brain tissue does not receive enough oxygen, nicotinamide adenine dinucleotide hydrogen cannot deprotonate, and only two adenosine triphosphate (ATP) molecules will be produced anaerobically, in contrast to the aerobic production of 32 ATP molecules. This alteration of the metabolic process can be sensed by increased lactate to pyruvate ratio, as glucose will be directly converted to lactate and not first to pyruvate, as in usual aerobic glycolysis. Ischemia is also detected by decreased glucose levels due to insufficient perfusion. Elevated glycerol levels indicate a failure in bioenergetics, as they increase when cells lack the energy to self-regulate. Brain pH (pH$_{bt}$) is controlled by a complex combination of different homeostatic mechanisms. Although the exact effect of trauma on these mechanisms is not fully understood, statistical data shows a significant correlation between prolonged low pH values and mortality. Prolonged pH values below 7.0 clearly indicate a metabolic disturbance. pH$_{bt}$ is measured with an optical fiber sensor, which is based on the pH-dependent light absorbance of phenol red. This sensor is no longer manufactured.
2. Intracranial Pressure Sensors

2.1 Clinically Approved Sensors

ICP monitoring is divided into ventricular, intraparenchymal, epidural, subarachnoid, and non-invasive pressure sensing, each one defining the localization of probe placement. Usually, the same sensors are used in different catheter alignments to measure ICP in different brain parts. Nowadays, three major sensing principles are used to monitor ICP in human tissue: fluid-based systems, implantable transducers, and Doppler sonography.\cite{17} This review is limited to the different sensing technologies used in implantable transducers, as invasive technologies provide the highest accuracy.\cite{18} The evaluation of fluid-based systems is left out, as those are the golden standard for many decades and have been extensively discussed in literature.\cite{19} In the following, the different sensing principles of implantable ICP transducers are introduced and compared.

2.1.1 Piezoresistive Strain Gauge Pressure Sensors

2.1.1.1 Semiconductor Strain Gauge Principle

The majority of invasive ICP transducers measure the pressure with a piezoresistive strain gauge element showed in Figure 1A. Prior to the review of the commercially available strain gauge sensors, the physical fundamentals of this measurement technique are introduced. The sensing principle of a semiconductor strain gauge is based on the measurement of the electrical resistance $R$. For metal or semiconductor, $R$ is given by

\[
R = \rho \cdot \frac{l}{A},
\]  

(Eq. 1)

where $\rho$ is the specific resistance, $l$ is the length, and $A$ is the cross-sectional area.\cite{20} When a cylindrical strain gauge is stretched like shown in Figure 1B, its specifying parameters ($\rho$, $l$, $r$) will change to

\[
l_{\text{stretched}} = l + \Delta l,
\]  

(Eq. 2)

\[
r_{\text{stretched}} = r - \Delta r,
\]  

(Eq. 3)
\[ \rho_{\text{stretched}} = \rho + \Delta \rho, \]  \hspace{1cm} (Eq. 4)

where \( r \) is the radius and \( \Delta l, \Delta r, \) and \( \Delta \rho \) are the differences in length, radius, and specific resistivity, respectively. Consequently, \( R \) will change too and its relative difference depending on the stretching is expressed by

\[ \frac{\Delta R}{R} = \frac{\Delta \rho}{\rho} + \frac{\Delta l}{l} - 2 \frac{\Delta r}{r}. \]  \hspace{1cm} (Eq. 5)

In general, strain gauges are defined by the ratio

\[ G = \frac{\Delta R/R}{\Delta l/l}, \]  \hspace{1cm} (Eq. 6)

where \( G \) is called the gauge factor.\[^{20}\] A distinction is made between metal strain gauges and semiconductor strain gauges. In contrast to metal strain gauges, where the change in resistivity is majorly achieved by \( \Delta l \) and \( \Delta r \), the significant parameter in a semiconductor is \( \Delta \rho \). This phenomenon is described by the piezoresistive effect. When a semiconductor is stretched, the spaces between the single atoms increase in the direction of the mechanical tension. This leads to a change of the semiconductor’s band structure. In the direction of the mechanical tension it flattens, and in the perpendicular direction it widens. As a result of the band structure variation, the charge carrier population densities redistribute through an electron transfer. The effective electron mass decreases in the flatter band structure, thus increasing the velocity of the charge carriers and decreasing the specific resistance of the semiconductor. The \( G \) factor of a semiconductor strain gauge is given by

\[ G_{\text{SC}} = \frac{\Delta R/R}{\Delta l/l} = 1 + 2\mu + \frac{\Delta \rho/\rho}{\Delta l/l}, \]  \hspace{1cm} (Eq. 7)

where \( \mu \) is the Poisson’s ratio.\[^{20}\]
2.1.1.2 Piezoresistive Strain Gauge ICP Sensors

The most established piezoresistive ICP sensors from Raumedic AG (Germany), Integra LifeSciences (USA) and Sophysa Ltd. (France) are introduced and compared. These ICP sensors are distributed in different configurations, depending on the desired positioning of the intracranial probe, while the pressure sensing element is always the same. Variations include the number of lumens used for sensing and drainage, as well as minor changes in the catheter’s diameter. The sensing element is located at the tip of the catheter in all configurations. The sensors can be fixed with a bolt in the skull at the insertion point.

The new version of the ICP measuring system from Sophysa Ltd, Pressio 2 (P2), can monitor pressure as well as temperature. Depending on the chosen configuration, the probe is equipped either only with a pressure sensing strain gauge element or with the strain gauge element and a thermistor. The P2 system is used for parenchymal or ventricular ICP monitoring, while the ventricular catheter can be placed into a polyamide sheath with a pre-inserted stylet and a lumen for CSF drainage. There is a possibility to purchase a catheter together with a tunneling needle or trocar for easier placement.\(^{[21]}\) The ICP measuring system from Raumedic AG is called Neurovent(-P) or Neurodur (ND), depending on the dedicated placement of the probe. The Neurovent-P (NTP) catheter series is developed for parenchymal ICP monitoring, while the Neurovent (NT) series is made for ventricular ICP monitoring. Both can be additionally equipped with a temperature sensor. The NTP catheter can also be equipped with an oxygen sensor. Similar to the P2 sensing system, a lumen for CSF drainage can be added to both catheters. There is also a possibility to put the catheters into a tunneling sleeve for easier placement. The ND sensor is designed for epidural placement and can be additionally equipped with a temperature sensor.\(^{[22]}\)

In contrast to the monitoring systems from Sophysa and Raumedic, the Codman Microsensor (CMS), which was originally designed by Codman & Shurtleff and is now sold by Integra LifeSciences, is only designed to monitor the ICP value. It is available in four different configurations: The basic kit is used for parenchymal and subdural placement and the ventricular kit is designed for ventricular placement with the possibility of CSF drainage. The technical specifications of the three ICP measurement systems introduced above are summarized in Table 2.\(^{[23]}\) All three introduced piezoresistive ICP sensors have been evaluated in-vitro. This section summarizes the following studies and provides a solid basis for further comparison.

The Raumedic ICP monitoring system was tested in a test bench study with 10 new NTP catheters. The aim of the
study was to observe the zero-drifts (initial and 5 days) and dynamic response properties of the sensors in a variating pressure environment. The test bench alignment consisted of a hydrostatic column to create a precisely calculated pressure. A three-way stopcock connected the hydrostatic column and an infusion pump with the pressure chamber, in which the sensors were placed. In all experiments, the room temperature was kept stable at 20°C. Due to a hardware fault, the 5 days zero drift could only be tested for 8 sensors, with a mean result of 0.6 ± 0.96 mmHg zero drift. The dynamic accuracy test revealed a high accuracy with a mean difference of less than 1 mmHg at pressure levels ranging from 0-50 mmHg levels. [24]

The CMS was compared with two other ICP sensors in a very similar test bench alignment as described above. Additionally to the CMS catheter, the Camino ICP monitoring system (Camino Laboratories) and the ICP monitoring catheter kit OPX-SD (InnerSpace Medical) were tested. The Camino ICP monitoring system is now sold by Integra LifeSciences and will be introduced later, as it is based on fiber-optic technology. The ICP monitoring catheter kit OPX-SD is not available anymore and is therefore not discussed in this review. Since only one of each catheter was tested, there is no statistical data. The different experiments included the evaluation of the 24 h zero-drift, temperature drift in the range from 27 °C-40 °C, frequency response, accuracy at a static and pulse pressure, and the slew rate. To manipulate the temperature in the testing environment, the pressure chamber was put into a water bath. The CMS results for the drift experiments showed a zero-drift of less than 0.8 mmHg/ 24 h and a temperature drift of nearly 0.026 mmHg/ °C. The frequency response was up to the mark in the range from 0-50 Hz, and the static pressure accuracy error was lower than 2 mmHg. The pulse pressure accuracy and slew rate test revealed very similar results for the CMS and the Camino monitoring system, with a slew rate of approximately 2200 mm Hg/s. [25]

Three Pressio catheters were compared with one CMS to investigate their zero-drift properties, frequency response, and accuracy at static and pulse pressure. The test bench alignment used for the evaluation did not differentiate significantly from the described above. The difference in 7 days zero drift was lower than 0.5 mmHg between the two sensors. The temperature drift results showed a drift of 0.2 mmHg/ 20°C for the CMS and 0.3 mmHg/ 20 °C for the Pressio catheter in the range from 20 °C to 40 °C. The frequency response experiments at 10 mmHg showed a 3-dB bandwidth from 0 to 21 Hz for the Pressio monitoring system. The static accuracy of the Pressio catheter was recorded to be better than 0.5 mmHg in the range from 0-100 mmHg. Only in the accuracy test with a pulsating
pressure, the Pressio transducer showed a delay in comparison to the CMS.\[26\]

Even though the technical specifications of the three sensors are very similar, the results of the different test bench evaluations, as well as clinical experiences, show significant differences.\[24-26\] All three sensors have acceptable zero-drift properties, with the NTP showing the best zero-drift performance in the in-vitro study.\[27\] The conducted lab experiments reveal that the sensors have a temperature dependence, which is in mean under 0.03 mmHg/°C and is acceptable, as, in clinical practice, the still recoverable temperature fluctuations are normally in the range from about 32-41 °C.\[28\] The in-vitro accuracy test revealed interesting results. Although all three sensors showed an acceptable accuracy, with the CMS having the lowest accuracy with < 2 mmHg, different trends were reported for a rising pressure.\[24-26\] A comparative summary of the in-vitro accuracy and zero-drift evaluations is given in Tables 3 and 4, respectively.

Several clinical studies were conducted, evaluating the three introduced ICP monitoring systems based on the strain gauge pressure sensing technology. The following is a summary of the reviewed in-vivo papers. The ICP monitoring products from Raumedic have been clinically evaluated in different studies. In contrast to the in-vitro evaluations, it is important to differentiate between the NTP and ND models when reviewing in-vivo studies, as the placement and thus the probe design have an essential effect on the clinical measurement results and the risk of complications.\[29\]

In clinical studies of the NTP, the main characteristics of interest were zero-drift over time, complication due to catheter placement, and MRI compatibility. The mean zero-drift after explantation was calculated to less than 1 mmHg in one study and to 0.86 ± 2.2 mmHg in another study. Both clinical evaluations were conducted with nearly 100 patients and did not record a correlation between the zero-drift and implantation duration.\[30\] Citerio et al. (2005) pointed out that in 22 out of 89 patients the zero-drift exceeded ± 3 mmHg, which is a significant difference from the in-vitro results in 2004 showing a mean zero-drift of 0.6 ± 0.96 mmHg.\[27\] Another clinical study tested the NTP to be MRI conditional at ≤ 2T with a better artifact distinction at 2T.\[31\] All clinical investigations recorded only a minimal number of complications with consequences for the patient, which could be traced down to catheter placement.\[24, 30-31\]

The ND probe was evaluated in a clinical study with 106 patients. The zero-drift results of the study ranged from -13 mmHg (only one sensor) to 6 mmHg with a median of 0 mmHg and an interquartile range of ± 1mmHg for a
total of 78 patients. No correlation between monitoring time or ICP value and the zero-drift was registered. Complications for the patient were minimal (insignificant hemorrhage in 3 cases and one infection). Only one out of 106 sensors malfunctioned and needed to be replaced.\[32\]

Over the years, many different studies have been conducted to evaluate the CMS clinically. For this review, only studies after the year 2000 were taken into regard. Two clinical studies focused on quantifying the zero-drift properties of the CMS, one with 128 patients and the other with 88 patients. In both studies, the CMS was placed in the parenchyma. Whereas one evaluation revealed a mean zero-drift of 0.9 ± 0.2 mmHg (P = 0.9; r = 0.002) with no correlation between zero-drift and the duration of use, the other did record a correlation (Spearman’s correlation coefficient = 0.342; P = 0.001) with a mean absolute zero-drift of 2 mmHg.\[33\] Several evaluations investigated the MRI compatibility of the CMS. The sensor showed limited usability in combination with an MRI if transmit-and-receive coils were used since unsuitable coils led to substantial heating.\[34\] One study focused on analyzing the complications due to probe implantation based on data from 549 patients, which was collected in an 8 year period. The results revealed a small number of complications, including hematomas, insignificant bleedings, and infections. The overall conclusion of this long-term evaluation was that the risk of complications with CMS is reduced.\[35\]

The Pressio ICP monitoring system was compared to the CMS and an extraventricular drain (EVD) in an in-vivo study, which included 30 patients. For the comparison, one half of the patients were monitored with the Pressio ICP monitoring system and the other with the CMS (15/15). Parallel to the intraparenchymal monitoring, every patient was additionally monitored with an EVD. The resulting mean differences between the intraparenchymal and ventricular sensing were -0.6 mmHg (with limits of agreement from ~ -8 mmHg to ~ +7 mmHg)\[3\] for the Pressio device and +0.3 mmHg (with limits of agreement from ~ -7 mmHg – 7 mmHg)\[2\] for the CMS. \[36\]

The in-vivo evaluations showed that all three sensors are safe for clinical use. Different studies recorded divergent accuracy and zero-drift performances for each sensor, which makes it hard to draw conclusions about the in-vivo performances. In general, the results are acceptable for all sensors and show that the piezoresistive pressure

\[1\] Rounded values to zero decimal places

\[2\] Rounded values to zero decimal places
measurement is a reliable approach for intracranial applications.

2.1.2 Pneumatic Pressure Sensors

2.1.2.1 Sensing Principle

The pneumatic ICP measurement principle is based on a technique first introduced by Marey in 1881 to measure blood-pressure invasively. The measuring system designed by Marey contained an air-filled probe with a small compressible rubber bubble at the end, and an external pressure sensing device, similar to the ICP monitoring system showed in Figure 2.\textsuperscript{[37]} With increasing blood pressure, the rubber bubble gets compressed, leading to a pressure increase insight the inner air channel of the probe. Thus, the blood pressure could be read externally by measuring the pressure insight the probe’s air channel. The physical basis of this measurement system is given by the ideal gas law:

\[
P \cdot V = n \cdot R \cdot T,
\]

(Eq. 8)

where \(P\) is the pressure, \(V\) is the volume, \(n\) is the number of moles of a gas, \(R\) is the ideal gas constant, and \(T\) is the temperature.

This law states, for a constant mass of a gas at a stable temperature, the product of volume and pressure will also be constant. If consequently the amount of air insight a pneumatic probe is kept stable, the pressure insight the air channel will change with a varying volume of the flexible air pouch.\textsuperscript{[38]} The same effect is used by modern pneumatic sensors, which use a piezoresistive semiconductor element in the monitoring device to measure the resulting pressure insight the air system. Modern pneumatic sensors can recalibrate intracranially, as the maximal possible volume of the air pouch is always known.

2.1.2.2 Commercial Sensors

The only manufacturer of pneumatic ICP measuring systems is Spiegelberg GmbH & Co. KG (SB), developing different catheter configurations for ventricular, parenchymal, and epidural placement. All ICP probes from SB are based on the same pneumatic measuring principle. Additionally, there is a possibility to choose between a tunneling and non-tunneling version for the parenchymal and ventricular probe. The ventricular catheter is always equipped with a CSF drainage lumen.\textsuperscript{[39]} Table 5 shows a summary of the technical specifications of the SB ICP monitoring system. The SB ICP transducer's accuracy, as well as its 24 h and 10 days zero drift, were analyzed in a bench test evaluation. All parameters were tested at different pressure levels. The accuracy was evaluated in the range from 0
to 80 mmHg (5 mmHg steps). The 24 h and 10 days zero-drifts were examined at a pressure ranging from 0-50 mmHg (10 mmHg steps). The results showed an increasing inaccuracy of the SB sensors with pressure values higher than 60 mmHg and maximum deviations of over 6 mmHg. The authors pointed out that the largest drifts occurred in the first 3 days and became smaller in the following 7 days. The mean 24 h zero-drift for the SB catheter was 2.1 mmHg, while the mean zero-drift over 10 days was 7 mmHg. The results of this in-vitro study show a significant increase in inaccuracy only for pressure higher than 60 mmHg, which is nearly three times the physiologic threshold (Table 1) and therefore acceptable. As the current version of the SB catheter recalibrates intracranially, the recorded high zero-drift is of no meaning.

In the in-vivo evaluation, the SB ICP catheter was compared with a CMS and an intraventricular fluid measurement system. This in-vivo evaluation was not conducted in a clinical environment with human patients but with 5 anesthetized and paralyzed sheep. All three transducers were placed concurrently in the sheep. The SB catheter and CMS were placed parenchymally. For the accuracy evaluation, the pressure readings of the three transducers were compared, while the ICP value was manipulated from 0 - 50 mmHg. The results revealed an average bias of -0.74 mmHg between the SB catheter and the intraventricular measurement. The average bias between the SB catheter and the CMS was 0.01 mmHg, leading to the conclusion that the SB transducer is comparable to both standard applications in clinical use.

A clinical study of the SB sensor was conducted on 87 patients. The aim of the study was to analyze the incidence of complications relatable to the implantation of the SB transducer. Additionally, the accuracy of the SB measurement system was compared to a parallel intraventricular measurement in 5 cases. No case was reported in which complications occurred that could be traced down to the SB catheter placement. The comparison to intraventricular measurement revealed a measurement difference of less than ± 3 mmHg in 99,6 % of the readings.

The conducted in-vivo studies record a different system accuracy in comparison to intraventricular measurement. Both results are based only on 5 catheters, which is a low quantity to draw conclusions about the accuracy. Whereas an accuracy within ± 1mmHg would be acceptable, an error of ± 3 mmHg in the physiologic range is not tolerable for clinical applications, as stated by The American National Standards Institute/ Association for the Advancement of Medical Instrumentation.
2.1.3 Intensity Modulated Fiber-Optic Pressure Sensors

2.1.3.1 Measurement Principle

Intensity-modulated fiber-optic sensors (FOS) were first introduced in the 1960s for different applications. Their sensing principle is the measurement of light intensity, which variates with the measured parameter. The publications from Lekholm and Lindstrom in 1969 and 1970 became the basis for the first commercial fiber-optic ICP sensor, developed by Camino Laboratories Inc. and patented in 1983.\textsuperscript{[43]} Even though Camino Laboratories Inc. does not exist anymore, the Camino ICP sensor is still available through Natus Inc. and is the only FOS approved for clinical ICP monitoring.

In a light intensity-modulated pressure sensor, like the Camino sensor, light emitted from an LED is guided through an optical fiber (illuminating fiber) and reflected at a flat mirror, which is placed on a pressure-sensitive membrane. The reflected light is captured with a second optical fiber (sensing fiber), placed parallelly to the illuminating fiber, and guided to a phototransistor. As the distance between the optical fiber and the mirror changes with the applied pressure on the membrane, the amount of reflected light into the sensing fiber and thus the sensed light intensity variates with pressure.\textsuperscript{[44]} Figure 3 shows the basic design and principle of the sensor. The used physical principles in the sensor tips are explained in detail below. The maximum angle of an out-coming beam from an optical fiber is given by

\[ \theta_0 = \arcsin(NA) , \]  

(Eq. 9)

where NA is the numerical aperture.\textsuperscript{[43c]} NA of an optical fiber is defined by

\[ NA = \sqrt{n_1^2 + n_2^2} , \]  

(Eq. 10)

with \( n_1 \) and \( n_2 \) as the refractive indices of the fiber core and coating.\textsuperscript{[43c]} Consequently, the radiated light from an optical fiber will follow a cone structure with an angle of \( 2\theta_0 \). This leads to the effect that the area illuminated with full intensity will get narrower with an increasing distance from the illuminating fiber, while a wider area will get
illuminated in general with the intensity decreasing from the center to the edge (Fig. 3 B). The reflection coefficient $Q$ determines the relative amount of initial illumination, which is captured by the output fiber and is defined by

$$Q = \frac{\int_{A_{12}} \frac{E_{(1)}^{(1)}}{E_0} \frac{E_{(2)}^{(2)}}{E_0} dA_{12}}{\int_{A} \frac{E_0}{E_0} dA},$$

(Eq. 11)

where $A$ is the area illuminated by one fiber, $A_{12}$ is the distance-depending area of overlapping illumination from the two fibers, $E_0$ is the illumination field with the full intensity from inside the fiber, and $E_0$ is the whole illumination field in front of the optical fiber with index (1) and (2) representing the illuminating and sensing fiber.\textsuperscript{[43c]} For the two operation modes, equation 12 is simplified to

$$Q \approx 0.14 \cdot (d/a)^{3/2} \quad \text{for} \quad (d \ll a),$$

(Eq. 12)

and

$$Q = 0.57 \cdot (d/a)^{-2} \quad \text{for} \quad (d \gg a),$$

(Eq. 13)

where $d$ is the distance between the optical fiber and the mirror and $a$ is the diameter of the optical fiber.\textsuperscript{[43c]}

2.1.3.2 Commercial Fiber-Optic Pressure Sensors

Camino ICP sensor is currently sold by Natus Medical Inc. in several catheter alignments. Three different catheter versions are available for parenchymal placement, of which one includes a temperature sensor and another gives a possibility for use in combination with the oxygen measurement system Licox, sold by Integra LifeSciences Corp. The Camino ICP sensor is also available for ventricular and subdural placement. The catheter for ventricular placement can be equipped with an additional temperature sensor, whereas the catheter for subdural placement is only available for ICP measurement.\textsuperscript{[45]} The technical specifications of the Camino ICP sensor are given in Table 6.

The Camino ICP sensor was tested in-vitro after a previous clinical analysis of its zero-drift. In the in-vitro experiments, the explanted sensors were placed in a syringe, which was sealed with epoxy glue and put in a water
bath with controlled temperature. The tests involved accuracy evaluations at a pressure range from 0 - 100 mmHg and a varying temperature from 22 °C to 40 °C. Additionally, the frequency response characteristics of the sensor were tested from 0 - 30 Hz. The results revealed an increase in absolute error with increasing pressure and a temperature drift. The difference in readings at 30° C and 40° C was up 0.5 mmHg in the clinically relevant range. The frequency response test showed a flat frequency response at 25 Hz and a "half-power" point at 43 Hz.\textsuperscript{46}

Another bench test evaluation proved the Camino ICP to react correctly to a pulsating pressure in the range from 5 - 50 mmHg by comparing its reading to a different ICP transducer.\textsuperscript{47}

Only the evaluations published since 2000 regarding the Camino ICP sensor are reviewed. The zero-drift properties of the Camino ICP sensor were investigated in several clinical studies. All evaluations recorded zero-drift issues with the Camino ICP sensor. In one study, over 39% of the investigated sensors had a zero-drift after explantation exceeding the technical specifications, and in another study, over 50% of the sensors had a zero-drift over 3 mmHg, with no correlation between implantation time nor a trend towards positive or negative zero-drift.\textsuperscript{48} The third evaluation of 624 sensors recorded a mean zero-drift of $7.3 \pm 5.1$ mmHg after explantation.\textsuperscript{46} Zero-drift seems to be a major problem of the Camino ICP sensor. A reason for the zero-drift issue could be a change of the mirror position with time due to pressure and other physical influences, as only the reflection path and the refractive index in the sensor tip influence the resulting light intensity and thus the pressure signal.

An investigation of the complications due to the implantation of the Camino ICP transducer revealed only a minimal number of infections, which is comparable to other ICP transducers.\textsuperscript{49} Mechanical malfunctions occurred in less than 5% of the sensors in a study with 1000 Camino ICP transducers and were mainly caused by a breakage of the optical fiber or dislocations of the fixations screw or probe.\textsuperscript{50}

2.1.4 Comparison of Clinical Intracranial Pressure Sensors

Strain-gauge ICP sensors show to be the most reliable out of current transducers used in clinical applications. They measure the pressure with high accuracy and provide acceptable zero-drift properties. The Spiegelberg ICP transducers are a cost-effective alternative to piezoresistive sensors with acceptable lower accuracy. The widely established Camino ICP sensor show a significant zero-drift over time in clinical studies, which is a disadvantage in comparison to other sensors.\textsuperscript{46, 48} Even though all sensors are tested to be MRI conditional, precautions are necessary before patients can undergo MRI screenings to reassure that the sensors do not heat up.\textsuperscript{34c} Several
evaluations reported the formation of artifacts on the screenings due to implanted sensors.\textsuperscript{34c, 51} The summarised comparison of the three clinically used ICP is listed in Table 7.

2.2 Intracranial Pressure Sensors in Development

Developments in MRI lead to its expansion in routine clinical use and thus to a requirement in MRI-resistant monitoring devices. Especially its advantage in soft tissue imaging and detection of neuronal damage makes it an important imaging tool in neurocritical care.\textsuperscript{52} Fiber optic pressure sensors (FOPS) have the advantage of being MRI-compatible. Several different FOPS are commercially available but not clinically used yet. FOPS provide the required accuracy to be used in medical applications. Table 8 gives an overview of the technical specifications of the currently available FOPS, which show potentials to be used clinically and found in online research in the future. As all of those sensors are based on Fabry-Perot interferometry, this sensing principle is explained in detail.

2.2.1 Sensing Principle

Fabry-Pérot interferometer (FPI) was invented in 1899 by the French physicists Charles Fabry and Alfred Pérot and provides the theoretical basis for many modern FOS. Sensors based on FPI use the effect of multi-beam interference to measure a distance or the refractive index $\eta$. In general, the interference phenomena describes the resulting irradiance from the superposition of two or more coherent light-waves (Figure 4A).\textsuperscript{53} The electrical field $E$ of a light-wave is an extremely fast oscillating quantity, which makes it very hard to measure. In contrast, the irradiance $I$ is easily measured, as it depends on the averaged electrical field over time. For a light-wave with the electrical field $E$, the irradiance is given by

$$I = \frac{1}{2} \varepsilon \cdot c \cdot |E|^2,$$

(Eq. 14)

where $\varepsilon$ is the electric permittivity constant and $c$ the speed of light.\textsuperscript{54} When two parallel and coherent light-waves with the electrical fields $E_1$ and $E_2$ are superposed, the resulting electrical field $E$ is simply given by

$$E = E_1 + E_2$$

(Eq. 15)

and thus the resulting irradiance $I$ is given by

$$I = I_1 + I_2 + 2 (I_1 I_2)^{\frac{1}{2}} \cos(\delta),$$

(Eq. 16)

where $\delta = k (r_2 - r_1) + (\phi_1 - \phi_2)$ is the phase difference defined by the optical path difference of the light-
waves $k(r_2 - r_1)$ and the phase difference of the electrical fields $(\phi_1 - \phi_2)$.[53] As the two light-waves are coherent, their phase difference $\Phi = (\phi_1 - \phi_2)$ is constant, and the resulting interference will only change with a varying optical path difference. With the assumption that $\Phi = 0$ and the irradiances $I_1$ and $I_2$ are equal, the maximum interference intensity $I_{\text{max}}$, called constructive interference, is calculated to

$$I_{\text{max}} = I_1 + I_2 + 2(I_1 I_2) = 4I_1 \quad \text{for} \quad k(r_2 - r_1) = 2m\pi,$$

(Eq. 17)

where $m$ is an integer. Under similar assumptions, the destructive interference $I_{\text{min}}$ (minimal interference) is calculated to

$$I_{\text{min}} = I_1 + I_2 - 2(I_1 I_2) = 0 \quad \text{for} \quad k(r_2 - r_1) = (2m + 1)\pi,[53]$$

(Eq. 18)

The effects of constructive and destructive interference are the fundamental principles that are used in Fabry-Pérot interferometry. In the FPI, two perfectly parallel mirrors form a cavity, in which EM waves are reflected infinitely often. The reflected waves will constructively and destructively interfere with each other, leading to a set of allowed stationary EM waves within the cavity.[53] The electrical field needs to be zero at the reflecting mirrors so that only an integer number $m$ of half ways can be fitted into the cavity with the length $L$: [55]

$$m\left(\frac{\lambda}{2}\right) = L ; \; m = 1, 2, 3, ...,$$

(Eq. 18)

where $\lambda$ is a wavelength. In a FOS, the Fabry-Pérot cavity is realized with two semi-reflecting mirrors at the tip of the fiber, which reflect the incoming light with a certain intensity (Figure 4B). Due to the described interference effects, the reflectance and thus the resonance of a certain wavelength is dependent on the optical path and can be expressed with the reflectance function:

$$R(\lambda) = \frac{R_1 + R_2 - 2\sqrt{R_1R_2}\cos(\delta)}{1 + R_1 + R_2 - 2\sqrt{R_1R_2}\cos(\delta)},$$

(Eq. 19)

where $\delta = \frac{2\pi}{\lambda} \cdot 2\eta L$ is the phase difference with the refractive index $\eta$.[56] Resonances will occur whenever the condition is met, which is the case for $\lambda_k = \frac{2L}{k}$. [56] The free spectral range (FSR) describes the wavelength separation between two adjacent resonated wavelengths and is given by[56]

$$\delta = 2\pi k, \; \text{with} \; k \in \mathbb{N}$$

(Eq. 20)

$$\Delta\lambda = \lambda_k - \lambda_{k+1} = \frac{\lambda_k \lambda_{k+1}}{2L},$$

(Eq. 21)

As the reflectance pattern is in general dependent on $\delta$ (Eq. 20), changes of parameters influencing the phase
difference will lead to a different $\lambda_k$. The total phase difference can be expressed by

$$\delta_{\text{total}} = \delta_{\text{initial}} + \Delta\delta_L + \Delta\delta_f + \Delta\delta_T,$$

(Eq. 22)

where $\delta_{\text{initial}}$ is the initial phase shift and $\Delta\delta_L$, $\Delta\delta_f$, and $\Delta\delta_T$ represent the phase difference changes due to a change in cavity length, frequency, and temperature, respectively.\textsuperscript{[57]} $\delta_{\text{initial}}$ is given by

$$\delta_{\text{initial}} = \frac{4\pi\eta L}{\lambda} = \frac{4\pi\nu L}{c}, \text{ with } \lambda = \frac{c}{\nu},$$

(Eq. 23)

where $\nu$ is the optical frequency and $c$ is the speed of light, and $\Delta\delta_L$, $\Delta\delta_f$, and $\Delta\delta_T$ are given by

$$\Delta\delta_L = \frac{4\pi}{\lambda} \left( \nu \Delta L + L \Delta\nu \right),$$

(Eq. 24)

$$\Delta\delta_f = \frac{4\pi}{c} \left( \eta + \nu \frac{\Delta\eta}{\Delta\nu} \right),$$

(Eq. 25)

$$\Delta\delta_T = \frac{4\pi}{\lambda} \left( \nu \frac{\Delta L}{\Delta T} + \nu \frac{\Delta L}{\Delta T} \right),$$

(Eq. 26)

where $\Delta\delta_L$, $\Delta\delta_f$, and $\Delta\delta_T$ are the differences in length, frequency, and temperature, respectively.\textsuperscript{[57]} In FPI based pressure sensors, the varying parameter $\Delta L$ changes due to the flexible membrane at the sensor tip, which will displace when pressure is applied. A schematic of the sensor tip with the flexible membrane is shown in Figure 4C.

The dependency of $\Delta L$ in the center of the sensor to the applied pressure is expressed by

$$y = \frac{3(1 - \nu^2)P}{16Eh^3} r^4,$$

(Eq. 27)

where $y$ is the central displacement of the membrane, $P$ is the pressure, $h$ is the membrane thickness, $r$ is the membrane radius, $E$ is Young's modulus, and $\nu$ the Poisson's ratio. The introduced commercialized sensors use different analysis methods to find out the cavity length.\textsuperscript{[56]}

2.2.2 Commercial FOPS

Fiso Technologies uses a Fizeau wedge, which spreads a spectrum of resonance distances on a charged coupled device (CCD), with the effect that the filtered light from the FPI resonates only at one point, where the Fizeau
wedge has the same cavity distance as the Fabry-Perot cavity. Therefore, each point on the CCD corresponds to a cavity length and thus to a pressure. The basic design of the Fizeau wedge is shown in Figure 4D. The same principle is also used by Opsens Medical, with the only difference that the light coming from the FPI is first polarized with a birefringent filter.\textsuperscript{58}

RJC Enterprises uses an LED with a bandwidth of about 60 nm to illuminate the FPI. The Fabry-Perot resonator is designed to exhibit only a minimal change with pressure so that the reflection change occurs within one reflection cycle (Figure 4E). This design allows measuring the cavity length by simply measuring the reflected intensity from the FPI, e.g., with a photodiode. \textsuperscript{59}

3. Intracranial Temperature Sensors

3.1 Clinically Approved Sensors Intracranial Temperature Sensors

3.1.1 Clinically Approved Intracranial Temperature Sensors

Clinically approved temperature sensors for intracranial applications are divided into two groups based on their sensing principle, thermistors, and thermocouples. Thermistors sense the temperature with a metal or semiconductor element, which variates its electrical resistivity with a temperature change. Thermocouples consist of two materials with different thermal properties at the sensing tip and measure the resulting voltage from a temperature-dependent electron flow between those materials.

3.1.2 Thermistor Sensors

3.1.2.1 Thermistor Sensing Principle

Thermistors (thermal resistors) are based on the electrical resistance properties of metals and semiconductors, which are temperature-dependent. The electrical resistance $R$ of a material is defined by its electrical conductivity given by

$$\sigma_e = e \cdot n_e \cdot \mu_e,$$

(Eq. 28)

where $e$ is the elementary charge, $n_e$ is the electron density, and $\mu_e$ is the electron mobility.\textsuperscript{60} $R$ is then given by
where $\rho$ is the specific resistivity, $l$ is the length, and $A$ is the cross-sectional area. \[^{61}\]

Thermal resistors are divided into three types: metal-resistors, semiconductor resistors with a negative thermal coefficient (NTC), and semiconductor resistors with a positive thermal coefficient (PTC). The difference between those three thermistor types lies in the physical principle, which leads to a thermal-dependent resistivity of the sensor.\[^{62}\] When comparing the different thermistors, an important parameter is the temperature coefficient $\alpha$, which defines the electrical resistance variation due to a temperature change and is given by the relation

\[
\frac{dR}{R_0} = \alpha R_0
\]  

(Eq. 30)

where $T$ is the temperature.\[^{63}\]

In metal thermistors, plasmon oscillations increase with a rising temperature, which leads to an electron mobility reduction of the interacting electrons with the relation\[^{63}\]

\[
\mu_e \sim T^{-1}.
\]  

(Eq. 31)

The electrical resistance of a metal thermistor increases with rising temperature. The most common metal thermistor in technical applications is the Pt100 resistance sensor. The platinum thermistor has a resistance of 100 $\Omega$ at a temperature of 0 °C, and its thermal dependence is given by a linear characteristic in the range from -200 °C ($R \sim 25 \, \Omega$) to +800 °C ($R \sim 360 \, \Omega$) with $\alpha \sim 0.0038 \, K^{-1}$. The Pt100 is often chosen as a reference sensor.

In the NTC semiconductor, the electron density $n_e$ is the temperature-dependent coefficient. With an increasing temperature, $n_e$ increases exponentially, which leads to the temperature-dependent electrical resistance defined by:

\[
R(T) = A \cdot \exp \left( \frac{B}{T} \right),
\]  

(Eq. 32)

where $A$ is the resistivity of the semiconductor at an infinite temperature and $B$ is a material constant in Kelvin.\[^{64}\]
$B$ can be experimentally determined by resistance measurements at two different temperatures and the following calculation

$$B = \frac{\ln \frac{R_2}{R_1}}{\frac{1}{T_1} - \frac{1}{T_2}}, \quad [\text{K}]$$

(Eq. 33)

where $R_1$ and $R_2$ are the resistivities at temperatures $T_1$ and $T_2$, respectively. Therefore, the sensitivity coefficient of an NTC thermistor results in [64]

$$\alpha_{NTC} = -\frac{B}{T^2}, \quad [\text{K}^{-1}]$$

(Eq. 34)

The PTC thermistor combines semiconducting properties, like in the NTC semiconductor, with ferroelectric properties. Underneath the Curie temperature $T_C$, it acts similar to the NTC semiconductor. However, if the temperature increases above $T_C$, its ordered structure breaks down, leading to an exponential rise of the electrical resistance with a further rising temperature. The sensitivity coefficient of a PTC thermistor above $T_C$ is given by

$$\alpha_{PTC} = +\frac{1}{R(T)} \cdot \frac{dR(T)}{dT}, \quad [\text{K}^{-1}]$$

(Eq. 35)

In biomedical applications, usually, the NTC thermistor with an approximate sensitivity coefficient of ~ -0.04 [K$^{-1}$] is the thermistor of choice. [66] NTC resistors are fabricated out of oxidized metals and are available at a lower price in comparison to PTC semiconductors or the Pt100 thermistor. Medical applications require only a limited sensing range, not exceeding 100 °C. The accuracy of 0.1 °C is sufficient in most cases. The advantages of a wide temperature sensing range, operation at high temperatures, and high sensitivity of PTC semiconductors and metal thermistors are not required. Figure 5 illustrates an example alignment of a medical catheter with a thermistor placed at its tip. [67]

3.1.2.2 Thermistor-Based Intracranial Temperature Sensors

Intracranial temperature sensors are not sold as single catheters since their clinical benefits are not sufficient enough
in comparison with the implantation risk. However, in combination with a \( PO_2 \) or an ICP sensor, they provide very valuable information about the patient’s condition. Thermistor sensors are used in catheters from Raumedic AG (Neurovent and Neurodur), Sophysa S.A. (Pressio), Hemedex Inc. (Bowman Perfusion Monitor), and Natus Inc. (Camino). Table 9 gives an overview of the technical specification of the different \( T_{bt} \) thermistor sensors.

Only one in-vitro study was found, which investigated the thermistor performance of intracranial sensors. In this evaluation, the NeuroVent P-Temp (Raumedic AG) (NTT) and the Licox temperature sensor (Integra LifeSciences) (LX) were tested. Only the results of the NTT sensor are of interest, as the LX sensor measures the temperature with a thermocouple. The focus of the study was to evaluate the accuracy and stability of the sensors by testing them in a water bath environment with a controlled temperature. The NTT proved to be accurate in the tested range from 30 - 45 °C with deviations of less than 0.25 °C. The 120 h zero-drift test at 37°C revealed that all sensors have high stability in this time period, with the NTT having a standard deviation of less than ±0.08 °C. The results prove the NTT sensor is a reliable tool for temperature measurement. \[68\]

3.1.3 Thermocouple Sensors

3.1.3.1 Thermocouple Sensing Principle

In 1821 Thomas Johann Seebeck described the thermoelectric effect by showing that a temperature difference between two soldering joints leads to a voltage difference \( U \). \[69\] Differences in the temperature and material-dependent electron working function of the two soldering joints leads to an electron flow. The resulting voltage is calculated from the electron density ratio of two metals, which is dependent on the temperatures and electrical potentials of the two soldered materials. The density ratio is given by

\[
\frac{n_A}{n_B} = \exp\left(\frac{e}{kT_1}(U_A - U_B)\right), \quad \text{with} \quad U_A - U_B = U_1, \tag{Eq. 36}
\]

\[
\frac{n_B}{n_A} = \exp\left(\frac{e}{kT_2}(U_B - U_A)\right), \quad \text{with} \quad U_B - U_A = U_2, \tag{Eq. 37}
\]

where \( n_A \) and \( n_B \) are the electron densities, \( e \) is the elementary charge, \( k \) is the Boltzmann constant, \( T \) is the temperature, and \( U_A \) and \( U_B \) are the voltages at the soldering joints. \[70\]
By inversion of the electron density ratio and the summation of the resulting voltages at each soldering joint, the resulting voltage difference is given by \[^{[71]}\]

\[
U = U_1 + U_2 = \frac{kT_1}{e} \ln \frac{n_A}{n_B} - \frac{kT_2}{e} \ln \frac{n_A}{n_B} = \frac{k}{e} \ln \frac{n_B}{n_A} (T_1 - T_2) 
\]

(Eq. 38)

where \(S_{AB}\) is the Seebeck coefficient defining the sensitivity of the thermocouple in \(\frac{J}{K}\).

To measure a temperature \(T_1\) using the thermoelectric effect, the temperature \(T_2\) must be known. Figure 6 illustrates the setup of a thermocouple with a reference temperature. Depending on the sensing materials of the thermocouple, it has different measurement characteristics. Majorly the thermal sensing range and sensitivity are influenced.\[^{[72]}\]

Table 10 summarizes the normed types of thermocouples that can be used in medical applications.

3.1.3.2 Thermocouple based \(T_{bt}\) sensors

The type K thermocouple is used in the Licox (LX) temperature sensor sold by Integra LifeSciences Inc. Apart from temperature, the LX sensor also measures the oxygen tension in brain tissue. In this chapter, only the temperature measurement characteristics of the sensor are discussed, as the review of oxygen sensors is covered in the next chapter. The LX sensor is specified to measure the temperature in the range from 30 to 40 °C with a resolution of 0.2 °C and long-term accuracy of ± 1 °C.

Two bench test studies could be found, which evaluated the accuracy of the LX temperature sensor. In results of one study revealed an overestimation trend of the LX temperature sensor, whereas the other evaluation showed the sensor to have a tendency to underestimate the temperature in the tested range from 33 °C to 37 °C with a mean error of \(-0.7\) °C.\[^{[68, 73]}\] The different results may result from different versions of the sensor, as the first was conducted in 2004 and the second one in 2007.

In one in-vivo review, the \(T_{bt}\) measurement differences between LX and Hemedex sensors were investigated. The aim of the study was to evaluate whether the differences in temperature readings can be explained by the accuracies and depth of placement only, or the differences occur because of other reasons. For the evaluation, LX and Hemedex

\[^{3}\] rounded value to 1 decimal place
sensors were placed simultaneously in six patients. As the LX sensor was placed about 3.5 mm deeper than the Hemedex probe, a calculated $T_{bt}$ gradient model was taken into regard. The results reveal that 95% of the readings lay within the accepted $\Delta T_{bt}$ interval when depth and specified sensor accuracies were respected. \textsuperscript{[74]}

3.1.4 Comparison Thermistor vs. Thermocouple

The comparison of the thermistor and thermocouple sensors used for intracranial applications revealed that the thermistor sensor is slightly more accurate, but the measurement performance is, in general, very similar. The results of a comparative in-vitro study from Alessandri et al. are summarized in Table 11.

3.2 Fiber-Optic Temperature Sensors in Intracranial Monitoring

3.2.1 Commercialized Fiber-Optic Temperature Sensors

Similar to FOPS, fiber-optic temperature sensors (FOTS) are fabricated completely out of materials, which will not experience any electromagnetic interference (EMI). EMI resistance, small size, biocompatibility, sufficient accuracy, and acceptable costs\textsuperscript{4} make FOTS very interesting for medical applications.\textsuperscript{[75]} Several different commercialized FOS exist, which allow temperature measurement in intracranial catheters. Table 12 gives an overview of the available sensors and fiber-optic technologies for temperature measurement for medical applications.\textsuperscript{[76]}

3.2.2 Fiber-Optic Temperature Measurement with Fluorescence Decay

FOTS based on fluorescence decay measure the temperature-dependent luminescent decay of a fluorescent dye. Various materials can be used for this kind of temperature measurement.\textsuperscript{[77]} In commercialized sensors, typically, a phosphorus-based compound is used.\textsuperscript{[75, 78]} For the temperature measurement, the luminescent material is placed at the tip of an optical fiber and is excited with EM radiation, usually in the ultraviolet spectrum range.\textsuperscript{[75, 79]} Depending on the luminescent material, it will emit EM radiation with a certain wavelength shift after the excitation, called Stokes shift.\textsuperscript{[80]} This emission process due to the relaxation of excited electrons is called fluorescence. In some materials, the fluorescence life-time $\tau_0$, in which EM radiation is emitted after an excitation, dependents on their temperature.\textsuperscript{[81]} With increasing temperature, non-radiative relaxation processes increase in those materials and lead to a decrease in $\tau_0$. For example, manganese activated magnesium fluorogermanate

\textsuperscript{4} depending on the OFS technology
phosphor will exhibit a nearly linear change in $\tau_0$ of about 4 ms from $\tau_0 \approx 5$ ms at $\sim -200$ °C to $\tau_0 \approx 1$ ms at $\sim 400$ °C.\textsuperscript{[82]} The excitation spectrum of phosphorus-based compounds is in the ultraviolet spectrum, whereas its emission spectrum reaches from 620 nm to 680 nm with a peak at about 665 nm.\textsuperscript{[81a]} Other phosphorus-based materials show similar temperature-dependent properties in scientific experiments.\textsuperscript{[81b, 83]} The measurement of $\tau_0$ is accomplished by a pulsating excitation signal (photodiode with an optical band-pass filter or laser) and the measurement of the intensity of luminescence in the emission spectrum of the dye (photodiode with an optical filter). $\tau_0$ is then calculated as the time difference between the end of one excitation pulse and the decrease to a set threshold of the emitted luminescence intensity from the fluorescence dye.\textsuperscript{[82]} A qualitative example of the measurement principle is shown in Figure 7A.

3.2.3 Fiber-Optic Temperature Measurement with Fabry-Pérot Interferometry

The Fabry-Pérot measurement of the optical path difference is also used for temperature measurement. In general, FOTS based on FPI measure either the temperature-dependent length difference $\Delta L$ of the cavity (capillary type) or a change in the refractive index $\Delta \eta$ (refractive index type) due to temperature (Eq. 26).\textsuperscript{[84]} Capillary type FOTS comprise an optical glass fiber with a high coefficient of thermal expansion, to which one to the refractive mirrors is fixated. An increase in temperature leads to an expansion of the cable and thus to a decrease in the cavity length $L$, which leads to a measurable optical path difference (Eq. 21 and 24).\textsuperscript{[85]} Refractive type FOTS sense an optical path difference due to a variating refracting index in the Fabry-Pérot cavity. In this kind of sensor, the Fabry-Pérot cavity is made of a translucent crystal, which exhibits a change in its refracting index due to variating temperature.\textsuperscript{[85]}

3.2.4 Fiber-Optic Temperature Measurement with Temperature Sensitive Long-Pass Filter Glass

Long pass filter glass (LPFG) transmits EM waves, which are larger than a threshold wavelength. In some glasses, like Hoya R68, this threshold wavelength variates with temperature. Wolthuis et al. introduced an OFTS in 1993, which uses an LPFG to variate the light intensity reflected from the sensor tip. In this measurement system, the glass is placed at the sensor tip and illuminated by a 674 nm LED. A shortwave reflecting dichroic filter reflects the transmitted light at the end of the glass back into the optical fiber. The intensity of the reflected light is measured with a photodiode. As the LPFG transmittance of the 674 nm long light-wave decreases with a rising temperature, the resulting light intensity is anti-proportional to temperature. Wolthuis et al. achieved an accuracy of 0.5 °C and
a sensing range from -100-250 °C with this measurement technique. An example of this sensor and the temperature-dependent transmittance spectrum of Hoyra R68 filter glass are shown in Figure 7B. This temperature sensing technology is used in commercialized sensors by RJC Enterprises.

3.2.5 Fiber-Optic Temperature Measurement based on temperature-dependent absorption by GaAs

Temperature measurement with the use of temperature-dependent EM radiance absorption of GaAs is similar to the temperature sensing technique with LPFG described above. GaAs absorbs photons if their energy is higher than its band-gap energy $E_g(GaAs)$. Therefore, EM waves are absorbed when their wavelength is smaller (energy higher) than

$$\lambda' = \frac{hc}{E_g(GaAs)},$$  \hfill (Eq. 39)

where $h$ is Planck’s constant and $c$ is the speed of light. This dependency shows a long pass filter characteristic of the GaAs. As the band-gap energy of GaAs is temperature-dependent, it is possible to get the temperature by measuring the transmitted or reflected wavelengths of the semiconductor. In general, the temperature dependence of the band-gap energy is given by

$$E_g = E_g(0) - \frac{aT^2}{T + \beta},$$  \hfill (Eq. 40)

where $E_g(0)$ is the energy gap at 0 °K, $\beta$ is the approximate 0 °K Debye temperature, and $a$ is an empirical constant. For GaAs, the thermal dependence of $E_g$ in the range from 0 – 973 °K was calculated to

$$E_g(GaAs) = 1.522 - \frac{5.8 \times 10^{-4}T^2}{T+300} \text{ eV}.$$  \hfill (Eq. 41)

Equations 41 and 42 prove, with an increasing temperature, GaAs will absorb longer wavelengths. Hence, the
temperature is measured by determining the shortest transmitted or reflected wavelength. In FOTS GaAs is illuminated at the sensor tip with broadband light, and the reflected light spectrum is analyzed. The reflected light is either guided through a separate fiber or a single fiber. The spectral analysis is achieved by specific spectrometers for the corresponding wavelengths.\[87\]

3.2.6 Fiber-optic Sensors in Development

Traditional methods to sense temperature using fiber-optic fibers are to monitor Bragg peak shifts to reflect the result of temperature change. However, the efficiency needs to be improved by increasing the length of the optical fiber or incorporating complicated fabrication methods. Another method to test temperature is to measure resonant wavelength. Resonance effects, e.g. whispering gallery modes, have also been applied for temperature measurements. However, these methods require complicated and highly accurate experimental result analysis. Recently, a portable rare-earth-doped glass optical fiber has been developed for in vivo temperature measurement of brain temperature based on rare-earth thermometry.\[89\] Although this device does not require complicated alignment, it is still in the laboratory stage. It is expected that the adaption of the device can completely meet the requirement for clinical use.

Most recently, bioresorable Fabry-Pérot interferometer pressure optical fiber sensors have been developed based on pressure-responsive defections of silicon nanomembranes that could induce the resonant peak shifts in response to intracranial temperature.\[90\] Due to their immobilized sensor-fiber interface, the Fabry-Pérot interferometer pressure fiber sensors provide the in vivo measurements with high accuracy and high stability compared to the traditional optical fibers sensors that may be easily affected by exterior interferences, such as loss of incident light intensity. However, the intracranial implanted optical fibers for long-term monitoring of temperatures remain a challenge in clinical use, because the open space of interface of the sensor and biological tissue can cause immune-mediated inflammatory responses.

4 Intracranial Oxygen Sensors

4.1 Commercialized Intracranial Oxygen Sensors

4.1.1 Electrochemical Oxygen Sensors

Oxygen Sensors, which are clinically used to measure $P_{bt} O_2$, are divided into two measurement principles:
Electrochemical sensing, based on the Clark electrode, and optical sensing, based on fluorescence quenching. The basic design of the electrochemical $PO_2$ sensor for medical applications was first introduced by Leland Clark in 1956.\textsuperscript{[91]} The Clark electrode is based on the reduction of oxygen at a charged cathode, placed in an electrolyte, and covered by an oxygen-permeable membrane. The resulting electrical current depends on the number of oxygen molecules that get reduced and allows to calculate the oxygen tension. Figure 8 shows an example of the Clark electrode.\textsuperscript{[92]} The essential effects that lead to the measurement current are the redox reactions at the electrodes.

The reduction reaction at the cathode is given by:

$$O_2 + 2e^- + H_2O \rightarrow H_2O_2 + 2OH^-, \quad (\text{Eq. 42})$$

$$H_2O_2 + 2e^- \rightarrow 2OH^-, \quad (\text{Eq. 43})$$

where $e$ are the released electrons from the cathode to the electrolyte. The oxidation reaction at the anode is given by

$$4Ag \rightarrow 4Ag^+ + 4e^-, \quad (\text{Eq. 44})$$

$$4Ag^+ + 4Cl^- \rightarrow 4AgCl, \quad (\text{Eq. 45})$$

where $e$ are the removed electrons from the electrolyte to the anode. The combination of the reactions given above leads to an electron current from the cathode through the electrolyte to the anode, which depends on the number of oxygen molecules available to catalyze the first reaction (Eq. 44). The resulting current is expressed by

$$i = \frac{n \cdot F \cdot A \cdot D \cdot \alpha \cdot \{PO_2\}}{x}, \quad (\text{Eq. 46})$$
where \( n \) is the net number of electrons involved in the reaction, \( F \) is the Faraday constant, \( A \) is the surface area of the cathode, \( D \) the diffusion coefficient, \( \alpha \) the solubility coefficient, and \( x \) the thickness of the membrane. The factors \( \alpha \) and \( D \) are both temperature-dependent. Consequently, the temperature of the system must be known or controlled so that \( \frac{nF\cdot A\cdot D\cdot \alpha}{x} \) is considered as constant. This will lead to a current \( i \), which is directly proportional to \( PO_2 \).\(^{[93]}\)

The Licox sensor, sold by Integra LifeSciences Corp., is the only sensor measuring \( P_{bt}O_2 \) with an electrochemical approach. It was originally developed by Gesellschaft für medizinische Sondentechnik GmbH, which has patented the technology in 1996.\(^{[94]}\) Additionally to the oxygen sensor, the LX probe also measures temperature with a thermocouple providing additional information about the patient. In this chapter, only the electrochemical sensor of the LX probe is analysed, as the thermocouple was already covered in chapter 3. The technical specifications for the \( PO_2 \) measurement of the LX sensor are given in Table 13.

Several scientific papers evaluated the LX sensor in vitro. Most of those studies tested the sensor at different temperatures and in varying oxygen environments, reporting the change in accuracy, response time, and zero-drift over time. The experiments of these studies are summarized below.

In one evaluation, 12 Licox sensors were compared to 12 Neurotrend sensors (Diametrics Medical Ltd., Buckinghamshire, UK)\(^5\). All experiments were conducted in a liquid-filled tonometer with a stable temperature of \( \sim 37 \, ^\circ C \). Experiments involved an accuracy test in the range from 1 % to 8 % \( O_2 \), evaluation of the 120 h zero-drift, and the quantification of the 90 % response time when switching from low to high \( O_2 \) concentration and the other vice versa. The results reveal a mean accuracy ranging from -4.5 % at 8 % \( O_2 \) to -9 % at 1 %, no significant zero-drift, and mean response times of 129 s and 174 s for low to high and high to low \( O_2 \) concentration changes.\(^{[95]}\)

6 LX sensors were analyzed in a two-chamber apparatus, where gas was bubbled through distilled water in the first chamber and passed through a sparger into the second chamber with the sensors. Accuracy and response times were evaluated in oxygen concentrations ranging from 2.5 % to 21 % and a varying temperature in the range from 33 \( ^\circ C \) to 39 \( ^\circ C \). The results reveal a mean measurement error of \( \sim -3.8 \, % \), with a trend to increase at higher

\(^5\)Neurotrend was a multiparameter sensor for the measurement of pH, \( PCO_2 \), \( PO_2 \), and temperature. The chemical concentration measurement is based on fiber-optic technology. Neurotrend is currently not sold anymore.
temperatures. Response times show a tendency to increase with higher $O_2$ concentrations.\[73\]

A third study compared 5 LX sensors with 5 Neurovent-PTO (NTO) sensors from Raumedic AG in a container filled with buffer solution. The results of the NTO sensor will be discussed in the next chapter, as it is based on the fluorescence quenching principle. The probes were first analyzed at a stable temperature of ~37 °C and $O_2$ concentrations ranging from 0.687 % to 5.6 %, and then at a varying temperature from 37° C to 40° C in stable 1.42 % and 2.81 % $O_2$ concentrations. The 90 % response time was recorded for a decreasing and rising $O_2$ concentration (1.42 % to 5.6 % $O_2$). Finally, a 10 days zero-drift experiment was conducted in a solution with 1.42 % $O_2$. The results reveal a mean error of about -0.5 ± 0.3 mmHg (averaged over all tested $O_2$ concentrations), a broader distribution of measurement errors with an increasing temperature, a minimal zero-drift over time, and mean response times of 78 s and 215 s for a rising and decreasing $O_2$ tension, respectively.\[96\]

The in-vitro evaluations of the Licox sensor show that the sensor provides a reliable method to measure the $P_{bt}O_2$ in the range from 0-150 mmHg with the specified accuracy from the manufacturer. The evaluations from Steawart et al. and Hoelper et al. report that the sensor in general under-evaluates the $PO_2$ value, whereas the evaluation from Purins et al. shows a general over-evaluation.\[73, 95\] Although the study from Purins et al. reveals an overall over-evaluation of the sensor, it records under-evaluating values at the $O_2$ concentration of 2.81 %. Still, these studies do not allow any assumption on the general trend. The different results may be due to a different bench test alignment or a measuring error of the reference sensor. The analysis of the response times shows that the sensor responds faster when the $O_2$ concentration increases in comparison to a decreasing concentration and takes longer to sense a higher $O_2$ concentration. Another essential characteristic shown in the studies by Stewart et al. and Purins et al. is the temperature dependence of the sensor. In one study, the mean measurement error increased, whereas in the other, the standard deviations. The temperature drift results are summarized in Table 14. As these results are recorded for temperature changes, which also occur in the human body, they are also important for neurocritical care units.

Several studies discussed the effectiveness of oxygen monitoring in various pathologies using the Licox sensor. Most of the studies analyzed the pathophysiology with regard to oxygen levels, the therapeutic benefits of oxygen monitoring, and therapeutic approaches.\[97\] Only two studies could be found examining the performance of the LX sensor in-vivo, which are summarized in the following.
One study compares the readings of the LX sensor with the fiber-optic Neurotrend sensor in 7 patients with SAH. The results reveal a mean $P_{bt}O_2$ measurement difference of about 7 mmHg (LX - Neurotrend). In this evaluation, LX proved to be the more reliable sensor in comparison to the Neurotrend probe. Only one Neurotrend sensor worked without any malfunction, whereas all LX functioned flawlessly.\[98\]

Another study compares the LX sensor with the NTO sensor. For the evaluation, the sensors were implanted simultaneously in 7 patients with SAH, and the readings were statistically evaluated. Additionally, the oxygen pressure reactivity index (ORx)$^6$ was calculated from the $P_{bt}O_2$ values. Each patient was monitored for a median of 9 days. The results show that the LX sensor measures the $P_{bt}O_2$ value with a mean difference of about 2.7 ± 10 mmHg lower than the NTO sensor. However, the difference is only about 0.03 ± 0.3 for the calculated ORx.$^{[99]}$

4.1.2 Fiber-Optic Oxygen Sensors

Fiber optic oxygen sensors that are used in intracranial applications are mostly based on an effect called fluorescence quenching. Prior to the review of fiber-optic $P_{bt}O_2$ sensors, the basic mechanisms of fluorescence and fluorescence quenching are explained below.

The physical effect of fluorescence was already observed in the 16$^{th}$ century and the first fluorescence compounds were described in the early 19$^{th}$ century.$^{[100]}$ Since then, this field has experienced much research, that the first commercial applications could be introduced at the end of the 20th century.$^{[101]}$ Fluorescence describes the emission of light by a substance, which absorbed electromagnetic (EM) radiation.$^{[102]}$ There are many different sensing technologies based on the fluorescence properties of different substances.$^{[103]}$ Figure 9A shows the Jablonski diagram and gives an explanation of the energetic transition states and relaxation mechanisms of an excited electron after absorption of EM radiation, which are fluorescence, inner conversion (IC), inter-combination, and phosphorescence.$^{[104]}$

When examining the fluorescence process, the Stokes shift is of high importance. Resulting from the interaction of the excited electron with the surrounding medium, it loses energy. Consequently, the emitted photon in the fluorescence process has got less energy (longer wavelength). This wavelength shift is called Stokes shift and is dependent on the physical condition of the molecule.$^{[80]}$ Other important parameters of the fluorescence process

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$^6$ Taking into account arterial pressure
include the fluorescence lifetime $\tau_0$ and the fluorescence quantum yields $\phi_F$. $\tau_0$ is the mean time, which an electron spends in the excited state and is given by

$$\tau_0 = \frac{1}{k_e + k_{NR}},$$  \hspace{1cm} (Eq. 47)

where $k_e$ is the rate of emitted photons and $k_{NR}$ is the sum of non-radiating relaxation processes from the electron state $S_1$ to the ground state $S_0$ (Fig. 9 A). $k_{NR}$ is given by

$$k_{NR} = k_{IC} + k_{ISC} + k_Q,$$  \hspace{1cm} (Eq. 48)

where $k_{IC}$, $k_{ICS}$, $k_Q$ are the rates of relaxation by IC, inter-combination, and quenching. The fluorescence quantum indicates how many of the absorbed photons are emitted again in the form of fluorescence photons and is given by

$$\phi_F = \frac{k_e}{k_a} = \frac{k_e}{k_e + k_{NR}},$$  \hspace{1cm} (Eq. 49)

where $k_a$ is the rate of absorbed photons.

Fluorescence sensing applications are always based on sensing either the fluorescence intensity, emission spectrum, or life time. These properties will change when the quantity of non-radiative energy transfer (NRET) processes variates. Quenching refers to the general reduction of the fluorescence process by an increase of NRET processes. There are different physical and chemical effects, which can lead to this increase. Dynamic quenching describes quenching processes due to molecular interactions with the environment or with other molecules that are responsible for fluorescence quenching. Examples for dynamic quenching are Förster resonance energy transfer (FRET), photoinduced energy transfer (PET), and energy transfer by collision with solvents.\cite{105} Static quenching refers to a quenching effect induced by molecular conversion.\cite{106}

The fluorescence measurement of oxygen is based on the dynamic quenching of a fluorophore due to collision with oxygen molecules.\cite{107} When the excited dye molecules collide in their excited state with oxygen molecules, the
energy of the excited electron is transferred to the oxygen molecule, which switches from its triplet state to the singlet state. The electron returns afterward to its ground state without emitting a fluorescence photon.\(^\text{[108]}\) If the concentration of oxygen molecules increases, \(k_Q\) increases. An increase in \(k_Q\) leads to a decrease in \(\phi_F\) and \(\tau_0\), which can be measured. Figure 9B shows the basic design of a fiber-optic \(PO_2\) sensor based on fluorescence quenching. The relationship of the luminescence intensity and luminescence lifetime of a fluorophore due to oxygen quenching, is given by the Stern-Volmer equation

\[
\frac{I_0}{I} = \frac{\tau_0}{\tau} = 1 + K_{SV} \cdot [O_2],
\]  
(Eq. 50)

where \(\tau_0\) is the luminescence lifetime without quenching, \(\tau\) is the luminescence time with quenching, \(I_0\) is the luminescence intensity without quenching, \(I\) is the luminescence intensity with quenching, \(K_{SV}\) is the Stern-Volmer constant (quantifies the quenching efficiency and therefore the sensitivity of the sensor), and \([O_2]\) is the oxygen concentration.\(^\text{[109]}\)

Several fluorophores can be used for \(PO_2\). In the clinical approved \(P_{bt}O_2\) sensor, the luminophor ruthenium is used as dye.\(^\text{[27]}\) Depending on the exact ruthenium complex used, the absorbance spectrum for its excitation is in the range from 300 to 500 nm, and the maximum of the emission spectrum (fluorescence emission) is in the range from 600 to 650 nm, with a life time of about 0.1 - 2 \(\mu\)s.\(^\text{[110]}\)

Currently, the only clinically approved sensor on the market, which senses \(P_{bt}O_2\) with the fluorescence quenching principle, is the Neurovent sensor from Raumedic in the PO, PTO, and TO configurations. All configurations are using the same sensing element and are therefore referred to as NTO in the following. The technical specifications of the NTO sensor are given in Table 15.

In one in-vitro evaluation, 5 NTO sensors were compared to 5 LX sensors in a container filled with a buffer solution. The experimental setup and conducted tests were explained in the previous chapter.\(^\text{[7]}\) In this chapter, the results of

\(^7\) The probes were analyzed at a stable temperature of about 37 °C in five different \(O_2\) concentrations ranging from ~ 0.7 % to 5.6 %. After that, the thermal dependence of the sensor’s accuracy was tested in the range from 37° C to 40° C in two different \(O_2\) concentrations (~1.4 %, ~2.8 % \(O_2\)). The 90 % response time was recorded for a
the NTO sensor are covered. The evaluation reveals a mean error of about -0.8 ± 1.6 mmHg (averaged over all tested $O_2$ concentrations). The recorded NTO mean response times are 56 s for an increasing $O_2$ concentration and 131 s for a decreasing $O_2$ concentration. In comparison to the LX sensor, the NTO standard deviations are more stable with a temperature rise. Differences range from -0.5 - 1.7 mmHg in the 2.8 % $O_2$ solution at 40 °C. Only a minimal rise in the $PO_2$ is recorded in the measurements after 10 days.[96, 111]

The in-vitro evaluation shows that the sensor provides a reliable application to measure $PO_2$. The results reveal that the Neurovent sensor seems to slightly over-evaluate $PtO_2$, while its accuracy is not temperature-dependent. Moreover, the standard deviation even decreased with higher temperatures.[96] The recorded response times are shorter for increasing $O_2$ concentration in comparison to decreasing $PtO_2$.[95, 111]

The Neurovent-PTO sensor is compared with the Licox sensor in a clinical study with 30 patients. To compare the readings of both sensors, each patient was monitored simultaneously by both transducers, which were implanted through a double-lumen bolt. Due to malfunctions and handling errors, the readings were only compared in 18 patients (2 LX sensors malfunctioned, 2 NTO sensors malfunctioned, and 11 NTO sensors were handled incorrectly). The results reveal a mean difference between the two sensors of about -1.2 mmHg with limits of agreement from -25.1-22.6 mmHg (LX - NTO). [112]

Another study compares the NTO with the LX sensor by implanting both sensors in 8 German landrace pigs. $PO_2$ values were recorded every minute, while the $O_2$ tension was manipulated with inhalation of 100 % $O_2$. The in-vivo results reveal a mean difference of -6.3 mmHg (LX- NTO) between the sensors. Both sensors responded equally to the $O_2$ increase, while the NTO had a 10 % higher response amplitude.[113]

When comparing the in-vitro evaluation results of the electrochemical and fiber-optic $PtO_2$ sensors, both sensing technologies show similar accuracy. The summarized accuracy results are given in Table 16. Differences appear in the observed thermal dependence and response times of the sensors. The evaluations, which tested the sensors in decreasing and rising $O_2$ concentration (~ 1.4 % to 5.6 % $O_2$). Finally, the zero-drift was tested by leaving the sensors in the 1.4 % $O_2$ solution for ten days with measurements every 24h.

\[\text{value was rounded to one decimal place}\]
different thermal environments, show that the Licox sensor is more sensitive to thermal changes than the NTO sensor. The study conducted by Purins et al. records higher standard deviations in the Licox group with rising temperatures, whereas the standard deviations in the NTO group decreased with increasing temperature. The fiber-optic sensors also seem to have better response time characteristics. In the same experiments, the mean response times of the NTO sensor are about 20 - 85 s faster in comparison to the Licox sensor. The results of the response time evaluations are summarized in Table 17. The in-vivo evaluations report the LX sensor reading to be slightly lower in comparison to the NTO.\textsuperscript{112-113}

4.2 Intracranial Oxygen Sensors in Development

Similar to the introduced oxygen sensor from Raumedic, other fiber optic developments are also based on fluorescence quenching technology. A variety of different fluorescence dyes can be used to sense the oxygen tension optically.\textsuperscript{114} However, only one other commercialized FOS could be found, which is meant to sense oxygen in biological tissue. The OxyLite monitoring system from Oxford Optronix is currently available for research purposes and is inter alia designed to sense the intracranial oxygen tension. Its general measurement principle is very similar to the Neurovent-O series from Raumedic, with the only difference that instead of a ruthenium dye, a platinum-based fluorophore is used at the sensor tip.\textsuperscript{115} The technical specifications of the OxyLite monitoring system are listed in Table 18. The platinum-based oxygen sensor is supposed to have higher accuracy than the ruthenium-based oxygen sensor from Raumedic AG. It is likely that in the future, more FOS based on fluorescence quenching by oxygen will get commercialized, as other fluorophores also showed a good performance in research studies.\textsuperscript{116}

Considering clinical feasibility of the FOS used for cerebral oxygen monitoring, challenges of its biosafety, anti-fouling property, signal stability, and real-time monitoring performance remain in the current researches. Recently, silica nanoporous membranes have been used to functionalize carbon fiber microelectrodes to develop implantable electrochemical sensors. This new type of sensor showed high current stability and fast response that could be used to continuously monitor oxygen levels \textit{in vivo}.\textsuperscript{117}

The measured oxygen level in brain replies on the inserted site in the brain that cannot reflect total oxygen content or cerebral metabolism. Malpositioned FOS in brain conveys a misleading result. Also, the minimally invasive method possesses potential contamination for long-term monitoring. Therefore, non-invasive technology such as
infrared spectroscopy of cerebral oxygenation, is an ideal method for continuous oxygen monitoring. Future direction to measure oxygen levels in brain is to integrate oxygen sensor with therapy functions. Moreover, the further exploration of foreign-body effect of the implantable oxygen sensors should be investigated, although the materials of the sensors are biocompatible.

5 Cerebral Blood Flow Sensors

5.1 Clinically Approved Cerebral Blood Flow Sensors

CBF is measured invasively by thermal diffusion flowmetry (TDF) and laser Doppler flowmetry (LDF). Currently, only a TDF probe is commercially available for clinical application, which is the Bowman Perfusion Monitor from Hemedex. Although a LDF sensor is also commercially available, it is not approved for clinical use yet.

For a better understanding of the TDF measurement principle, first, the design of a thermal diffusion probe (TDP) is explained. The TDP consists of two thermistors, which are placed at a distance from each other, as illustrated in Figure 10A. For the CBF measurement, the first (active) thermistor is heated to about 2 °C above the tissue's temperature, while the second (passive) thermistor measures the temperature difference in a set distance (Figure 10B). The CBF is then calculated from the power, which is needed to keep a fixed temperature difference $\Delta T$:

$$\text{CBF} = K \left( \frac{1}{U} - \frac{1}{U_0} \right),$$  \hspace{1cm} (Eq. 51)

where $K$ is a constant and $U$ is the voltage. To distinct the amount of energy dissipation by heat convection from heat conduction, the tissue's heat conduction properties need to be determined first. This is important, as the CBF is only proportional to the heat dissipation by convection and not to the overall heat loss. In general, this is achieved by a preceding no-flow calibration. The Bowman Perfusion Monitor obviates the need for the calibration process by determining the tissue's thermal conductivity from the initial propagation rate of the thermal field every 30 min.\[118\]

The Bowman Perfusion Monitor from Hemedex (BPMH) is the only invasive sensor available for clinical CBF measurement. It is available with the QFlow 500 Perfusion Probe and either a single-, dual- or quad-lumen bolt for combination with other sensors. As TDF is based on temperature measurement, the BPMH also provides a
temperature signal. The technical specifications of the BPMH are summarised in Table 19.

One clinical evaluation was found, which investigated the accuracy of the BPMH between calibration cycles in 75 patients with SAH. The statistically analyzed data reveals a mean zero-drift of 2.3 ml/100g per minute in the 30 minutes interval between the self-calibration of the probe. Furthermore, the readings show an exponential drift trend over each cycle in each patient. Also, a significant difference in the measured results was registered with different software versions, which implies that zero-drift is a result of inaccurate calculation. The recorded upward drift has clinical relevance, but recalculation is possible since the drift follows a stable exponential function.\[119\]

5.2 Cerebral Blood Flow Sensors in Development

LDF provides the only other invasive and commercialized method to measure the cerebral blood flow with a single sensor.\[115\] Currently, one LDF monitoring system called OxyFlow is available from Oxford Optronix but not yet approved for clinical use.\[120\] LDF sensors are used to measure the velocity of blood cells and thus calculate the blood flow. Based on the principle of the Doppler shift, the frequency change of reflected laser light from the tissue is measured, providing information about the velocity of the reflecting objects.

The LDF probe comprises two optical fibers, which are separated by a short distance, as shown in Figure 11. The first optical fiber is used to illuminate the tissue with low-power laser light, whereas the second fiber is used to sense the backscattered light and return it to the detector where the frequency shift is spectrally analyzed. The physical principle of a frequency shift that a wave undergoes when it is emitted by a moving object was first described by Christian Doppler in 1842.\[121\] The same principle is used in LDF. When the laser light is scattered at the red blood cells (RBC), the reflected light will undergo a frequency shift (Doppler shift) \(\Delta \nu\), depending on the reflection angle and the velocity of the RBC, which is shown in Figure 11. The Doppler shift is expressed by

\[
\Delta \nu = \eta V \frac{\cos(\alpha_s) - \cos(\alpha_i)}{\lambda_i},
\]

(Eq. 52)

where \(\eta\) is the refractive index, \(V\) is the velocity vector of RBS, \(\alpha_s\) is the scattering angle, \(\alpha_i\) incidence angle of the laser beam and the velocity vector of RBC, and \(\lambda_i\) is the laserbeam wavelength. In the tissue, a spectrum of Doppler-shifts and non-Doppler-shifts is measured as a result of different reflection angles, different velocities, and a non-moving tissue. Non-shifted frequencies are used as a reference value, and the Doppler-shifted frequencies are used
to calculate the velocity of RBC.\textsuperscript{[122]} The commercialized LDF sensor provides higher accuracy in comparison to TDF. Table 20 lists the technical specifications of the OxyFlow monitoring device from Oxford Optronix.

Compared to minimally invasive cerebral blood flow sensors, non-invasive optical method, such as diffuse correlation spectroscopy (DCS) shows great potentials to monitor microvascular cerebral blood flow by detecting reflected light at the tissue surface to a blood flow index in the tissue. This non-invasive DCS avoids the risk of potential inflammatory responses for long-term use, so that it is suitable for all ages. Also, the cost for DCS is low compared to MRI or PET monitoring. However, the current DCS technology is restricted in depth and spatial sensitivity that affects deep brain tissue perfusion.\textsuperscript{[123]} Recently, a fiber-less diffuse speckle contrast flowmeter has been proven to provide a low-cost, simple, and flexible approach to continuous monitoring of cerebral blood flow variations in deep tissues through the intact scalp and skull.\textsuperscript{[124]} In comparison with DCS that has rigid optical fiber bundles, this diffuse speckle contrast flowmeter contains soft electrical wires, which could be integrated with wearable sensors for continuous monitoring of free-moving animals.\textsuperscript{[125]}

6 Outlook on Intracranial Metabolism Sensors

6.1 Introduction to Metabolism Sensors

The monitoring of cerebral metabolism is achieved with a technique called microdialysis (MD). With the help of an MD catheter, the concentration of chemical substances can be measured by extracting them from the tissue. Conclusions about cerebral metabolism are drawn from monitoring the concentrations of molecules involved in the metabolism process. Currently, MD is mainly performed for research purposes and is not only used to monitor metabolism parameters but also to measure the concentrations of a variety of different molecules and proteins with the aim to gain a better understanding of neurophysiology.\textsuperscript{[126]} Many of the conducted clinical studies reveal benefits from MD, as early diagnosis of ischemia and better-targeted therapies for patients with SAH.\textsuperscript{[127]} With the emergence of commercialized and easy to handle analytical tools, MD has the potential to become a routine monitoring technology in clinics.

Whereas the molecule extraction process is similar in the different available applications, the analyzing principles differ. Constant monitoring of the analyte is achieved with an electrochemical analyzing device based on the Clark electrode.\textsuperscript{[128]} In contrast, periodic concentration analysis can be done by fluorescence sensing. First, the basic principle of the MD catheter is explained in more detail, and secondly, the physical basics of electrochemical and
optical fluorescence molecule concentration measurement are introduced.

6.2 Microdialysis Principle

6.2.1 Microdialysis Catheter

The fundamental physical principle used in the microdialysis catheter is that solutes follow the concentration gradient from an area of high concentration to an area of lower concentration. The outer tube of the MD catheter contains a part with a semipermeable membrane, which separates the tissue, including the analyte of interest from the solution insight the catheter without the analyte. Due to the two different concentrations of the analyte molecules, a concentration gradient will rise, initiating the analyte to diffuse through the semipermeable membrane into the insight of the catheter. The diffusion rate is thereby given by

\[ J = \frac{\Delta C_{1-3}}{R_1 + R_2 + R_3}, \]  
(Eq. 53)

where \( J \) is the flux, \( \Delta C_{1-3} \) is the overall concentration difference between the investigated tissue and the solution insight the catheter, and \( R_1 - R_3 \) the diffusion resistances of the tissue, semipermeable membrane, and the solution, respectively. The resistance to the diffusion of the analyte is given by

\[ R = \frac{\delta r}{D_{eff} \phi S}, \]  
(Eq. 54)

where \( \delta r \) is the length over which the diffusion occurs, \( D_{eff} \) is the diffusion coefficient, \( \phi \) the volume fraction, and \( S \) the surface area of the membrane. Finally, the proportional difference of the analyte concentration between the investigated tissue and the fluid insight the catheter \( E_d \) is given by

\[ E_d = \frac{C_{out} - C_{in}}{C_{ext} - C_{in}} = 1 - \exp \left[ -\frac{1}{Q_d (R_1 + R_2 + R_3)} \right], \]  
(Eq. 55)

where \( Q_d \) is the perfusate flow rate, \( C_{out} \) the analyte concentration in the dialysate outlet, \( C_{in} \) the analyte
concentration in the dialysate inlet, and \( C_{\text{ext}} \) the analyte concentration in the undisturbed external tissue.\[130b\]

Constant perfusion with about of the solution insight the catheter, also called perfusate, reassures that no concentration equilibrium is achieved and that the analyte is transported to the analyzing device. Thereby, it is important to choose a flow rate, which will reassure that a detectible amount of the analyte can diffuse into the perfusate. Typical perfusion rates vary from 0.3 to 3 \( \mu \text{L/min} \), and depend on the extracellular concentration of the analyte, the membrane area, and the membrane material.\[131\] Membranes are defined by their permeability, which limits the size of molecules that can diffuse through it. Typical limits for the molecular mass are lower than 20,000 Da. Semipermeable membranes in this permeability range are fabricated out of regenerated cellulose, polycarbonate-ether, or polyacrylonitrile.\[131\] The perfusate is majorly made with artificial cerebrospinal fluid (aCSF), which does not contain the analyte of interest. The correct composition of the perfusate is important to reassure that the homeostatic balance of the tissue is not disturbed.\[131\]

Figure 12A shows an example of the microdialysis catheter. The microdialysis pump controls a constant flow of the perfusate, which is guided through the inner tube into the outer tube, where the analyte can diffuse through the semipermeable membrane. The analyte is then transported through the outer tube to the analyzing unit. The diffusion process of the analyte from the extracellular fluid into the catheter is shown in Figure 12B.

6.2.2 Electrochemical Analyser

The continual electrochemical analyzer consists of an array of electrodes, to which the perfusate with the analytes is directly guided from the microdialysis catheter. Each electrode either measures the concentration of one of the analytes of interest or is a reference electrode. Figure 12C shows an example of the setup of the analyzer, whereas Figure 12D shows a schematic example of an analyzing electrode. As previously mentioned, the measurement principle of the electrodes is based on the revolutionary work from Leland Clark on enzyme electrodes published in 1962.\[132\] Clark et al. explained the possibility to sense different analytes with a simple pH or \( PO_2 \) electrode by using membrane layers with trapped enzymes. The enzymes would react with the analyte of interest and change the pH or \( PO_2 \) value, thus enabling to measure the analyte concentration. This exact method, combined with several other membranes, is used in modern electrochemical analyzers. The measurement principle of the electrodes used for the analysis of cerebral metabolism parameters is explained in more detail below.

The general electrode design to measure glucose, lactate, pyruvate, or glycerol is the same. The electrodes consist
of 5 different layers, of which one is a layer with immobilized oxidase enzymes. Depending on the analyte of interest, a different enzyme is used in that layer. For example, to measure glucose, immobilized glucose oxidase enzymes are used, and for the measurement of lactate, pyruvate, and glycerol lactate oxidase, pyruvate oxidase, and glycerol oxidase are used, respectively. To control the number of analyte molecules, which can enter the oxidase layer, it is covered with a diffusion limiting membrane. For example, a 10 μm thick poly-HEMA membrane is used to reassure that the diffusion resistivity for the analyte is higher than for oxygen so that the whole amount of the analyte is oxidized in the oxidase layer. The oxidase enzymes form hydrogen peroxide and an oxidase product of the analyte. Before the actual measurement in the bottom layer can take place, which is based on the oxidation of the hydrogen peroxide molecules at a platinum electrode, the solute needs to be filtered first. A layer between the oxidase membrane and the platinum electrode, preferably only permeable to hydrogen peroxide, reassures that no other molecules can penetrate to the platinum electrode and falsify the measurement. Finally, the hydrogen peroxide molecules are oxidized at the platinum electrode and create a measuring current, as the electrode is polarized at an electrical potential versus a reference electrode, where electro-oxidation occurs. To further minimize the error of measurement, the electrode is covered with a catalase membrane at the top. This layer converts the hydrogen peroxide, which does not diffuse to the platinum electrode but upwards, in hydrogen and oxygen, and therefore preventing it from entering the next measurement electrode and falsify the reading.[128]

A continuous electrochemical analyzer based on the measurement principle described above is available from M Dialysis AB. The technical specifications of the MD LOKE are summarized in Table 21 to give an overview of the electrochemical monitoring accuracy.

6.2.3 Optical Analyzer

In contrast to the electrochemical analyzer, the optical system does not measure the analyte concentration continuously but in time intervals of at least 2 minutes.[133] The estimation of the analyte concentration is based on sensing the emitted fluorescence intensity of a reagent, which is proportional to the amount of analyte catalyzing a chemical reaction to create fluorescence molecules.

The optical measurement system comprises an illuminating unit, a measurement cuvette, and a sensing photodiode. The schematic design of the optical analyzer is shown in figure 12 C. Depending on the analyte of interest, either a 530 nm or 375 nm light-emitting LED is used to excite the fluorescence molecules in the cuvette. The light is
guided through an optical filter, which is impervious to the fluorescence emission spectrum. The emitted fluorescence is then sensed by a second optical conductor, impermeable to the excitation light. A photodiode measures the fluorescence intensity by converting it to an electrical signal. The intensity of the emitted luminescence in the cuvette depends on the number of fluorescence molecules, which are produced due to an enzymatic reaction of the reagent with the analyte. Similar to the electrochemical analyzer, different oxidase enzymes are used to sense the different analytes. In general, each measurement starts with mixing a fixed amount of the sample with the reagent in the cuvette by automated aspiration of both substances and rapidly moving both into the cuvette. In the cuvette, a series of chemical reactions is catalyzed by the analyte. First, the analyte molecules will get oxidized by the oxidase enzymes. Then peroxidase enzymes will trigger a reaction between the formed hydrogen peroxide, phenol, and 4-amino-antipyrine to form a red-violet quinoneimine and emits fluorescence. For example, for the measurement of glucose concentration, 5 μL samples are mixed with 14.5 μL reagent, and after 12 s, the fluorescence emission is measured. \[134\]

M Dialysis AB also sells an optical analyzer. The device is called ISCUS flex and is available on the market for many years. In contrast to the electrochemical analyzer, ISCUS flex provides a possibility to measure glycerol and glutamate. The accuracy of the device variates with concentration. The results of the internally conducted glucose and lactate accuracy tests by M Dialysis AB are summarized in table 22 and the general technical specifications are summarized in Table 23.

7. Conclusion

Monitoring of neurophysiology is a helpful tool to early diagnose pathophysiology’s leading to SBI and thus influence the patients healing process. With further understanding of the brain’s physiology, different parameters gain importance in neurocritical care and are routinely measured in clinics. Monitoring devices need to be accurate and reliable to provide significant information for the correct treatment. Currently, ICP, \(P_{bt}O_2\), and \(T_{bt}\) are the most frequent invasively monitored parameters in routine neurocritical care. Invasive intracranial sensors provide the highest measurement accuracy today however, they also show drawbacks.

Clinical and bench test evaluations show that established ICP sensors have a zero-drift and are only MRI compatible if special precautions are taken. Strain-Gauge sensors are currently the most reliable in this field. Fiber optic pressure sensors, which are based on FPI, show potentials for future clinical applications, as they have a
significantly lower zero-drift and can be used in MRI without limitations. Companies like Fiso Technologies and Opsens Medical already offer suitable FPI based pressure sensors, which can be used in intracranial catheters. Temperature sensors in currently available intracranial catheters show all very similar acceptable properties with limited accuracy. Different FOTS could be used for future applications, as they provide similar accuracy and resolution, while being MRI compatible. FPI, as well as a long-pass optical filter, and reflection at GaAs seem to be more suitable fiber optical sensing approaches, as they provide higher accuracy. Electrochemical and fiber-optic sensors both measure oxygen tension with a measurement error of several percent and high response times. Both principles have proved themselves in clinical use. The fiber-optic approach showed a faster response time, which is favorable. Also, new sensing dyes, including the platinum-dye used in a sensor by Oxford Optronix or other dyes, are currently under development, which can provide more accurate and faster responding sensing elements. New fiber-optic devices have better measurement specifications and show potential to be used in intracranial catheters. Especially their MRI compatibility, low zero-drift and high accuracy are an advantage in comparison to the most established sensors.

Biocompatibility of the fiber-optic sensors is priority for clinical use. High flexibility and mechanical biocompatibility of the fiber-optic probes could allow for long-term continuous monitoring. Compared with commercial silicon optical fibers, hydrogel optical fibers have shown great promises as implantable sensors that can be used to continuously monitor in vivo.[135] Therefore, the hydrogel optical fibers can be fabricated to intracranial sensors for continuous monitoring of neurophysiology. Although the fiber optical sensors have been clinically used for brain monitoring, the method is invasive that is always associated with patient discomfort and risk of inflammatory responses for a long-term use. Wearable and wireless devices are promising alternatives for continuous and cost-effective detection of intracranial signals without pain conditions that could help patients with chronic diseases to improve cognitive performances and long-term therapy.[136] The wearable and wireless devices have seamlessly integrated with mobile devices, such as smartphone. Utilizing the external mobile devices shows potentials to detect brain activity patterns in a real-time manner that can help diagnose and treatment conditions associated with brain diseases.

Microdialysis proofs to be a helpful tool to investigate the metabolism in brain tissue. Currently it is a worthy tool for researchers to understand biochemical processes in the healthy and injured brain. Complicated operation,
limited measurement frequency are a challenge for future clinical use. With further research on cell metabolism in the injured brain and new analyzers providing the possibility of continuous monitoring, microdialysis could be used routinely in future applications for early diagnosis of pathophysologies in neurocritical care.

Currently, most clinically-used brain monitoring devices measure a single parameter. However, brain dysfunction always involves abnormal changes in multiple biomarker levels. As a consequence, different implantable devices are required for simultaneous monitoring of multiple biomarkers, increasing the risk of bleeding and infection. Therefore, a multiplexed sensor which is able to simultaneously monitor multiple parameters in the brain is necessary for future studies.

**Table 1.** Overview over parameters of interest in neurocritical care with physiologic ranges, threshold values, clinical significance, and invasive monitoring technologies. [4a, 7, 137]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Physiologic range</th>
<th>Threshold (TH)</th>
<th>Clinical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial pressure (ICP)</td>
<td>0-20 mmHg</td>
<td>&gt; 20-25 mmHg</td>
<td>ICP over the TH could lead to ischemia and herniation</td>
</tr>
<tr>
<td>Cerebral perfusion pressure (CPP)</td>
<td>60-70 mmHg</td>
<td>&lt; 60 mmHg</td>
<td>CPP under the TH could lead to ischemia</td>
</tr>
<tr>
<td>Cerebral blood flow (CBF)</td>
<td>~ 50 mL/100 g per minute</td>
<td>&lt; 20 mL/100 g per minute</td>
<td>Indicator of ischemia and helps to differentiate vasospasm from hyperemia</td>
</tr>
<tr>
<td>Brain temperature (T_{bt})</td>
<td>34 - 39 °C</td>
<td>&gt; ~ 39 - 40 °C</td>
<td>Indicator of inflammation and stroke, and therapeutic parameter</td>
</tr>
<tr>
<td>Brain tissue oxygen tension (P_{btO2})</td>
<td>30 - 48 mmHg</td>
<td>&lt; 20 mmHg</td>
<td>Indicator of regional hypoxia and marker for ischemic risk</td>
</tr>
</tbody>
</table>
Brain tissue pH (pH<sub>bt</sub><sup>[137d]</sup>)
7.2 - 7.5 pH < 7.0 pH
Low pH indicates a metabolic disturbance

Brain tissue carbon dioxide tension (P<sub>btcO₂</sub>)<sup>[137e]</sup>
35 - 45 mmHg
Hypercapnia: > 44 mmHg
Hypercapnia indicates increased CBF and ICP
Hypocapnia: < 35 mmHg
Hypocapnia indicates decreased ICP<sup>[138]</sup>

Glucose<sup>[4a]</sup>
~ 1.7 ± 0.9 mmol/L ~ 0.8 mmol/L
Decreased glucose levels indicate ischemia

Lactate<sup>[4a]</sup>
~ 2.9 ± 0.9 mmol/L ~ 8.9 mmol/L
Increased levels of lactate indicate ischemia and hypoxia

Pyruvate<sup>[4a]</sup>
~ 166 ± 37.5 μmol/L ~ 30.7 μmol/L
Decreased levels of pyruvate indicate ischemia and hypoxia

Lactate to pyruvate ratio (LPR)<sup>[4a]</sup>
~ 23 ± 4 ~ 30
Increased LPR indicates ischemia and hypoxia

Glycerol<sup>[4a]</sup>
~ 20 - 50 mmol/L ~ 2.3 mmol/L
Elevated glycerol levels indicate a failure in cellular bioenergetics and severe tissue damage

Table 2. Summarized technical specifications of the ICP sensors from Raumedic AG (NeuroVent & NeuroDur), Integra LifeSciences Corp. (Codman Microsensor), and Sophysa S.A. (Pressio 2).<sup>[21-22, 45, 139]</sup>
### Table 3. Accuracy evaluations of the Neurovent ICP series, Codman Microsensor and Pressio ICP monitoring system.

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Tested pressure range</th>
<th>Recorded trend at static pressure</th>
<th>Mean error at static pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurovent-P</td>
<td>0 - 50 mmHg</td>
<td>increasing pressure</td>
<td>0.66 ± 0.85 mmHg (Overestimation)</td>
</tr>
</tbody>
</table>

- Sensing range: -40 to +400 mmHg (-50 to +250 mmHg (Monitor display range))
- Sensitivity: 5 μV /V/mmHg (N/A)
- Accuracy: ± 1 mmHg (N/A) ± 2 %
- Zero drift: Ø 0.6 mmHg/ 5 days ≤5 mmHg/ 30 days in-vitro: < 0.05 mmHg/ 7 days in-vivo: -0.7 ± 1.6 mmHg/ 100 h
- Frequency response: > 200 Hz >200 Hz >100 Hz
- Recalibration: extracranial extracranial extracranial
- MRI compatibility: ≤3T ≤3T N/A
- Tip size: NPT: 5F (1.67 mm) ≤ 1.3 mm ≤ 0.7 mm or 3 mm (diameter)
  NPT: 6-9F (2.3 mm) (diameter)
  ND: 5.8×2.1 mm
Codman MicroSensor 0 - 100 mmHg Decrease in absolute accuracy with increasing pressure <2 mmHg (Underestimation)

Pressio 0 - 100 mmHg Drift from overestimation to underestimation with increasing pressure < 0.5 mmHg

Table 4. In-vitro zero- and temperature drift results of the Neurovent ICP series, Codman Microsensor and Pressio ICP monitoring system in the pressure range from 0 to 20 mmHg.[25-27]

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Long term mean zero-drift</th>
<th>Thermal drift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurovent-P</td>
<td>0.6 ± 0.96 mmHg (after 5 days)</td>
<td>≈ 0.2 mmHg/20°C</td>
</tr>
<tr>
<td>Codman MicroSensor</td>
<td>&lt; 1 mmHg after 24 h</td>
<td>≈ 0.026 mmHg/°C</td>
</tr>
<tr>
<td>Pressio</td>
<td>&lt; 0.05 mmHg difference to Codman MicroSensor</td>
<td>≈ 0.3 mmHg/20°C</td>
</tr>
</tbody>
</table>

Table 5. Summary of the technical specifications of the Spiegelberg ICP monitoring system.[39]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spiegelberg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>0 to 1000 mmHg</td>
</tr>
<tr>
<td>ICP measurements</td>
<td>mean/ systolic/ diastolic</td>
</tr>
<tr>
<td>Recalibration</td>
<td>intracranial</td>
</tr>
<tr>
<td>MRI compatibility</td>
<td>≤3T</td>
</tr>
</tbody>
</table>
ventricular: 7F-10F (2.33-3.33 mm)
parenchymal & epidural: 4F (1.33 mm)

Table 6. Technical specifications of the Camino ICP Monitor.[45]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Camino Fiber Optic Transducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>-100 to 125 mmHg</td>
</tr>
<tr>
<td></td>
<td>-10 to 50 mmHg: ± 2 mmHg</td>
</tr>
<tr>
<td>Accuracy</td>
<td>51 to 125 mmHg: ± 6 mmHg</td>
</tr>
<tr>
<td></td>
<td>measurement: 5 μV/V/mmHg</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>display: ± 1 mmHg or 1% of monitor reading (whichever is greater)</td>
</tr>
<tr>
<td>MRI compatibility</td>
<td>conditional at 1.5 and 3 T</td>
</tr>
<tr>
<td>Tip size</td>
<td>4F (1.33 mm)</td>
</tr>
</tbody>
</table>

Table 7. Comparison of Clinically Established ICP Sensors

<table>
<thead>
<tr>
<th>Sensor types</th>
<th>Strain-Gauge Sensors</th>
<th>Pneumatic Sensors</th>
<th>Fiber-Optic Sensors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Raumedic</td>
<td>Sophysa</td>
<td>Spiegelberg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integra LifeSciences Gaeltec</td>
<td>Natus Medical</td>
</tr>
<tr>
<td>Accuracy in the physiologic range</td>
<td>≤ ± 1 mmHg</td>
<td>~ ±(1- 3) mmHg</td>
<td>~ ± 2 mmHg</td>
</tr>
<tr>
<td>Temperature drift</td>
<td>0.2 - 0.3 mmHg/ 20 °C</td>
<td>no temperature drift</td>
<td>≤ 0.5 mmHg/ 10 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Zero-drift over time</td>
<td>&lt; 1 mmHg/ 24 h (acceptable)</td>
<td>intracranial recalibration</td>
<td>high in-vivo zero drift</td>
</tr>
<tr>
<td>MRI compatibility</td>
<td>compatible</td>
<td>compatible</td>
<td>compatible</td>
</tr>
<tr>
<td>Minimal tip size</td>
<td>3-5F (1.00-1.67 mm)</td>
<td>4F (1.33 mm)</td>
<td>4F (1.33 mm)</td>
</tr>
<tr>
<td>Clinical experience</td>
<td>reliable</td>
<td>Cost-effective alternative</td>
<td>high zero-drift to SGS, but less accurate</td>
</tr>
</tbody>
</table>

**Table 8.** Overview of fiber optic pressure sensors suitable for medical applications.\[140\]

<table>
<thead>
<tr>
<th>Sensing technology</th>
<th>FPI &amp; Fizeau wedge (white light)</th>
<th>FPI &amp; microshift (LED)</th>
<th>FPI &amp; birefringent wedge white light</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>FISO Technologies</td>
<td>RJC Enterprises</td>
<td>OpSens Medical</td>
</tr>
<tr>
<td></td>
<td>FOP-M200 (M200)</td>
<td>Model 60</td>
<td></td>
</tr>
<tr>
<td>Sensor models</td>
<td>FOP-M260 (M260)</td>
<td>Model 62</td>
<td>OPP-M200</td>
</tr>
<tr>
<td></td>
<td>FOP-MIV (MIV)</td>
<td>Model 40</td>
<td></td>
</tr>
<tr>
<td>Sensing range</td>
<td>-300 - 300 mmHg</td>
<td>-50 - 300 mmHg</td>
<td>-300 - 350 mmHg</td>
</tr>
<tr>
<td>Accuracy</td>
<td>sensor: ± 1 mmHg</td>
<td>± 2 mmHg or 2 %</td>
<td>± 1 mmHg</td>
</tr>
<tr>
<td></td>
<td>system:±3mmHg or 3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature drift</td>
<td>&lt; 0.3 mmHg/ °C</td>
<td>0.15 mmHg/ °C</td>
<td>0.2 mmHg/ °C</td>
</tr>
<tr>
<td></td>
<td>M200 &amp; M260: 0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution</td>
<td>mmHg</td>
<td>0.1 mmHg</td>
<td>0.2 mmHg</td>
</tr>
<tr>
<td></td>
<td>MIV: &lt; 0.3 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sampling rate</td>
<td>up to 250 Hz</td>
<td>100 Hz</td>
<td>250 Hz</td>
</tr>
</tbody>
</table>
(with possibility to extend)

Operating conditions:

- Humidity: 0 - 100 %
- Temperature: 15 - 45 °C

M200: 272 (polyimide)  Model 60: 508
M260: 310 (polyimide)  Model 62: 324
MIV: 635 (polyimide)   Model 40: 273
Tip diameter in μm

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neurovent/Neurodur</th>
<th>Pressio</th>
<th>BMP</th>
<th>Camino</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>25 - 45 °C</td>
<td>20 - 45 °C</td>
<td>25-46°C</td>
<td>30-42°C</td>
</tr>
<tr>
<td>Resolution</td>
<td>0.01 °C</td>
<td>0.1 °C</td>
<td>0.005 °C</td>
<td>0.2 °C</td>
</tr>
<tr>
<td>Accuracy</td>
<td>± 0.1 °C</td>
<td></td>
<td>25 - 45 °C: ± 0.2 °C</td>
<td>± 0.3 °C</td>
</tr>
<tr>
<td>Response time</td>
<td>&lt; 150 s</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;30s/2°C</td>
</tr>
<tr>
<td>Tip size</td>
<td>5F (1.67 mm)</td>
<td>≤ 0.7 mm</td>
<td>3F (1.00 mm)</td>
<td>4F (1.33 mm)</td>
</tr>
</tbody>
</table>

Table 9. Summary of technical specifications of thermistor elements in sensors from Raumedic AG, Sophysa S.A., Hemedex Inc., and Natus Inc.\textsuperscript{[21, 45, 141]}

<table>
<thead>
<tr>
<th>Thermocouple Type</th>
<th>Temperature Range in °C</th>
<th>Sensitivity in μV/°C</th>
<th>Standard Tolerance in °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>K</td>
<td>NiCr-Ni</td>
<td>20 - 50</td>
<td>≈ 40</td>
</tr>
</tbody>
</table>

Table 10. Normed thermocouple types that are used in medical applications.\textsuperscript{[72]}
Table 11. Summarized results of the in-vitro accuracy evaluation of the Neurovent thermistor and Licox thermocouple in a direct comparison study (2004) in the temperature range from 30-40 °C.[68]

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Observed Trend</th>
<th>Min. Mean Error</th>
<th>Max. Mean Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeuroVent</td>
<td>Overestimation</td>
<td>+ 0.13 ± 0.05 °C at 42 °C</td>
<td>+ 0.24 ± 0.06 °C at 30 °C</td>
</tr>
<tr>
<td>Licox</td>
<td>Overestimation</td>
<td>+ 0.48 ± 0.44 °C at 36 °C</td>
<td>+ 0.54 ± 0.47 °C at 39 °C</td>
</tr>
</tbody>
</table>

Table 12. Overview over different fiber-optic sensors for temperature measurement, which are available on the market and suitable for medical applications. [78, 115, 127, 142]

<table>
<thead>
<tr>
<th>Sensing technology</th>
<th>Fluorescence decay</th>
<th>Fabry-Pérot Interferometry</th>
<th>Long Pass Filter Glass</th>
<th>Reflection at GaAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Advanced Energy Industries</td>
<td>FISO</td>
<td>RJC Enterprises</td>
<td>FISO Technologies</td>
</tr>
<tr>
<td>Sensor models</td>
<td>STB Probe</td>
<td>FOT–L–SD (SD)</td>
<td>Model 120</td>
<td>THR-NS</td>
</tr>
<tr>
<td></td>
<td>STM Probe</td>
<td>FOT-L-BA (BA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MicroProbe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Sensing range in °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy in °C (possible up to ±0.5)</td>
<td>±2</td>
<td>±0.5</td>
<td>±0.3</td>
<td>±0.5</td>
</tr>
<tr>
<td>Resolution</td>
<td>0.01 °C</td>
<td>0.1 °C</td>
<td>0.1 °C</td>
<td>0.1 rms</td>
</tr>
<tr>
<td>Response time in ms</td>
<td>STB: 250</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>STM: 700</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MicroProbe: &lt; 200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.5 (Tefzel®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tip diameter in mm</td>
<td>STM: 1.5</td>
<td></td>
<td>0.8</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>(Teflon)</td>
<td></td>
<td>(PTFE)</td>
<td>(polyimide)</td>
</tr>
<tr>
<td></td>
<td>MicroProbe: 0.25 (polyester)</td>
<td></td>
<td>1.7</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>(PTFE) (polyimide)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 13. Technical specifications of the Licox sensor.[143]
Sensing range: 0 to 150 mmHg

Accuracy:
- 0 – 20 mmHg: ±2 mmHg
- 21 – 50 mmHg: ±10 mmHg
- 51 - 150 mmHg: ± 13 mmHg

Sensitivity:
- measurement: 5 μV/V/mmHg
- display: ± 1mmHg or 1 % of monitor reading (whichever is greater)

Recalibration: extracranial

Tip diameter:
- oxygen probe: 0.6 mm
- combined oxygen & temperature probe: 0.65 mm
- oxygen probe for tunneling: 0.8 mm

Table 14. Summary of in-vitro accuracy results of the Licox sensor in different thermal environments. [73, 96]

<table>
<thead>
<tr>
<th>Tested °C Range</th>
<th>Observed Trend</th>
<th>Min. Mean Error</th>
<th>Max. Mean Error</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 °C – 39 °C</td>
<td>Decrease in accuracy with higher temperature</td>
<td>-2.5% ± 3.3% at 33 °C</td>
<td>-5.2% ± 3.3% at 39 °C</td>
<td>[73]</td>
</tr>
<tr>
<td>37 °C – 40 °C</td>
<td>Increase in standard deviations with higher temperatures</td>
<td>N/A</td>
<td>N/A</td>
<td>[96]</td>
</tr>
</tbody>
</table>

Table 15. Technical Specifications of the Neurovent PO2 sensor.[22]
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Raumedic NTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>0 to 150 mmHg</td>
</tr>
<tr>
<td></td>
<td>0 - 120mmHg: ± 3 mmHg</td>
</tr>
<tr>
<td>Accuracy</td>
<td>120 - 150 mmHg: ± 10 %</td>
</tr>
<tr>
<td>Zero drift</td>
<td>≤ 1.5 mmHg in 5 days</td>
</tr>
<tr>
<td>Recalibration</td>
<td>N/A</td>
</tr>
<tr>
<td>Response time</td>
<td>≤ 200 sec</td>
</tr>
<tr>
<td>Recalibration extracranial</td>
<td></td>
</tr>
<tr>
<td>MRI compatibility</td>
<td>≤ 3T</td>
</tr>
<tr>
<td>Tip size</td>
<td>5F (1.67 mm)</td>
</tr>
</tbody>
</table>

**Table 16.** Summary of accuracy results in in-vitro evaluations of the Licox and Neurovent PO2 sensors.

<table>
<thead>
<tr>
<th>Tested Sensor</th>
<th>Tested $O_2$ Range</th>
<th>Observed Trend</th>
<th>Min. Mean Error</th>
<th>Max. Mean Error</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licox</td>
<td>1 to 8 %</td>
<td>Underestimation</td>
<td>-4.5 ± 2.8 % at 8</td>
<td>-9 ± 6.3 % at 1 %</td>
<td>[144]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurovent</td>
<td>0.7 to 5.6 %</td>
<td>Overestimation</td>
<td>4 ± 1.9 % at 5.6</td>
<td>15.6 ± 2.9 % at</td>
<td>[96]</td>
</tr>
<tr>
<td>$P_tO_2$ sensor</td>
<td>0.7 to 5.6 %</td>
<td>Overestimation</td>
<td>0.3 ± 3.2 % at 5.6</td>
<td>5.3 ± 14.6 % at</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 17. Summary of the 90% response times in in-vitro evaluations of the Licox and Neurovent PO$_2$ sensors.

<table>
<thead>
<tr>
<th>Tested Sensor</th>
<th>Tested $O_2$ Range</th>
<th>Observed Trend</th>
<th>Min. Mean Error</th>
<th>Max. Mean Error</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licox</td>
<td>1 to 5 % &amp; 5 to 1 %</td>
<td>higher response times when concentration decreases</td>
<td>129 ± 27 sec (low to high)</td>
<td>174 ± 26 sec (high to low)</td>
<td>[144]</td>
</tr>
<tr>
<td></td>
<td>at 2.5 %, 9 %, and 21 %</td>
<td>increase in response times at higher concentration</td>
<td>109 ± 20 sec at 2.5 %</td>
<td>120 ± 17 sec at 21 %</td>
<td>[73]</td>
</tr>
<tr>
<td>Neurovent</td>
<td>1.4 to 5.6 % &amp; 5.6 to 1.4 %</td>
<td>higher response times when concentration decreases</td>
<td>78.2 ± 21 sec (low to high)</td>
<td>215 ± 63 sec (high to low)</td>
<td>[96]</td>
</tr>
<tr>
<td>$P_tO_2$ sensor</td>
<td>1.4 to 5.6 % &amp; 5.6 to 1.4 %</td>
<td>higher response times when concentration decreases</td>
<td>56 ± 22 sec (low to high)</td>
<td>131 ± 42 sec (high to low)</td>
<td>[96]</td>
</tr>
</tbody>
</table>

Table 18. Technical Specifications of the OxyLite monitoring system from Oxford Optronix.[115]
<table>
<thead>
<tr>
<th>Parameter</th>
<th>BPMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>0 – 200 ml/ 100 g per min</td>
</tr>
<tr>
<td>Resolution</td>
<td>&lt; 0.2 ml/ 100 g per min</td>
</tr>
<tr>
<td>Accuracy</td>
<td>10 % of full scale (200 ml/ 100 g per min)</td>
</tr>
<tr>
<td>Volume of measurement</td>
<td>~ 0.3 ml</td>
</tr>
<tr>
<td>Recalibration</td>
<td>intracranial</td>
</tr>
</tbody>
</table>

Table 19. Technical Specifications of the Bowman Perfusion Monitor from Hemdex.[141]
### Table 20. Technical Specifications of the OxyFlow monitoring system from Oxford Optronix.\[^{120}\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OxyFlow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitation wavelength</td>
<td>785 ± 10 nm</td>
</tr>
<tr>
<td>Laser power from probe tip</td>
<td>&lt; 0.5 mW</td>
</tr>
<tr>
<td>Accuracy</td>
<td>± 5 %</td>
</tr>
<tr>
<td>Update time</td>
<td>2 sec</td>
</tr>
<tr>
<td>Sampling frequency</td>
<td>200 Hz</td>
</tr>
<tr>
<td>Measurement averaging</td>
<td>200 ms (Flow)</td>
</tr>
<tr>
<td>Zeroing</td>
<td>automatic</td>
</tr>
<tr>
<td>Tip size</td>
<td>500 μm</td>
</tr>
</tbody>
</table>

### Table 21. Technical Specifications of the electrochemical analyzer MD system LOKE from M Dialysis AB.\[^{145}\]

<table>
<thead>
<tr>
<th>Sensed molecule</th>
<th>Glucose</th>
<th>Lactate</th>
<th>Pyruvate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensing range</td>
<td>0.2 – 15 mM</td>
<td>1 – 10 mM</td>
<td>10 – 150 μM</td>
</tr>
<tr>
<td>Accuracy</td>
<td>± 30% or 0.1 mM</td>
<td>± 30% or 2 mM</td>
<td>± 30% or 10 μM</td>
</tr>
<tr>
<td>(whichever is greater)</td>
<td>(whichever is greater)</td>
<td>(whichever is greater)</td>
<td></td>
</tr>
</tbody>
</table>
**Table 22.** Summary of the tested glucose and lactate measurement accuracy in comparison to established laboratory analyzers (Cobas Mira S), which was conducted by M Dialysis AB.\cite{134b}

<table>
<thead>
<tr>
<th>Tested Concentration in mmol/L (rounded to zero decimal places)</th>
<th>Glucose Accuracy</th>
<th>Lactate Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-5.3%)</td>
<td>(-7.3%)</td>
</tr>
<tr>
<td>3</td>
<td>(-4.3%)</td>
<td>(-7.3%)</td>
</tr>
<tr>
<td>5</td>
<td>(+3.6%)</td>
<td>(-3.6%)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 23.** Technical Specifications of the electrochemical analyzer MD system LOKE from M Dialysis AB.\cite{133}

<table>
<thead>
<tr>
<th>Sensed molecule</th>
<th>Glucose</th>
<th>Lactate</th>
<th>Pyruvate</th>
<th>Glycerol</th>
<th>Glutamate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear sensing</td>
<td>0.1 - 25 mM/L</td>
<td>0.1 - 12 mM/L</td>
<td>10 - 1500 μM/L</td>
<td>10 - 1500 μM/L</td>
<td>1 - 150 μM/L</td>
</tr>
<tr>
<td>Amount of sample (μL)</td>
<td>0.5</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Amount of reagent (μL)</td>
<td>14.5</td>
<td>14.8</td>
<td>14.5</td>
<td>14.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Delay time</td>
<td>12 sec</td>
<td>17 sec</td>
<td>17 sec</td>
<td>17 sec</td>
<td>17 sec</td>
</tr>
</tbody>
</table>
Figure 1. A Piezoresistive Effect: (1) shows the unstretched strain gauge with the length $l$, the diameter $2r$, and the cross-sectional area $A$; (2) shows the stretched strain gauge with the length $l + \Delta l$, the cross-sectional diameter $2r - \Delta 2r$ and the force $F$. B Strain Gauge Pressure Sensor: The configuration of a pressure sensor based on strain gauge pressure measurement. The diaphragm will be stretched depending on the pressure $p_1$ of the external environment, therefore changing the electrical resistivity, measured at the electrical contacts. C ICP catheter with Strain Gauge sensor: An example of an ICP catheter with a strain gauge pressure sensor at the tip and a flexible membrane, which bends proportionally to the ICP. D Photograph of two different piezoresistive ICP sensors: (a) Codman MicroSensor, (a) NeuroVent-P sensor. Reproduced with permission.[146] Copyright 2011, Springer Nature.
**Figure 2.** Pneumatic ICP Sensing Scheme: The figure illustrates a pneumatic pressure measuring system as Spiegelberg used it to measure the ICP. The hollow catheter is filled with air and equipped with an elastic air pouch at the tip, which will deform if pressure is applied to it. The pressure inside the catheter depends on the pressure applied at the catheter tip and is measured in the monitoring device.
Figure 3. A FOS based on intensity modulation. The schematic illustrates a pressure monitoring system with an intensity modulation FOS. In this setup, a light-emitting photodiode is powered by a power and control unit. The emitted light is guided through a first optical fiber (illuminating optical fiber) and reflected at a flat mirror into the second optical fiber (sensing optical fiber). The sensing optical fiber guides the light to the sensing element, which is either a photodiode or a phototransistor. As the reflecting mirror is fixed on a pressure-sensitive membrane, its distance to the optical fibers will change with pressure, and thus the amount of reflected light into the sensing optical fiber will change too. As a result, a pressure-dependent light-intensity will be converted by the sensing element into an electrical current and displayed on the monitor. B Intensity modulation principle: The figure shows the reflection process at a mirror placed in distance $d$ in front of the optical fibers in more detail. The light is first guided through the illuminating fiber with the reflection index $\eta_1$ of the core and $\eta_2$ of the cladding, which determine the $NA$ of the fiber. Consequently, the light in front of the illuminating fiber is emitted within a cone structure with the top angle of $2\theta_0 = 2 \arcsin(NA)$. The full intensity is focused in the center of the cone, getting
narrower with distance. The distribution of the light intensity at the reflecting mirror is shown with the function $E_p/E_0$. The reflected amount of light into the sensing fiber will thus depend on the distance $d$.

**Figure 4.** A Fabry-Pérot interferometry: The figure shows the general principle of white light Fabry-Pérot interferometry, where two semi-reflecting mirrors are separated by a distance $L$. The filtered light escaping the cavity is focused by a lens on an optical detector. The sensed EM spectrum includes the resonated wavelengths separated by a wavelength difference, which is dependent on the distance $L$. B FPI sensor tip: In this figure, a simplified example of a FOPS tip is illustrated. The FOPS's Fabry-Pérot cavity is realized with a micro-machined glass structure. The glass structure is combined with an optical fiber and put in a polyimide sheath. Optionally, the sensor can be covered with a protecting gel. C Fabry-Pérot cavity: Figure C shows the micro-machined glass cavity in more detail. The glass forms a drum structure.
and is covered with a flexible membrane. When pressure is applied, the distance of the cavity decreases.

D Fizeau wedge: This figure shows the basic design of the Fizeau wedge used to find the resonance Fabry-Pérot cavity distance. E FOP-MIC pressure sensor: This figure shows a 3D model of the FOP-MIC pressure sensor from Fiso Technology Inc. Reproduced with permission.[84] Copyright 2009, Hindawi Publishing Corporation.

**Figure 5.** Catheter with a thermistor at the tip: This figure shows an example of a medical catheter for temperature measurement (not to scale), where the thermistor is placed at the catheter tip and connected with electric cables for monitoring purposes.
Figure 6. A Thermocouple principle: This figure illustrates the basic principle of a thermocouple, where two different materials A and B are soldered together at the measurement point and connected by a third material C with a voltmeter. B Catheter with a thermocouple at the tip: The figure shows an example of a medical catheter for temperature measurement (not to scale), where the thermocouple consisting of two materials is placed at the catheter tip and connected with the guiding wire to the voltmeter.
Figure 7. A temperature measurement principle with fluorescence decay: At the top of this figure, the temperature-dependent fluorescence process is shown, where the violet waves represent the excitation and the red waves the emission. With a higher temperature, the thermal relaxation of excited electrons will increase, thus decreasing the relaxation due to luminescence emission and shorten the luminescence lifetime. At the bottom of the figure, a simplified example of an FOTS is shown, in which the fluorescent dye is placed in the sensor’s tip. B Temperature measurement principle with longpass filter glass: This figure shows the qualitative reflection spectrum of a temperature-dependent LPFG, with the LED measurement wavelength $\lambda$ chosen in the variating part of the reflection spectrum and $T_1 < T_2 < T_3$ the temperatures of the glass. On the right, a simplified example of a FOTS is shown, where the LPFG is placed at the sensor tip, and a reflective mirror is placed at its end. C Temperature measurement principle
with GaAs: On the left of this figure, the reflection spectrum of GaAs is shown, which absorbs a longer wavelength with higher temperature $T$. On the right, a simplified GaAs FOTS is shown, where the illuminating broadband light is transmitted through a first optical fiber and reflected at a GaAs semiconductor into the sensing optical fiber.

**Figure 8.** Clark Electrode: In the Clark Electrode, a platinum cathode and a silver anode are placed in an electrolyte and sealed with an insulating cap. At the tip, an oxygen-permeable membrane lets oxygen molecules diffuse in- and out-sight of the sensor. A voltage is applied to the electrodes. The oxygen molecules react with the charged cathode and get electrolytically reduced, which results in an electrical current. This current is the indicator for oxygen pressure. Depending on the number of oxygen molecules, which can diffuse into the sensor because of the concentration gradient, the intensity of the resulting electrical current will change.
Figure 9. A Jablonski Diagram: When a molecule is excited with EM radiation in its absorption spectrum, one electron moves from its ground state $S_0$ to its vibrionic state $S_1$ or a higher excitation state. Within some picoseconds, the electron moves, because of oscillation relaxation, to the lowest energetic state $S_1$ from where it can return to the ground state by emitting energy in the form of a photon. This process is called fluorescence. Another process is called inner conversion (IC), where the electron moves back to its ground state by converting its energy only to oscillation energy and emits no radiation. A third process is called inter-combination, where the electron moves to a triplet state $T$ because of spin-orbit coupling. From the triplet state, the electron can return to its ground state by emitting a photon. This emission is called phosphorescence and is differentiated from fluorescence, as it takes longer. B Ruthenium Oxygen Sensor: The ruthenium dye is illuminated with sinusoidal 450 nm monochrome light through an optical fiber. The ruthenium molecule shifts to its excited state, from where it returns back to its ground state by emitting light at about 600 nm. Some of the ruthenium molecules collide with oxygen molecules and transfer their excitation energy to the oxygen molecule. The ruthenium returns back to its ground state.
without emitting fluorescence (quenching) and thus the emission intensity and fluorescence lifetime are decreased. The quenching quantity is dependent on the number of oxygen molecules. The oxygen tension can be measured by sensing either the luminescence intensity with an optical detector or by sensing the phase shift between the excitation and emission signal.

Figure 10. A Thermal diffusion probe: This figure shows the schematic design of a thermal perfusion probe, where an active thermistor is placed at the sensor’s tip; and a passive thermistor is placed at a 5 mm distance from it. B Thermal field of the TDP: This figure illustrates the decreasing thermal field of the heated active thermistor, which is sensed by the passive thermistor at a 5 mm distance.
**Figure 11.** Laser Doppler flowmetry: A. the laser reflection at an RBC with the corresponding frequency shift. B. a simplified example of the sensor tip is illustrated, which includes the illuminating and sensing optical fiber.

**Figure 12.** A microdialysis principle: This figure shows the setup of the MD process. An MD pump is used to perfusate the MD catheter with an analyte-free solution. The analyte of interest will diffuse through the semipermeable catheter and be guided to the chemical analyzer, which is an electrochemical device.
B Analyte diffusion: This figure visualizes the diffusion process of the analyte. The black arrow shows the analyte's way following the concentration gradient passing different cells and blood vessels (V). The gray catheter membrane separates the human tissue from the perfusate. C Optical analyzer: In this figure, the measurement cuvette with the optical analyzing unit is shown. The analyte and the reagent enter the cuvette through the inlet tubing and undergo a series of enzymatic reactions inside it. The resulting fluorescence is measured by excitation of the solution inside the cuvette with LED light and measuring the intensity of emitted luminescence with a photodiode. D Chemical sensing electrode: This figure shows the chemical sensing electrode with its multiple layers, where (1) is the perfusate including the analyte of interest, (2) is the catalase membrane, (3) is the poly-HEMA membrane, (4) is the oxidase membrane, (5) is a layer only permeable for hydrogen peroxide, and (6) is the platinum electrode.

Acknowledgements

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References


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Detection of different physiological parameters in brain is essential to early diagnosis and monitor of brain diseases or injuries. This article reviews the established and ongoing technologies of optical biosensors that could be used to brain monitoring including intracranial pressure, brain temperature, oxygen level, cerebral blood flow, and cerebral metabolism.