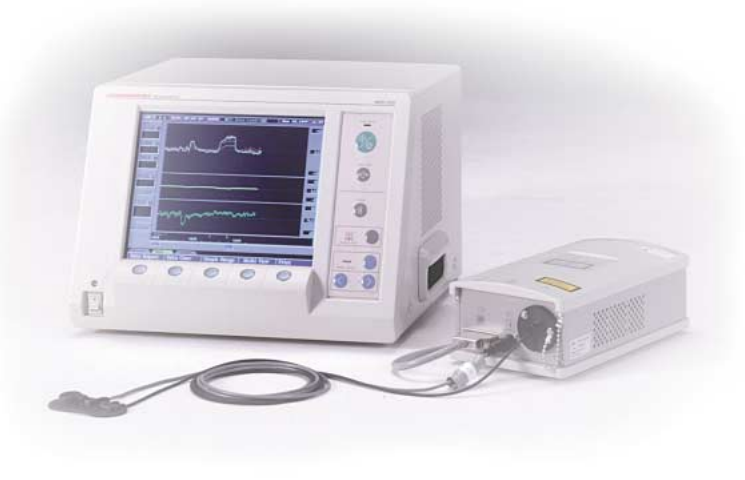
NIRO NEWS

HAMAMATSU

NIRO News No. 1, September 1999



ABOUT NIRO NEWS

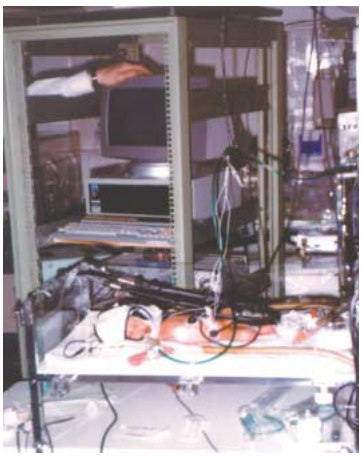
Seven years have passed since Hamamatsu first launched a Near Infrared Oxygenation Monitor (NIRO monitor) in Japan. Since then, engineers at Hamamatsu have made a number of improvements in NIRO monitors by incorporating the opinions of many doctors representing a variety of specializations in different countries. Today, Hamamatsu's NIRO monitors are being used by many doctors including anesthesiologists, surgeons and pediatricians. However, despite the increasing interest and usage of NIRO monitors and substantial improvements in the interpretation of measurement data, some problems remain. To address these problems and help users utilize NIRO monitors more effectively, we decided to publish a newsletter called NIRO NEWS in order to inform our NIRO users of the latest developments in the monitors in a timely way. We invite doctors to incorporate the contents of this publication in presentations at academic meetings, etc.

We believe that this technology to measure oxygenation of deep tissues with a small amount of light has the capability to assist professionals make dramatic improvements in medical and health care fields in the future. We would also like to use NIRO NEWS as a vehicle to communicate with doctors and incorporate the opinions we receive through this newsletter into the development of devices, thereby contributing to the growth of this field as effectively as we can.

HISTORY OF NIRO

It has been said that a tissue oxygenation monitor may have been developed as early as the beginning of the twentieth century. However, a cerebral oxygenation monitor, the most important such device from a clinical point of view, was first described in 1977 by F.F. Jöbsis in the U.S. Although the principles employed in cerebral oxygenation monitors are nearly the same as the principles employed in monitoring oxygenation in other parts of the body, the cerebral oxygenation technique did not materialize for several decades because the highly sensitive light measuring technology required for the measurement of deep tissues (brain) was not established for a long time.

Since our company was founded in 1953, engineers at Hamamatsu Photonics K.K. have been accumulating the knowledge necessary to develop a wide range of technologies as a manufacturer specializing in the measurement of light. In order to apply these technologies to the development of cerebral oxygenation monitors, we began research studies on these technologies in the 1980s, in cooperation with David T. Delpy, Professor of Medical Physics and Bioengineering, University College London. In 1987, we engineers at Hamamatsu succeeded in developing and producing the model NIR-1000 Cerebral Oxygenation Monitor ahead of any other company in the world, and we began to sell this system in Europe. In 1992, we obtained approval for the NIRO-500 Cerebral Oxygenation System, the successor to the NIR-1000, under the Pharmaceutical Affairs Law of Japan, and Hamamatsu started to sell this system in Japan. The system was used in Europe, America, and principal countries in Asia, and earned a good reputation. At the same time, we received some requests to modify the device. Based on these requests, we made a number of improvements in the system, and we completed the NIRO-300, the current model, in 1998. In order to satisfy the very specialized requirements for cerebral oxygenation monitors, we have been incorporating components especially developed for light detectors and light sources (semiconductor lasers), which are the nucleus of monitors, rather than using general-purpose parts. Although it is time consuming, we take pride in designing and producing products that include the development of essential components, at the same time attaching great importance to fundamental research and evaluations related to measuring methods.



Clinical experiment using a protomodel (University College London, 1986)

EXPLANATION OF THE PRINCIPLE

Measurement principle of NIRO-300

The NIRO-300 can measure the following:

(1) Changes in concentration

- Changes in oxygenated hemoglobin: ΔO_2Hb
- Changes in deoxygenated hemoglobin: ΔHHb
- Changes in total hemoglobin: ΔcHb
- Changes in difference between oxidized and reduced cytochrome oxidase: $\Delta CtOx$

(2) Tissue oxygenation index (TOI)

TOI (= O_2Hb/cHb)

In order to measure TOI values, we developed the probe shown in Figure 1. An emission probe made of fiber optics irradiates laser beams, and a detection probe, which is placed several centimeters from the emission probe, detects faint light that has passed through tissues. As shown in Figure 1, the detection probe has a light sensor (photodiode) consisting of three small sensors.

Changes in concentration are calculated from changes in light intensity detected by the center sensor, and TOI values are calculated from the light attenuation slope along the distance (ρ) from the emitting point, ∂A/∂ρ, detected by the three sensors. For more information on calculation methods, please consult the references noted throughout this newsletter.

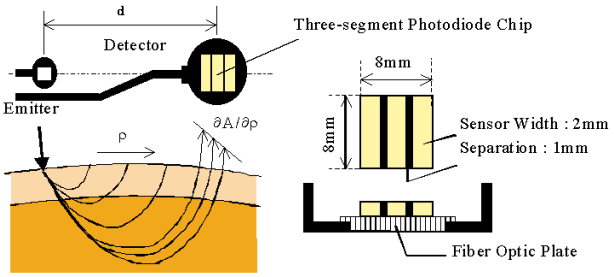


Figure 1. Measurement principle and structure of a probe

Design principles

We designed Hamamatsu's NIRO devices according to the principles cited in the following explanations:

(1) Reliable measurement of deep tissues

The brain consists of deep tissue enclosed by the scalp and skull. In order to measure brain tissue reliably, it is important that the distance between the emission point and the detection point be as long as possible. The NIRO-300 has been designed with highly sensitive light sensors in order to enable measurement, in most cases, with the distance of 5 cm. In addition, the irradiation intensity to the skin has been reduced to an extremely low level as described below.

(2) Usage of safe irradiation intensity

The NIRO-300 is designed and manufactured with an irradiation intensity lowered to comply with Class 1 of the international laser standards (IEC-825), essentially safe levels for a human body, in consideration of the following variables: a) accidental irradiation into eyes; b) use on newborn infants; and c) long-term measurements.

(3) Reliable measurement of the TOI

As described above, the TOI is calculated from the slope (∂A/∂ρ) of light attenuation (A) along the distance (ρ) from the emitting point. Therefore, accurate measurement of the slope is indispensable for the reliability of the TOI. This reliability has been achieved by considering the following points:

❑ Minimizing the effects of head shape upon measurement

Variations in the shape of the human head and non-uniformity on surfaces less affect measurement results because the detection area (8×8 mm) is quite short and narrow compared with the distance from the emission point (40 to 50 mm).

❑ Achievement of reliable measurements

Although the slope can be measured with two sensors, we manufacture the NIRO-300 with three sensors to monitor the linearity of the slope because the linear slope is a precondition for reliable measurements. If the linearity degenerates into a certain level, a message is displayed. Thus, the reliability of measurement is secured.

❑ Increasing measurement accuracy

In order to direct the spatial distribution of light coming from the skin toward the sensor without distorting it, and in order to measure the slope accurately, we use optical fiber plates in the incident window.

EVALUATION OF MEASUREMENT DATA

Presently, there are no immediate standards (commonly called "Gold Standards") for in vivo measurement with oxygenation monitors using near infrared spectroscopy (NIRS), because such standards are based upon experience with a variety of devices and/or methods which do not presently exist in sufficient numbers. This situation makes it difficult to evaluate data measured with NIRS devices. Regrettably, the NIRO-300 is no exception: it is not currently possible to evaluate data measured with the NIRO-300 by comparing such data with a Gold Standard. However, it is a precondition for measuring devices to provide accurate results, at least in in-vitro evaluations and comparative evaluations with NIRS devices having different principles. Based on this philosophy, we conducted the following evaluations:

(1) *In vitro* evaluation

Propagation of light in tissue is determined by absorption and scattering characteristics in the tissue. In this experiment (Figure 2), we used a "tissue phantom " prepared by adding blood having the same concentration (absorption coefficient) as living tissues into an intralipid solution having the same scattering coefficient as living tissues. During this experiment, oxygen saturation of the phantom was changed via the fermentation of yeast fungi and the bubbling of oxygen gasses, and simultaneously measured with the NIRO-300 (TOI values) and a blood gas analyzer (SO_2 values).

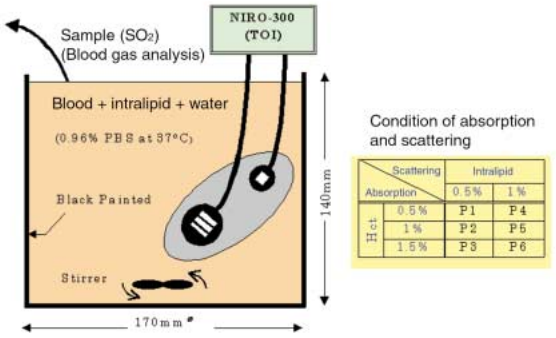


Figure 2. Experiment with tissue phantom

As shown in Figure 3, data from the NIRO-300 closely conforms to data from the blood gas analyzer. We also conducted the experiment by changing phantom conditions, and we obtained the same results.

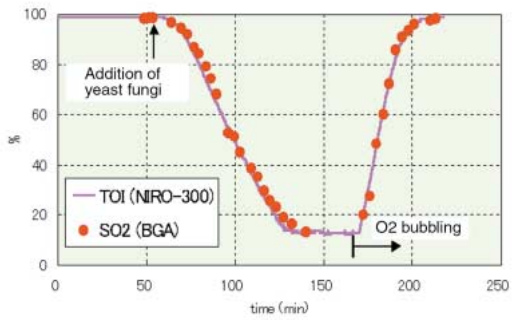


Figure 3. Comparison of data from the NIRO-300 with data from a blood gas analyzer

(2) Comparison with NIRS devices designed under different principles

NIRS devices designed with several different kinds of measuring methods are available, each having various merits such as practicality with cost-effectiveness and/or high performance for scientific research. Time-resolved spectroscopy (TRS) is said to be superior in quantification among NIRS methods. TRS, a method used primarily for scientific research, is the method we used to compare results obtained with the NIRO-300. In the experiment shown in Figure 4, simultaneous measurements with the NIRO-300 and a TRS device were conducted by attaching probes originating from both systems to the forearm at two points adjacent to each other and changing oxygenation by using a blood pressure cuff.

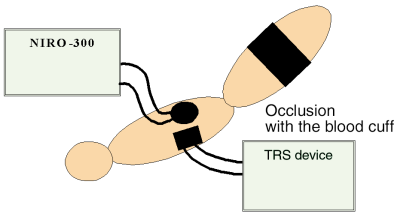


Figure 4. Simultaneous measurement with NIRO-300 and a TRS device

As shown in Figure 5, data from the NIRO-300 closely conformed to data from the TRS device, both in arterial and venous occlusion.

(This report was originally presented in SPIE BIOS '99.)

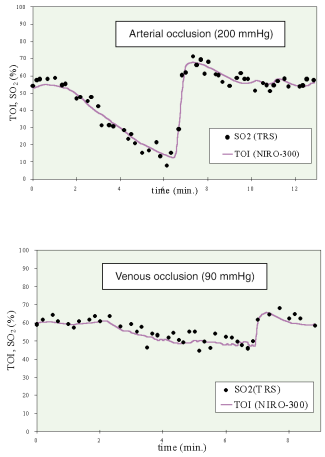


Figure 5. Comparison of data from the NIRO-300 and data from a TRS device

As described above, the NIRO-300 demonstrated accurate measurement performance, at least in the measurement of uniform media and in comparison with NIRS devices designed under principles differing from those used in designing the NIRO-300. We believe this is a requisite for a measuring device and a precondition for the evaluation of clinical data.

Q & A

Q. Does the NIRO-300 measure the brain ?

Because near infrared lights have higher transmissivity in living bodies than visible light, they can penetrate the skull and pick up information inside it. In this case, the longer the distance between the emission point and detection point is, the larger the percentage of light in detection signals that goes through deep tissue (brain) becomes.
The NIRO-300 has been designed to collect as much information as possible in the brain, and measurement with a distance of 5cm between the emission and detection points is possible in most instances.
There is a report on the correlation between cerebral blood flow and NIRO data in simultaneous measurement with PET. According to the report, when the distance between the emission point and the detection point is 4 cm, NIRO data are closely correlated with cerebral blood flow at a depth of 1 cm from the brain surface[1]. On the other hand, to elucidate which areas of the brain are to be measured, a study was made by conducting simultaneous measurement with MRI[2].

1) Kersten Villringer et al.: Assessment of local brain activation; A simultaneous PET and near-infrared spectroscopy study. Adv Exp. Med. Biol. 413, 143-153, 1997
2) Andreas Kleinschmidt et al.:, Simultaneous Recording of Cerebral Blood Oxygenation Changes During Human Brain Activation by Magnetic Resonance Imaging and Near-infrared Spectroscopy. J. Cerebral Blood Flow and Metabolism16: 817-826, 1996

Q. Does an electric knife affect measurement?

Noises generated by an electric knife affect measurement for the following reason. Because signals are transmitted from the detection probe to the measurement unit (MU) via electrical signals, measurements that involve the detection and amplification of faint light may be disturbed by electrical noises such as those from an electric knife.
In such cases, the electrical noise from the knife apparently has the effect of excessively amplifying the detected signal, resulting in the display of error messages such as “Signal Overflow” after which all the data became zero.
When the electric knife is turned off, the NIRO-300 device immediately resumes normal operation, and measurements continue as before. In this case, change in data can be seen on graphs by plotting normal data with envelope curves.

Q. What is the unit of concentration changes?

Changes in concentration of tissue ingredients are measured by the Modified Beer-Lambert law as follows:

$\Delta A = \varepsilon \cdot \Delta C \cdot L$

where,
ΔA : Change in detected light
ε : Molar absorption coefficient ($\mu M^{-1} \cdot cm^{-1}$)
ΔC : Concentration change ($\mu M = 10^{-6}$ mole)
L : Pathlength (cm)

When the pathlength is known, the data obtained is the concentration change, ΔC (μM) .
($\Delta C = \Delta A/\varepsilon/L$)

When the pathlength is not known, the data obtained is the relative change in concentration , $\Delta C \bullet L$ ($\mu M \cdot cm$).
($\Delta C \bullet L = \Delta A/\varepsilon$)

In the NIRO-300 system, data (O_2Hb, HHb, cHb, and CtOx) are displayed as concentration changes by inputting a pathlength into the machine. When a pathlength is not input, the data are displayed as relative concentration changes. TOI values do not depend on the pathlength.

Q. What is pathlength?

A pathlength is a mean distance along which light travels from the emission point to the detection point. In tissues, light does not travel straight; instead it travels scattered at different angles. For this reason, pathlength L becomes longer than a straight line (distance) d that links the emission point to the detection point.
It is said that pathlength L is nearly in proportion to distance d. The proportion constant is called the differential pathlength factor DPF. Usually, the pathlength L is calculated by assuming the DPF, i.e. L=DPF∗d, and the value is input to NIRO-300. The report shown below regarding DPF value has been published[3]. For reference, examples of DPF values, which should be regarded as average values, are given below.

Adult head:	5.93
Adult forearm:	3.59
Head of newborn infant:	3.85

3) P van der Zee et al:, Experimentally Measured Optical pathlengths for Adult Head, Calf and Forearm and the Head of the New Born Infant as a Function of Inter optode Spacing. Adv. Exp. Med. Biol., 316, 143-156, 1992

EXPENDABLE SUPPLIES

New probe holder (type S)

In addition to type-I and type-T probe holders, more flexible type-S probe holders will be available. Because the cable is removed from the top of the probe holder, the probes can be more easily attached to small subjects such as the head of a newborn infant.

Product	Model	Remarks
Probe holder	Type I, A7383	The cable is removed from the side.
Probe holder	Type T, A7384	The cable is removed vertically.
New product (optional) Probe holder,	Type S, A7928	The cable is removed from the top.

Light attenuator

There are patients whose tissues transmit light rather well, which may cause excessive incident light to reach the detector. In such cases, measurement is made possible by attaching the light attenuator to the emission probe.

New emission probe

The emission probe has been improved so that it withstands larger mechanical stresses.

NIRO-300 online software

New online software enables the user to incorporate NIRO-300 data into a Windows PC. The user can then readily graph the data and save them in PC files.

High-speed sampling

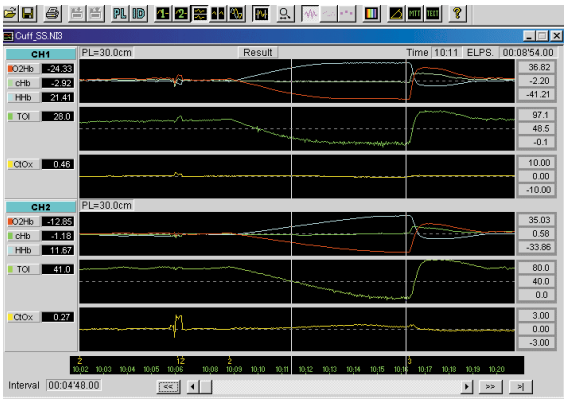
The maximum measurement speed has been improved from 2 Hz to 6 Hz, enabling the measurement of rapidly-changing phenomena.

Detection fiber adapter

Standard detection probes are manufactured with electronic circuits inside them. By using the detection fiber adapter, fiber optics can be used as detection probes in the same way as in the emission probes. Thus, since all probes have fiber optics, the following measurements are made possible:

- Measurements in narrow regions where standard probes are not applicable
- Simultaneous measurement with MRI
- Experiments on small animals

When the defection fiber adaptor is used, only concentration changes in hemoglobin and cytochrome are measurable.



Examples of online software screens

TOPICS

Sixth NIRO workshop held

On January 16, 1999, a NIRO workshop sponsored by Hamamatsu Photonics was held at Ochanomizu Square, Tokyo. The workshop was the first NIRO workshop organized since the NIRO-300 was launched. Many doctors who are actually using the NIRO-300 and NIRO-500 systems presented data obtained using these systems. In previous workshops, many reports offered by doctors were about experiments and research. This time, however, there were many reports on clinical subjects, indicating for the first time that usage of the NIRO-300 has moved a step closer to clinical applications.

Hamamatsu Photonics made a presentation at BIOS '99

In January 1999, BIOS '99, the annual symposium on biomedical optics, was held in San Jose, California, under the sponsorship of SPIE. Every year, many NIRS researchers come together to make presentations on state-of-the-art technologies. Engineers from Hamamatsu Photonics presented reports on the measurement principle of the NIRO-300, on the explanation of the NIRO-300 device, and on experiments to evaluate the performance of theNIRO-300. A summary of the presentation is reported in this issue. (S. Suzuki, et al.:, Tissue Oxygenation Monitor using NIR Spatially Resolved Spectroscopy, Proc. SPIE Vol.3597, pp.582-592, 1999)

US Aviation Medicine Association

A steep climb and steep dive of aircraft causes sudden gravitation changes. Now, NIRO devices are being used for the study of blackouts (G-LOC) caused by such changes. At the meeting of the US Aviation Medicine Association held in Detroit in May, 1999, data measured with a NIRO device designed to be loaded onto an aircraft were presented by Dr. A. Kobayashi of theDefense Agency (Aeromedical Laboratory). This device, called the NIRO-300G, was made by remodeling the NIRO-300 especially for use in aircraft. In order to load the NIRO-300 onto an aircraft, it was reduced in size and weight and converted to battery-operation (with more than one hour of battery life). Although there have been earlier reports on measurements in a centrifugal accelerator for the training of astronauts, this was the first experiment in the world that conducted measurements in an actual combat plane while it was flying. In addition to Dr. Kobayashi's presentation, Hamamatsu Photonics presented a technical report on the device, which also attracted the attention of the audience.

A. Kobayashi et. al., In-Flight Cerebral Oxygen Status:Continuous Monitoring Near Infrared Spectroscopy, Aviation, Space, and Enviromental Medicine, Vol.7; No.2, pp.177-183, Feb.2000

List of theses related to NIRO

If you would like to see the list of theses related to NIRO systems, please contact our company and we will be happy to send it to you.

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