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IN VIVO PHOTOACOUSTIC SPECTROSCOPY OF THE SKIN

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Resume — Un spectromètre photoacoustique utilisant un détecteur différentiel permet de mesurer in vivo les spectres d'absorption optique de la peau humaine. Sa conception et ses caractéristiques sont décrites ; les premiers résultats expérimentaux sont présentés.

Abstract — We describe the conception and the characteristics of an open-ended photoacoustic detector developed for doing in vivo measurements of skin optical absorption. Preliminary results are presented.

As soon as he introduced the modern photoacoustic spectroscopy, Rosencwaig attempted to demonstrate the usefulness of this new method in medical sciences such as dermatology. He soon mentionned the feasibility of performing in vivo measurements on human skin, by the use of an open-ended cell.

In spite of this, almost all the cutaneous applications of photoacoustic detection have been done on excised epidermal samples. These studies have shown that the photoacoustic spectrum reveals the absorption band of proteins at about 280 nanometres and depends on the hydration of the sample through its thermal properties. The photoacoustic signals produced by drugs or sunscreens give their optical absorption in situ, that is on and in the epidermis and their diffusion coefficient in stratum corneum.

At the time being, only Campbell et al. and Pines and Cunningham reported in vivo measurements. The major difficulty in doing in vivo photoacoustic measurements lies in the fact that the microphone is sensitive to the body's movements. We undertook to study the real possibilities of such in vivo cutaneous photoacoustic spectroscopy. After various approaches, this led us to construct a photoacoustic detector using a differential microphone between two identical cells. Its characteristics allow us to measure different in vivo signals with good reproducibility and signal to noise ratio.

I - EXPERIMENTAL SET-UP

The originality of the spectrometer resides in the conception of the photoacoustic cell which must be considered so as to optimize the signal to noise ratio. One of the important features of the conception of this cell is to maximize its sensitivity by the optimization of its dimensions. According to Aamodt et al. and to Quimby and Yen, the optimal dimensions of the cell at 20 Hz modulation frequency and in standard temperature and pressure conditions are 1.6 mm long and 7 mm large. This 20 Hz threshold was chosen because the vibrations of the skin are too substantial at any lower frequencies. This choice also means that it is possible to use theoretical models of the photoacoustic effect based on the Rosencwaig-Gersho theory. The microphone should be in contact with the gaseous volume specified above by means of a small acoustic pipe.

Having defined the dimensions which optimize the sensitivity of the cell, we must now consider the second aspect of its conception : to minimize the noise and synchronous background signal produced by the microphone. The synchronous background is usually the most difficult to reduce. It can be generated by absorption of light within the cell by a body other than the studied sample, such as the sidewalls or the microphone itself. Another synchronous background can be produced by the light modulator.
Using an open cell raises problems of damping external sounds and vibrations. When the cell is applied to the body under scrutiny, the gaseous volume delimited by the cell and the surface being analysed must be perfectly sealed with regard to the outside atmosphere in order to obtain a photoacoustic signal. As long as this hermetic seal can be achieved, insulation against outside sounds will be satisfactory. On the other hand, it is impossible to insulate the cell from the vibrations of the body under scrutiny, the surface of which inevitably forms one of the internal walls of the cell. It is therefore essential to use a modulation frequency at which the vibrations of the skin are small, although it must not be forgotten that as the modulation frequency rises, the signal becomes weaker. It is also advantageous to seek out zones of skin where vibration is weakest. In spite of all these precautions, the level of noise detected on the surface of the skin made the first photoacoustic cells virtually impossible to use.

In order to reduce the effect of the skin vibrations on the measured signal, a differential method was applied, using a close-talking microphone: the Knowles BW1789. This microphone includes two sound ports, one on each side of the diaphragm, and the signal it delivers depends on the pressure difference between the two sides of this diaphragm. The microphone is fitted to the cutaneous detector, in between two identical cells, one of which is closed by the light guide, the other by a volume-adjusting screw. This screw should enable the responses of the two cells to be equalized, at the frequency in use, so as to minimize noise. The sketch of the photoacoustic detector is shown in Fig.1. Its dimensions have been optimized according to the criteria set out above. It is attached to the surface of the skin by a double-sided adhesive tape in which two holes have been bored opposite the cells, and the whole apparatus can be fastened to the forearm by means of an armband.
The characteristics of the detector enable the performance of the photoacoustic spectrometer to be considered, and will be used for feasibility studies of the various applications which are considered. The sensitivity of the detector was measured on a thin black body, obtained by blackening a plexiglass holder over a flame. At 20 hertz, the sensitivity of the cell is 430 pascals per watt, and expresses the ratio between the r.m.s. values of variations in acoustic pressure and incident light power. This sensitivity varies as a function of the modulation frequency. The theoretical decrease in 1/f is verified at frequencies higher than 25 hertz, as could be foreseen from the size of the cell. At lower frequencies, the thermal losses occurring in the walls of the cell weaken the signal. The spectrum of the noise density delivered by the microphone is estimated from the r.m.s. value of the output voltage of the lock in amplifier, with a time constant of 100 milliseconds, which corresponds to a bandwidth of 1.25 hertz.

While the noise was being measured, all the instruments were operating, the cell sealed against the studied sample and the modulated light beam shut off by a blind. Various types of noise are detected on a vibration-free sample: a wide-band noise with frequencies above 150 hertz, 50, 100 and 260 hertz parasites, a 1/f noise with a knee at approximately 30 hertz, and a narrow-band noise between 30 and 60 hertz. This spectrum is the direct result of the different sources of noise referred to above, except for the synchronous background, which would appear to be produced by the light scattered or reflected by the sample itself, and which depends on the nature of the latter.

Whilst the cell was attached to the forearm of a volunteer, the noise level is higher, whatever the frequency used, although a much more substantial level can be observed at low frequencies (below 20 hertz), and this is due to involuntary movements of the forearm.

Fig. 2 shows the sensitivity to noise density ratios corresponding to the two foregoing situations. When the cell is placed on an isolated base, this ratio reaches its maximum values at 30 hertz (approximately 2000) and 90 hertz (approximately 1500). When the cell is attached to a forearm, this ratio is, in a typical case, ten times smaller, and has two maxima, one at 25 hertz (about 200) and the other at 80 hertz (about 120). The sensitivity to noise density ratio is poor at low frequencies (40 at 10 hertz) and at high frequencies (less than 50 over 300 hertz).
a constant or with a sinusoidal current delivered by the power supply unit controlled by a function generator. When the lamp is supplied with a constant current the light is modulated by the use of a mechanical chopper placed before the monochromator or the interference filter. The energy of the light-beam produced is 50 watts, of which more than 30 watts consist of infra-red radiations, which are filtered out by a watertank 5 centimetres thick with quartz windows. The beam is then focused by a UV silica lens, onto either the entrance slit of a holographic-grating monochromator, with a light-guide at the exit slit, or directly on the light guide placed behind an interference filter. The used light-guide is made of UV silica, is 1 metre long, and the diameter of the bundle of fibers is 4 millimetres. The end of the light guide forms one of the walls of the cutaneous photoacoustic detector.

![Diagram of the photoacoustic spectrometer](image)

The electrical signal produced by the microphone in the cell is analyzed by a two-phase lock-in amplifier. The amplitude and phase of the photoacoustic signal are then plotted on an XY recorder. The X-scan is controlled either by the time-base of the monochromator, or by the sweep output of the function generator during a frequency analysis. A AC/DC and logarithmic converter can be used for recording the noise spectra at the output of the lock-in amplifier, as well as the frequency-variation graphs of the photoacoustic signal, expressed in logarithmic coordinates. As the amplitude of the photoacoustic signal is proportional to the energy of the sample, each spectrum must be corrected by a point by point division with a previously recorded spectrum of a black body.

RESULTS AND DISCUSSION

Preliminary applications of the cutaneous detector were performed on small-sized solids attached to the cell with double-sided adhesive tape. Spectra were recorded for different solids: coloured cards, glass optical filters, whole green leaves on the plant. They all show that the open detector can easily be used for making spectroscopic studies of the surface of inert and vibration-free solids. Simply using double-sided adhesive tape provides satisfactory insulation of the cell from external sounds. The delocalization of photoacoustic spectroscopy resulting from the use of a light guide and an open cell enable the method to be applied to various original situations, as it no longer requires the use of small samples enclosed within a cell.

The characteristics of the cutaneous detector and the thermal properties of skin enable one to envisage the possibility of taking cutaneous measurements. The thermal effusivity of skin is close to that of water 7, and the maximum photoacousticsignal measured at the surface of the skin ought to be about three times weaker - ratio of the thermal effusivities - than the signal produced by the reference mentionned in
the previous chapter. The ratios of the saturated signal to noise relative to incident light energy of 1 milliwatt and a bandwidth of 1 hertz should therefore be 70 at 25 hertz and 25 at 80 hertz.

The mean energy available in UVB (280-320 nm) and UVC (200-280 nm) radiation, correlate with intensities of more than 100 watts per square metre and the effect of these intensities on the exposed areas must be carefully controlled. It is well known that such radiation gives rise to numerous photobiological reactions, such as the inhibition of nucleic acid and protein synthesis, the induction of skin cancer, and the formation of erythemas.

The preliminary experimental results we present were obtained on the forearm of volunteers who remained stationary throughout the measurements. Fig. 4 shows the photoacoustic spectrum of the skin measured in vivo. The non-corrected spectrum is shown, as well as the signal at 470 nm recorded during 5 minutes, 80 Hz; 16 nm; 10s.

Fig. 5 shows the photoacoustic spectrum of merbromin (dibromohydroxymercuri fluorescein disodium salt) on the skin. The spectrum obtained on the untreated skin is shown for comparison, as well as the photoacoustic spectrum of the used merbromin aqueous solution (2 %), measured with our conventional photoacoustic spectrometer and quantized according to a previously described methodology.
CONCLUSION

These first experimental results show that photoacoustic signals can be measured in vivo, and with satisfactory signal-to-noise ratios. Reduction of the noises caused by the subject's skin vibrations has been achieved by using a differential microphone, and this in turn has made possible to obtain the first in vivo photoacoustic measurements of the absorption of the skin itself, and of an optical absorption spectrum of a medicinal substance applied to the surface of the skin of subjects having volunteered to remain immobile throughout the period necessary for the measurements to be taken. The diagnostic use of photoacoustic detection techniques nevertheless remains limited by the detector's sensitivity to skin vibrations. Another mode of detection ought to be able to eliminate this drawback: photothermal detection using infrared radiometry, which was already being used in the nineteen fifties for measuring the thermal properties of the skin.

However, these early results can be seen to be encouraging, and from them can be considered various applications of photoacoustic spectroscopy such as the bilirubin level in newborn's jaundice, photosensitivity of the skin to UV radiation or phototherapies of skin diseases like psoriasis and cancer.

REFERENCES