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Tissue temperature monitoring during Interstitial Photodynamic Therapy

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ABSTRACT

During δ-aminolevulinic acid (ALA) based Interstitial Photodynamic Therapy (IPDT) a high light fluence rate is present close to the source fibers. This might induce an unintentional tissue temperature increase of importance for the treatment outcome. In a previous study, we have observed, that the absorption in the tissue increases during the treatment. A system to measure the local tissue temperature at the source fibers during IPDT on tissue phantoms is presented.
The temperature was measured by acquiring the fluorescence from small Cr^{3+}-doped crystals attached to the tip of the illumination fiber used in an IPDT-system. The fluorescence of the Alexandrite crystal used is temperature dependent. A ratio of the intensity of the fluorescence was formed between two different wavelength bands in the red region.
The system was calibrated by immersing the fibers in an Intralipid solution placed in a temperature controlled oven. Measurements were then performed by placing the fibers interstitially in a pork chop as a tissue phantom. Measurements were also performed superficially on skin on a volunteer. A treatment was conducted for 10 minutes, and the fluorescence was measured each minute during the illumination. The fluorescence yielded the temperature at the fiber tip through the calibration curve. The measurements indicate a temperature increase of a few degrees during the simulated treatment.

Keywords: interstitial photodynamic therapy, temperature-dependent fluorescence, Cr^{3+}-ions

1. INTRODUCTION

The aim of this study is to present results of an optical method to monitor tissue temperature behaviour during simulated Photodynamic Therapy (PDT) treatments superficially on skin, but also interstitial PDT illumination in a piece of meat.

1.1 Interstitial Photodynamic Therapy (IPDT)

Photodynamic therapy, PDT, is a method for treating locally situated tumours.[1] The patient is given a photosensitising drug a certain time period before the treatment. The photosensitiser can be administered in different ways. After some time the photosensitiser has selectively accumulated in the tumour and the treatment is initiated. By illuminating the tumour, with light of a wavelength matching an absorption peak of the photosensitiser, the photosensitiser is excited. The photosensitiser can interact with other molecules and an energy transfer is therefore possible. If the energy is transferred to an oxygen molecule, this molecule can be excited from a triplet ground state to a first singlet excited state. This singlet state is very reactive and can oxidise proteins and cell constituents, which can lead to cell necrosis or apoptosis in the tumour.
The main advantages of PDT are that the treatment is selective, can be repeated and that the treated areas heal fast. A major disadvantage is that only superficial tumours can be treated and with tumour thickness only up to a few millimetres. A possible solution to this problem is to use interstitial photodynamic therapy, IPDT, where optical fibers are inserted into the tumour mass. This will give the advantage to enable treatment of more solid tumours, either primary tumours or e.g. liver metastases.[2]

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1.2 Why is it important to monitor the temperature locally?

During an IPDT treatment procedure a high light fluence rate is present close to the source fibers, especially when using bare end cut fibers.[3] This might induce an unintentional tissue temperature increase of importance for the treatment outcome. In addition, an increase in the measured absorption coefficient has been seen during IPDT treatments, in a recent study.[3] The increase in the absorption coefficient could be an effect of tissue deoxygenation, changes in blood flow, local bleeding or temperature increase close to the fiber tips.

The goal of an IPDT treatment is not to have a hyperthermal, but a photochemical effect, on the lesion. If a small bleeding occurs at the fiber tip, the absorption coefficient will increase drastically and this could lead to an abrupt temperature increase. Such bleeding would reduce the efficacy of the treatment, since most of the light would be absorbed in the blood right at the fiber tip.

In an earlier published study, the blood perfusion and the temperature were measured during superficial PDT, both on patients with lesions and on skin on volunteers[4]. The temperature was studied with an infrared camera and an increase in temperature 1-4 °C could be seen during the treatment. This small temperature increase shows that there is no hypothermal effect during the treatment when an initial temperature was about 35 °C. The infrared camera only monitor the really superficial layer of the skin and in deeper lying tissue the temperature could actually be higher. With a thermometer based on an optical technique, the temperature could actually be measured at other deeper locations.

2. MEASUREMENT PRINCIPLES

One way to measure the temperature with an optical technique is to use crystals, which fluorescence is temperature dependent. To be able to measure the temperature locally in the tissue where the treatment fibers are located, a small crystal can be attached to the fiber tip. In this study a crystal doped with Cr^{3+}-ions was used. Cr^{3+}-ions in ionic crystals interact strongly with the crystal field and the lattice vibrations. The crystal field arises because of the influence on the Cr^{3+}-ion from the neighbouring ions. The interaction between the Cr^{3+}-ions and the crystal field arises due to the fact that there are no outer shells to shield the three valence electrons. As a result Cr^{3+}-activated materials are characterised by a wide absorption spectrum, from UV to infrared. This has two advantages, the possibility to choose excitation source and that a small drift in the excitation source will not cause a significant change in the fluorescence intensity. Because of the strong crystal field interaction, the energy gaps of the electronic levels of Cr^{3+} can vary from one host crystal to another. The temperature dependence of the fluorescence lifetime varies with the energy gap and will thus differ for different Cr^{3+}-doped materials. Different Cr^{3+}-doped crystals show different temperature dependence in the fluorescence signal. Among the different crystals, Alexandrite seems to show good temperature sensitivity in the interesting temperature range (15 – 100 °C) in this case.[5]

A Jablonsky diagram of Alexandrite is shown in Figure 1. The ground state in Cr^{3+} is always $^4A_2$, independent of the strength of the crystal field. Two excited energy levels are involved, following excitation at 635 nm: $^4T_2$ and ^2E. The energy splitting between these two low-lying states is denoted $\Delta E = E(^4T_2) - E(^2E)$. ΔE varies strongly with the strength of the crystal field and can be both negative and positive. The emission spectrum of Cr^{3+} consists of two different features, a broad spectral band and two sharp peaks, so called R-lines. The broad band originates from the vibrational transitions, $^4T_2 \rightarrow {}^4A_2$, where ions in the $^4T_2$ state decay to the empty vibrational levels of the $^4A_2$ state. The R-lines appear because of a further split of the ^2E state into two levels, E and $2\bar{A}$, separated by a small energy gap. The R_1-line is the transition $E \rightarrow {}^4A_2$ and the R_2-line comes from the transition $2\bar{A} \rightarrow {}^4A_2$. [5] Lattice vibrations in the crystal interact with the electronic levels of the Cr^{3+}-ion. The effects of this are the initiation of vibrational transitions, radiationless transitions and phonon scattering. The first of these effects produces broad bands in the spectra, the second effect leads to a temperature dependent decrease of the fluorescence lifetimes of the R-lines and both the second and third effect can cause a thermal broadening of the R-lines.[6]

In Alexandrite, the lowest excited state of the Cr^{3+}-ions is the ^2E state (Figure 1). At low temperatures the emission is dominated by the transition $^2E \rightarrow {}^4A_2$ (the R-lines), yielding an effective long fluorescence lifetime, since the transition is parity and spin forbidden. The $^4T_2$ state has a much shorter lifetime than the ^2E state. When the temperature increases, a higher percentage of the Cr^{3+}-ions will populate the $^4T_2$ state according to the Boltzmann distribution. Consequently more ions will decay through the $^4T_2 \rightarrow {}^4A_2$ path, resulting in a decrease of the fluorescence lifetime. Thus, at low temperatures the thermally activated populations of the ^2E and $^4T_2$ states determine the fluorescence properties. [5]

This phenomenon can also be seen in the intensity of the fluorescence. The fluorescence, corresponding to the R-lines, will decrease when less ions will follow the path $^2E \rightarrow {}^4A_2$. This can be used as a measure of the temperature by forming a dimensionless ratio for the intensities from the R-lines divided by the intensity at longer wavelengths.

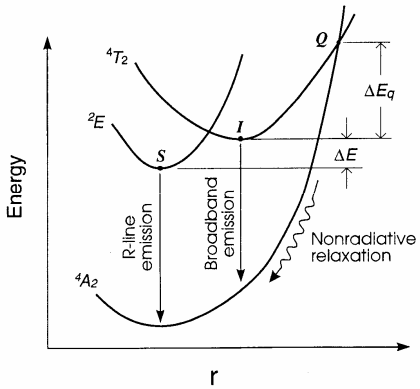

Figure 1. The energy levels as a function of nearest neighbour distance for a crystal with a high crystal field strength (See Ref 5).

An evaluation of the method measuring the temperature with fluorescence from crystals has been reported earlier.[7] In that study fluorescence lifetime measurements were performed. In this study we go one step further and use an integrated system developed for IPDT to measure the fluorescence and calculate an intensity ratio of the fluorescence to give a value of the actual temperature. There are commercially available fiber based thermometers using optical techniques to measure temperature dependent fluorescence, which can be used for temperature monitoring.[8] The concept we use in this study is that the crystal is located on the fiber tip of the fiber delivering the treatment light during a real IPDT treatment.

3. MATERIAL AND METHODS

3.1 Material

In this section the Interstitial Photodynamic Therapy system used will be described and also a short description of how the crystal was attached to a bare end fiber tip will be given.

3.1.1 IPDT system

An instrument for interstitial photodynamic therapy has been developed by the company SpectraCure AB (Ideon Research Park, Lund, Sweden). A general schematic drawing of the instrument is shown in Figure 2. The instrument uses a maximum of six bare end optical fibers that are used to deliver the therapeutic light into the tumour mass. The same fibers can also be used in order to perform diagnostic measurements during the treatment session.[3] The therapeutic light unit consists of six diode lasers emitting at 635 nm with an individual maximum output power of 200 mW. While in treatment mode, light from the therapeutic light unit is guided into the light distribution module and further coupled into the six 400 μm diameter fibers, which are inserted in the tumor.

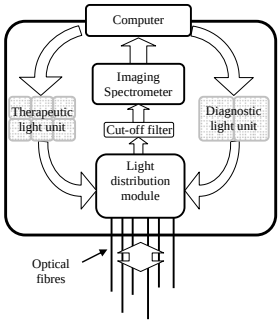

Figure 2. A schematic description of the interstitial photodynamic therapy system used for the experiments (See Ref 3).

In the measurement mode, light from the diagnostic light unit is coupled into one of the "patient fibers" via the light distribution module. After interacting with the sample the fluorescence light is collected by the other fibers and coupled into an imaging spectrometer covering the spectral range between 620 and 810 nm. A cut-off filter (Schott RG665) is used to attenuate the intense laser light at 635 nm from the laser light source. Wavelength calibration of the spectrometer is carried out using an HgAr lamp to determine the relation between wavelength and pixel number in the horisontal direction of the CCD chip.[3]

3.1.2 Attachment of crystal to fiber tip

For the measurements, an end cut fiber with a core diameter of 400 μm (Fiberguide Industries, USA), was used. A small Alexandrite crystal was glued to the clear cut fiber tip, using the glue (Nordland Optical Adhesive 68, Norland Products) which needed to cure in UV-light for 30 minutes.

3.2 Calibration of fiber

The set-up used for temperature calibration is shown in Figure 3. The calibration was performed in the temperature interval 15 – 50 °C. Two fibers were immersed in an Intralipid solution of 1.28 % in a vessel. The distance between the fibers was approximately 12 mm. Initial tests were performed to investigate the influence of different scattering coefficients, by changing the Intralipid concentration. Different distances were also tested to study the effect of the distance between the two fibers. One fiber was used only for delivering the excitation light and the other one, with an attached piece of crystal, was used for detection of induced fluorescence light. The vessel and the fibers were placed inside a temperature controlled oven (FN300 Nüve Microprocessor). To monitor the actual temperature in the Intralipid, two thermistors were also placed in the vessel, close to the fibers. After approximately 45 minutes the temperature had stabilized in the solution, the laser in the IPDT system was turned on and was illuminating through fiber 1. The induced fluorescence light from the crystal was detected through fiber 2 in Figure 3, and an image was acquired with the detection unit. For each temperature, two different powers (90 mW and 130 mW) of the laser light were tested, in order to monitor the influences of the power in the fluorescence light. Then the temperature of the oven was increased and the procedure was repeated.

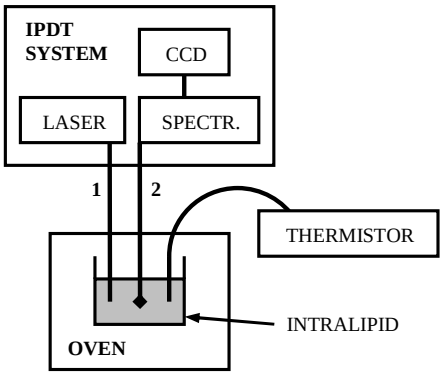

Figure 3. The set-up used for calibration. The fiber used for illumination of the laser light (denoted 1) and the fiber with a piece of crystal (marked 2) are shown.

3.3 Evaluation of a fluorescence spectrum

The evaluation of the temperature was performed by using the concept of forming a dimensionless ratio. A summation was made for the intensities in two different wavelength bands, marked with Area 1 and Area 2 in Figure 4. A ratio was then formed between the two values from Area 1 and Area 2 for each measured temperature.

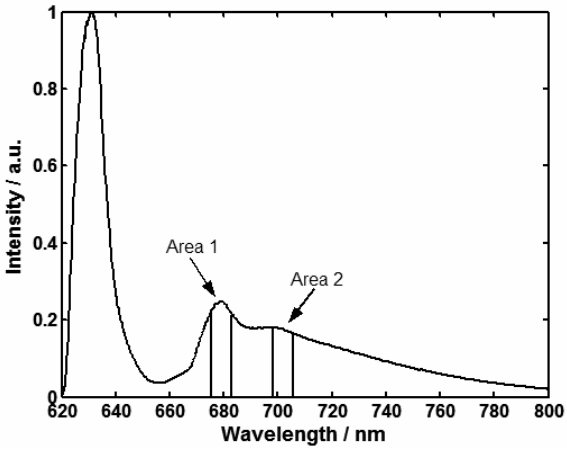

Figure 4. A fluorescence spectrum from alexandrite showing the wavelength bands used for forming a ratio.

3.4 Experiment

For the experiments performed in this study, two different arrangements of the two fibers were used. In arrangement A, see Figure 5a, the end cut fiber, denoted with 1 in the figure, was used for illumination during the simulated treatment. The other fiber (denoted 2), with a crystal attached to the fiber tip, was used to monitor the temperature. The treatment light was used to induce fluorescence in the crystal. The fluorescence light was guided through the fiber into the detection unit in the IPDT system. With this arrangement the temperature was monitored in the spot where the doped fiber was placed, which means a small distance from the treatment fiber.

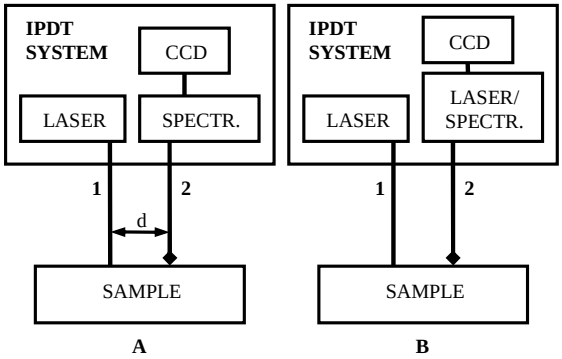

Figure 5. Two different arrangements of the fibers are shown. In A, the illumination fiber is denoted 1 and the detection fiber with the crystal is marked 2. In the arrangement in B, the illumination fiber is the doped fiber, (2), measuring the temperature in the same spot where the treatment takes place. The fiber, denoted 1, in B, is only used for inducing fluorescence in the crystal when a temperature measurement is performed.

In fiber arrangement B, see Figure 5b, the fiber with a piece of crystal attached to the tip (denoted 2), was used for illumination during the treatment. This fiber was illuminating the whole time except during the temperature measurements, when it was used for detection of fluorescence light. The other fiber, denoted 1 in Figure 5b, was placed approximately 2 mm apart from the first fiber. Fiber 1 was only illuminating during the temperature measurements to induce the fluorescence in the crystal at the other fiber tip. With this set-up the temperature is monitored where the illumination fiber is located and not at a small distance as in arrangement A.

3.4.1 Simulation of a superficial treatment on skin

Both the fiber arrangements were used for the investigation on skin. With arrangement A, (Figure 5a), the two fibers were placed in close contact with the skin on the arm of a healthy volunteer. In the first measurement, a power of 130

mW through the illumination fiber was used, and detection of fluorescence light, with the doped fiber, was performed each 10 seconds during 2 minutes. This was done to see how the temperature increases in the beginning of the illumination period. In the following three measurements the distance between the two fibers was changed (see distance d in Figure 5a) with the values of 1 and 3 mm. The power from the illumination fiber was measured to 130 mW and the illumination was continued during 10 minutes. A fluorescence measurement was acquired each minute. The temperature of a larger area of the skin was monitored using an infrared camera (uncooled, AGEMA 570 Elite, Flir Systems Inc), which was saving a temperature image every minute.

In the experiment using fiber arrangement B, two different powers, 75 mW and 110 mW, were used for illumination in order to monitor how the temperature changed as a result of different treatment power. One temperature measurement was performed before the treatment, to get information about the initial temperature. The treatment started by illuminating with the doped fiber (denoted 2 in Figure 5b). After 1 minute the other fiber (denoted 1 in Figure 5b) started to illuminate. Detection of induced fluorescence light from the crystal was performed through fiber 2. The illumination was continued as before and a temperature measurement was recorded each minute during the treatment. After 10 minutes the treatment was interrupted, but the measurements continued for a few minutes to study the temperature change without any illumination.

3.4.2 Simulation of an interstitial treatment in meat

In the final experiments, regarding interstitial treatment, measurements were performed using a pork-chop as a tissue phantom. The two fibers were placed next to each other inside the meat. By using fiber arrangement A, a 10 minutes treatment was performed. In this case an output power from the illumination fiber was 130 mW and the depth of the fibers in the meat was approximately 12 mm. Two experiments were also conducted with arrangement B. In the first experiment the depth of the fibers was 18 mm and a power of 110 mW. The treatment continued during 20 minutes. In the last experiment the fibers were placed at a depth of 10 mm and a power of 110 mW, but only for 10 minutes. A temperature measurement was performed each minute.

4. RESULTS AND DISCUSSION

4.1 Calibration curve for fiber with attached crystal

A calibration curve is shown in Figure 6, with the dimensionless ratio as a function of the corresponding temperature. For the calibration curve different fluorescence excitation powers were used. It can be seen in the figure that the influence of the power is very weak. The reason for that might be the formation of a dimensionless ratio, with the main advantage of cancelling out environmental effects. Tests were also performed when changing the distance between the fibers and different scattering in the Intralipid. The results, not presented here, show that the distance, between the illumination and detection fiber, does not affect too much, more when the distance is too big so the detected fluorescence signal becomes too weak, and noise disturbs the measurements. A different scattering power of the Intralipid phantom does not affect the ratio either. A quadratic polynomial was fitted to the acquired data points. This curve was later used as a calibration curve for determining the temperature measured during the tissue measurements.

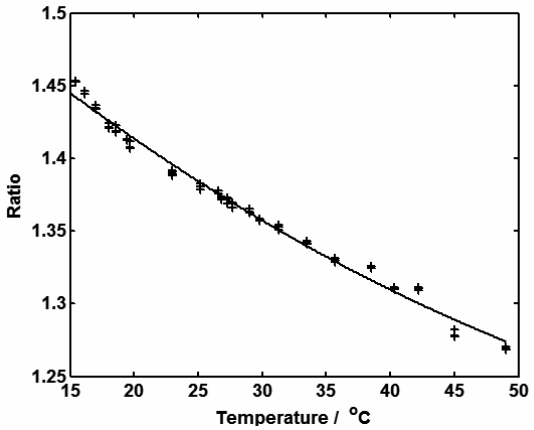

Figure 6. A calibration curve for the fiber with an attached crystal is shown. Measured values (crosses) and the fitted calibration curve (solid line) to these values are shown.

4.2 Superficial measurements on skin

The absolute temperature as a function of time can be seen at a small distance from the illumination fiber during a two minute long session on skin (Figure 7). A quadratic polynomial has been fitted to the measured values. As can be seen the temperature is increasing during the first two minutes and it is stabilizing at later times.

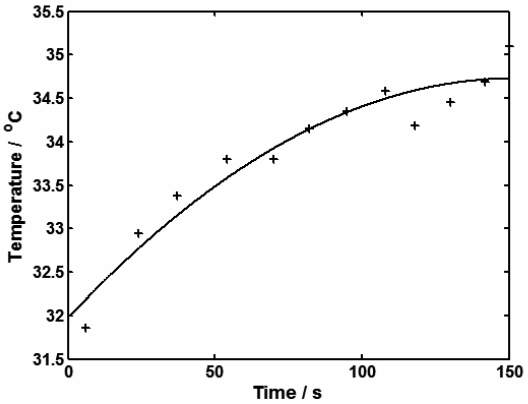

Figure 7. The temperature increase during the first two minutes of superficial illumination on skin is shown. Measured temperatures (crosses) and a fitted line to the measured values are shown.

The temperature increase can be seen as a function of time when changing the distance between the illumination and the doped detection fiber (denoted d in Figure 5A) for two different simulated treatment sessions, in Figure 8. When changing the distance between the two fibers, the temperature in different spots from the illumination spot will be monitored. As can be seen the temperature is increasing the closer to the illumination fiber the detection fiber is located.

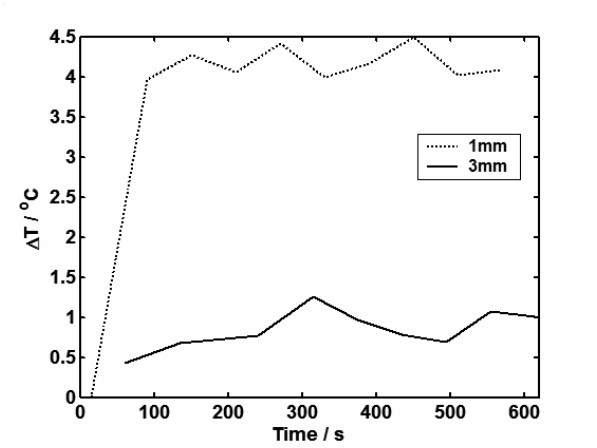

Figure 8. The measured temperature increase at two different fiber separations.

An infrared image is shown after 5 minutes of a superficial treatment on skin (Figure 9). The same figure presents a graph of the temperature increase as a function of distance in the infrared image. As can be seen the increase is about 4 °C close to the middle, which can be related to the same increase seen in Figure 8 for the distance 1 mm. Further out the increase is not of that high value. This shows how important it is to monitor the temperature in the right spot where the illumination is.

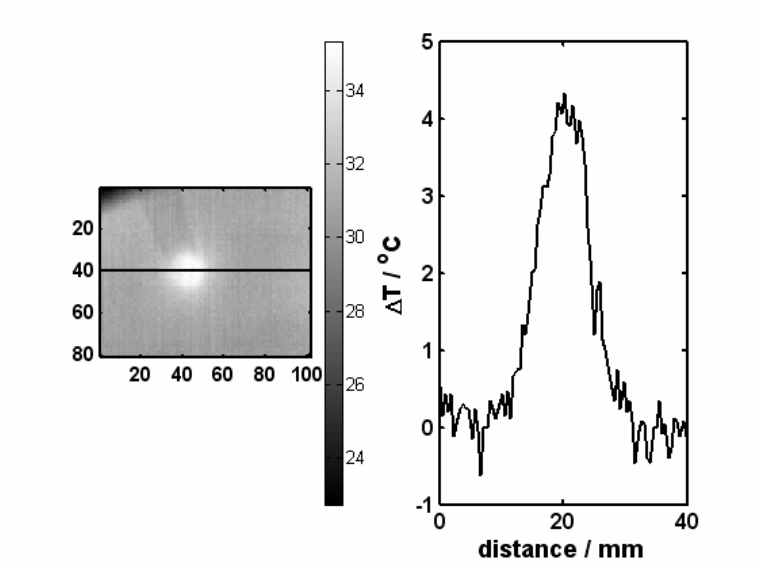

Figure 9. An infrared image is shown 5 minutes after the start of a superficial treatment on skin (left). The temperature increase is shown as a function of distance (right). The solid line in the left image corresponds to the cross section showed in the right graph.

It is interesting to see the temperature increase when using two different powers, as shown in Figure 10. In this figure the illumination fiber is the same as the doped fiber, (see fiber arrangement in Figure 5b), which means that it is the local temperature where the illumination fiber is located that is monitored. As can be seen, the temperature increase is larger when using the power of 110 mW compared to a power of 75 mW. This is not an unexpected behaviour when more energy is delivered to the tissue with a higher power. Another interesting feature is that the temperature increase is stabilized after 3 minutes for the power of 75 mW and after 4 minutes with the power of 110 mW, and for the rest of the treatment the temperature is rather constant. This can be explained by a balance between energy deposition due to light absorption and energy dissipation due to the blood flow where the illumination fiber is located. If the increase, as can be seen in the graph, is about 2-4 °C, the blood perfusion will increase to the area of the fiber to remove some of the extra heat. This might take about 3-4 minutes. The laser illumination was stopped after 10 minutes, but a few extra

temperature measurements were performed to see how the temperature was decreasing. It seems like the temperature decreased even below the initial temperature. An explanation to this can be the increased blood perfusion in the area stimulated by the procedure. Only a few minutes after the treatment was interrupted, it seems like the temperature is stabilized again and probably will reach the initial temperature after a short while. A change in the blood perfusion to the initial perfusion will probably take a few minutes.

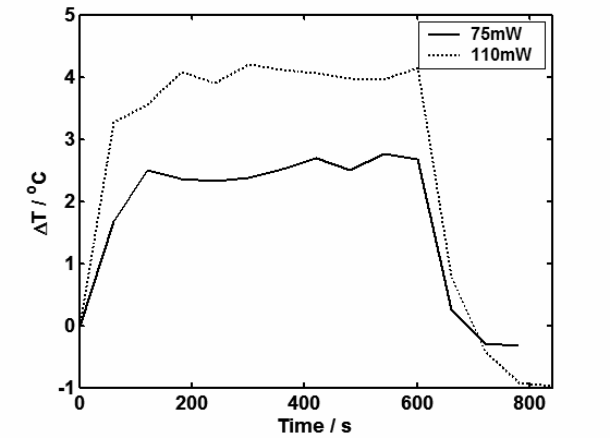

Figure 10. The temperature increase as a function of time conducted at two different powers, 75 and 110 mW.

The reason that the temperature increase is shown instead of an absolute temperature is that there is a difference in the initial temperatures on different locations of the skin.

4.3 Interstitial measurements in meat

The temperature increase during an interstitial treatment in a piece of meat is shown in Figure 11. Three different curves are shown, corresponding to three different treatment sessions. Two of the treatments were conducted for 10 minutes and one for 20 minutes. As can be seen in the graph, the temperature is increasing during the whole session. This can be compared to the superficial measurements on skin where the temperature increase is stabilized after a while as the blood perfusion most probably removes the heat. In interstitial treatment in meat there is no convection or blood perfusion which can stabilize the temperature, instead there will be an increase during the whole treatment. The measurements on meat symbolise thus no entirely realistic scenario because of the lack of tissue perfusion.

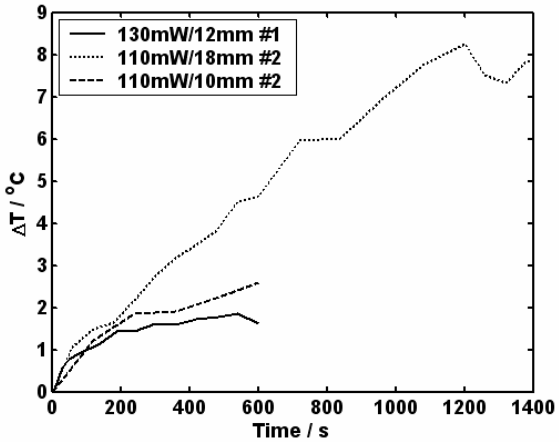

Figure 11. The temperature increase for 3 different interstitial treatments performed in a piece of meat. The power/depth and the arrangement used are shown in the legend.

5. CONCLUSIONS

In this study we have shown that tissue temperature can be measured with an optical technique based on the detection of temperature dependent fluorescence light from the Alexandrite crystal. Simulations of superficial treatments on skin, using a bare cut fiber delivering 110 mW light power at 635 nm, showed that the temperature increase is about 2-4 °C for a treatment of 10 minutes. After 3-4 minutes the temperature remains almost constant most likely due to an increased blood perfusion to the area where the illumination fiber is located.

Simulations of interstitial treatment in meat were also conducted, showing the similar temperature increase, but continuing through the entire treatment. In these cases an increase was shown for the whole treatment as no blood flow is existent in the meat.

In the study we worked with two different fiber arrangements used for treatment. In the first arrangement the illumination fiber was not the same as the doped fiber. With this arrangement the temperature is not measured right at the illumination fiber where the light fluence rate is high. With the second arrangement, where the illumination fiber is also the crystal doped fiber, the temperature will be monitored exactly at the fiber tip where a high fluence rate is located. A big temperature increase will only occur in a distance of a few hundred micrometers from the tip of the illumination fiber.[9] This means that the fiber arrangement B (see Figure 5B) is the best for monitoring the local temperature at the fiber tip.

Future work in the project involves more temperature measurements on simulated superficial treatments on volunteers to get a better statistics. Also more interstitial measurements in meat will be conducted. The robustness of the attachment of the crystal to the fiber tip is also an urgent question to be solved. So far, we have seen that only using glue to attach the crystal is not enough. The fiber tip becomes very fragile.

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