

## Extended Theory of Selective Photothermolysis

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**Background and Objective:** We present a new theory of selective thermal damage of non-uniformly pigmented structures in biological tissues. Spatial separation of the heavily pigmented areas and the target requires limitation of the pigment temperature and heat diffusion from the pigmented to the targeted areas.

**Study Design/Materials and Methods:** A concept of selective target damage by heat diffusion is presented for three target geometries: planar, cylindrical, and spherical. An in vitro experiment is described in which the dependence of thermal damage on pulsewidth at constant fluence was evaluated.

**Results:** The in vitro experiment showed that the size of the damage zone for similar hair follicles was pulsewidth-independent over a very broad range of pulsewidths (30–400 ms). We formulated a new theory (extended theory of photothermolysis) to interpret the experimental results.

**Conclusions:** Based on this new theory, the treatment pulsewidth for non-uniformly pigmented targets is significantly longer than the target thermal relaxation time (TRT). The theory provides new recommendations for photoepilation and photosclerotherapy parameters. *Lasers Surg. Med.* 29:416–432, 2001.

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**Key words:** photothermolysis; photoepilation; photosclerotherapy

### INTRODUCTION

For many years electromagnetic radiation (EMR) from lasers, lamps, and other EMR sources (including microwave ones) has been used to treat a variety of medical conditions in ophthalmology, dermatology, urology, otolaryngology, and other specialties. For example in dermatology EMR sources have been used to perform a wide variety of procedures including hair removal, treatment of various pigmented lesions, removal of unwanted veins, tattoo removal, and skin resurfacing. For all these treatments, a natural or artificial chromophore present in the body is heated by absorption of either monochromatic or broadband EMR. Typical natural chromophores include water, melanin, hemoglobin, protein, lipid, etc. Artificial chromophores can include dye, ink, carbon particles, etc. For example, heating of a chromophore may result directly in the destruction of a tattoo or a

pigmented lesion. In these cases, the treated target for destruction and the chromophore occupy the same area. These cases are very well described by the theory of selective photothermolysis (SP) [1]. The theory of SP provides a quantitative description of optical treatments such as those mentioned above. The aim of SP is to provide permanent thermal damage of targeted structures with the surrounding tissue held intact. To satisfy the above criterion, the EMR pulsewidth  $\tau$  must be small compared to the thermal relaxation time (TRT) of the whole target. Actually, if the condition  $\tau \ll \text{TRT}$  is met, the heat generated within the target due to EMR absorption does not flow out of the structure until it becomes fully damaged (coagulated, injured). The above approach provides both selective damage and minimum light energy deposition.

However, the use of such a short pulsewidth becomes inapplicable when the target absorption is non-uniform over its area and a part of the target exhibits weak or no absorption, but the other part exhibits significant absorption. If this is the case, the weakly absorbing part of the target has to be damaged by heat diffusion from the highly pigmented/strongly absorbing one (hereafter called the heater or absorber). An example of such a target is the hair follicle (HF) [2]. The highly absorbing areas consist of melanin-bearing structures, (i.e., the hair shaft (HS) and the matrix cells). The other follicular tissues including the stem cells do not contain an appreciable amount of any chromophore that absorbs in the red/near-IR. These targets (tissues) can be damaged by heat diffusion from the HS or the matrix cells to the surrounding follicular tissues. Another example is the treatment of telangiectasia or leg veins with a wavelength near the maximum hemoglobin absorption. Permanent closure of a vascular malformation or a vein probably requires coagulation of the vascular or vein wall [3,4]. In this case, coagulation of the wall requires heat diffusion from the blood to the wall.

In this paper, we will demonstrate the heat diffusion concept by presenting the results of a simple in vitro experiment involving a HF. Then, we will discuss the mechanism and the requirements for selective damage of biological structures by heat diffusion. We will prove these

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new concepts using thermal diffusion theory for isolated plane, cylindrical, and spherical targets. We will apply this theory to high-density targets. Finally, as an example, we will apply this new theory to the cases of HF and spider vein treatment. For readers who are interested in the mathematical details, we have included formulas in the Appendix.

The goal of the following experiment was to evaluate the effects of pulse duration and irradiance for a constant fluence on different anatomical structures of the HF. The thermal damage after laser exposure was evaluated by histochemical demonstration of lactate dehydrogenase (LDH) activity.

## MATERIALS AND METHODS

Post-mortem scalp skin of one donor with light skin and dark brown hair was used for the experiments. The sample was procured 8 hours post mortem, frozen and stored at  $-80^{\circ}\text{C}$ . The average hair density was  $244 \pm 26$  hairs/cm<sup>2</sup>, and the average hair diameter was  $68 \pm 12$   $\mu\text{m}$ . The hair of the post-mortem scalp sample was clipped to a length of approximately 0.5 mm. From this sample, 6-mm punch biopsies were obtained each containing an average of  $69 \pm 7$  hairs. The biopsies were placed into human, hairless, post-mortem back skin of  $3 \times 3$  cm<sup>2</sup> size and 1.5-cm thickness that was serving as a frame. In order to obtain good fit, an opening was prepared in the back skin using a 5-mm skin punch. The entire sample was placed on a temperature-controlled plate. A 120- $\mu\text{m}$  thermocouple was located below the biopsy to monitor the temperature of the specimen. The exposure was performed when an equilibrium temperature of  $30 \pm 1^{\circ}\text{C}$  was measured.

The exposures were performed with an 800 nm diode laser prototype with 9 mm spot size and a sapphire window maintained at room temperature. The fluence was kept constant at 35 J/cm<sup>2</sup> for all exposures. The pulsewidth was 30, 100, 200, 350, 400, and 500 ms equivalent to an irradiance of 1170, 350, 175, 100, 90, and 70 W/cm<sup>2</sup>. Before and after each exposure, a dermatoscopic image with crossed polarizing filters was taken (Dermaphot, Heine, Germany).

### Histochemical Technique

The samples were processed in horizontal frozen sections of 15- $\mu\text{m}$  thickness, and a histochemical evaluation of LDH activity was performed as described by Balogh et al. [5]. Representative micrographs were taken at a level close to the bulge.

## RESULTS

Evaluation of the dermatoscopic images demonstrated a strong dependence of pulsewidth on the alterations of the clipped HSs. For 30-ms pulsewidth, the HSs were ablated, and a brownish chromophore was released from the ablated HSs (browning). For 100-ms pulsewidth, only coarse HSs or HSs located in the same follicular unit of coarse HSs and adjacent HSs demonstrated some alterations such as apparent thickening and darkening. For

exposures with pulsewidths of 200 ms and longer, no HS alterations were observed at the surface after laser exposure.

Micrographs demonstrating LDH activity at the bulge level are shown in Figure 1a–e. HFs with similar HS diameter were selected. The inner root sheath (IRS) and the HS do not possess LDH activity at the bulge level and therefore do not stain blue. Thermal damage of the outer root sheath (ORS) or perifollicular cellular structures can be assessed by a sharply demarcated pale zone with loss of LDH activity. Selective loss of LDH activity of the ORS was observed for all pulsewidths from 30 to 400 ms. Some HFs also had a thin perifollicular cuff with loss of LDH activity. No significant variation of damage-zone diameter was observed with increasing pulsewidths for damaged single HFs at a fixed fluence of 35 J/cm<sup>2</sup>. The extent of the thermal damage for each HF was correlated to the coarseness and pigmentation of the HS. However, for pulsewidths longer than 200 ms, the percentage of damaged HFs decreased with increasing pulsewidths. For a pulsewidth of 500 ms corresponding to an irradiance of 70 W/cm<sup>2</sup>, no decrease of LDH activity was observed for any structure at the bulge level. For HFs that were located within a few hundred microns of each other, inter-follicular tissue damage was observed for all pulsewidths. This interfollicular damage was related to HS diameter, pigmentation, distance, and local HF density.

## THEORY AND DISCUSSION

As we can see from the experiment discussed above, the damage-zone size for similar HFs is pulsewidth-independent over a very broad range of pulsewidths (30–400 ms). Based on the classical theory of SP [1], this behavior is very typical for pulsewidths significantly shorter than the target TRT. However, in our case, the pulsewidths are close to or longer than the TRT (not shorter). The TRT of a HF with a diameter of 200–300  $\mu\text{m}$  is 25–55 ms; our 400-ms pulsewidth is approximately a factor of 7 longer than the maximum TRT. The next surprising result is that, even for relatively high-density targets such as scalp HFs, the thermal damage is still selective for pulsewidths where  $\tau \gg \text{TRT}$ . This experimental result stimulated us to investigate the thermal damage process of a target (such as a HF) that has a structure with spatial separation between part of the target and the pigmented area. As we show below, a new theory (the extended theory of SP) was required to correctly interpret our experimental results.

### Method of Selective Target Damage by Heat Diffusion

Thermal damage of this type of target (with separation between part of the target and the pigmented area) requires deposition of sufficient heat energy into the absorbing area and good heat exchange between this area and the targeted external structures. Heat deposition depends on the absorption coefficient of the absorber and the EMR power density. Heat exchange depends in turn on the distance between the heater and the outermost part of the target and on the heat transmission coefficient

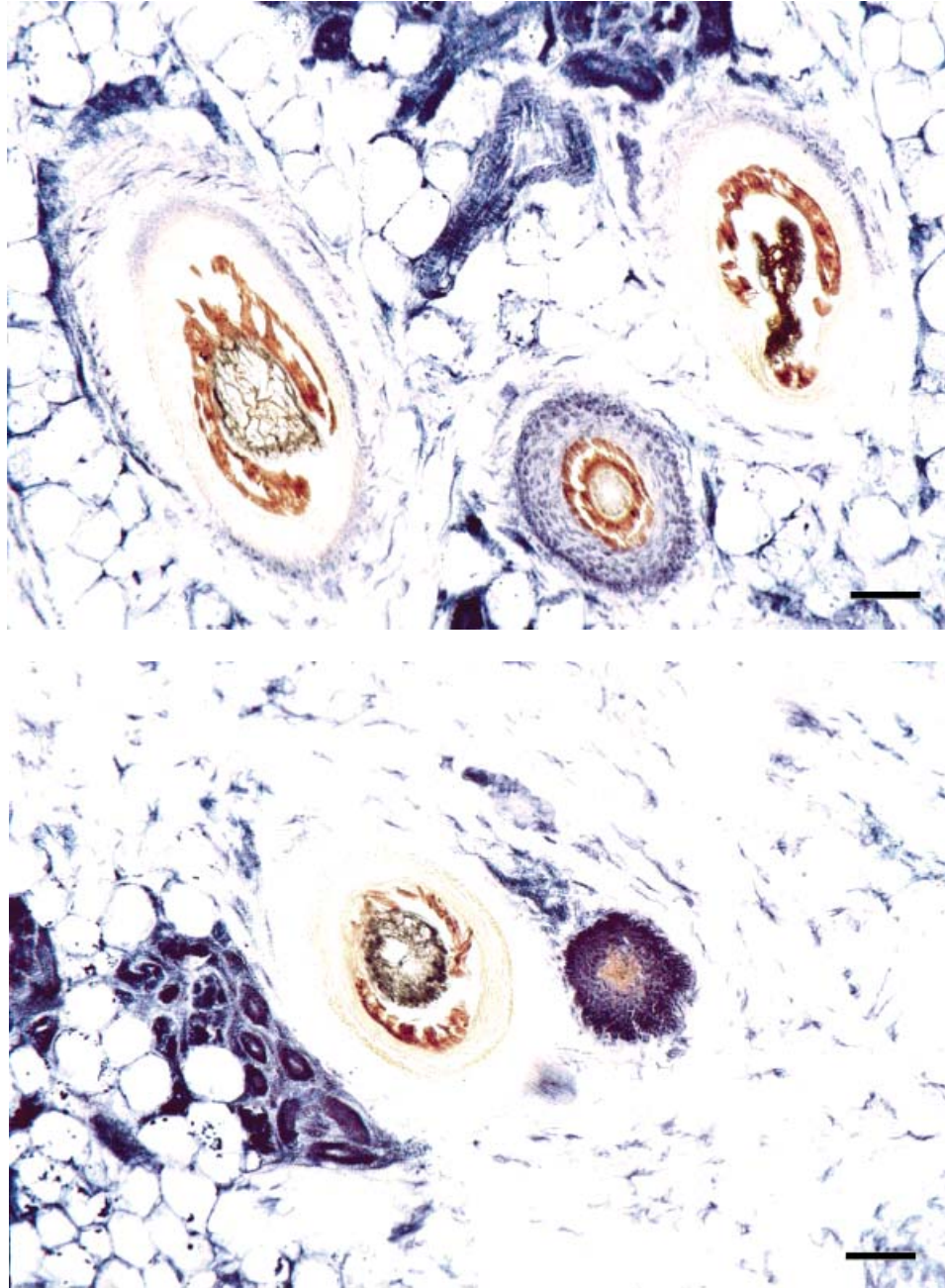


Fig. 1. Thermal damage pattern of HF at bulge level demonstrated by loss of LDH activity, fluence was  $35 \text{ J/cm}^2$ . Bar,  $100 \mu\text{m}$ . There is selective damage of the HF over a wide range of pulsewidths, and the extent of thermal damage depends on HS diameter and pigmentation. (A)  $\tau = 30 \text{ ms}$ ,  $I = 1170 \text{ W/cm}^2$ . Right HF demonstrates almost complete damage of ORS, HS structurally disintegrated with browning, fragments of HS partly protruded through ruptured IRS, no perifollicular damage. Left HF presents vacuoles within HS, no browning, IRS ruptured, partial loss of LDH activity of ORS and no perifollicular damage. Middle HF with fine and light pigmented HS does not demonstrate any HS alteration or loss of LDH activity. (B)  $\tau = 100 \text{ ms}$ ,  $I = 350 \text{ W/cm}^2$ . Right HF without any HS alteration or loss of LDH activity of ORS.

Left HF with vacuoles within HS, IRS ruptured, loss of LDH activity of entire ORS and a thin cuff of perifollicular tissue. (C)  $\tau = 200 \text{ ms}$ ,  $I = 175 \text{ W/cm}^2$ . No HS alterations for both HF. Right HF with minor loss of LDH activity of ORS. Left HF with partial loss of LDH activity of ORS. No perifollicular damage. (D)  $\tau = 200 \text{ ms}$ ,  $I = 175 \text{ W/cm}^2$ . No HS alterations for both HF. Right HF with partial loss of LDH activity of ORS. Left HF with complete loss of LDH activity of ORS. Interfollicular damage of these adjacent HF with only  $300 \mu\text{m}$  interfollicular distance. Note more pronounced pigmentation of HSs than in Fig. 1C. (E)  $\tau = 350 \text{ ms}$ ,  $I = 100 \text{ W/cm}^2$ . No HS alterations for both HF, IRS not damaged, partial loss of LDH activity for both HF, more pronounced loss for HF with more pigmented HS.

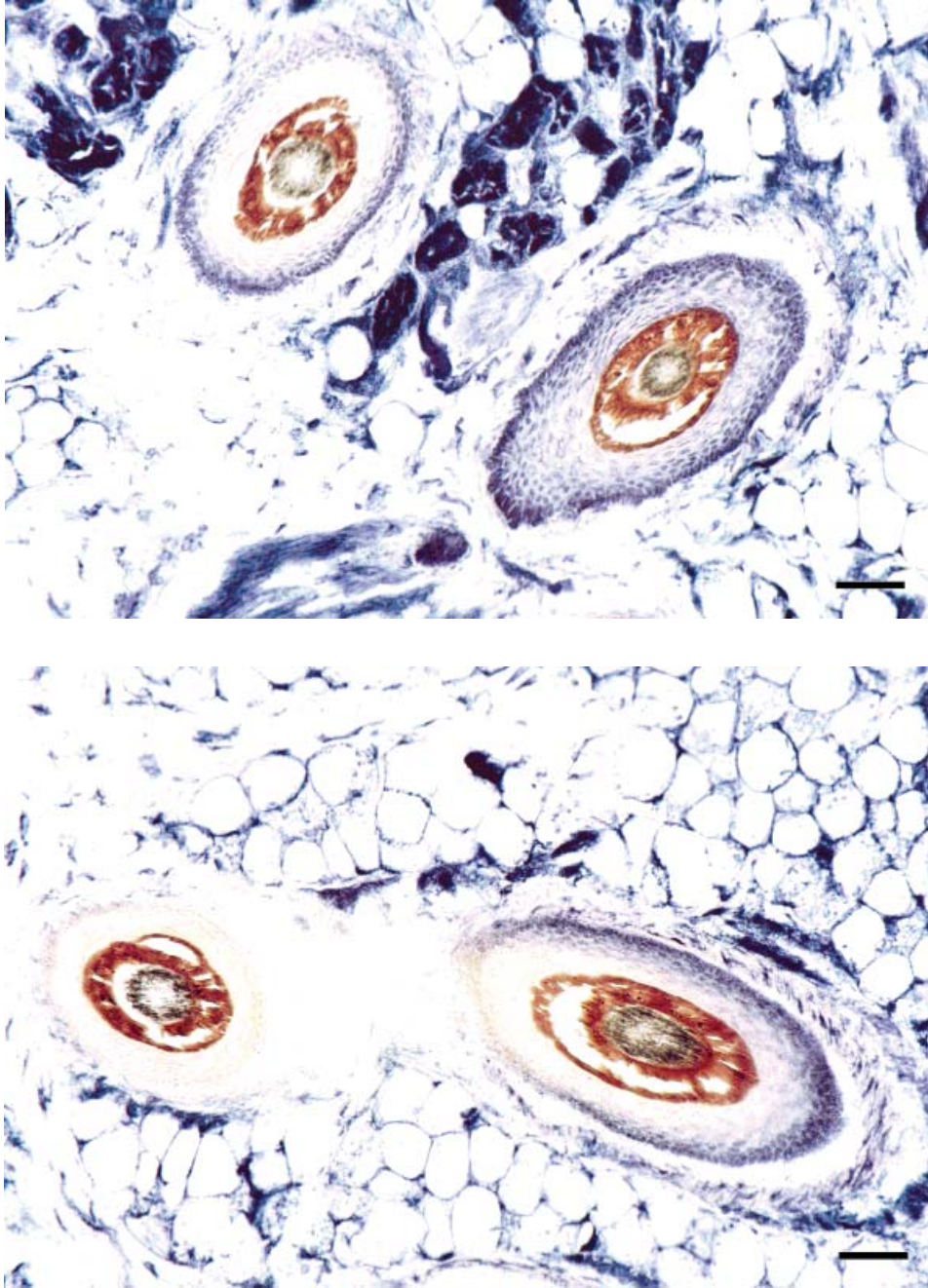


Fig. 1. (Continued)

between the absorber and the intervening tissue. However, at a sufficiently high temperature both the heater absorption coefficient and the heat transmission coefficient from the heater to the other targeted tissues may become lower due to phase transitions and destructive processes such as bleaching, melting, boiling, and bubble formation. This results in inefficient use of EMR energy for phase transition processes within the absorber and the intervening tissue. To prevent these undesirable effects, the heater peak temperature has to be limited to a

prescribed value,  $T_{1\max}$ , called hereafter the “heater absorption loss temperature” that is the temperature of heater absorption loss.  $T_{1\max}$  of most natural chromophores (e.g. melanin, hemoglobin, and water) exceeds  $100^{\circ}\text{C}$ . Simultaneously, to ensure permanent damage of the whole target, the temperature should exceed a second prescribed value, the damage temperature  $T_2$ , throughout the target area. This temperature is lower than the heater absorption loss temperature  $T_{1\max}$ . More precisely, the damage temperature,  $T_2$ , is the temperature at which

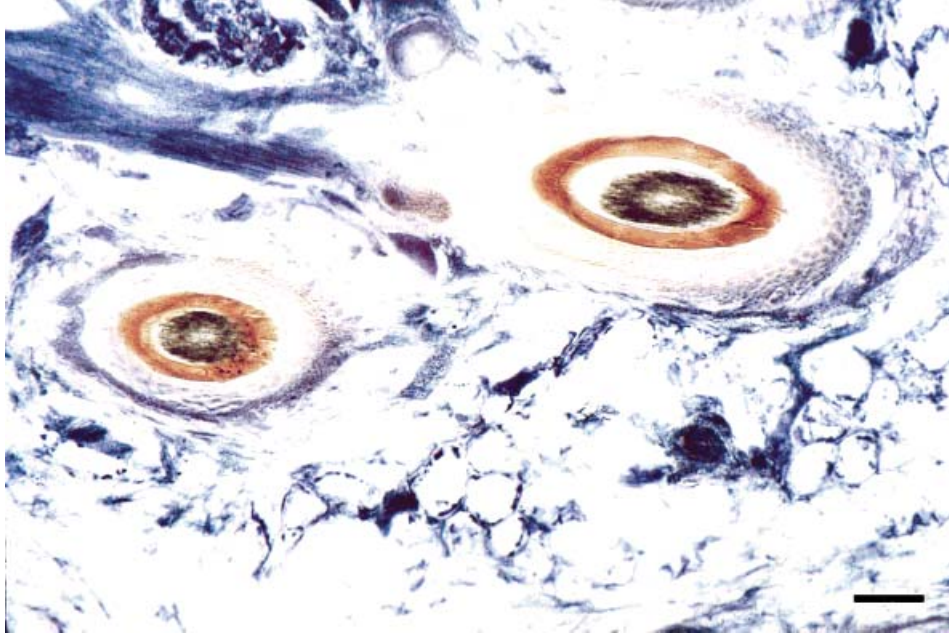


Fig. 1. (Continued)

irreversible thermal damage of the target occurs. We suggest that the basic damage mechanism in soft tissue is the denaturation of proteins. As an alternative to the rigorous Arrhenius rate process integral [6], the dynamic denaturation process may be described approximately by using the simpler damage-temperature concept. For human-skin collagen,  $T_2$  is about 65–75°C and for cells  $T_2$  is about 60°C if the exposure duration is several tens of milliseconds [6]. Furthermore, the tissue temperature should not exceed the water boiling point to prevent formation of vapor bubbles that could insulate the absorbing area from the surrounding tissue. Strictly speaking, vapor bubbles can transfer heat from the absorbing area to the target, but this process is unpredictable because vapor bubbles can move in different directions.

To meet the temperature limitations described above, the EMR power must be limited, (but sufficient to heat the target up to the damage temperature) and, therefore, the EMR pulse has to be made sufficiently long to deliver enough energy. We define the thermal damage time (TDT) of the target to be the time required for irreversible target damage with sparing of the surrounding tissue. For a non-uniformly absorbing target structure, the TDT is the time when the outermost part of the target reaches the target damage temperature  $T_2$  through heat diffusion from the heater. Because the heat-diffusion front becomes blurred when propagating into the tissue, part of the heat energy will leave the target. Therefore, the heated area will be larger than the damaged area. However, we demonstrate below that target damage can still be selective even though the TDT is many times as long as the TRT of the whole target. Apparently, the optimum EMR pulsewidth,  $\tau_0$ , should be shorter than or equal to the TDT. So, in contrast to the standard theory of SP, non-uniformly pigmented

structures have to be treated by long EMR pulses: the pulsewidth must typically be longer than the target TRT. In addition, the EMR power should be limited to prevent reduction of the heater absorption by bleaching, vaporization, etc.

Figure 2 shows the general structure of a “target” that is thermally denatured by heat diffusion from a “heater”. The heater includes a natural or artificial chromophore (pigment) with a high photon absorption coefficient. The target exhibits weak EMR absorption. The distance between the heater and the target is  $d$ . Photons from the EMR source are absorbed by the heater. As discussed in the previous section, the EMR power density has to be adjusted so that during the time of treatment the heater temperature  $T_1$  does not exceed the temperature  $T_{1\max}$  where the absorption coefficient may begin to drop. The

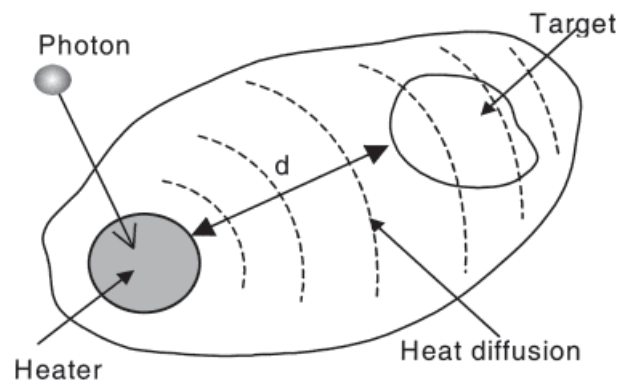


Fig. 2. General structure of biological target with space separation between target and absorber (heater).

heat propagates from the heater to the target due to either thermal diffusion or two other possible mechanisms. The two other mechanisms are hot ablation products emanating from the heater or steam. In this paper, we concentrate exclusively on the thermal diffusion mechanism. The process of target thermal damage is finished when its temperature reaches  $T_2$ , while the temperature of the surrounding tissue remains below its damage temperature. In general, it is not possible to damage the target without damaging the tissue between the target and the heater. For this target type, precise selective damage of the target is impossible. But if the treated target is a layer or a shell of tissue roughly symmetrical with respect to the heater, the target damage can be made precisely selective. This means that the damage zone covers the whole target without extending beyond it. After the end of the EMR pulse, the target temperature at the outermost point goes on growing until it reaches a maximum. The time delay between the end of the EMR pulse,  $t = \tau_0$ , and the moment when the temperature of the outermost point is reached the maximum temperature  $T_2$  is denoted by  $\varepsilon$  and thus  $\text{TDT} = \tau_0 + \varepsilon$ . Therefore, the EMR pulsewidth is equal to or shorter than the TDT. This delay  $\varepsilon$  is roughly equal to the propagation time of the heat front from the heater to the target  $\varepsilon \cong d^2/k$ , where  $k$  is the thermal diffusivity of the tissue ( $k \cong 0.1 \text{ mm}^2/\text{sec}$ );  $\varepsilon$  is therefore close to the target TRT. As we shall see subsequently, TDT is significantly longer than the TRT in most cases. So, for selective treatment the pulsewidth should be approximately equal to the TDT:  $\tau_0 \cong \text{TDT}$ . The TDT depends in turn on  $T_1$ ,  $T_2$ , and the target size. For a better understanding of this dependence we first look more closely at heat diffusion from the heater to the target. Specifically, we focus on a target comprising a heavily pigmented long cylinder of diameter  $d_1$  and a surrounding treated area of diameter  $d_2$  (Fig. 3). This simple geometry can be used to model thermal damage of HF by HS heating or blood vessel destruction. We consider two heating modes. The first mode utilizes a "rectangular EMR pulse" (Fig. 4a) and the second one utilizes a "rectangular temperature pulse" (Fig. 4d). In the case of the rectangular EMR pulse, the heater temperature grows during the EMR pulse and reaches  $T_1$  at the end of the pulse (Fig. 4b). In the case of the rectangular temperature pulse, the temperature of the heater is constant during the EMR pulse, which requires a special pulse shape (Fig. 4c). For both heating modes, the heater temperature is below the heater absorption loss temperature  $T_{1\text{max}}$  so the absorption coefficient of the heater does not change.

The sequence of thermal profiles during the heating process is depicted in Figure 3. The input parameters for modeling are  $d_1 = 70 \mu\text{m}$ ,  $d_2 = 210 \mu\text{m}$ . The temperature  $T_1$  is  $100^\circ\text{C}$  (the boiling point of water). The damage temperature is  $65^\circ\text{C}$ , which is the average protein denaturation temperature in the 10–1000 ms pulsewidth range. We assume that the EMR absorption is confined to the heater and that the thermal properties of the heater, the target and the surrounding tissue are the same. Heat diffusion from the heater takes place simultaneously with

the growth of the heater temperature due to light absorption. This process is described well by the heat conduction equation. Figure 3a,b show the temperature profiles in the cylindrical target and the surrounding tissue at different instants of time for the rectangular EMR pulse and the rectangular temperature pulse, respectively. Curve 1 in both figures is the temperature profile at the time equal to the TRT of the whole target. The later time is  $\text{TRT} = d_2^2/16k$ . In our case the  $\text{TRT} = 27 \text{ ms}$ . We can see that at the time instant  $t = \text{TRT}$  the boundary temperature of the target is still significantly below the damage temperature. Curve 2 in both figures is the temperature profile at the moment when the boundary temperature of the target reaches the damage temperature  $T_2$ . At this moment, the whole target becomes damaged but the surrounding tissue is still intact. It is this time that has been defined above as the TDT. In our case  $\text{TDT} = 0.63 \text{ second}$  for the rectangular EMR pulse and  $\text{TDT} = 0.16 \text{ second}$  for the rectangular temperature pulse. Based on this example, we can make two main conclusions. First, the ratio  $\text{TDT}/\text{TRT}$  is about 23 and 6 for the rectangular EMR pulse and the rectangular temperature pulse modes, respectively. Therefore, in both modes the pulsewidth  $\tau = \text{TDT}$  is significantly longer than the TRT of the entire target. Second, at the time instant when  $t = \text{TDT}$  the heated area is significantly larger than the damaged target. These observations present a striking contrast to the classical case of SP. The distinction above is a result of the spatial separation of the heavily pigmented and the treated areas. Actually, in contrast to the classical case, the basic damage mechanism is now heat diffusion rather than direct heating by EMR absorption. The heat diffusion front is not sharp and, therefore, heat is spreading outside the damaged area; however, the damage is still rather selective.

We have described the difference in treatment modality between uniformly and non-uniformly pigmented targets. The new extended theory of selective thermal damage of non-uniformly pigmented structures in biological tissue postulates the following:

1. The EMR wavelength should be chosen to maximize contrast between the absorption coefficient of the pigmented area and that of the tissue surrounding the target. This postulate is identical to the case of classical SP.
2. The EMR power should be limited to prevent absorption loss in the pigmented area, but it must be sufficient to achieve a heater temperature higher than the target damage temperature.
3. The pulsewidth should be made shorter than or equal to the TDT, which can be significantly longer than the TRT of the target.

### Treatment Parameters for Planar, Cylindrical, and Spherical Targets

Heat diffusion is strongly dependent on the heater and target geometry. In this section, we discuss three basic

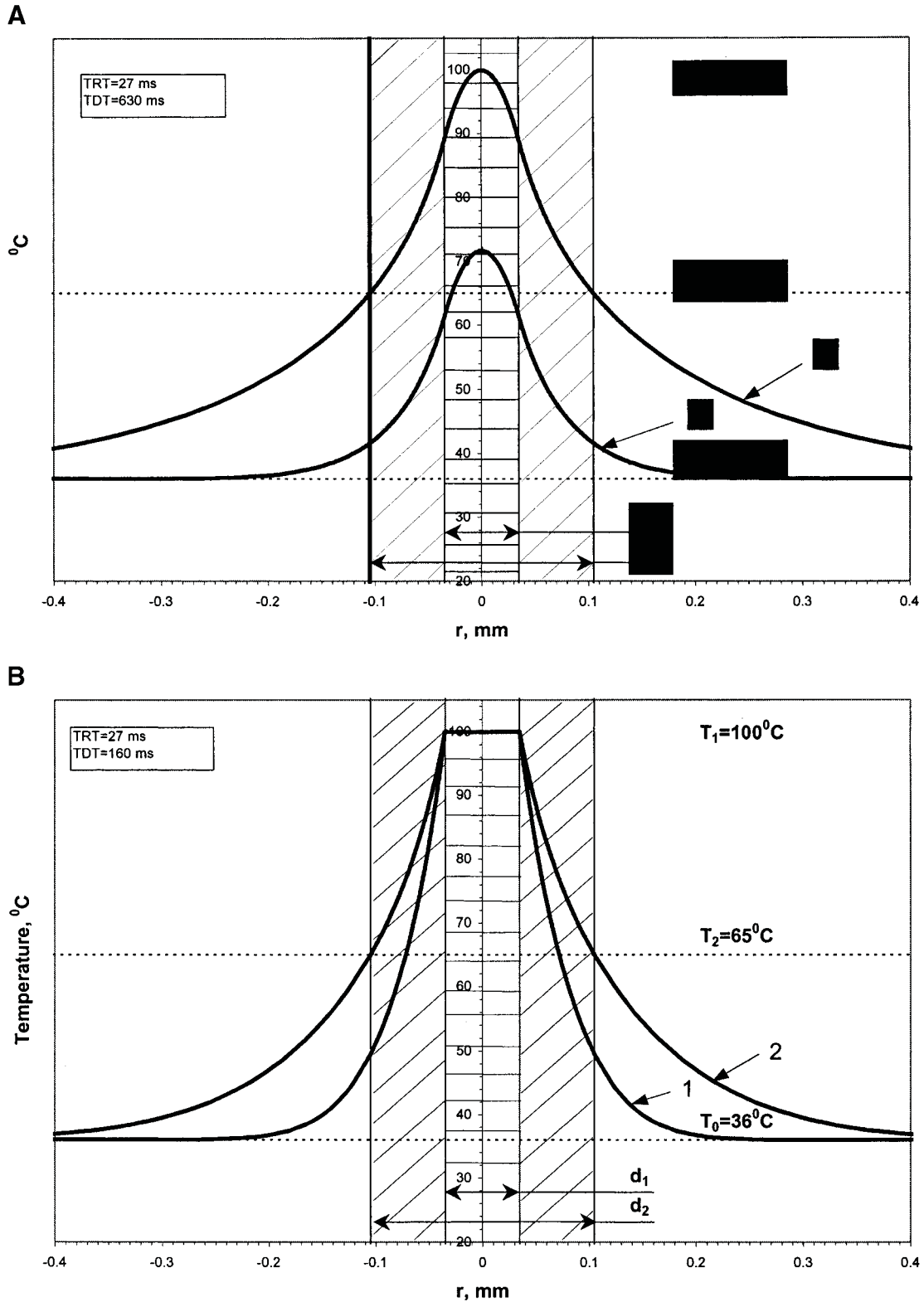


Fig. 3. Temperature distribution in the tissue with cylindrical absorber with diameter 0.07 mm and target with diameter 0.21 mm. (A) Shows the temperature distribution for a rectangular EMR pulse at two points in time: bottom curve at  $t = \text{TRT} = 27.5$  ms and top curve at  $t = \text{TDT} = 1.6$  seconds. (B) Shows the temperature distribution for a rectangular

temperature pulse at two points in time: bottom curve at  $t = \text{TRT} = 27.5$  ms and top curve at  $t = \text{TDT} = 0.36$  seconds. Maximum temperature of the absorber is  $T_1 = 100^{\circ}\text{C}$ . Damage temperature is  $T_2 = 65^{\circ}\text{C}$ . Initial temperature is  $T_0 = 37^{\circ}\text{C}$ . The absorption of surrounding heater tissue was neglected.

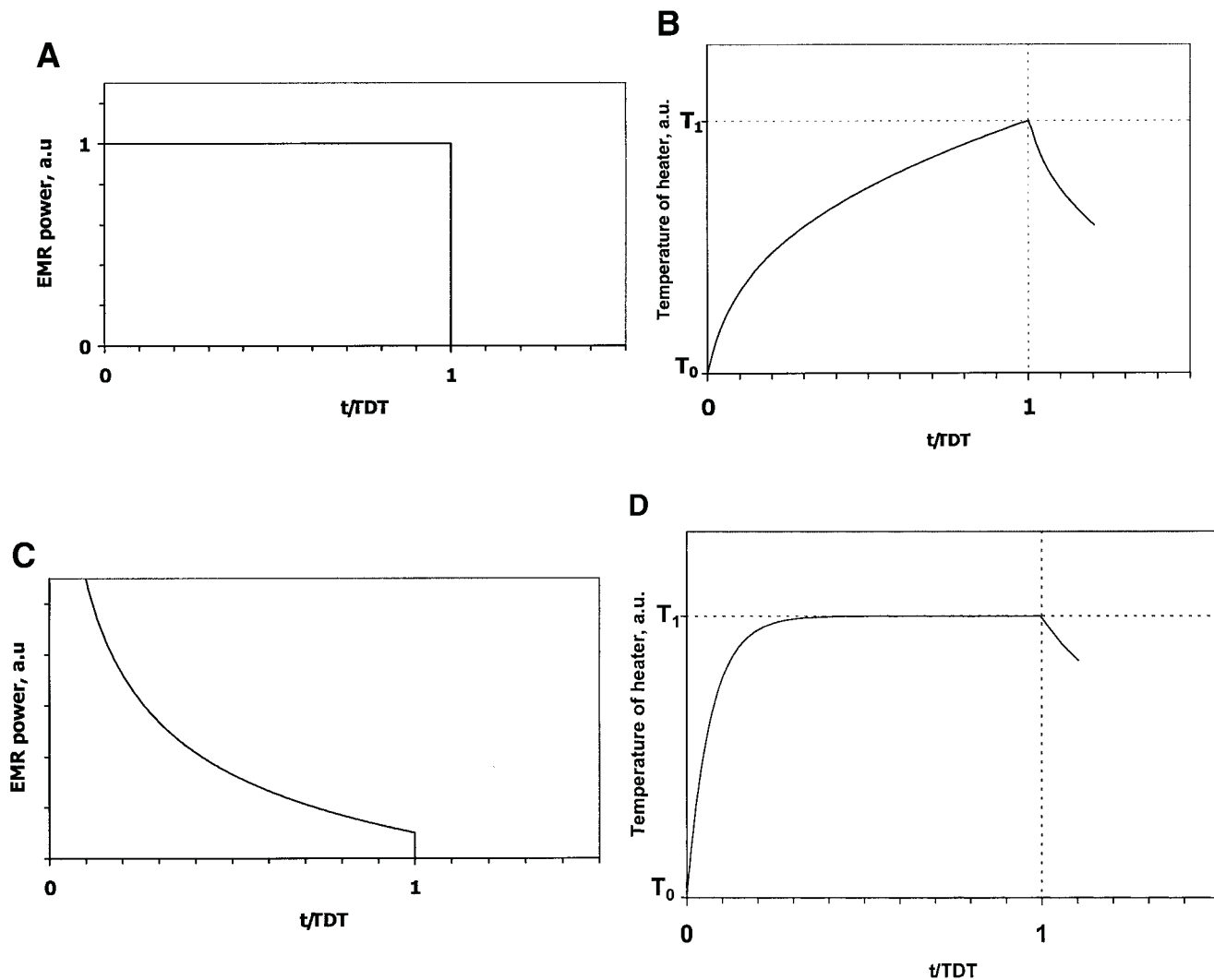


Fig. 4. Time dependence of EMR power and temperature of the heater (absorber). Two basic cases are shown: (A) rectangular EMR pulse and (D) rectangular temperature pulse. (B) Shows heater temperature as a function of time that is produced by a rectangular EMR pulse. (C) Shows EMR power as function of time that produces a rectangular temperature pulse at the heater.

geometries: planar, cylindrical, and spherical (Fig. 5). In all cases, we assume a heater with size  $d_1$  located in the center of a target with size  $d_2$ . We define the ratio  $x = d_2/d_1$  to be the geometrical factor of the target. As before,  $T_1$  is the maximum temperature of the pigmented area, and  $T_2$  is the target damage temperature ( $T_1 > T_2$ ). As we show in the Appendix, the target TDT can be expressed by the following formula:

$$TDT = TRT \times r(x, \Delta)$$

where  $r(x, \Delta)$  is a function of the geometrical factor  $x$  and temperature factor  $\Delta$  defined as  $\Delta = (T_2 - T_0)/(T_1 - T_0)$ .  $T_0$  is the target and heater temperature before irradiation. Normally  $T_0$  is body temperature and is equal to 37°C. TDT is proportional to the TRT. In the Appendix, we present formulas for the TDT of planar, cylindrical, and spherical targets. Figure 6 shows the ratio  $r(x, \Delta) =$

TDT:TRT as a function of geometrical factor  $x$  for two heating modes: rectangular EMR pulse and rectangular temperature pulse. The calculation parameters were  $T_1 = 100^\circ\text{C}$ ,  $T_2 = 65^\circ\text{C}$ ,  $T_0 = 37^\circ\text{C}$  ( $\Delta = 0.52$ ).

We emphasize that in the framework of our analytic theory, the ratio  $r(x, \Delta)$  does not depend on the size of the entire target and the tissue thermal properties. Several important conclusions follow from Figure 6.

First, the ratio TDT/TRT is an increasing function of geometrical factor  $x$ .

Second, the actual value of this ratio is very different for plane, cylindrical, and spherical targets. For a plane target, the TDT is several times higher than the TRT. The TDT exhibits appreciable growth with increasing the target dimensionality. It is implied herein that the planar, cylindrical, and spherical targets are one-, two-, and three-dimensional, respectively.



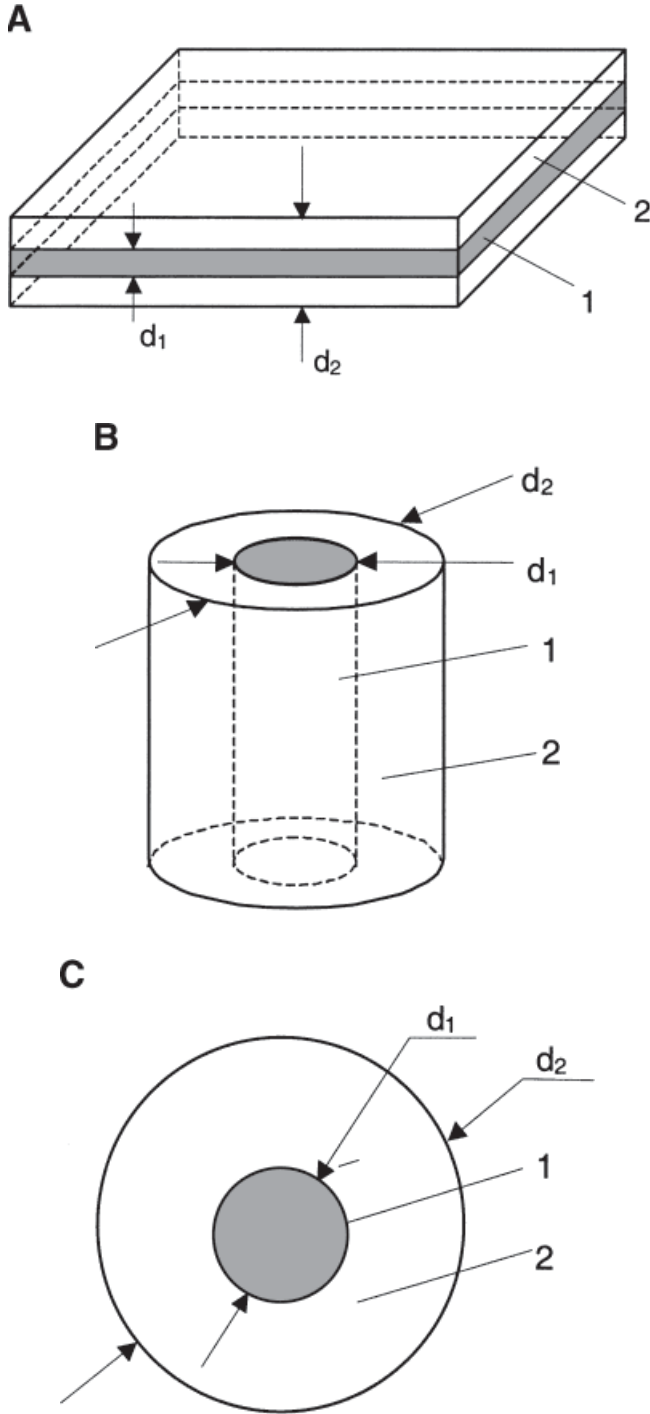


Fig. 5. Three types of target with different geometry: (A) planar, (B) cylindrical, (C) spherical. 1 is the heater (absorber); 2 is the target;  $d_1$  is size of the heater;  $d_2$  is size of the target.

Third, for the same TDT/TRT, the relative size of the damaged zone  $x$  is smallest for the spherical target. Next in this order is the cylindrical target. The plane target exhibits the largest damage area. The relative size  $x$  of the damaged zone around the heater decreases when increas-

ing the target dimensionality. The later two conclusions are intuitively apparent. Actually, conductive heating of a weakly absorbing tissue should proceed more effectively for a low-dimensional target. This "dimensionality" concept is a useful target parameter. It is also applicable to non-symmetrical targets. The temperature profile is sharper and better localized for the spherical heater compared to the cylindrical one and it is better for the cylindrical than the planar heater. For the classical case of SP, the target geometry is not important because thermal damage is confined to the same area as the EMR absorption and direct heating. In our case, thermal damage due to heat diffusion is confined to an area that is distinct from the heater. The dependence of heat diffusion on heater geometry is very strong.

Fourth, the ratio TDT/TRT depends strongly on heating mode. The rectangular EMR pulse mode (Fig. 4a) represents the gentlest heating mode because the heater temperature reaches maximum  $T_1$  at the end of the pulse (Fig. 4b). The ratio TDT/TRT is a maximum for this mode. The rectangular pulse mode (Fig. 4d) represents the most aggressive heating mode because the heater temperature reaches a maximum just after the beginning of the pulse and the maximum heater temperature takes place during the EMR pulse. The ratio TDT/TRT is a minimum for the rectangular temperature pulse mode. As mentioned above the rectangular temperature pulse mode can be realized by using an EMR pulse with a special temporal profile. The initial power density should be very high to raise the heater temperature abruptly (for a time interval of the order of or shorter than the TRT). After the maximum temperature is reached, the power density should undergo a steep fall to prevent overheating. Then, to maintain the heater temperature at the prescribed level (Fig. 4d), the power density should fade gradually to compensate the heat flow out of the heater. The pulse power should be precisely adjusted to keep maximum temperature of the heater  $T_1$  below the temperature of heater absorption loss  $T_{1max}$ . The power depends on heater absorption and size and the EMR attenuation in tissue (see Appendix). In reality, it is probably difficult to exactly create these two modes. Thus, the real value of TDT can be between these two extreme cases.

The ratio TDT/TRT depends on the temperature factor  $\Delta = (T_2 - T_0)/(T_1 - T_0)$ . Table 1 shows the influence of initial target temperature  $T_0$  and maximum heater temperature  $T_1$ . All calculations were done for a cylindrical target with the same size as Figure 4 for the rectangular EMR pulse. The TDT increases by a factor of 2.6 by precooling from 37 to 27°C and decreases by a factor of 2.3 by preheating to 45°C. The fluence should be changed at the same time. If the heater temperature can reach a high value without losing absorption, the TDT can be significantly reduced. The ratio TDT/TRT is about 1.5–2 (TDT = (1.5–2)·TRT) for the case when the heater temperature is 200–250°C. In biological tissue, such a high temperature can be expected in melanin in the HS or in an artificial chromophore such as carbon. But we must

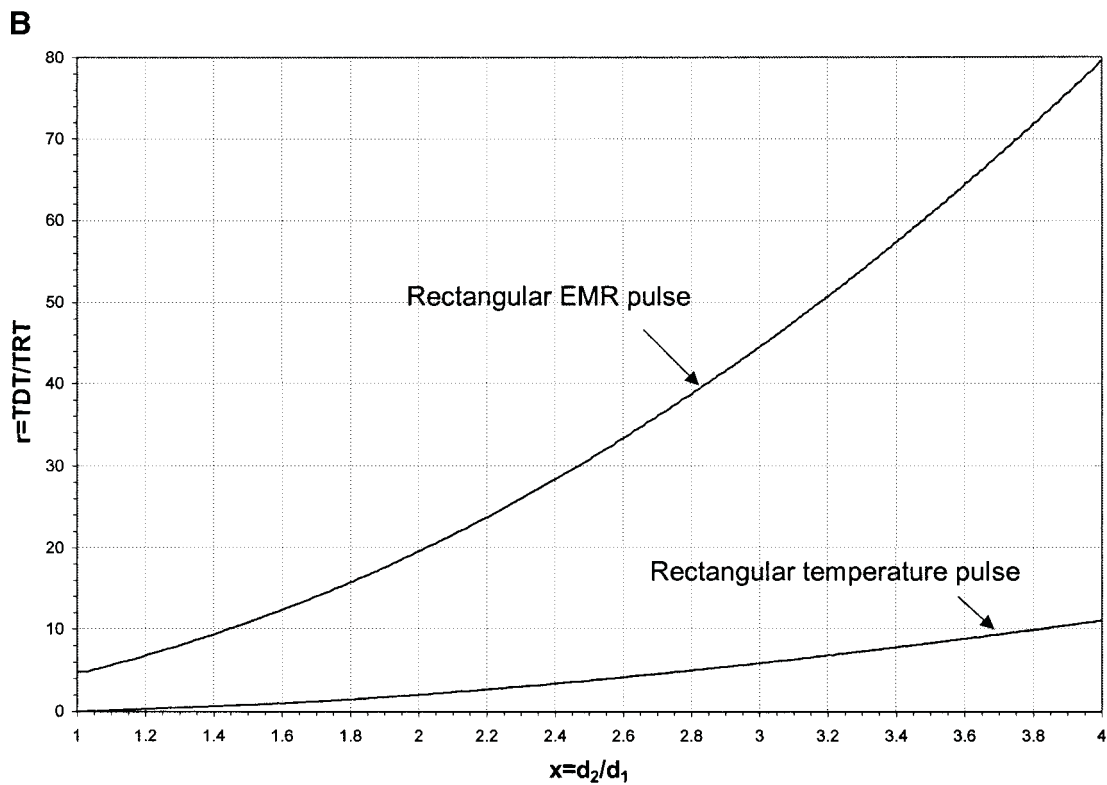
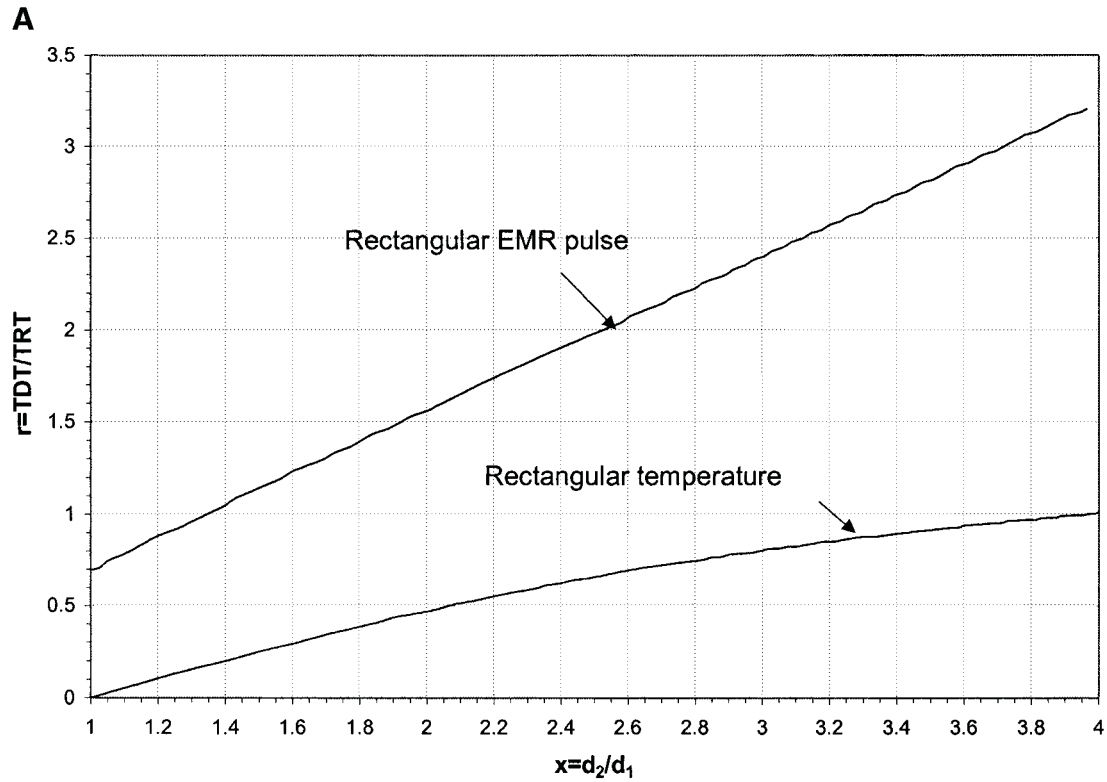


Fig. 6. The ratio  $r$  of TDT and thermal relaxation time (TRT) as a function of ratio  $x$  of size of the target  $d_2$  and size of the heater  $d_1$  for different target geometries: (A) planar, (B) cylindrical, (C) spherical. Ratio  $r = \text{TDT}:\text{TRT}$  is given for two heating modes: rectangular EMR pulse and rectangular temperature pulse.

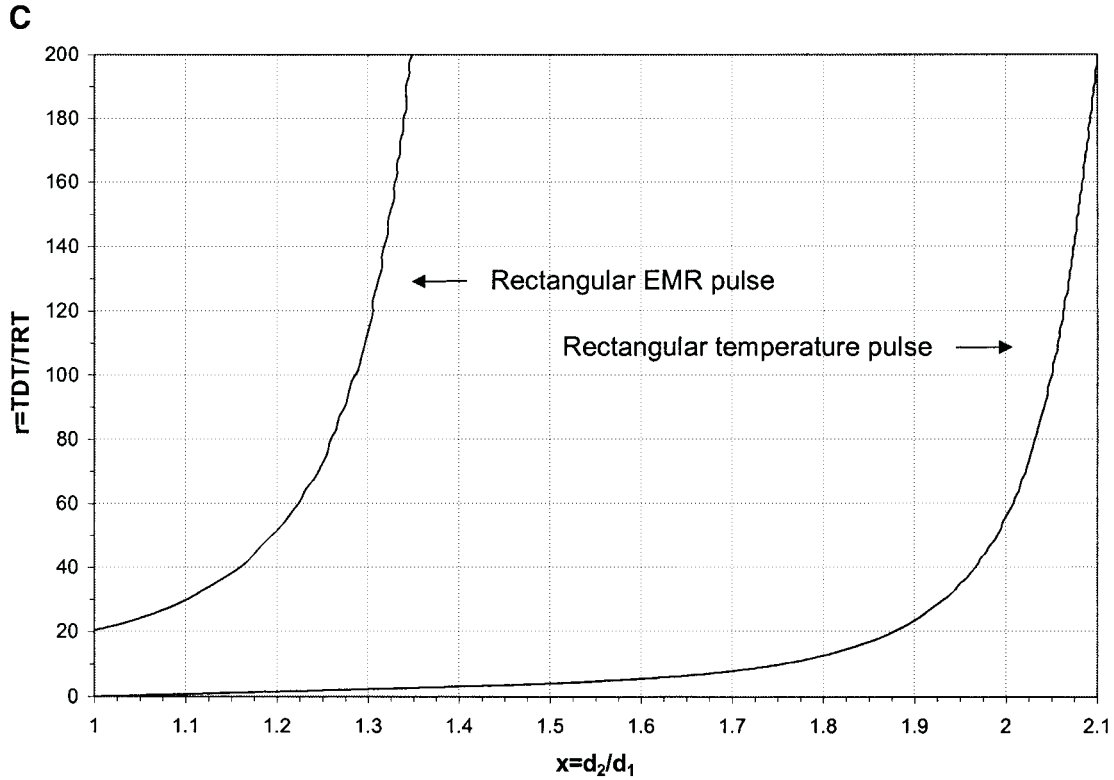


Fig. 6. (Continued)

remember that the thermal diffusivity can drop in the tissue surrounding the heater due to water vaporization. So this case is very difficult to predict.

As we have shown above, heat diffusion from the heater is very different for different target geometries. The heater temperature should depend on the heater geometry. Figure 7 shows the heater center temperature as a function of pulsewidth for a rectangular EMR pulse with the same power. Spherical, cylindrical, and planar heaters have equal: size  $d_1$ , thermal properties, and EMR absorption coefficient. The TRT of the heater  $\tau_r$  depends on geometry, and the ratio is 1:2:3 for spherical, cylindrical, and planar heaters, respectively. If the pulsewidth  $\tau$  is significantly shorter than the TRT of the heater ( $\tau \ll \tau_r$ ) the temperature rises of all the heaters exhibit the same elevation of temperature. However, as shown in Figure 7, the temperature behavior of heaters with different geometries is very different for pulsewidth

equal to or longer than  $\tau_r$ . A steady state heater temperature for a rectangular EMR pulse is possible only for a spherical heater. For cylindrical and especially for planar heaters, the temperature is continuously rising when the pulsewidth is increasing (the power density should be constant, the energy density should be proportional to the pulsewidth). This is because 3D heat diffusion from the spherical heater (in contrast with 2D and 1D heat diffusion from the cylindrical and planar heaters respectively) can compensate constant heating from the rectangular EMR pulse. This phenomenon is very important for uniform targets when the heater and target are the same. For example, the temperature of epidermis (planar target) for a rectangular optical pulse at a wavelength strongly absorbed by melanin will continuously rise during a long pulse ( $\tau \gg \tau_r$ ). However, for a spherical target such as the hair bulb matrix, the temperature will stabilize at a steady-state level. To produce a constant

**TABLE 1. TDT as Function of Temperature Factor**

Initial temperature $T_0$ , °C	Maximum temperature of the heater $T_1$ , °C	Temperature of damage $T_2$ , °C	Temperature factor $\Delta$	TDT/TRT
37	100	65	0.44	21
27 (precooling)	100	65	0.52	53
45 (preheating)	100	65	0.36	9.1
37	200	65	0.17	2.0
37	240	65	0.14	1.5

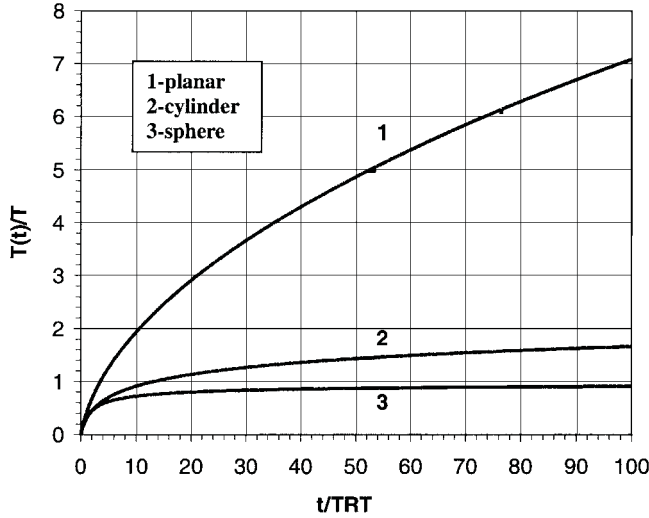


Fig. 7. Increase of heater temperature  $T(t)$  normalized to steady state and temperature of spherical heater increase  $T_0$  as a function of heating time for rectangular pulse and different type of heaters with the same size: (1) planar, (2) cylinder and (3) sphere.

heater temperature (rectangular temperature pulse as shown in Figure 4d), the EMR pulse shape must be special (Fig. 4c) with a strong peak in the beginning and decaying amplitude.

### Mechanism of Selective Damage of High Density Targets by Heat Diffusion

Since the results obtained in the above sections were presented just for isolated targets, it is important to see the effect of high-density targets. As shown above, non-pigmented targets located close to pigmented areas can be destroyed by heat diffusion. However, heat flux will leak out of the target and the heating area will be larger than the target. This increases the risk of overheating the tissue surrounding the target and thus the risk of unselective damage. Very roughly the fluence to produce unselective bulk tissue damage  $F_{NS}$  is  $(d_3/d_2)^n$  times higher than the fluence required to produce selective damage  $F_S$ , where  $d_2$  and  $d_3$  are the target size and distance between target centers, and  $n$  is 1, 2 or 3 for planar, cylindrical, and spherical targets, respectively. So as a first approximation,  $F_{NS}/F_S$  is proportional to the ratio of target volume and tissue bulk volume and is independent of pulsewidth. The risk of unselective damage increases in the following order: spherical, cylindrical, and planar targets.

More precisely, consider this problem for the ideal model of cylindrical targets with equal spacing. Figure 8 shows the dependence of  $F_S$  and  $F_{NS}$  on the density factor  $y = d_3/d_2$  for a rectangular temperature pulse. As seen from Figure 8,  $F_S$  decreases as a function of  $y$ . This effect is explained by the influence of heat fluxes from neighboring targets. But at the same time, the  $F_{NS}$  is continuously dropping as function of density factor  $y$ . So approximately for  $y < 4$  the range of safe fluences is going to be very narrow and the risk of unselective damage will

increase. In the case of short pulse/high-power irradiation where the chromophore is ablated, the energy delivered to the tissue is therefore limited. This provides additional protection in the case of high-density target treatment.

### Applications of the Extended Theory of SP

Now we are going to discuss applications of the new theory. Thus far, we have considered at some length the method of selective photodamage of unpigmented targets in the tissue. We will present two examples where the new theory can be applied: photoepilation and photosclerotherapy.

**Photoepilation.** Photoepilation utilizes light to cause thermal or mechanical damage of HF's. To achieve hair growth delay, it is sufficient to either damage matrix cells of anagen HF's or coagulate blood vessels of the papilla or possibly to destroy part of the ORS [2]. For permanent hair-follicle damage, in accordance with current knowledge, it is necessary to damage stem cells that are located in the bulge area at the interface of the ORS and the connective tissue sheath [7]. One can also irreversibly damage a HF at the level of the dermis by replacing it with connective tissue.

The matrix cells produce the HS. The matrix cells contain melanosomes that produce hair melanin. The concentration of melanin in the matrix cells is significantly higher than in the HS. Melanin is distributed uniformly and densely in the matrix cells. So for a pulsewidth longer than the TRT of individual melanosomes ( $1 \mu s$ ), the matrix cells act as a uniformly pigmented target. This is a typical example of a target where standard SP theory is applicable. For selective and effective treatment, the energy and

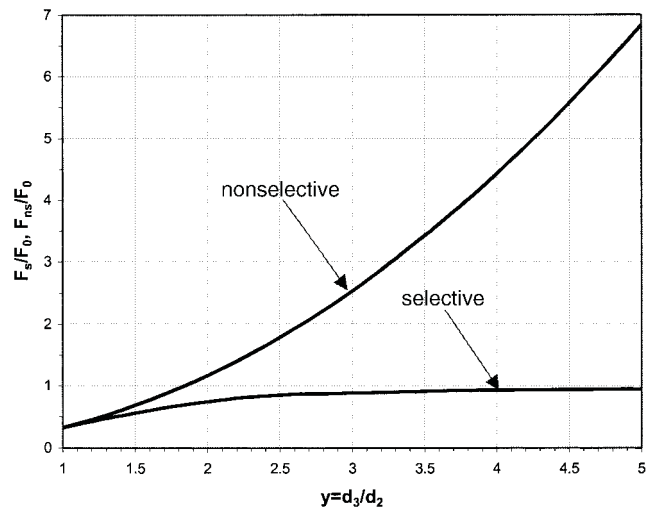


Fig. 8. Damage fluence for high density targets as a function of density factor  $y$  (ratio of distance between centers of targets  $d_3$  and size of the target  $d_2$ ). Figure shows dependence of damage fluence for selective  $F_S$  (bottom curve) and nonselective  $F_{NS}$  (top curve) damage on density factor  $y$ . Both curves are normalized to the damage fluence of individual target  $F_0$ . Calculations were done for a cylindrical individual target with parameters the same as those used for Figure 3.

**TABLE 2. Optimum Pulsewidth for Hair-Follicle Treatment**

Hair type/diameter	TRT of HS, ms	TRT of HF, ms	TRT of hair matrix, ms	Halting HS growth		Permanent hair-follicle destruction	
				TDT of papilla blood vessel, ms		TDT of stem cell, ms	
				Rectangular temperature pulse	Rectangular light pulse	Rectangular temperature pulse	Rectangular light pulse
Fine/30 $\mu$	0.6	5.4	<0.3	0.5	1.5	30	115
Medium coarse/70 $\mu$	3	27	<2	2.7	8.5	170	610
Large coarse/120 $\mu$	9.6	87	<5	8	21	510	1800

pulsewidth have to be significantly shorter than the TRT of the matrix cells. The matrix cells form a dome-shaped structure with the smallest cells close to half of the HS diameter  $d_h$ . So the TRT of the hair matrix can be estimated as the TRT of a layer with thickness  $d_h/2$ , that is  $d_h^2/32k$ . The pulsewidth values for effective treatment are presented in Table 2.

Another method of halting HS growth is to coagulate blood vessels in the papilla. The loop of blood vessels in the papilla is located in the center of the matrix cell dome. Blood absorption is significantly lower than melanin absorption in the neighboring matrix cells because of the small vessel size. So the most effective method of papilla blood vessel coagulation is to utilize heat diffusion from the matrix cells that absorb light. This is a typical case where the extended theory of SP can be applied. The highly pigmented heater (the matrix cells) and the lightly pigmented target (the blood vessels) are separated by distance about  $d_h/2$ . We calculated the TDT of the hair papilla blood vessels using our thermal diffusion model assuming the maximum heater temperature to be  $T_1 = 100^\circ\text{C}$  and the blood vessel coagulation temperature to be  $T_2 = 65^\circ\text{C}$ . The TDT values for different hair sizes and heating modes are presented in Table 2. We can see a significant difference in optimum treatment pulsewidth for: (1) the matrix cells by direct light absorption and (2) the papilla blood vessel loop by heat diffusion.

Let us now consider damage of hair stem cells. They are located in the basal cell layer of the ORS of the lower isthmus. The stem cells do not have any pigment that can effectively absorb light in the therapeutic window (600–1200 nm), which is also the best wavelength range for photoepilation [2]. However, the stem cells can be damaged by heat diffusion from the melanin-rich HS or an artificial chromophore inside the IRS. This case is very well described by the cylindrical model that we considered in some detail above. The optimum treatment pulsewidth of the stem cells is close to the TDT of the follicle structure. If we assume that the maximum HS temperature is  $T_1 = 100^\circ\text{C}$  and the damage temperature of the stem cells is  $T_2 = 65^\circ\text{C}$ , we can calculate the TDT as shown in Table A2 (approximate formulas give us slightly lower values than the exact modeling we presented in Figure 6b). Calculation results for a follicle with a ratio of follicle diameter to HS diameter of  $x = 3$  are presented in Table 2.

To estimate power density  $P$  and fluence  $F$  for the rectangular light pulse case, we can use formulas from Table A2 (see Appendix ) that we can simplify for the follicle case as:

$$P = \frac{32}{\mu_a q} \cdot \frac{x^2}{\text{TRT}} \cdot \frac{T_1 - T_0}{\ln(1.4x^2 \cdot \frac{\text{TDT}}{\text{TRT}})} [\text{W}/\text{cm}^2]$$

$$F = P \cdot \text{TDT} [\text{J}/\text{cm}^2]$$

where  $\mu_a [\text{cm}^{-1}]$  is the HS absorption coefficient,  $q$  is the ratio of the radiance at the target location to the input power density (attenuation factor). For our calculation, we use typical treatment conditions: wavelength is 800 nm, dark hair with  $\mu_a = 100 \text{ cm}^{-1}$ ,  $x = 3$ ,  $q = 1$  (bulge level of follicle),  $T_1 = 100^\circ\text{C}$ ,  $T_2 = 65^\circ\text{C}$ , and  $T_0 = 36^\circ\text{C}$ . Using the formulas shown above, we calculate the following values: power density is 560  $\text{W}/\text{cm}^2$  for 30  $\mu\text{m}$  fine hair, 100  $\text{W}/\text{cm}^2$  for 70  $\mu\text{m}$  terminal hair, and 35  $\text{W}/\text{cm}^2$  for 120  $\mu\text{m}$  coarse hair. For these hairs with equal melanin concentration and different diameters, the fluence necessary to damage the stem cells is the same. The fluence value is 40  $\text{J}/\text{cm}^2$ . The pulsewidth value appears in Table 2 as the TDT for a rectangular light pulse. We can see from Table 2 that selective and complete hair-follicle damage can be achieved over a very broad range of pulsewidths. For example, for a HS diameter of approximately  $d_1 = 70 \mu\text{m}$  and a HF diameter of  $d_2 = 210 \mu\text{m}$ , this range is 170–610 ms, which is significantly longer than the TRT (27 ms). In our in vitro experiment, we observed nearly complete damage of similar size follicles for pulsewidths in the 30–400 ms range with an identical fluence of 35  $\text{J}/\text{cm}^2$ . The main differences between theory and experiment for short pulses can be explained by differences in the maximum HS temperature used in the theoretical model ( $T_1 = 100^\circ\text{C}$ ) and the HS temperature reached in the experiment. For a pulsewidth shorter than 100 ms, we saw a significant change in the HS structure. This implies that the HS temperature was higher than  $250^\circ\text{C}$ . For this temperature the TDT is very close to the TRT (see Table 1). If the energy of the ablation products is not too high, most of them release their energy inside the HF and heat up the follicle structure. So all the absorbed energy was utilized to heat the follicle structure (including IRS and ORS). For a pulsewidth significantly shorter than 30 ms

with the same fluence, we can expect more HS ablation and escape of the HS ablation products from the HF. In this case, the damaged volume of the HF should decrease with decreasing pulsewidth and, for very short pulses, it should be limited to the HS. The differences between theory and experiment for pulses longer than 400 ms can be explained by the low power density ( $<100 \text{ W/cm}^2$ ) of the laser pulse, which was not sufficient to heat the HS close to  $100^\circ\text{C}$ .

**Photosclerotherapy.** Photosclerotherapy produces thermal or mechanical damage of the vessel structure due to light absorption by blood [8]. The blood hemoglobin exhibits selective light absorption over a wide wavelength range. Optimum vessel closure can be achieved by denaturation of the endothelium that is in direct contact with blood. This case is well described by the standard theory of SP [1]. Other authors have suggested that permanent vessel closure requires denaturation of the vessel wall structure [3,4]. These structures do not contain any strongly absorbing chromophores and can be damaged by heat diffusion from blood. Therefore, we will apply the extended theory of SP to estimate treatment parameters for different vein sizes. As a first approximation, the vein can be modeled by a cylinder. However, this is true just for limited constrained cases depending on the light wavelength and vein size. The cylindrical model is valid if the light penetration depth in the blood exceeds the vessel internal diameter  $D$ . In this case, the blood is heated uniformly. If scattering of the blood is lower than absorption, the light penetration depth is roughly equal to the inverse blood absorption coefficient  $1/\mu_a$ . Thus the cylindrical model can be used when  $D < 1/\mu_a$ . In this case, the heater diameter is  $d_1 = D$  and the target diameter is  $d_2 = D + 2w$ , where  $w$  is the vessel-wall thickness. If  $D \gg 1/\mu_a$ , the heated zone is a cylindrical blood layer, in contact with the vessel wall. The heated-zone thickness is approximately equal to the penetration depth  $1/\mu_a$ . This case can be roughly described by the planar model with heater thickness  $d_1 = 1/\mu_a$  and target thickness  $d_2 = 1/\mu_a + 2w$ . Analytic evaluation of the TDT using the expressions of Table A1 is possible in the rectangular light-pulse case when the whole blood volume is uniformly irradiated. If this is the case the cylindrical target model is applicable. In the opposite limiting case of very strong blood absorption, only a thin layer of blood adjacent to the vessel wall is irradiated. In the later case one may apply the planar model. At that, the analytic and numeric results show rather good agreement. In other cases both the TDT and the input flux were evaluated numerically. The maximum heater temperature is  $T_1 = 100^\circ\text{C}$  (limited by blood coagulation and vaporization), vessel wall denaturation temperature is  $T_2 = 65^\circ\text{C}$ , and the initial body temperature is  $T_0 = 37^\circ\text{C}$ . The calculations were performed for two wavelengths  $\lambda$ :  $\lambda = 577 \text{ nm}$  (maximum hemoglobin absorption), where  $1/\mu_a = 43 \mu\text{m}$  and moderate hemoglobin absorption  $\lambda = 1060 \text{ nm}$ , where  $1/\mu_a = 1400 \mu\text{m}$  [9,10]. To estimate the power density and fluence for a rectangular light pulse, we can use formulas from Table B and direct modeling for a rectangular temperature pulse.

TABLE 3. Optimum Pulsewidth for Treatment of Spider Veins

Diameter of vein, mm	Wall thickness, mm	TRT of blood volume, ms	TDT of vein and fluence F								
			$\lambda = 577 \text{ nm}$			$\lambda = 1060 \text{ nm}^*$					
			Rectangular temperature pulse		Rectangular light pulse		Rectangular temperature pulse		Rectangular light pulse		
0.1	0.035	0.5	TDT, ms	F, J/cm <sup>2</sup>	TDT, ms	TDT, ms	F, J/cm <sup>2</sup>	TDT, ms	F, J/cm <sup>2</sup>	TDT, ms	F, J/cm <sup>2</sup>
0.25	0.08	4	40	10	130	40	20	40	590	140	1090
0.5	0.12	35	150	6	515	150	15	150	335	610	615
1	0.15	260	215	4	740	215	6	215	115	1200	200
			240	4	670	240	5	240	50	2400	90

\*We can predict that TDT and F will be on the same order for another important wavelength ( $\lambda = 800 \text{ nm}$ ) because the absorption coefficients for vein blood at  $\lambda = 800 \text{ nm}$  and  $\lambda = 1060 \text{ nm}$  are similar.

Calculation results for different types of spider veins are presented in Table 3.

As we see from Table 3, the TDT of the entire vein wall structure is shorter for the 577-nm wavelength that coincides with the strong hemoglobin absorption peak. The TDT can be very long, typically for large veins. The perfusion factor can also be important but is neglected in the present study. Blocking of the blood flow can be important for optimum treatment with such a super long pulse. The large veins need significantly lower fluence, power density, and longer pulsewidth than small veins. This dependence is even stronger for light with low absorption in hemoglobin. The water absorption of surrounding tissue can be important for long treatment wavelengths ( $\lambda > 750$  nm) due to parallel non-selective heating by water absorption that can increase the tissue temperature  $T_0$ . As we showed above, the TDT will be shorter in this case and the fluence will be lower.

The parameters for spider-vein treatment suggested by our new theory are very different compared to typical clinical parameters used for photosclerotherapy and should be clinically proven.

Following from Tables 2 and 3, the treatment time (pulsewidth) for HF's and spider veins is on the order of several hundreds of milliseconds. As was shown in [11], parallel cooling of the epidermis (simultaneous heating by light absorption and heat removal by heat diffusion into the skin and cooling agent) is very effective in this pulsewidth range. This cooling mode is important for epidermal protection and makes the procedure more effective because high fluence can be delivered through the epidermis.

## CONCLUSIONS

The following are the conclusions:

1. Our in vitro experiment demonstrated that the hair-follicle damage pattern for fixed fluence is selective and

pulsewidth-independent over a broad pulsewidth range; this range is 1–10 times the hair-follicle TRT.

2. A new theory of selective thermal damage of non-uniformly pigmented structures of biological tissues is presented in this paper. We call this theory the extended theory of selective photothermolysis (ESP).
3. The extended theory of SP, is important for biological targets with space between all or part of the target and the pigmented area of the tissue. So, in contrast with the standard theory of SP, the target is destroyed by heat diffusion from the pigmented area to the target but not by direct heating from EMR.
4. The main principles of the extended theory of SP are: (i) The EMR wavelength should be chosen to maximize contrast between the absorption coefficient of the pigmented area and that of the tissue surrounding the target. This postulate is identical to the case of classical SP. (ii) The EMR power should be limited to prevent absorption loss in the pigmented area, but it must be sufficient to achieve a temperature of the pigmented area higher than the target damage temperature. (iii) The pulsewidth should be made shorter than or equal to the TDT. The TDT is the time required for irreversible target damage with sparing of the surrounding tissue. The TDT can be significantly longer than the TRT of the entire target.
5. The power and shape of the EMR pulse are important for successful treatment, in contrast with the standard theory of SP where just fluence is important.
6. Treatment parameters are power-and pulsewidth-dependent and are not just dependent on target size, absorption, and thermal properties but on their geometry as well.
7. For highly dense targets, it is important to limit fluence to prevent non-selective damage. Selective treatment of very high density targets is not possible because the gap between the fluence of selective and non-selective treatment is too small.

TABLE A1.

Variable	Dimensionality	Name	Assumptions and relations
$k$	$\text{cm}^2 \text{s}^{-1}$	Thermal diffusivity	Assumed to be the same all over the target
$\rho$	$\text{g cm}^{-3}$	Density	Assumed to be the same all over the target
$c$	$\text{J}/(\text{g } ^\circ\text{K})$	Specific heat	Assumed to be the same all over the target
$\mu_a$	$\text{cm}^{-1}$	Tissue absorption coefficient	Assumed to be zero outside the heater
$q$	a.u.	The ratio of radiance to the input power density	
$d_1$	cm	Thickness or diameter of the heater	
$d_2$	cm	Thickness or diameter of the target	$d_2 > d_1$
$d_3$	cm	Mean spacing between the targets	$d_3 > d_2$
$T_0$	$^\circ\text{C}$	Initial temperature of both the target and the surrounding tissue	$T_0 = 37^\circ\text{C}$
$T_{1\text{max}}$	$^\circ\text{C}$	Temperature of heater absorption loss	$T_{1\text{max}} = 100^\circ\text{C} - 250^\circ\text{C}$
$T_1$	$^\circ\text{C}$	Maximum temperature of the heater (absorber)	$T_2 < T_1 \leq T_{1\text{max}}$
$T_2$	$^\circ\text{C}$	Temperature of irreversible damage of the tissue	$T_2 = 70^\circ\text{C}$
$\Delta$	a.u.	Temperature factor, temperature ratio	$\Delta \equiv \frac{T_2 - T_0}{T_1 - T_0} < 1$
$x$	a.u.	Geometrical factor, diameter ratio	$x \equiv d_2/d_1 > 1$

TABLE A2.

		Approximate expression for a particular target geometry			
N	Quantity	Notation [dimensi- onality]	Planar	Cylindrical	Spherical
1	TRT of the heater	$\tau_r$ [S]	$\tau_r = \frac{d_1}{8 \cdot k}$	$\tau_r = \frac{d_1}{16 \cdot k}$	$\tau_r = \frac{d_1}{24 \cdot k}$
2	TRT of the target	TRT [S]	$\text{TRT} = \frac{d_2^2}{8 \cdot k} = x^2 \cdot \tau_r$	$\text{TRT} = \frac{d_2^2}{16 \cdot k} = x^2 \cdot \tau_p$	$\text{TRT} = \frac{d_2^2}{24 \cdot k} = x^2 \cdot \tau_r$
3	TDT	TDT [s]	$\text{TDT} = \frac{\text{TRT}}{2 \cdot x^2} \cdot \left[ \left( \frac{D - \Delta}{1 - \Delta} \right)^2 - 1 \right]$ ,	$\text{TDT} = \frac{\text{TRT}}{x^2} \cdot \exp \left( \frac{D - 0.3 \cdot \Delta}{1 - \Delta} \right)$ ,	$\text{TDT} = \begin{cases} 0.9 \cdot \frac{\text{TRT}}{x^2} \left[ \left( \frac{1 - \Delta}{D - \Delta} \right)^2 - 1 \right], & D - \Delta > 0 \\ \infty, & D - \Delta \leq 0 \end{cases}$
			$D = \exp(-x^2) + 1.8 \cdot x \cdot \text{erf}(x)$	$D = 0.6 + 2 \cdot \ln(x) - \text{Ei}(-1.4 \cdot x^2)$	$D = 0.7 \cdot \frac{\text{erf}(1.3 \cdot x)}{x}$
4	Input power density	$P$ [W/cm <sup>2</sup> ]	$P = \frac{\rho \cdot c}{\mu \cdot q} \cdot \frac{1.1 \cdot x^2}{\text{TRT}} \cdot \frac{T_1 - T_0}{\sqrt{1 + 2.1 \cdot x^2 \cdot \frac{\text{TDT}}{\text{TRT}} - 1}}$	$P = \frac{\rho \cdot c}{\mu \cdot q} \cdot \frac{x^2}{\text{TRT}} \cdot \frac{T_1 - T_0}{\ln(1 + 1.4 \cdot x^2 \cdot \frac{\text{TDT}}{\text{TRT}})}$	$P = \frac{\rho \cdot c}{\mu \cdot q} \cdot \frac{0.3 \cdot x^2}{\text{TRT}} \cdot \frac{T_1 - T_0}{1 - \frac{1}{\sqrt{1 + 1.2 \cdot x^2 \cdot \frac{\text{TDT}}{\text{TRT}}}}}$
5	Input fluence	$F$ [J/cm <sup>2</sup> ]	$F = P \cdot \text{TDT}$	$F = P \cdot \text{TDT}$	$F = P \cdot \text{TDT}$



8. The extended theory of SP suggests a significantly longer treatment time (pulsewidth) than classical SP. In dermatology, it provides the additional benefit of epidermal protection due to parallel cooling.
9. The extended theory of SP presented in this paper is also useful for electrothermolysis (electrode is heater) and certain cases of magnetic and acoustic treatment of tissue.

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## APPENDIX

### Procedure to determine the amplitude and the duration of the rectangular EMR pulse: brief summary

The present Appendix summarizes the EMR pulse parameters for the treatment of the basic targets exhibiting a high degree of symmetry, i.e., the planar, cylindrical, and spherical ones.

The notations and the basic parameters of the problem are explained in Table A1.

Our analysis was based on the heat conduction equation. We have found approximate analytic solutions of TDT and input power density  $P$ .

The final expressions for the important variables in question are outlined in simplified form in Table A2 below. It is implied that the thermal constants, i.e., the density, the thermal diffusivity, and the thermal conductivity do not vary significantly within the target and the surrounding tissues.

The present discussion is restricted to rectangular EMR pulses only. Our goal herewith is to determine the pulsewidth and the pulse amplitude. This may be performed in the following order:

1. Based on the target geometry, the size of the pigmented area (heater)  $d_1$ , size of the target  $d_2$ , distance between targets  $d_3$ , the geometrical factor  $x = d_2/d_1$  and density factor can be determined.
2. Based on the thermal properties of the target and chromophore, the temperature of pigmented area absorption loss  $T_{1\max}$ , temperature of target damage  $T_2$ , initial tissue temperature  $T_0$ , the temperature factor  $\Delta = (T_2 - T_0)/(T_1 - T_0)$  can be determined.
3. Using these parameters and formulas, we can use the formulas in Table A2, rows 1–3 to determine  $\tau_r$ , TRT, and finally TDT. As explained above, the TDT is approximately equal to the optimum duration of the EMR pulse  $\tau_0$ .
4. Based upon an estimate of the EMR attenuation factor at the depth of target  $q$  and the absorption coefficient of pigmented area  $\mu_a$  and the heater temperature  $T_1$ , the power density on the skin  $P$  using can be determined by using the formulas from Table A2 row 4. The power density should be limited in order to not bleach the pigmented area, but it should be significantly high to rich the temperature of target damage  $T_2$ .
5. Treatment fluence is given by  $F = P \cdot \text{TDT}$  or  $F = P \cdot \tau_0$

In contrast to both the planar and cylindrical targets, the TDT for the spherical target may be evaluated to infinity (see Table A2, row 3, rightmost column). This means that one cannot ensure the safety of the heater in an attempt to damage the whole target. After a part of the target becomes damaged, the heater temperature reaches the crucial value  $T_1$ . This gives rise to phase transitions, bleaching, bubble formation, and other nonlinear processes lying outside the scope of this paper. Therefore, our simple theory provides the means to describe thermal damage of sufficiently small spherical targets only. More precisely, for a given value of  $\Delta$  the diameter ratio  $x$  must not exceed the value obtained from the equation  $D = 0$ , where variable  $D$  is a function of  $x$  determined by the last expression of Table A2, row 3, rightmost column.

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