Pulse Duration Dependent Mid-Infrared Laser Ablation for Biological Applications


Abstract— There are significant benefits to medical laser surgeries performed with mid-infrared wavelengths, including the ability to select laser parameters in order to minimize photochemical and thermal collateral damage. It has been shown that a wavelength of 6.1 micrometers (µm) is optimal when high ablation efficiency and minimal collateral damage is desired in biological soft tissues. Historically, free electron lasers were the only option for ablating tissue at this wavelength due to their ample pulse energy and average power. In recent years new sources are being developed for this wavelength that can successfully ablate tissue. These alternative sources have different pulse structures and pulse durations than free electron lasers, motivating investigation of how these parameters affect the ablation process. Here, we present the pulse duration dependence for mid-IR laser ablation of biological tissues at a wavelength of 6.1 µm on a tissue phantom of cooked egg white. The crater shape, depth, and volume all changed in a significant, non-monotonic manner as the laser pulse duration was increased from 100 ns to 5 µs.

Index Terms— Mid-infrared laser ablation, pulse duration, Pockels cell, tissue ablation, crater shape, crater depth, crater volume, Free Electron Laser (FEL), Optical Parametric Oscillator (OPO).

I. INTRODUCTION

There are many properties of biological tissues that affect pulsed laser ablation. Tissue optical properties determine the internal energy distribution that initiates the ablation process[1]. The structure and morphology of tissue also affects energy transport within its constituents[2] and, along with mechanical and thermal properties, controls the response of tissue to pulsed heating and phase transformation[1]. Strong absorption of energy in tissues occurs in both the ultraviolet and mid-infrared wavelength regions; however, due to the potential mutagenic effects of ultraviolet wavelengths, mid-infrared laser radiation is preferred for many types of tissue, in particular in tissues with high cellularity[3]. The wavelengths of greatest interest for mid-infrared pulsed laser ablation have traditionally been at 2.1, 2.94, 6.1, 6.45, and 10.6 µm due to either the ability to remove tissue with little concomitant thermal damage or the availability of laser sources at these wavelengths[1, 3-14]. The absorption of mid-IR radiation at 2.1, 2.94, and 10.6 µm is primarily associated with strong water absorption; however, water and protein both absorb at 6.1 and 6.45 µm which coincide with the amide-I and amide-II absorption bands of protein respectively[1]. The promising results first obtained at the Vanderbilt University Mark-III free electron laser (FEL) were initially attributed to the absorbance of the protein in addition to the water in the tissue[4]. The absorption of collagen is twice that of water at 6.1 µm and six times that of water at 6.45 µm. In addition, the water absorption at 6.1 µm is 3.5 times higher than it is at 6.45 µm. Recent work has shown that 6.1 µm wavelength light gives improved tissue ablation with minimal thermal damage for numerous tissue types[9, 14-21]. To date, the Vanderbilt FEL has been used for a total of eight human surgeries including neurosurgery and ophthalmic surgery[6, 22-27]; however, the prohibitive size and cost of an FEL limits its practicality for medical uses. Although the wavelength range described here allows for selective excitation of amide bands, the lifetimes of these vibrations are only in the picosecond range[28-31]. Recently, researchers have shown that mid-IR laser ablation in the picosecond pulse duration range may have benefits in efficient ablation related to vibrational excitation to both hard and soft tissues[32, 33]; however, on the time scale of the FEL pulsewidth (100 ns to 5 µs), selective excitation is relatively unimportant and thermal processes dominate.
Alternative laser sources in the 6-8 µm range are currently being developed and tested for numerous medical applications, including an Er:YSGG pumped ZnGeP₂ crystal optical parametric oscillator (OPO)[9, 34], an Er:YAG pumped AgGaSe₂ OPO[35, 36], and a Raman-shifted Alexandrite laser[37]. Recently quantum cascade lasers have been shown to provide numerous wavelengths in the region of interest; however, these lasers are currently limited to spectroscopy applications due to their cw operation and energy limitations[38-40]. In addition to wavelength, a critical parameter that needs to be specified in the development of these laser sources is the pulse duration. We have previously shown that the micropulse structure of the FEL (each 5 µs macropulse consists of ~14,000 micropulses approximately 1 picosecond in duration delivered at 2.85 GHz) plays a negligible role in the ablation characteristics of the FEL[7, 8]; however, the role of the macropulse duration in achieving efficient tissue ablation and minimal collateral damage has not been well defined. Therefore, it was our goal with this research to explore the pulse duration dependence for 6.1 µm laser ablation of biological tissues.

The pulse duration of the ZGP:OPO system (λ=6.1 µm) used in previous work was 100 ns[9]. When compared to ablation using the FEL, significant differences were found in the ablation rate as well as in the size and shape of the ablation craters produced in cornea. The ZGP:OPO showed a significantly higher ablation rate with all other parameters being held constant except for the repetition rate. To determine the effect of pulse duration on crater size, shape, and ablation efficiency, we needed to vary the pulse duration over the range from the 5 µs native FEL macropulse to the 100 ns width of the ZGP:OPO. Given the large macropulse energy available with the FEL, it is possible to shorten the FEL macropulse to as little as 100 ns and still have enough energy to ablate tissue with a single pulse. By using a Pockels cell, we were able to slice a portion of the FEL macropulse and thus produce pulses with variable durations from the maximum 5 µs to as short as 100 ns over a range of pulse energies[41, 42]. Previous research using gelatin as a tissue phantom yielded only limited results for analysis due to melting and re-coagulation of the gelatin following ablation; even when measurements were performed on craters made in gelatin with a single laser pulse, accurate results were not always obtained. Therefore, we decided to use cooked egg white as our tissue phantom since its water/protein constituency mimics that of biological soft tissue and it does not melt and re-coagulate during or following laser ablation.

II. MID-INFRARED LASER ABLATION

A. Laser System

The laser system used for ablation was the Vanderbilt Mark III Free Electron Laser (FEL)[4, 43-45]. The laser was operated with a 30 Hz pulse repetition frequency, a 2.856 GHz micropulse repetition frequency, and an emission wavelength centered at 6.1 µm. The laser beam was sent through a 6 mm diameter, λ=4-8 µm Pockels cell (II-VI Inc., Saxonburg, PA), operated with a high voltage Behlke switch triggered by a TTL pulse synchronized with the FEL pulse train and an electrical one-shot box operating a fast shutter to select single macropulses. A digital delay generator (Stanford Research Systems, DG535) was used to trigger the Pockels cell and shorten the 5 µs FEL laser macropulse to the pulse durations of interest down to 100 ns. After confirming that the spatial beam profile resembled a Gaussian, the laser beam radius was analyzed using a knife-edge measurement[46] in front of a pyroelectric detector (J-25, Molelectron Inc.), and determined to be ~47 µm (+/- 5% due to detector uncertainty) for all of the experiments performed.

B. Ablation Threshold Measurements

The laser ablation threshold was measured on both water and cooked egg white using a red HeNe laser beam directed tangentially across the target surface at the FEL laser ablation location. The red HeNe beam reflected from ablated water and/or egg white passed through an optical iris to a CCD detector. The CCD detector signal was then sent to an oscilloscope for analysis. The laser pulse energy was adjusted until the signal due to reflected light from the ablated sample was seen; this gave an accurate reading for the ablation threshold at all pulse durations investigated between 5 µs and 100 ns.

We first determined the threshold of ablation for both water and cooked egg white at the different 6.1 µm pulse durations. Due to the loss of energy with shorter pulses out of the Pockels cell, we decided to use as small a spotsize as was practical (~47 µm radius). Nine pulse durations were used between 100 ns and 5 µs as shown in figure 1. For cooked egg white irradiated with pulses at 6.1 µm in wavelength, the threshold energy for ablation was determined to be 50 +/- 10 µJ at the spot size used, giving a threshold radiant exposure of approximately 0.72 J/cm². There was no significant change in the threshold for the ablation of egg white over the range of pulse durations used as seen in figure 1.

III. PULSE DURATION DEPENDENCE OF CRATER FORMATION, DEPTH, AND SHAPE

A. Crater Formation

A single pulse at 6.1 µm was used to ablate a fresh piece of cooked egg white that was placed on a translation
stage and kept at room temperature (21 °C). A micrometer was used to move the translation stage a distance of 1 mm between subsequent laser pulses. The energy was changed between 75 and 225 μJ using a ZnSe polarizer/attenuator (II-VI Inc.). The pulse energy was measured using a J-25 detector (Molectron Inc.).

B. Crater Depth Measurements

The crater depth was measured and averaged for a minimum of 10 craters at each pulse duration and pulse energy with an Olympus Fluoview laser scanning confocal microscope with FV300 software and an Olympus BX-VCB motion controller which allowed for depth measurement with a precision of 10 nm. Given the 100 mJ of energy available in a 5 μs pulse from the FEL, we were able to compare single pulse ablation craters for all pulse durations over a wide range of pulse energies all well above the ablation threshold energy (75, 100, 175, and 225 μJ). Comparison of craters made with equal pulse energies but widely different pulse widths revealed substantial differences in their shape, and prompted a detailed characterization of the pulse duration-dependence of ablation craters produced with these laser parameters. The results (figure 2) show that the deepest craters were made at 1,000 and 2,000 ns in pulse duration. The shallowest craters were produced with pulse durations of 100 ns and 5,000 ns.

C. Crater Shape Measurements

While crater depth is a common parameter for determining the overall ablation rate, the shape of the crater must also be measured in order to determine the volume of material removed (and hence get a handle on the overall ablation efficiency). The crater shape was measured using the same laser scanning microscope as described above. The

![Fig. 2. The single pulse induced crater depth in μm produced as a function of pulse duration (ns) at 75, 100, 175, and 225 μJ of energy per pulse. A minimum of 10 craters were averaged for each point. The error bars are the standard deviation for the ten craters. The deepest craters were found at 1,000 and 2,000 ns in pulse duration.](image-url)
diameter of the crater was measured beginning at the surface of the egg white and then measured repeatedly at deeper and deeper locations in the crater until the bottom of the crater was seen. This was repeated for a minimum of three craters at each pulse duration. All crater shapes were analyzed at a constant pulse energy of roughly 3 times the ablation threshold (175 µJ) for reproducibility.

The average diameter was then plotted as a function of depth to construct a cross section through the crater. The resulting crater shapes revealed a pulse duration dependence shown in figure 3. The deepest craters are again seen at 1,000 and 2,000 ns; however, there was a marked change in the shape of the craters through this range of pulse durations. The craters get wider as the pulse duration gets shorter, with the widest crater being seen at 100 ns. This crater was more than twice the diameter of the Gaussian beam diameter that was used to create it. In addition, the widest short pulse crater is almost hemispherical, quite unlike the narrow, conical-shaped crater produced by the longest (5,000 ns) pulse.

D. Crater Volume Measurements

Each crater shape is approximated by a curve specifying the radius as a function of the crater depth. We calculated volumes by integrating over the crater depth using a polynomial function to fit the radial profile that was determined in the crater shape analysis as described above. The integration was performed using Microlab Origin 6.0 software. The total volume of the single pulse craters was calculated from the data and plotted as a function of pulse duration; these results are shown in figure 4. For each pulse energy, the volume of tissue removed increases with a decreasing pulse duration. The largest volume of tissue was removed with the 100 ns pulse and the smallest volume was removed with the 5,000 ns pulse duration. A sharp decrease in crater volume occurred near 1,000 ns, which corresponds to the shape change seen in figure 3; this may coincide with the onset of steady-state tissue ejection and plume screening[10].

E. Mathematical Modeling

Multiple physical mechanisms could impact the pulsewidth-dependence of crater depth and shape. To better understand these mechanisms, we constructed a phenomenological model based on time-delay partial differential equations. This model includes a transition from blow-off type behavior – i.e. material removal occurs only after the pulse – to a process of continuous material removal during the pulse and its associated plume screening.

The model is simplified because the role of thermal diffusion is minimal. Egg white is largely denatured protein and should have a thermal diffusivity similar to that of protein, \( \alpha = 8.1 \times 10^{-8} \text{m}^2/\text{s} \) [47]. Even for the longest pulses used here, the characteristic thermal diffusion distance is just \((\alpha T)^{1/2} \approx 0.6 \mu \text{m}\), much smaller than any of the observed crater dimensions. Thermal diffusion would not become important until the pulsewidths approached the characteristic thermal diffusion times: \( t_{\text{radial}} \sim w^2/\alpha \sim 2.7 \text{ ms} \) based on a 1/e beam radius of 47 µm; and \( t_{\text{axial}} \sim \delta^2/\alpha \sim 170 \text{ µs} \) based on an absorption depth of 3.7 µm. Given these estimates, our model excludes thermal diffusion.

Existing mathematical models can reproduce the range of observed crater shapes, but fail to account for the pulsewidth-dependence, and do not reproduce the correct coupling of crater shape and depth. For short pulsewidths (100-500 ns), we observe rounded craters that are in reasonable agreement with a blow-off model [48]:

\[
\frac{z(r)}{r} = \ln \left( \frac{F(r)}{H_{\text{abl}}} \right)
\]

where \( z(r) \) is the crater depth at distance \( r \) from the beam axis, \( F(r) \) is the fluence \( \delta \) is the absorption depth and \( H_{\text{abl}} \) is the threshold energy density for material removal. To match the observed crater depths, one must assume an extremely low \( H_{\text{abl}}(\lesssim 10^4 \text{J/cm}^2) \) and/or dynamic optical properties that yield a dramatic increase in the absorption depth. To match the observed trends in crater depth, one would need to assume a pulsewidth-dependence for one or both parameters. For longer pulsewidths, we observe craters that transition from Gaussian to sharply peaked trumpet shapes. These shapes can all be reproduced by “steady-state” models that assume continuous material removal at a rate that is proportional to the projection of the intensity normal to the current crater surface [49, 50]:

\[
\frac{z(r,t)}{t} = \frac{F(r)}{H_{\text{abl}}} \left[ 1 + \left( \frac{z(r,t)}{r} \right)^2 \right]^{-1/2}
\]

These models assume the absorption depth is small compared to the size of the crater; neglect surface reflection, and neglect any absorption or scattering in the ejected material. Nonetheless, the models yield Gaussian-shaped craters at near-threshold fluence and sharply peaked trumpet-shaped craters at higher fluence. One can get a similar range of crater shapes by recasting this model as a condition on the slope of the final crater wall[51]. For a given fluence, both versions of the model predict identical crater shapes regardless of pulsewidth. This becomes clear if one casts the model in integral form and switches the integration variable to \( t/\tau \):

![Fig. 4. The crater volume for each of the nine pulse durations is shown in 10^4 µm^3 versus pulse duration in nanoseconds. The error bars are the standard deviation for the average of at least three craters for each pulse duration.](image-url)
The model thus cannot reproduce the observed transition in crater shape at constant fluence, but variable pulsewidth. Furthermore, the steady-state models yield results in which deeper craters are always sharper – in contradiction with the experimental results.

To better match our experimental results, we thus constructed a hybrid of the blow-off and steady-state models. We chose the most straightforward combination by assuming that there is a shortest time, \( \tau_{\text{eject}} \), at which material removal begins. At \( t = \tau_{\text{eject}} \), material is removed according to a blow-off model. After this time, material is removed continuously at a rate that depends on the projection of the intensity normal to the crater surface and screening by previously ablated material. Mathematically, the model can be expressed as:

\[
z(r, t) = \ln \left( \frac{F(r)}{H_{\text{abl,BO}}} \right)_{\text{eject}} + \frac{\partial z(r, t_{\text{eject}})}{\partial t} \left( 1 + \frac{\partial z(r, t_{\text{eject}})}{\partial r} \right)^{\frac{1}{2}} S(r, t - \Delta_2)\]

where \( S(r, t - \Delta_2) \) is a function that accounts for plume screening, and \( \Delta_1 \) and \( \Delta_2 \) are delays that respectively account for the time required to form a well-defined crater interface and a highly attenuating plume of ejected material. We investigated several screening functions and found that the best results were obtained by integrating all of the material removed and distributing this material in an annular plume – similar to that observed upon impact ejection from a fluid surface[52]. The mathematical form for this screening function is:

\[
S(r, t - \Delta_2) = e^{\left( \frac{1}{2} \int_0^{\tau_{\text{eject}}} \left( z(r, t - \Delta_2) \right)^2 r dr dt \right) \text{plume}}
\]

where \( \delta_{\text{plume}} \) is the absorption depth of the plume and the integrals calculate the total amount of material in the plume up to time \( t - \Delta_2 \). The normalized function \( P(r) \) contains all information about the annular shape of the plume and was assumed to be a Gaussian of width \( w \) centered at \( r = w \).

These partial differential equations were cast as coupled time-delay ordinary differential equations with radial derivatives approximated by finite differences. The equations were then numerically integrated in Mathematica (Wolfram, Champaign, IL). Integration of the ejected material in the plume was performed out to a radial distance of \( 5w \).

Figure 5 shows model solutions for a particular set of global parameters (details in figure caption). These parameters were chosen to match the trends in crater shape and depth observed in experiments. The crater shapes transition from rounded to Gaussian to sharply peaked and the crater depth first increases with pulsewidth and then decreases, with a maximum crater depth of \( 120 \mu m \) reached at \( \tau = 1000 \) ns.

If one varies each temporal parameter from its selected value, one observes characteristic changes in the crater shapes and depths. \( \tau_{\text{eject}} \) and \( \Delta_1 \) determine the pulsewidth scale on which the crater shape transitions from rounded to Gaussian. \( \Delta_1 \) and \( \Delta_2 \) then determine the pulsewidth scale on which the craters become sharply peaked. For the longest
pulses, both the slope factor and the plume screening function are necessary to generate sharply peaked craters even as the crater depth decreases. If one excludes plume screening in the model (e.g. by letting $\delta_{\text{plume}} \to \infty$), the craters for $T > 2000$ ns still become sharply peaked, but they all have the same depth. If one includes plume screening with a uniform plume, the long pulse craters become shallower, but also more rounded. Only screening with an annular plume matches the trends in both the crater shape and depth.

The model presented here is phenomenological. More fundamental modeling would require an explicit consideration of the kinetics of explosive vaporization in a mechanically constrained tissue, the time-dependent shape of the ejected plume and the impact of this plume on how incoming radiation reaches the underlying tissue. The equilibrium properties of water and steam are very well known; however, the kinetics of the phase transition are not as well understood, particularly under the extreme conditions of laser ablation. These are active areas of research and future results should improve the ability to model the relevant hydrodynamics.

IV. OBSERVATIONS AND BENEFITS FOR FUTURE LASER DEVELOPMENT

The observed transition from a wide, nearly hemispherical crater shape to a narrow, conical shape suggests that two different mechanisms for ablation are involved over this range of pulse durations. The short pulses deliver the entire pulse energy (3 times the ablation threshold) to a small volume of tissue before significant heat diffusion can take place; this results in an explosive phase change, which would leave a hemispherical crater. This mechanism acts like a “blow off” model which would remove a larger volume of material[53]. With the longer pulses, a slower mechanism such as an equilibrium state of evaporative boiling may occur (‘steady state’ model)[53]. In this case, tissue would be removed in a continuous fashion as long as energy required for boiling is being deposited in tissue faster than it is being lost through diffusion and plume screening. This argument is supported by the proximity of the thermal diffusion time to the $5 \mu s$ pulse width at the $6.1 \mu m$ wavelength[54]. Since the laser intensity is weaker around the edges of the beam, longer pulse durations limit ablation to the central portion of the irradiated spot, where losses from heat diffusion and plume screening could still be overcome. Therefore, a small, narrow crater would be produced. The abrupt change in crater shape seen at pulse durations around 1,000 ns is consistent with the onset of large amounts of material being removed (and strong plume screening). The shrinking crater size observed with pulses longer than ~1,000 ns can be explained by the loss of incident laser radiant exposure to plume screening. Previous work showed the development of a water plume prior to the end of the 5000 ns pulse during ablation of water using the FEL that causes plume screening during the long FEL pulse duration[7].

While the largest volume of material was removed with the shortest pulses, the deepest craters resulted from the intermediate pulse durations. We propose the following explanation: with the shortest pulses, tissue may reach radiant exposures well in excess of the threshold needed for ablation; the extra energy would be lost to pressure waves in the bulk of the tissue or to kinetic energy of material in the plume. With longer pulses, there is more time for energy transfer into deeper regions of the tissue, so that more of the available laser energy could be used to remove tissue from underneath the center of the irradiated area. This could result in the deeper (but narrower) craters found with intermediate laser pulse durations. In addition, thermal lensing becomes more of a pronounced interaction in tissue with longer pulse durations. As a result, the laser beam divergence may increase which will reduce the area of the tissue that reaches the ablation threshold [55-57]. These factors could lead to a deeper and narrower crater shape for the intermediate pulse durations as compared to the short pulse durations.

V. CONCLUSION

Using the Vanderbilt Mark III free electron laser (FEL) and cooked egg white as our tissue phantom allowed us to perform a thorough study of the laser pulse duration dependence of ablation at $6.1 \mu m$ in wavelength. We were able to compare nine different pulse durations from 5,000 ns down to 100 ns. The 100 ns pulse duration is comparable with the pulse durations typically used in alternative laser sources, such as the ZGP:OPO laser system, in this mid-infrared wavelength range. This work did not cover the ~10 ns range, where several new mid-IR generation schemes are being developed. Our results suggest that such short pulses might result in even larger total volumes and shallower craters. We were able to vary single pulse energies from just above the threshold for ablation to four and a half times the threshold, and performed a detailed comparison of crater depth, crater shape, and crater volume at a fixed pulse energy three and a half times the ablation threshold. We found that the deepest craters were achieved at 1,000 ns while the largest crater volume was removed with 100 ns pulses, suggesting that a short pulse at 6.1 $\mu m$ is preferred for removing large surface areas of tissue, while a longer pulse is preferred for a deep and narrow cut. Mathematical modeling with a hybrid of blow-off and steady-state models and the inclusion of plume screening is able to reproduce the observed trends in both crater shape and depth. The results obtained in this work provide a great potential for understanding tissue removal in laser medical applications in the mid-infrared region of interest.

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