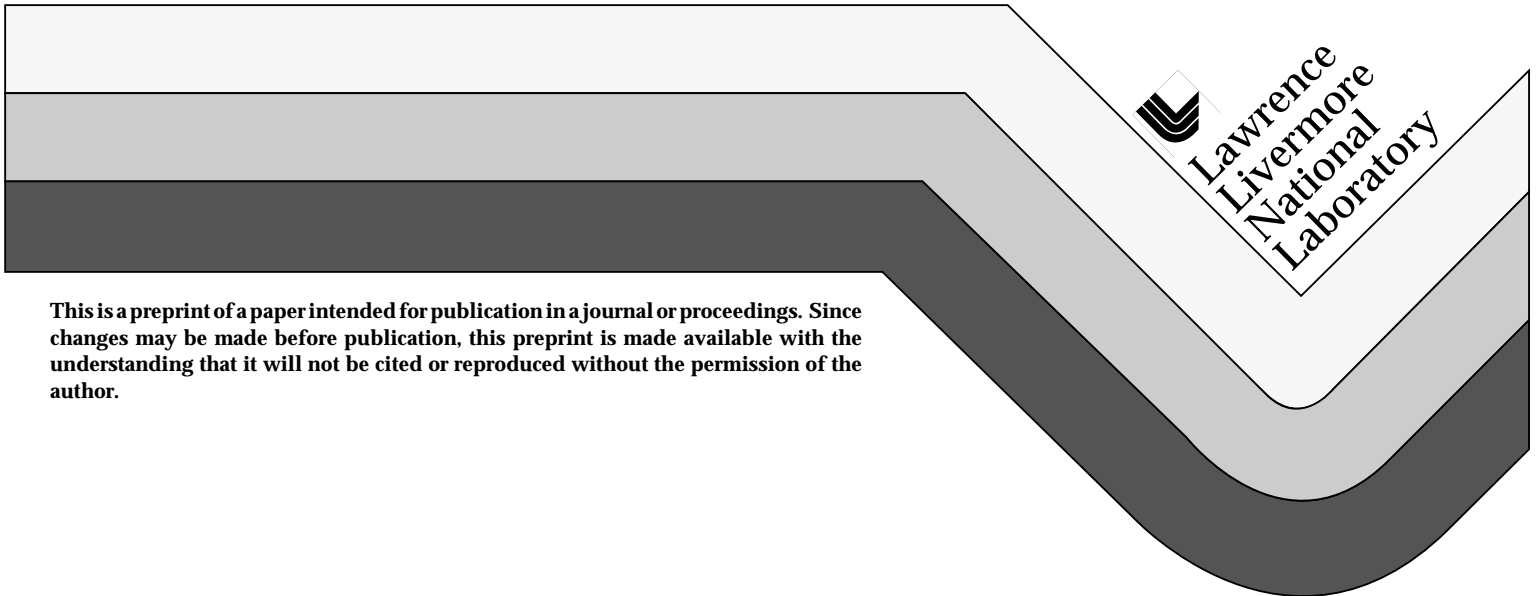


Computational Modeling of Stress Transient and Bubble Evolution in Short-Pulse Laser Irradiated Melanosome Particles

M. Strauss, P. A. Amendt, R. A. London,
D. J. Maitland, M. E. Glinsky, C. P. Lin,
and M. W. Kelly

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Computational modeling of stress transient and bubble evolution in short-pulse laser irradiated melanosome particles

Moshe Strauss

*Nuclear Research Center, Negev, P. O. Box 9001, Beer Sheva, Israel, and
University of California Davis, Department of Applied Science, Livermore, CA 94550*

P. A. Amendt, R. A. London, D. J. Maitland, and M. E. Glinsky

Lawrence Livermore National Laboratory, Livermore, CA 94550

C. P. Lin and M. W. Kelly

*Wellman Laboratories of Photomedicine, Massachusetts General Hospital,
Harvard Medical School, Boston, MA 02114*

ABSTRACT

Laser injury by sub-nanosecond pulses in the eye and skin is related to strongly absorbing pigment particles such as melanin with dimension of order 10-15 nm. Single melanosomes, with size of approximately 1 μm and containing many such melanin particles, were isolated in water and irradiated with 100 psec pulses. [Lin and Kelly, SPIE 2391, 294 (1995)]. Using time resolved imaging techniques, they observed the emission of a strong shock wave followed by rapid bubble expansion on a nanosecond timescale. The shock had a supersonic speed of approximately 2700 m/sec and an initial pressure of nearly 35 kbars. The shock wave can induce further tissue damage in addition to that produced by the bubble expansion and reduce the threshold for laser damage in the retina. In this work we simulate the system by using the hydrodynamic computer code LATIS with a realistic equation of state for water. We simulate both isolated melanin particles and whole melanosomes. Our melanosome model considers a spherical structure of order 1 μm in diameter with a uniform energy. This is consistent with the fact that the melanin particles are not stress confined while the melanosome is almost stress confined; thus, the pressure builds up uniformly in the melanosome. The details of the dynamics of the supersonic shock wave emission and rapid bubble evolution on both the melanin and melanosome scales are investigated. Comparison between modeling and experiments is presented. In order to achieve peak pressures and shock speeds comparable to the reported values, it is necessary to model the melanosome as having an absorption coefficient of approximately 6000 cm^{-1} , which is somewhat high compared to values reported in the literature of $500 - 2000\text{ cm}^{-1}$. Another way to achieve agreement with experiment is if the superposition of shock waves from the many melanin particles inside the melanosome produces a stronger shock than calculated by assuming a smooth absorption, as in our melanosome model. A better experimental determination of the values of linear and non-linear absorption coefficients for a single melanosome is needed in order to decide between the two approaches.

Keywords: melanin, melanosome, retinal injury, stress transient, shock wave, vapor bubble, cavitation

1. INTRODUCTION

In various microsurgery applications a short laser pulse generates a shock wave that is later followed by a fast vapor bubble expansion. In ophthalmology and dermatology, photomechanical damage can result from absorption of laser light by melanin granules of 10-15 nm radius which generate local hot spots. These strong absorption centers are the sources for shock waves and vapor bubbles.^{1,2} In intra-ocular surgery, photo-disruption of tissue is obtained by plasma generation in the laser focus, which induces similar hydrodynamic behavior.^{3,4}

The objective in this work is to study retinal injury by sub-nanosecond laser pulses absorbed in the retinal pigment epithelium (RPE) cells. The absorption centers in the RPE cell are melanosomes of order 1 μm radius. Each melanosome includes many melanin particles of 10-15 nm radius, which are the local absorbers of the laser light and generate a discrete structure of hot spots. To relax the hot spot pressure, each melanin emits a shock wave and a vapor bubble into the melanosome. The superposition of the dynamics induced by the ensemble of hot spots represents the average melanosome behavior. Each melanin is in a non-stress confined state and superposes a pressure field on the melanosome scale. The melanosome, which is stress confined, builds up a large uniform stress field. What emerges from the melanosome is a single supersonic shock wave which rapidly decays to a sonic wave. Later in time, a single vapor bubble expands out from the melanosome.

In the work of Lin and Kelly, single bovine melanosomes were isolated in water and irradiated with 30-100 psec laser pulses.^{2,5} Using methods of time-resolved imaging microscopy, they observed the shock wave and fast bubble expansion with 1 μm spatial resolution. By measuring the radius of the shock at various times, they obtained the average shock speed. A 1 nanosecond average speed of 2700 m/sec was observed, corresponding to initial pressures approximately equal to 35 kbars for a 2 J/cm² laser fluence.⁵

In this work we use the hydrodynamic code LATIS (LAsEr-TISsue interaction modeling) and a water equation of state (EOS) to first simulate the small melanin particle of 15 nm responsible for initiating the hot spot and the pressure field.^{6,7,8} We next simulate an average melanosome of 1 μm scale which is consistent with a superposition of pressure waves generated by the hot spots from the many melanin particles inside the melanosome. Supersonic shocks and fast vapor bubbles are generated in both cases: the melanin scale and the melanosome scale. The hot spot behavior induces a shock wave pressure stronger than with a uniform deposition of laser energy.

In this sub-nanosecond laser pulse range with strong shock wave generation, there is a reduction in the laser fluence threshold compared with longer laser pulses, where only bubble expansion is observed.¹ This may be related to the strong stress wave released from the melanosome, which propagates for long distances in the cell (several microns) and is absorbed in sub-cellular structures. Strong internal reflections and significant tensile damage may then occur.

The paper is organized as follows. In Section 2 we consider the physical model; Section 3 presents our simulation results for a melanin particle; Section 4 considers the computational results for an average melanosome system; Section 5 discuss the damage mechanism and threshold condition; and we summarize in Section 6.

2. THE PHYSICAL MODEL

2.1 The absorption mechanism

We consider a sub-nanosecond laser pulse which is absorbed in the RPE layer lying just below the retina. This layer includes 10 μm sized cells which are responsible for the absorption of light by the retina and suppression of internal reflections. Strong photomechanical interaction of short pulse lasers with the RPE layer may result in retinal injury.

The RPE cells absorb light via the melanosomes, which have an ellipsoidal shape with a typical average radius R_m of order 0.5 μm for humans and 1.15 μm for the bovine case.⁵ Each melanosome includes approximately 10^3 - 10^4 melanin granules. For a melanosome with a radius of 0.5 μm and $N_g=2000$ melanin particles, the average inter-particle spacing is $R_{av}=R_m/(N_g)^{1/3}\approx 0.04 \mu\text{m}$.

For laser light near 532 nm the average absorption coefficient for a melanosome is in the range of 500-2500 cm^{-1} , depending on the type of melanin particle.^{9,10} However, Sliney and Palmisano found for bovine melanosomes an absorption coefficient of 4100 cm^{-1} at 694 nm, which can be extrapolated to a much higher value of 9600 at 530 nm.^{10,11} Recently, bovine RPE melanosomes were found to be about 4-fold more dense in melanin absorbers than cutaneous melanosomes (but with absorption coefficient of $\sim 2350 \text{cm}^{-1}$.) For a 0.5 μm melanosome with 2000 melanin particles of 15 nm, only 3% of the volume is absorbing the laser energy. For an average melanosome absorption coefficient of $2 \times 10^3 \text{cm}^{-1}$ the melanin value is $3.6 \times 10^4 \text{cm}^{-1}$. Thus the melanin temperature can be higher by an order of magnitude than the average melanosome temperature. This hot spot structure can impose a stronger stress wave, explosive vaporization and fast bubble expansion, which contrasts strongly with the behavior predicted by averaging the laser absorbed energy uniformly over the melanosome. However, strong dissipation of the granule shock waves can effect a uniform distribution of the absorbed energy. We believe that if the dissipation is significantly limited the hot spots can act as sources for an enhanced shock wave leaving the melanosome.

2.2 Shock wave relations

Two types of relaxation times are important in identifying the relevant dynamics of the system: thermal relaxation and stress relaxation. Thermal conductivity changes the temperature in a structure of size d on a characteristic thermal relaxation time $t_{th} = d^2 / (4a)$, where in water $a = 1.4 \times 10^{-3} \text{cm}^2/\text{sec}$.¹ For a melanin granule of size 15 nm, $t_{th} = 400$ psec and for a melanosome of radius 0.5 μm , $t_{th} = 0.5 \mu\text{sec}$. Thus, for laser pulses below 100 psec the melanin particle is almost thermally confined while the melanosome is completely thermally confined.

The stress relaxation time is defined for a structure of size d by $t_s = d / C_s$, where C_s is the sound speed which in water is 1500 m/sec. For a granule of size 15 nm, $t_s = 10$ psec, and for a melanosome of 0.5 μm , $t_s = 300$ psec. For laser pulses shorter than 100 psec the melanin stress is relaxed, while the melanosome stress is almost confined. Thus, pressure released by the melanin hot spots uniformly accumulates on the melanosome scale.

Fast hydrodynamic expansion of the individual granule vapor bubbles and bubble merging can effectively increase the thermal conduction and thus enable a more uniform spreading of energy in the melanosome.

To obtain an average speed of 2700 m/sec over 1 nanosecond as observed by Lin and Kelly,^{2,5} the initial shock speed should be close to 3500 m/sec. For a shock wave in water, the following relations hold between the shock speed U_s , the fluid speed (particle speed) U_p , and the pressure P ,¹²

$$U_p = \frac{1}{2} (U_s - C_s) \quad (1)$$

$$P = \rho_0 U_s U_p \quad (2)$$

$$P = P_1 \left(\frac{r_1}{r} \right)^2 \quad (3)$$

where P_1 is the pressure value at initial point r_1 . Inserting $U_s = 3500$ m/sec and $C_s = 1500$ m/sec in eq. (1), we obtain a particle speed $U_p = 1000$ m/sec. Early in the bubble expansion, the bubble speed U_b is close to the particle speed $U_p = 1000$ m/sec. The initial shock pressure at the front is found from eq. (2) to be 35 kbars for $\rho_0 = 1$ g/cm³.

3. SIMULATION OF A MELANIN GRANULE

We simulate a melanin granule of radius 15 nm heated by a 100 psec laser pulse using the LATIC hydrodynamic code. For a laser fluence of 2 J/cm² and absorption coefficient of 4×10^4 cm⁻¹, 1 pJ of energy is absorbed. A water EOS is used for the melanin and the surrounding medium. The EOS is hybrid in the sense of including both the tensions (or negative pressures) in the system by including Van der Waals loops and the liquid-vapor equilibrium with use of a Maxwell construction.⁸

Figures (1a), (1b) and (1c) represent the pressure, density and temperature, respectively, as a function of radius for times 0.02, 0.05, 0.1, 0.2 and 0.3 nsec. A supersonic shock wave is emitted from the melanin granule. The radius $R_{qv} = 0.04$ μ m is defined as half of the melanin inter-particle spacing in the melanosome. Up to this distance the shock is supersonic with a speed of 2500 m/sec, a maximum pressure of 2.5 kbar, and a temperature of 4000 ⁰C. After this distance the melanin contributions start to overlap. This shock speed decays rapidly by 100 psec to a sonic speed.

In fig. (1b) a fast vapor bubble is apparent from the growing low density region around the center. Close to the bubble edge there is a 10% rise in density above the ambient 1 g/cm³ value. This density rise propagates with the shock wave. The average bubble expansion speed after reaching a distance $R_{qv} = 0.04$ μ m is 500 m/sec. The bubble expands to its maximum radius according to the Rayleigh theory.¹³ The temperature inside the bubble starts as a hot spot with a value near 10⁴ ⁰C and decays as the bubble expands and transfers its energy to the exterior region.

The melanin particle possibly contains only lipids and behaves under laser action as a solid material without boiling. Hydrodynamic motion is induced by fast thermal conduction of heat from the melanin to the surrounding water. For a 1 pJ simulation with 15 nm melanin radius, we find similar results between a protein melanin and a water-filled granule except for a time delay related to the thermal conduction of the energy out of the melanin.

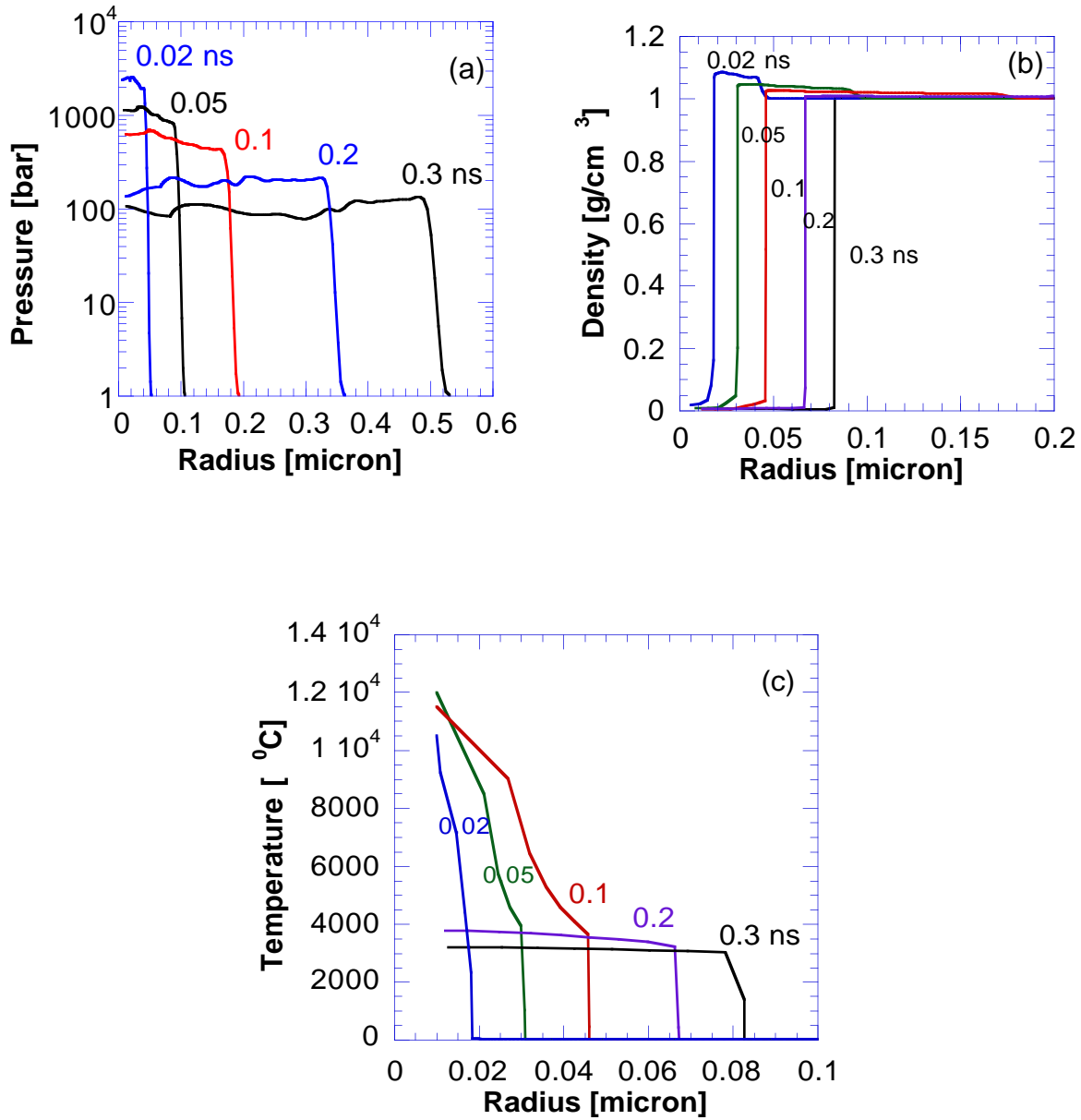


Fig. 1. Melanin granule pressure (a), density (b) and temperature (c) vs. radius r for times 0.02, 0.05, 0.1, 0.2, 0.3 nsec. Melanin absorbed energy is 1 pJ, radius is 15 nm and laser pulse length is 100 psec.

4. SIMULATION OF A MELANOSOME

4.1 Uniform distribution of laser energy

We consider a 100 psec pulse laser with fluence 2 J/cm^2 interacting with an isolated $0.5 \text{ }\mu\text{m}$ melanosome in water. We expect from the experimental results to obtain an initial pressure of 35 kbar and an average shock speed over 1 nanosecond of 2700 m/sec. For an average absorption coefficient of 2000

cm^{-1} the absorbed energy is 2 nJ. We first consider a melanosome with the absorbed energy spread uniformly.

Figures (2a), (2b) and (2c) present the pressure, density and temperature as functions of radius for times of 0.1, 0.4, 0.7 and 1 nsec. A shock wave is emitted from the heated region with an average speed of 2000 m/sec over 1 nsec. From fig. (2a) and (2b) the initial pressure after 0.1 nanosecond at the bubble boundary is about 15 kbars. This pressure decays after 1 nanosecond to a value of 2 kbar. The pressure decays as $1/r^\alpha$, where initially $\alpha=2$ for a strong shock and later $\alpha=1$ for an acoustic wave. The initial pressure of 15 kbar and the average shock speed of 2000 m/sec are lower than seen in experiment.

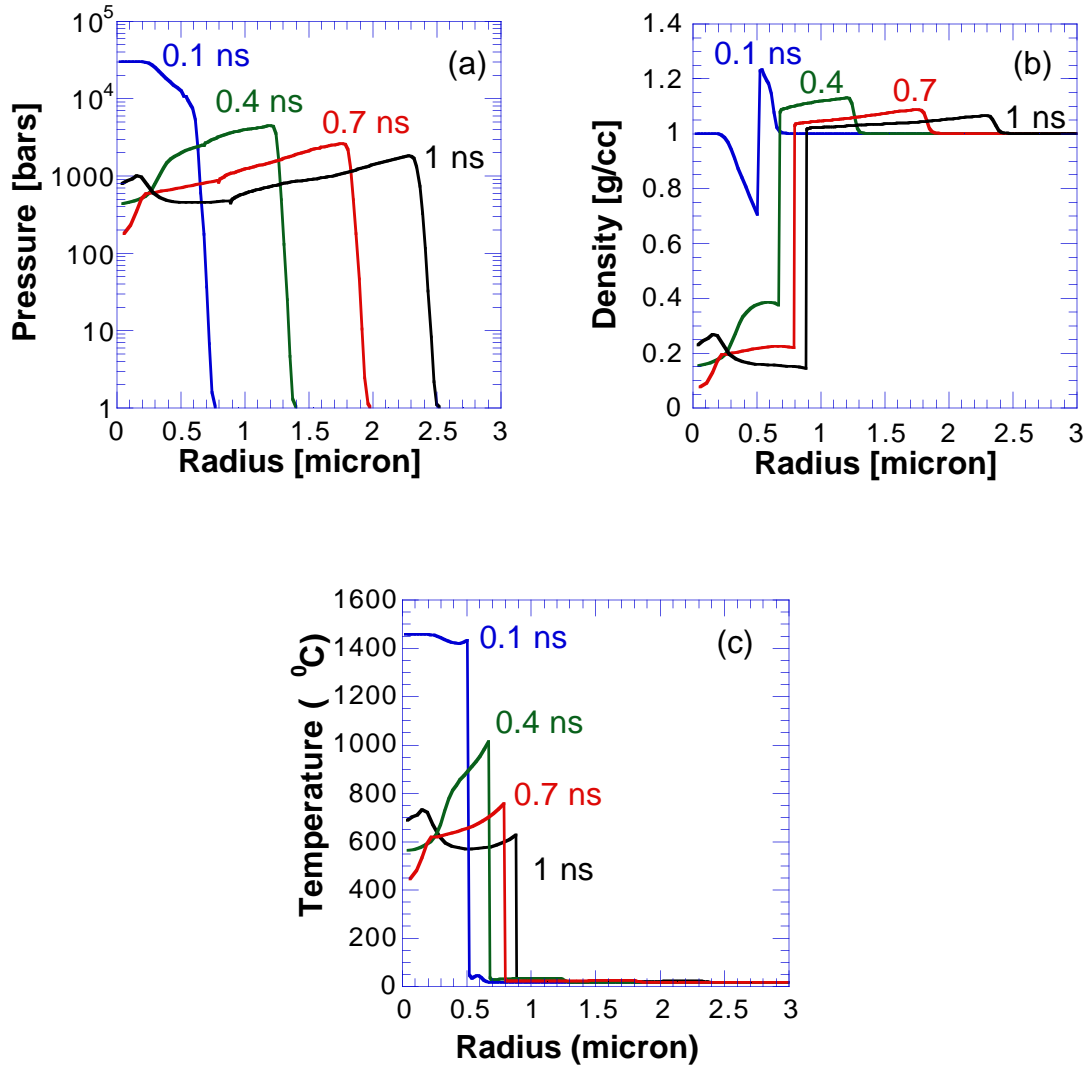


Fig. 2. Melanosome pressure (a), density (b) and temperature (c) vs. radius for times 0.1, 0.4, 0.7, and 1 nsec. The absorbed energy is 2 nJ, the radius is $0.5 \mu\text{m}$ and the pulse length is 100 ps.

In fig. (2b), a bubble expansion is obtained with a average speed after 1 nanosecond of 400 m/sec. The density rise in the shock wave region starts close to the bubble boundary and propagates with the shock speed. The density increases after 100 psec to 1.25 g/cm^3 and decays after 1 nanosecond to 1.05 g/cm^3 . The

temperature in Fig. (2c) in the heated region is initially 1450 °C at 100 psec and decays with the bubble expansion.

A mechanism must be identified to increase the simulated average shock speed to the experimental value of 2700 m/sec. Several models were tested. We first considered a single shell structure of width 10 nm located at the melanosome boundary at 0.5 μm. The energy of 2 nJ was distributed throughout the shell. The average shock speed obtained was 2100 m/sec which is similar to the previous case.

We next considered a thermally conducting solid core of radius 0.5 μm without hydrodynamic motion, representing the lipid, and a heated shell of 10 nm on the boundary of the core. We did not obtain any significant change in the results. We tried depositing the energy uniformly in the solid core and, again, ignored the hydrodynamic motion. In this case, the energy conducts out of the heated region and induces hydro motion. For this case the heat conduction is so slow that no significant motion was obtained.

Human melanosomes have an average radius of 0.5 μm, but for the bovine melanosome considered in the experiment the average radius is somewhat larger at 1.15 μm.⁵ For the same absorption coefficient of 2000 cm⁻¹ the absorbed energy by each bovine melanosome of radius 1.15 μm is 24 nJ. We simulated this case for a uniform distribution of energy. The average shock speed over 1 nanosecond obtained increased to 2150 m/sec. This result is still significantly lower than the experimental value.

Another possibility is that the laser absorption coefficient in the melanosome is higher than expected by a factor of 3 and is 6000 cm⁻¹. For a radius of 0.5 μm and fluence of 2 J/cm² the absorbed energy is 6 nJ and the average shock speed obtained is 2350 m/sec. For a radius 1.15 μm with the same absorption coefficient the absorbed energy is 72 nJ and we find an average shock speed of 2650 m/sec. This value is very close to the experimental result of 2700 m/sec. We can conclude that a higher absorption coefficient can explain the difference between theory and experiment and should be tested experimentally. Evidence for a higher absorption coefficient has been suggested in Ref. 11.

4.2 Hot spot structure

The melanin granules absorb the laser energy and generate a matrix of hot spots with average separation $2R_{av}$. For a melanosome of radius 0.5 μm with 2000 granules, $R_{av} = 0.04$ μm. Shock waves are emitted from the hot spots and collide at an average distance R_{av} . The superposition of these waves form a uniform shock wave over the melanosome. The shock wave emitted from a single granule has speed close to 2500 m/sec and reaches a distance of R_{av} in 10 psec. These colliding shocks presumably involve a lot of energy dissipation and heating of the melanosome. During this heating of the melanosome, the bubble expands from each granule with speed close to 1000 m/sec and reaches a radius of 0.025 μm.

It is possible that the hot spot structures emit a superposed shock wave stronger than in the case of a uniform distribution of the absorbed energy. In this case, the dissipation of the granule shock waves must be limited. If the measurement of the absorption coefficient still does not show a large increase, then a mechanism involving the hot spot structure is likely the cause for the enhanced shock wave.

5. DAMAGE MECHANISM AND THRESHOLD CONDITION

Damage induced by short pulse lasers is related to the emission of shock waves and bubble expansion. The shock wave decays rapidly as $1/r^\alpha$, where α is between 1 and 2. The stress wave which is left after the decay of the shock wave decreases as $1/r$ and can cause damage in a 10 μm cell. The stress wave damage is obtained when the wave transmits through a sub-cellular structure and is internally reflected.

This reflection induces a tensile wave of strength P_T :

$$P_T = P \cdot R_f (1 - R_f) \quad (4)$$

where R_f is the reflection coefficient between the sub-cellular structure and its surroundings, $R_f = (1-U)/(1+U)$, $U = Z_1 Z_2$, and $Z = \rho C_s$ is the acoustic impedance. Here, ρ is the density, C_s is the sound speed, and the indexes 1 and 2 denote the outer and inner regions, respectively, of the sub-cellular structure. A tensile wave P_T larger than 10 bars may cause local damage. The damage depends on the duration of the tensile stress and on the local displacement and the elasticity of the medium. For a stress wave with a local pressure of 200 bars and an impedance mismatch of 10%, $U=0.9$, P_T is 10 bar, and damage can occur. For a 1 kbar stress wave at 1 μm , a $1/r$ decrease in the stress amplitude will generate damage at a 5 μm distance.

Similar damage can result from bubble expansion. For an absorbed laser energy of 2 nJ, and with a uniform energy deposition in a melanosome of radius 0.5 μm , the maximum bubble radius can be estimated from fig. 2(b) and use of the Rayleigh relation,¹³

$$\left(\frac{R_M}{R}\right)^3 = \frac{3\rho}{2P_\infty} U^2 + 1 \quad (5)$$

Here, R and U are the local bubble radius and speed, respectively, R_M is the maximum radius, and P_∞ is the ambient pressure which for many cases can be replaced by the average material strength. Equation (5) can be used only when the bubble radius is much larger than the initial radius. The expansion time is $t_M = 0.91 (\rho/P_\infty)^{1/2} R_M$. For the 2 nJ, case a bubble of 5 μm radius can be generated, causing a large region of damage in the cell.

Figures (3a), (3b) and (3c) represent the pressure, density and temperature as a function of radius for the case of a 0.5 μm radius melanosome absorbing 0.2 nJ. Here the system starts from an initial temperature of 140 $^\circ\text{C}$. For this case the bubble dimension is below 1 μm and 0.2 nJ is close to the threshold for bubble formation. The experimental limit for bubble formation is for a fluence of 0.05 J/cm^2 .⁵ If the two limits are the same then the relation between the theoretical absorbed energy and the experimental fluence requires an absorption coefficient on the order of 8000 cm^{-1} . This analysis indicates the possibility that the absorption coefficient is significantly higher than previous measurements have indicated.

It is possible that for a 1 μm structure such as a melanosome, the boiling temperature is higher than considered and is closer to the critical temperature of 370 $^\circ\text{C}$. In this case, the threshold for bubble formation would be higher.

For temperatures below boiling, strong stress waves can still be obtained. A rise of 100 $^\circ\text{C}$ induces a pressure close to 1 kbar. This pressure can still cause long-range damage on a cellular scale. Below boiling, stress waves emitted in a spherical geometry by the melanin granules within the melanosome include tensile components. These tensile waves can generate damage especially inside the melanosome and further reduce the threshold fluence. Tensile damage below boiling requires further study.

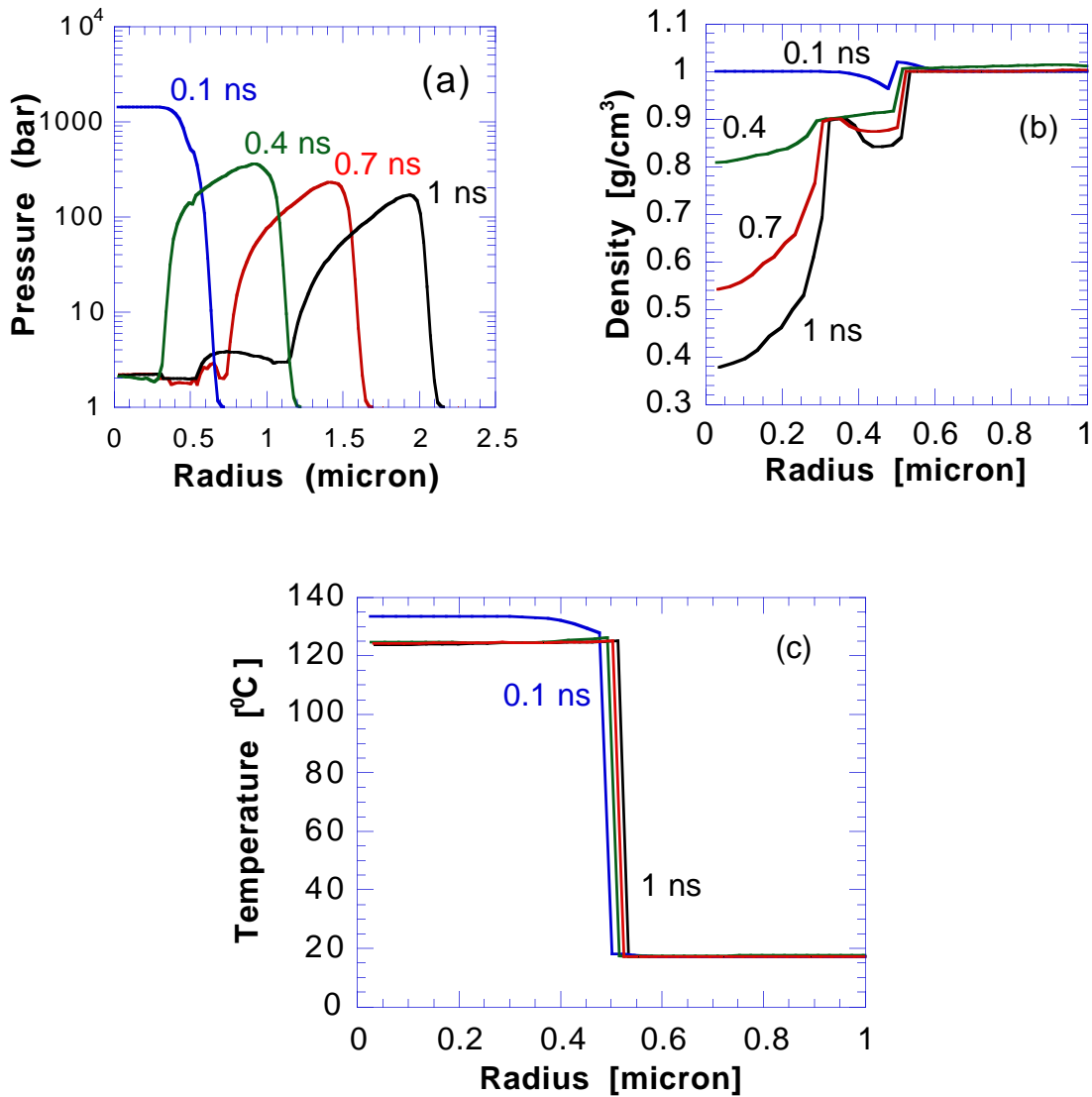


Fig. 3. Melanosome pressure (a), density (b) and temperature (c) vs. radius r for times 0.1, 0.4, 0.7, 1 nsec. The absorbed energy is 0.2 nJ, the radius is 0.5 μm and the laser pulse length is 100 psec.

6. CONCLUSIONS

We find that an absorption coefficient in the range $6000\text{-}8000\text{ cm}^{-1}$ can explain the enhanced shock wave emitted by the melanosome. An experimental and theoretical effort should be considered to identify the mechanism for generating shock wave enhancement. An experiment to measure a single melanosome absorption coefficient during laser irradiation would be very useful. An enhanced absorption may be related to linear and nonlinear mechanisms, such as plasma generation in the melanin granules.

We should also consider the possibility that hot spot emission of shock waves by melanin granules can superpose to increase the amplitude of the emitted shock relative to a uniform deposition of laser energy. This is a possibility if the amount of dissipation from the granular shock wave collisions is limited.

The determination of the threshold for damage from stress wave propagation and bubble expansion in real cells requires the knowledge of various cell properties: sound speed, densities, elastic-plastic response under tension and shear and viscosity. Experiment should measure these properties.

We find that hydrodynamic simulations are useful for identifying the physical properties of laser irradiation of sub-micron structures and to quantify cell threshold conditions for damage.

7. ACKNOWLEDGMENTS

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Technical Information Department • Lawrence Livermore National Laboratory
University of California • Livermore, California 94551

