Low-density plasma formation in aqueous biological media using sub-nanosecond laser pulses

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We demonstrate the formation of low- and high-density plasmas in aqueous media using sub-nanosecond laser pulses delivered at low numerical aperture ($NA=0.25$). We observe two distinct regimes of plasma formation in deionized water, phosphate buffered saline, Minimum Essential Medium (MEM), and MEM supplemented with phenol red. Optical breakdown is first initiated in a low-energy regime and characterized by bubble formation without plasma luminescence with threshold pulse energies in the range of $E_p \approx 4\text{--}5\ \mu\text{J}$, depending on media formulation. The onset of this regime occurs over a very narrow interval of pulse energies and produces small bubbles ($R_{\text{max}}=2\text{--}20\ \mu\text{m}$) due to a tiny conversion ($\eta < 0.01\%$) of laser energy to bubble energy E_B . The lack of visible plasma luminescence, sharp energy onset, and low bubble energy conversion are all hallmarks of low-density plasma (LDP) formation. At higher pulse energies ($E_p=11\text{--}20\ \mu\text{J}$), the process transitions to a second regime characterized by plasma luminescence and large bubble formation. Bubbles formed in this regime are 1–2 orders of magnitude larger in size ($R_{\text{max}} \geq 100\ \mu\text{m}$) due to a roughly two-order-of-magnitude increase in bubble energy conversion ($\eta \approx 3\%$). These characteristics are consistent with high-density plasma formation produced by avalanche ionization and thermal runaway. Additionally, we show that supplementation of MEM with fetal bovine serum (FBS) limits optical breakdown to this high-energy regime. The ability to produce LDPs using sub-nanosecond pulses focused at low NA in a variety of cell culture media formulations without FBS can provide for cellular manipulation at high throughput with precision approaching that of femtosecond pulses delivered at high NA. © 2014 AIP Publishing LLC.
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Pulsed laser microbeam irradiation of aqueous media is used in many biological applications including targeted cell lysis, molecular delivery, cellular microsurgery, and cellular stimulation.^{1–4} These processes are typically initiated by plasma formation resulting in shock wave emission and cavitation bubble generation.^{5,6} To achieve high precision, nano- to micro Joule femtosecond duration laser pulses are often delivered at large numerical apertures ($NA \geq 0.8$) to form low-density plasmas (LDPs) with high spatial confinement.^{5,7,8} However, femtosecond laser sources are costly and cannot be delivered at low numerical aperture due to self-focusing that leads to laser beam filamentation and significant jitter in the focal volume position and intensity.^{9–11} This limits the delivery of femtosecond laser pulses at low numerical apertures for applications, such as micromachining and cellular micromanipulations, that require precise modifications over large areas at high throughput.^{9,12}

While the delivery of nanosecond pulses at low NA may provide a less costly and more reproducible means to perform cellular manipulation at high throughput, current studies indicate that nanosecond optical breakdown is typically associated with large cavitation bubbles and extended ($>100\ \mu\text{m}$) regions of cellular damage, even when using high numerical apertures.^{13,14} This is consistent with experimental studies demonstrating that the high energies/irradiance required to initiate optical breakdown using nanosecond

pulses inevitably generates vigorous avalanche ionization leading to the formation of a highly ionized plasma.^{5,15} Interestingly, even though the mechanism is uncertain, reports have documented the effective use of sub-nanosecond pulses, delivered at low numerical aperture and scanned over large areas, to provide cell lysis and molecular delivery with high throughput and precision.^{12,16}

To understand the processes underlying the biomedical applications of optical breakdown, several groups have investigated plasma formation and bubble dynamics in deionized (DI) water to examine the mechanism, energetics, and dynamics of laser-induced plasma formation.^{15,17,18} The underlying presumption has been that plasma formation in DI water is substantially equivalent to that in aqueous biological media which may contain salts, amino acids, and/or exogenous dyes. While a few studies have examined the impact of aqueous media composition on optical breakdown,^{19–21} no study has systematically examined the characteristics of optical breakdown in media formulations used for cell culture or demonstrated precise cellular manipulation using sub-nanosecond pulses. Such an investigation is not only of fundamental interest but also relevant to understanding the reports of exquisitely precise cellular manipulation achieved using pulsed laser microbeam irradiation at low numerical apertures.^{12,16}

To investigate these issues, we examine optical breakdown produced by 500 ps duration pulses of $\lambda=532\ \text{nm}$

radiation focused at $\text{NA} = 0.25$ in DI water and various aqueous media formulations relevant for cell culture. Using both optical pump-probe measurements and time-resolved imaging, we demonstrate LDP formation in DI water as well as in several aqueous media formulations relevant for cell culture. Specifically, we examine optical breakdown dynamics in DI water, phosphate buffered saline (PBS) and minimal essential media (MEM). We further examine the effects of MEM supplementation with phenol red, an exogenous dye used as a pH indicator, and/or fetal bovine serum (FBS), which is used to provide additional proteins and growth factors for sustained cell culture.

We used an optical pump-probe technique to detect and characterize the dynamics of plasma and bubble formation as shown in Fig. 1. We directed the emission of a passively Q-switched, frequency-doubled Nd:YAG microchip laser (Teem Photonics PNG-M031012-CT2) emitting 500 ps duration pulses at $\lambda = 532 \text{ nm}$ through a $10\times$, 0.25 NA microscope objective (Zeiss CP-Achromat) into a liquid-filled cuvette to generate optical breakdown. A continuous-wave HeNe laser beam ($\lambda = 632.8 \text{ nm}$) served as an optical probe and was delivered collinearly with the Nd:YAG laser beam into the microscope objective after passing through a beam expander. After passing through the focal volume, the diverging He-Ne probe beam was focused onto the surface of a photodiode by a plano-convex lens. The photodiode signal was recorded for 20–100 laser pulses at each pulse energy. The Nd:YAG microchip laser pulse energies were recorded using an energy detector (Coherent J5-09-050).

The pump-probe measurements were corroborated with time-resolved imaging of the optical breakdown process using a procedure described in Ref. 1. The pulsed laser microbeam was formed by directing the Nd:YAG microchip laser beam through a $20\times$, 0.4 NA microscope objective (Zeiss CP-Achromat) to the aqueous sample placed on the stage of an inverted microscope (Zeiss Axiovert S100 2TV). We used an iris to under fill the rear aperture of the objective and provide focusing conditions equivalent to the 0.25 NA

FIG. 1. Schematic of pump-probe experiments. $L1 = 25 \text{ mm}$ focal length lens; $L2 = 250 \text{ mm}$ focal length lens; $L3 = 30 \text{ mm}$ focal length lens; $L4 = 25 \text{ mm}$ focal length lens; $L5 = 20 \text{ mm}$ focal length lens; $P1$ = polarizer; $PD1$, $PD2$ = photodiode and $M1$ – $M5$ = mirrors.

objective used in the pump-probe measurements. This arrangement enables initiation of optical breakdown at 0.25 NA while providing wide-field image acquisition with a larger 0.40 NA .

The pump-probe measurements were sensitive to refractive index changes generated by the pulsed laser microbeam irradiation of the focal volume. With increasing pulse energy, we observed two signal types characterized qualitatively as: *unipolar signals* (Fig. 2(a)) that rise and return to baseline within $2 \mu\text{s}$ or *bipolar signals* (Fig. 2(c)) that also rise and return to baseline rapidly but is also followed by one or more signal oscillations after a period greater than $\sim 15 \mu\text{s}$. The use of time-resolved photography and direct visual observation confirmed that unipolar signals represent optical breakdown in a low-energy regime resulting in bubble formation alone, while bipolar signals represent optical

FIG. 2. (a) Unipolar photodiode signal and (b) corresponding time-resolved images in DI water for $E_p = 6.5 \mu\text{J}$. Arrows in (a) correspond to the times in (b) $t_1 = 26 \text{ ns}$; $t_2 = 740 \text{ ns}$ (R_{max}); $t_3 = 1410 \text{ ns}$. (c) Bipolar photodiode signal and (d) corresponding time-resolved images for $E_p = 19.6 \mu\text{J}$ in DI water. Arrows in (c) correspond to the times in (d) $t_1 = 65 \text{ ns}$; $t_2 = 11400 \text{ ns}$ (R_{max}); $t_3 = 20100 \text{ ns}$.

TABLE I. Threshold pulse energies E_{th} , threshold irradiances I_{th} , and sharpness values S for bubble formation and plasma luminescence regimes in DI Water, PBS, MEM, MEM w/ phenol red, MEM w/10% FBS, and MEM w/both phenol red and 10% FBS.

Media	Bubble formation			Plasma luminescence		
	E_{th} (μ J)	I_{th} (W mm $^{-2}$)	S (μ J $^{-1}$)	E_{th} (μ J)	I_{th} (W mm $^{-2}$)	S (μ J $^{-1}$)
DI water	5.22	1.97×10^9	>10	19.34	7.31×10^9	1.88
PBS	4.93	1.86×10^9	>10	14.56	5.50×10^9	1.32
MEM	4.02	1.52×10^9	>10	14.30	5.40×10^9	0.67
MEM with phenol red	8.17	3.09×10^9	>10	>17	$>6.42 \times 10^9$	NA
MEM with 10% FBS	...	...	...	5.26	1.99×10^9	4.70
MEM with phenol red and 10% FBS	...	...	...	6.86	2.59×10^9	2.54

breakdown in a higher energy regime resulting in both bubble formation and visible plasma luminescence. Simultaneous bubble formation and visible plasma luminescence is associated with high-density plasma formation initiated by pico-/nano second duration pulses.^{6,15,17} The bubble oscillation times T_{osc} were measured from the photodiode traces as indicated in Fig. 2(a)/2(c). Time-resolved photography (Fig. 2(b)/2(d)) confirmed that selection of these time points accurately delimit T_{osc} . The maximum bubble radius R_{max} is determined from T_{osc} using the Rayleigh formula for inertially-controlled bubble growth $R_{max} = T_{osc}[(p_{\infty} - p_v)/3.35\rho]^{1/2}$, where p_{∞} and p_v are the atmospheric and vapor pressures, respectively, and ρ is the water density.²² The Rayleigh formula predictions for R_{max} are in full agreement with the bubble sizes recorded from the time-resolved images.

For each media composition tested, we classified the photodiode signal type and determined the probabilities of bubble formation alone as well as bubble formation accompanied by plasma luminescence versus pulse energy E_p . This pulse-energy-dependent probability for bubble formation and plasma luminescence $p(E_p)$ was fit to a Gaussian error function (GEF).^{1,15} The GEF is parameterized by the threshold energy E_{th} , which generates bubble formation or plasma luminescence with 50% probability, and the sharpness S .¹ Table I summarizes the threshold pulse energy, the threshold irradiance, and the sharpness of these two plasma formation regimes for each media composition.

Pump probe measurement of DI water and PBS (0.15 mol/l) revealed distinctly different threshold energies for the onset of bubble formation vs. plasma luminescence. Values for the bubble oscillation time T_{osc} and maximum bubble radius R_{max} were determined from these signals and Fig. 3 provides the variation of R_{max} versus E_p for both media. Bubble formation was first detected for $E_p = 5.22$ and 4.93μ J for DI water and PBS, respectively, corresponding to $R_{max} = 10.9$ and 7.0μ m, respectively. Bubble formation alone was observed for E_p values as large as 19.75 and 15.0μ J in DI water and PBS, respectively. Larger pulse energies resulted in an abrupt change to bipolar photodiode signals coincident with the appearance of plasma luminescence and a dramatic increase in R_{max} from ~ 30 – 40μ m to $>130 \mu$ m.

For sustained culture, cells require minimal essential medium (MEM), an aqueous solution that includes amino acids, salts, and glucose. MEM is routinely supplemented with phenol red, a non-essential, visible pH indicator that absorbs $\lambda = 532$ nm radiation for standard cell culture pH of

7.4.²³ Moreover, many cell types require additional proteins and growth factors in the form of FBS. For these reasons, we examined the energetics and dynamics of optical breakdown for several cell culture media compositions containing these elements.

Figure 4 shows R_{max} versus E_p for four media compositions: MEM, MEM with 28μ M phenol red, MEM with 10% FBS, and MEM with both 28μ M phenol red and 10% FBS. For MEM alone, optical breakdown commences with the appearance of a unipolar signal at 4.02μ J with the formation of bubbles with $R_{max} = 2.2 \mu$ m which is comparable to the diffraction-limited focal volume radius of the probe beam (1.3μ m). Starting at pulse energies of $E_p \sim 11 \mu$ J, we occasionally observe bipolar photodiode signals coincident with plasma luminescence that occurs concurrently with an abrupt increase in R_{max} from $\sim 40 \mu$ m to $>120 \mu$ m. For $E_p \geq 15 \mu$ J, plasma luminescence is observed consistently along with the production of large bubbles ($R_{max} \sim 150 \mu$ m). The addition of phenol red to MEM results in a significant increase in the minimum pulse energy for bubble formation alone ($E_{th} = 8.17 \mu$ J) corresponding to a significant increase in the bubble radius $R_{max} = 10.7 \mu$ m. Addition of FBS to MEM eliminates the formation of low-density plasmas and the onset of optical breakdown results in both visible plasma luminescence and the formation of moderately-sized bubbles ($R_{max} \sim 60 \mu$ m). The threshold energy for optical breakdown was measured as 5.26μ J for MEM with FBS alone and 6.86μ J for MEM supplemented with both phenol red and FBS.

FIG. 3. Maximum bubble radius R_{max} vs. laser pulse energy E_{th} in deionized water and phosphate buffered saline. Pulse energies below 4.93μ J did not result in bubble formation. Open symbols represent experimental trials where only bubble formation was observed while filled symbols represent trials where both bubble formation and plasma luminescence were observed.

FIG. 4. Maximum bubble radius $R_{\max}$ vs. laser pulse energy E_{th} in MEM, MEM with 28 μM phenol red, MEM with 10% FBS, and MEM with both 28 μM phenol red and 10% FBS. Open symbols represent experimental trials where only bubble formation was observed while filled symbols represent trials where both bubble formation and plasma luminescence were observed.

Our data clearly establish the existence of two plasma formation regimes resulting from the irradiation of aqueous samples with single 500 ps pulses emitted by a Q-sw Nd:YAG microchip laser at $\lambda = 532$ nm and focused at 0.25 NA. For all aqueous media compositions lacking supplemental FBS, pulse energies below 11 μJ result in optical breakdown producing only relatively small bubbles with $R_{\max} = 2\text{--}40$ μm . Further increases in laser pulse energy produce both visible plasma luminescence and the formation of much larger bubbles with $R_{\max} \geq 100$ μm . In Table II, we summarize the energy ranges that delimit these two regimes, provide the corresponding bubble sizes, and calculate the conversion efficiency, η , of laser pulse energy to bubble energy as $\eta = 100 \times (E_B/E_p)$, where $E_B = \frac{4\pi}{3}(p_{\infty} - p_v)R_{\max}^3$.²²

Table II shows that the low-energy regime is characterized by the generation of tiny bubbles due to minuscule conversion efficiencies $\eta = 10^{-5}\% - 10^{-1}\%$. These low bubble energy conversion efficiencies, as well as the absence of visible plasma luminescence, are hallmarks of LDP generation in which the rate of free electron generation via multi-photon and avalanche ionization processes is counteracted by electron-hole recombination which limits the free electron

density in the focal volume.^{8,24} Our use of sub-nanosecond pulses to form LDPs is likely due to the short cavity length of the Q-sw microchip laser that promotes single-frequency operation free of mode beating resulting in a smooth and reproducible temporal pulse shape.²⁵ For all the media formulations tested, we find a high-energy regime characterized by both bright plasma luminescence and larger bubble formation with conversion efficiencies $\eta \geq 2\%$. The formation of luminescent plasmas with significantly larger conversion efficiencies indicate the formation of full-density plasmas where the higher laser intensity drives free electron generation through avalanche ionization and thermionic emission at rates that exceed electron-hole recombination.⁵

The production of microscopic bubbles via LDP formation using 500 ps laser microbeam irradiation at 0.25 NA is unprecedented and approaches the precision achieved using femtosecond pulses.^{8,24} For example, Vogel and co-workers have shown that irradiation of DI water using femtosecond pulsed microbeams at 0.9 NA resulted in maximum bubble radii of $R_{\max} = 1\text{--}5$ μm for $\lambda = 1040$ nm and $R_{\max} < 1\text{--}3.5$ μm for $\lambda = 520$ nm.⁸ Moreover, the LDP formation with sub-nanosecond pulses at low NA enables rapid and precise cellular modification over large areas which is simply not possible using femtosecond laser irradiation without implementation of strategies to mitigate self-focusing and laser beam filamentation.¹¹

The lower threshold energies observed for plasma formation in PBS as compared to DI water are likely mediated by the ionic characteristics of PBS. In DI water, no electron donors are present and the initial free electrons must be generated by multiphoton ionization of the water molecules, leading to a very sharp threshold.^{20,21} The addition of small concentrations of salt (~ 0.15 M) provides electron donors within the media thereby lowering the optical breakdown threshold energy.²⁰

The chief difference between MEM and both DI water and PBS is its amino acid content (579 $\mu\text{g}/\text{ml}$), especially the content of aromatic amino acids tyrosine, tryptophan, and phenylalanine, which display significant two-photon absorption at $\lambda = 532$ nm.²⁶ It is likely that two-photon absorption by the aromatic amino acids in MEM provides a source of free electrons at lower irradiances and leads to a lower energy threshold for LDP formation in MEM (4.02 μJ) as

TABLE II. Ranges of maximum bubble radii and conversion efficiencies for each media composition.

Media		Bubble formation			Plasma luminescence		
		$R_{\max}$ (μm)	E_p (μJ)	η (%)	$R_{\max}$ (μm)	E_p (μJ)	η (%)
DI water	Min	10.9	5.22	0.0102	142.5	19.04	6.01
	Max	43.5	19.75	0.173	162.0	20.0	9.29
PBS	Min	7.00	4.93	0.0033	132.0	14.0	6.30
	Max	29.4	15.0	0.0495	164.0	15.49	6.78
MEM	Min	1.6	4.02	4.49×10^{-5}	123.0	11.0	6.25
	Max	28.8	15.0	0.065	149.0	16.0	8.18
MEM with phenol red	Min	10.7	8.17	6.20×10^{-3}	96.8	11.0	3.43
	Max	33.2	17.0	0.089	163.0	17.0	10.5
MEM with 10% FBS	Min	...	...	...	75.1	5.12	3.43
	Max	...	...	...	100.0	6.10	6.83
MEM with phenol red and 10% FBS	Min	...	...	...	76.2	6.23	1.80
	Max	...	...	...	100.0	8.03	6.37

compared to PBS (4.93 μJ) and DI water (5.22 μJ). The addition of 10% FBS to MEM limits the optical breakdown process to the production of full-density plasmas initiated at $E_p \approx 5.1 \mu\text{J}$. The proteins and additional amino acids in FBS provide additional electron donors beyond those present in the MEM. This is because bovine serum albumin, a globular protein, is the major component of FBS and displays significant two-photon absorption at $\lambda = 532 \text{ nm}$.²⁶ This enhances the rate of multiphoton ionization at lower irradiances which outstrips the rate of electron-hole recombination leading to avalanche ionization, the generation of full-density plasmas, and formation of moderate to large bubbles due to the higher conversion efficiency of laser energy to bubble energy.²⁷

The addition of phenol red to the aqueous medium narrows considerably the energy interval in which unipolar photodiode signals are observed. The attenuation of the incident laser radiation by phenol red, which has an absorption peak near $\lambda = 532 \text{ nm}$, requires higher pulse energies in order to generate the focal volume irradiances needed for plasma formation. Once formed, the linear absorption by phenol red enables thermionic emission to contribute to generation of free electron and supplements avalanche ionization as mechanisms for full-density plasma formation at higher pulse energies.²⁸

In conclusion, we have demonstrated the generation of low-density plasmas in a number of biologically relevant aqueous media compositions using sub-nanosecond laser pulses emitted from a passively Q-sw frequency-doubled Nd:YAG microchip laser delivered at low numerical aperture. Low-density plasma formation was achieved in DI water, PBS, and MEM with or without phenol red supplementation. However, media supplemented with 10% FBS provides additional proteins that act as electron donors leading directly to avalanche ionization, luminescent plasmas, and moderate to large bubble formation. The energetics and spatial confinement of the low-density plasmas that we form using sub-nanosecond laser pulses approach those produced by femtosecond pulses. Moreover, the greater ease with which sub-nanosecond pulses can be focused at low NA facilitates its application to large fields of view and opens the opportunity for cellular applications in biological media that require both high precision and high throughput. These results further suggest that cellular irradiation should be performed in media without FBS to facilitate precise cellular modifications.

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