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Plasmonic Intracellular Delivery

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Abstract

This chapter describes the significance of plasmonics to the field of intracellular delivery. We begin by discussing the significance of intracellular delivery, its applications in biology and medicine, and the currently available intracellular delivery techniques. Next, we discuss the field of plasmonic intracellular delivery, beginning with the discovery of optoporation. In optoporation, a laser beam is tightly focused onto a cell membrane to generate a transient pore, through which membrane-impermeable cargo can enter the cell. To improve the throughput of this technique, plasmonic materials were used for their ability to efficiently absorb laser light and generate spatially confined electric fields. Here, we describe the process by which plasmonic materials absorb laser light energy and generate plasmons. These plasmons transfer their energy to their surroundings, resulting in a rise in temperature and the subsequent creation of a bubble or shockwave. Finally, we describe how the properties of plasmons and plasmon-mediated effects facilitate cell poration for intracellular delivery.

Keywords: plasmonic, thermoplasmonic, intracellular delivery, cell poration, cell membrane perforation, cell transfection

1. Introduction

Plasmonic materials have found utility in biological applications ranging from photothermal therapy (killing cancer cells) to bio-sensing to intracellular delivery [1–3]. The ability to deliver membrane-impermeable cargoes into cells is a critical step in the development of many therapeutics and an important problem in the field of biology [4–7]. Light-activated thermoplasmonic nanostructures are a potential solution to this problem and can be used to deliver a range of cargoes into a range of cell types at high efficiency and high throughput, with spatial selectivity, while maintaining cell viability [8–10].

2. Currently available intracellular delivery techniques

The delivery of membrane-impermeable cargoes such as nanoparticles, genetic materials, or functional proteins directly into cells is a critical step for applications in biology and medicine [4]. For instance, the delivery of gene-editing tools could be used to manipulate cells and tissues for regenerative medicine or engineer cells for personalized cell therapies [4–7]. Intracellular delivery methods include biological vectors such as viruses, chemical modifications of delivery cargoes such as lipofection, and physical techniques such as microinjection, electroporation, and optoporation [11–24]. While research efforts have led to a continuous increase in efficiency and sophistication, each of the currently available approaches has its own advantages and disadvantages. To this point, no platform technology exists that combines high-efficiency delivery, high-throughput processing, low-toxicity, versatility with respect to type of cell and cargo, and simple, cheap and affordable production. The research presented in this thesis is an attempt toward developing a solution to this problem.

Viral-based delivery is a popular biological technique that offers high-efficiency delivery at high throughput. However, it is limited in terms of cargo-carrying capacity, the ability to only deliver genetic material, the requirement to customize the virus for each cargo and cell type, and the potential for immunologic and oncogenic risks [11–15].

Lipofection, a chemical method, offers high throughput but varies in efficiency depending on cell type, can require complex chemical customization depending on the cargo, and risks endosomal trapping of the cargo [7, 25, 26].

Electroporation, the most widely used physical delivery method, offers high-efficiency delivery and high throughput for a range of cargo types, but can lead to high cell death, particularly for sensitive cell types [27, 28]. Nucleofection, a variation of electroporation, offers improved viability but can require expensive customized reagents and can still be low viability for the most sensitive cell types. Ultrasound-mediated methods offer a low-cost high-throughput technique for delivering membrane-impermeable cargo into cells [12]. However, the cavitation dynamics are not spatially localized, which can lead to nonuniform results and high cell death. Other physical methods such as microinjection, nanowire-mediated delivery, and microfluidic squeezing are promising, but offer limited throughput and/or reproducibility [14, 29–32].

3. Laser-mediated cell poration for intracellular delivery

Optoporation, a physical delivery technique, utilizes a tightly focused laser beam to create a transient pore in the cell membrane [18, 19, 33, 34]. This technique offers high delivery efficiency, high cell viability and is versatile with respect to cargo and cell type. However, each cell has to be porated individually by focusing the laser beam directly onto the membrane, causing optoporation to have an extremely low throughput. Modifications, including the use of active flow in microfluidic channels and a nondiffracting beam, slightly increase the throughput but not to the scale necessary for applications such as cell therapy, which can require on the order of 10^8 cells [35, 36].

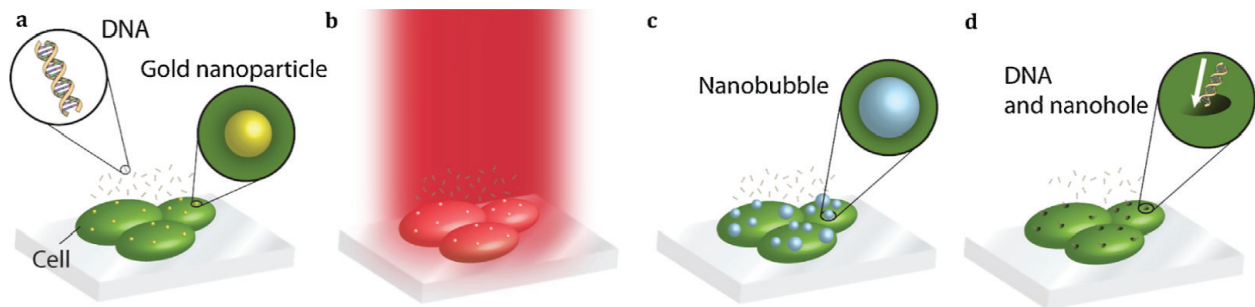


Figure 1. Schematic of gold nanoparticle-mediated intracellular delivery. (a) Gold nanoparticles adhere to the cell membrane. (b) The gold nanoparticles are illuminated by a pulsed laser system. (c) Laser illumination of the gold nanoparticles leads to the formation of a bubble around the gold nanoparticle. (d) The bubble creates a temporary pore in the cell membrane, through which membrane-impermeable cargo can enter. Reprinted with permission from [1]. Copyright 2013, Elsevier.

Laser-activated thermoplasmonic nanostructures improve the throughput of optoporation by efficiently absorbing the laser energy at multiple localized hotspots, generating a rise in temperature, and transferring the energy to the surrounding medium [2, 8–10, 31, 37–39]. This transfer of energy to the surrounding solution results in the creation of a bubble or pressure wave that can generate sufficient mechanical stress to create a transient pore in the cell membrane, through which membrane-impermeable cargo can diffuse into the cell [1, 3, 8–10, 40]. This process is shown briefly in **Figure 1**, and the physics of this process will be explained in greater detail in the following section of this thesis. Gold nanoparticles are the most commonly used plasmonic nanostructures for intracellular delivery and have been successfully used to porate cell membranes for a range of cell types [37, 38, 41–46]. Gold nanoparticles potentially outperform other physical techniques by offering high efficiency, viability, and throughput [1, 45]. However, the gold nanoparticles remain in the cell after delivery as metallic residue and can form aggregates, and the long-term toxicity of these gold nanoparticles is still not fully understood [47, 48].

Laser-activated nanostructured substrates bypass this potential toxicity problem, as cells can be cultured on the substrates, porated, and removed from the substrates (which remain intact) after intracellular delivery without leaving metallic particles within the cells [31, 39, 49–52]. In this thesis we explore the fabrication of various thermoplasmonic nanostructured substrates for intracellular delivery and use the fabricated substrates to deliver a wide range of membrane-impermeable cargoes (dyes, dextrans, proteins, etc.) to a wide range of cell types (HeLa CCL2 cells, induced pluripotent stem cells (iPSCs), etc.).

4. Physics of plasmonic intracellular delivery

4.1. Properties of localized surface plasmons

Plasmonic structures have proven valuable in intracellular delivery as well as numerous other applications requiring the ability to generate electric fields in a highly localized manner [1]. These structures are capable of supporting plasmons, or quanta of plasma oscillations.

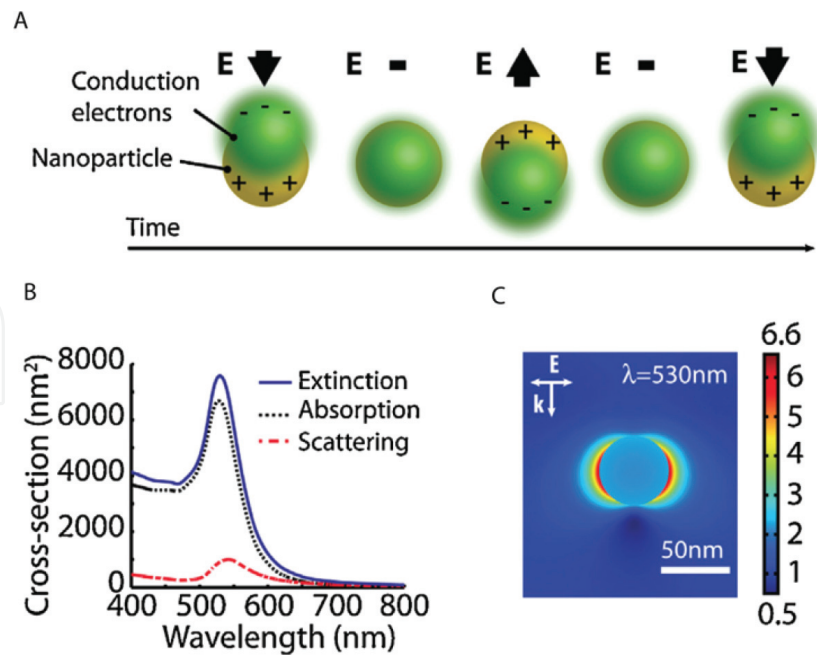


Figure 2. (a) Principle of localized surface plasmons. At any point in time, the gold nanoparticle experiences a uniform electric field. The electrons accelerate in the direction of the electric field and are displaced from the positive lattice ions. The electrons are then attracted back to the positive lattice ions by Coulomb forces. This electromagnetic oscillator is called a plasmon. (b) The gold nanoparticles are illuminated by a pulsed laser system. (c) For a gold nanoparticle with a 50-nm diameter, resonance occurs at a wavelength of approximately 550 nm [1]. Copyright 2013, Elsevier.

Plasmons can be described classically as the collective oscillations of free electrons with respect to the positively-charged ion lattice in a metallic nanoparticle in the presence of an oscillating electromagnetic field [53, 54].

It is simplest to picture a spherical metallic nanoparticle immersed in an aqueous environment in the presence of an electromagnetic wave, such as laser light. If the diameter of the nanoparticle is less than half the wavelength of the light, then at any point in time the entire nanoparticle will experience a uniform electric field pointing in one direction, as shown in **Figure 2a**. The free electrons in the metallic nanoparticle will accelerate in the direction of the uniform electric field. As a result, the electrons are displaced from the positively-charged lattice ions of the metallic nanoparticle. The electrons experience an attractive Coulomb force that drives them back toward the positively-charged lattice ions, and this movement results in a collective oscillation of the free electrons with respect to the fixed positively-charged lattice ions. The oscillator is termed a localized surface plasmon, and the electromagnetic wave, for instance laser light, is the driving force.

For this phenomenon to occur, the real part of the permittivity, ϵ_r , of the plasmonic material must be negative (a condition satisfied by metals), and the real part of the permittivity of the surrounding material must be positive (a condition satisfied by dielectrics) [1]. This allows the following boundary condition in electrodynamics to be satisfied:

$$(D_1 - D_2) \cdot \hat{n} = D_{1,\perp} - D_{2,\perp} = \sigma_f \quad (1)$$

given that

$$D = \varepsilon E \quad (2)$$

where D is the electric displacement field, E is the electric field, ε is the permittivity of the material, σ_f is the free charge density and \hat{n} points in the direction from medium 2 to medium 1 [55].

When the eigen frequency of the collective electron oscillation, or the plasma frequency, matches the frequency of the electromagnetic wave, the system is said to be in resonance. Resonance results in enhanced absorption of the laser light energy by the metallic nanoparticle, and a greater near field enhancement, as shown in **Figure 2b** and **c** [1]. The resonance wavelength is affected by the shape, size and material of the nanoparticle as well as the dielectric constant and refractive index of the environment [1, 56]. Although resonance results in more efficient absorption and a higher near-field enhancement, resonance is not a necessary condition for the thermoplasmonic cell poration described in this thesis [57].

4.2. Interactions of laser pulses and plasmonic structures in an aqueous environment

4.2.1. Energy transfer from light source to plasmonic nanostructure to aqueous environment

When a plasmonic nanostructure in an aqueous environment is illuminated with laser light, the resulting absorption of laser energy and near-field enhancement initiates a series of energy transfers. Depending on the conditions of the laser pulse, these energy transfers can result in the creation of a shockwave or vapor bubble [1, 57–59]. In our theoretical discussions, we will use water as the aqueous environment, as cell media is water-based and biological tissue has a refractive index (1.36–1.39) comparable to that of water (1.33) [60].

First, the photons in the laser light are absorbed by the electrons in the plasmonic nanostructure, causing them to collectively oscillate, generating plasmons. The plasmons generate an enhanced near field. For ultrashort pulses in the fs regime, the peak intensities of the laser pulses and therefore of the enhanced near-field can be high enough to photo-ionize the water and generate a plasma [1]. Because the research presented in this thesis makes use of a ns-pulsed laser system rather than a fs-pulsed laser system, we will not focus on the effects of the enhanced near-field. We will instead focus on other effects of laser energy absorption by the plasmonic structure. As the plasmon oscillations decay, the energy is transferred into a distribution of nonthermal electrons (**Figure 3**) [1]. Over approximately 500 fs, the nonthermal electrons decay into a population of thermalized electrons via electron–electron scattering. It takes 1–3 ps for the thermalized electrons to couple with the phonon lattice of the plasmonic nanostructure and reach thermal equilibrium. According to Boulais et al., over a timescale of approximately 100 s of ps, thermal energy is transferred from the phonon lattice to the surrounding medium. However, it is worth noting that the characteristic timescale over which energy is transferred from a gold plasmonic nanostructure to water can vary depending on the laser system used and the laser power.

The research presented in this thesis makes use of a ns-pulsed laser system with 11-ns pulses. These pulse widths are relatively long compared to the electron-phonon coupling

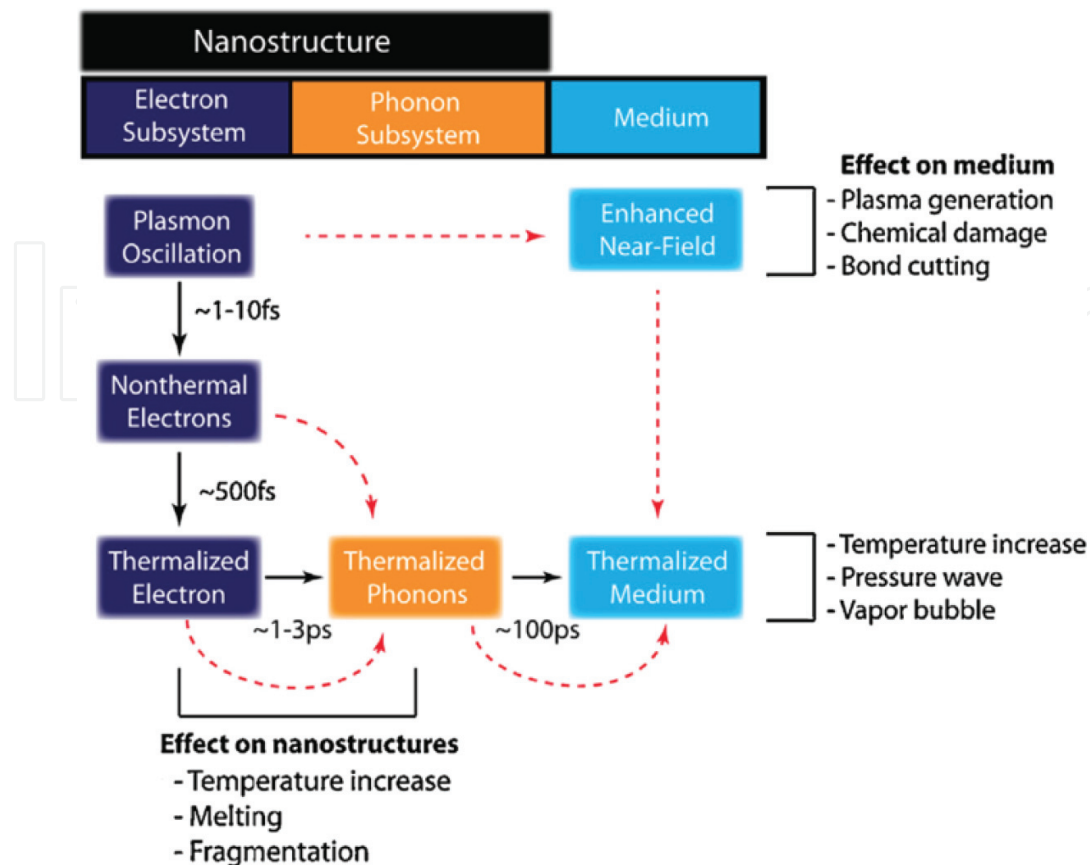


Figure 3. Energy transfers following laser illumination of a plasmonic nanostructure. The photons in the laser light couple with the electrons in the plasmonic nanostructure, generating plasmon oscillations. The plasmons decay into a nonthermal electron distribution, which thermalizes within 100s of fs. The thermalized electrons transfer energy to the phonon lattice of several ps. The phonons transfer thermal energy to the surrounding medium within a timescale on the order of 100 ps. This can result in effects such as temperature increase, the formation of a pressure wave, and/or the formation of a vapor bubble. Reprinted with permission from [1]. Copyright 2013, Elsevier.

time and the time over which the thermalized phonon lattice couples to the surrounding medium. These subsystems therefore reach thermal equilibrium during the lifetime of the laser pulse, and the laser pulse can be considered as heating the electrons, phonon lattice, and surrounding medium at the same time.

4.2.2. Heat-mediated bubble and/or shockwave formation

Absorption of laser energy by a plasmonic nanostructure can result in a temperature increase that generates a shockwave or a bubble, among other possible effects [1, 3, 8–10, 40]. The exact event that results from the laser energy absorption is dependent on the conditions of the laser pulse—most importantly, the fluence and the width of the laser pulse. **Figure 4** shows the various effects on a plasmonic gold nanoparticle immersed in water after absorption of an incoming laser pulse, ranging from a relatively low fluence on the left to increasingly higher fluences on the right [3].

The laser fluences used in the research presented in this thesis are sufficient to cause protein denaturation and to generate acoustic waves and water vapor bubbles, and we will therefore

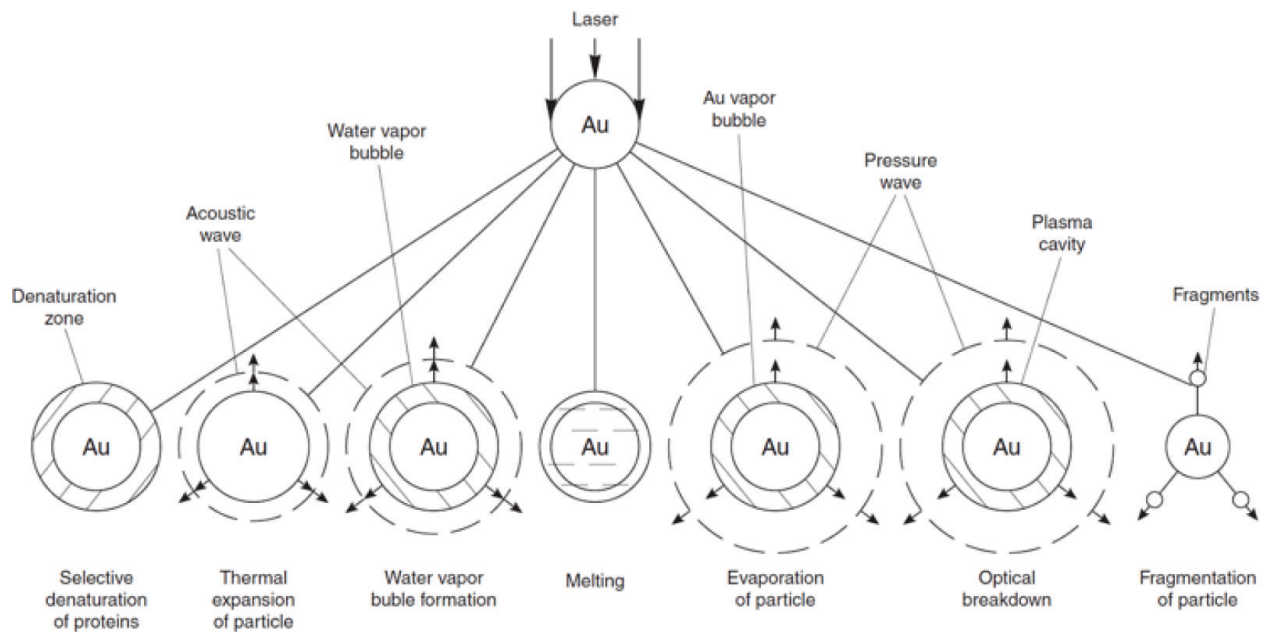


Figure 4. Various effects of laser illumination of plasmonic gold nanoparticle in liquid environment. Laser fluence increases from left to right. Reprinted with permission from [3]. Copyright 2008, Astro Ltd.

focus the discussion in this section on these events. Because the research presented in this thesis is based on the use of an 11-ns pulsed laser system, we will restrict the discussion to mechanism processes that can be initiated by laser pulses of this width.

Proteins can denature at temperatures above 50–160°C [3]. The distance from the plasmonic material at which proteins are denatured is also dependent on the width of the laser pulse. For instance, proteins 18 nm away from a gold nanoparticle illuminated with a microsecond laser pulse of sufficient energy are denatured, whereas only proteins up to 4 nm away from a gold nanoparticle illuminated with a femtosecond pulse are denatured [3]. In the case of nanosecond pulses, as are used in the research presented here, proteins 6 nm away from a gold nanoparticle are denatured [3]. This is because heat is able to diffuse further for longer pulse widths; in other words, shorter pulse widths result in greater thermal confinement.

When the plasmonic material absorbs light from a pulsed laser source, the material undergoes thermal expansion. If the rate of thermal expansion is greater than or approximately equal to the speed of sound in the surrounding media, compression waves can form, known as the photoacoustic effect [3]. These acoustic waves can form at lower temperatures, and thus at lower fluences, than those required for bubble formation [3].

If the laser fluence is high enough for the surrounding media to reach 90% of the critical temperature, ($T_c = 373.9^\circ\text{C}$) bubbles can be generated via phase explosion, which is a combination of spinodal decomposition and homogenous nucleation [1, 61–63]. Thermal energy is deposited rapidly into the system, and the water temperature rises rapidly as a consequence. The heating occurs too rapidly for the water to build up pressure at a sufficient rate, and the pressure drops below the saturation pressure. The system crosses the binodal line into the metastable region, and crosses the kinetic spinodal line into the unstable region. In the

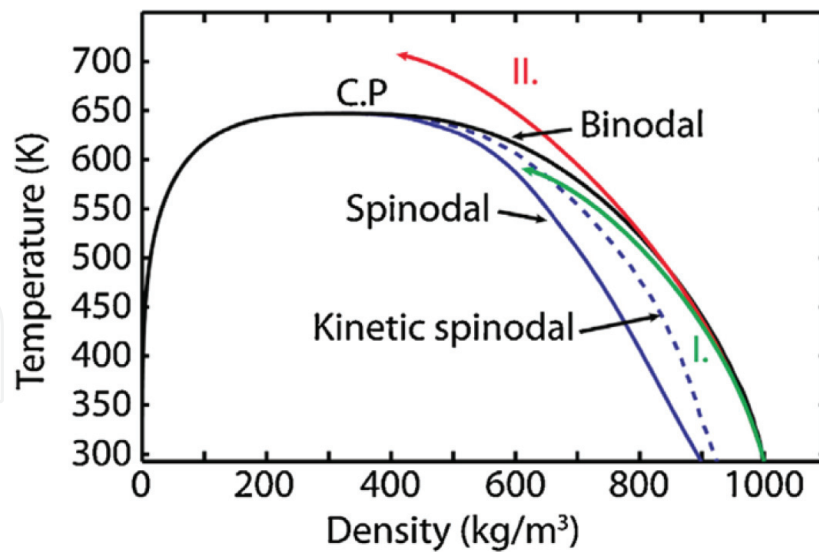


Figure 5. Density-temperature phase diagram for water. The green line labeled “I” shows the trajectory for phase explosion. The system crosses the binodal line into the metastable region before crossing the kinetic spinodal line into the unstable region, where there is no energy barrier between the two phases. The red line labeled “II” shows the trajectory for trivial fragmentation. CP is the critical point. Reprinted with permission from [1]. Copyright 2013, Elsevier.

unstable region, there is no energy barrier between the liquid and vapor phases. The water relaxes into an equilibrium state of both liquid and vapor. This process is accompanied by an increase in pressure, termed phase explosion. The green line in **Figure 5** represents the pathway of this process [1].

For nanosecond pulses and longer, the damage caused to the cells is most likely due to bubble formation and collapse, and not due to the formation of acoustic shockwaves. This is because the timescale for the shockwaves generated by a nanosecond pulse (on the order of 10^9 s) is longer than the characteristic relaxation time for thermomechanical stress in biological tissues (10^{11} – 10^{12} s) [3].

4.2.3. Bubble dynamics

For a nanosecond laser pulse, bubbles can grow and collapse on the timescale of 100 ns to 5 μ s [3]. The bubble grows due to its high relative temperature and pressure, but loses energy as it grows due to friction with the surrounding liquid. The pressure of the surrounding liquid and surface tension eventually cause the bubble to collapse, which occurs over approximately the same timescale as the bubble’s growth [1]. When the bubble collapses, it can generate a shockwave [3]. It is also possible for the bubble to contract and expand repeatedly, resulting in bubble oscillations [3].

The formation of a bubble or pressure wave can be measured using pump-probe spectroscopy [1]. Pump-probe spectroscopy measures scattered light, or a drop in transmitted light. The lifetime of the drop in transmitted light is equivalent to the lifetime of a bubble, which can be used to calculate the diameter of the bubble [1]. Operating under the assumptions that the surrounding liquid is incompressible and there is no heat or mass transfer from the bubble

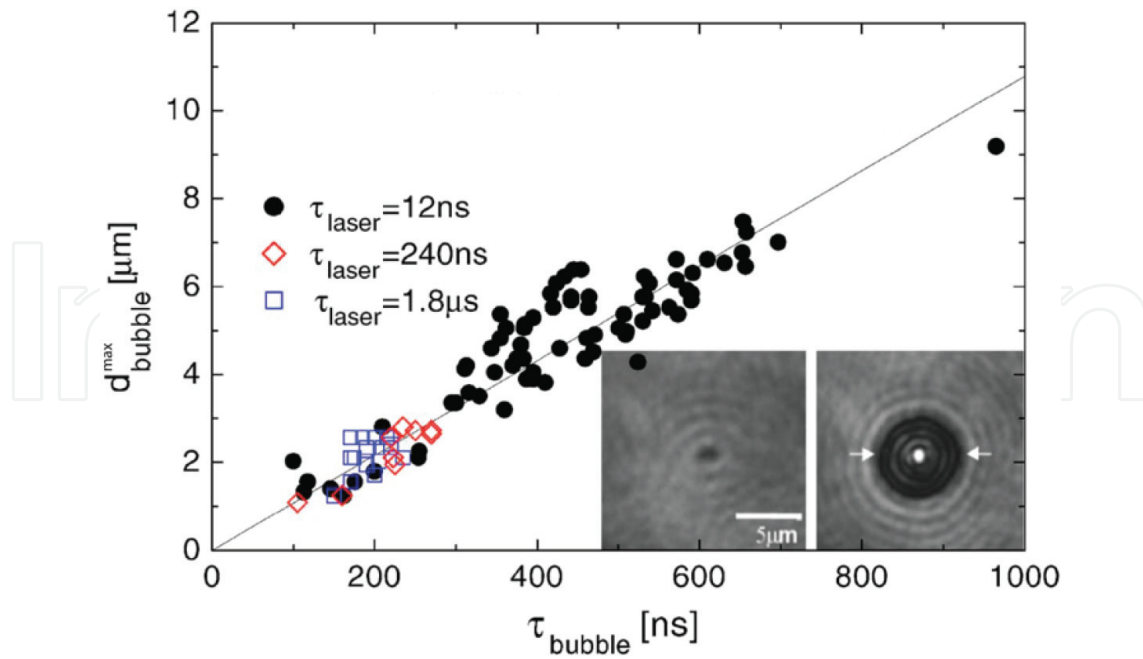


Figure 6. Plot showing fit of Rayleigh-Plesset equation to experimental data measuring the maximum diameters and lifetimes of bubbles generated by light-irradiated melanosomes. Photographic image on left shows melanosome before irradiation; image on right shows melanosome and bubble after irradiation. Ambient pressure of 101 kPa, saturated vapor pressure of 2.33 kPa, and water density of 998 kg/m³. Reprinted with permission from [1]. Copyright 2013, Elsevier.

(water vapor has relatively low heat conduction), and given that the temperature T of the surrounding water is 293 K, the mass density $\rho_L = 998 \text{ kg/m}^3$ and the saturation pressure $\rho_{sat} = 2.3 \text{ kPa}$ for water, one can simplify the Rayleigh-Plesset equation to obtain the following relation between the lifetime of a bubble and its diameter [1]:

$$\tau_{bubble} = 0.0915 \left(\frac{s}{m} \right) d_{bubble}^{max} \quad (3)$$

This estimation is well supported by experimental results, as shown in **Figure 6** [1].

The growth and collapse of thermoplasmonic bubbles can generate sufficient thermomechanical stress to porate cells [1, 3, 8, 9, 40]. In addition to this effect, the formation of a vapor bubble affects the interaction between the incoming laser light and the plasmonic nanostructure by modifying the refractive index of the system and by scattering the incoming light and reducing the absorption of light by the plasmonic structure [1, 3]. The presence of the bubble also prevents significant heat conduction to the surrounding liquid, because the vapor of the bubble consists of relatively low thermal conductivity [1].

5. Conclusion

The challenge of delivering membrane-impermeable cargoes into living cells is an important problem in the fields of biology and medicine [4–7]. Over the past few decades, solutions such

as viral vectors, lipofection, electroporation, nucleofection, microfluidic squeezing, and micro-injection have offered potential solutions to this complex and critical problem [11, 14–17, 19, 20, 22–24, 28, 29, 35, 64–66]. However, there is still a need for a high-efficiency, high-throughput, low-toxicity, cost-effective intracellular delivery technique that is applicable to a range of cells types for a range of cargoes. Plasmonic nanostructured surfaces may be a promising alternative to the currently available intracellular delivery techniques and utilize the unique ability of plasmonic structures to absorb laser light energy and transfer the energy to a confined volume within the nearby surrounding medium [31, 39, 49–52]. Upon illumination with a short laser pulse, the laser light energy is strongly absorbed by the plasmonic nanostructures, resulting in a rise in temperature [1, 57–59]. Thermal energy is transferred to the surrounding medium; if the rise in temperature is sufficient, a bubble is formed in the surrounding medium [1, 57–59]. The subsequent growth and collapse of the bubble can generate sufficient thermomechanical stress to create a transient pore in nearby cell membranes [1, 3].

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