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Simulating Traumatic Brain Injury (TBI) using laser-induced shockwave under quantitative phase microscopy

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ABSTRACT

Traumatic brain injury (TBI) occurs when an external shock causes injury to the brain. The mechanism of the disease is not completely understood yet. Studies have shown that astrocytes play various roles following brain injury. However, the exact functional role of them after TBI is still a matter of debate. Laser-induced shock waves (LIS) can create a precise controllable mechanical force that is capable of injuring or lysing cells to simulate the brain injury at the cellular level. Here, we propose a system that enables us to induce injuries in CNS cells with LIS and observe the whole process under a Quantitative phase microscope (QPM). Our system is also capable of adding another laser for optically trapping the cells to keep them at a certain distance from the center of the shockwave, as this distance is one of the important factors which determines the level of injury.

Keywords: TBI, QPM, LIS, Astrocytes, bTBI

1. INTRODUCTION

Traumatic Brain Injury is considered one of the crucial public health problems, as it is the common reason of death or impairment 1, 2. As there is an increase in blast Brain Traumatic Injury (bTBI) as a result of exposure to improvised explosive devices (IEDs) in wars, various models are being proposed to study this type of brain injury 3, 4. Laser-Induced Shockwave can be named as one of the proposed methods to simulate bTBI, both in vivo and in vitro. Despite the ease of implementation of the actual force in animal studies in vivo, by the use of LIS to apply a precise and measurable force, in vitro models make it possible to narrow down the aim of studying TBI to the single-cell response 5, 6.

Laser-induced shockwave is generated when a laser light with a high power irradiates a fluid in a short time. If the irradiance is higher than the fluid's optical breakdown, photo-ionization results in a plasma formation and the temperature and pressure difference of the plasma and the rest of the fluid creates a cavitation bubble which can expand hundreds of micrometers. This expansion causes a shockwave in the fluid, which is called LIS 7, 8.

To have a precise and direct measurement of the amount of damage we have integrated the shockwave system into a Quantitative Phase Microscopy (QPM). QPM enables measuring the surface fluctuations of the cells quantitatively by quantifying the optical pathlength delays caused by the cell through a Linnik interferometer. As this technique is label-free, no fluorescent dyes or probes are used; therefore long time imaging can be done without photobleaching or interfering with the cells normal condition 9, 10, 11, 12.

2. SETUP

The developed setup is a laser system, for generating shockwaves, integrated into a QPM system. For this study, the QPM in the system works in its reflectance mode. The details of the setup can be found in ref 13. The shockwave system is comprised of a laser system, beam expander, a half-wave plate polarizer to control the laser power, an oscilloscope connected to a photodiode to measure the laser power, a mirror for reflecting the light into an objective lens, and an objective lens to focus the light into the cell medium.

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3. RESULTS

Real height of the cells can be measured by estimating the refractive index of the cell in QPM images 12. Figure 1 shows a constructed 3D image of astrocyte cells, taken with 20x magnification. Cell growth cones, filopodia and lamellipodia, can be clearly seen in this image. Figure 2, displays a constructed 3D image of cells 30 seconds

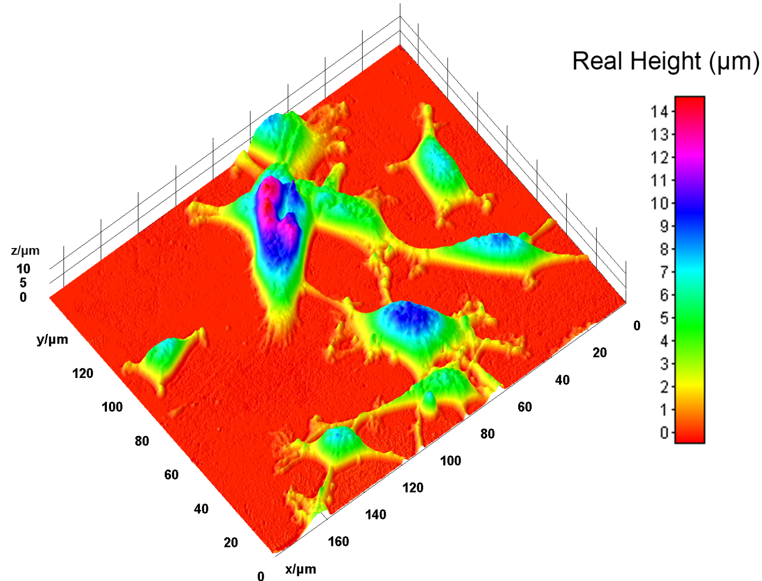

Figure 1. **(a)** Constructed 3D image of astrocyte cells.

after the shockwave. The shockwave was generated by a nano pulsed laser (Flare 532-40-100, Coherent, Sana Clara, CA), producing pulses of $1.7ns$ at $\lambda = 532nm$, focused with 40x water immersion objective lens (C Achroplan NIR 40x/0.80 W, Zeiss). The increase in the level of damage in the cells closer to the blast area can be observed in this figure. Figure 3 shows the displacement of an astrocyte cell which is located $10\mu m$ away from the center of the shockwave. The displacement was calculated by subtracting the cell heights before and after the shockwave. Therefore, two images with the time interval of 0.3 seconds were chosen, one before and one after the shockwave. The shockwave was generated by a nano pulsed laser (Flare NX, Coherent, Sana Clara, CA). Although the amount of the damage is less than the one with the $\lambda = 1030nm$ laser, as figure 3 shows, we can precisely measure the instant changes in the thickness of the cell as we go further from the center of the shockwave.

4. DISCUSSION

In this study, we described a new method to study traumatic brain injury. Our system is capable of applying exact controllable forces and directly measuring the resulted damage. The proposed model can be expanded to study different aspects of neural cell injury. For instance, as the system is equipped with a pulsed laser system, we can apply axonal injuries to nerve cells and quantitatively measure the changes in the neural growth cone which has an important role in the process of nerve regeneration in neurodegenerative diseases 14. Also, fluorescent microscopy can be done using the QPM setup. In the future, we can use LIS paired with FRET imaging to study the intracellular calcium signalling in response to the injury simultaneous with direct measurement of the level of damage 15, 16.

5. CONCLUSION

In conclusion, we have developed a novel model to simulate and TBI. By introducing a laser system to a quantitative phase microscope, we can generate controllable damage using LIS and have a direct way of to

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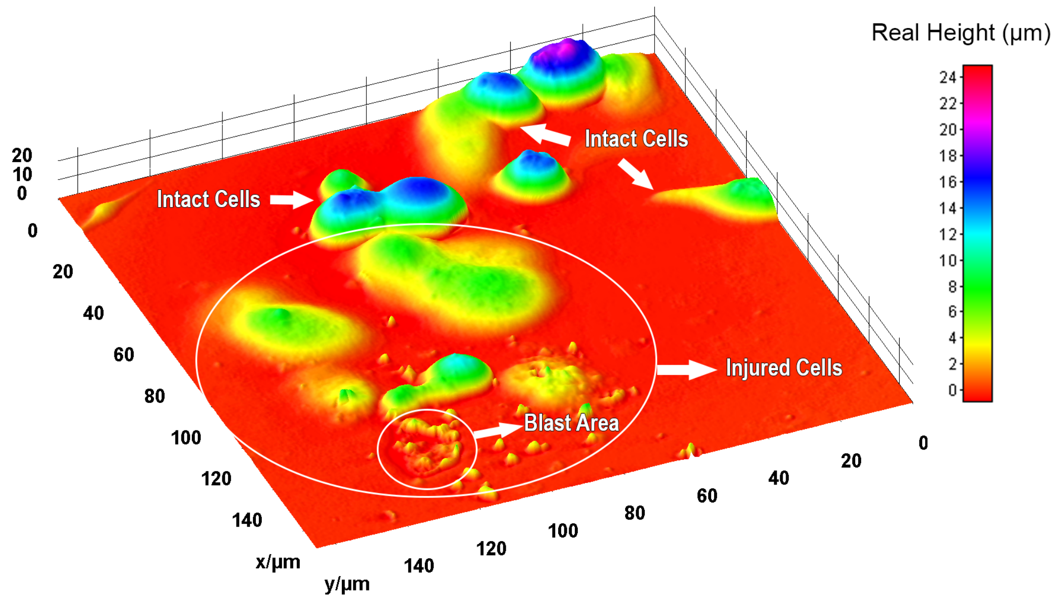

Figure 2. Constructed 3D image of astrocyte cells after shockwave.

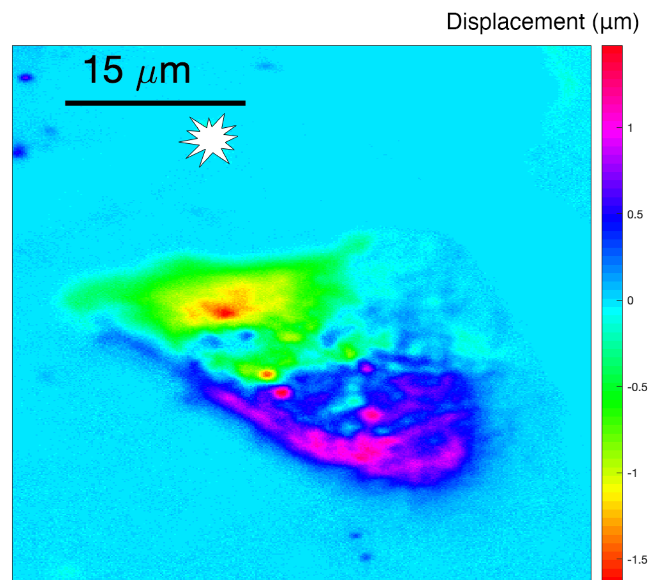

Figure 3. Height displacement of a cell right after a shockwave. The center of the shockwave is shown with a star.

measure the amount of this precise damage, by measuring the real height of the injured cells in real-time. Furthermore, it can be combined with other techniques, like fluorescent microscopy, which enables studying multiple biological aspects in the brain cells, following an injury.

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