Determining the mechanism of the optical opening of the blood brain barrier using gold nanospheres in mice

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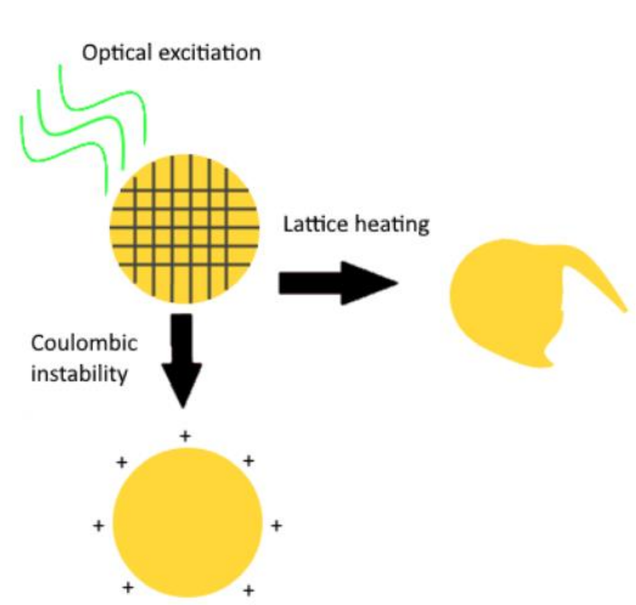
Introduction

Nanoparticles are increasing in popularity as a useful candidate for low invasive treatments. The blood brain barrier (BBB) is difficult to penetrate with traditional pharmaceuticals, and here we will demonstrate one possible mechanism to pass through the BBB. Gold nanoparticles (15nm-45nm) are capable of generating intense heat within their local "neighborhood" due to its interaction with light. We are able to exploit this property and use it to temporarily open the BBB due to heat shock. Although the biological response is not well understood, we are presenting a potential answer to the physical mechanism.

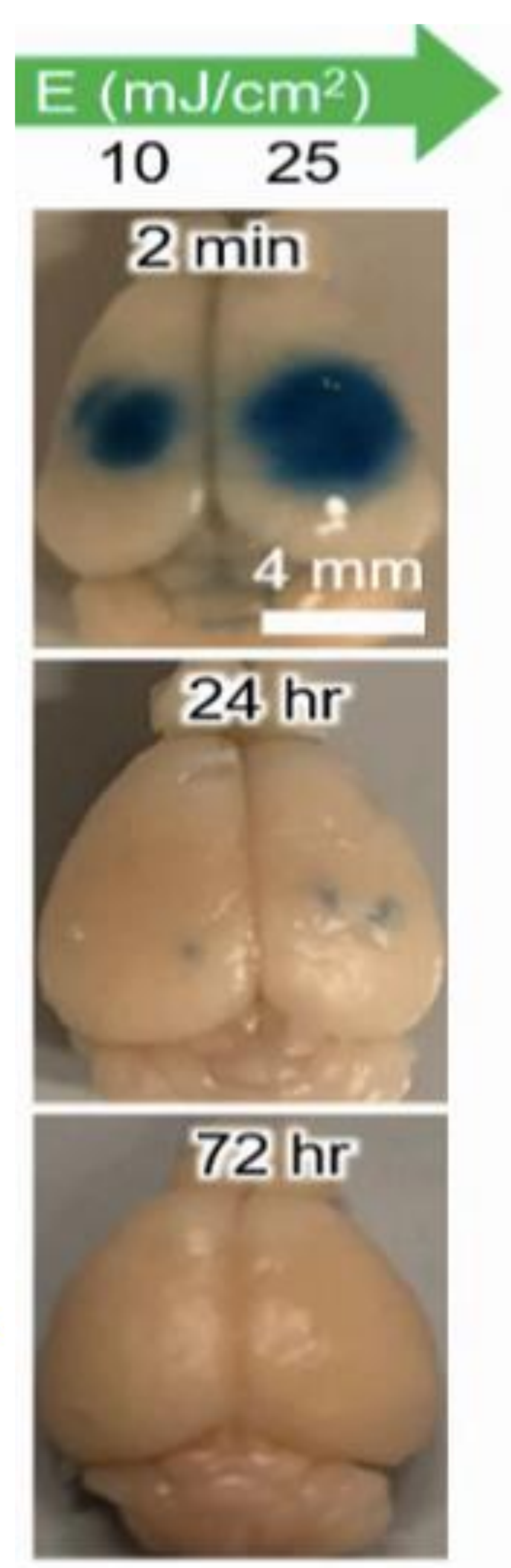
A two-temperature model is best used to describe the heating affects of gold in response to optical stimulation. The model considers electron-phonon excitation which leads into lattice coupling and heating.

Purpose

Picosecond laser pulses coupled with gold nanoparticles are capable of penetrating the BBB. There are two mechanisms that can describe this process, the biological response as well as the heat transfer of the nanoparticles. Here we are only considering the physical mechanism of the particles with a picosecond pulse. The scientific community generally agrees on how gold behaves to nanosecond and femtosecond laser pulses, but in the picosecond range, there is much disagreement. Here we are presenting a two-temperature model of particle heating.



The two-temperature model of nanoscale heating.



Pennetration of the BBB. Photo credit to Xiaoqing Li.

Materials and methods

The synthesis of 15 nm gold nanospheres is done using the following procedures:

-The following methods are performed on a heated stir plate

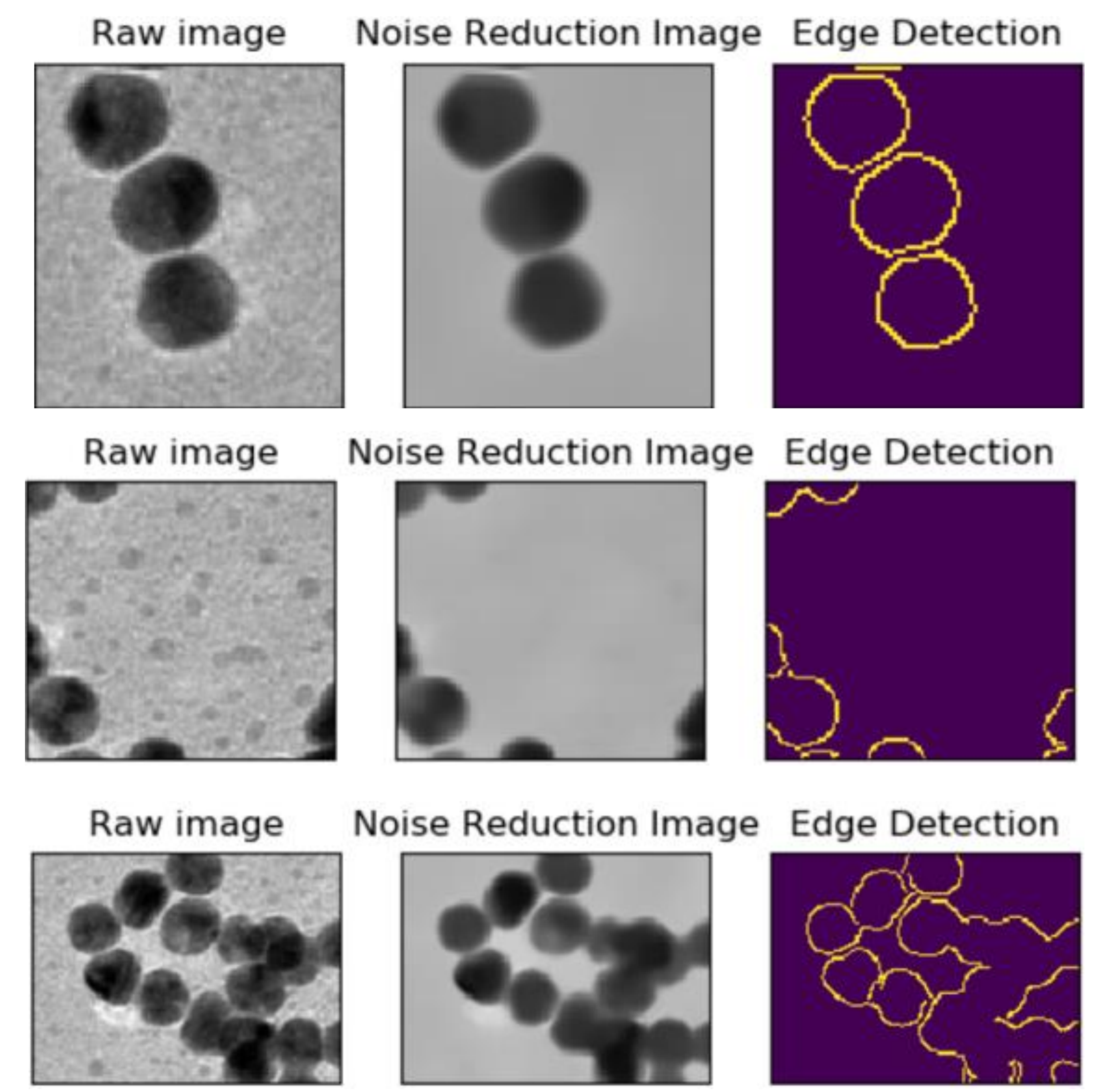
-In a 250 mL Erlenmeyer flask add approximately 90-95 mL of Millipore water and pipette in 1 mL of 33mg/ml solution of sodium citrate

-Once the water is at a boil, pipette in 1 mL of gold (III) chloride solution and remove from heat, but continue stirring

-Wait for solution to cool down.

For the computer vision portion of this experiment, we used python along with the OpenCV libraries to process and analyze images. Raw TEM images were fed into the edge detection algorithm and were processed to analyze the edges and clusters of nanoparticles. Machine learning was used to try to get an accurate count of the nanospheres and used the TensorFlow and Keras libraries. The motivation to use a computer algorithm to count particles was to reduce the manual time to document the distribution and sizes of particles both pre and post excitation.

TEM images were done with the equipment provided in BSB.



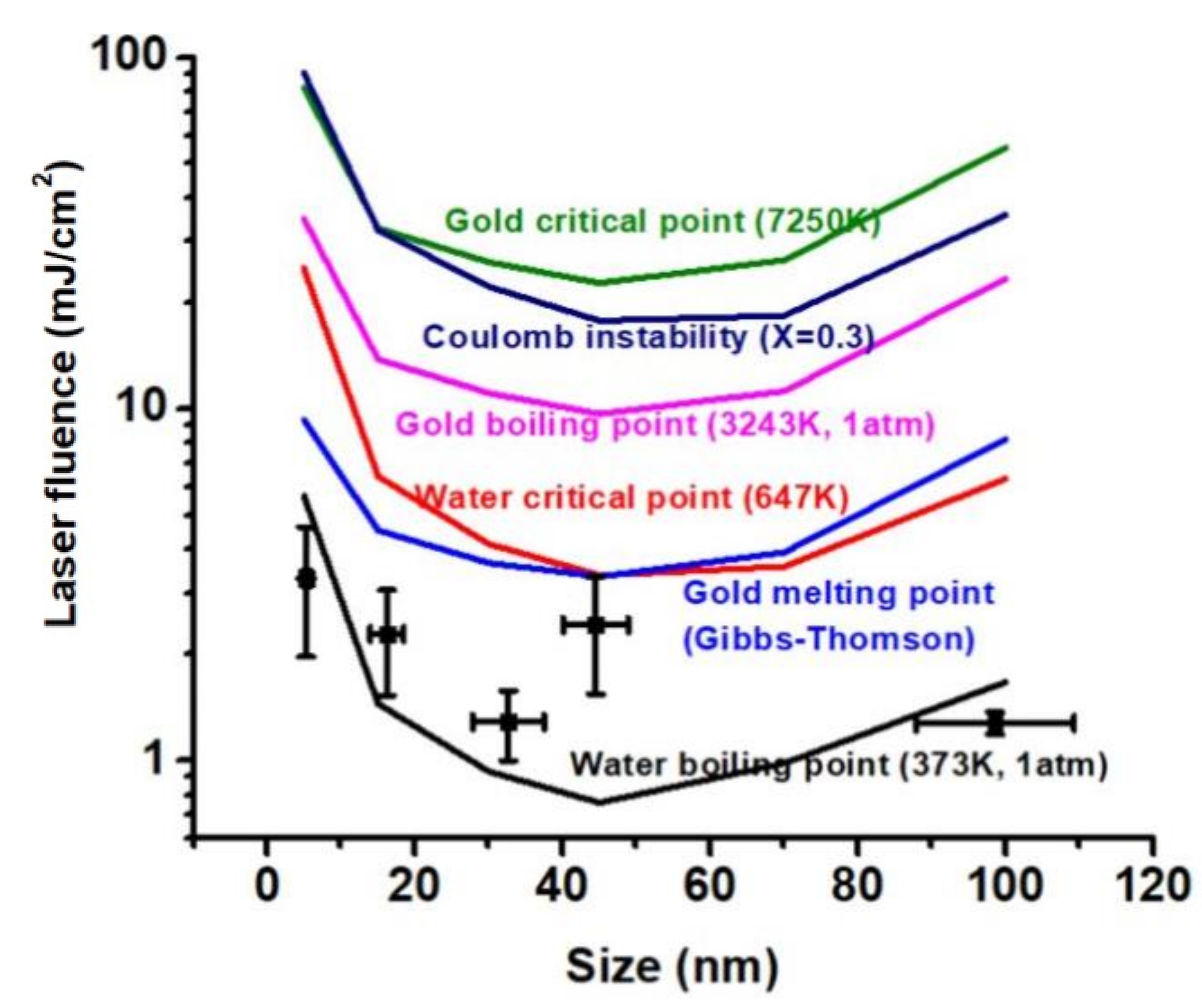
Results

It was determined that in the picosecond range, we can see a hybrid of deformation mechanisms particularly seen in nanosecond and femtosecond excitation. The fragmentation behavior seems to be dependent on laser fluence (mJ/cm^2), with higher laser fluences yielding charge effects and low laser fluence yielding lattice effects. We determine a deformation pattern using the Rayleigh instability factor. This describes a threshold at which a particle begins to separate into multiple particles. This factor is used to describe either solid or liquid phase particles, although the magnitude of the factor differs between the phases.

It should be noted that in the figure, that it seems that the gold particles are still in a solid phase during this experiment, and in order for Coulombic effects to be demonstrated, laser energies must be higher.

$$X = \frac{N_\varepsilon^2}{N_e} * \frac{e^2}{16\pi\sigma r_{ws}^3}$$

Where X is the dimensionless Rayleigh instability factor



Square points indicate the experimental values of gold particles under the picosecond excitation regime. Figure credit to Dr. Peiyuan Kang

Conclusions

It is still puzzling to understand the effects that picosecond excitation has on gold nanoparticles, but strides are made to understand at least some of its behaviors. The main variables shown today were laser fluence and size dependencies. Laser fluence is the driving factor for charge effects. It is still very difficult to analyze the deformation patterns in these gold particles as the time frame in which the undergo these transformations are in the nanosecond scale. More work will need to be done in order to describe and understand the transient mechanisms these gold particles are exposed to under picosecond excitation.

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Improved Working Model for Interpreting the Excitation Wavelength- and Fluence-Dependent Response in Pulsed Laser-Induced Size Reduction of Aqueous Gold Nanoparticles

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