Optical neural stimulation using the thermoplasmonic effect of gold nano-hexagon

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Abstract: The use of nanoparticle photothermal effect as adjuvants in neuromodulation has recently received much attention, with many open questions about new nanostructures’ effect on the action potential. The photothermal properties of hexagonal gold nanoparticles are investigated in this work, including the absorption peak wavelength and light-heat conversion rate, using both experimental and simulation methods. Furthermore, the ability to use these nanostructures in axonal neural stimulation and cardiac stimulation by measuring temperature changes of gold nano-hexagons under 532 nm laser irradiation is studied. In addition, their thermal effect on neural responses is investigated by modeling small-diameter unmyelinated axons and heart pacemaker cells. The results show that the increase in temperature caused by these nano-hexagons can successfully stimulate the small diameter axon and produce an action potential. Experiments have also demonstrated that the heat created by gold nano-hexagons affects toad cardiac rhythm and increases T wave amplitude. An increase in T wave amplitude on toad heart rhythm shows the thermal effect of nano hexagons heat on heart pacemaker cells and intracellular ion flows. This work demonstrates the feasibility of utilizing these nanostructures to create portable and compact medical devices, such as optical pacemakers or cardiac stimulation.

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1. Introduction

Plasmonic nanoparticles (NPs) are absorbing from the fundamental science point of view as well as in applications such as optics, medicine, clinical diagnosis, and therapy due to their localized surface plasmon resonances (LSPRs) [1–3]. The properties of LSPR include resonance wavelength and spectral range, which vary depending on the shape, such as nanospheres, nanorods, nanobars, nanostars, nanoprism, and the size of the plasmonic NPs [4–6]. Among these different shapes, nanostars have displayed extraordinary properties and highly enhanced electromagnetic fields with promising applications in biosensing, bioimaging, and biodetection [7,8]. To guarantee these NPs in the biomedical area, intensifying local electric fields is used, especially around their tips and sharp corners [9,10] and red shifting in the resonance answer by adjusting the size of particles and corners.

Various neurological disorders such as Parkinson’s disease, hearing loss, and heart arrhythmia are common diseases globally controllable by neural stimulation. In the last decade, infrared neural stimulation (INS) has shown significant potential for neural modulation [11–14]. In addition, optical methods can be considered as an alternative way for electrical heart pacemakers. Infrared radiation (IR) has been shown to raise heart rate in embryonic quail [15], rabbits [16], and rats [17]. Cause primary underlying mechanism of infrared neural stimulation is based on thermal effects, so nano heaters can be helpful for enhancing the photothermal effect. During INS, the photothermal effect of gold nanorods was demonstrated to increase neural activity in cells and nerves [18–21]. Carbon nanoparticles have also been shown to enhance the INS of the sciatic nerve [22]. In addition, a two-dimensional structure based on gold nanorods helps us benefit from INS for regulating membrane depolarization [23].
In all these procedures, neural stimulation by plasmonic nano heaters’ physical phenomena has not been clearly explained. As a result, gold nano-hexagons (AuNHs), a novel type of nanoparticle, are employed in the proximity of neurons to simulate their effect in this medium, making these nano heaters more sensitive to neural stimulation. First, AuNHs’ photothermal effects, temperature behavior, and heat diffusion in the cellular environment are studied. Then, according to these results, the possibility of using these nanoparticles in axonal neural stimulation was evaluated. Finally, the effects of heating on cardiac action potential were simulated. The results are evaluated by an animal study wherein the increase in temperature by AuNHs under 532 nm irradiation on the toad heart area was studied. These results show the potential of AuNHs as an effective structure on axonal and cardiac tissues. According to recent developments in the compact platform design for neural stimulation [24,25], this study could be considered an early stage study to design portable optical heart pacemakers based on nanoparticles.

2. Material and methods

2.1. Synthesis of gold nano-hexagons

In the fabrication of AuNHs, Cetyl trimethylammonium bromide (CTAB), Tetrachloroauric acid (HAuCl₄), Sodium hydroxide (NaOH), ascorbic acid (C₆H₈O), silver nitrate (AgNO₃), and acetone (C₃H₆O) were used. The synthesis method followed in this project was the same as the protocol used by Trigari et al. [26–28]. The synthesis of AuNHs is based on the reduction of HAuCl₄. AuNHs preparation was started by making a 3 mL solution of CTAB (50mM) and HAuCl₄ (2mM) mixture in water. The color of this solution was dark yellow. Afterward, 80 µL of NaOH (0.25 M) and 200 µL of ascorbic acid (40 mM) were added to the solution. By adding NaOH and ascorbic acid, the solution became colorless. In the last steps of the synthesis, 60 µL of AgNO₃ (10 mM) and 65 µL acetone were added to the solution. All the solutions were prepared in HPLC water. The solution containing NHs was kept at 25°C overnight to complete the reduction of AuNHs.

2.2. Neural activity simulation

2.2.1. Axonal action potential

An unmyelinated axon with a diameter of 5µm was modeled using the modified Hodgkin-Huxley model. In the original Hodgkin-Huxley (H-H) model, the membrane capacitance is constant. However, H-H equations were rewritten based on temperature-dependent capacitance to describe the increase in axon’s temperature due to nanostructures generated heat. Based on presented results in [29], the relation between membrane capacitance and temperature is defined as follows based on Curie–Weiss law:

\[
C_m = c_o + \frac{k}{\delta T},
\]

where \(\delta T\) is defined in this as follows:

\[
\delta T = T_c - T,
\]

wherein \(k = 2.2 \mu F/cm^2\), \(c_o = 0.8 \mu F/cm^2\) and \(T_c = 31°C\) according to Ref. [30]. Thus, temperature changes over time for short pulses can be defined as follows [31]:

\[
T = \Delta T \gamma t \quad t < t_{pulse}.
\]

\[
T = \Delta T \beta \left\{ \varphi e^{-n_1 t} + (1 - \varphi) e^{-n_2 t} \right\} \quad t > t_{pulse}.
\]

\(\Delta T\) denotes the amount of the temperature changes and constant parameters \(n_1 = 0.015\), \(n_2 = 0.03\), and \(\varphi = 0.454\). The parameters \(\gamma\) and \(\beta\) are also numbers between 0 and 1 that change
with temperature changes. The total currents through the membrane (based on the H-H model) are defined as follows:

\[ I = C_m \frac{dV}{dt} + I_Na + I_K + I_L + I_H. \]  

(4)

Wherein ionic currents are sodium, potassium, leakage currents. Effect of the heat of nanoparticles under irradiation on membrane capacity is considered as \( I_H \).

### 2.2.2. Cardiac action potential

The behavior of Purkinje fibers under thermal stimulation was studied to simulate the variation of cardiac action potentials. For this purpose, Hodgkin-Huxley based equations from Ref. [32] were used.

\[ I = C_m \frac{dV}{dt} + I_{Na} + I_{K1} + I_{K2} + I_{Cl}. \]  

(5)

That there are sodium and chloride currents and two types of potassium currents.

In this study, the neural models were simulated by NEURON software [33]. All parameters employed in the simulation are shown in Table 1 and Table 2 in the Appendix section.

### 2.3. Photothermal effect simulation

The pyGDM tool kit was used to calculate the total heat generated inside the nanostructure. pyGDM is based on the Green dyadic method (GDM) and calculates the total field \( E(r, \omega) \), inside a nanostructure [34]:

\[ E(r, \omega) = E_0(r, \omega) + \sum_{j=1}^{N} G(r_i, r_j, \omega) \chi(e)(r_j, \omega) E(r_j, \omega)V_{cell}. \]  

(6)

Where \( E_0(r, \omega) \) is the electric field of the incident light, \( G(r_i, r_j, \omega) \) is a tensor describing the environment that nanostructure is located inside that, and \( \chi(e)(r_j, \omega) \) is the dielectric function of nanostructure material. The total electric field inside the nanostructure is calculated using meshing nanostructure in cubic sections. Where \( V_{cell} = d^3 \) is the volume of every single mesh with the height of \( d \). When a nanostructure is irradiated, a part of the light is scattered, and the other part is absorbed. The absorbed part eventually turns into heat. The total heat generated inside the nanostructure is given by:

\[ Q(\omega) = \int_V q(r, \omega) dr = \frac{\omega}{8\pi} \int_V \epsilon'(r)|E(r, \omega)|^2 dr. \]  

(7)

Where \( q(r, \omega) \) is the volumetric power density of heat generation and \( \epsilon'(r) \) is the imaginary part of permittivity of nanostructure material. The temporal change in temperature of axons adjacent to nanoparticles may therefore be estimated as follows:

\[ \frac{\partial T}{\partial t} = \frac{k}{\rho c_p} \frac{\partial^2 T}{\partial x^2} + \frac{Q_V}{\rho c_p}, \]  

(8)

where \( T \) is temperature change and \( Q_V \) is volumetric heat generated by nanoparticles. Aqueous environment parameters were used to calculate heat diffusion because 60% to 90% of neural cells are composed of water [35]. \( k = 0.6 \ \text{W/mK} \) is thermal conductivity, \( c_p = 4182 \ \text{J/kgK} \) is specific heat and \( \rho = 997 \ \text{kg/m}^3 \) is the density of water.
2.4. AuNHs temperature change experiment

A continuous 532 nm laser (53220, Mahfanavar, Iran) was used to illuminate AuNHs. The laser was set at a distance of 5 cm from the top of the AuNHs. The laser beam diameter is 3 mm, and its power density is $80 \text{ mW cm}^{-2}$. The temperature was measured by a thermocouple (TM-916, LUTRON electronic enterprise co, Taiwan). All experiments are performed four times a week to ensure the stability of temperature changes of AuNHs.

3. Results and discussion

TEM images for AuNHs samples were recorded a week after fabrication for the sample with 80 µL of NaOH and sample without NaOH, as shown in Fig. 1(A).

![TEM images of AuNHs](image)

Figure 1(A) shows the absorption spectrum of AuNHs. The prominent peak at 530 nm belongs to the Au absorption, and the shoulders appear due to the sharp corners of the polygonal. In addition, the heat distribution was calculated, and as can be seen in Fig. 1(C) in gold hexagonal nanoparticles, significant heat was generated at the corners of the structure. Temperature increases of up to 6°C were seen after 20 minutes of irradiation, as illustrated in Fig. 2(A). The temperature increased with a steep slope in the first 6 minutes of irradiation at a rate of $0.86 \text{ °C min}^{-1}$. The AuNHs also lost heat with a slope of $0.91 \text{ °C min}^{-1}$ in around 4 minutes after the laser radiation was turned off. The experiment is carried out at a temperature of around 23°C in the laboratory.

3.1. Heat generation and distribution of AuNHs

The first one requires predicting the appropriate wavelength for heating the nanoparticles used in this study. The suitable wavelength can be computed by using Eq. (7). Figure 2(B) depicts
Fig. 2. (A) Temperature hysteresis diagram of AuNHs. A considerable rise occurred within the first 6 minutes after starting the irradiation at a rate of 0.86 °C/min. Also, after the laser radiation was turned off, AuNHs temperature decreased at a rate of 0.91 °C/min. (B) The influence of wavelength on single AuNH heat generation. (C) Heat generation inside the AuNH via radiation with a wavelength of 532 nm. With a power density of 80 mW/cm², roughly 15 pW heat inside the nanostructure was generated (Variation of for different versus power density). (D) Temperature variations in distances near nanoparticles in the watery environment after 5 ms putting beside AuNHs.

the spectral heating of these nanoparticles. As shown in this figure, the best wavelength for photothermal conversion is about 550 nm. It is compatible with the absorption spectrum of the AuNHs, as shown in Fig. 1(B). Then heat generation inside a single AuNH for different laser power densities (λ at 532 nm) was calculated as depicted in Fig. 2(C). Finally, based on the maximum observed temperature rise of 6°C in the experiment, the heat diffusion equation was used to estimate the radial distribution of temperature around the nanoparticles, as shown in Fig. 2(D). Figure 2(D) shows that temperature significantly decreases at a distance of 100 µm around AuNHs. Heat transfer in 5 ms was calculated considering the importance of thermal gradient for neural stimulation.

Assuming heated AuNHs are located in a neural environment to calculate the temperature rise in AuNHs surroundings. The one-dimensional heat diffusion equation is solved up to a distance of 200 µm from the AuNHs. Water’s thermal conductivity and thermal diffusivity were used because the cell environment is composed mainly by water. As shown in Fig. 2(D), a significant increase in temperature can be seen at a distance of around 20 µm from AuNHs. It means axons with a diameter of up to 20 µm could be significantly affected by the thermal effects of AuNHs.
3.2. Axonal neural stimulation

An unmyelinated axon with a diameter of 5 µm was modeled to investigate the potential of nerve stimulation with heating as well as the behavior of neural responses. A temperature-dependent Hodgkin-Huxley model was defined for this axon. According to the temperature variations observed in the experimental and simulation results, placing the axon next to the nanoparticles for 5 ms induced about 6 °C increase in temperature to the modeled axon. Figure 3(A) shows that action potential was generated with a 6°C increase in axon temperature, and the axon was successfully stimulated.

By repeating the experiment for temperature increase between 3 to 6 °C, it was observed that to generate AP in the axon, it is required to increase the temperature at least about 5.3 °C. This corresponding to other nanostructures like gold nanorods that have been reported to have led to successful neural stimulation in temperature increasing range under 10 °C [18,21]. As shown in Fig. 3(B), a 5 °C increase in temperature could not stimulate the axon. Because the temperature drops as the distance from the AuNHs increases, nerve stimulation will be unsuccessful if the axon distance from the nanostructure exceeds 5µm. The temperature increase at a distance of 10µm from AuNHs in 5 ms is about 4.8 °C, which is insufficient to generate AP. In addition, to study the current induced in the membrane, induced currents were calculated using a 6 and 3 °C increase in temperature on the axon. Figure 3(D) shows that if the temperature increase doubles, the induced current to the membrane is quadrupled. These results confirm the potential of gold hexagonal nanoparticles for stimulation of neural fibers.
3.3. Cardiac neural stimulation

Heart rhythm phases directly depend on heart muscle activity showing intracellular ion changes of heart cells. So an experimental animal study was done on the toad heart to explore the effects of AuNHSs on heart rhythm. Three immature Eurasian green toads (weight 50-70 grams) were utilized and fixed horizontally. The use of anesthetics (such as ether and chloroform) disrupts the toad’s regular cardiac rhythm. So no anesthesia was utilized in this trial. A continuous 532 nm laser with a 3 mm beam diameter and a power density of $100 \text{ mW/cm}^2$ irradiated AuNHSs to increase their temperature. The laser was fixed at a distance of 5 cm from the top of the toad. First, the toad heart area was illuminated for 5 minutes just by laser. Then AuNHSs were added and distributed on the heart area to determine the different effects of AuNHSs heating and laser radiation. A two-dimensional nanoplasmonic structure was fixed on top of the heart area for heart activity recording. According to the required time for increasing the AuNHSs temperature, the heart area was irradiated for more than 5 minutes. The experimental setup can be seen in Fig. 4(D). All animals participating in this study were cared for according to the ethics committee of Shahid Beheshti University, Iran.

![Figure 4](https://example.com/figure4.png)

**Fig. 4.** (A) Toad heart rhythm with 532 nm laser irradiation. (B) Toad heart rhythm with gold nano hexagons under 532 nm irradiation on the toad heart area. (C) Change in membrane voltage of Purkinje fibers due to increased temperature. APD time is shortened as the temperature increases. (D) Experimental setup for toad heart stimulation.

Results of toad heart stimulation with AuNHSs show significant changes in toad heart activity. Despite that laser irradiation without AuNHSs had no significant effect on heart rhythm, irradiation of AuNH in the toad heart area affected heart rhythm. Figure 4(A) shows toad heart rhythm under laser with the wavelength of 532 nm irradiation that could not be seen any effect on its
phases amplitude under the impression of laser radiation. T wave amplitude was impacted by an increase in temperature on the toad heart area owing to AuNHs photothermal effect, as illustrated in Fig. 4(B).

In comparison to toad heart rhythm before stimulation with AuNHs, T wave amplitude significantly has increased. T wave amplitude increase is due to some biological effects on the toad heart. For exploring these biological effects, cardiac action potential was simulated. According to the results published in Ref [36], an increase in the temperature by prolonged irradiation of infrared laser reduces membrane capacity. Therefore, decreasing membrane capacity on cardiac AP shape was studied considering that temperature reduced the membrane capacity. For this purpose, membrane voltage adjustments were recorded by setting three different membrane capacities for the cardiac model. The initial membrane capacity of the model was 12.8 µF, but it was changed to 11.9 and 10.7 µF, and membrane voltage was recorded. Figure 4(C) shows that decreased membrane capacity reduces action potential duration (APD) time. When membrane capacity decreased to 11.9 and 10.7 µF, APD about 21 and 46 ms reduced, respectively. It has been shown that reducing APD time affects T wave amplitude [37,38]. There are a few reasons those are the cause of reducing AP durations. The first one is related to the increase in temperature and heating that in our work, our nano hexagons increased the temperature by almost 6 °C. It has been shown by Ref. [39] that increasing the temperature is effective in reducing the duration of AP. As a result, the amplitude of the T wave increases. So, probably, the heat effect of AuNHs is the first reason for increasing T wave amplitude. Increased intracellular calcium ion concentration is another factor that decreases APD [40]. It has been shown that temperature increase by IR laser led to an increase in intracellular free Ca$^{2+}$ concentration in ventricular cardiomyocytes and cortical neurons [41,42]. It seems that photothermal effects of AuNHs affected intracellular Ca$^{2+}$ concentration in the toad heart. In summary, our results show the effects of AuNHs photothermal on heart cells and cardiac activity. Moreover, this study can be considered as an early study for non-invasive optical pacing based on nanoparticles.

4. Conclusion

In this study, the photothermal effect of hexagonal gold nanoparticles such as absorption spectrum and the light-heat conversion rate were studied. Furthermore, cardiac and axonal action potentials were modeled, and the effects of thermal stimulation on them were investigated. The results showed that irradiation of AuNHs under continuous 532 nm laser led to about 6°C increase in temperature. In addition, it was shown that in this range of increase in temperature, gold nano-hexagons could successfully stimulate small diameter axon fiber. Finally, thermal stimulation of the toad heart with AuNHs increased T wave amplitude on its heart rhythm. Changes in heart rhythm are probably related to increasing Ca$^{2+}$ intracellular concentration due to the photothermal effect of hexagonal gold nanoparticles.

Appendix

A. Cardiac action potential

- Sodium current

\[ I_{Na} = (g_{Na} - 140)(V - V_{Na}) \]  
\[ V_{Na} = \frac{RT}{zF} \ln \left( \frac{[Na^+]_o}{[Na^+]_i} \right) \]  
\[ g_{Na} = \chi_{Na_{max}} m^3 h \]

- Chloride current

\[ I_{Cl} = g_{Cl}(V - V_{Cl}) \]
• Voltage and time-dependent potassium current:

\[ I_{K1} = g_{K1}(V - V_{Na}) \]  \hspace{1cm} (13)

\[ g_{K1} = g_{k1max}n^4 \]  \hspace{1cm} (14)

• Voltage-dependent potassium current

\[ I_{K2} = g_{K2}(V - V_{K2}) \]  \hspace{1cm} (15)

\[ V_{Na} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i} \]  \hspace{1cm} (16)

R is the universal gas constant, T is the temperature, z is the number of elementary charges of the ion, and F is the Faraday constant. \([K^+]_o\) and \([Na^+]_o\) are the extracellular concentration of potassium and sodium. \([K^+]_i\) and \([Na^+]_i\) are the intracellular concentration of potassium and sodium.

| Table 1. Parameters used in the cardiac model |
|---------------------------------------------|
| Parameter                  | Value                |
|----------------------------|----------------------|
| Resting potential         | -80 (mV)            |
| Cl Reversal Potential     | -60 (mV)            |
| Na Reversal Potential     | 35 (mV)             |
| K Reversal Potential      | -100 (mV)           |
| \(g_{Na_{max}}\)          | 0.4 (s/cm^2)        |
| \(g_{K1_{max}}\)         | 1.2 (s/cm^2)        |
| \(g_{Cl}\)                | 0.000075 (s/cm^2)   |
| Initial membrane capacitance | 12.8 \(\mu\)F   |
| \([K^+]_i\)               | 95 mM               |
| \([K^+]_o\)               | 2.5 mM              |
| \([Na^+]_i\)              | 7.5 mM              |
| \([Na^+]_o\)              | 111 mM              |

B. Axonal action potential

\[ I_k = g_k(V - V_K), \]  \hspace{1cm} (17)

\[ I_{Na} = g_{Na}(V - V_{Na}), \]  \hspace{1cm} (18)

\[ I_l = g_l(V - V_l), \]  \hspace{1cm} (19)

which \(g_k\), \(g_{Na}\), and \(g_l\) denote the conductivity of the potassium, sodium, and leakage currents, respectively. \(V_K\), \(V_{Na}\), and \(V_l\) are the reversal potentials of the potassium, sodium, and leakage channels.
Table 2. Parameters used in the axonal model

| Parameter                  | Value                  |
|----------------------------|------------------------|
| Axon diameter              | 5 μm                   |
| Electrical current         | 4 nA                   |
| Resting potential          | -65 (mV)               |
| Leak Reversal Potential    | -54 (mV)               |
| Na Reversal Potential      | 50 (mV)                |
| K Reversal Potential       | -77 (mV)               |
| Na conductance $x_2$       | 0.12 (s/cm$^2$)        |
| K conductance $x_1$        | 0.036 (s/cm$^2$)       |
| Leak conductance $x_3$     | 0.003 (s/cm$^2$)       |
| Axon Initial Temperature   | 21 °C                  |
| Initial membrane capacitance| $1 \mu F$               |
| $Q_{10}$                   | $3 \frac{10^{-11} F}{m}$|

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Data availability. Data underlying the results presented in this paper are not publicly available at this time but may be obtained from the authors upon reasonable request.

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