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Laser-ablative synthesis and photoheating characterization of TiN NPs for biomedical applications

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ABSTRACT

Titanium nitride (TiN) nanoparticles (NPs) prepared by methods of laser ablation in liquids present a novel object, which promises attractive biomedical applications. Here, we review our recent advances in the elaboration of femtosecond laser ablation technique from a TiN target in liquid medium (here, isopropanol) to maximize the efficiency of TiN NPs synthesis and optimize their characteristics. Our experiments showed that the synthesis productivity is dependent on lateral velocity of laser beam scanning during laser ablation with the achievement of productivity saturation at a certain relatively high velocity. The observed phenomenon was attributed to the interaction of laser pulses with cavitation bubbles generated during the ablation process. In addition, we assessed photo heating properties of the synthesized TiN NPs in the near-IR range. It was found that TiN NPs with sizes in 20-50 nm range have the highest heating rate and can be heated to maximal temperatures. As demonstrated by our recent tests *in vitro* and *in vivo*, this size range is optimal for biomedical applications, which promises successful applications of these nanoparticles in phototherapy and imaging modalities.

Keywords: titanium nitride, nanoparticles, laser ablation in liquids, photo heating

1. INTRODUCTION

Transition metal nitrides and especially titanium nitride (TiN) have recently gain huge attention as a promising alternative to conventional noble metal plasmonic materials such as gold or silver¹. Among the most prominent advantages of TiN, one could mention its low cost, high availability, superior mechanical characteristics, thermal stability and good plasmonic properties. Good biocompatibility of this material renders possible the manufacturing of TiN-based implants², surgical and food-related tools³, while excellent plasmonic photoheating properties of TiN nanoparticles (NPs) are important for biomedical applications related to the development of biological imaging^{4,5} and photothermal therapy (PTT)^{6,7} modalities. In particular, the latter modality implies the conversion of external light stimuli into heat by nanomaterials accumulated in the tumor area, which causes a cancer cell kill. Furthermore, PTT could be easily combined with photoacoustic imaging (PAI) modality, based on acoustic wave generation by nanomaterials upon heating^{8,9}, which makes possible an efficient imaging of tumor area in order to monitor the therapeutic outcome.

TiN nanoparticles (TiN NPs) look much more promising than traditional noble metal-based nano agents for both PTT and PAI due to several advantages. First, plasmonic feature and related highest photothermal conversion efficiency of small (dozens to hundred nm) TiN NPs is in near-IR region^{10,11}, exactly in the region of relative biological transparency, whereas the relevant plasmonic feature of spherical noble metal NPs is in the visible-UV where biological tissues are highly scattering and absorptive¹². Second, TiN is a refractory material and therefore TiN NPs do not change their properties during PTT, while gold nanostructures especially those ones having complex geometries (e.g., nanorods), often change their shape upon even mild heating and lose their IR plasmonic properties¹³. Third, TiN is about 1000 times cheaper than noble metals like gold and easily available, which makes its translation to “real world” applications much more accessible.

Projected biomedical applications require careful safety evaluations of NPs. Generally, the toxicity of nanomaterials depends on several factors including size, shape, surface charge and chemistry, presence of stabilizing agents and synthesis byproducts. Conventional methods for the synthesis of colloidal TiN NPs are based on chemical routes^{14,15}. Such methods are rather complicated due to the necessity of running several preparation steps and employment of hazardous reagents,

which can cause residual contamination of NPs. Alternative fabrication methods require redispersion in aqueous solutions and stabilization by similar wet chemistry techniques.

Laser ablation is a “green” physical technique for NPs synthesis, which offers an exceptional level of purity^{16–18}. This method profits from natural generation of nanoclusters under ablation of a solid target by laser irradiation in liquid ambient. The technique does not require any specific chemicals for the synthesis; therefore, it can avoid any residual contamination of NP surface. We recently applied methods of ultrashort (femtosecond, fs) laser ablation from a TiN target in liquids to produce stable colloidal solutions of spherical TiN NPs with controllable size from hundred down to 4 nm^{19,20} and performed their thorough characterization²¹. We also performed a comprehensive safety assessment of the laser-synthesized TiN NPs, which demonstrated their biocompatibility both *in vivo* and *in vitro*²². It is worth noting that the high biocompatibility is a characteristic feature of nanomaterials prepared by laser ablation in liquids, according to our data^{23,24}.

Here, we report our recent progress in the elaboration of fs laser-ablative synthesis of TiN NPs in liquids and the assessment photo-heating properties of the synthesized NPs under different conditions. We believe that ultrapure TiN NPs prepared by laser ablation in liquids could be considered as a new appealing candidate for PTT and PAI applications.

2. EXPERIMENTAL METHODS

2.1 Synthesis of nanoparticles

TiN NPs were synthesized using fs Yb: KGW laser (1030 nm wavelength, 270 fs pulse duration, 30 μJ pulse energy, 10–20 kHz repetition rate, TETA 10 model, Avesta, Moscow, Russia). A TiN target was fixed vertically on the wall of a glass vessel filled with 14 mL of analytical grade isopropanol. A 3 mm wide beam from the laser was focused by a 100 mm F-theta lens on the surface of the target through a side wall of the vessel. The thickness of the liquid layer from the entrance glass to the target surface was 3 mm. The laser beam was moved over the target surface (scanned) by galvanometric mirrors. The scanning pattern was a spiral with outer diameter 20 mm and inner diameter 2 mm. Velocity of the laser movement was varied between 100 and 4000 mm/s to study the efficiency of the laser ablative synthesis. The ablation duration was 5 min.

Different size fractions were separated by centrifugation technique. The synthesized NPs were initially centrifuged at 1 000 g for 10 min. The sediment was later used as “large” NPs fraction. The supernatant was taken and centrifuged again at 10 000 g for 15 min. The sediment from the second step was later used as “medium” NPs fraction, while the supernatant was used as “small” NPs fraction. The pellets (formed by sedimented NPs) from both centrifugation steps were redispersed in isopropanol using ultrasonication step.

2.2 Characterization of nanoparticles

Morphology, size, and composition of the synthesized TiN NPs were characterized by scanning electron microscopy (SEM) system (MAIA 3, Tescan, Czech Republic) coupled with an energy dispersive spectrometry (EDS) detector (X-act, Oxford Instruments, High Wycombe, UK). Electron images were obtained at 30 keV accelerating voltage, while EDS spectra were measured at 15 keV.

Optical extinction spectra of the colloidal solutions were measured using an ML 122 spectrophotometer (SOL Instruments, Belarus) in quartz cuvettes with 10 mm optical path.

Mass concentrations of produced colloidal solutions were measured by the atomic absorption spectroscopy method (the titanium content in samples was detected) using a Lumex MGA-1000 device.

2.3 Photo heating of nanoparticles

The photoheating of the synthesized TiN NPs in physiologically relevant near-IR region was studied using radiation from a 830 continuous wave (CW) home built laser source. One ml of a colloidal solution of TiN NPs, placed into a sealed quartz cuvette with 10 mm optical path length, was irradiated by a collimated laser beam with 10 mm diameter. The laser power was measured before the cuvette using a power meter (PM100D, Thorlabs) with thermal power sensor (S425C, Thorlabs). Temperature of the colloidal solutions was measured using an IR thermal camera (Flir C3). The thermal readings were corrected to background temperature.

3. RESULTS AND DISCUSSION

To synthesize TiN NPs, we used methods of fs laser ablation in isopropanol. Details of the experimental procedure are described in the Experimental Methods section. Laser ablation of the TiN target in this solvent resulted in a fast dark blue coloration of the solution in the ablation cuvette, evidencing the formation of TiN NPs. A typical SEM image of the synthesized NPs is shown in Fig. 1A. One can see that the NPs had spherical shape. EDS analysis (Fig. 1B) qualitatively confirmed chemical composition of the synthesized TiN NPs. Here, main signals presented in the spectrum corresponded to nitrogen (N), titanium (Ti) and oxygen (O). The presence of O could be explained by surface oxidation of the NPs. Large silicon (Si) peak in the spectrum originated from the Si substrate, while carbon (C) signal was related to organic contamination of microscope vacuum chamber or the sample itself due to the presence of traces of solvent after its evaporation.

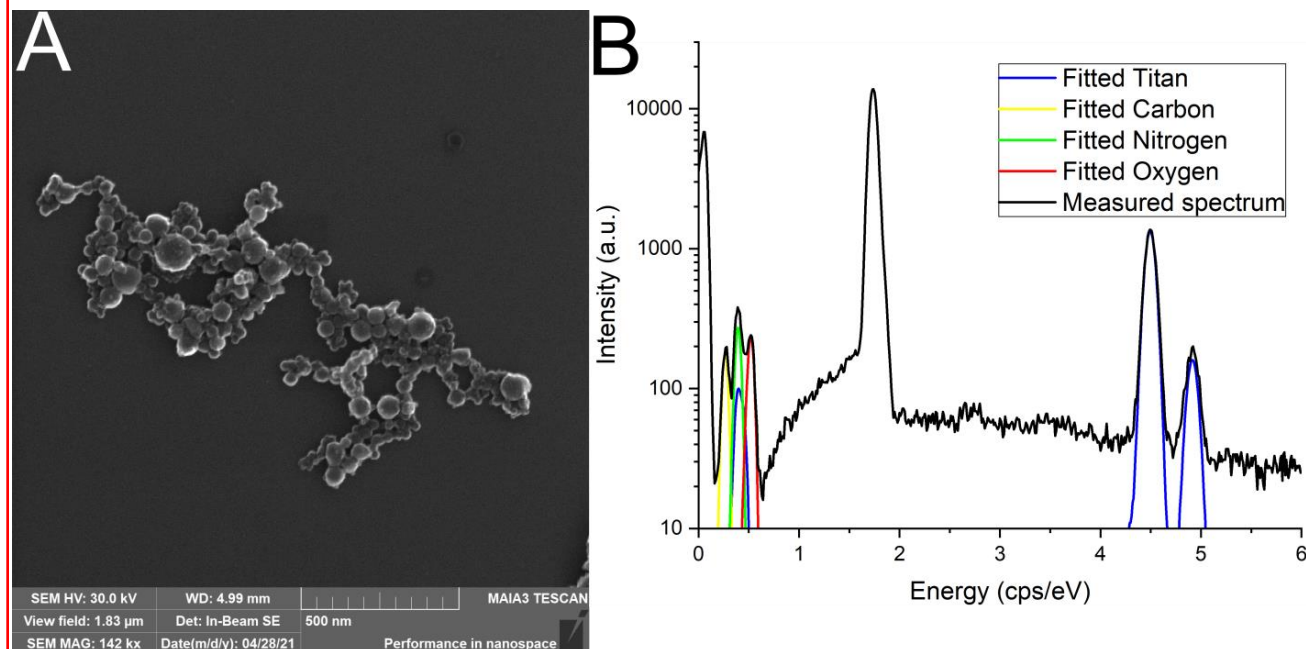


Figure 1. Physicochemical characterization of TiN NPs. (A) Typical SEM image and (B) EDS spectrum of NPs after synthesis. Measured EDS spectrum (black line) is decomposed into spectra of different chemical elements, which are present in the composition of NPs: titan (blue), nitrogen (green), oxygen (red) and carbon (yellow).

Then, we studied how the velocity of laser beam scanning affects the productivity of the laser-ablative synthesis at different repetition rates of laser pulses. For this, we made a series of experiments, in which a TiN target was ablated by a laser beam scanned at different velocities, while the duration of experiment was fixed (5 min), but. We assessed productivity by measuring optical extinction of the obtained colloidal solutions at 700 nm, which roughly corresponded to the position of the plasmonic peak of synthesized TiN NPs. Results obtained for two different repetition rates of laser pulses (10 and 20 kHz) are presented in Fig. 2. As one can see, the dependence of the productivity on the velocity of laser scanning is similar in both cases: the productivity initially raises with increase of laser speed but then comes to saturation at higher velocities. At the same time, our data show that the laser speed required for the saturation of the ablation productivity should be doubled (from 750 to 1500 mm/s) to compensate effects associated with the repetition rate doubling.

The observed data can be explained by scattering of radiation from consecutive laser pulses by cavitation bubbles, which emerge after the interaction of pulsed laser radiation with the solid material in liquid ambience. The cavitation bubbles appear when hot material ablated by a laser radiation (temperature of the material can be up to dozens of thousands Kelvins²⁵) expands from the ablation target into a liquid. The onset of the cavitation bubble expansion typically starts several hundred ns after the beginning of laser-target interaction, while the lifetime of the bubble lasts from hundreds of microseconds to a few milliseconds, depending on energy and duration of laser pulses²⁶. The maximal size of the cavitation bubble can be up to several mm. The size value depends on energy and duration of laser pulses, as well as on roughness of the target surface.

If a new laser pulse comes while the cavitation bubble, formed the previous laser pulse, is still “alive”, it will be partly scattered and absorbed by the bubble. Therefore, the amount of material ablated by the upcoming laser pulse will be greatly reduced. However, if the upcoming laser pulse comes much later than the previous laser pulse, it can avoid the interaction with the cavitation bubble, even if the bubble is still “alive”. Therefore, the speed of laser scanning is increased, the productivity of laser ablative process also increases due to the decrease of spatial overlapping between the cavitation bubble and the upcoming laser pulse. However, when the speed of laser beam displacement is sufficient for a complete spatial separation between the cavitation bubble and the upcoming laser pulse, the productivity reaches the maximum value and becomes independent of further increase of laser velocity. When the repetition rate of laser pulses increases, time between consecutive laser pulses decreases and higher speed of the laser beam displacement is required to reach the maximal productivity, which explains the observed data.

Based on the obtained data, we can conclude that 1 000 mm/s speed of laser scanning is enough to reach the maximal productivity of laser ablative synthesis of TiN NPs in isopropanol with 10 kHz repetition rate (other laser parameters are specified in Experimental Methods section), while 2 000 mm/s speed is required for 20 kHz repetition rate.

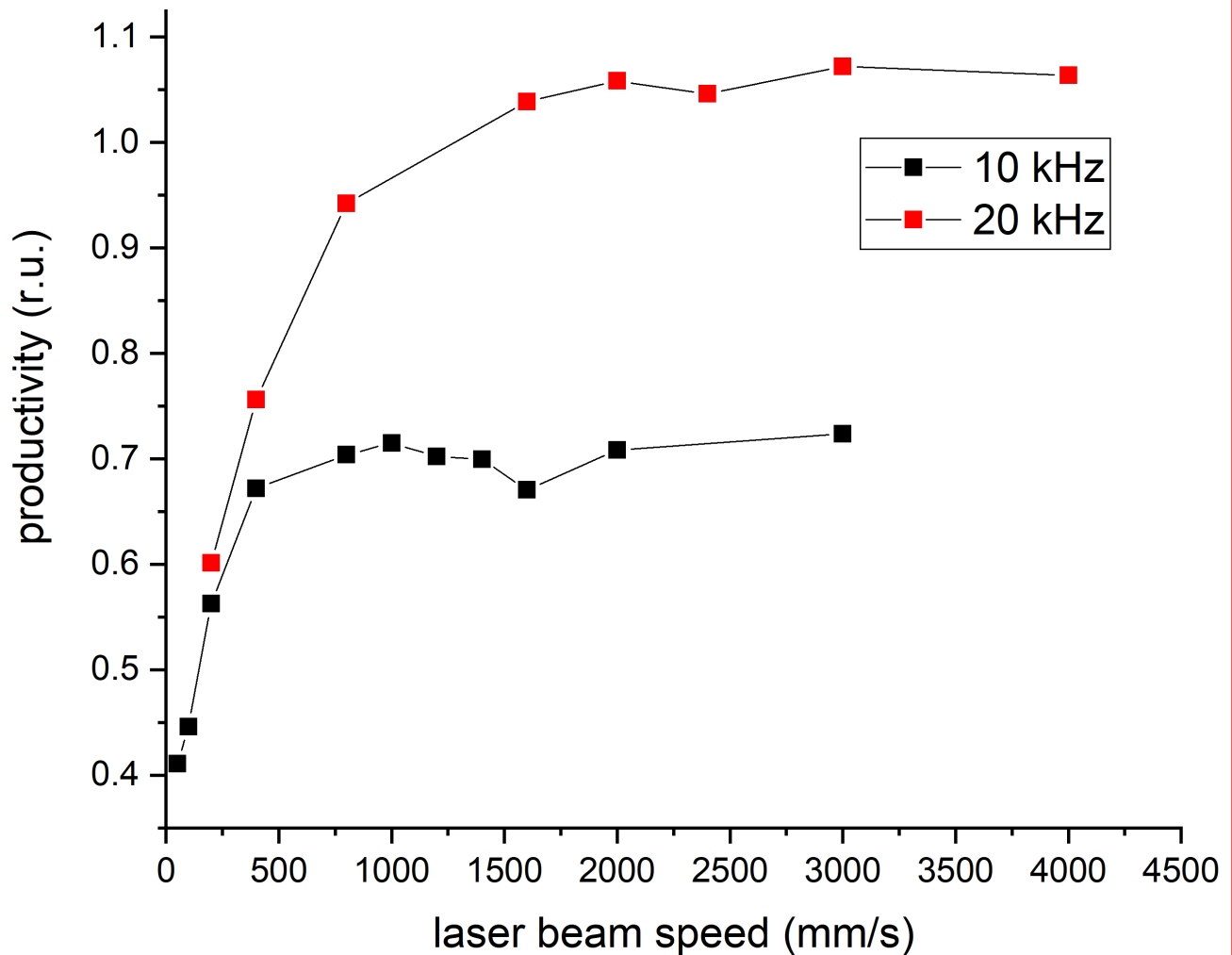


Figure 2. Dependence of the productivity of laser ablative synthesis on the velocity of laser beam displacement for different repetition rates of laser pulses: 10 kHz (black squares) and 20 kHz (red squares).

In our study, we also explored the heating rate of TiN NPs under their irradiation by near-IR light. First, we measured kinetics of heating and cooling of the colloidal solutions of TiN NPs as functions of power of near-IR radiation. We prepared a colloidal solution of TiN NPs with 1 optical density (OD) at 830 nm and irradiated it with different power of 830 nm CW laser for 500 seconds, then turned off the laser radiation and measured the cooling kinetics. The obtained

results are shown in Fig. 3. As one can see from Fig. 3A, the increase of laser power led to a progressive increase of both the maximal achievable temperature increment and the initial heating rate of the colloidal solutions. The maximal temperature increase changed from 4 °C to 30 °C, while laser power was increased from 0.25 W to 2 W. At the same time, the initial heating rate increased almost linearly under the increase of laser power, as shown in Fig. 3B. It is worth noting that the heating of isopropanol without NPs was negligible under the laser radiation, as shown by a pink line in Fig. 3A. Indeed, the irradiation of the solvent by 1 W laser beam for 260 seconds led to its heating only by 0.6 °C. Therefore, the observed heating was almost entirely conditioned by the presence of TiN NPs in the solvent.

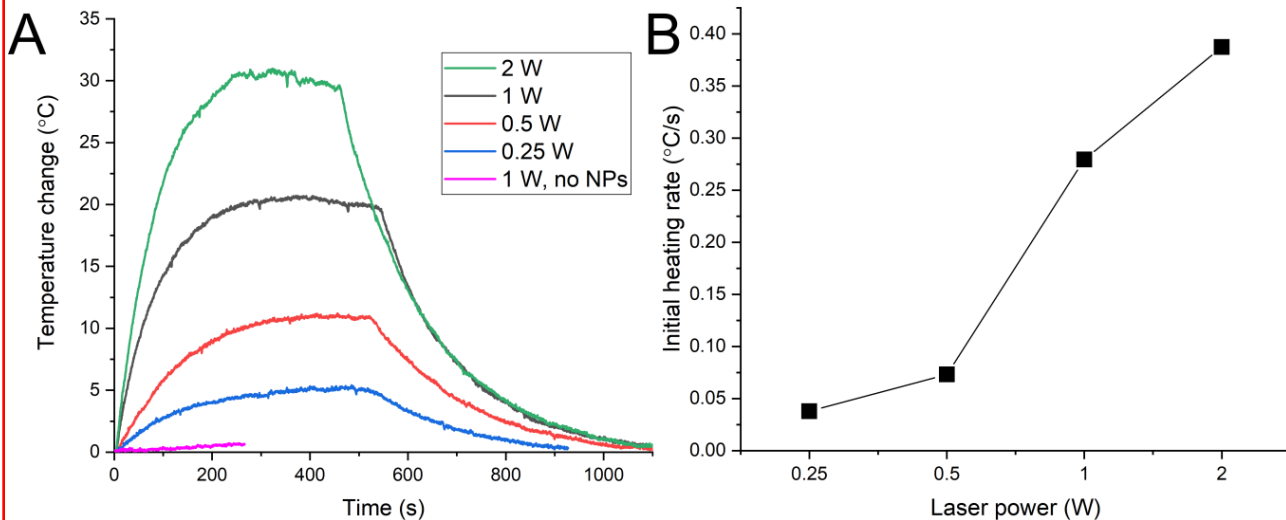


Figure 3. Heating of TiN NPs under irradiation by 830 nm CW radiation. (A) Curves of heating and cooling of TiN NPs with 1 OD at 830 nm with different laser power: green line – 2 W, black line – 1 W, red line – 0.5 W, blue line – 0.25 W. Pink line represent heating of a solvent without NPs by laser radiation with 1 W power. (B) Initial heating rate of the colloidal solutions of TiN NPs for different power of laser radiation.

Finally, we studied how the size of TiN NPs affects their near-IR photo heating. We divided the synthesized TiN NPs into three size fractions, as described in Experimental Methods section, which were labelled as “small” TiN NPs (<50 nm) fraction, “medium” TiN NPs (50-100 nm) fraction, and “large” TiN NPs (>100 nm) fraction. We adjusted concentrations of all three fractions to make their optical extinction equal at 830 nm. Then, we irradiated the colloids with 0.5 W of the same collimated near-IR laser for 600 seconds and measured the cooling kinetics after the irradiation offset. The obtained results are shown in Fig. 4. As one can see, the maximal temperature increase clearly depended on the TiN NPs size. Indeed, the increase of the NPs size was accompanied by the decrease of the maximal temperature increment. This could be explained by the decrease of relative contribution of optical scattering to the total optical extinction under the decrease of the NPs size. Such a phenomenon could be related to different scaling of absorption and scattering: the NPs absorption is generally scaled with NPs size r as r^3 , while NPs scattering is scaled as r^6 . Therefore, even NPs with equal optical extinctions at a particular laser wavelength could be heated unequally due to different contribution of absorption and scattering to their total extinction. The obtained data suggest that in order to maximize the heating efficiency one should use smaller TiN NPs. Nevertheless, one should take into account that TiN NPs with sizes less than ca 20 nm have much smaller optical extinction in the near-IR region, as it shown experimentally in our earlier publications¹⁹ and elsewhere¹⁰, which is due to the formation of a thin oxide coating on the surface of TiN NPs during their aging. The thickness of the film depends on synthesis conditions and storage time, but it is typically within 2-6 nm range. The titanium oxide coating serves as an efficient isolator having a wide bandgap and not absorbing radiation in the IR range. To conclude, TiN NPs with sizes between 20 and 50 nm have the best performance as sensitizers of near-IR photo heating, which favors their use in projected biomedical applications. Indeed, this size range is large enough not to offer a prompt elimination of NPs from the blood stream via renal filtration, but these sizes are small enough to provide the internalization by cells not only via phagocytose or micropinocytosis, but also by various endocytosis mechanisms such as caveolae or clathrin mediated endocytosis.

It is worth noting that the presented research continues a cycle of studies devoted to the synthesis, characterization and assessment of novel laser-synthesized nanomaterials for biomedical applications. In our recent studies we focused on synthesis of nanomaterials for nuclear and radiative medicine applications. Examples include samarium oxide NPs²⁷ and

elemental bismuth (Bi) NPs²⁸, which can be used either as carriers or agents in radionuclide therapy, or as sensitizers in radiative diagnostics and therapy. In another line of studies^{23,29}, we already evaluated laser-synthesized Au NPs presenting another promising object for a variety of biomedical applications, including the treatment of neurodegenerative diseases³⁰, energy converters for pacemakers³¹, probes in SERS-based identification of target biomolecules^{32,33}. As follows from our analysis, Au NPs also present a safe object, which does not cause any damage of organs or tissues despite their residual accumulation in organs of mononuclear phagocyte system²³. In yet another series of studies^{24,34,35}, we assessed laser-synthesized silicon (Si) NPs, whose intrinsic semiconductor properties make possible a series of unique imaging³⁶ and therapy³⁷ functionalities. Our evaluation showed that Si NPs are not only safe, but also biodegradable as they can rapidly decay into orthosilicic acid and excrete from the organism with the urine³⁸. In contrast to Au- and Si-based NPs, which have already been widely studied and explored in biomedical applications, TiN NPs present a new material, which however has superior photothermal and photoacoustic characteristics compared to other plasmonic counterparts and thus can radically advance cancer phototheranostic modalities.

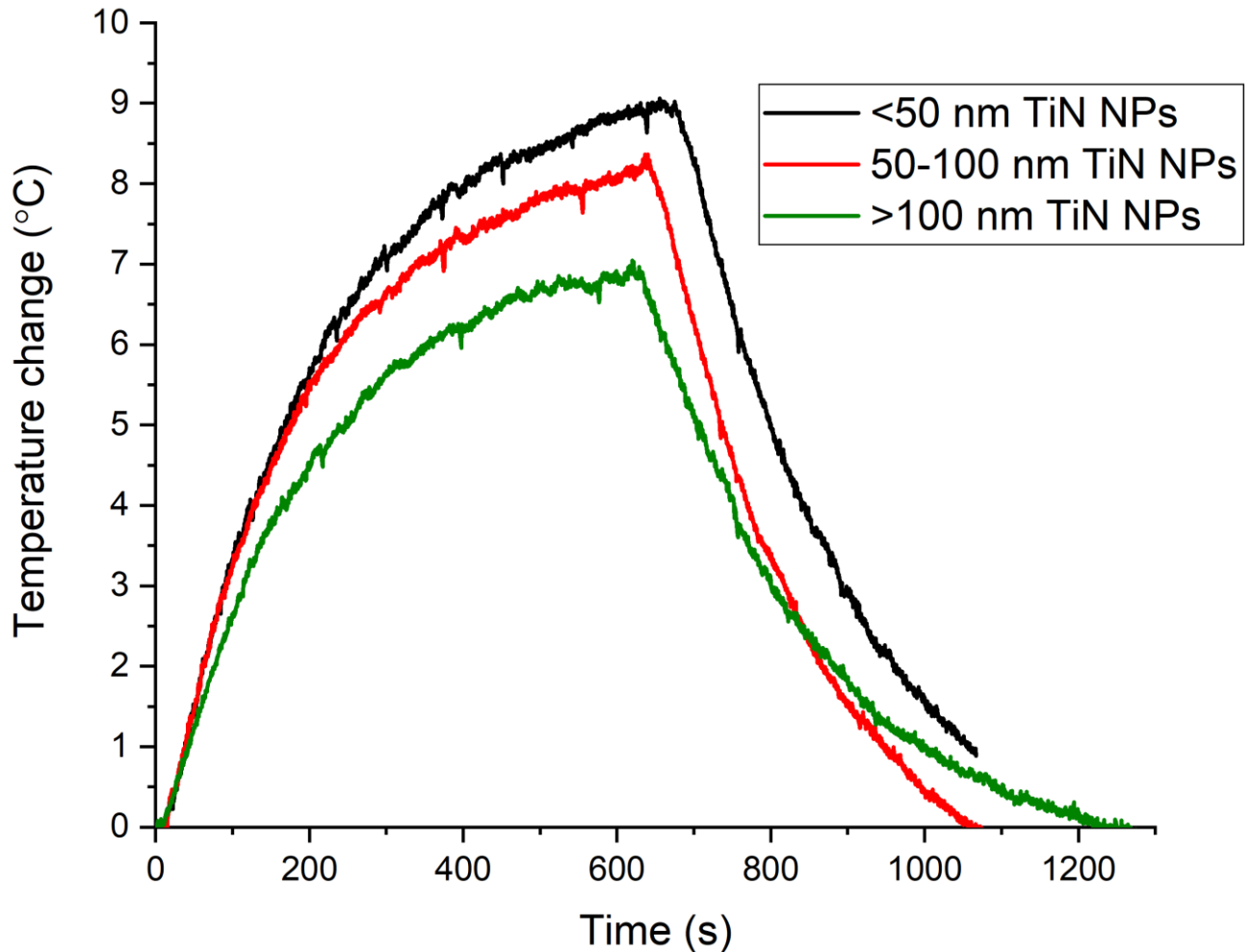


Figure 4. Heating of colloidal solutions of TiN NPs with different sizes by 0.5 W of 830 nm CW radiation. Black line – “small” fraction of TiN NPs (<50 nm), red line – “medium” fraction of TiN NPs (50-100 nm), green line – “large” fraction of TiN NPs (>100 nm).

4. CONCLUSIONS

We elaborated methods of fs laser ablation from a TiN target in organic solvents (here, isopropanol). We found that the productivity of the laser synthesis reaches the saturation point at a certain velocity of laser beam scanning along the target. This “saturation velocity” increases with the increase of the pulse repetition rate. The observed phenomenon is explained

by screening of radiation from consecutive laser pulses by cavitation bubbles. We also found that laser-synthesized TiN NPs with sizes in 20-50 nm range have the best near-IR photo heating properties. This size range is usually considered as the most suitable for biological systems, which gives a promise for the development of novel phototherapy and imaging modalities profiting from superior properties of TiN NPs compared to other plasmonic counterparts.

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