Gold nanoparticles as nanosources of heat

Guillaume Baffou

GOLD NANOPARTICLES
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Guillaume BAFFOU
Institut Fresnel, CNRS,
Aix Marseille Univ,
Centrale Marseille,
Marseille, France
guillaume.baffou@fresnel.fr

Under illumination at their plasmonic resonance wavelength, gold nanoparticles can absorb incident light and turn into efficient nanosources of heat remotely controllable by light. This fundamental scheme is at the basis of an active field of research coined thermoplasmonics and encompasses numerous applications in physics, chemistry and biology at the micro and nano scales.

Heat generation in plasmonics

When a metal nanoparticle is illuminated, its free electrons oscillate at the frequency of the electric field of the incoming light. This electronic oscillation is responsible for a re-radiation of light, an important feature of metal nanoparticles, but it also means an electronic current in a metal, which naturally gives rise to heat generation via Joule effect. This photothermal effect can be further enhanced when shining the nanoparticle at its plasmonic resonance wavelength. This resonance occurs, *e.g.*, around 500 nm for gold nanospheres, but it can be red-shifted by engineering the morphology of the nanoparticles, which makes the beauty of the field of research called plasmonics. Gold demonstrated many benefits compared to other plasmonic materials. It features unequalled photothermal efficiencies, the plasmonic resonance can be shifted in the infrared (ideal for biomedical applications) and chemical functionalization of gold is easy. For these reasons, almost all the applications involving heat generation in plasmonics have been based on the use of *gold* nanoparticles. *Figure 1a* illustrates the principle of gold nanoparticle heating using light.

For a long time, heat generation in plasmonics was considered as a side effect that had to be minimized in regards to the optical effects like light scattering or, more importantly, optical near-field enhancement. It was only in 2002 that some important conceptual ideas were proposed, the most famous one being the possibility to cure cancer (see further on). Then, the community realized that heating on the nanoscale could yield countless applications, with some imagination. That time corresponds to the birth of thermoplasmonics [1,2], a still rapidly growing field of research today.

The main challenge: measuring nanoparticles' temperature

Heating gold nanoparticles is straightforward, one just needs to shine them with light. The challenge is not here. The real difficulty rather consists in controlling the temperature increase. Probing temperature on the micro and nano scales is not simple. When thermoplasmonics was born, in the early 2000s, temperature probing on the nanoscale was mainly the job of scanning thermal microscopy (SThM). This technique consists in using a nanometric thermocouple at the apex of a tip and scan it over a sample. But this approach would have been very invasive to measure the temperature of nanoparticles. For this reason, other techniques had to be invented.

Most of the temperature microscopy techniques for plasmonics have

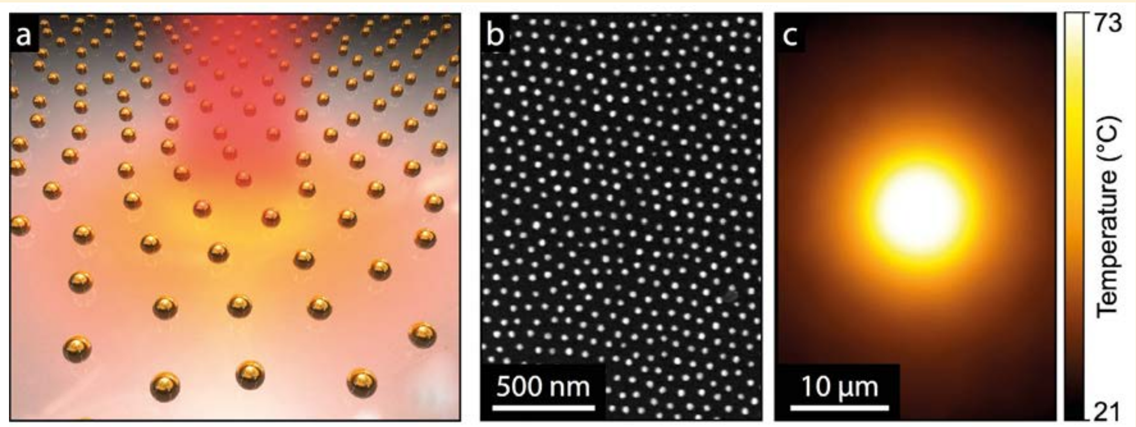

Figure 1. (a) Artistic view of an assembly of gold nanoparticles on a glass susbtrate. (b) Scanning electron microscope image of gold nanoparticles. (c) Temperature profile generated by the assembly of nanoparticles upon illumination.

been developed since 2009 and most of them are based on fluorescence measurements [4]. Since most fluorescence properties depend on temperature (intensity, spectrum, excited-state life time, polarization anisotropy), it becomes possible to disperse fluorescent molecules at the vicinity of metal nanoparticles and then map the fluorescence in order to map the temperature, provided a calibration law was previously determined. But this kind of technique implies a modification of the sample, and fluorescence properties are not only dependent on temperature, which may yield artefacts. Some other thermal measurement techniques have thus been developed based on Raman spectroscopy, refractive index variations, infrared radiation, X-ray absorption spectroscopy, microwave spectroscopy of nanodiamonds, etc. Today, the panel of temperature mapping techniques is very large and enables a more accurate use of plasmonic nanoparticles as nanosources of heat compared to a decade ago. *Figure 1b-c* gives an example of a temperature measurement performed on gold nanoparticles using a label-free microscopy technique based on quantitative wavefront sensing.

This large panel of techniques, involving a large variety of physical processes, illustrates an important aspect of thermoplasmonics: the multidisciplinarity. Working in thermoplasmonics usually implies working at the interface between different fields of Science as detailed in the next section.

The countless temperature-induced effects in science

Almost any field of science features some thermal-induced effects. Thus, almost any field of science can be addressed on the nanoscale, with a new glance, to hopefully uncover new applications, when using plasmonic nanoparticles as nanosources of heat. This is why the field of thermoplasmonics has been very active this last decade, motivating researchers from physics, chemistry and biology working at the interface between nanooptics and thermodynamics.

More precisely, as soon as a nanoparticle is heated, subsequent processes can occur in the surrounding environment, such as nanobubble formation, stress wave generation, enhancement of chemical reactions, microscale fluid convection, enhanced Brownian motion, liquid superheating (i.e., heating above the boiling point of a liquid without boiling), thermal radiation, microscale thermophoresis of colloids and biomolecules, modification of the metabolism of living cells. All these processes have been at the basis of research studies and recent applications, as described in the next section.

Cancer therapy and other promising applications

Photothermal cancer therapy was one of the first proposed application involving plasmonic nanoparticle heating. In 2003, two different groups led by Jennifer L. West and Charles P. Lin concomitantly proposed to internalize gold nanoparticles in tumors and subsequently shine an infrared laser to heat the nanoparticles and burn the tumor [3]. As biologists have the ability to achieve specific binding of nanoparticles to cancer cells, this approach can yield the specific destruction of the cancer cells, and not of the healthy surrounding cells and tissues, at least in theory. The principle of this application is depicted in *Figure 2*. Many investigations have been conducted on the level of cells in culture or living mice endowed with subcutaneous tumors. In 2010, a start-up was built, named Nanospectra, aimed at carrying out clinical trials. 7 years later, the results have not been disseminated yet. Several difficulties may indeed limit the applicability of this technique: first, the difficulty to control and to measure the temperature distribution in tissues. Temperatures up to 46 °C have to be achieved in the whole tumor location; while lower temperatures would result in a partial destruction of the tumor, which is not desired; and higher temperatures may be hazardous in the presence of vital organs in the vicinity of the treated volume. Second, human body is not transparent. Using infrared light helps going deeper compared to visible light, but it still remains difficult to go beyond 1 cm, making it difficult to treat some types of cancers. Interestingly, photothermal therapy does not only consist in treating cancer and gold nanoparticle heating has been used recently to treat other pathologies, such as atheroma or acne, with very good efficiencies.

Photoacoustic imaging is a biomedical imaging modality based on the photoacoustic effect, which consists of the emission of acoustic waves following a local and rapid absorption of a light pulse by efficient light absorbers such as blood vessels, tumors, melanin, dyes, etc. By collecting the sound waves following a pulse of light using a set of acoustoelectric transducers, it is possible to reconstruct in three dimensions the morphology of the absorbing medium. First proofs of concept date from the early 80s. The idea to use gold nanoparticles as contrast agents in photoacoutic imaging came later, in 2001. The benefits of using gold nanoparticles are two-fold: (i) gold nanoparticles are excellent photothermal contrast agents and their absorption can be tuned in the near-infrared, *i.e.* in the biological transparency window, allowing deep imaging in tissues. (ii) It allows imaging of specific targets, like a tumor, by active targeting of the nanoparticles conjugated with antibodies that will specifically attach to the region of interest. This way, regions characterized by weak endogenous photothermal contrast can be made visible for photoacoustic imaging thanks to the use of gold nanoparticles. Gold nanoparticles were injected intravenously a couple of hours prior to imaging. Since 2010, most of the efforts have been devoted to find more efficient metallic nanoparticles by playing with the nanoparticle morphology or nature, and expanding the range of applications of plasmon-assisted photoacoustic imaging, from cancer diagnosis to imaging of atherosclerotic plaques, brain function and image-guided therapy.

Nanochemistry depicts the generation of chemical reactions involving a nanometric spatial scale, either because the products are, for instance, nanoparticles or because the chemical reaction occurs at a nanometric scale. This second picture matches an application of plasmonic nanoparticles in nanochemistry. As most chemical reactions are catalyzed by heating, according to the Arrhenius law, gold nanoparticles as nanosources of heat can be used to very locally enhance a chemical reaction, even at the nanoscale. The interest of such an approach is three-fold. (i) Heating at the nanoscale makes it possible to achieve very fast thermal dynamics due to a reduced thermal inertia (the smaller the heated volume, the faster the heating and subsequent cooling). (ii) Heating a reduced volume makes it possible to superheat a liquid reaction medium above its boiling point, without boiling, opening the path for solvothermal chemistry at

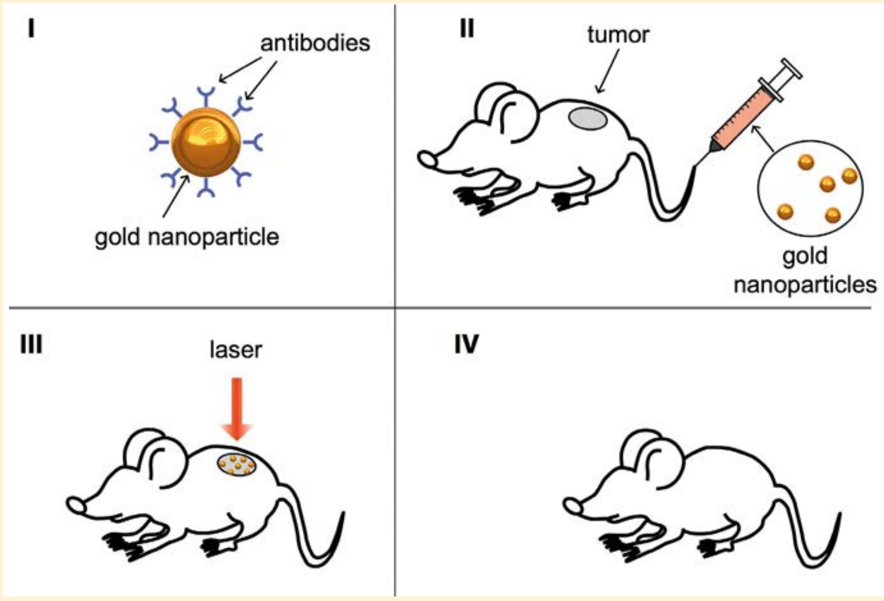

Figure 2. Process of photothermal therapy illustrated on a mouse. (a) Schematic of a nanoparticles coated with antibodies associated to specific receptors of the membrane of cancer cells. (b) Tail-injection of a gold nanoparticle solution in a mouse endowed with a sub-cutaneous tumor. (c) Laser heating of the tumor, once the nanoparticles are agglomerated in the cancer cells. (d) After several treatments, the tumor is destoyed.

ambient pressure. (iii) Heating at the nanoscale enables the formation of products with a nanometric spatial resolution, opening the path for original lithography techniques. Applications of plasmonics in nanochemistry do not only involve photothermal effects. Plasmonic nanoparticles under illumination can also act as efficient light enhancers at the nanoscale, favouring photochemical reactions at their vicinity, and efficient sources of hot electrons, catalyzing redox processes with a nanoscale spatial resolution.

Photothermal imaging is based on the probing of local variations of refractive indices produced by optical heating of an absorbing medium. In 2002, Michel Orrit's team introduced the use of nanoparticles as efficient photothermal contrast agents [5]. Nanoparticles as small as a few nanometers, normally invisible using standard optical microscopes because too small, can be made visible upon heating because a much larger volume surrounding the nanoparticles exhibits a variation of its refractive index. This seminal achievement gave birth to a novel label-free imaging technique in biology. While fluorescent tags used in cell biology tend to rapidly photobleach during imaging, gold nanoparticles can live (almost) forever. If attached to, *e.g.*, membrane proteins, the diffusion of the proteins in the membrane can be followed during hours, which provides valuable and additional information compared to a fluorescent labelling that could not be used for long acquisitions due to photobleaching.

What's next?

Interestingly, new developments in thermoplasmonics are still being proposed by the community, even 15 years after the birth of the thematic. There exist three recent and promising research thematics that are worth mentioning here and that should animate a large community in the next decade. First, *gold* has been the candidate of choice for most applications in thermoplasmonics. But its low-temperature melting point prevents from using it in high-temperature applications. For this reason, the community is currently looking for other possible plasmonic materials that would exhibit equivalent or better properties, but which would sustain much higher temperature increases. For the time being, no better material has been confidently found, but one may expect new discoveries in the near future, presumably by using metal alloys merging the benefits of different materials. Second, gold nanoparticles have been recently used to induce thermophoresis at the microscale. Thermophoresis denotes the motion of molecules or colloids induced by a temperature gradient in fluids. Although the origins of *thermophoresis* in liquids are still an active matter of debate, several applications have already been developed. Recently, Frank Cichos's team managed to advantageously use gold nanoparticles under illumination to create retroactive thermophoretic traps capable of confining the motion of biomolecules under the field of view of a microscope [5]. Third, more and more experiments are reported involving the plasmonic heating of living cells in culture. The state of a living cell is highly dependent on the temperature. Studying the effect of temperature on living cells may imply bulky apparatus, based on resistive heating of the sample holder, characterized by a large thermal inertia. Heating cells using gold nanoparticles and a laser beam offers important advantages. (i) Heating dynamics can be as fast as approximately 1 ms, which enables the study of very fast thermally induced processes in cells. (ii) One cell at a time can be heated, or even subcellular compartments, opening the path for new kinds of fundamental research in single cell thermal biology and thermogenetics. ■

FURTHER READING

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