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Design of a New Nanostructure for Theranostic Applications

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Abstract—**Medical applications of metal nanoparticles are the subject of intense research due to their unique properties which make them suitable for both diagnostic and therapeutic use. One such property is the Surface Plasmon Resonance (SPR) which results in strong enhancement of the absorption and scattering of electromagnetic radiation. The combination of metal type, size, and shape characteristics provides unique tunability of a nanostructure's optical properties. Several types of nanoparticles have been explored for medical and biological applications. Here we present a theoretical investigation of a novel metal nanostructure which has the unique property of distinct absorption and scattering plasmon bands. This could be beneficial for combined diagnostic and therapeutic applications since the diagnostic and therapeutic laser wavelengths can be decoupled for increased efficacy and safety. For this purpose, it is desirable to have the most intense scattering, with minimal absorption, in the near-infrared for imaging and the opposite in the red, for therapy. The efficiency factor for various metals, shapes and sizes was first calculated using the Discrete Dipole Approximation (DDA) method. From the results, nanostructures consisting of combinations of cubes and small spheres were considered to have the desired property and were thoroughly investigated. The number (diameter) and material (silver or gold) of the nanospheres were varied in order to obtain the optimum nanostructure with distinct absorption and scattering plasmon band. Given its properties, this nanostructure have the potential to be used for enhancement of various imaging and therapeutic methods.**

Keywords—nanocube; nanosphere; silver; gold; absorption; scattering; imaging; therapy

I. Introduction

Metal nanoparticles can have unique optical properties due to the existence of Surface Plasmon Resonance (SPR). By varying the size, shape, metal type, external medium, and the coupling and interactions between adjacent nanoparticles, the SPR frequency can range from visible to near-infrared (NIR) wavelengths [1, 2]. Most of the research effort focuses on noble metals, such as silver and gold, since they exhibit strong absorption and scattering enhancements which can be exploited in imaging, sensing, and therapeutic applications [3, 4]. Gold nanostructures have been extensively studied as potential theranostic agents [5-7]. Recent reports discuss the synthesis, preparation, and surface modifications necessary and suggest potential applications in sensing, e.g. with Surface Enhanced Raman Spectroscopy (SERS) [8], imaging, e.g. with Optical Coherence Tomography (OCT) [9] and therapy, e.g. with photothermal therapy [10].

Optical medical imaging and spectroscopic applications can significantly benefit from using NIR light, which minimizes absorption and scattering and therefore allows deeper penetration of the incident radiation into tissue. Photothermal applications, on the other hand, could benefit from nanostructures having strong absorption with limited scattering, for better efficiency. Here we present a theoretical investigation of a novel metal nanostructure which has the property of distinctly separated absorption and scattering plasmon bands. This could be beneficial for combined diagnostic and therapeutic applications since the diagnostic and therapeutic laser wavelengths can be decoupled for increased efficacy and safety. For this purpose, it is desirable to have the most intense scattering, with minimal absorption, in the near-infrared for imaging and the opposite in the red, for therapy. Such a structure would allow independent control of imaging and therapy for combined theranostics.

Several metal nanostructures, gold and silver, nanospheres, nanoshells, nanorods, nanocubes and tetrahedral, have been investigated so far. Their optical properties have been extensively studied using electrodynamic methods. Extinction spectra were calculated for various metals, sizes and shapes and compared with experimental results [1, 2, 11-13]. Small nanospheres, exhibit mostly absorption plasmon bands in visible range [2, 14]. As the size increases, scattering becomes more intense, overlapping with absorption which is not optimal for theranostic applications. Silver is mostly a scattering material but its SPR is in the visible wavelength range [15]. Gold SPR is shifted to longer wavelengths, but with, again, overlapping absorption and scattering spectra. Similar is the case for most nanostructures investigated so far [13-16]. A nanostructure having distinct absorption (at visible wavelengths) and scattering (at NIR wavelengths) plasmon bands, suitable for combined theranostic applications, has not yet been described.

II. METHODOLOGY

A. *Discrete Dipole Approximation (DDA)*

The Discrete Dipole Appoximation (DDA) method was used to investigate the optical properties (absorption, scattering and extinction) of various metal nanostructures. The DDA can address with any arbitrary shape, composition and external medium as long as some criteria are satisfied. Briefly, a target is geometrically approximated by a cubic lattice of N polarizable point dipoles, localized at r_i, and each characterized by a polarizability α_i, where i = 1, 2, …, N. There is no restriction regarding the localization of the polarizable point dipoles however a sufficient number of dipoles (N) must be used. A large enough N assures an interdipole separation (d) small compared to any structural dimensions of the target and the wavelength of the incident light (λ) [17, 18].

Complex 3N-coupled linear equations ($\mathbf{A}'.\mathbf{P}=\mathbf{E}$) are solved using iterative methods and the polarizations (P) can be determined. Absorption, scattering and extinction cross-sections (C_{abs}, C_{sca} and C_{ext}) can then be evaluated [18]. The efficiency factors are used to explore the spectral characteristics of absorption, scattering and extinction. These factors are defined as $Q_{abs/sca} \equiv C_{abs/sca} / \pi\alpha_{eff}^2$ and $Q_{ext} = Q_{abs} + Q_{sca}$ where α_{eff} is the effective radius which represents the radius of a sphere having a volume equal to that of the nanostructure and is given by $a_{eff} = (3V_{str}/4\pi)^{1/3}$. The code DDSCAT adapted by Draine and Flatau [18] was used to solve the complex linear equations of the DDA and calculate the efficiency factors.

Fig. 1 demonstrates the set up of a combined nanostructure considered for calculations viewed from the side (x-y plane, Fig. 1(a)) and front (z-y plane, Fig. 1(b)) where k represents the propagation of incident radiation, E the electric field and B the magnetic field. For the calculations the incident radiation (k) was assumed to propagate along the +x direction while the incident polarization (E) was assumed to be along the y or z-axis. An average value of the efficiency factors was obtained between the two polarizations states. The various dielectric functions (or refractive indices) of the nanostructure materials must be included to the calculations. The refractive indices were taken from the E. D. Palik [19]. When small nanospheres were considered for calculations, the dielectric function has been modified to include the surface damping effect, as described in [20, 21]. All calculations assumed water (n_{med} = 1.33) as the external medium.

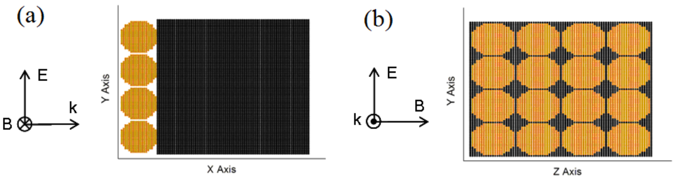

Figure 1. Set up of a combined structure for DDA calculations. Combined nanostructure of 16 small spheres arranged along x-axis, in front of a cube, viewed from the (a) side (x-y plane) and (b) front (z-y plane).

III. RESULTS AND DISCUSSION

The SPR plasmon band depends on the material, size and shape of a nanostructure. In order to find a theranostic nanostructure which has the characteristic property of distinct absorption and scattering spectra, a series of calculations have been performed to investigate several options.

A. *Simple metal nanostructures*

First, the efficiency factors were calculated for various metals, such as silver (Ag), gold (Au), aluminum (Al), and nickel (Ni), shapes, such as nanospheres, nanocubes and tetrahedral, and sizes ranging from 50 to 120nm. The characteristic properties of the wavelength of peak efficiency (λ_{max}), value of peak efficiency, and the profile of each spectrum were recorded.

Fig. 2 shows the absorption, scattering and extinction efficiency factors of some nanostructures. A gold nanocube (Fig. 2(a)) has overlapping absorption and scattering spectra in the visible range, while a distinct scattering peak at λ_{max} = 0.720μm is observed, with a value of 6.5 and minimal absorption in the near-infrared range. The silver nanocube (Fig. 2(b)) has two scattering peaks, one distinct scattering peak at λ_{max} = 0.570μm with a value of 6.9 and one broader, red-shifted at λ_{max} = 0.700μm with a value of 6.2, while the absorption has a small peak in the visible range. The aluminum tetrahedron (Fig. 2(c)) has blue shifted, overlapping peaks, with the wavelength of peak efficiency at approximately 0.435μm. On the other hand, nickel nanosphere (Fig. 2(d)) has very broad, overlapping plasmon peaks, ranging all over the visible spectrum, with λ_{max} = 0.460μm. The differences observed between the optical responses of materials derive from the electronic structure and the free conducting electrons of each metal.

B. *Combined metal nanostructures*

It is clear from Fig. 2 that each nanostructure has different characteristics, and by varying the parameters of material, shape and size, presents with unique optical properties. However, none of the nanostructures was found to have distinct absorption and scattering plasmon bands so combined nanostructures have been further considered. To create the desired nanostructure, small nanospheres and a gold nanocube, with properties chosen from the previous calculations, were combined. Small nanospheres were chosen as the absorption structure since they provide adequate absorption in the visible wavelength range [2, 14]. A gold nanocube with an effective radius 74.4nm (Fig. 2(a)) was chosen chosen as the scattering structure, since it provides strong scattering in the desired imaging range. Parameters such as the number, size (diameter) and material (silver or gold) of the small nanospheres were varied in order to obtain the optimum nanostructure with distinct absorption and scattering plasmon bands. The small nanospheres, unless otherwise noted, are considered to be arranged on the front face of the nanocube, along x-axis, as seen in Fig. 1(a, b).

Fig. 3(a-c) shows the absorption, scattering and extinction efficiency factors for thr nanocube combined with small silver nanospheres of varying numbers and diameters. It is observed

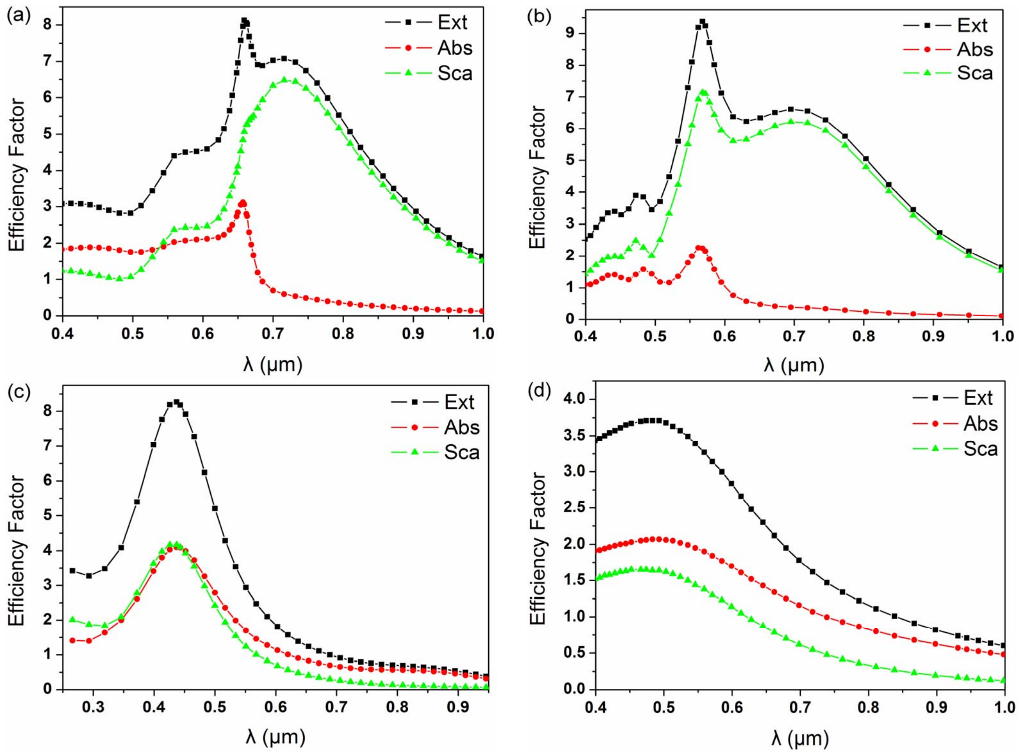

Figure 2. Efficiency factors of (a) gold nanocube, $\alpha_{eff} = 74.4$nm, (b) silver nanocube, $\alpha_{eff} = 74.4$nm, (c) aluminum tetrahedron, $\alpha_{eff} = 30.4$nm and (d) nickel nanosphere, $\alpha_{eff} = 50$nm.

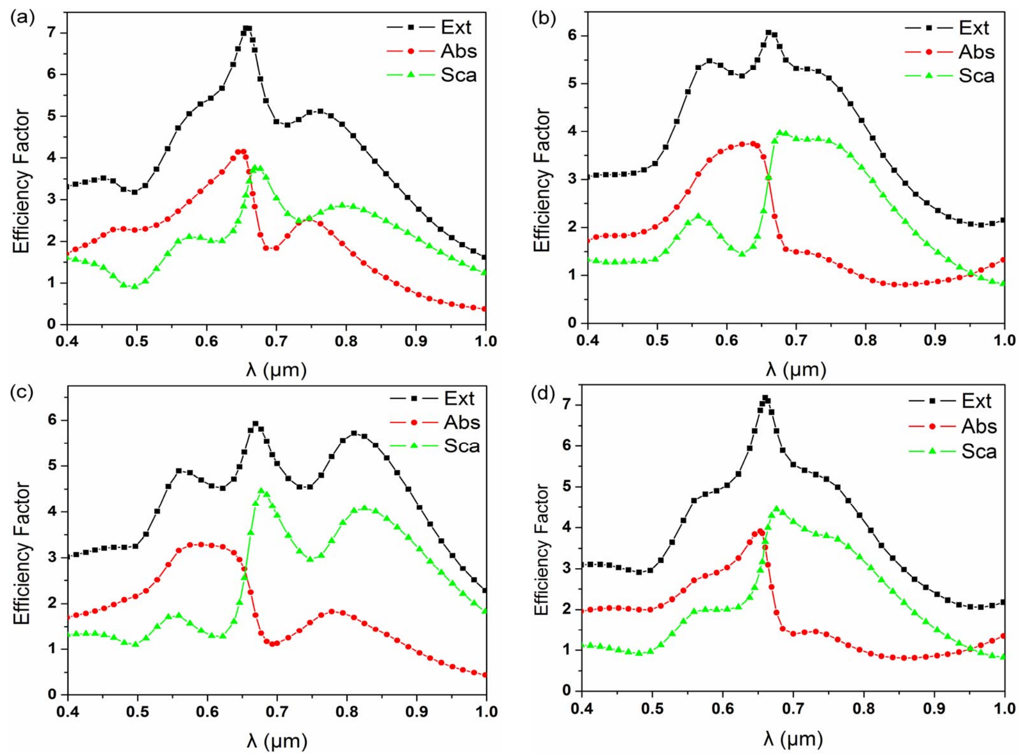

Figure 3. Efficiency factors of gold nanocube combined with (a) 4 (60nm diameter), (b) 16 (30nm diameter), (c) 64 (15nm diameter) silver (Ag) nanospheres, and (d) 16 (30nm diameter) gold (Au) nanospheres.

that as the number of nanospheres increases, absorption is dominant for all three nanostructures but overlaps with small scattering peaks in the visible wavelength range. In the NIR wavelength range, scattering is enhanced with its peaks becoming more pronounced, while the absorption has an unusual pattern, first decreases and then slightly increases with small peaks overlapping with the scattering spectrum. The results for a gold nanocube combined with 16 gold nanospheres are shown in Fig. 3(d). The absorption and scattering plasmon bands slightly differ from those of the combination with silver nanospheres. The other combinations, with gold nanospheres, give similar results with Fig. 3(a, c) and are not shown.

In order to evaluate the separation of absorption and scattering maxima, the ratios of efficiencies were calculated for two wavelengths, commonly used in imaging and therapeutic applications (Table 1). A combination of the highest possible rations, for both wavelengths, is desired. From Fig. and Table 1, one can deduce that the best possible theranostic nanostructure is a gold (Au) nanocube (α_{eff} = 74.4nm) combined with 16 (30nm diameter) silver (Ag) nanospheres.

TABLE I. RATIO OF ABSORPTION TO SCATTERING, AND VICE VERSA, FOR THE TWO WAVELENGTHS OF INTEREST.

	Q_{abs}/Q_{sca} at $\lambda = 0.635\mu m$	**Q_{sca}/Q_{abs} at $\lambda = 0.785\mu m$**
Cube with 4 silver (Ag) spheres	1.781	1.354
Cube with 16 silver (Ag) spheres	2.366	3.233
Cube with 16 gold (Au) spheres	1.583	3.242
Cube with 64 silver (Ag) spheres	1.992	1.947

The simulations described so far assumed that the small nanosphere were arranged along x-axis, on the front face of cube. The case where the nanospheres arranged along a different axis was also investigated. Fig. 4 shows the efficiency factors of the Au nanocube combined with 16 (30nm diameter) Ag nanospheres arranged perpendicular to the z-axis. The spectra changed significantly. The absorption spectrum broadens whereas the scattering is more intense for most of the wavelength range. More importantly, the separation in the absorption and scattering spectra is less distinct. These results imply that the response of the combined nanostructure depends on the arrangement of nanospheres on the nanocube in relation to the incident radiation direction.

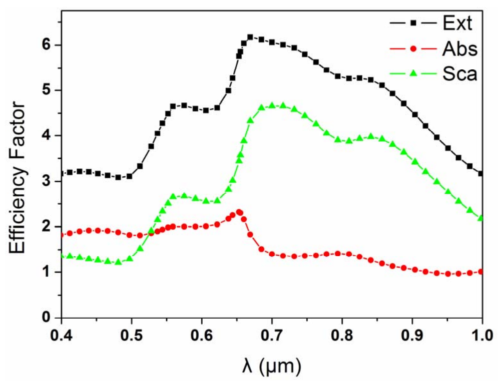

Figure 4. Efficiency factors of a gold nanocube combined with 16 (30nm diameter) silver nanospheres arranged along the z-axis

Fig. 5 shows the absorption and scattering spectra of an Au nanocube covered on all sides by 6x16 (30nm diameter) Ag nanospheres. A broad, uniform absorption spectrum over the entire spectral range is observed, overlapping with a scattering spectrum which has two distinct peaks at λ_{max} = 0.555μm and 0.865μm. The distinction between absorption and scattering spectra is again lost.

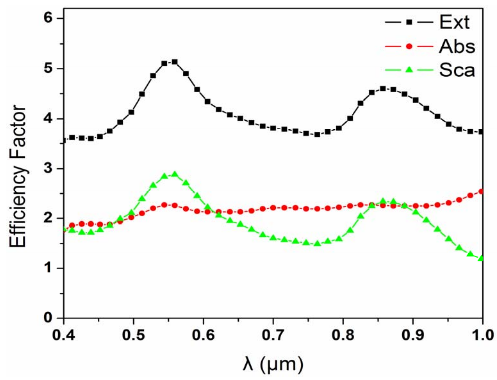

Figure 5. Efficiency factors of an Au nanocube (α_{eff} = 74.4nm) covered with 6x16 Ag (30nm diameter) nanospheres

IV. CONCLUSION

The purpose of this work was to theoretically design a nanostructure which could be used for theranostic purposes, for combined imaging (NIR wavelengths) and therapy (visible wavelengths) applications. First, the efficiency factors of various metals, shapes and sizes were calculated. Absorption and scattering plasmon bands were found to overlap, to some degree, in the visible range while, for NIR wavelengths, scattering was dominant. None of the common metal nanostructures was found to have distinct spectra, so combinations were considered next. A gold nanocube of an effective radius 74.4nm was chosen as the scattering structure and was combined with small nanospheres (absorption structure) along one side. A detailed investigation was performed, where parameters such as the number (and diameter), material (silver and gold), and arrangement of small nanospheres were varied. Even though the optical properties of the proposed combined nanostructure appear to be orientation dependent, the complex gold nanocube with 16 (30nm diameter) silver nanospheres was found to exhibit the desired property of distinct absorption and scattering plasmon bands.

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