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Gold-Based Core@shell Heteronanostructured Materials for Biomedical Engineering Application: Recent Trends & New Perspectives

Déogratias Ntirikwendera[1*], Solange Mukeshimana[2], Jean Claude Uwamahoro[1]

[1]Department of Physics, School of Science, University of Rwanda-College of Science and Technology (UR-CST), Kigali, Rwanda
[2]Department of Mathematics, School of Science, University of Rwanda-College of Science and Technology (UR-CST), Kigali, Rwanda
Email: *irikwende@yahoo.fr

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Abstract

Core@shell nanoparticles are advanced functional materials with modified properties combined into a single unity leading to their enhanced physico-chemical properties. In biomedical field, bi/tri/or multi-metallic Gold-Based Nanocrystals (GBNCs) and metamaterials, with core@shell heteronanostructures exhibit superior plasmonic properties with a broad range from sensing technology to nanomedicine. In this review paper, we investigated the recent trends of gold nanoparticles with a particular focus on core@shell heteronanostructured materials and their application in biomedical engineering. All properties are due to their size, shape, and structure-dependent Localized Surface Plasmon Resonances (LSPRs); owing to the enhancement of the plasmonic properties of isotropic and anisotropic Au NPs, including Quantum dots that are tailored to generate electromagnetic "hots sports"; highly sensitive for the diagnostic and therapeutic applications.

Subject Areas

Physics, Biochemistry

Keywords

Core@shell, Heteronanostructures, Surface Plasmon Resonance, Quantum Dots, Biomedical Engineering

1. Introduction

Gold (Au) and silver (Ag), noble metals Nanoparticles (NPs) have attracted huge interest in scientific community owing to their tunable plasmonic optical properties and large range of applications from biosensing technology, electronic and biomedicine [1] [2]. The ability of these materials to confine resonant photons to induce the coherent surface Plasmon oscillation of their conduction band electrons leads to a fabulous Plasmon resonance phenomenon, which can radiate light (commonly known as Mie Scattering) [3]. Meanwhile, gold-based nanostructured materials play a crucial role in sensing biomedical field owing to their fabulous optical properties resulting from their Localized Surface Plasmon Resonance (LSPR). Au-based nanostructured materials with LSPR peaks in the Near-Infrared Region (NIR, 650 - 900 nm); in this particular range of wavelengths, light can readily penetrate deep into soft tissues because of low absorption from blood and water as well as the low scattering phenomenon from soft tissue in the body [4]. To tune the LSPR peak of Au nanostructures to the Near-Infrared Region (NIR), not only size is concerned but also a careful control of the shape or aspect ratio of non-spherical nanoparticles, or fine-tuning of the shell thickness in hollow or core@shell nanostructures lead to Au nanostructures with enhanced/or improved physico-chemical properties for biomedical applications [5]. Moreover, excellent stability, biocompatibility, ease of functionalization of their surface, low toxicity, and drug transferability are important features of gold-based nanoparticles, which attracted scientific community for various applications [6].

Maintaining the Integrity of the Specifications Faraday in 1857 pioneered the foundation for the systematic chemical synthesis of colloidal Nanoparticles (NPs) with his experimental observation of the formation of a pure deep red-colored colloidal gold solution obtained by reduction of an aqueous solution of chloroaurate ($AuCl_4^-$) using phosphorus in CS_2 in a two-phase. He realized that the solution was completely different from the golden yellow color of intrinsic gold bulk material [7]. However, the scientific foundation about the origins of these colors arising from gold metal nanostructures was not well known. Over the past few decades, interestingly, studies have demonstrated that “fine particles of Au” can also be tailored and engineered to display an entire spectrum of varying colors, where “nano-gold” colloids exhibit different colors with different shapes; nanorods, Nanos hells, nanocages at different concentrations.

Maxwell’s equations, which describe light-matter interactions, marked an important step in the theoretical understanding of various colors exhibited by metal nanoparticles. Mie developed the first analytical formalism for calculating the electromagnetic response of spherical objects [8]-[10]. Understanding why these core/shell nanostructures have gained the attention of scientific community. We provide discussion of the physical foundation and relevant properties of gold nanoparticles for biomedical use. In particular, the Localized Surface Plasmon Resonance (LSPR) phenomena are tailored to enhance the properties of gold/core-shell materials with or without anisotropic shapes. In addition, gold-based quantum dots are also discussed in bio-imaging and therapy.

Although this review presents a simplified approach of understanding Gold-based core/shell nanostructures, we highlight also gold-based quantum dots, fluorescent semiconductors nanocrystals, their specific methods of preparations, including Molecular Beam Epitaxy (MBE), Metal Organic Chemical Vapor Deposit (MOCVD) their application *in vitro* and *vivo* imaging techniques [11]. Besides, this review article makes an awareness of how gold-based materials are treasure on earth and no one can ignore how expensive are the medical services even for one simple medical treatment. The rapid population growth in Africa, and the increase in different chronic diseases such as prostate Cancer, diabetes, asthma, high blood pressure, etc. drive the uptake of research in various gold-based Nanomaterials in the development of point-of-care medical devices and sensors.

Herein, we present a comprehensive review of recent trends of research on gold-based core/shell heteronanostructures and their particular use in biomedical engineering. We start with a general understanding introduction to Gold-based nanoparticles, various configurations, discussion on Mie theory, which lies the foundation of explanation of the behavior of Nanoparticles core@shell, Localized surface Plasmon resonance and its related sensing technology, and finally AuNPs' optical properties relevant to biomedical application are discussed.

2. Types of Au-Nanomaterials Configurations and Their Potential Use in Biomedical Field

Figure 1 represents the scheme of different types of commonly studied Gold-Based Nanoparticles (GBNPs). Typically, **Figure 1(a)** represents the conventional spherical Au NPs which have a polycrystalline structure with a poorly defined, quasi-spherical shape, especially prepared as colloidal samples by reducing $HAuCl_4$ by strong reducing agent in a solution phase. In these materials, there is essentially no sharp corner or edge on the entire surface of the particle [12]. In recent years, different research groups found a particular interest in the synthesis of Au nanospheres as a pure sample and with a well-controlled size mainly due to their simplicity in modeling their optical properties, leading to novel properties of these nanoparticles. The coating of Au core with other metals Leads to Au@shell_1@shell_2 with enhanced properties and functionalities owing to their particular use in medical imaging namely X-rays and optical imaging, Fluorescence. Note that a wide range of combination of materials with close interaction is possible; typically the combination including inorganic/inorganic, inorganic/organic, organic/inorganic, and organic/organic materials have been developed [13]. The choice of shell material of the core@shell nanoparticle is generally strongly dependent on the end application and use.

Gold Nanorods (Au NRs) highlighted in **Figure 1(b)** have an anisotropic shape, with the positions of their longitudinal Localized Surface Plasmon Resonance (LSPR) peaks highly sensitive to the aspect ratio. Au NRs@shells resulting from their coating with other metals are highly researched by different research groups owing to their therapeutic uses. AuNRs with sharp edges in **Figure 1(c)**

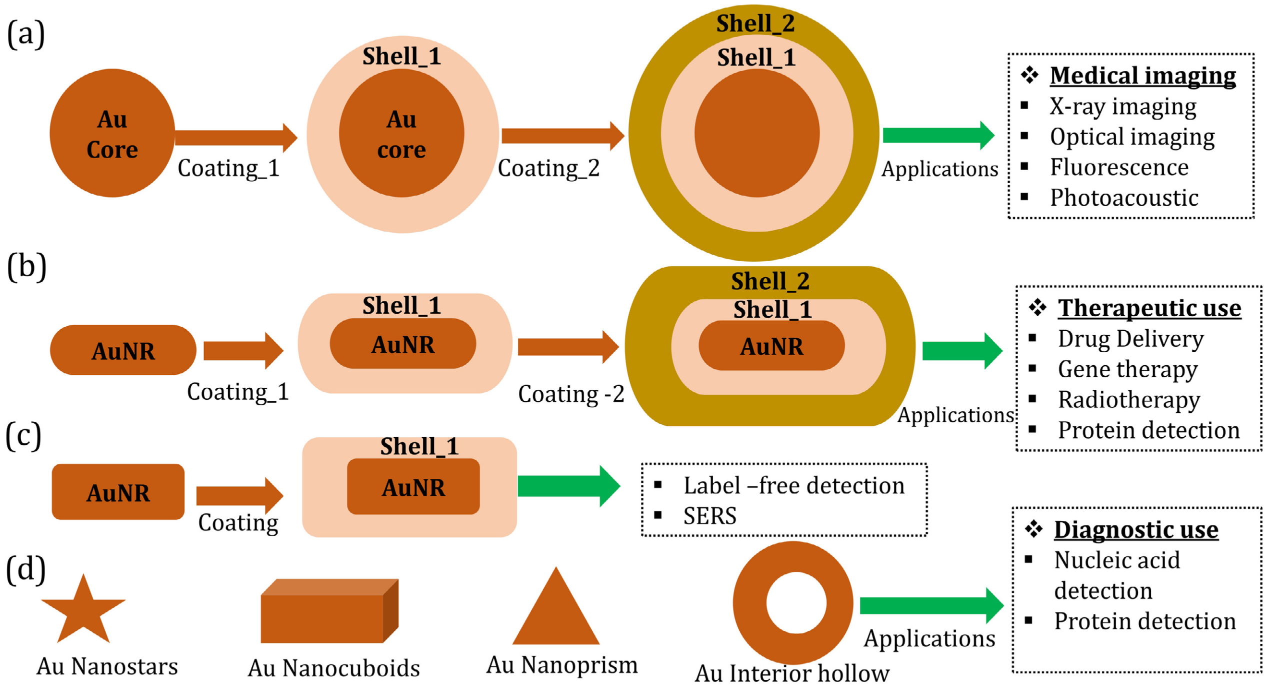

Figure 1. Scheme of different types of Au NPs. (a) Gold core nanospheres (Au NSs) which coated with two other metallic shells to enhance its functionality. ((b) (c)) Gold nanoparticles with round and sharp edges respectively. (d) Other shapes of Au NPs.

find their particular interests in Label free detection and Surface Enhancement Raman Scattering (SERS). Moreover, Gold Nanoplates (Au NTs) are plate-like nanostructures enclosed by two relatively large basal (111) planes, together with low aspect ratios [14].

Meanwhile, Au nanostructures that exhibit tunable LSPR properties similar to those of Au nanoshells but have hollow interiors and/or porous walls make find their particular application in different medical technologies involving encapsulation, controlled release, and drug delivery [15]. Nanoboxes, nanocages, and nanoframes are the typical classes of these nanostructures that depend on the porosity of their walls. Galvanic displacement reaction is the most important synthesizing technique for these materials. Various scientific papers reports on the synthesis of Au nanocrystals with polyhedral shapes, including cubes, octahedral, tetrahedral, cuboctahedral, decahedral, and icosahedra [16]. The later find their particular application in medical diagnostic.

3. Core@shell Nanostructured Materials Synthesizing Techniques

Since a few decades, Core@shell nanostructures attracted attention of the scientific community owing to the enhanced properties over their simple nanoparticles [17]. For the synthesizing of nanomaterials two general approaches namely "**bottom up**" and "**top down**" have been widely used [18].

In biomedical engineering, the core material coated with another material on top of it leads to integrated materials with enhanced physico-chemical properties such as less cytotoxicity, bio, and cyto-compatibilty, increased thermal and chemical stability, enhanced dispersibility, much better conjugation with bioactive molecules, etc. [19]. Moreover, the coating of a benign material on top of the core makes the nanoparticles much less toxic and bio-compatible. Sometimes, the shell layer not only acts as nontoxic layer but also improve the core material property. In the case of semiconductor core@shell materials, the effect of coating the core materials leads to enhanced optoelectronic properties with diverse applications [20].

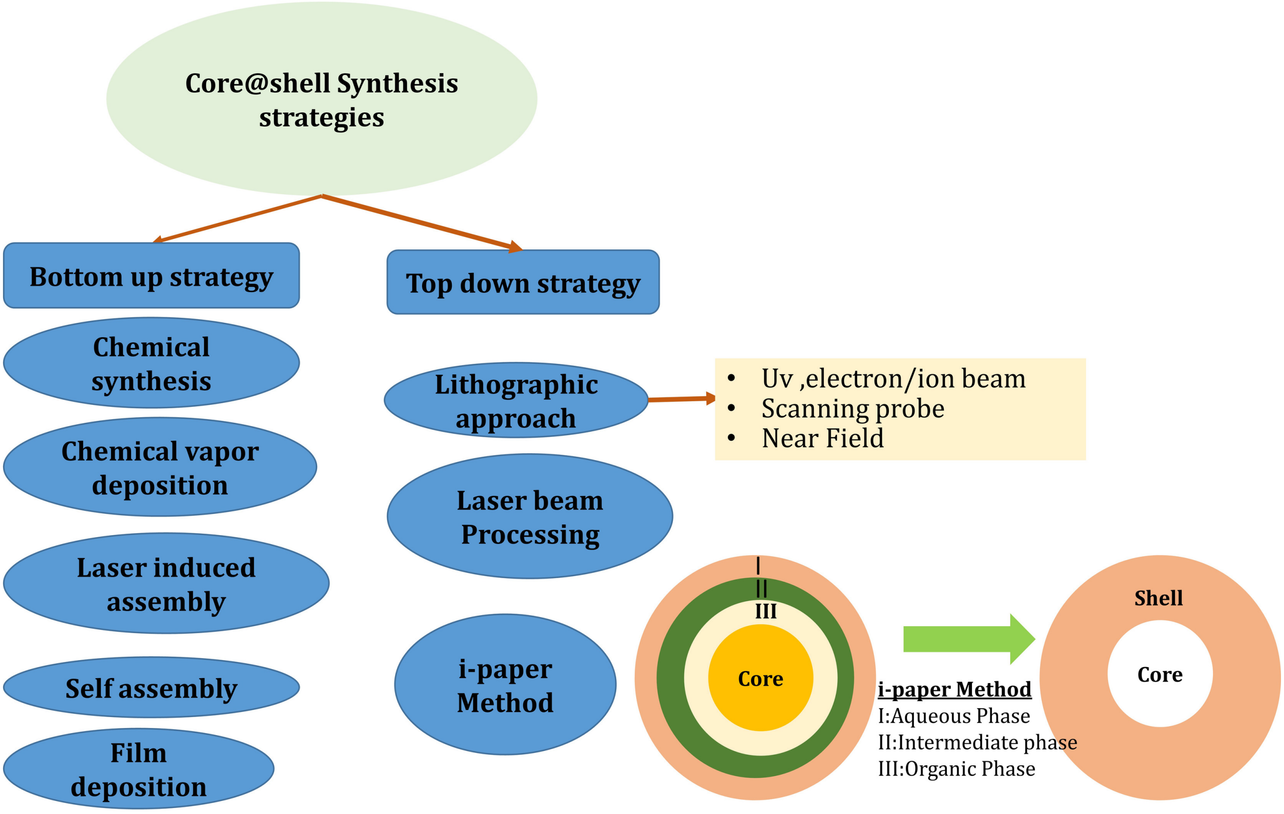

Figure 2. Schematics illustration of mostly used core@ shell synthesis strategies including intermediate-phase assisted phase exchange and reaction strategy for synthesizing versatile core@metal-shell nanostructures.

One of the most experimental challenging in core@shell nanostructures is the precise control of shell over the core materials synthesis, which includes self-nucleation of shell components and inhomogeneous growth over core NPs, which set requirements of both slow growth rate of shell and controllable surface reactivity of core NPs [21]. The latter group proposed a robust strategy for the synthesis of core@shell nanostructures with the precise control of shell layer by layer. The so called "intermediate-phase assisted phase exchange and reaction", i-paper method highlighted in scheme Figure 2, has been demonstrated to be an attractive strategy for synthesizing a wide range of Nanoparticles (NPs) because it combines advantages of both aqueous and organic phase synthesis. All reagents are mixed together in a reaction vessel with vigorous stirring to form a macroscopic homogeneous thermostable mixture.

The key for the success of this proposed method is the judicious choice of an intermediate-phase reagent so that it can coordinate transport of ion (M^{n+}) and atom (M0) species to govern shell growth dynamics and can have better compatibility with core NPs surface to ensure homogeneous growth. Typically, core NPs are passivated by long chain alkyls ligands such as oleic acid or oleylamine and well dispersed in fatty acid (Phase III). Precursors, soluble metallic inorganic salts in distilled water (Phase I), facilitate the shell growth over the core. For phase transfer, metallic iron such as RCOONa is typically selected to be an effective phase transfer agent. Once Phase II reagent is identified, Phase I with metal ions, sodium linoleate, Phases II and III reagents are mixed together in a reaction [21].

4. The Theoretical Foundation of the Behavior of Core@shell Nanostructures

4.1. Mie Theory and Quasi-Static Approximation for Spherical Nanoparticles

Gustav Mie theory provides a complete theoretical description of the optical properties of spherical nanoparticles [10]. The resultant scattering (C_{sca}) and extinction (C_{ext}) cross section efficiencies are given by:

$C_{sca} = \frac{2\pi r^2}{x^2}\sum_{n=1}^{\infty}(2n+1)\left(|a_n|^2+|b_n|^2\right)$ (1) and $C_{sca} = \frac{2\pi r^2}{x^2}\sum_{n=1}^{\infty}(2n+1)\Re_e(a_n+b_n)$ (2) in which the parameter $x = \frac{2\pi r\varepsilon_m}{\lambda}$ (3), where r is the radius of the particle a_n and b_n are the Mie scattering coefficients which may be described in terms of spherical Bessel function and n corresponds to the mode of excitement. In quasi-static regime, the dipole approximation is equal to the first order Mie calculation (n = 1) in Equations (1) and (2). The scattering cross-section (C_{sca}) can be obtained from the conservation relation $C_{ext} = C_{sca} + C_{abs}$ (4). In the quasi-static regime, the scattering and absorption can be calculated as $C_{abs} = \kappa\Im m(\alpha)$ (5) and $C_{sca} = \frac{k^4}{6\pi}|\alpha|^2$, where $k = 2\pi\sqrt{\varepsilon_m}/\lambda$ is the wave vector. The polarizability of sphere α_{sph} used in Equation (5) is given by the dipolar Clausius-Mossoti equation:

$$\alpha_{Sph} = 4\pi r^2\left(\frac{\varepsilon_{exp}-\varepsilon_m}{\varepsilon_{exp}+2\varepsilon_m}\right) \tag{6}$$

4.2. Mie-Gans Theory for Ellipsoids

Mie theory gives exact solutions of Maxwell's equation for Spherical particles and few exceptions for long cylinders [8]. In the quasi-static approximation, Gans proposed a geometric factor which allows the determination of response for oblate and prolate ellipsoids. In many papers roads like nanoparticles (Nanorods) are addresses as prolate ellipsoids, and the polarizability is described by introducing the polarizing factor $L_{x,y,z}$ into Equation (6):

$$\alpha_{Sph} = \frac{4\pi}{3} abc \left(\frac{\varepsilon_{exp} - \varepsilon_m}{\varepsilon_m + L_{x,y,z}\left(\varepsilon_{exp} + 2\varepsilon_m\right)} \right) \tag{7}$$

where a, b, c reflect the length of the particle along x, y, z axes respectively. $L_{x,y,z}$ denotes the depolarization along the semi-axes in a Cartesian frame, with increased displacement expected along the elongated axis (x) for ellipsoidal particles such that:

$$L_x = \frac{1-e^2}{e^2} \left(\frac{1}{2e} \ln \frac{1+e}{1-e} - 1 \right) \tag{8}$$

where $e = \sqrt{1-(b/a)^2}$.

4.3. Heterogeneous Bimetallic System

Improved tunability of metallic nanoparticles is possible with the combination of more than one metal either by: a) Coating a shell-layer of an alternative material, with dielectric ε_{Shell} on to a core with dielectric ε_{core} to form a core@shell particle or 2) through alloying two materials together to provide novel electronic properties. In the former case, the previously described dielectric polarizability of an ellipsoid ($\alpha_{x,y,z}$) Equation (7) can be modified within the electrostatic limit to give:

$$\alpha_x = V \frac{\left(\varepsilon_{Shell} - \varepsilon_m\right)\left[\varepsilon_{Shell} + \left(\varepsilon_{Core} - \varepsilon_{Shell}\right)\left(L_{Core}^x - fL_{Shell}^x\right)\right] + f\varepsilon_{Shell}\left(\varepsilon_{Core} - \varepsilon_{Shell}\right)}{\left[\varepsilon_{Shell} + \left(\varepsilon_{Core} - \varepsilon_{Shell}\right)\left(L_{Core}^x - fL_{Shell}^x\right)\right]\left[\varepsilon_m + \left(\varepsilon_{Core} - \varepsilon_{Shell}\right)L_{Shell}^x\right]\varepsilon_{shell}\left(\varepsilon_{Core} - \varepsilon_{Shell}\right)} \tag{9}$$

where the depolarization factors L_{Shell}^x shell and L_{core}^x core are representative of the depolarization factors for the core and shell, respectively; V is the volume of the entire particle $V = \frac{4\pi a_{shell} b_{shell} c_{shell}}{3}$ and f is the volume fraction $a_{core} b_{core} c_{core} / a_{shell} b_{shell} c_{shell}$ occupied by the inner ellipsoid as expected, when $\varepsilon_{shell} = \varepsilon_{core}$ and $f = 1$ Qualitatively, one would expect the extinction profile for a heterogeneous composite structure to be a combination of the two individual spectra of the component metals.

5. Optical Properties of Au NPs Relevant for Biomedical Applications

5.1. Photoluminescence

Luminescence is a process that involves the electronic transition between two different energy levels and thus the emission of electromagnetic radiation [22]. Photoluminescence is a result of light absorption where the emission can be described as either fluorescence or phosphorescence depending on the relaxation mechanism. The size of Au nanostructure has a large impact on its photoluminescence properties. When the size of Au nanostructure decreases to approximately 2 nm, the spatial confinement of free electrons by the nanostructure results in discrete, size-dependent energy levels, and thus tunable photoluminescence [23].

Gold nanostructures with a variety of shapes or morphologies, including conventional particles, rods, plates, shells, cages, and stars, have all been reported with photoluminescence properties. In particular, fluorescent Au clusters are excellent optical probes for the detection of biological species owing to their large Stokes shifts, low toxicity, and high emission efficiency [24]. The photo stability and biocompatibility of Au NCs are superior in comparison to some semiconductors quantum dots, organics dyes, etc.; while its photoluminescence can be readily tuned from the visible to the NIR region [25].

5.2. Sensing Properties Based on LSPR

Localized Surface Plasmon Resonance (LSPR) is a well-knownphenomenon in nanomaterials and is heavily exploited for diverse applications as highlighted in the scheme illustrated in **Figure 3**. Precisely it occurs when light impinges on nanoparticle, the free electrons of the metal are immediately sensed by the electromagnetic field and begin to oscillate collectively relative to the lattice of positive ions at the same frequency as the incident light. This phenomenon can occur in any nanomaterial with an adequately high density of free electrons, including those made of metals and heavily doped semiconductors [26]. These resonances, associated with noble metal nanostructures such as gold and silver, create sharp spectral absorption and scattering peaks as well as strong electromagnetic near-field enhancements.

The tailoring of LSPR properties of different nanostructures are controlled by

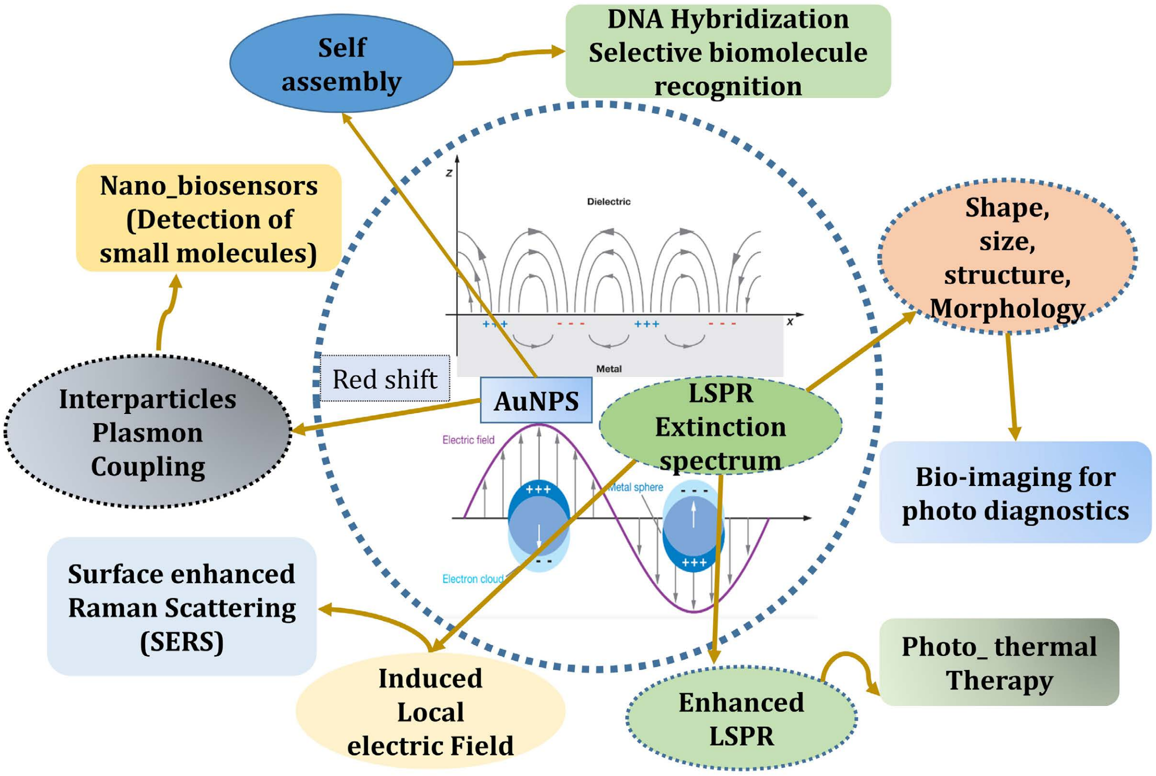

Figure 3. Illustrative scheme of localized surface Plasmon resonance and its associated sensing technology.

a number of parameters, including the size, shape, structure, morphology, as well as the environment surrounding the surface of the nanostructure [27]. This allows bimolecular photodiagnostics. Indeed, the LSPR properties depend strongly on the particle size. According to Mie theory, for spherical particles of radius R much smaller than the wavelength of light $2\pi R = \lambda$ the magnitude of the scattering cross-section is proportional to R6, while absorption is proportional to R3. Because of the prefactors, for the smallest particles, LSPR extinction is dominated by absorption, and as particle size increases, scattering takes over. For gold Nano spheres, this transition occurs at around 80 nm in particle diameter [28]. The Plasmon resonance line width also varies with particle size, due to a combination of interband transitions, which contribute to increased line width for small particles, and higher order (nondipole) Plasmon modes, which contribute to increased line width for larger particles.

In addition, the LSPR sensitivity is also determined by the particle shape. Particular, higher refractive index sensitivities are produced with nanoparticles with sharp tips and sharp corners. The driving factor for interest in nanoparticle shapes with sharp features or tips is mainly the occurrence of a red shift in the Plasmon resonance, which further increases the refractive index sensitivity [29]. Another additional advantage is that sharp features are used for molecular detection at the microscopic level due to the fact that a sharp tip creates a localized sensing/mode volume of highly enhanced electrified intensity.

The alteration of the medium surrounding the nanostructure leads to LSPR shift of Au NPs and this opens the door for AuNPs to be applied in optical sensing. For biomedical applications, scientists are most interested in Au nanostructures with LSPR peaks in the near-infrared regionNIR (650 - 900 nm). At these wavelengths, light can readily penetrate deep into soft tissues because of the low absorption from blood and water as well as the low scattering from soft tissue [4]. The vast majority of LSPR sensing experiments have been carried out on gold or silver nanoparticles. Gold is often chosen because of its chemical stability and resistance to oxidation, but silver has sharper resonances and higher refractive index sensitivity. That is why the combination of gold and silver into core shell nanostructures leads to versatile materials with enhanced sensing properties.

Note that the LSPR sensitivity for the nonspheroidal particles cannot be described analytically; electrodynamic simulation and experimental observation can be carried out to investigate their sensitivity. Both “label free” and “labeled” strategies can be employed for the detection of analyte molecules based on the “blue shift” of LSPR. By modifying the surface of Au nanoparticles with different probes, such a “labeled” assay can also be used for the detection of proteins, small molecules, and ionic species. As an example in our recent work [30], Simulation, using Density Function Theory (DFT) in comsolmultiphysic software, and experimental work, using seed mediated approach, showed that sharp-featured Au@Ag core/shell in_cuboid and out_cuboid lead to a label-free ultrasensitive SERS detection of protein single-point mutations. This technique was proved to be an effective way to prepare Au@Ag NCs with sharp features and different sizes. Experimental observation through TEM and STM images proved that the array of Au@Ag NCs can self-assembly to the ordered quartic symmetry structure on the surface. Furthermore, in the same group, using "vacuum-tuned-atmosphere induced dip coating method", an assembly of Au@Ag core/shell nanocubes can be converted into multi-dimensional superstructures which exhibited the label-free ultrasensitive SERS detection for the different mutants of IAPP8-37 proteins under low pressure conditions [31].

Moreover, refractive Index Sensing application of LSPR-active particles is to detect changes in the bulk refractive index of their environment through shifts in the LSPR peak wavelength [32]. LSPR peaks are typically detected by spectral extinction measurements on a dense film or spectral scattering measurements on single nanoparticle. There has also been some interest in the LSPR sensing capabilities of nanostructures exhibiting Fano resonances in their extinction spectra [33]. Fano resonances arise in asymmetrical nanostructures (such as nonconcentric core/shell particles) when a typical, "bright" Plasmon mode which couples to light, interferes with a "dark" Plasmon mode, which does not couple to light. The result is a sharp dip in the extinction, which is theoretically predicted to have extremely high refractive index sensitivity [29].

Furthermore, an anisotropic plasmonic metal/semiconductor hybrid photocatalyst such as Au@CdSe Nano dumbbell with precise control of their topology and heterointerface could lead to light harvesting and Photo Electrochemical (PEC) hydrogen generation beyond the visible region with excellent performance [34].

5.3. Sensing Based on Surface-Enhanced Raman Scattering

Surface Enhanced Raman Scattering (SERS) is a powerful technique for low-concentration chemicals and biomolecules detection through the enhancement of Electromagnetic fields (E-field) generated by the Localized Surface Plasmon Resonance (LSPR) effect [35]. To find the SERS active substrate, the enhancement mechanisms should be considered, namely the long-range Electromagnetic (EM) effect and the short-range Chemical (CH) effect [36]. Thus, both of the sharp features and "hot sites" created by LSPR coupling in Nano gaps between adjacent Nanoparticles (NPs) are simultaneously operative in SERS [37] [38]. Au and Ag-based NPs as SERS substrates have received extensive attention for biological detection, mainly owing to their strong LSPR effect in the visible and Near-Infrared regions (NIRs) and their controllable sharp shapes [39].

Au stars [40], Ag Nano bars [41]-[43], Ag octahedral [44] [45], Au triangular Nano plates [14] [46] [47], and Au NPs aggregate system, etc. with more surface roughness have been developed as SERS substrates. In addition, for the LSPR coupling in the Nano gaps, Au NPs arrays [48], Au Nano bridged Nano gap particles have also been reported. Compared with sensors based on photoluminescence, detection based on SERS shows even higher sensitivity, both label-free and

Raman reporter assays have been explored for SERS-based detection. In a label-free assay, the analyte molecules can be identified according to a pattern of their SERS peaks. The SERS substrates can be individual Au nanostructures or their aggregates, which tend to offer a stronger Raman enhancement than individual nanostructures due to the formation of hot spots.

6. Gold-Based Core@shell Quantum Dots and Their Use in Biomedical Field

Nanocrystals Quantum Dots (NCQDs) represent an ultimate class of advanced materials where electron confinement phenomena in all the 3 directions, at the nanoscale level, are more important. Since last few decades, these materials interested the scientific community and their properties, which are intermediate between molecular and bulk form of matter, depend heavily on their preparation techniques [5]. Typically, Self-Assembled Quantum Dots (SAQDs) present superior photo physical properties, hence find a particular application in optoelectronic devices, photodiodes. They are mainly synthesized by a heteroepitaxial growth and Molecular Beam Epitaxy (MBE) and Metal Organic Chemical Deposit (MOCVD) techniques are commonly used [49]. The degrees of freedom of charge carriers in these materials can be controlled efficiently with higher accuracy. Furthermore, Colloidal Quantum Dots (CQDs) with the size ranging from 2 - 4 nm can be obtained different Chemical routes. They are mainly prepared by coating the core material with another materials leading to Quantum dots in core shell configurations. These materials present excellent optical performance with good photo-stability, high-Quantum Yield (QY), long fluorescent lifetime, among other relevant properties which are important for biomolecules detection (see **Figure 4**).

Quantum dots nanoparticles are intensively research in biomedical sciences

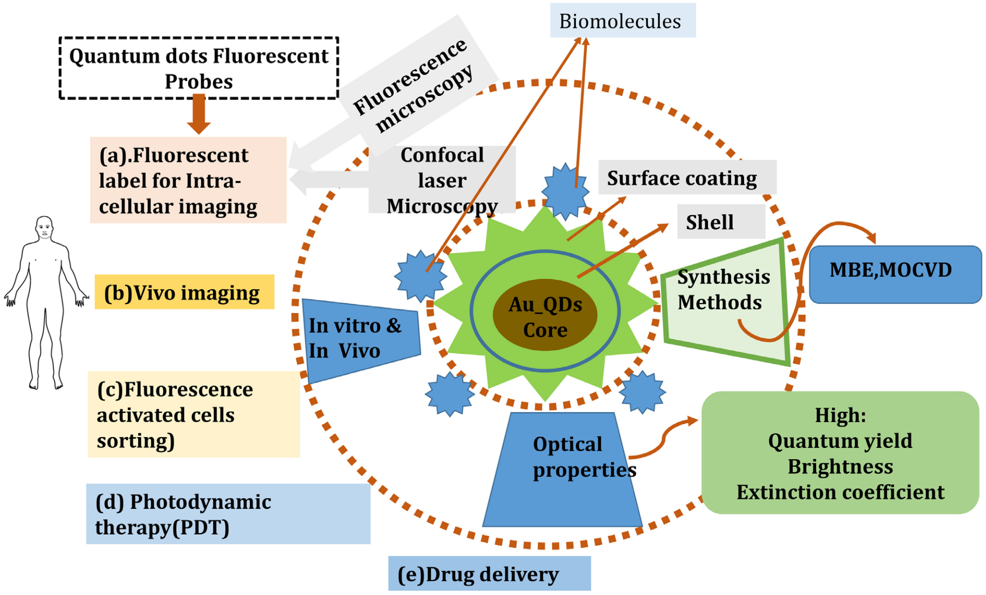

Figure 4. Scheme of Gold Quantum Dots (AuQDs) as fluorescent probe in medical imaging.

for their practical use *in vitro* diagnosis tissue imaging, molecular, cellular, supplying drugs, and theranostics systems among others. Furthermore, their capability to cover large surfaces areas because of the aspect ratio, and their nanoplatforms conjugated with various probes leads to their effective use in ultrasensitive bioassays and diagnostic. Another common use of QDs is as optical indicators for development of biosensors, using them as luminescent markers for detecting target biomolecules. The successful use of QDs for the detection of tumor biomarkers and the imaging of tumor cells has great potential for applications of these nanomaterials in the early diagnosis of cancer, with an accurate forecasting and visual tracking of tumor reduction and elimination. Due to their different, high brightness, large surface area, and flexibility for various conjugations, QDs can play multiple roles in the development of drug delivery systems [50]. They can serve as agents for monitoring the administration of the drug, and they can act as carriers. They can also integrate with functionalized ligands to increase the cellular consumption of the drug in the target organ. Therefore, the integration of QDs as nanovectors can significantly improve drug capacity by providing the multifunctional drug-drug complex, excellent stability, and good biocompatibility.

Gold quantum dots found their interest in biomedical nanotechnologies because they exhibit the same properties as Au NPs such as their inertness, non toxicity, controlled dispersity, high surface area to volume ratio. These properties allow them to be good candidates, useful for imaging and diagnoses, delivery of therapeutic agents, sensitizing cells and tissues to treatment regimens, monitoring, and guidance of surgical procedures. However gold quantum dots present advantages over other QDs of being no fluorescent. Meanwhile their colorimetric properties induced by Surface Plasmon Resonance (SPR) depending on particle size, shape, solvent and ligand, dielectric properties, surface functionalization, surrounding medium, and agglomeration, make them useful in biological systems detection applications, such as hybridization assays, DNA sequencing, genetic disorders, immunoblotting, flow cytometry, etc. [23] [49].

The NIR facilitates certain biomedical applications, such as *in vitro* imaging (and the formation of deep tissue images), and can, therefore, be used in diagnostics and photodynamic therapy. Silver chalcogenide (Ag_2X) with X = S, Se, Te have low toxicity compared to convention QDs such as CdTeS; CdSe, CdS. Hence, they represent a class of materials which is paramount importance for future application in biomedical field.

7. Gold-Based Core@shell Nanoparticles for Cancer Imaging and Therapy

Today, different types of cancers including Prostate, blood and breast cancers attack an important number of population in different countries. Cancer is the main cause of death in economically developed countries and the second cause of death in developing countries [51]. The smoking behavior, one of the cancer-causing factors is prohibited in many public areas. Various imaging technologies along with imaging contrast agents have been or are being developed and used for clinical settings to enable precise cancer diagnosis and prognosis. Hence, there is an urgent need for effective way of diagnosis and treatment of cancer and intensive research on this disease gained attention of different research groups in Biomedicine. In particular due to their less cytotoxicity excellent biocompatibility and disparity for high quality particles; enhanced optical electronic, magnetic particles among other; core-shell NPs are especially promising for cancer imaging and therapy [52] [53].

8. Gold Core@shell Structures for Bio-Imaging

Bio-imaging technique is used to visualize tissue and/or cell functionality in order to detect earlier stage of a disease of to guide a therapy for a better treatment. For this purpose, X-ray radiography, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), ultrasounds, and optical imaging are commonly used. However, with the advancement of science and technology, core shell nanostructures exhibit peculiar properties which are crucial for medical imaging. As a typical example, for effective cancer imaging, core-shell nanostructures present advantages of better biocompatibility, easy functionalization, colloidal stability in physiological conditions, low aggregation in blood vessels, and a long shelf life over their nanoparticles counterparts. Nowadays the advances in nanotechnology allow for precise engineering of critical features of core-shell particles, with precise properties and functionalities. For example, the composition, the size, the morphology, and the surface chemistry can all be precisely tailored, not only to improve their solubility and stability in physiological conditions but also to influence their pharmacodynamics and pharmacokinetics behaviors [54].

9. Anisotropic Gold-Based Core@shell: Nanocages, Nanorods & Hybrid Structures

Anisotropic gold core-shell nanostructures include also other structures apart from nanorods, which are rods-like structures. These include gold nanocages which are particularly characterized by hollow interiors and ultrathin and porous walls; they represent another class of nanostructures with tunable LSPR peaks in the NIR region; mainly synthesized by galvanic replacement reaction, these materials present a particular interest in study for their use in biomedical field because of their cavity, which exhibits the opportunity for these materials to be used in delivering drugs or the ranostic agents [12]. These materials are also used in cancel therapy owing to their tissue penetration near NIR radiations. Furthermore, gold-based nanoshell showed a particular use in photothermal therapy. Note that the combination of gold with other elements such as Iron, and SiO_2 leads to Au@Fe and Au@SiO_2 NPs with magnetic properties of a ferromagnetic material and the optical property of gold make such hybrid NPs to be widely used for theranostic applications [55].

10. Conclusions and Future Perspectives

This review paper investigated the recent trends of gold-based core@shell heteronanostructures and their particular use in biomedical engineering. This class of materials has gained attention of scientific community over the past few decades and has become one of the most active and innovative research subjects in various areas of nanoscience and engineering. The main purpose of coating shells on core materials is to protect the core against environmental influences and the stabilization of the core properties; hence to change the material properties and functionalities. Owing to their size-, shape-, and structure-dependent Localized Surface Plasmon Resonances (LSPRs), the plasmonic properties of isotropic and anisotropic Au NPs, including Quantum dots, are tailored to generate electromagnetic "hots sports", which are highly sensitive for the diagnostic imaging and therapeutic applications. Gold-based core-shell nanostructures are promising a revolution in biomedical field.

However, different features of these materials including the toxicity of various core/shell nanostructures in human body, and their stability are not well documented, this needs a careful investigation for a proper use of these nanoparticles. In addition, there is an urgent need for synthetic approach with high monodispersity of materials, easily reproducible at high scale. Most core/shell nanostructures are prepared in the milligram terms and their synthesis in large amounts is not clarified. This would hinder their commercialization at large scale. Furthermore, the synthesis of these materials in aqueous solution and their stability need a further investigation.

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Authors' Contributions

All authors contributed equally to the writing and validation of this article.

Conflicts of Interest

The authors declare no conflicts of interest.

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