The ‘nanobig rod’ class of gold nanorods: optimized dimensions for improved \textit{in vivo} therapeutic and imaging efficacy

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Abstract
Currently, gold nanorods can be synthesized in a wide range of sizes. However, for the intended biological applications gold nanorods with approximate dimensions 50 nm $\times$ 15 nm are used. We investigate by computer simulation the effect of particle dimensions on the optical and thermal properties in the context of the specific applications of photoacoustic imaging. In addition we discuss the influence of particle size in overcoming the following biophysical barriers when administrated \textit{in vivo}: extravasation, avoidance of uptake by organs of the reticuloendothelial system, penetration through the interstitium, binding capability and uptake by the target cells. Although more complex biological influences can be introduced in future analysis, the present work illustrates that larger gold nanorods, designated by us as ‘nanobig rods’, may perform better at meeting the requirements for successful \textit{in vivo} applications compared to their smaller counterparts, which are conventionally used.

(Some figures may appear in colour only in the online journal)

1. Introduction
One of the most important properties of gold nanoparticles (AuNPs) is the intense absorption of light at specific wavelengths, due to the phenomenon of localized surface plasmon resonance (LSPR). Additionally, these particles are relatively biological inert, and by using different conjugation strategies, such as PEGylation \cite{1–3}, where antibodies are attached on their surface, they can be used to target specific biomolecules.

SPR occurs when light of a specific frequency sets free electrons of the AuNP surface into collective resonant oscillations (plasmons). The resonant frequency is uniquely defined by particle size, shape \cite{4–6} and dielectric environment. At resonance, the interaction of the incident light and the AuNP is high, leading to narrow absorption and/or scattering peaks in the spectra. In asymmetric AuNP, plasmons can be created along the different axes of the particle, giving rise to multiple plasmon bands in the spectra. For example, in gold nanorods (AuNRs) \cite{7, 8}, resonant oscillations can occur along the short axis and the long axis, causing a transverse peak (TP) and a longitudinal peak (LP) respectively in the spectra. The TP is situated in the green region of the spectrum; the LP is red-shifted and tunable with aspect ratio (a.r.) \cite{4} to occur in the near infrared region (NIR). The NIR wavelength region is interesting for applications in tissue, since absorption ($\mu_a$) and scattering ($\mu_s$) coefficients of tissue are relatively low in this region, allowing high penetration of light for imaging into tissue...
In literature, we find that larger AuNRs (larger $r_{\text{eff}}$) are optimum for diagnostic and/or therapeutic purposes. The temperature rise around irradiated particles can also produce therapeutic effects. CW (continuous wave) light irradiation can be used to cause cell death in the process of hyperthermia [18, 19, 4, 20].

For these biomedical applications, various methods have been researched in pre-clinical studies whereby the NPs can be functionalized [21] by conjugating them with antibodies, thereby imparting them with the capability to target disease sites such as cancer [22, 12].

The ability to detect the disease or to effect a complete therapeutic action is dependent on the extent of interaction that the NPs will have with light, a phenomenon for which NPs can be tailored by appropriate choice of physical features such as size and a.r.. Also important is the extent to which a therapeutically relevant concentration accumulates homogeneously throughout the disease area. This requires design of physical and biochemical features of the NPs, which calls for some understanding of the physiology in normal and tumor tissue, and in their respective vasculature.

In general, for biomedical application of NPs the following steps are required for deployment of NPs for diagnostic or therapeutic purposes.

(i) Synthesis of the NPs.
(ii) NP bioconjugation with disease specific antibodies (mAb).
(iii) Topical or systemic administration of mAb-NPs.
(iv) Circulation in blood stream.
(v) Extravasation at disease site through leaky vasculature.
(vi) Transport in tumor.
(vii) Binding to the targeted cells.
(viii) Triggering of NPs present at the diseased site (tumor) with light, for detection or therapy.

Currently AuNRs can be synthesized with large variations in physical dimensions (length, width and a.r.), each variant having specific optical properties [6]. Typically, the entire ‘optical diagnostic and therapeutic window’ in the NIR spectrum can be covered by AuNRs with aspect ratios ranging from 2.5 to 5, and effective radii ($r_{\text{eff}}$) from 5 to 35 nm [23, 7, 6]. The $r_{\text{eff}}$ of an AuNR is the radius of a sphere having the same volume as the particle [24].

The immediate question is which particles among these are optimum for diagnostic and/or therapeutic purposes. The goal of this paper is to provide a possible solution to this problem.

Using computer simulations and analysis of data reported in literature, we find that larger AuNRs (larger $r_{\text{eff}}$), while still preserving appropriate a.r., can largely meet the requirements for successful use in biological applications. These particles, designated by us ‘nanobig rods’, have better physical, optical and thermal properties compared with the commonly used gold nanorods, which have $r_{\text{eff}}$ smaller than half the mean free path of electrons in gold. Next to the improved optical responses, we also consider the effects particle dimensions can have on in vivo behavior, such as on extravasation, uptake by cells and thermal stability in laser fields.

2. Materials and methods

2.1. Simulation of optical properties of AuNRs

The DDSCAT 6.1 [24] package (an implementation of the discrete dipole approximation method) was used to simulate the optical properties of AuNRs. The method discretizes a particle into dipoles, and the electromagnetic field scattered by the nanoparticle is calculated taking into account dipole–dipole and dipole–light interaction. The approach allows the interaction of light with arbitrarily shaped particles to be modeled and simulated, with a knowledge of parameters such as the dielectric function of the material, refractive index of media and particle orientation relative to incident electromagnetic field. For simulating AuNRs, we used the dielectric function of bulk gold [25], and water with a refractive index of 1.33 was considered as the embedding medium [8].

3. Criteria for choosing sizes of gold nanorods

3.1. Optical properties

In in vivo biomedical applications, collections of particles are involved. The absorption coefficient $\mu_a$ [9] of such an ensemble is wavelength dependent [26] and is calculated as the product of particle concentration ($N$) and absorption cross-section ($C_{\text{abs}}$) of the particle ($\mu_a = NC_{\text{abs}}$), where

$$C_{\text{abs}} = \pi r_{\text{eff}}^2 \eta Q_{\text{abs}}$$  \hspace{1cm} (1)

with $Q_{\text{abs}}$ the absorption efficiency of the particle. To maximize light interactions with the NRs embedded in tissue, the following requirements for the NR need to be fulfilled:

- the LP peak has to be located in the NIR spectral region, where background tissue optical properties, $\mu_a$ and $\mu_s$, are lower than in the visible range [27, 28];
- the optical interaction coefficients, $\mu_a$ and $\mu_s$, should be as high as possible, to increase the light induced effect necessary for detection or therapy.

AuNRs are currently synthesized using various modifications [6] to a seed-mediated silver-assisted growth protocol [29], resulting in variously sized rods. We modeled a wide range of AuNRs with $r_{\text{eff}}$ (5–35 nm) and aspect ratios (2.5–4) to include these different particles.

For in vivo optical imaging and photothermal applications, 800 nm is a wavelength that is typically used [9, 30]. In this NIR region, tissue has relatively low $\mu_a$ and
μs. Further, sources of 800 nm in the nanosecond regime are readily available for photoacoustic imaging by pumping OPO crystals. CW laser sources with emission wavelength at 800 nm are also reported in studies of hyperthermic effect [31, 32]. For these reasons we make comparisons between AuNRs which show their LP peaks around this wavelength.

Figure 1 shows as a function of \( r_{\text{eff}} \) the spectral locations of the LP absorption peaks for AuNRs with a.r. 3, 3.25, 3.5, 3.75 and 4. As observed earlier [33], not only the a.r. but also the volume of the NR determines the position of the LP peak. The LP peaks red-shift with increasing \( r_{\text{eff}} \), but the region around 800 nm is covered only by AuNRs with a.r. between 3 and 4, possessing \( r_{\text{eff}} \) between 11 and 35 nm.

The values of simulated absorption (\( Q_{\text{abs}} \)) and scattering (\( Q_{\text{sca}} \)) efficiencies at the LP peaks for a.r. 3–4 as a function of \( r_{\text{eff}} \) are shown in figures 2(a) and (b). Irrespective of a.r., \( Q_{\text{abs}} \) values have a peak around \( r_{\text{eff}} = 17.5 \) nm. The diameter of such a particle is close to the mean free path of electrons in gold (\( \approx 42 \) nm [34]).

\( Q_{\text{sca}} \) increases with increasing \( r_{\text{eff}} \), but NRs with \( r_{\text{eff}} < 10 \) nm can be considered pure absorbers, as \( Q_{\text{sca}} \) is negligible in comparison with \( Q_{\text{abs}} \). For \( r_{\text{eff}} > 27 \) nm (see figure 2), scattering is larger than absorption. This is the consequence of radiation damping effects, which occur in larger particles [35], a behavior also seen in gold nanospheres [36].

Figure 3 depicts the optical properties in the form of \( Q_{\text{abs}} \) and \( Q_{\text{sca}} \) values at 800 nm for particles with a.r. between 3 and 4, and \( r_{\text{eff}} \) between 11 and 35 nm. From figure 3(a) we can identify an optimal combination of a.r. = 3.75 and \( r_{\text{eff}} = 17.5 \) nm for obtaining the LP peak at 800 nm with the highest \( Q_{\text{abs}} \). As shown above, for thermal response upon irradiation, \( \mu_a \) is the most important parameter.

We calculated further the \( \mu_a \) for solutions containing particles simulated in figure 1, using the \( Q_{\text{abs}} \) and \( Q_{\text{sca}} \) from figure 3 at the same particle concentration (\( 10^9 \text{ ml}^{-1} \)). The result displayed in figure 4 shows that collections of particles with the combination of a.r. of 3.75 and \( r_{\text{eff}} = 17.5 \) nm are not actually optimal, with particles with a.r. of 3.5 and \( r_{\text{eff}} = 25 \) nm possessing higher \( \mu_a \) and \( \mu_s \). It can be observed that increasing the \( r_{\text{eff}} \) and decreasing the a.r. will not increase \( \mu_a \). The geometrical cross-section in this case will not counterbalance sufficiently lower \( Q_{\text{abs}} \). Particles with a.r. = 3 and \( r_{\text{eff}} = 35 \) nm may be used for example only in scattering based detection systems.

Thus, from the optical imaging or photothermal perspective, larger AuNRs are more favorable than the commonly used smaller AuNRs.

The length and width of this AuNR assuming a hemispherically capped cylinder geometry are 100 nm and 28.5 nm respectively. We qualify these particles as ‘nanobig rods’ for a clear identification in further discussion. We also name AuNRs with \( r_{\text{eff}} \) smaller than 17.5 nm ‘nanosmall rods’ for differentiation in the discussion. As a rule of thumb we define the ‘nanobig rods’ as being those AuNRs with \( r_{\text{eff}} \) greater than half of the mean free path of electrons in gold.

We will further compare the commonly used ‘nanosmall rods’ with the proposed ‘nanobig rods’. The dimensions of these particles are summarized in table 1.
Figure 3. (a) Simulated absorption efficiency $Q_{abs}$ and (b) scattering efficiency $Q_{sca}$ at 800 nm as functions of effective radii ($r_{eff}$) and aspect ratios.

Figure 4. Simulated absorption coefficient $\mu_a$ (cm$^{-1}$) (a) and scattering coefficient $\mu_s$ (cm$^{-1}$) (b) calculated at 800 nm for a collection of $10^9$ ml$^{-1}$ rods as a function of $r_{eff}$ and a.r. at 800 nm.

Table 1. Actual dimensions of gold nanorods occupying the classes ‘nanosmall rods’ and ‘nanobig rods’ with aspect ratios and effective volumes that provide plasmon peaks at 800 nm.

| $r_{eff}$ | a.r. | Length (nm) | Width (nm) | Size class       |
|----------|------|-------------|------------|------------------|
| 11       | 4.0  | 50          | 12.5       | ‘Nanosmall rods’ |
| 24       | 3.5  | 100         | 28.5       | ‘Nanobig rods’   |

3.2. Circulation in the blood, extravasation and interstitial penetration

3.2.1. Circulation of AuNRs in blood. Upon intravenous administration of AuNRs, the particles are distributed via the vascular system to various organs and tissues in the body. During this transport, the AuNRs interact with various blood components such as cells and proteins. Nanoparticles coated with hydrophilic, neutral polymers such as PEG possess relative stealth properties in the blood [37]. The steric stabilization of the particles with the polymers prevents or minimizes adsorption of proteins such as opsonin ligands, which could otherwise interact with macrophage cell receptors and thereby mark a particle for uptake. We have recently shown that PEGylation of AuNRs prolongs the blood circulation half-life of the particles to 19 h, while the non-PEGylated AuNRs are trapped rapidly within minutes in the liver and spleen [38, 1].

Particles can be bioconjugated with specific antibodies to attach to targeted cells. However, it has been shown that the presence of antibodies on the surface of particles increases their chances of being recognized and engulfed by macrophages in the RES (reticuloendothelial system) [39, 40]. It was also shown that the uptake level of bioconjugated nanoparticles by macrophages is proportional to loading of antibodies on the surface [41]. Only at low densities of antibody coverage can sufficient target binding to tumor cells be achieved while maintaining minimal macrophage interaction.

At this point, there is no literature comparing RES uptake of AuNRs of various sizes; most studies have used the ‘nanosmall rod’ particles (65 nm × 11 nm [37], 50 nm × 15 nm [42], 56 nm × 13 nm [43]).

Another issue with smaller nanoparticles represents their capacity to cross the brain–blood barrier (BBB). This phenomenon is not desired if not specifically targeted. As discussed in recent publications [44–47], particles smaller than 20 nm can cross the BBB and can also be found in retinal layers. Larger particles such as ‘nanobig rods’ (width > 20 nm) will have lower probability to cross the BBB.

In the spleen, studies have shown that particles between 100 and 150 nm are more efficiently filtered by the splenic
Unlike normal vasculature, angiogenic blood vessels associated with carcinoma are in general poorly organized with chaotic branching and are dilated, tortuous and leaky. The vessels can have gaps as large as 10 μm between endothelial cells [49–51]. Moreover, fenestration sizes vary from patient to patient, depend on the type of cancer and change over time.

Solid tumors have interstitial hypertension, which reduces the convection of the particles across the vessel walls. The progressively higher pressures from the periphery to the center of the tumor are due to the proliferation of cancer cells and impaired lymphatics. For the NRs to infiltrate the tumor, the particles will have to traverse this fluid interspersed with chaotic networks of collagen and elastin fibers [49, 52]. Movement in this region is by diffusion and convection; however, convective transport progressively reduces towards the center of the tumor due to the elevated pressures.

Experimental studies using 90 nm liposomes have shown that these could penetrate only distances of 10–20 μm from the microvasculature in mice, forming relatively static perivascular clusters [53]. It has been estimated that such large particles could take months to traverse 1 mm of tumor tissue, while smaller structures such as an IgG molecule with a hydrodynamic radius of 5 nm would take a considerably shorter 2–3 days [54]. Thus, it is evident that smaller sizes of the NRs will be favorable for interstitial penetration. Data presented in literature on extravasation of nanoparticles show that larger particles tend to remain localized at the vascular bed and do not extravasate deep into the tumor [41]. This could make the case against ‘nanobig rods’, since the spatial heterogeneity of particle distribution in tumors can affect the visualization of tumors by photothermal methods by not revealing the entire tumoral volume. However, their presence at the tumor periphery can provide indications about the tumor size.

3.2.2. Extravasation. Unlike normal vasculature, angiogenic blood vessels associated with carcinoma are in general poorly organized with chaotic branching and are dilated, tortuous and leaky. The vessels can have gaps as large as 10 μm between endothelial cells [49–51]. Moreover, fenestration sizes vary from patient to patient, depend on the type of cancer and change over time.

3.2.2.1. Thermal response during pulsed laser irradiation

Pulsed lasers can induce larger temperatures in nanoparticles because heat will accumulate faster than losses across the surfaces. The temperature rise of the particles can be sufficient to cause vaporization of surrounding water/tissue layers [73, 65, 74]. When particle concentrations are high enough, bubble formation and subsequent collapse can cause damage to cells. With high laser intensities, the temperature rise can be so high that reshaping of the NRs into shorter NRs and into spheres may occur. The melting and/ or fragmentation [75, 76] causes a drastic change in the optical properties, with the disappearance of the LP peak in an ensemble collection of irradiated AuNRs.

The stability of the NRs in a laser field depends on the melting point of the particles, which in turns depends on their size and coating [77]. The energy \( Q_m \) and temperature required \( (T_m) \) for melting of AuNRs can be calculated using [77, 78]

\[
Q_m = \rho V (c_p[T_{NR} - T_0] + \Delta H_f) \quad (2)
\]

\[
T_{NR} = T_b \left(1 - \frac{r_S}{8 \pi r^3_{eff}}\right) \quad (3)
\]

where \( \rho \) is bulk density (19 300 kg m\(^{-3}\)), \( c_p \) is heat capacity (129 J kg\(^{-1}\) K\(^{-1}\)), \( \Delta H_f \) is enthalpy of fusion (6.5 × 10\(^4\) J kg\(^{-1}\)), \( T_b \) is the bulk melting temperature (1330 K), and \( r_S \) and \( r_{eff} \) are the core radius and effective radius of the NRs.
Table 2. Typical sizes of AuNR synthesizable with different protocols.

| Reference | Length (nm) | Width (nm) | Effective radius (nm) | Aspect ratio | Position of LP (nm) | Class          |
|-----------|-------------|------------|-----------------------|--------------|-------------------|----------------|
|           | 10–30       | 5–10       | 4–8                   | 2.2–4        | 670–790           | ‘Nanosmall rods’ |
| [85]      | 41–52       | 14–20      | 11–15                 | 2.3–3.6      | 675–850           | ‘Nanosmall rods’ |
| [81]      | 52–187      | 20–30      | 15–34                 | 2.2–6.7      | 724–1080          | ‘Nanobig rods’  |

Table 3. Performance of the two NR classes in the selection criteria.

| Feature                      | ‘Nanobig rods’ | ‘Nanosmall rods’ |
|------------------------------|---------------|-----------------|
| LP at 800 nm                 | ++            | +               |
| Circulation in blood         | ?             | ?               |
| Extravasation at tumor       | +             | ++              |
| Interstitium transport       | +             | +               |
| Target cell uptake           | ?             | ?               |
| Lower number for contrast effect | ++         | +               |
| Thermal stability            | ++            | +               |
| Quality of synthesis         | +             | ++              |

4. Concluding remarks

We have identified a size class, ‘nanobig rods’, which has several advantages compared to their smaller counterparts, ‘nanosmall rods’, which are used conventionally. The discussed performance of these two size classes for various features is summarized in table 3.

Some performance indicators can be conflicting and a judicious balance between the different criteria has to be found. The extent of mAb loading on a particle, which depends on the surface area, e.g. will improve the adhesion to the target cells. On the other hand, enhanced immunogenicity of the particle with more mAbs may increase uptake by the RES and thus lower the final dose arriving in the tumor. Moreover, as shown in [87], the bioconjugation improves the internalization rather than extravasation.

Finally, modulation of the microenvironment of the tumors may improve the uptake of the AuNRs. Some examples of vascular manipulation have been described to improve delivery of drugs and/or drug containing nanocarriers to solid tumors. Transient normalization [88] of the abnormal structure of tumor vasculature is known to improve perfusion and thereby drug delivery. The use of vasodilatation factors [89], or abnormalization approaches that increase vascular permeability for instance by using growth factors or cytokines [50], or heat [90, 91], are known to increase accumulation and transport of NPs. A final approach of vascular manipulation is the approach that aims at lowering the interstitial hypertension using lytic enzymes [92, 49].

Additional experiments and theoretical calculations are necessary to show which of ‘nanobig rod’ and ‘nanosmall rod’ particles are better suited for biological applications. Techniques similar to particle swarm optimization (PSO) [93] may be used to optimize the size of gold nanorods for biological applications. However, if we take into account only the optical and thermal properties, the ‘nanobig rod’
particles have better properties for biological applications than ‘nanosmall rod’ ones.

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References

[1] Lankveld D P, Rayavarapu R G, Krystek P, Oomen A G, Verharen H W, van Leeuwen T G, de Jong W H and Manohar S 2011 Blood clearance and tissue distribution of pegylated and non-pegylated gold nanorods after intravenous administration in rats Nanomedicine 6 339
[2] Jokerst J V, Lobovkina T, Zare R N and Gambhir S S 2011 Nanoparticle pegylation for imaging and therapy Nanomedicine 6 715–28
[3] Green H N, Martyshkin D V, Rodenburg C M, Rosenthal E L and Mirov S B 2011 Gold nanorod biocjugates for active tumor targeting and photothermal therapy J. Nanotechnol. 2011 1
[4] Huang X, Neretina S and El-Sayed M A 2009 Gold nanorods: from synthesis and properties to biological and biomedical applications Adv. Mater. 21 4880
[5] Jain P K, Huang X, El-Sayed H and El-Sayed M 2008 Noble metals on the nanoscale: optical and photothermal properties and some applications in imaging, sensing, biology, and medicine Acc. Chem. Res. 41 1578
[6] Perez-Juste J, Pastoriza-Santos I, Liz-Marzan L M and Mulvaney P 2005 Gold nanorods: synthesis, characterization and applications Coord. Chem. Rev. 249 1870
[7] Prescott S W and Mulvaney P 2006 Gold nanorod extinction spectra J. Appl. Phys. 99 123504
[8] Ungureanu C, Rayavarapu R G, Manohar S and van Leeuwen T G 2009 Discrete dipole approximation simulations of gold nanorod optical properties: choice of input parameters and comparison with experiment J. Appl. Phys. 105 102032
[9] Li C and Wang L V 2009 Photoacoustic tomography and sensing in biomedicine Phys. Med. Biol. 54 59
[10] Qin Z and Bischof J C 2012 Thermophysical and biological responses of gold nanoparticle laser heating Chem. Soc. Rev. 41 1191
[11] Yang X, Stein E W, Ashkenazi S and Wang L V 2009 Nanoparticles for photoacoustic imaging WIREs Nanomed. Nanobiotechnol. 1 360–8
[12] Manohar S, Ungureanu C and Leeuwien T G V 2011 Gold nanorods as molecular contrast agents in photoacoustic imaging: the promises and the caveats Contrast Media Mol. Imaging 6 389
[13] Huang G, Yang S, Yuan Y and Xing D 2011 Combining x-ray and photoacoustics for in vivo tumor imaging with gold nanorods Appl. Phys. Lett. 99 123701
[14] Su R, Lioppo A, Ermilov S A, Brecht H P, Larin K and Oraevsky A A 2011 Optoacoustic tomography in preclinical research: in vivo distribution of highly purified peg-coated gold nanorods Proc. SPIE-OSA Biomedical Optics
[15] Yeager D, Karpiouk A, Wang B, Amirian J, Sokolov K, Smal1ing R and Emelianov S 2012 Intravascular photoacoustic imaging of gold nanorod-labeled atherosclerotic plaques Photons Plus Ultrasound: Imaging and Sensing; Proc. SPIE 8223 82231Q
[16] Mallidi S, Luke G P and Emelianov S 2011 Photoacoustic imaging in cancer detection, diagnosis, and treatment guidance Trends Biotechnol. 29 213
[17] Tung L, Wei Q, Wei A and Cheng J X 2009 Gold nanorods as contrast agents for biological imaging: optical properties and surface conjugation and photothermal effects Photochem. Photobiol. 85 21
[18] Li M L, Wang J C, Schwartz J A, Gill-Sharp K L, Stoica G and Wang L V 2009 In vivo photoacoustic microscopy of nanoshell extravasation from solid tumor vasculature JBO Lett. 14 010507
[19] Mallidi S, Larson T, Tami J, Joshi P P, Karpouki A, Sokolov K and Emelianov S 2009 Multiwavelength photoacoustic imaging and plasmon resonance coupling of gold nanoparticles for selective detection of cancer Nano Lett. 9 2825
[20] Oldenburg A L, Hansen M N,Ralston T S, Wei A and Boppart S A 2009 Imaging gold nanorods in excised human breast carcinoma by spectroscopic optical coherence tomography J. Mater. Chem. 19 6407–11
[21] Tiwari P M, Vig K, Dennis N A and Sin S R 2011 Functionalized gold nanoparticles and their biomedical applications Nanomaterials 1 31
[22] Rayavarapu R, Petersen W, Ungureanu C, Post J, van Leeuwen T and Manohar S 2007 Synthesis and biocjugation of gold nanoparticles as potential molecular probes for light-based imaging techniques Int. J. Biomed. Imaging 29817 29817
[23] Harris N, Ford M J, Mulvaney P and Cortie M B 2008 Tunable infrared absorption by metal nanoparticles: the case for gold rods and shells Gold Bull. 41 5
[24] Draine B and Flatau P 2004 User Guide to the Discrete Dipole Approximation Code DDCSAC 6.1 arXiv:astro-ph/ 0409262v2
[25] Palik E D 1991 Handbook of Optical Constants of Solids (Boston, MA: Academic)
[26] Ungureanu C, Amelinik A, Rayavarapu R G, Sterenborg H J C M, Manohar S and van Leeuwen T G 2010 Differential pathlength spectroscopy for the quantitation of optical properties of gold nanoparticles ACS Nano 4 4081
[27] Vo-Dinh T 2002 Biomedical Photonics Handbook (London: Taylor and Francis)
[28] Franceschini M A, Gratton E, Hube1 D M and Fantini S 1999 Near-infrared absorption and scattering spectra of tissues in vivo Proc. SPIE 3597 526–31
[29] Nikoobakht B and El-Sayed M A 2003 Preparation and growth mechanism of gold nanorods (NRs) using seed-mediated growth method Chem. Mater. 15 1957
[30] Dickerson E, Dreden E, Huang X, El-Sayed I, Chu H, Pushpakanth S, McDonald J and El-Sayed M 2008 Gold nanorod assisted near-infrared plasmonic photothermal therapy (PPTT) of squamous cell carcinoma in mice Cancer Lett. 269 57
[31] Choi W J, Kim J Y, Kang C, Byeon C C, Kim Y H and Tae G 2011 Tumor regression in vivo by photothermal therapy based on gold-nanorod-loaded, functional nanocarriers ACS Nano 5 1995
[32] Cole J R, Mirin N A, Knight M W, Goodrich G P and Halas N J 2009 Photothermal efficiencies of nanoshells and nanorods for clinical therapeutic applications J. Phys. Chem. C 113 12090
[33] Jain P K, Lee K S, El-Sayed I H and El-Sayed M A 2006 Calculated absorption and scattering properties of gold nanoparticles of different size and shape and composition: applications in biological imaging and biomedicine J. Phys. Chem. B 110 7238
[73] Liu X, González M G, Niessner R and Haisch C 2010 Strong size-dependent photoacoustic effect on gold nanoparticles by laser-induced nanobubbles Appl. Phys. Lett. 96 174104

[74] Liu C, Li Z and Zhang Z 2009 Mechanisms of laser nanoparticle-based techniques for gene transfection a calculation study J. Biol. Phys. 35 175

[75] Akchurin G, Khlebtsov B, Akchurin G, Tuchin V, Zharov V and Khlebtsov N 2008 Gold nanoshell photomodification under a single-nanosecond laser pulse accompanied by color-shifting and bubble formation phenomena Nanotechnology 19 015701

[76] Didychuk C L, Ephrat P, Chamson-Reig A, Jacques S L and Carson J J L 2009 Depth of photothermal conversion of gold nanorods embedded in a tissue-like phantom Nanotechnology 20 195102

[77] Link S and El-Sayed M 2000 Spectroscopic determination of the melting energy of a gold nanorod J. Chem. Phys. 114 2362

[78] Qi W and Wang M 2004 Size and shape dependent melting temperature of metallic nanoparticles Mater. Chem. Phys. 88 280–4

[79] Alekseeva A V, Bogatyrev V A, Dykman L A, Khlebtsov B N, Trachuk L A, Melnikov A G and Khlebtsov N G 2005 Preparation and optical scattering characterization of gold nanorods and their application to a dot-immunogold assay Appl. Opt. 44 6285

[80] Jana N R, Gearheart L and Murphy C J 2001 Seed-mediated growth approach for shape-controlled synthesis of spheroidal and rod-like gold nanoparticles using a surfactant template Adv. Mater. 13 1389

[81] Pérez-Juste J, Liz-Marzán L M, Carmie S, Chan D Y C and Mulvaney P 2004 Electric-field-directed growth of gold nanorods in aqueous surfactant solutions Adv. Funct. Mater. 14 571

[82] Xia Y, Xiong Y, Lim B and Skrabalak S E 2009 Shape-controlled synthesis of metal nanocrystals: simple chemistry meets complex physics? Angew. Chem. Int. Edn 48 60

[83] Grzelczak M, Pérez-Juste J, Mulvaney P and Liz-Marzán L M 2008 Shape control in gold nanoparticle synthesis Chem. Soc. Rev. 37 1783

[84] Brioude A, Jiang X C and Pileni M P 2005 Optical properties of gold nanorods: DDA simulations supported by experiments J. Phys. Chem. B 109 13138

[85] Rayavarapu R G, Petersen W, Chin P, Janssen H, van Leeuwen F W B, Manohar S and van Leeuwen T G 2010 In vitro toxicity studies of polymer-coated gold nanorods Nanotechnology 21 145101

[86] Sharma V, Park K and Srinivasarao M 2009 Shape separation of gold nanorods using centrifugation Proc. Natl Acad. Sci. 106 4981

[87] Kirpotin D B, Drummond D C, Shao Y, Shalaby M R, Hong K, Nielsen U B, Marks J D, Benz C C and Park J W 2006 Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models Cancer Res. 66 6732–40

[88] Jain R K 2005 Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy Science 307 58

[89] Sonveaux P 2008 Provascular strategy: targeting functional adaptations of mature blood vessels in tumors to selectively influence the tumor vascular reactivity and improve cancer treatment Radiother. Oncol. 86 300

[90] Kong G, Braun R D and Dewhirst M W 2000 Hyperthermia enables tumor-specific nanoparticle delivery: effect of particle size Cancer Res. 60 4440

[91] Li L, ten Hagen T L, Schipper D, Wijnberg T M, van Rhoon G C, Eggermont A M, Lindner L H and Koning G A 2010 Triggered content release from optimized stealth thermosensitive liposomes using mild hyperthermia J. Control. Release 143 274

[92] Jain R K 1990 Physiological barriers to delivery of monoclonal antibodies and other macromolecules in tumors Cancer Res. 50 814

[93] Kessentini S, Barchiesi D, Grosjes T and de la Chapelle M L 2011 Selective and collaborative optimization methods for plasmonics: a comparison PIERS Online 7 291