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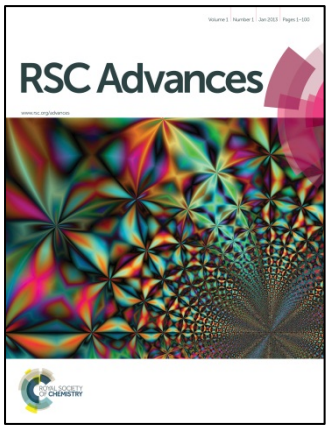

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ARTICLE

Enhancement of Tumor Smart-Targeting Efficiency based on Optical Communication between Signaling and Receiving Nanoparticles (Modeling and Analysis)

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According to our knowledge in this work for the first time, optical communication between signaling and receiving nanoparticles is analyzed and simulated for tumor smart-targeting. The original aim is the smart communication between receiving nanoparticles far from the tumor and signaling nanoparticles in nearby of tumor which can be concluded to an effective detection and treatment of cancerous tumor. The latter case can be contributed to the effective targeting by signalling nanoparticles and tune drug delivery by receiving agents. In this method, gathering of nanoparticles more in the tumor site is realized by the optical force that is contributed to the interaction between optical field and nanoparticles around tumor in such a way that enhance the population of nanoparticles toward the tumor. Moreover the manipulation of the optical force is controlled by the engineering of plasmon hybridization of core-shell nanoparticles. Unlike to the recent smart-targeting which is based on the biological cascade; in this work the communication between agents is optically done, so the construction of fake sites in the normal tissues will be diminished and avoided from the harmful effect on them.

Introduction

As everybody knows cancer maintains its standing as the second leading cause of death in the world, researchers have continued their quest for purely safe and more effective treatments. Among the most promising advances has been the rise of nanomedicine, the application of tiny materials and devices whose sizes are measured in the billionths of a meter to detect, diagnose, and treat cancer and other disease [1-4]. Compared with other available therapies [5-9] such as chemotherapy, radiotherapy, and surgery, nanomedicine has proven to be especially promising in fighting cancer. In preclinical trials, nanomaterials have produced purely safe and more effective imaging and drug delivery, and they have enabled researchers to precisely target tumors while sparing patients' healthy tissue [2-4]. In addition nanotechnology can be used to significantly improve the sensitivity of magnetic resonance imaging, making hard-to-find cancers easier to detect. The drug delivery is the most important case in the treatment of cancer, so this case must be regulated with high precisely targeting and imaging (smart-targeting). It has been proved that the main disadvantage of common method such as chemotherapy is related to use of non-targeted drug for killing of cancerous tumor cells [6-9]. But in the nanomedicine field to avoid main disadvantage of common method therapy, the targeting of specific site has been done with targeting procedures. Two popular methods including passive and active targeting have been used for this. In the case of passive targeting which uses permeability and retention effect to detect target, the targeting efficiency is very small. But in the recent years to improve passive targeting efficiency, the active targeting which the synthesized nanoparticles (NPs) must be functionalized with any biological agents such as proteins, peptides, anti-body, and enzymes for specific actions, has been used. It is notable that the active targeting method is benefit for mono-functional NPs tasks. It menas that any NPs should apply on targeting or drug delivery, no for two cases simoultaneously. It is related to this, if the several biological agents are attached on NPs' surface to construct of a multi-functional nanobio-sensors to simultaneously doing of several tasks, the multi-functionality can be eventuated to increase of the NPs' size larger than 350 nm which is severely limited in the biological

applications [1-3], [10-17]. To solve of the latter problem, two functionalized NPs (NPs with signaling and receiving capability such as detection and drug delivery performances, respectively) with small size rather than a multi-function nanobio-sensors have been assembled to do simultaneously several predefined aims as a tumor smart-targeting. The tumor smart-targeting means that the large amount of signaling and receiving nanoparticles with detection, imaging, and drug delivery agents are precisely accumulated in the tumor location especially for small tumors. In the recent years, some works related to the the smart-targeting were done which show a high efficiency rather than active targeting. Step-by-step of the latter approach are shortly stated as: I. Incidence of external electromagnetic wave, II. Heat generation by targeting NPs, III. Disturb tumor vessel, IV. Coagulation enzyme activity and construction of route communication between signaling and receiving NPs [14]. This method has some advantages such as smart drug delivery system, high efficiency targeting with different type of NPs, and signaling between them. But it is notable that NPs could be confused and target the fake sites and then the false signals from fake sites can be sent. So the coagulation cascade method can lead to burning and disturbing of normal tissue due to fake targeting of NPs. To improve of the latter disadvantage, our group proposes a new method: in this method coagulation cascade is used as coarse targeting (effective active targeting) and then the smart-targeting is initiated. In the smart-targeting approach, the external electromagnetic source is used with a lower energy and finally the optical force [23-26] causes to the communication between tumor targeted NPs (signaling NPs in the nearby of tumor) and non-targeted NPs (receiving NPs and fake targeted signaling NPs). In this approach the non-uniform electrical field will produce by active targeted NPs and in the nearby of tumor present a great optical force which applies on any non-targeted NPs to attract them toward the tumor site. It has been shown that because of active targeting and targeting due to coagulation cascade some percent of the signaling NPs are accumulated in the nearby of tumor. It is observable that the gradient electrical field arose by targeted NPs in the closeness of tumor is higher than other areas; so it causes to attract of non-targeted NPs to the tumor site. It has been proved that by controlling of electromagnetic field incidence, the applied optical force on NPs could be managed and which be used to move of any NPs to the desired point. It is clear that the approaching of non-targeted agents to tumor depends on the electrical field gradient, NPs radius, and distance of non-targeted NPs from the tumor. Furthermore it has been studied that the optical force has two components, including gradient and scattering forces in which the scattering force always acts along the direction of propagation of light but the direction of gradient force could be manageable. It is notable that to attract of non-targeted agents to the tumor site, the two factors of gradient force should be controlled: intensity and direction of gradient force. In this work, the two latter key factors are engineered by using of core/shell NPs and engineering of plasmon-plasmon interaction (hybridization) in the near-field of targeted NPs [27-28].Our sure things show that by engineering of core's plasmon and plasmon of outer shell, the amount of gradient and scattering force can be dramatically changed, so the amount of intensity and direction of applying force on non-targeted NPs can be manageable. In the following theoretical section and simulation results including optical force details and its effect on NPs and moreover, firefly algorithm (FA) for simulation of optical communication between NPs are perused with some extra details. Furthermore in this work, the Liver: Murine [29] as host material, R3327-AT [29] as tumor and *Au/SiO$_2$/Au* [18] as core/shell NPs are used. It is noteworthy that this simulation work is modulation of the interaction of light with matter, simulation of the trajectory of incident photons in real tissue, and targeting method (smart targeting) which are performed by MIE theory, [27-28, 30] Monte Carlo (MC), [31-35] and FA, [36-39] respectively.

Background and Methods

In this work, the interaction between electromagnetic wave and matter is used as a premise of presenting study and are analyzed by MIE theory. A plane wave with $|E_0|<100$ *v/m* in the *z-direction* is applied on core/shell nanostructure (*Au/SiO$_2$/Au*). With supposition of Hertz vector, the related Maxwell's equations for mentioning cases are solved and in the following, by consideration of the related boundary conditions (Equation 1), the three essential parameters including E_{inc}, E_{sca}, and E_{int} are calculated as [27-28, 30]:

$$(E_{inc}+E_{sca})\times e_r|_{r=R_s}=(E_{\text{int}})\times e_r|_{r=R_s};\quad (H_{inc}+H_{sca})\times e_r|_{r=R_s}=(H_{\text{int}})\times e_r|_{r=R_s} \qquad (1)$$

where E_{inc}, E_{sct}, E_{int}, H_{inc}, H_{sct}, H_{int}, e_r, R_s are the electromagnetic field components (incident, scattering, and internal), constant vector, NPs' radius to satisfy of Maxwell's boundary conditions. After calculation of scattering coefficients a_n and b_n for *TM* and *TE* modes, the other parameters for interaction of NPs with wave including absorption cross section, scattering cross section, Pöynting vectors, and so on are analyzed in the near- and far-fields. In this study, the considered NPs are designed to be in the plasmon resonance state, so the poles of scattering coefficients have an important role in our plan due to investigation of plasmons. Moreover, the plasmon-plasmon interaction is used in considering nanostructure, so by engineering of space layer thickness between *Au* core plasmon and *Au* shell plasmon, the strength of plasmons interaction could be managed. Our sure things show that the plasmon interactions have a dramatic influence on optical force components. It will be shown that the gradient optical force is approaching to maximum amount in the plasmon frequency. It has been proved that two modes including symmetric and anti-symmetric modes are raised after plasmon interaction and their places and magnitudes would be altered based on plasmons interactions strength. It is related to managing of sizes, materials, structures, and space layer thickness in nanostructure. For example, in the weak state of plasmons interactions, the core's and shell's plasmons are independently resonance and there in no interaction between each other. The weak and strong coupling states will be

investigated in the next section and their effects are perused on optical force components. In the following, the optical force is theoretically perused in details.

Optical force

The optical force contains two essential components, including gradient and non-gradients or scattering force which is related to the applying of electromagnetic field on dipole particles. The mentioned forces are applied on uncharged NPs in the external fields. It has been reported that by applying of the external field, the moving of NPs will be accessible and have different applications such as optical tweezers and NPs detection by optical force. The time-average force on a dipole in harmonic electromagnetic field can be defined as [23]:

$$< F > = (1/4).\mathrm{Re}(\alpha).\nabla \mid E \mid^2 + (k/2).\mathrm{Im}(\alpha).\mathrm{Re}(E^* \times B) + (1/2).\mathrm{Im}(\alpha).\mathrm{Im}[(E^*.\nabla)E] \quad (2)$$

Where F, α, E, B, and k are optical force, polarizability, electrical field, magnetic field, and wave vector, respectively. In this equation, the first term in the right hand is gradient force and the next terms cooperatively titled as scattering force. For proving of Equation 2, we begin with an expression for negative gradient of the classical dipole-field interaction Hamiltonian:

$$< F > = (1/2).\sum_i e_i \,\mathrm{Re}[\alpha.E\,(\partial E/\partial x_i)^*] \quad (3)$$

where i is the Cartesian component. By simplification of Equation 3, we have:

$$< F > = \sum_i e_i \,\mathrm{Re}(\alpha)(\partial \mid E \mid^2/\partial x_i) + (1/2).\sum_i e_i \,\mathrm{Im}(\alpha).\mathrm{Im}[E^*(\partial E/\partial x_i)] \quad (4)$$

In this equation, the first term is related to gradient force and the second is contributed to scattering force. It is notable that for satisfying of our plan, it is sufficient that the gradient force is designed to be considered greater than scattering force and moreover is applied in the opposite direction of scattering force. The next important section is the motion of NPs based on applying of optical force. It has been proved that their motion is based on momentum alteration which is related to the reflection and refraction of waves in the NPs boundary. When electromagnetic wave is applied on NPs surface, the Δp_{photon} is transferred and then based on momentum conservation, the particle undergoes an equal and opposite momentum change by $-\Delta p_{photon}$. This momentum change exerts a force on the particle which is given by the rate of change of momentum of the particle. Two types of forces arise at the interface due to the light-matter interaction. First one is the scattering force (F_{sca}) which acts along the direction of propagation of light, and the second one is the gradient force (F_{grad}) which pulls the particle towards the higher intensity region. The equation of motion of a polarizable particle with mass m moving in a viscous medium and experience the gradient and scattering forces exerted by the electromagnetic force is presented as:

$$m\,d^2r/dt^2 = 6\pi\eta R_{NPs}(dr/dt) + F_{grad} - F_{sca} \quad (5)$$

Where m, r, t, η, R_{NPs}, F_{grad}, F_{sca} are NP's mass, position, medium viscosity, NP's radius, gradient force and scattering force, respectively. The first term in the right hand for motionless particle is the Stoke force and can be supposed that this force is higher than random force (Brownian force). But in this work, for managing of NPs' position due to optical force, the FA is used which is perused in details in the following section.

Fire Fly algorithm

In this section, the brief exploration of FA is presented. In the FA, there are two important sections: the variation of light intensity and attractiveness which should be fitted based on our work's parameters. In the simplest case for maximum optimization problems, the brightness I of a firefly at a particular location x can be chosen as I(x) α f(x). However the attractiveness β is relative; it should judge by the other fireflies (in our plan, the fireflies are attributed to NPs). Thus it will vary with the distance r_{ij} between firefly i and firefly j. In addition, light intensity decreases with regard of the distance from its source, and light is also absorbed in the media, so the attractiveness will be varied with the degree of absorption**.** For a given medium with a fixed light absorption coefficient γ, the light intensity I vary with the distance r [36-39], for this we have:

$$I = I_0 e^{-\gamma r} \quad (6)$$

where I_0 is the original light intensity. As the firefly's attractiveness is proportional to the light intensity seen by adjacent fireflies, we can now define the attractiveness β of a firefly by:

$$\beta = \beta_0 e^{-\gamma r} \quad (7)$$

where β_0 is the attractiveness at $r = 0$ (target point or tumor site in our study). For distance between any two i^{th} and j^{th} fireflies at x_i and x_j, respectively in the *2D* Cartesian coordination, we have:

$$r_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2} \quad (8)$$

The attraction of i^{th} firefly to the most attractive (brighter) firefly j^{th} (the tumor attractiveness is brighter than other points because the rate of accumulation of NPs in this region is so high due to active targeting) is determined by:

$$x_i = x_i + \beta_0 e^{-\gamma r_{ij}}(x_j - x_i) + \alpha\varepsilon_i \quad (9)$$

where the second term is due to the attraction. The third term is a factor with a being of randomization parameter (ε_i) which is a vector of random numbers drawn from a Gaussian distribution or uniform distribution and α is the state of agent's divergence. In the following, the optical force role in the attraction of non-targeted NPs to the tumor site is fitted on FA's relations. At first, the location of tumor, which is given through the active targeting and coagulation cascade by signaling agents is considered, then the approaching of non-targeted agents to the tumor site is simulated based on tumor site's attractiveness. For this, the essential parameters of FA should be defined based on our study. It means that the attractiveness, medium absorption, and FA's divergence factor must be fitted to our work. It is mentioned that the NPs' near-field state is used to calculate of optical force and this field has an evanesce state in the far-field. Exponential decay of the evanescent wave intensity at a distance from an interface can be written as:

$$\gamma = \alpha_m.\sqrt{n_{NPs}^2.\sin^2\theta_i - n_M^2} \quad (10)$$

where α_m, n_{NPs}, θ_i, n_M are medium absorption coefficient, NP's refractive index, incidence angle, and medium refractive index, respectively. By approaching of receiving agents to the tumor site, the brightness augmentation because of NPs' extra accumulation is shown which is due to increasing of gradient

force. So, it will be caused to attraction of other agents with a high tendency toward tumor site. It is notable that the tumor site attractiveness could be contributed to the amount of field in nearby of it which is produced by targeted NPs in the near-field state and based on plasmonic conditions. Moreover NPs' convergence and divergence tendency factor to- and from the tumor site could be related to gradient and scattering force as below:

$$\beta_0 = F_{grad} / F_{grad} + F_{sca} \quad , \quad \alpha = F_{sca} / F_{grad} + F_{sca} \qquad (11)$$

Results and Discussion

Our simulations have shown that the tumor smart-targeting is much effective than active targeting and targeting after the coagulation cascade. In the latter approach the signaling NPs (with detection or imaging agents) detect the desired point (optimum destination) and then using a communicative approach to call receiving NPs (contain drug delivery or photothermal agents) toward the target point. In the other words signaling modules at first, target the tumor and then broadcast the tumor's location to other agents in order to collect them. In this method the signaling NPs have detection and imaging capabilities and receiving agents can have the drug delivery and other possibilities. In the recent year a good work was published [14] in which communication between signaling and receiving NPs was done by coagulation cascade effects. In this work the signaling and receiving modules could selectively activate the coagulation cascade in the tumor: signaling NPs that target tumors and convert external electromagnetic energy into heat to locally disturb tumor vessels to call other receiving NPs. They explored the potential to route communication to the receivers through two molecular pathways in coagulation by developing peptide coating that recognizes fibrin directly and peptide that targets the coagulation enzyme activity by acting as a substrate for the coagulation *transglutaminase factor XIII*. Their interesting things were the coupled smart signaling and receiving NPs which could communicate among each other to do simultaneous works. As an important result, it was experimentally studied the accumulation of receiving NPs to the region of coagulation. In this case the fold enhancement of receiving NPs is approaching to maximum amount in the 45°C and going to decrease by increasing of temperature higher than 45°C. This case explored that the higher temperature accelerated intravascular coagulation and occlusion and diminishing the perfusion required for delivery of receiving NPs into tumors. It is notable that the coagulation effect can be limited by increasing of temperature. But based on our knowledge the mentioned work didn't consider the fake coagulation effect. It means that the previous work did not take into account fake coagulation. Due to the presence of specific receptors both in cancer and normal cells (common problem) [18-19], NPs could be confused and false signals can be sent (Figure 1). So this paper proposes a new protocol where communication is enabled by optical force between two NPs. To achieve this, signalling NPs need to be strongly plasmonically active; such NPs are core-shell NPs. It is obvious that the using of high intensity external electromagnetic wave due to any local fake coagulation sites beside of the target point can be eventuated to harmful effects on normal tissue. Neither we can use of coagulation cascade effect due to its drawbacks (high temperature and its effects on tissue [20-22]) as a smart-targeting approach, while this case will be used as a coarse targeting method to initiate the smart-targeting by another harmless method. For solving of the latter disadvantage, a new method is presented which uses the optical force to communicate between receiving and signaling NPs. It has been mentioned that with the supposition of active targeting, some of the injected signaling NPs are accumulated in the tumor site and then by using of the coagulation cascade as the coarse targeting method, the receiving NPs are located either in nearby of the tumor or in the fake sites (Figures 1 and 2). Because of the accumulation of signaling NPs due to active targeting, by the incidence of the electromagnetic wave, the NPs produce a high scattering near-field intensity. Moreover, the produced gradient field is becoming so high rather than other area because of the core/shell NPs and their plasmon resonance. It means that by designing of the NPs based on plasmon-plasmon interaction, the maximum amount of gradient force can be attainable. The simulation results have shown that the applied gradient force lead to the attraction of non-targeted NPs to target point. It is notable that the gradient intensity in the nearby of tumor is certainly greater than fake points; this is because in the normal coagulation cascade approach, the accumulation of NPs in the tumor is higher than fake sites. Moreover, our approach is harmless because we use near-field scattering produced by NPs rather than high power incident external electromagnetic field. For instance, the electrical component of near-field scattering is approximately *700 v/m*, while the incident field amplitude is about of *90 v/m*. It is related to the using of plasmon resonance frequency and plasmon-plasmon interaction between the NPs' core and shell. The near-field scattering intensity will be intensified by approaching of the other NPs to the target point. For designing of core/shell NPs, the multi-shells nanostructure of $Au/SiO_2/Au$ is used. It has been proved that due to use of *Au* noble metal in the core and outer shell of the structure, the core plasmon and outer shell plasmon have an interaction with each other by considering of SiO_2 spacer layer thickness. In the interaction states either strong or weak plasmonic coupling, the two modes (anti-symmetric and symmetric) are produced because of the plasmon–plasmon interactions. Also, it has been shown that the specification of two modes have differed from each other due to their interaction strength. It will be shown that by changing of the spacer layer thickness, the plasmonic interaction is altered, so the optical force amplitude will be altered. It is shown when the strength of plasmonic interaction is increased which contributes to the decreasing of the spacer layer thickness, the scattering force is increased unlike of the gradient force. Decreasing of the gradient force is related to the increasing of the plasmonic interaction. In regard of these points, we need to a nanostructure with a high spacer layer thickness, it means that the NPs with the weak plasmonic coupled states would be

considered for our plan. Also, for a better illustration, the two different states for spacer layer thickness are considered *d=5 nm* and *d=30 nm* and the simulations are done for the plane wave incidence at the *z-direction* with $|E_0|$<90 v/m. The results of the simulations are illustrated in Figure 3. In this Figure, gradient and scattering forces for two plasmonic hybridization states as the strong and weak interactions are simulated. In Figures 3 a and b (correspond to layer thickness of 5 nm), the gradient and scattering forces are investigated in the strong plasmonic coupling modes. Their results are related to the altering of scattering and internal field in the core/shell structures. Also, it is notable that because of *Re* (α_p)>*Im* (α_p), where α_p is the NPs polarizability, and incidence in the visible to NIR spectra, the gradient force originally is greater than the scattering force. But in the weak plasmonic hybridization between core and shell plasmons (Figures 3 c and d), the scattering field is increased. It contributes to the increasing of gradient force while the scattering force is decreased. It means that by designing of core/shell NPs, the higher amount of gradient force is attainable and so could be easily applyed to attract of NPs toward tumor. Additionally, by increasing of gradient force, the large area for attracting of NPs toward the tumor site will be easily scanned. Finally, for better illustration of optical communication between signaling and receiving NPs, *25000* incidence photon (~$3*10^{-4}$ w/cm^2) trajectories are simulated by simultaneously using of MC and FA algorithms in the real tissue. The two tests with consideration of different NPs plasmons coupling are considered. In each test, the photon interaction with matters (host media, tumor, and inserted NPs) such as transmission, reflection, absorption and scattering are perused. In all simulations, the two wavelength *560* nm and *800* nm are considered for exciting and fluorescence emission, respectively. In our work, for simplicity, the simulation area is considered *1cm x 1cm* of host medium. In our simulation approach, the fake accumulation of signaling NPs at some sites differ than tumor because of inaccurate coagulation effect is modeled by random parameters in the MC algorithm. The fake sites targeted by signaling NPs after active targeting and coagulation effect which are simulated by MC, are schematically illustrated in Figure 2. In the following, the communication between targeted NPs and non-targeted NPs is simulated by modulation of MC approach and FA. In these simulations which are illustrated in Figure 4 and 5, the communication between the signaling and receiving NPs is investigated. In these figures, the approaching of receiving NPs toward signaling NPs site (tumor closeness) is shown in the four different records (a-d). It is shown that the improvement of optical gradient force is notable in the tumor location after each records and furthermore, this parameter to be vanished in the fake site after each record.

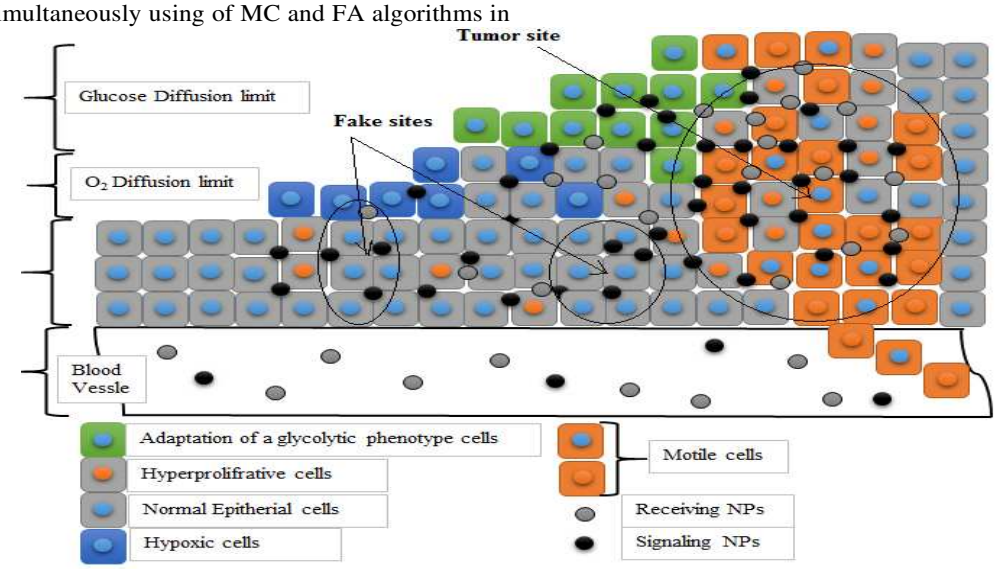

Figure 1. Schematic illustration of tumor and fake area for cell–environment interactions in carcinogenesis. Early carcinogenesis proceeds from normal tissues through initiation to a hyperplastic state to interstitial neoplasia, progressing to carcinoma in situ [4].

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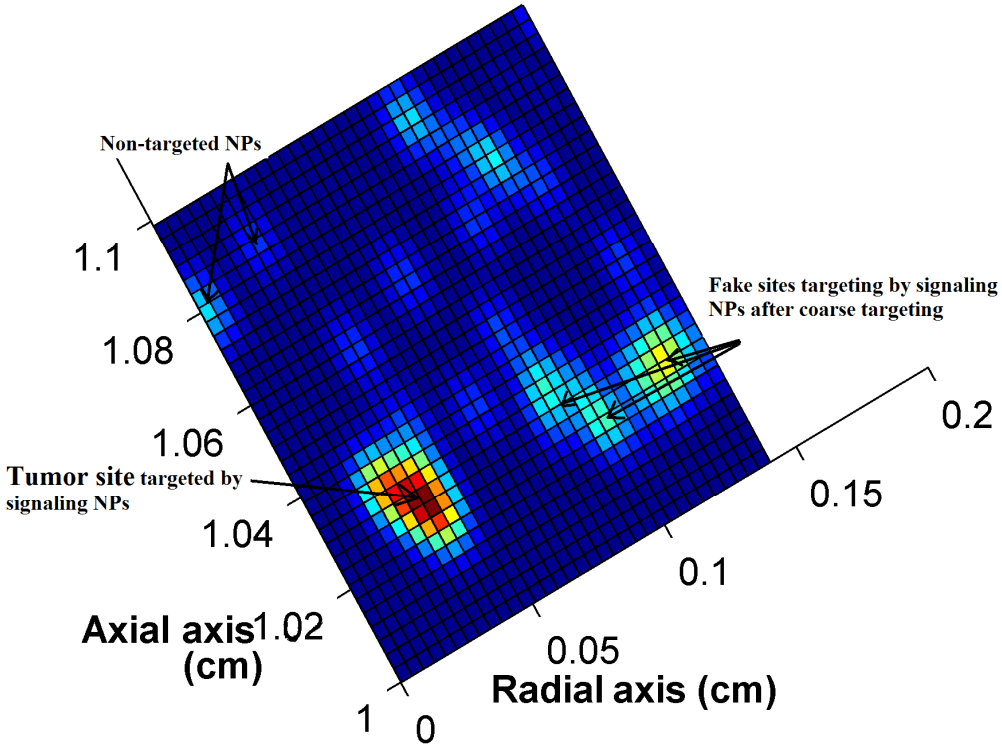

Figure 2. Schematic illustration of tumor and fake sites targeted by signaling NPs and non-targeted NPs (MC simulation results)

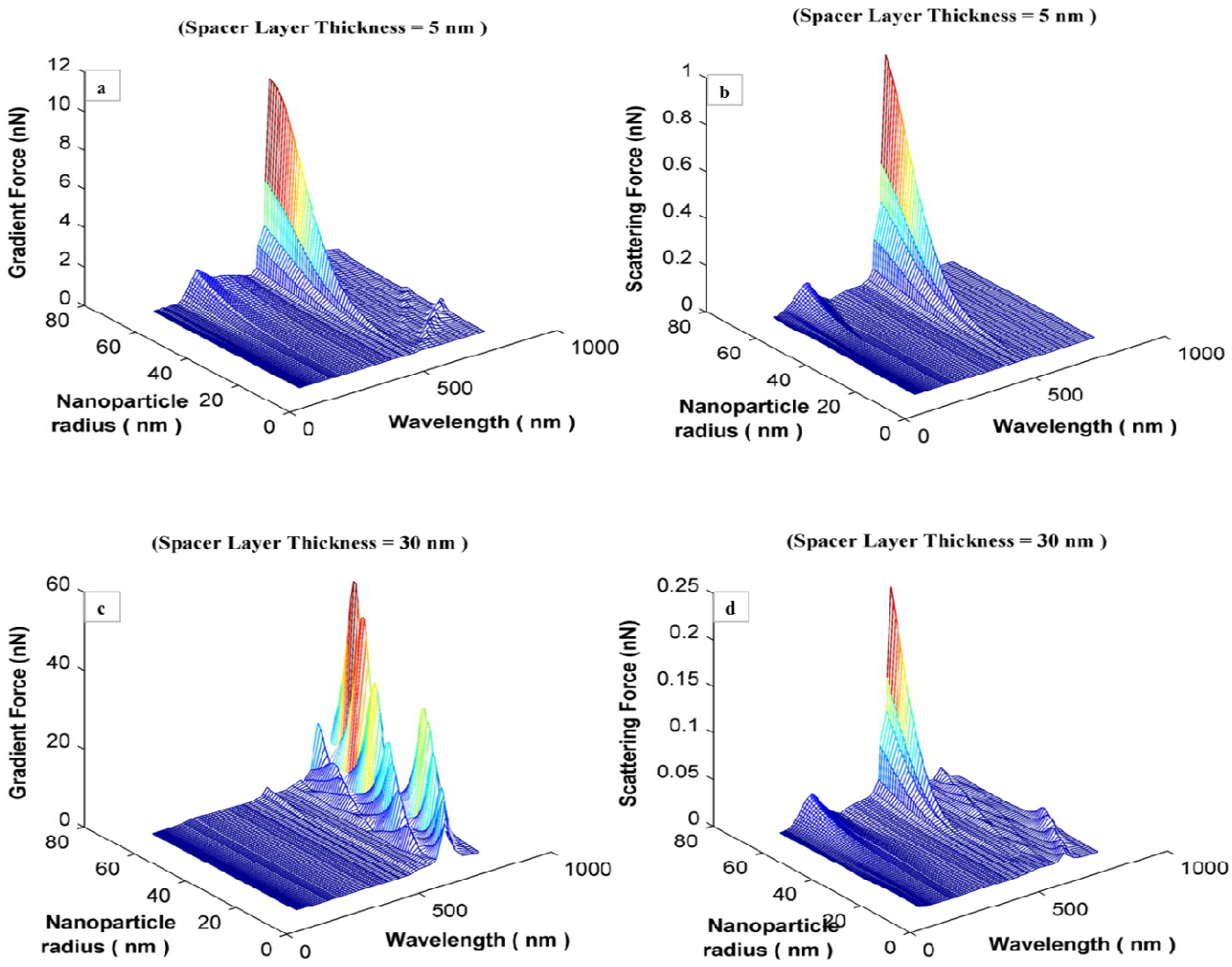

Figure 3. Au/SiO2/Au NPs engineering of gradient and scattering forces based on spacer layer thickness alteration;
a) Gradient force: spacer layer thickness 5 nm, b) Scattering force: spacer layer thickness 5 nm, c) Gradient force: spacer layer thickness 30 nm, d) scattering force: spacer layer thickness 30 nm

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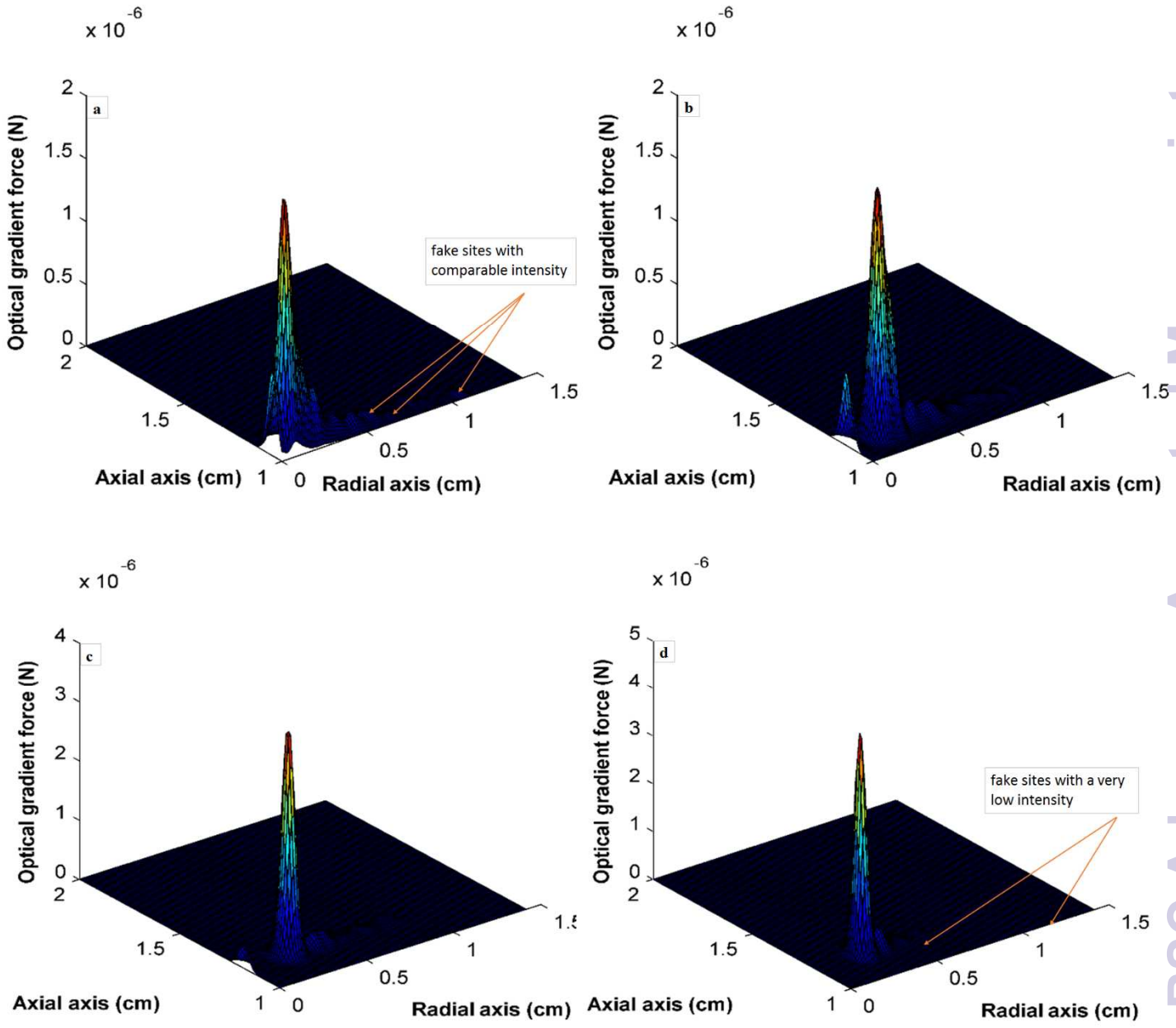

Figure 4. Tumor site targeting by signaling and receiving NPs; optical communication between NPs in the weak regime plasmonic; Gradient force a) record 1, b) record 2, c) record 3, d) record 4

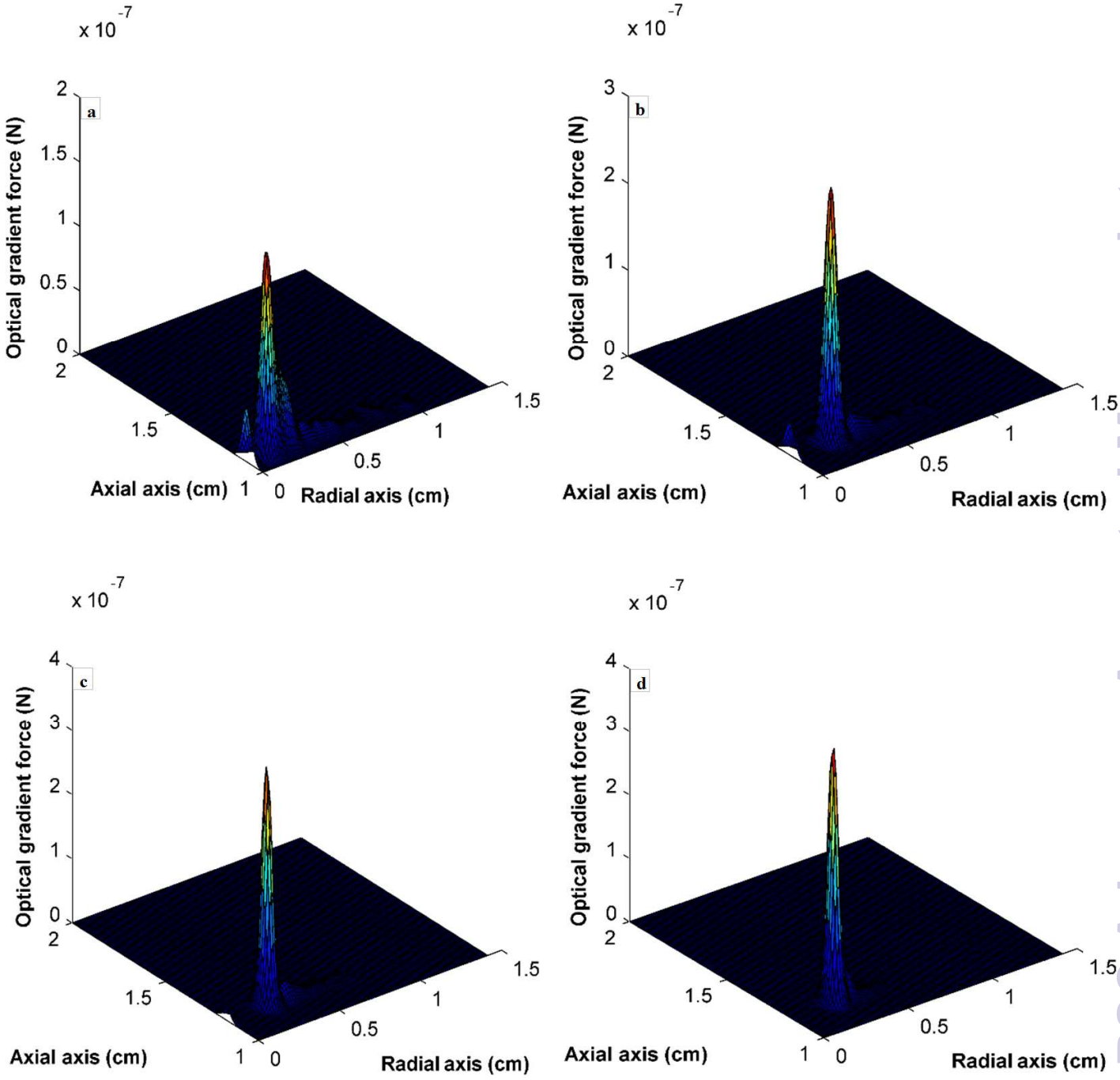

Figure 5. Tumor site targeting by signaling and receiving NPs; optical communication between NPs in the strong regime plasmonic; Gradient force a) record 1, b) record 2, c) record 3, d) record 4

At last it is shown that by using of the gradient force produced in the tumor site and applying of it on receiving NPs or fake located signaling NPs, some roam NPs will be attracted to the tumor site. This attraction chance is perused in the FA section and strictly affected by the medium absorption coefficient and NPs distance from the tumor site. The simulation results are

divided into two diverse sections including NPs with weak and strong plasmonic coupling modes, which are illustrated in Figure 4 (a-d) and Figure 5 (a-d) respectively. It is easily seen that in the weak coupling state (Figure 4); the amount of gradient force is so high, and therefore the tendencies of NPs toward the tumor site is done with high alacrity rather than strong coupling.

Conclusions

In this article, our results show that by engineering core/shell NPs, optical force can be used to enable communication between non-targetting (receiving) NPs and drug carrying NPs and attract them to the tumor site. To achieve effective use of the optical force, core shell NPs with weak plasmon coupling should be employed. Namely, for such NPs gradient force is higher than scattering force and in such way non-targetted NPs can approach tumor side with higher affinity and precision and in addition, larger tumor areas can be covered. Finally, use of smart targeting through communication between signaling and targetting NPs diminishes appearance of the fake targetting sites, which might have overall harmful effects.

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