

Engineering Plasmonic Nanoparticles for Nanomedical Applications

by

Emre Doruk ÖNAL

A Dissertation Submitted to the
Graduate School of Sciences and Engineering
in Partial Fulfillment of the Requirements for
the Degree of

Doctor of Philosophy

in

Physics



KOÇ ÜNİVERSİTESİ

September 20, 2020

**Engineering Plasmonic Nanoparticles for
Nanomaterial Applications**

Koç University

Graduate School of Sciences and Engineering

This is to certify that I have examined this copy of a doctoral dissertation by

Emre Doruk ÖNAL

and have found that it is complete and satisfactory in all respects, and
that any and all revisions required by the final
examining committee have been made.

Committee Members:

Assoc. Prof. Kaan GÜVEN (Advisor)

Prof. İrşadi AKSUN

Prof. Özgür MÜSTECAPLIOĞLU

Assoc. Prof. Emre TAŞGIN

Prof. Hakan Özgür ÖZER

Date: _____



Vires in Numeris...

ABSTRACT

Engineering Plasmonic Nanoparticles for Nanomedical Applications

Emre Doruk ÖNAL

**Doctor of Philosophy
in Physics**

September 20, 2020

Localized surface plasmon resonances grant plasmonic nanoparticles rich features that attract the attention of numerous researchers from wide ranging disciplines. Remotely triggered nanoscale heat production and strong optical contrast generation are the key attributes that render gold nanoparticles (AuNPs) widely popular especially in nanomedical applications such as photothermal cancer therapy and diagnosis. AuNPs are programmable via surface modifications to selectively target cancer cells facilitating the implementation of non-invasive cancer diagnosis and treatment at a cellular level. The variability of cancer types and the corresponding unpredictability in the structuring of the tumor tissue across individual patients represent one of the greatest challenges for the nonspecific approaches in the diagnosis and treatment of cancer. Personalized treatment strategies have been attracting special attention due to the highly irregular nature of cancer. The main motivation of this thesis is to address the increasing need for identifying the optimum AuNP morphology in the dynamic application landscape that is consistently transformed by technological developments and continuously varying demands of the changing implementation environment.

The scope of this thesis covers a progressively evolving approach based on numerical simulations to establish an understanding of the interaction between the morphological features and the resulting optical properties of a plasmonic nanoparticle. Plasmonic nanoparticles of various geometries are simulated via the Lumerical and MNPBEM package for MATLAB within the 500-3000 nm spectrum spanning the entire range of biological transparency windows available. The simulations generate data pertaining to the optical properties of plasmonic nanoparticles including absorption, scattering and extinction cross-sections per individual particle; transmission, reflection and absorption for periodic array of nanoparticles; electric field in the near vicinity of the nanoparticles; and the electric current density flowing through the nanoparticle under the localized surface plasmon resonance condition. The scope of nanoparticle geometries explored in this thesis ranges from cartesian particles such as nanobars to elementary NP geometries, i.e. spherical, disk-shaped, and cylindrical nanoparticles both as monolithic, standalone structures and as self-assembling complex nanoplatforms.

Engineering of large absorber silver nanobars resonant beyond 1500 nm, a wavelength range strongly dominated by scattering nanoparticles, is one of the key novelties of this thesis work. The contour design approach generates a significant change in the optical characteristics by enhancing absorption while simultaneously suppressing scattering in plasmonic nanoparticles. Another key contribution of this thesis work, building on top of the contour design approach, is the theoretical demonstration of the viability of implementing AuNP mediated cancer diagnosis and treatments in the lately discovered long wavelength transparency windows (1600-2400 nm) for the first time in literature. The design framework for engineering AuNPs constructed through a deductive analysis of an extensive dataset of fundamental AuNPs based on a data scientific perspective, represents the final key contribution of the thesis with the objective to provide guidance for future researchers working on implementations of AuNPs in a wide range of applications.

ÖZETÇE

Nanomedikal Uygulamalar Odaklı Plazmonik Nanoparçacık Mühendisliği

Emre Doruk ÖNAL

Fizik, Doktora

20 Eylül 2020

Lokalize yüzey plazmon rezonanslarının plazmonik parçacıklara kazandırdığı zengin özellikler birçok farklı disiplinden araştırmacının dikkatini çekmeyi başarmıştır. Uzaktan tetiklemeli nano boyutta ısı ve güçlü optik kontrast üretimi altın nanoparçacıkların (ANP) ısı ısı tanı ve tedavi gibi uygulamalarda nanotıp alanında öne çıkmasına neden olan temel nedenlerdir. ANP'ların yüzey modifikasyonları aracılığıyla kanser hücrelerini seçilimli hedeflemeye programlanması hücresel düzeyde girişimsel olmayan kanser tanı ve tedavi uygulamalarına olanak sağlamıştır. Kanser türleri arası değişkenlik ve buna bağlı hastadan hastaya farklılık gösteren tümör dokusu yapılanmasındaki öngörülemezlik geleneksel kanser tanı ve tedavi yaklaşımlarının karşılaştığı en önemli zorluklardan birini temsil eder. Kanser hayli düzensiz doğası kişiselleştirilmiş tedavi stratejilerini son yıllarda özellikle dikkat çekici kılmıştır. Bu tez çalışması teknolojik gelişmelere ve değişen uygulama koşullarının durmaksızın farklılaşan gerekliliklerine tutarlı olarak dönüşüm geçiren dinamik uygulama alanlarında kullanılmak üzere en uygun ANP biçimlerinin belirlenmesine olan artan ihtiyaca hitap etmek amacıyla hazırlanmıştır.

Tezin kapsamı plazmonik nanoparçacıkların biçimsel nitelikleri ve bunlar sonucunda ortaya çıkan optik özellikleri arası etkileşimi kavramaya yönelik sayısal simülasyonları temel alan dereceli gelişen bir yaklaşımı içine alır. Değişen geometrilerdeki plazmonik parçacıklar bütün bilinen biyolojik saydamlık pencerelerini kapsayan 500-3000 nm aralığındaki ışık spektrumunda Lumerical ve MATLAB için yazılmış MNPBEM paketi kullanılarak simüle edilmiştir. Yapılan simülasyonlarda tekil nanoparçacıkların soğurma, saçılım ve sönümleme kesitleri; periyodik dizilişli nanoparçacıkların iletim, yansıma ve soğurulması; nanoparçacık yakın çevresindeki elektrik alanı ve lokalize yüzey plazmon rezonansı kaynaklı nanoparçacıkta oluşan elektrik akım yoğunluğu başta olmak üzere plazmonik nanoparçacıkların optik nitelikleriyle ilintili veri üretilmiştir. Bu tezde irdelenen nanoparçacık geometrileri hem tek parçalı bağımsız hem de öztoplanımlı karmaşık yapıdaki küresel, disk-biçimli ve silindirik temel nanoparçacık geometrilerinden nanobar gibi kartezyen geometrilere uzanan bir yelpazeyi kapsamaktadır.

Çoğunlukla saçılgaç nanoparçacıkların hakim olduğu 1500 nm dalga boyunda çınlayan büyük boyutlu soğurucu gümüş nanoparçacıkların mühendisliği bu tez araştırmasının kilit yeniliklerinden birisidir. Çerçeve tasarım yaklaşımı plasmonik nanoparçacıkların saçılımlarını baskılarken soğurma özelliklerini artırmasıyla parçacıkların optik niteliklerinde kayda değer değişimler ortaya çıkarır. Bu tez çalışmasının esaslı katkılarından bir diğeri, çerçeve tasarım yaklaşımı üzerine kurgulanan ANP aracılı kanser tanı ve tedavi uygulamalarının son zamanlarda keşfedilen uzun dalgaboyu saydamlık pencerelerinde (1600-2400 nm) teorik olarak gerçekleştirilebilirliğinin literatürde ilk defa kanıtlanmasıdır. ANP mühendisliği odaklı tasarım iskeleti kapsamlı temel ANP veri setinin veri bilimi bakış açısıyla yapılan çıkarımsal analizi sonucu oluşturulmuştur. Tasarım iskeleti ANP'ların geniş uygulama alanlarına uyarlanması çalışılan bir çok araştırmacıya gelecekte yol göstermeyi hedefleyen bu araştırma tezinin son asli katkısını temsil eder.

ACKNOWLEDGMENTS

I am incredibly grateful for all the great people this thesis brought into my life and for all the wonderful people that brought me to writing this thesis. I will start with the people that sadly could not witness the completion of the path they started me on. Erdem Kurbanoglu without his foresightedness I would have never left Ankara to study at Koc University, may he rest in peace. Kürşat Necip Kaynak without whom I would have never set foot into the realm of physics. I treasure all the wonderful memories, yet I always wish we had time for more, I hope he finally finds peace.

One of the proudest decisions I have ever made was asking my advisor Kaan Güven if I could work with him in my PhD. I had the great fortune to spend almost 7 years working with one of the most gentlemanly, thoughtful, and inspiring persons I have ever known. I will always cherish every opportunity to bounce ideas with his great intellect that has been the source of creativity presented in this thesis.

I am thankful for the insightful comments of Özgür Müstecaplıoğlu and İrşadi Aksun that guided me in the tricky journey of writing this PhD thesis. I proudly bear the marks of the great researchers I worked with, Ersin Yurtsever who taught me the value in asking the right questions, Ali Serpengüzel who showed me that there is much more to the tables than the eye can see and many others, for the sake of brevity, remain unstated. I would also like to thank Ayşe abla and Emine hanım for the invaluable support behind the stage, I am forever indebted.

Arzu Angı, Buse Kaynak, Hüseyin Serhat Tetikol, Güneş Aydındoğan, Cem Yetişmişoğlu and the wonderful members of SCI 131, I am grateful for all the colors you have added to my life.

I would simply not be if it were not for the unquestioned support of my wonderful family at every step of the way. Şebnem, Nevzat and Sarp Önal, you are the unsung heroes of this thesis. My dear wife Ezgi, without you all this would have no meaning, you are the champion of the darkest hours of this journey, I treasure your constant support and love above anything.

TABLE OF CONTENTS

TABLE OF CONTENTS	ix
LIST OF FIGURES	xii
LIST OF TABLES	xv
ABBREVIATIONS	xvi
SYMBOLS	xviii
Chapter 1: INTRODUCTION	1
Chapter 2: PLASMONIC NANOPARTICLES IN BIOLOGICAL APPLICATIONS	5
2.1. Localized Surface Plasmon Resonance (LSPR)	5
2.2. Biological Transparency Windows (BTWs)	6
2.3. Plasmonic Nanoparticles (NPs) in Cancer Diagnosis and Therapy	7
2.3.1. New Approaches to Cancer: Nanomedicine	7
2.3.2. Plasmonic Material of Choice: Gold	8
2.4. Functionalities of Gold Nanoparticles (AuNPs)	8
2.4.1. “Die Zauberkugeln” (The Magic Bullets) - Targeted Payload Delivery	8
2.4.2. Locating the Enemy: Imaging & Diagnostics	9
2.4.3. Monitoring the Administration of Treatment	9
2.4.4. Thermal Dosimetry: Real-Time Temperature Monitoring	10
2.4.5. Light-Triggered Hyperthermia: Heating the Cancer Cells from within.....	10
2.5. Engineering AuNPs: Tailoring Properties to Fit the Application	11
2.5.1. Tuning the Operational Wavelength to the BTW: Resonance Wavelength....	11
2.5.2. Pharmacokinetics & Physicochemical Properties: NP Morphology.....	12

2.5.3. Quantifying Absorption & Scattering in AuNPs.....	12
2.5.4. AuNP Multi-modality: Combining Therapy & Diagnostics – Theranostics...	13
2.5.5. Quantifying Toxicity & New Performance Metrics for AuNPs.....	13
2.5.6. Cellular Uptake: Morphology and New Approaches in Fabrication	14
Chapter 3: CONTOUR DESIGN: ABSORPTION ENHANCEMENT IN NAs	16
3.1. Introduction: Absorption & Scattering in Plasmonic NAs	17
3.2. Contour Design in Dipole NA: Tuning LSPR in a Multitude of Ways	20
3.3. Periodic Contour NA Arrays	27
3.4. Mechanics of Scattering Suppression & Absorption Enhancement	29
3.5. Refractive Index of the Hollow: Further Scattering Suppression.....	31
3.6. Scattering Suppression in Self-Assembling NAs	33
3.7. Conclusion: Features of the Contour Design Approach.....	35
Chapter 4: DEEP TISSUE CANCER THERAPEUTICS IN NIR-III & -IV	36
4.1. Introduction: Fighting Cancer with Heat Generated by Gold Nanoparticles	37
4.2. Constructing Absorber Gold Nanobars in NIR-III & -IV.....	39
4.3. Self-Assembling NPs: Nano-Disk Chains (NDCs) & Nano-Ring Chains (NRCs)	43
4.4. Peripheral Heating & Selectivity Analysis of BTWs.....	45
4.5. Fabrication and Potential Use Cases for Contour AuNPs.....	47
4.6. Conclusion: Facilitating Deep Tissue PTT with Smart NP Designs.....	48
Chapter 5: NP DESIGN FRAMEWORK: A DATA SCIENTIFIC APPROACH	49
5.1. Introduction: Constructing a Design Framework for Engineering AuNPs	50
5.2. Deconstructing the Framework: NP Geometries & Design Parameters	50
5.2.1. Elementary Geometries for AuNPs & Degeneracy of the LSPR Modes.....	51
5.2.2. Taxonomy of NP Properties: Feature vs. Target Variables	52

5.3. Expounding the Dataset: Spanning the Design Space	53
5.3.1. Exploring the Boundaries of the Feature Space	54
5.3.2. Characteristics of the Target Space	55
5.4. A Dual-Perspective Design Approach: Fabrication vs. Clinical Applications.....	57
5.4.1. Fabricational Perspective: Geometry-Centric Optimization	58
5.4.2. Operational Perspective: Wavelength-Centric Optimization.....	61
5.5. Design Parameter Sensitivity Analysis: Tuning for Multiple Functionalities.....	64
5.5.1. Correlation Magnitude: Free vs. Tuning Feature Variables	66
5.5.2. Direction of Correlation & The Law of Diminishing Marginal Returns.....	68
5.6. The Final Piece of the Framework & Demonstration on Hypothetical Scenarios	70
5.6.1. Scenario 1: Transforming AuNDs to Longer Operational Wavelengths.....	72
5.6.2. Scenario 2: Most Suitable Morphology at NIR-IV	75
Chapter 6: CONCLUSION	77
BIBLIOGRAPHY	80
APPENDIX A: DUAL-PERSPECTIVE DESIGN: SUPPLEMENT	115
A.1 Geometry-Centric Comparison of Solid vs. Hollow AuNPs.....	115
A.2 Wavelength-Centric Comparison of Solid vs. Hollow AuNPs	116
APPENDIX B: BIVARIATE ANALYSIS OF ELEMENTARY AuNPs	117
B.1 Gold Nanospheres & NanoSphericalShells: AuNSs & AuNSSs	117
B.2 Gold Nanorings: AuNRs	118
B.3 Gold Nanotubes: AuNTs	119

LIST OF FIGURES

Figure 3.1: The effects of contour design in scattering suppression & absorption enhancement of plasmonic dipole NAs	19
Figure 3.2: A schematic view of the contour dipole antenna under linearly polarized plane wave illumination with outer NA ($L_x \times L_y \times L_z$) and hollow ($W_x \times W_y$) size parameters.	20
Figure 3.3: (a-b) A schematic view of the plain dipole and the contour dipole antenna. The scattering, absorption, and extinction cross section of the dipole (c) and the contour dipole nanoantennas (d-f). The outer dimensions of the nanoantennas are the same: $L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$. The contour size $W_x \times W_y$ changes by (d) $240 \times 40 \text{ nm}$, (e) $300 \times 60 \text{ nm}$ (f) $360 \times 80 \text{ nm}$, as illustrated by the insets.	22
Figure 3.4: Effect of changing dipole NA length- L_x (first column) and width- L_y (second column) on the resonance wavelength (a, b), σ_{Scat} , σ_{Abs} & σ_{Ext} (c, d), and the relative scattering efficiency ($\text{RSE} = \sigma_{\text{Scat}}/\sigma_{\text{Ext}}$). Insets illustrate alterations in NA length and width. 23	
Figure 3.5: (a) RSE of a dipole NA as a function of its length (L_x) and width (L_y). (b) The expanded RSE of a contour dipole NA which is based on the parent dipole with dimensions: $L_x \times L_y = 400 \times 100 \text{ nm}$ (marked by the black rectangular region in (a)). $\text{RSE} > (<) 0.5$ indicates predominantly scatterer (absorber) NAs.	25
Figure 3.6: The scattering (a), absorption (c) and extinction (e) cross sections of the dipole NA as a function of its length (L_x) and width (L_y). The black rectangles indicate the location of the parent dipole ($L_x \times L_y = 400 \times 100 \text{ nm}$) which is used to construct the contour dipole NA. The scattering (b), absorption (d) and (f) extinction cross sections of the contour dipole antenna as a function of hollow length (W_x) and width (W_y). The dashed arrow in panels (a-f) indicate the direction for scattering suppression. (g) The scattering, absorption and extinction cross sections of the contour dipole NA as a function of contour width at fixed contour length $W_x = 300 \text{ nm}$	26
Figure 3.7: (a) The schematic of the periodic contour dipole NA array. The transmission (b), reflection (c) and absorption (d) of the NA array as a function of the hollow length (W_x) and width (W_y). (e) Demonstration of the reflection/absorption crossover by widening the hollow at a fixed length $W_x = 300 \text{ nm}$. Periodicity in both directions ($P_x = P_y = 800 \text{ nm}$) and parent dipole NA dimensions ($L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$) are fixed.	28
Figure 3.8: Comparison of the (a, b) real part of the x-component of the electric field, (c, d) electric field magnitude, (e, f) the current density for the dipole (first column) and the contour	

dipole (second column) NA. The NAs have the same outer dimensions ($L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$) and the contour dipole has a hollow region ($W_x \times W_y = 240 \times 80 \text{ nm}$). The arrows in (a, b) indicate the induced electric dipole moments. (g) The total current integrated through the cross section of the dipole nanoantenna (blue curve) and the contour dipole NA (red curve). All figures are plotted at the respective resonance of the NAs. 29

Figure 3.9: The effect of a lossless dielectric medium with refractive index (n_{Hollow}), filling the hollow region of the contour dipole on the scattering, absorption and extinction cross section spectra: (a) $n_{\text{Hollow}} = 1$ (reference), (b) $n_{\text{Hollow}} = 1.8$, (c) $n_{\text{Hollow}} = 2.5$, as illustrated by the insets. The contour dipole has the same design as given in Figure 3.8. 31

Figure 3.10: (a) The effect of the refractive index of the medium filling the hollow region on (a) the extinction, absorption and scattering cross sections, (b) the relative scattering efficiency and (c) the resonance wavelength of the contour dipole antenna. Inset illustrates the contour NA geometry and the hollow refractive index (n_{Hollow}). The antenna dimensions are as given in Figure 3.8. 33

Figure 3.11: The extinction, scattering and absorption spectra of (a) the dipole antenna ($L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$) (b) an assembly of four identical nanodisks ($R_{\text{disk}} \times h_{\text{disk}} = 100 \times 30 \text{ nm}$) (c) an assembly of four identical nanorings ($R_{\text{out}} \times R_{\text{in}} \times h_{\text{disk}} = 100 \times 70 \times 30 \text{ nm}$). The nanodisk chain (middle inset) can be considered as a dipole nanoantenna (top inset) contoured from the outside and the nanoring chain (bottom inset) can be considered as a dipole NA contoured from both the outside and the inside. 34

Figure 4.1: Illustrating PTT in NIR-III & -IV 37

Figure 4.2: Schematic of (a) solid (NB), (b) 50% contour (50% CNB), and (c) 70% contour nanobars (70% CNB) and (d–f) their respective absorption efficiency (ϕ_{Abs}) as a function of the nanobar dimensions. Black lines border respectively the regions where the nanobar is resonant in NIR-III or NIR-IV. 40

Figure 4.3: Benchmarking the solid nanobar (NB, triangle) and contour nanobars (CNB, star, circle) in terms of absorption efficiency (ϕ_{Abs}), nanobar length, and absorption cross section (σ_{Abs}) in NIR-III and NIR-IV. The distribution of data points due to a large number of solid and contour nanobars provides visual cues on the merits of contour design. Compared to the nanobars, most of the contour nanobars provide better ϕ_{Abs} (a) and smaller size (b) and accumulate more along the maximum σ_{Abs} trend (c). Note also that the maximum σ_{Abs} trend shows a universal behavior, independent of the nanobar design. 41

Figure 4.4: Comparison of the optical cross sections (absorption and scattering) of solid nanobar (NB), contour nanobar (CNB), nanodisk chain (NDC), nanoring chain (NRC), designed for NIR-III and NIR-IV, respectively. The change in the ordering of the cross section curves from part a to part b and from part e to part f indicates that the contour design transforms the dominant response of the solid nanobar from scatterer to absorber in both NIR III and IV. For the nanoring chains (d, h), scattering is almost completely suppressed, rendering them as highly efficient absorber nanoparticles. 43

Figure 5.1: Schematic for Categorizing Plasmonic NP Properties 53

Figure 5.2: Primary and Derived Target Space of AuNP Dataset	56
Figure 5.3: AuNP Optimization Pathways for the Manufacturer & the Operators	58
Figure 5.4: Geometry Centric Investigation of the AuNP Dataset	60
Figure 5.5: Wavelength Centric Investigation of the AuNP Dataset.....	62
Figure 5.6: Correlation Matrices for Elementary AuNPs Properties.....	65
Figure 5.7: Bivariate Analysis of AuND Properties	73
Figure 5.8: Bivariate Analysis of AuNC Properties	75
Figure A.1 Geometry Centric Investigation of the AuNP Dataset: Solid vs. Hollow Elementary Geometries.....	115
Figure A.2 Wavelength Centric Investigation of the AuNP Dataset: Solid vs. Hollow Elementary Geometries.....	116
Figure B.1 Bivariate Analysis of AuNSs & AuNSSs Properties with respect to FR	117
Figure B.2 Bivariate Analysis of AuNRs Properties with respect to AR	118
Figure B.3 Bivariate Analysis of AuNRs Properties with respect to FR.....	118
Figure B.4 Bivariate Analysis of AuNTs Properties with respect to AR	119
Figure B.5 Bivariate Analysis of AuNTs Properties with respect to FR	119

LIST OF TABLES

Table 4.1: Comparison of Total Attenuation Length (μm) of Various Tissues in the BTWs .	38
Table 4.2: Comparison of the Absorption Cross Section (σ_{Abs}) and Heating Efficiency per Mass (HEPM) in All BTWs of Plasmonic Nanoparticles (RIS: rod-in-shell, NB: nanobar, CNB: contour NB, NDC: nanodisk chains, NRC: nanoring chains)	45
Table 4.3: Peripheral Heating and Selectivity: Comparing the Absorption Coefficients of Rat Brain Tissue with and without NPs	46
Table 5.1: Feature Space of Elementary AuNP	55
Table 5.2: Correlation Magnitude for Elementary AuNPs: Identification of Tuning & Free Feature Variables	67
Table 5.3: Correlation Direction for Elementary AuNPs	69
Table 5.4: A synopsis of bivariate analysis of primary features and target variables	71

ABBREVIATIONS

LSPR	Localized Surface Plasmon Resonance
SPP	Surface Plasmon Polariton
NIR	Near Infrared (biological transparency wavelength range)
Au	Gold
Ag	Silver
NP	Nanoparticle
NA	Nanoantenna
NC	Nanocylinder
NT	Nanotube
ND	Nanodisk
NR	Nanoring
NS	Nanosphere
NSS	Nanosphericalshell
NB	Nanobar
CNB	Contour Nanobar
NDC	Nanodisk Chain
NRC	Nanoring Chain
RIS	Rod-in-Shell
PTT	Photothermal Therapy

PPTT	Plasmonic Photothermal Therapy
PDT	Photodynamic Therapy
PAI	Photoacoustic Imaging
AR	Aspect Ratio
FR	Filling Ratio
EPR	Enhanced Permeability and Retention
HEPM	Heating Efficiency per Mass
SEPM	Scattering Efficiency per Mass
MNPBEM	Metallic Nanoparticle Boundary Element Method
LSPR	Longitudinal Surface Plasmon Resonance
TSPR	Transverse Surface Plasmon Resonance
SC	Selectivity Contrast
BTW	Biological Transparency Window
PCE	Photothermal Conversion Efficiency
OCA	Optical Contrast Agent
PTA	Photothermal Transduction Agent
MPE	Maximum Permissible Exposure
PS	Photosensitizer
PCE	Photothermal Conversion Efficiency

SYMBOLS

σ_{Abs}	Optical Absorption Cross-Section
σ_{Scat}	Optical Scattering Cross-Section
σ_{Ext}	Optical Extinction Cross-Section
λ_{Res}	Resonance/Operational Wavelength
λ_{Eff}	Effective Resonance Wavelength
I	Incident Light Intensity
P	Absorbed/Scattered Power
ϕ_{Abs}	Absorption Efficiency Coefficient
ϕ_{Scat}	Scattering Efficiency Coefficient
μ_{brain}	Absorption Coefficient of Human Brain Cells
μ_{NP}	Absorption Coefficient of NP-doped Brain Cells

Chapter 1:

INTRODUCTION

Interaction of light with small particles fascinated the humankind for centuries dating back to the Roman artisans in circa 200 AD whom accidentally mixed ground gold and silver particles/dust to molten glass. The resulting mysterious material today known as dichroic glass produced artistic objects that showed different colors when looked at and looked through. Lycurgus cup is one of the earliest dating examples known in history and it managed to preserve its mysterious for centuries defying the efforts of many greatest scientists [1]–[3]. Until Michael Faraday finally realized that the color transformations were caused by the colloidal gold nanoparticles. He published his findings in the first scientific paper on gold nanoparticles, shedding some light on how small gold particles highly dependently on their size and shape can reflect, absorb and refract light of varying wavelengths [4], [5]. Even today understanding the mechanics of light-matter interactions that make the sky blue [6]–[9] and the clouds white [10] provide great inspiration to young students of physics like myself to pursue their studies in the field of nanophotonics.

Nanophotonics has its roots in optics and focuses on the interaction of light with matter at near or subwavelength scale. The field has grown significantly over the years attracting researchers from a wide range of backgrounds including physics, chemistry, biology and medicine [11]. Metallic NPs due their strong scattering properties were one of the building blocks of the nanophotonics research. These new objects were initially used as scaled down RF antennas to emit, receive and control light at nanoscale and termed nanoantennas [12]. Earlier works in the field as well as the Chapter 3 of this thesis work are heavily influenced by optics ideology which is evident in the nomenclature including the naming of the NP as dipole nanoantennas. Although nanoantennas are rather similar in functionality to their RF counterparts, operationally exhibit significant differences due to the finite conductivity of metals and the consequent plasmonic effects at or near optical wavelengths [13]. These fundamental

differences generate an abundance of research opportunities and potential applications that eventually led to the formation of a spinoff field: Nanoplasmonics [14], [15].

One of the fundamental shortcomings of nanoplasmonics is the inherently lossy nature of metallic nanoantennas at the optical spectrum [16], [17]. This phenomenon which has been considered by the nano-optics community as a hindrance for optical applications that needs to be minimized turned out to be exploitable and highly advantageous for producing heat at a nanoscale [18], [19]. The changing perspective attracted significant interest especially for potential applications in cancer diagnosis and therapy initiating the dawn of a new field: Thermoplasmonics [20]. The use of plasmonic NPs as a targeted and non-invasive cancer therapy tool was first proposed in 2003 [21], [22] and the term plasmonic photothermal therapy (PPTT) is introduced to the scientific literature. PPTT or as more commonly referred to today as photothermal therapy (PTT) is the central focus of this thesis work. At its core PTT is based on selective internalization of gold NPs (AuNPs) by the targeted cancer cells that are triggered by external light source to generate heat inducing high temperatures inside the tumor cells to harm and eventually destroy the cancerous tissue. Chapter 2 serves as an extensive introduction to PTT and other biological applications utilizing plasmonic NPs regarding the vast diversity of backgrounds of the potential readers.

The simplicity of the idea behind PTT attracted many researchers from various backgrounds to the field which lead to a rapid growth, especially in the early years. The expansion phase of the research topic is accelerated by new discoveries such as biological transparency windows where human tissue is considerably transparent and suitable for conducting PTT as well as production techniques that enables the fabrication and utilization of wide range of NPs in different geometries and sizes. Such advances raised awareness and curiosity for engineering and designing plasmonic NPs optimized for the targeted application. Chapter 2 aims to introduce the reader to designing AuNPs for expanding PTT and other nanomedical applications from the perspective of a computational physicist.

The interdisciplinary nature of the subject presents 4 key perspectives from the 4 contributing disciplines targeting different challenges: design, fabrication, adaptation, and implementation. Chemistry is the principal discipline focusing on the challenge of fabrication and functionalization of plasmonic NPs. A top-down approach based on lithographic techniques dominated the field in the early days which is reflected in our early studies (Chapter 3). Later,

advancements in chemical methods introduced bottom-up fabrication techniques that can produce wide range of AuNP morphologies with strong control over the NP dimensions including most of the AuNP designs proposed in Chapter 3, Chapter 4, and Chapter 5. I believe solution-based techniques will keep evolving and further expand the space of fabricatable AuNPs with increasing complexity and diminishing cost of production paving the way for a personalized cancer treatment utilizing AuNPs tailored specifically to the needs of the patient.

Adaptation of the NPs to the biological medium is another critical challenge in the progression of PTT. Biology as a discipline concentrates on the interaction between the synthesized AuNPs and living cells, focusing on identifying and overcoming challenges of working in a biological medium, i.e. the constraints on AuNP design such as selective internalization mechanisms of the NPs by the targeted cells, and the critical NP mass that induce cytotoxicity.

Medicine is the discipline that is responsible for implementation of PTT at the clinical stage and studies the interaction of plasmonic NPs with the various systems and organs of the human body, focusing on challenges such as removal of NPs after completing the execution of PTT with minimal retention.

Identifying the best performing NP tailored for a specific application under the constraints of fabrication processes together with medical and biological conditions, i.e. designing NPs, is the challenge of physics. The main purpose of this thesis is to establish a framework for engineering AuNPs that provides guidance for future researchers from all contributing disciplines in determining the optimum NP suited for their goal in a practical manner.

Chapter 3 demonstrates one of our first approaches to engineer the optical properties and expand the limits of AuNPs by theoretically showing the possibility of constructing NPs that operate at longer wavelengths while preserving the absorber nature and suppressing scattering. The work in this chapter has been published in the following manuscript:

E. D. Onal and K. Guven, "Scattering Suppression and Absorption Enhancement in Contour Nanoantennas," *ArXiv e-prints*, p. 1511.01312, 2015.

Chapter 4 expands on this idea and shows the viability of PTT in NIR-III & -IV for the first time in literature through an extensive comparative analysis, applying the constraints of the biological tissue and addressing the possible cellular internalization problems with self-

assembling designs. Some of the work in this chapter has been published in the following manuscript:

E. D. Onal and K. Guven, “Plasmonic photothermal therapy in third and fourth biological windows,” *J. Phys. Chem. C*, vol. 121, no. 1, pp. 684–690, 2017, doi: 10.1021/acs.jpcc.6b10060.

Chapter 5 is a comprehensive and methodical analysis of NP design culminating on the insights of the previous chapters. The most significant contribution is the introduction of a deductive approach to the analysis of AuNP properties utilizing data scientific methods. Unlike the inductive approach which aims to create models based on our physical intuition about the motion of oscillating electrons, the deductive approach aims to create a model based on a large dataset of AuNP simulations free from our intuitions and biases. Some of the findings of this approach are quite intriguing and reveal unexpected pathways in designing efficient AuNPs for target applications. Moreover, these findings pose challenging questions for future researchers in discovering the underlying physical phenomena.

This thesis is also a testament to the evolution of the nanoplasmonics as a field and you will witness the change in terminology as you read through the chapters that is in line with the field moving away from the influence of optics to become the interdisciplinary topic it is today.

Chapter 2:

PLASMONIC NANOPARTICLES IN BIOLOGICAL APPLICATIONS

The aim of this chapter is to provide the necessary understanding of the interdisciplinary concepts that form the basis of this thesis work covering topics from physics, chemistry, biology, and medicine.

2.1. Localized Surface Plasmon Resonance (LSPR)

Plasmons refer to the quantization of the collective oscillations of an electron gas (plasma), in practical terms the conduction electrons of metals collectively oscillate in response to an external electromagnetic field [23], [24]. These oscillations when confined to a surface (metal-dielectric interface) are called surface plasmons. Surface plasmons with their high sensitivity to the boundary conditions display unique characteristics. Confining surface plasmons further to the surface of metallic NPs leads to localized surface plasmon resonances (LSPR) [25]. The electric field of an incident radiation causes the conduction electrons in the metallic NP to shift from the positive lattice centers to cancel the electric field inside the metal. Coulomb interaction between the negatively charged electron and the positively charged nuclei lattice induces a restoring force that results in the conduction electrons collectively oscillate back and forth on the metallic NP surface until the energy is dissipated via Joule heating to heat or radiation to reemission of light corresponding to the absorption and scattering properties of plasmonic NPs [26]. In earlier works influenced by engineering and optics, including Chapter 3, these collective electron oscillations are also referred to as the dipole plasmon resonance of the particle differentiating the phenomenon from the bulk and surface plasmon excitations in reference to the radiation patterns of elementary electric dipole [27].

Due to the high surface to volume ratios, metallic NPs exhibit significantly different electromagnetic and chemical properties compared to the bulk of the metal [28], [29]. In

addition, concentrating light to scales smaller than the wavelength leads to interesting phenomena for subwavelength light manipulation both at the near-field and the far-field. Due to the resulting near-field enhancements, nanoscale light induced heat generation and rich spectral responses plasmonic NPs are employed in wide variety of applications from sensing to cancer therapy and diagnosis [30].

The properties of plasmonic NPs and the spectral location of LSPR depend on internal factors such as the material composition, geometry and size of the NP as well as on external factors such as the refractive index of the environment and the influence of other NPs [31]–[35]. Nobel metals such as gold and silver have been the most widely used materials in plasmonic NPs due to their good plasmonic performances, high chemical stability and the advanced chemical methods in fabricating NPs in various morphologies with precise control over their dimensions [36], [37]. Further details on the properties of plasmonic NPs will be provided in the later sections of this chapter.

2.2. Biological Transparency Windows (BTWs)

Tissue transparency is one of the key challenges in utilizing AuNPs in nanomedical applications [38], [39]. The incident radiation that induces LSPR attenuates due to the presence of absorbing and scattering elements of the biological medium, limiting the effectiveness of imaging and therapeutic applications [40]. Near-infrared (NIR) spectrum offers light penetration in the order of millimeters within specific wavelength bands where human body is most transparent. These wavelength bands are referred to as optical or biological transparency windows (BTW) allowing photon penetration deep in to the tissue [41]. The first BTW (NIR-I) in the wavelength band of 700–950 nm was discovered in 2001 [42]. The photodetectors, light sources and other optical elements working in NIR-I has been widely available. The recent developments in optical instruments such as InGaAs sensors facilitated the discovery of new BTWs at longer wavelengths: NIR-II (1000–1350 nm) in 2009, NIR-III (1600–1870 nm) in 2014 and NIR-IV (2100–2300 nm) in 2016 [43]–[46]. The longer wavelength photons carrying less energy have great potential for superior tissue penetration depth and enhanced maximum permissible exposure (MPE). Nevertheless, the latest BTWs remain relatively underexplored with the exception of NIR-II attracting some attention for deep tissue therapeutic and imaging applications [47]–[51]. Chapter 4 presents one of the pioneering works in exploring the

potentials of AuNPs for nanomedical applications in NIR-III & -IV by engineering NPs that overcomes the optical limitations and addresses the imposed biological constraints.

2.3. Plasmonic Nanoparticles (NPs) in Cancer Diagnosis and Therapy

“There’s plenty of room at the bottom” - Richard Feynman, Caltech 1959 [52]

2.3.1. New Approaches to Cancer: Nanomedicine

Cancer is globally a major cause of death with roughly 40% of people being diagnosed with it at some point in their lives [53]. The growing number of cancer patients and cancer related deaths are the driving forces for developing better and more effective diagnosis and therapy techniques beyond the conventional strategies such as chemotherapy, radiotherapy and surgery [54], [55]. The conventional approaches remain limited in their efficiency due to the heterogeneous nature of cancer and by their unintended impact on healthy tissue and the immune system of the patient [56]. Consequently, recent cancer research efforts focus on developing innovative approaches as standalone or complementary therapeutic strategies by increasing precision while lowering side effects. Photothermal therapy (PTT) is one of the most promising candidates among the next generation cancer therapeutics together with immunotherapy, photodynamic therapy (PDT), gene therapy [57]–[63].

PDT and PTT are non-invasive, selective phototherapies that utilize photosensitizers (PSs) accumulated in cancer tissue. The targeted PSs are remotely activated by external irradiation at specific wavelengths to induce selective damage via reactive oxygen species for PDT or via heat for PTT while minimizing injury to healthy cells [64]–[69]. PDT has a significantly limited operational wavelength window compared to PTT as PS molecules that generate ROS are activated by higher energy photons with wavelengths in NIR-I (650–900 nm). NIR-I is the most limited of all known BTWs both in terms of tissue penetration and MPE [70], [71]. Similarly, PTT utilizing molecular PSs suffer from the same limitations that apply to PDT. Plasmonic NPs have gained popularity as the preferred photothermal transduction agents (PTAs) for PTT as a result of their ability to overcome many of the limitations faced by molecular PSs. LSPR induced in noble metal NPs such as gold and silver greatly enhance the radiative properties causing the absorption and scattering cross-section of such NPs orders of magnitude stronger than their molecular (optical dyes) counterparts [72]–[74].

2.3.2. Plasmonic Material of Choice: Gold

Gold has received the greatest attention in cancer nano-medicine as a material of choice for plasmonic NPs due to strong biocompatibility coupled with low systemic and cellular toxicity [75], [76]. From the clinical point of view gold has a well-established track record and a long history in the medical sciences with considerable success in treating rheumatoid arthritis and lately cancer [77], [78]. Gold NPs (AuNPs) are also widely studied in chemistry and has a well-established literature on methods for fabrication of wide variety of shapes and sizes as well as extensive surface modification techniques [79].

2.4. Functionalities of Gold Nanoparticles (AuNPs)

2.4.1. “Die Zauberkekeln” (The Magic Bullets) - Targeted Payload Delivery

AuNPs present excellent versatility for phototherapeutic applications. One key area of flexibility is the functionalization of the AuNPs to offer multiple modalities on a single platform complementing the primary function of light induced heat generation. Payload delivery is one of the most utilized extended functionalities of AuNPs enabling targeted delivery of drugs, genes and PSs to cancerous cells and preventing accumulation in the healthy tissue [80]–[86]. The concept of targeted drug delivery was first introduced by Paul Ehrlich in 1954 inspired by his visit to Karl Maria von Weber's opera “Der Freischütz”. He named the delivery system “Zauberkekeln” (Magic Bullets) in reference to the character “Freikugeln”. As a medical doctor in 1950s his primary candidate for the magic bullets were antibodies but the targeted drug delivery concept took off decades later with the advances in nanoparticles [87]–[90].

Biocompatibility is a critical feature of AuNPs for targeted delivery across biological barriers by shielding the payload from the immune system and giving a long blood circulation time. The prolonged circulation increases the odds of passive accumulation in cancerous tissue and improves the specificity to tumor cells while minimizing unwarranted side-effects [91]–[96]. The large surface to volume ratio of the AuNPs supports rich chemistry for surface modification offering active targeting of NPs to accumulate in specific tumor tissue [97], [98]. Even though active targeting enhances the NP accumulation in cancer cells, the leaky vasculature formed by the rapidly growing tumor allows passive diffusion and accumulation

of AuNPs in the cancer tissue caused by enhanced permeability and retention (EPR) [99], [100].

2.4.2. Locating the Enemy: Imaging & Diagnostics

Imaging and cancer cell diagnostics are another functionality for AuNPs that has attracted significant attention in the scientific community [73], [101], [110], [111], [102]–[109]. AuNPs provide imaging modality through two distinct mechanisms: optical imaging and photoacoustic imaging (PAI). Optical imaging applications of the cancer cells are built on the scattering properties of the AuNP acting as optical contrast agents (OCAs). OCAs are a powerful diagnostic tool enabling real-time monitoring of the tumor tissue for evaluation of treatment administrations such drug or gene delivery, PTT, and PDT [112]–[114]. Optical imaging strategies suffer from the strong optical scattering of the biological tissue and offer limited penetration depth whereas ultrasonic scattering of the biological tissue is much weaker can yield deeper tissue imaging. PAI is built upon this premise and utilizes AuNPs as PTAs to generate acoustic waves. Photo triggered heat generated by the AuNP causes thermo-elastic expansion on the surrounding medium and produces ultrasonic waves which after propagating through the tissue received by the ultrasonic transducer to reconstruct an image of optical absorption [115]–[120].

Detection of cancer at an early stage has a major impact on the wellbeing of the patient and alleviates some of the social and economic burden on the society. As a non-invasive diagnostic tool minimizing surrounding tissue damage and systemic toxicity, AuNPs display great potential for cancer diagnostics as an alternative or complementary tool to the conventional cancer treatment schemes. In addition to being standalone diagnostic tools, the imaging modalities of AuNPs also enhance their utilization in therapeutic applications such as PTT. The diagnostic-therapeutic multifunctionality enables real-time monitoring of the registered therapy and the effectiveness on the tumor tissue.

2.4.3. Monitoring the Administration of Treatment

The diagnostic functionalities of AuNPs further extends with additional surface modifications including the attachment of luminescent temperature-sensing probes to transmit high resolution, real-time temperature data from the tumor microenvironment during the PTT application [121]–[128]. Continuous temperature feedback data coming from the tumor

environment is extremely valuable in controlling hyperthermia to maximize damage to the cancer cells while keeping the temperature induced damage to the healthy tissue at a minimum [66], [67], [83], [129], [130]. The overall effectiveness of PTT improves significantly by the advancement of complementary strategies such as adjusting laser dosage and guidance via imaging functionality of AuNPs. Due to the heterogenous nature of cancer tissue, accumulation of the AuNPs in the tumor can vary greatly depending on the patient. The decision of when to initiate the laser irradiation to stimulate PTT is aided by the guidance data showing the sufficient accumulation and localization of the intravenously introduced AuNPs in the tumor tissue. Great importance is attributed to PTT guidance and development of new guidance strategies. The current research increasingly focus on advancing multi-modal imaging-guided PTT [131].

2.4.4. Thermal Dosimetry: Real-Time Temperature Monitoring

Aside from minimizing collateral damage to healthy tissue, adaptive laser dosage is critical for determining the cellular death pathways of the tumor cells. Heat generated in PTT induces cell deaths via two different mechanisms depending on the temperatures reached inside the cell which is controllable by the irradiation intensity. Necrosis is the undesirable pathway for tumor cell ablation that is caused by high intensity of heat generated by AuNPs and results in the rupturing of the cell membrane. The following release of intracellular content causes inflammation and unwanted immune response [132], [133]. Apoptosis on the other hand, cripples the activities of a cell and induces signals for the immune system to dispose of the cell securely. As the integrity of the cellular membrane remains intact, apoptosis minimizes inflammation and is the preferred pathway for light induced cellular ablation in PTT applications emphasizing the role of real-time temperature monitoring and adaptive laser dosage [134]–[137].

2.4.5. Light-Triggered Hyperthermia: Heating the Cancer Cells from within

Multiple functionalities discussed in the previous sections all add to the success of AuNPs and PTT as a nanomedical cancer treatment. Nanoparticle-mediated PTT relies on the conversion of external laser illumination into heat by the AuNPs inside the tumor cells. AuNPs accumulate in tumor tissue through active or passive targeting following an intravenous or intratumoral administration. The heat generated by LSPR in AuNPs increase the temperature inside the tumor cells causing irreversible damage with high selectivity. The resulting photothermally

induced apoptosis instigates tumor regression. In clinical applications the effectiveness of the PTT relies on controlling the temperature rise inside the tumor which is determined by three major factors: photothermal conversion efficiency (PCE) of AuNPs, AuNP concentration in the tumor microenvironment, and the laser dosage delivered to the AuNPs in the tumor. Researchers from all contributing disciplines study these factors to develop strategies and improve PTT effectiveness such as administration of appropriate laser dosage, image-guidance to identify tumoral localization, biocompatibility for minimizing toxicity and promoting long circulation time to foster accumulation in cancer tissue [133], [138].

Electromagnetic properties of AuNPs such as LSPR wavelength, absorption/scattering cross-sections are the key features that contribute to the success and effectiveness of PTT. These properties are controlled by the morphology of the AuNP and can be tailored to achieve better light-to-heat conversion, deeper tissue penetration. Designing AuNPs with the objective of optimizing optical properties for the targeted application is the main contribution of physics and this thesis to the advancement of PTT. Well-engineered AuNPs can significantly amplify the characteristic advantages of PTT as a non-invasive, highly selective, and externally controllable nanomedical tool in treating cancer [139].

2.5.Engineering AuNPs: Tailoring Properties to Fit the Application

Initial studies on designing AuNPs, from the perspective of physics, simply focused on maximizing the absorption to generate as much heat as possible from the incident radiation. The progressing experiments and clinical studies revealed that working in the biological domain introduces significant constraints into NP design such as operating in certain wavelength spectrum, i.e. biological transparency windows (BTW).

2.5.1.Tuning the Operational Wavelength to the BTW: Resonance Wavelength

LSPR resonance is the mechanism that amplifies the optical properties of AuNPs. One crucial aspect of designing AuNPs is the tuning of the resonance to match the operational wavelength of the PTT. AuNPs offer extraordinary versatility in tuning the resonance wavelength ranging from NIR-I (650 nm) at the lower end to NIR-IV (2500 nm) at the far end spectrum. Among other things, the resonance wavelength of a AuNP strongly depends on its size. The strength of this dependency varies significantly across different geometries such that certain geometries

like gold nanospheres (AuNS) display extremely limited variability and restricted to operate solely in NIR-I. On the other hand, cylindrical NPs (AuNC) successfully scale up to cover the whole biological transparency range (650nm – 2500 nm). The tuning of the resonance frequency is not an isolated process and in almost all cases significantly alters the other features of the AuNP. The interdependency of optical features is a great source of complication for engineering AuNPs and demonstrates the circular nature of the design construct.

2.5.2. Pharmacokinetics & Physicochemical Properties: NP Morphology

Another critical constraint in designing AuNPs is the physicochemical properties that affects the interaction of the AuNPs with the biological environment. Physicochemical properties such as the NP size, shape and the surface chemistry strongly influence the cellular internalization, pharmacokinetics and biodistribution of the AuNPs [140]–[147]. Heterogeneity of cancer causes the pharmacokinetics constraint to be imprecise and inconclusive [75], [76]. The optimum NP morphology can differ considerably and needs to be evaluated case by case depending on the cancer type and the structuring of the tissues of the patient. AuNPs show great potential in development of personalized cancer treatments due to their versatility [114]. Establishing an extensive design framework for AuNPs is critical to address the variable needs imposed by the biological medium in designating the optimum NP morphology for the specific application. This demonstrates the fluidity of NP engineering as there is no universal design that is applicable to all PTT applications with great efficiency.

2.5.3. Quantifying Absorption & Scattering in AuNPs

“It’s bigger on the inside!” – TARDIS: Time And Relative Dimension In Space [148]

The interaction of AuNPs with the incident radiation results in two primary process: scattering and absorption, i.e. a beam of light propagating through an ensemble of NPs loses its energy to scattering and heating/absorption. In the scattering process, the incident electromagnetic field induces oscillations of the NP electrons resulting in generation of radiation. On the other hand, the absorption process occurs as the electron oscillation dissipates energy through heat. Both scattering and absorption remove power from the incident radiation and causes attenuation which is referred to as extinction ($\text{Extinction} = \text{Absorption} + \text{Scattering}$). These processes are quantified by the optical cross section which is a geometric quantity that relates the incident light to scattered and absorbed power. The absorption/scattering cross section of a AuNP

represents the effective area over which the NP absorbs/scatters incident radiation. The absorption/scattering cross section of a plasmonic nanoparticle at the peak of its LSPR can be several orders of magnitude larger than its geometrical cross section [149]–[152]. This phenomenon is the underpinning of the great potential of plasmonic NPs in nanomedical applications. The plasmonic NPs that look tiny to the biological tissue are perceived dramatically larger by the incident electromagnetic radiation. They truly are bigger on the inside, much bigger!

2.5.4. AuNP Multi-modality: Combining Therapy & Diagnostics – Theranostics

Serving multiple purposes on a single nanoplatforms is one of the most attractive features of AuNPs in nano-medical applications. The additional modalities such as image-guidance, diagnosis, real-time temperature and biodistribution monitoring, targeted delivery of drugs and PSs for light triggered release in cancer tissue significantly improve the effectiveness of the treatment. Temperature increase caused by PTT is shown to significantly enhance the efficiency of other therapeutic strategies such as PDT, chemotherapy, and immunotherapy. These highly synergistic effects are the main motivation behind the efforts to combine multiple modalities, diagnostics, and therapy (theranostics) techniques. Combination theranostics also lower the required dosage of each contributor for effective treatment decreasing complications and side-effects [153], [154], [163]–[167], [155]–[162].

The performance of additional modalities relies on different features of AuNPs and requires a multi-parameter optimization in the design stage to achieve multiple objectives simultaneously. The interdependent nature of the optical properties of AuNPs exponentially increases the complexity of the task of engineering AuNPs for multiple modalities.

2.5.5. Quantifying Toxicity & New Performance Metrics for AuNPs

“Sola dosis facit venenum” (The dose makes the poison) – Paracelsus: Father of Toxicology [168]

AuNPs have been increasingly used in medical applications in the past decades and even introduced to consumer food and drink products in the recent years for anti-inflammatory purposes [169]–[171]. With the increasing number of clinical and cosmetic applications, the toxicity of the AuNPs at a systematic and cellular level is an increasingly important issue.

Nanotoxicology emerged as a major research field to assess the potential in-vivo and in-vitro toxicity of AuNPs. The wide variability of NP morphology, surface chemistry, targeted cell types and experimental conditions renders the task of predicting the toxicity of AuNPs rather difficult, leading to conflicting conclusions [145], [172], [181], [182], [173]–[180]. Relating physical characteristics such as size and shape to the toxicity of a AuNP remains an open question. The appropriate choice of a dose metric for quantifying AuNPs toxicity against a physical metric of mass, particle number or surface area is still widely disputed [183]–[186]. The challenge from the NP design perspective is in incorporating the dose metric to the optimization of optical properties. The absorption/scattering cross sections measure the optical performance of a AuNP per induced toxicity for a dose metric of particle number. Evaluation of optical performance per induced toxicity for the dose metrics of NP mass and surface area requires the introduction of new performance metrics. Normalizing absorption/scattering cross section by NP mass/surface area effectively produces the new optical performance metrics that measure the heat/scattering generated per gram of gold or per surface area under the toxicity constraints of the biological medium. Similar to the concept of wave function collapse following an observation [187], introduction of a new metric collapses the space to evolve around the optimization of the newly-defined metric which adds extra dimensions to the challenge of engineering AuNPs and will be the focus of discussion in later chapters.

2.5.6. Cellular Uptake: Morphology and New Approaches in Fabrication

Cellular uptake of AuNPs is another decisive issue in the realization of an effective PTT application. Quantifying the AuNP uptake and incorporating parametrically into the design framework is a significant challenge due to the innate complexity of cellular internalization pathways that is complicatedly dependent on NP size, shape, surface chemistry, tissue type and other elements in the composition of the biological environment. Understanding the interactions and internalization pathways of AuNPs is one of the most important open research questions in nanomedicine. The ramifications of NP uptake extend beyond cellular level affecting the post-treatment accumulation in specific tissue and organs. At a systematic level, the removal of AuNPs by the immune system shown to be highly morphology dependent but from the perspective of physics the disputed inference has little quantitative applicability to the design framework [183], [188], [197]–[201], [189]–[196].

One way to incorporate the cellular internalization constraints into the optimization of AuNP

optical properties is through defining the morphology space based on the constructs facilitated by various fabrication techniques. Two competing techniques based on top-down and bottom-up synthesis form the foundation of AuNP fabrication. Top-down production is a physical approach to the AuNP fabrication that utilizes lithographic techniques to generate the desired nano-patterns from larger macro-scale structures [202]. Optical properties of AuNPs are strongly dependent on morphology and small deviations in particle geometry or dimensions can lead to significant variation in NP performance. The major advantage of top-down fabrication is the precise control over the NP dimensions and uniformity of the fabricated NPs which is a crucial feature in tuning the AuNPs for their intended purposes [203]. The high precision comes at a cost of expensive machinery investments and high production costs per particle reducing applicability for large scale manufacturing required for nanomedical applications [204], [205]. In contrast, the bottom-up techniques based on chemical synthesis provide low-cost and scalable solutions for mass production of AuNPs. Bottom-up fabrication also facilitates vertical integration of post-production processes such as surface functionalization for increasing biocompatibility or attaching targeting agents to target specific cells/sites [206]–[208].

The two fundamental techniques define the boundaries of available geometries for designing AuNPs. Development of inventive techniques that coordinate AuNP components to form complex structures in-situ is the decisive development that adds a new dimension to the AuNP design framework. Self-assembling AuNPs allows construction of large and complex structures piece by piece inside the tumor cell that otherwise as a whole is extremely difficult to be internalized. The groundbreaking concept has rightfully attracted significant interest from the scientific community that lead to the development of intricate techniques to assemble AuNP with high precision to form complex structures. The expanding possibilities for NP morphology consequently redefine the boundaries of attainable optical properties and opens new frontiers in nanomedical applications for AuNPs [209].

Chapter 3:

CONTOUR DESIGN: ABSORPTION ENHANCEMENT IN NAs

The aim of this chapter is to introduce a design approach that numerically demonstrates the existence of large NPs with strong affinity to absorb majority of the incident radiation. The initial curiosity that nucleated this research was inspired by the discussions with Ali Serpengüzel who provided the motivation to tabulate existing NPs which consequently highlighted the absence large absorber NPs. In the early days, the consensus in the optics community was that the greater part of the incident radiation is absorbed by the small nanoantennas (NAs) while large NAs scattered most of it. The advancing nanotechnology propelled the search for ever smaller antennas for manipulating light in increasingly smaller scales. The optics community perceived the absorbing qualities of the NAs more of a nuisance that needs to be minimized rather than a feature. Prior to PTT and PDT and the discovery of longer wavelength biological transparency windows, losses in NAs to absorption were a challenge that needs to be overcome with limited incentives to search for large absorber NAs.

The expanding application spectrum of NAs demand versatile design approaches to tailor the antenna properties for specific requirements. The design efforts primarily concentrated on shifting the operation wavelength or enhancing the local fields by manipulating the size and shape of the NA. This chapter shows a design path to control the absorption and scattering characteristics of a dipole NA by introducing a hollow region inside the nanostructure. The resulting contour geometry can significantly suppress the scattering of the dipole NA while enhancing its absorption simultaneously. Out of two NAs that couple to equivalent amount of the incident radiation, the solid NA scatters 84% of the coupled power (absorbing the remaining 16%) whereas the contour NA scatters only 28% of the coupled power (absorbing the remaining 72%). This constitutes the transformation from scatter to absorber nanoantenna. The scattering of a contour NA can be further suppressed by incorporating a lossless dielectric in the hollow region without altering its absorption.

This chapter also demonstrate the applicability of scattering suppression and absorption enhancement features of the contour design in other NA geometries such as the self-assembly compatible nanoantenna structures of nanodisk and nanoring chains. The benefits of the contour design can be readily utilized in diverse applications, including bioplasmonics, medical diagnosis/therapy, cloaked sensing, photovoltaics and thermoplasmonics.

3.1.Introduction: Absorption & Scattering in Plasmonic NAs

Advances in nanotechnology paved the way to the miniaturization of antennas which provided the means to manipulate light at the subwavelength scale. The NAs are being used in a wide range of applications: from sensing and cloaking to information processing, and even medical diagnosis and therapy [210]–[212]. The working principle of the plasmonic NA is in their ability to confine light beyond the diffraction limit in the form of localized surface plasmon resonances (LSPRs) [213]. These resonances enhance the local electromagnetic field significantly and become particularly sensitive to changes in the local dielectric environment. Tailoring the properties of a NA for the vast variety of applications relies heavily on a careful design approach which involves three major parameters: shape, size, and material. NAs in various shapes have been developed for numerous application purposes in the last two decades. Bowtie NAs are designed to induce high local electromagnetic fields in between the sharp tips to be used in sensing applications; helical NAs are employed in polarization conversion; multilayer dolmen nanostructures are shown to work as plasmonic rulers, and optical Yagi-Uda antennas are utilized to enhance and direct the emissions of a nanoemitter [214]–[217]. The size of the NA primarily affects the operation wavelength and bandwidth. In radio frequency and microwave regimes, the dimensions of the antenna are directly related to its operation wavelength. However, in the optical regime, the field penetration into the metal body is significant due to the excitation of localized surface plasmons. This field penetration leads to an effective resonance wavelength which takes into account the optical properties of the metal [218], [219]:

$$L = \frac{\lambda_{eff}}{2}. \quad (3.1)$$

The material of choice for optical NAs has been dominated by gold and silver due to their small Ohmic losses and inertness under atmospheric conditions. However, there is a growing interest

to incorporate new materials for better fabrication characteristics and enhanced heat stability [220]–[223]. The losses in metallic NAs are significant and inevitable. Considerable amount of research has focused on circumventing this problem by introducing a gain medium, employing superconductors, or constructing all-dielectric NAs [224], [225]. On the other hand, the lossy nature of the metals can be put into use in devices specifically designed for absorption purposes such as solar energy harvesting [226], metamaterial perfect absorbers [227] and high optical field generators for near-field microscopy [228].

NAs that absorb a significant proportion of the incident radiation are utilized in the recently emerging field of thermoplasmonics which exploits the Joule heating caused by the plasmon resonances [229]–[231]. The resultant nanoscale heat sources found use in biological applications such as selective photothermal cancer cell treatment [21], [232], [233] and light controlled plasmonic drug delivery [234]. In chemistry, absorber NAs act as nanosources of heat, electrons and strong optical near-fields to control reactions in a nanoscale precision [235]. Designing highly absorptive plasmonic structures for thermoplasmonic applications initiated interest in refractory plasmonic materials to account for the melting point depreciation in nanoscale structures [236], [237]. Absorber NAs are also used in photovoltaic systems to trap solar radiation in the form of localized surface plasmons, which generate strong near-fields and enhance the creation of electron-hole pairs in the semiconductor [238]. Similarly, in solar thermophotovoltaic devices, instead of creating electron-hole pairs, absorber NAs convert sunlight into heat which via a thermal emitter is coupled to the photovoltaic cell for power generation [239]. Theoretically, the heat generated in the plasmonic nanostructures under continuous illumination is directly related to the absorption cross section (σ_{Abs}) and the incident light intensity (I) [240], [241]:

$$P = I \cdot \sigma_{Abs} . \quad (3.2)$$

Plasmonic NAs are also widely utilized in sensing applications. Free-standing NAs resonant in the biological transparency windows (650–1350 nm) serve as real-time, in-situ spectroscopy for in depth investigation of cellular processes [242]. There is also a growing interest in the self-assembly of NAs, especially inside living cells, by using nanoparticles attached to polymer or biomolecule templates, in particular when the resulting NA system is too large to go through the cell membrane [243]. In-vitro diagnostic devices based on arrays of plasmonic NAs have also been reported [244]. In recent years, considerable effort is focused on cloaking the NA

sensors to decrease the scattering and disturbance on the probed environment [245]–[248]. Unlike ideal cloaking where the presence of an object is completely shielded from the surrounding electromagnetic field, in sensor cloaking the aim is to minimize the scattering caused by the NA while preserving the coupling to the incident radiation [249]. This concept of “seeing without being seen” [250] has potential applications in communication technologies and in biological/medical imaging by lowering noise and interference [251].

In view of the aforementioned applications, designing low-scattering NAs that has strong coupling to the incident field is crucial for increasing the efficiency in sensing applications. On the other hand, thermoplasmonic and photovoltaic applications can benefit considerably from enhancing the absorption cross section of a NA. This chapter demonstrates the scattering suppression and absorption enhancement in plasmonic NAs by introducing a hollow region into the structure, which results in a contour geometry. While several contour NA structures have been studied in the past for shifting resonances to achieve deep subwavelength light modulation, for manipulating the damping of the plasmonic resonances, and for improving refractive index sensing capabilities [252]–[255], this study exposes the significant freedom gained by a simple contour design to extend and tune the scattering and absorption properties of a NA, without altering its outer dimensions. To the best of our knowledge, these features have not been exploited systematically before.

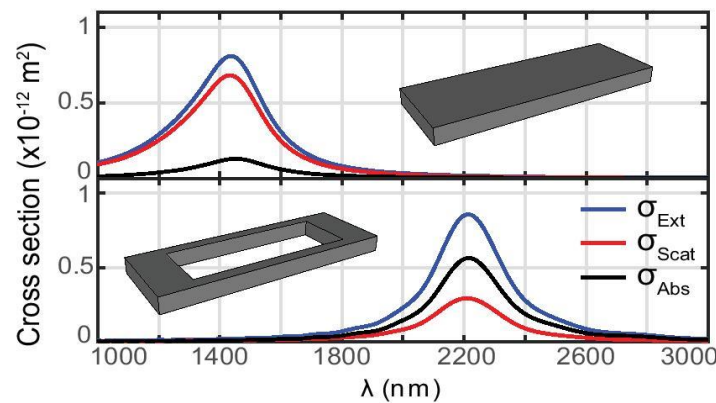


Figure 3.1: The effects of contour design in scattering suppression & absorption enhancement of plasmonic dipole NAs

The rest of the chapter is structured in 5 sections: Section 3.2 provides a comparative study on the scattering suppression and absorption enhancement in dipole and contour dipole NAs. Section 3.3 presents the effects of the contour geometry on the transmission/reflection

properties of a periodic array of contour NAs. Section 3.4 gives a qualitative description of the mechanisms providing the scattering suppression and the absorption enhancement based on the local electric field and the induced current distributions of the contour NA. In section 3.5 the effects of a dielectric-filled hollow on the scattering and absorption of the NA is discussed. Section 3.6 highlights the general applicability of the contour design by illustrating its use in self-assembling NA structures.

3.2. Contour Design in Dipole NA: Tuning LSPR in a Multitude of Ways

“more and more with less and less until eventually you can do everything with nothing.” – Ephemeralization by R. Buckminster Fuller

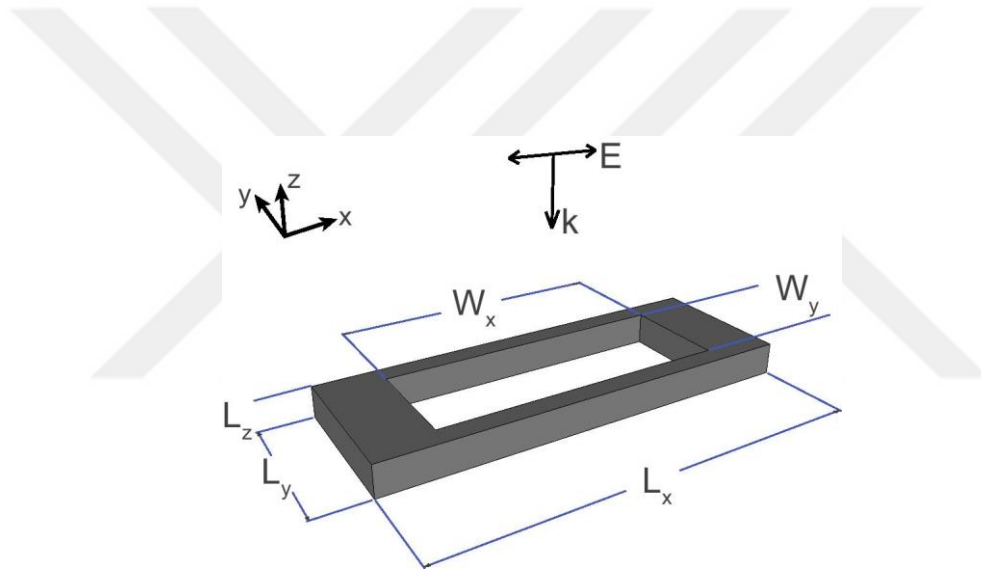


Figure 3.2: A schematic view of the contour dipole antenna under linearly polarized plane wave illumination with outer NA ($L_x \times L_y \times L_z$) and hollow ($W_x \times W_y$) size parameters.

The structures used for this study are referred to as dipole NAs since only the fundamental electric dipole mode is excited under linearly polarized plane-wave illumination. We present a numerical study of silver NAs in near-infrared region. The simulations are performed using the Lumerical FDTD software in the wavelength range of 1000 - 3000 nm [256]. Free standing NAs without any substrate are studied to eliminate complications such as resonance shift and broadening. In all of the performed simulations the NA height (L_z) is fixed at 30 nm. NAs of varying length ($L_x = 300\text{--}700$ nm) and width ($L_y = 20\text{--}250$ nm) are studied. All contour dipole NA designs are based on the same parent dipole structure ($L_x \times L_y \times L_z = 400 \times 100 \times 30$ nm)

with varying hollow dimensions ($W_x = 100\text{--}360$ nm, $W_y = 20\text{--}80$ nm). For modelling the complex refractive index of silver, we use Brendal-Bormann model which is shown to be in good agreement with experimental observations in the studied wavelength range [257]–[259].

The extinction cross section (σ_{Ext}) of an object is a measure of its effective shadowing area and calculated by:

$$\sigma_{\text{Ext}} = \frac{P_{\text{Tot}}}{P_{\text{Tot}}} \cdot \quad (3.3)$$

where P_{Tot} is the total energy loss from the incident beam and I is the incident light intensity. One of the contributions to this loss of intensity is due to redirection of the propagating beam which is related to the scattering cross section:

$$\sigma_{\text{Scat}} = \frac{P_{\text{Scat}}}{I} \cdot \quad (3.4)$$

where P_{Scat} represents scattered power by the object. Due to energy conservation the rest of the power loss must be due to the absorption of the object and by definition the absorption cross section is [260]:

$$\sigma_{\text{Abs}} = \sigma_{\text{Ext}} - \sigma_{\text{Scat}} \cdot \quad (3.5)$$

We calculated the scattering and extinction cross sections (σ_{Scat} & σ_{Ext}) of the dipole and contour dipole NAs using the FDTD simulations and consequently obtained the absorption cross section (σ_{Abs}). Comparing the extinction, scattering and absorption cross sections of a dipole and three contour dipole NAs (of the same outer dimensions) revealed the changes induced by the presence and varying size of the hollow region (Figure 3.3 d-f): The resonance wavelength is red-shifted with increasing hollow size. As the outer dimensions remain intact, this resonance shift enables deeper subwavelength control of light by contour dipole NA ($L_{\text{contour}} = 400$ nm = $\lambda_{\text{Res}}/5.5$) compared to a dipole NA of the same size ($L_{\text{dipole}} = 400$ nm = $\lambda_{\text{Res}}/3.5$). Increasing the hollow size transforms the NA from scatterer to absorber in character, as the absorption surpasses the scattering cross section (Figure 3.3e, f). Furthermore, the extinction cross section remains roughly constant throughout the crossover of the scattering and absorption cross-sections. This implies that, by starting with a proper sized dipole NA, one can carve out a hollow region to produce a contour NA with tailored scattering and absorption

cross sections, at the desired operation wavelength, while preserving the extinction cross section.

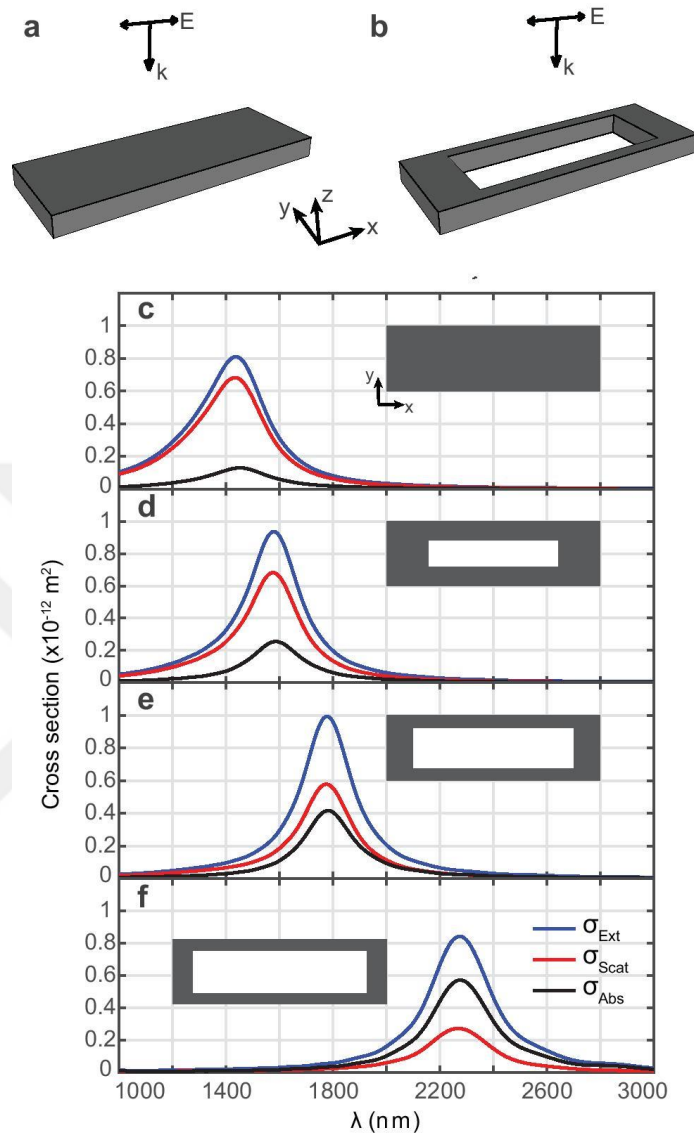


Figure 3.3: (a-b) A schematic view of the plain dipole and the contour dipole antenna. The scattering, absorption, and extinction cross section of the dipole (c) and the contour dipole nanoantennas (d-f). The outer dimensions of the nanoantennas are the same: $L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$. The contour size $W_x \times W_y$ changes by (d) $240 \times 40 \text{ nm}$, (e) $300 \times 60 \text{ nm}$ (f) $360 \times 80 \text{ nm}$, as illustrated by the insets.

Conventional design approaches for manipulating the resonance wavelength and the scattering behavior of dipole NAs focus on dimensional alterations of the structure. To contrast the effects of the contour geometry, we present a comparative study on the effects of changing the length and the width of a dipole NA on the resonance wavelength, relative scattering efficiency and

scattering, absorption and extinction cross sections of a dipole NA (Figure 3.4). Figure 3.4a, c & e show the effects of changing the NA length (L_x), at a fixed width ($L_y = 100\text{nm}$). The resonance wavelength as well as the scattering and absorption cross sections change linearly whereas the relative scattering efficiency ($\text{RSE} = \sigma_{\text{Scat}}/\sigma_{\text{Ext}}$) remains constant with the changing NA length. We introduced RSE as a measure of the extent of scattering in the extinction cross section. An RSE smaller than 0.5 indicates to an absorber NA, contrarily a scatterer NA has an RSE larger than 0.5. Figure 3.4b, d & f illustrate the effects of changing the NA width (L_y), at a fixed length ($L_x = 400\text{ nm}$). Significant variation of the relevant parameters is achieved only for narrow NAs ($L_y < 50\text{ nm}$). We will compare the narrow dipole NAs to the contour dipole structures later in this section.

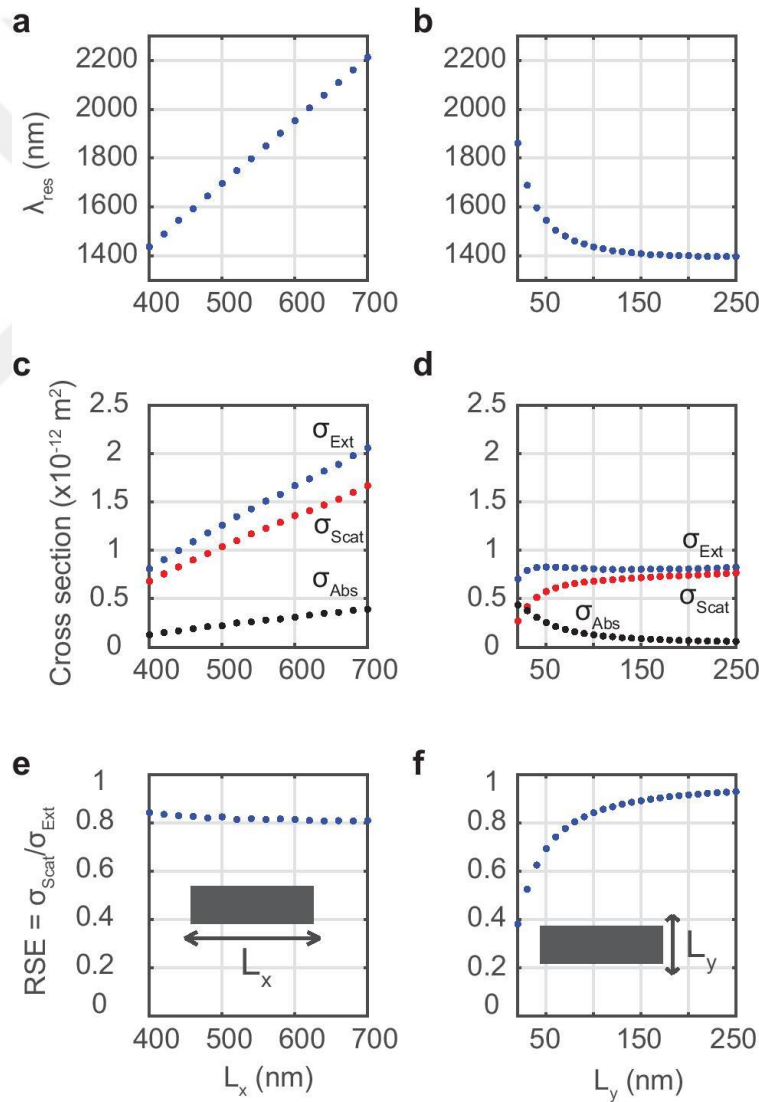


Figure 3.4: Effect of changing dipole NA length- L_x (first column) and width- L_y (second

column) on the resonance wavelength (a, b), σ_{Scat} , σ_{Abs} & σ_{Ext} (c, d), and the relative scattering efficiency ($\text{RSE} = \sigma_{\text{Scat}}/\sigma_{\text{Ext}}$). Insets illustrate alterations in NA length and width.

The control over the RSE of a dipole NA based on length and width alterations is limited to narrow structures only (Figure 3.5a). Figure 3.5 illustrates the extent of freedom gained by the contour design approach in modifying the RSE of a parent dipole NA (marked by the black rectangle with dimensions: $L_x \times L_y = 400 \times 100\text{nm}$). The dipole NA acts as a scatterer ($\text{RSE} > 0.5$) almost in the entire range of the axes. This observation is also consistent with the calculations based on Mie theory for nanospheres and nanoshells which indicates that small particles ($L \leq \sim \lambda/20$) are predominantly absorbers whereas larger particles act as scatterers [27]. The RSE of the contour dipole NA can be suppressed from 0.84 for the parent dipole (marked by the black rectangle in Figure 3.5a) to 0.32 by enlarging the hollow region (Figure 3.5b). Note that when $W_y > 70\text{ nm}$, the RSE can be brought below 0.5 and the selected constant RSE curves are running horizontally. Evidently, the width (W_y) rather than the length (W_x) of the hollow region governs the change in the RSE. We will elucidate this dependence later on while discussing the local field and current density of the contour dipole antenna.

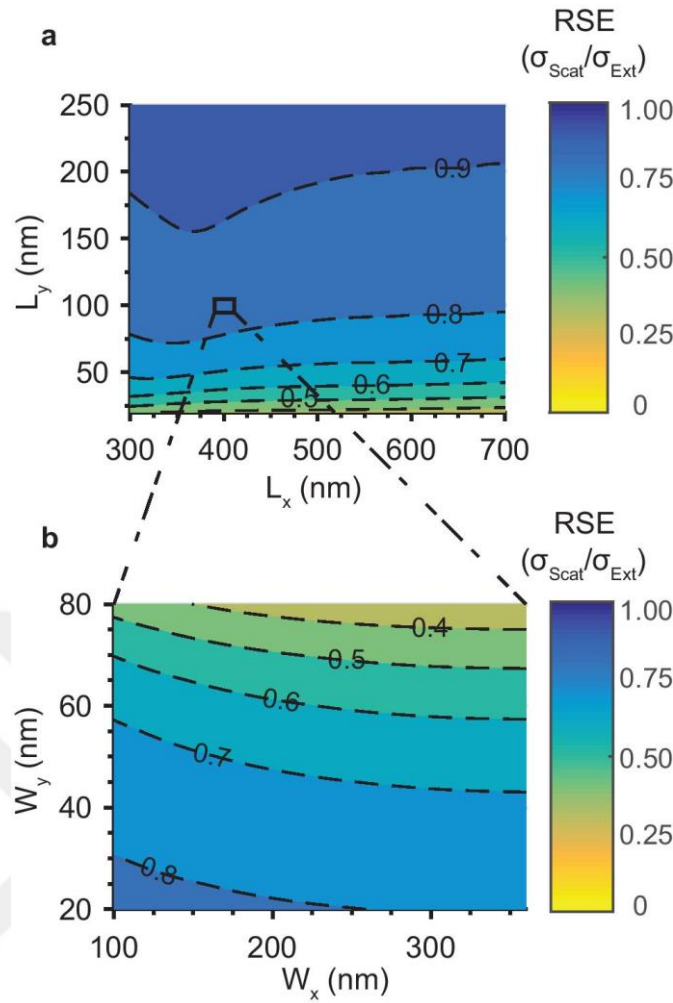


Figure 3.5: (a) RSE of a dipole NA as a function of its length (L_x) and width (L_y). (b) The expanded RSE of a contour dipole NA which is based on the parent dipole with dimensions: $L_x \times L_y = 400 \times 100$ nm (marked by the black rectangular region in (a)). RSE $>$ ($<$) 0.5 indicates predominantly scatterer (absorber) NAs.

We conclude this section by summarizing the modification of the scattering, absorption and extinction cross sections of the dipole and the contour dipole NA by their respective design parameters as shown in the first and second columns of Figure 3.6. The black rectangular regions in the figures of the first column, mark the location of the parent dipole structure ($L_x \times L_y = 400 \times 100$ nm) of the contour dipole NAs in the second column. Thus, the second column of figures can be seen as the expansion of the rectangular region through the contour design and signifies the additional range gained in the corresponding parameters. The similarity of the scattering and extinction cross section profiles of the dipole NA (Figure 3.6a, e) emphasizes its scattering character. The vertical running contour curves in Figure 3.6a, e indicate that the

properties of the dipole NA are mainly governed by its length and the NA width becomes effective only below 50 nm. The absorption cross section remains small and relatively insensitive to the changes in the design parameters (Figure 3.6c). The significance of the contour NA design is in the scattering and absorption cross section profiles which exhibit inverse and comparable variations as a function of contour parameters (Figure 3.6b, d). Consequently, the extinction cross section remains almost constant (Figure 3.6f). The horizontal running contour curves indicate that the cross sections are dictated by the width of the hollow. To demonstrate the scatterer to absorber transition in contour dipole NAs, we plot the cross sections as a function of hollow width (W_y) at fixed hollow length ($W_x = 300\text{nm}$). Figure 3.6g clearly shows the crossing of σ_{Scat} & σ_{Abs} .

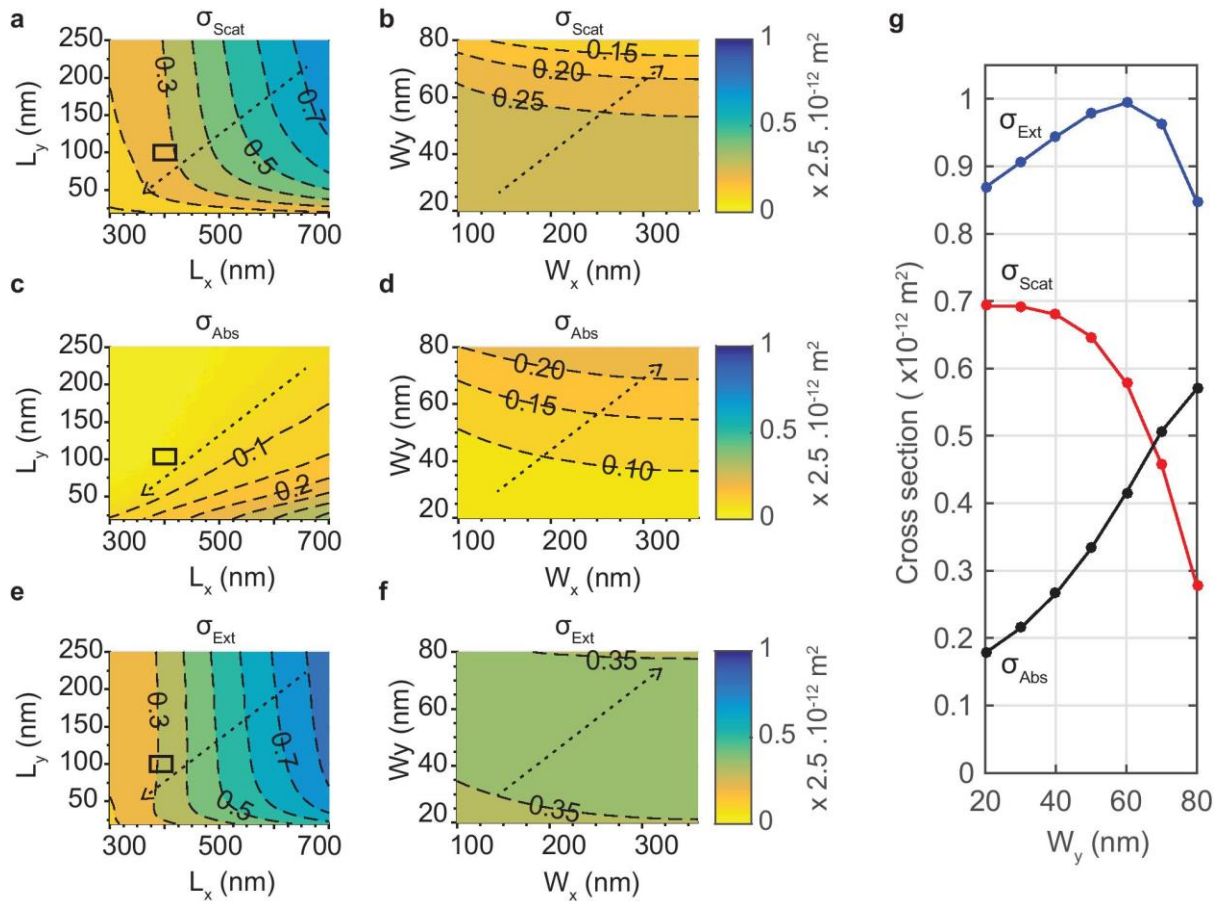


Figure 3.6: The scattering (a), absorption (c) and extinction (e) cross sections of the dipole NA as a function of its length (L_x) and width (L_y). The black rectangles indicate the location of the parent dipole ($L_x \times L_y = 400 \times 100 \text{ nm}$) which is used to construct the contour dipole NA. The scattering (b), absorption (d) and (f) extinction cross sections of the contour dipole antenna as a function of hollow length (W_x) and width (W_y). The dashed arrow in panels (a-f) indicate the direction for scattering suppression. (g) The scattering, absorption, and extinction cross

sections of the contour dipole NA as a function of contour width at fixed contour length $W_x = 300\text{nm}$.

In cloaked sensing applications, suppression of scattering without compromising on the coupling to the incident field is essential. The contour NA design constitutes a viable path for scattering suppression. The dashed arrows in Figure 3.6a, b indicate the directions to be taken to suppress the scattering in the dipole and contour dipole NAs. The arrows in the lower panels, mark the trend in absorption and extinction cross sections (Figure 3.6c-f) along the scattering suppression path for each NA respectively. The scattering suppression path for the dipole NA fails to preserve the extinction cross section. However, the contour dipole NA preserves the extinction cross section which represents the coupling to the incident field. The utilization of contour dipole NAs in cloaked sensing applications will be discussed in more detail in the later sections.

3.3.Periodic Contour NA Arrays

Periodic NA arrays provide a functional layer with application-specific reflection, transmission and absorption properties and their usage is already reported in optical nanocircuits [261], sensors [262]and photovoltaics [263]. The electromagnetic response of the NA array is primarily determined by that of the unit cell (constituent nanoantenna). The refractive index of the substrate and the periodicity of the array account for the secondary factors that influence the electromagnetic response of the NA array [264], [265]. In order to relate to the results presented in the previous section and to focus on the effects of the contour design, we consider a free-standing contour nanoantenna array with a typical periodicity of $P_x = P_y = 800\text{nm}$ (Figure 3.7a). The transmission (T) and reflection (R) under normal incidence are calculated from the FDTD simulation and the absorption (A) is determined by the relation:

$$A = 1 - (T + R) . \quad (3.6)$$

The extinction (E) is given by:

$$E = R + A = 1 - T . \quad (3.7)$$

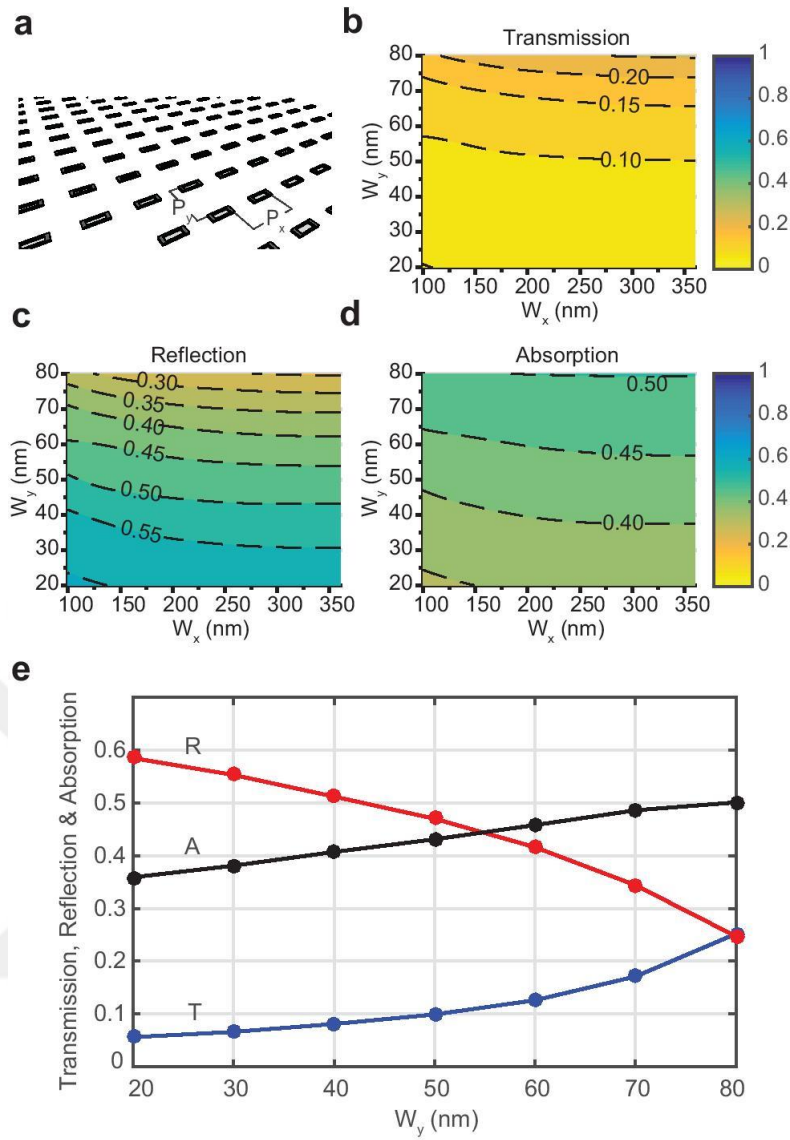


Figure 3.7: (a) The schematic of the periodic contour dipole NA array. The transmission (b), reflection (c) and absorption (d) of the NA array as a function of the hollow length (W_x) and width (W_y). (e) Demonstration of the reflection/absorption crossover by widening the hollow at a fixed length $W_x = 300$ nm. Periodicity in both directions ($P_x = P_y = 800$ nm) and parent dipole NA dimensions ($L_x \times L_y \times L_z = 400 \times 100 \times 30$ nm) are fixed.

Figure 3.7b, c & d show the transmission, reflection, and absorption as a function of the hollow dimensions. In accordance with the results of a single contour dipole antenna (Figure 3.6g), the periodic array exhibits a crossover from reflective to absorptive behavior (Figure 3.7e). Unlike the response of the single contour dipole NA, the extinction (transmission) of the periodic array shows a decreasing (increasing) trend with increasing hollow width (W_y).

3.4. Mechanics of Scattering Suppression & Absorption Enhancement

For a qualitative understanding of the mechanism behind the scattering suppression and the absorption enhancement, we investigate the electric field and the current density distribution of the dipole and the contour dipole NAs at their respective resonance wavelengths. The dominant electric field component along the direction of incident polarization (E_x) shows the electric dipole moments induced in each nanostructure (Figure 3.8a, b).

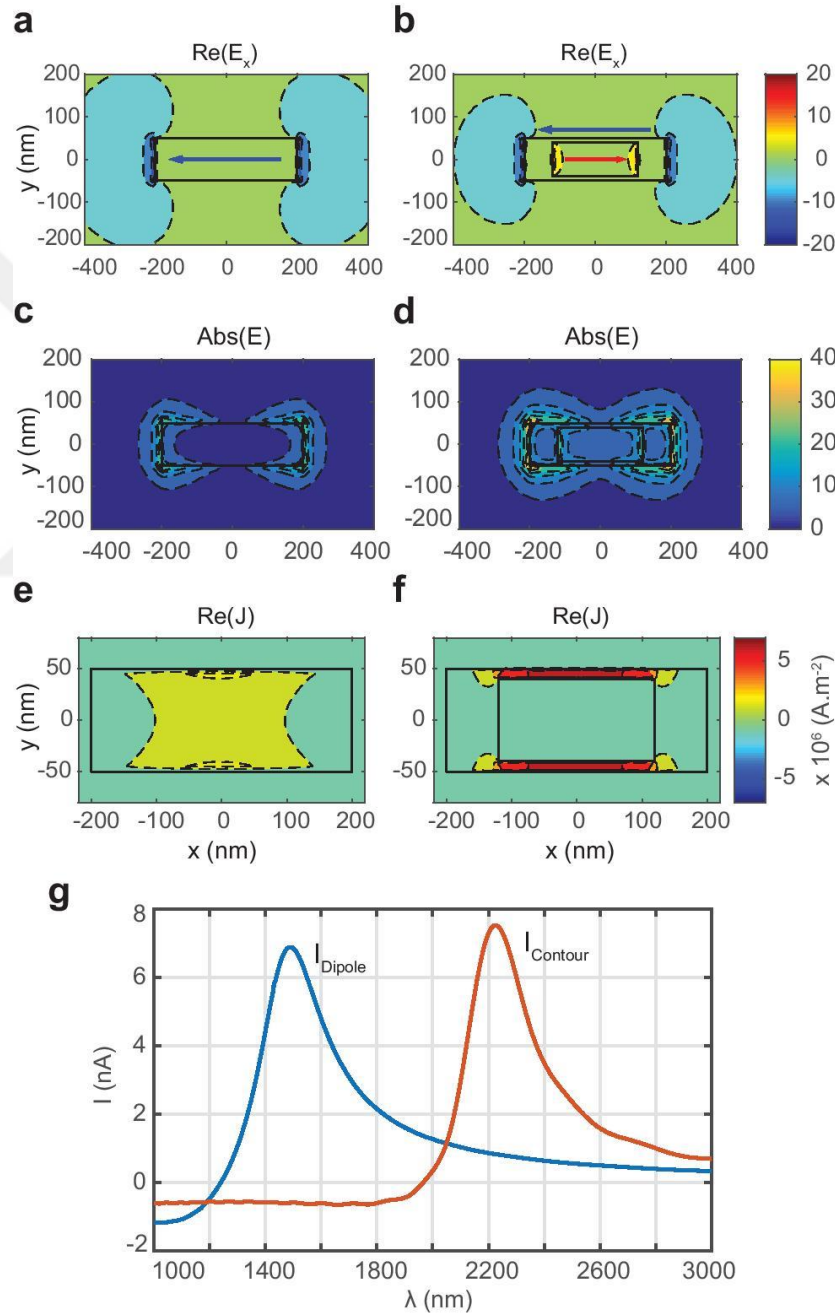


Figure 3.8: Comparison of the (a, b) real part of the x-component of the electric field, (c, d)

electric field magnitude, (e, f) the current density for the dipole (first column) and the contour dipole (second column) NA. The NAs have the same outer dimensions ($L_x \times L_y \times L_z = 400 \times 100 \times 30 \text{ nm}$) and the contour dipole has a hollow region ($W_x \times W_y = 240 \times 80 \text{ nm}$). The arrows in (a, b) indicate the induced electric dipole moments. (g) The total current integrated through the cross section of the dipole nanoantenna (blue curve) and the contour dipole NA (red curve). All figures are plotted at the respective resonance of the NAs.

The electric fields at both ends of the dipole NA are oriented in the same (-x) direction, which defines a dipole moment indicated by the blue arrow (Figure 3.8a). The contour NA possesses an additional opposing dipole moment (red arrow) which is induced across the hollow region (Figure 3.8b). Since the scattering (i.e. the radiated energy) of the NA is proportional to the square of the net dipole moment, reducing the net dipole moment suppresses the scattering of the contour NA. A similar scattering suppression is utilized in plasmonic cloaking of sensors, where the dipole moment of a dielectric NA is reduced by the opposite polarization induced in the surrounding plasmonic cloak with negative permittivity:

$$P_{\text{cloak}} = (\epsilon_{\text{cloak}} - \epsilon_0) E_{\text{incident}} \cdot \quad (3.8)$$

The enhancement of absorption can be inferred from the on resonance current density profiles of the nanostructures. The contour geometry restricts the surface current flow to narrow channels whereas the current flow is spread over the entire surface of the dipole NA (Figure 3.8e, f). As the contour geometry has considerably smaller cross-sectional area (1/5 of the dipole), by Pouillet's law:

$$R = \frac{\rho L}{A} \cdot \quad (3.9)$$

its electrical resistance increases by the same amount [266]. Applying the Ampere's law on a rectangular path at the yz-plane outlining each NA at their respective resonances, reveals that the dipole and the contour dipole NA have a similar amount of current flow (Figure 3.8g). The same amount of current passing through a region of increased resistance increases the Ohmic losses:

$$P = I^2 R \cdot \quad (3.10)$$

and significantly enhances the absorption in the contour dipole structure. Note that, the

absorption cross section remains relatively unaffected by the hollow length change, whereas the increasing hollow width increases the absorption significantly (Figure 3.6e).

The binary effect of the hollow as a scattering suppressor and absorption enhancer in the contour dipole NAs, makes these structures promising candidates for noninvasive sensing and communication applications. Scattering suppression reduces the noise and the disturbance in the environment of measurement whereas increased absorption preserves the extinction cross section and maintains strong coupling to the incident radiation. The induced strong local fields increase the interaction with matter for near-field spectroscopic applications (Figure 3.8c, d).

3.5. Refractive Index of the Hollow: Further Scattering Suppression

Increasing the refractive index of the hollow region by incorporating a dielectric medium enables the construction of contour dipole NAs with even lower relative scattering efficiencies (Figure 3.9).

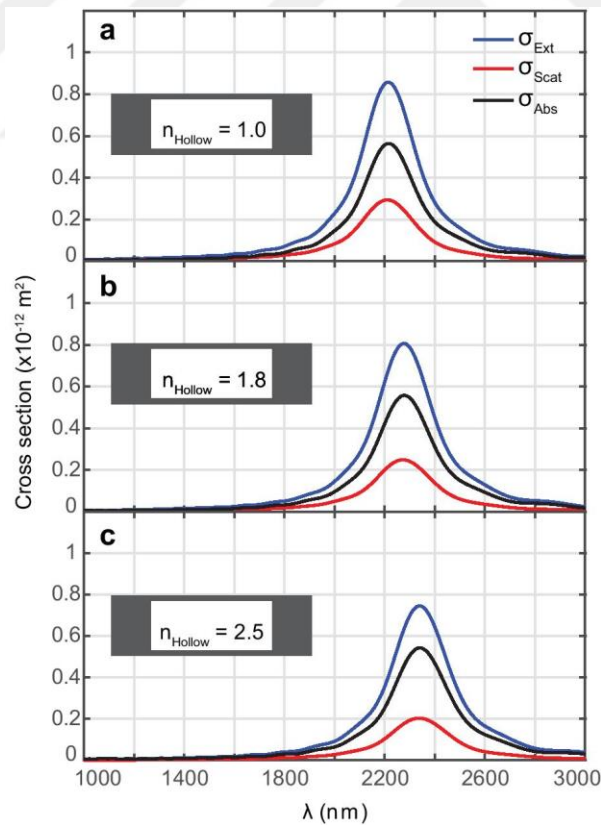


Figure 3.9: The effect of a lossless dielectric medium with refractive index (n_{Hollow}), filling the hollow region of the contour dipole on the scattering, absorption and extinction cross section

spectra: (a) $n_{\text{Hollow}} = 1$ (reference), (b) $n_{\text{Hollow}} = 1.8$, (c) $n_{\text{Hollow}} = 2.5$, as illustrated by the insets. The contour dipole has the same design as given in Figure 3.8.

Unlike the changes corresponding to the dimensional alterations of the hollow, the scattering suppression induced by increasing the refractive index of the dielectric (n_{Hollow}) preserves the absorption rather than the extinction cross section (Figure 3.10a). Conservation of absorption cross section while suppressing the scattering of a NA adds another functionality to the contour design and enables the independent manipulation of scattering from absorption cross section. The RSE of the contour dipole NA can be further reduced (Figure 3.10b) and the resonance wavelength shifts towards slightly larger wavelengths (Figure 3.10c).

The scattering suppression mechanism in contour dipole NAs is attributed to the cancellation of antiparallel polarization vectors induced across the NA:

$$P_{\text{Antenna}} = (\epsilon_{\text{Antenna}} - \epsilon_0)E_{\text{incident}} . \quad (3.11)$$

and the hollow:

$$P_{\text{Hollow}} = (\epsilon_{\text{Hollow}} - \epsilon_0)E_{\text{incident}} . \quad (3.12)$$

that result in a diminished net polarization [267].

$$P_{\text{Net}} = P_{\text{Antenna}} - P_{\text{Hollow}} . \quad (3.13)$$

Increasing the refractive index of the hollow:

$$n_{\text{Hollow}} = \sqrt{\epsilon_{\text{Hollow}}} . \quad (3.14)$$

produces a larger polarization vector inside the hollow dielectric and further reduces the net polarization of the contour dipole structure. The reduced net dipole moment causes the additional depreciation in scattering cross section. On the other hand, absorption cross section remains unaffected as the cross-sectional area for the flow of resonating charges is preserved. Changing the hollow refractive index constitutes an alternative design path to further suppress the scattering of a dipole NA without enhancing its absorption.

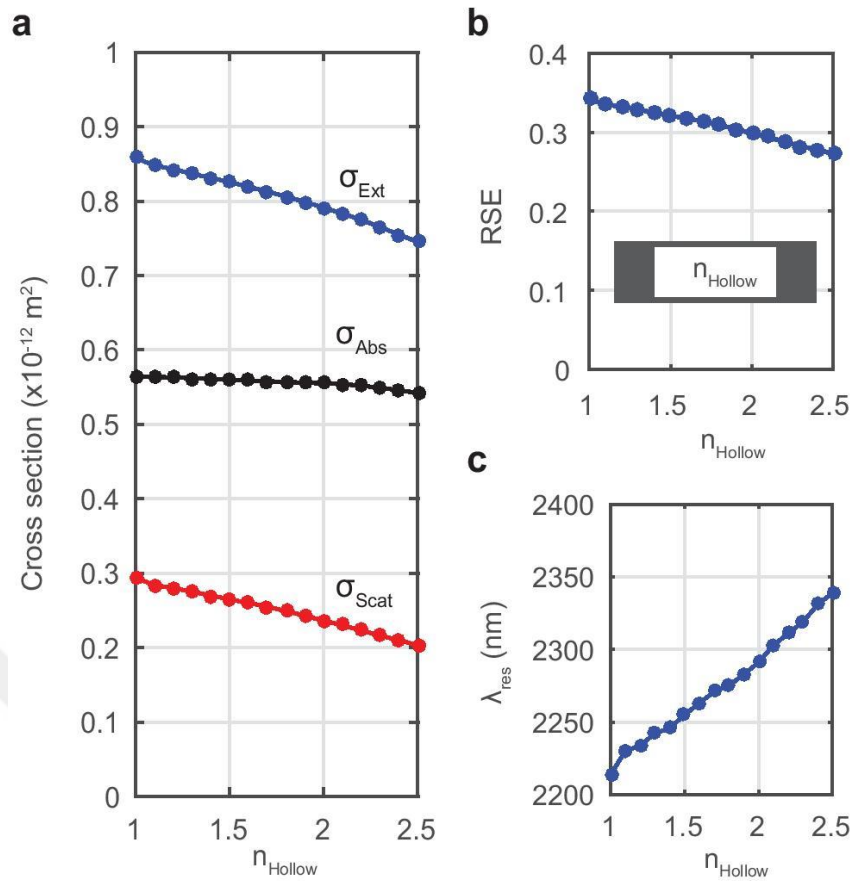


Figure 3.10: (a) The effect of the refractive index of the medium filling the hollow region on (a) the extinction, absorption and scattering cross sections, (b) the relative scattering efficiency and (c) the resonance wavelength of the contour dipole antenna. Inset illustrates the contour NA geometry and the hollow refractive index (n_{Hollow}). The antenna dimensions are as given in Figure 3.8.

3.6. Scattering Suppression in Self-Assembling NAs

With the advancing self-assembly techniques, more and more research is focused on producing self-assembling counterparts of top-down constructed plasmonic NAs [268]–[270]. Replacing a dipole NA with a chain of nanoparticles achieves light modulation in deeper subwavelength regime by shifting the resonance to longer wavelengths while preserving the size of the structure [271]. This resonance shift is attributed to the prolonged path for charge oscillations on the surface of the nanoparticle chain. Replacing the solid nanoparticles with nanoshells increases the resonance wavelength further. The oscillating electrons are restricted to move along the even longer path on the outer surface of the nanoshells [272].

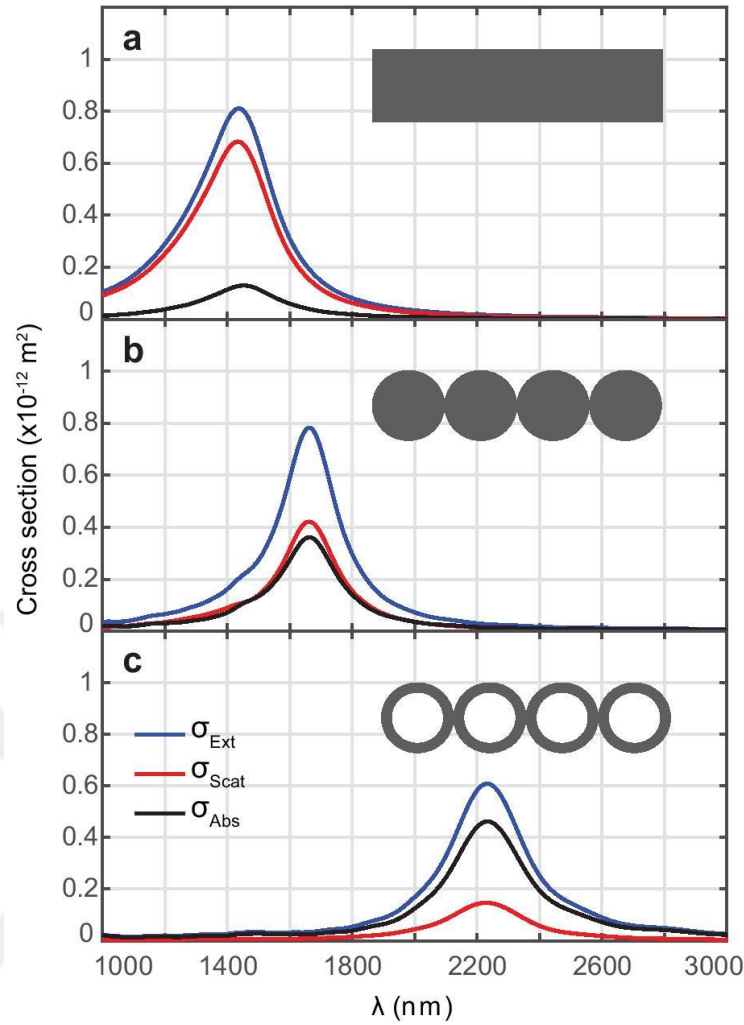


Figure 3.11: The extinction, scattering and absorption spectra of (a) the dipole antenna ($L_x \times L_y \times L_z = 400 \times 100 \times 30$ nm) (b) an assembly of four identical nanodisks ($R_{\text{disk}} \times h_{\text{disk}} = 100 \times 30$ nm) (c) an assembly of four identical nanorings ($R_{\text{out}} \times R_{\text{in}} \times h_{\text{disk}} = 100 \times 70 \times 30$ nm). The nanodisk chain (middle inset) can be considered as a dipole nanoantenna (top inset) contoured from the outside and the nanoring chain (bottom inset) can be considered as a dipole NA contoured from both the outside and the inside.

In addition to changing the resonance wavelength, replacing dipole NAs with nanodisk and nanoring chains causes a significant scattering suppression and absorption enhancement (Figure 3.11a-c). Relative scattering efficiency is dramatically reduced from 0.84 for the dipole NA to 0.57 for the nanodisk chain and further to 0.28 for the nanoring chain. Apart from being promising candidates for subwavelength light modulation, nanoring chains significantly suppress scattering and enable the construction of self-assembling, deep subwavelength, absorber NAs. These self-assembling, low-scattering nanoantenna systems also has great

potential for cloaked sensing applications especially in biological systems to monitor cellular processes where current cloaked sensor designs are either too large to pass through the cell membrane or too difficult to construct inside the cell using the available self-assembly techniques.

3.7. Conclusion: Features of the Contour Design Approach

We propose the contour antenna geometry as a design scheme to tailor the scattering and absorption properties of the dipole NAs. The primary feature of this design is to suppress the scattering of the NA which can be utilized in low-scattering sensors to reduce noise in optical communication and spectroscopic applications. Absorption enhancement is another feature of the contour geometry that is beneficial in photovoltaic and thermoplasmonic applications where the absorption of the electromagnetic field is critical. The absorption enhancement and the scattering suppression occur simultaneously in contour NAs causing little variation in the extinction cross section. In other words, the contour geometry determines how the extinction is distributed between the scattering and absorption cross sections. A predominantly scatterer NA can be transformed to become absorber in character, while the antenna extinction is preserved ($RSE_{\text{Dipole}} = 0.84$, $RSE_{\text{Contour}} = 0.28$). This provides the optimal conditions for cloaked sensing applications where reduced scattering yet strong coupling to the external field is required.

Chapter 4:

DEEP TISSUE CANCER THERAPEUTICS IN NIR-III & -IV

This chapter aims to demonstrate the pioneering efforts in theoretically establishing the viability of constructing AuNPs facilitated by the contour design proposed in Chapter 3 for nanomedical applications in the lately discovered biological transparency windows (BTWs): NIR-III (1600-1900 nm) & NIR-IV (2100-2300 nm). The two longer wavelength BTWs have a significant advantage in deeper light penetration into the tissue but the limited availability of optical instruments restrained their utilization in PTT and other applications.

Nanoparticle-assisted photothermal therapy poses a nontrivial optimization problem in which the light absorption efficiency of the NP needs to be maximized subject to various constraints that are imposed by the application environment. Upscaling the typical absorber-dominant NP designs (e.g., rod, sphere) that operate in the first and second transparency windows is not a viable option as they become increasingly inefficient absorbers while their size gets prohibitively large for internalization into certain cell strains. This chapter addresses this issue by contemplating on a versatile approach for designing both monolithic and self-assembling absorber dominant nanostructures for the new transparency windows. These NPs are lithographically fabricatable; additionally, they are adaptable to low-cost, mass production compatible chemical growth methods while accomplishing up to 40% size reduction and 2-fold increase in absorption efficiency compared to the conventional nanobar design. The overall photothermal performance in NIR-III & -IV exhibits significant improvements over NIR-II.

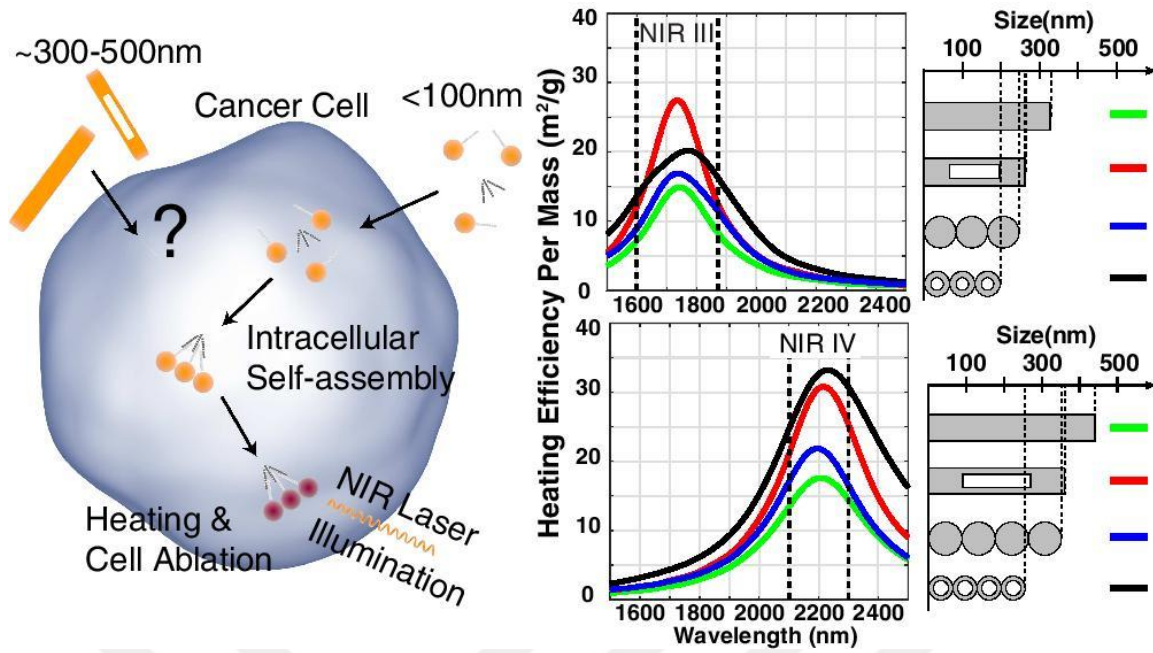


Figure 4.1: Illustrating PTT in NIR-III & -IV

4.1.Introduction: Fighting Cancer with Heat Generated by Gold Nanoparticles

Hyperthermia therapy is based on increasing the temperature of a malignant tissue above its standard value (37°C) to hinder cellular processes. In this context, incorporating metallic NPs that convert electromagnetic radiation into heat via plasmonic resonances has been widely investigated in the past decade.

The optical response of a NP is characterized by its scattering (σ_{Scat}) and absorption cross sections (σ_{Abs}). The heating power of a metallic NP under continuous wave illumination is related to the incident light intensity and the absorption cross section of the NP [240]:

$$P = I \cdot \sigma_{\text{Abs}} . \quad (4.1)$$

The efficiency of PTT is determined by these two parameters. The amount of light intensity reaching the NP inside a human body is limited by the attenuation of biological tissue whereas the absorption cross section depends on the size, shape, and material properties of the NP. Among various materials, gold is the dominant choice for NPs especially in biological applications due to its chemical inertness, biocompatibility, and ability to support localized surface plasmon resonance (LSPR). Several studies indicate that a rod-like design is the most

efficient geometry for PTT applications [273]–[275]. More recently, NPs with large flat surfaces are shown to demonstrate better internalization properties which led us to replace nanorods with nanobar structures as potentially a more suitable geometry for PTT applications [188].

The light penetration problem into the human body is overcome either by using optical fibers inserted through the body to transmit light into tumors or by utilizing external illumination at specific wavelength bands where human body is most transparent. These wavelength bands are called the biological transparency windows and located in near-infrared (NIR) region of the spectrum. So far, PTT is experimentally demonstrated in NIR-I (700–950 nm) [42] and NIR-II (1000–1350 nm) [45] which were discovered in 2001 and 2010 respectively. Recently, advancing photodetectors and optical instruments led to the discovery of new transparency windows at longer wavelengths: NIR-III (1600–1870 nm) and NIR-IV (2100–2300 nm) in 2014 and 2016 [43], [44]. Although radiation in NIR-I and -II is successfully used in PTT applications, utilizing NIR-III and -IV provides significantly better light penetration in various tissue types compared to NIR-I and -II (Table 4.1). To the best of our knowledge, the publication that constitutes the core part of this chapter is the first published study exploring the NPs that can operate in the NIR-III and -IV for PTT applications.

Table 4.1: Comparison of Total Attenuation Length (μm) of Various Tissues in the BTWs

	Total Attenuation Length (μm) (L_{Att})			
Tissue Type	NIR-I	NIR-II	NIR-III	NIR-IV
Fibula^a	58	92	114	114
Prostate Normal^b	191	331	673	723
Prostate Cancer^c	115	137	175	176
Breast Normal^b	169	217	274	274
Breast Cancer^c	81	124	160	143
Rat Brain^c	192	259	290	248
Pig Brain^b	190	235	279	291
^a [276], ^b [277], ^c [44]				

The objective of this chapter is to fill this gap by investigating NP designs that can efficiently operate in these bands. As revealed in this study, upscaling the existing NP designs of NIR-I or II to the NIR-III and -IV is not a feasible solution due to inefficiencies in photothermal conversion and cell intrusion.

Total attenuation length (L_{Att}) is a metric for quantifying the tissue penetration of radiation and represents the distance where the incident light intensity (I_0) reduces by a factor of $1/e$:

$$I = I_0 e^{-\frac{L}{L_{Att}}} . \quad (4.2)$$

The following sections exhibit an extensive study of several NP designs from solid and contour-shaped gold nanobars to self-assembling gold nano-disk- and nanoring chains. The electromagnetic simulations are performed by a commercial software (Lumerical) which implements a high-frequency finite difference time domain (FDTD) solver [256]. The light excitation is linearly polarized along the long axis of the NP. The frequency dependent complex dielectric function of gold is approximated by the Brendal–Bormann model which is shown to be in very good agreement with experimental observations in the studied wavelength range [257]–[259]. The refractive index of the environment is set to 1.40 which corresponds to that of living cells [278].

4.2. Constructing Absorber Gold Nanobars in NIR-III & -IV

The LSPR of a NP can be adjusted spectrally across the BTWs by modifying its size or geometry. For rod-like NPs, there is almost a linear relation between the NP length and its LSPR wavelength. However, simply scaling up the NP designs reported for PTT applications in NIR-I and II is not enough to adopt them to NIR-III and -IV because of two fundamental drawbacks.

The first drawback is that scaling alters the NPs' dominant response character at its LSPR: Solid gold nanobars (or nanospheres) that are good absorbers (absorb most of the incident radiation) in NIR-I become scatterers (absorb some of the incident radiation but scatter more of it) when scaled to NIR-III or IV. Figure 4.2d demonstrates this phenomenon where the absorption efficiency coefficient:

$$\phi_{Abs} = \frac{\sigma_{Abs}}{\sigma_{Abs} + \sigma_{Scat}}. \quad (4.2)$$

of a solid gold nanobar (Figure 4.2a) is plotted as a function of its length and width. The majority of solid nanobars for NIR-III and -IV are scatterers ($\phi_{Abs} < 0.5$). The preceding chapter established that a contour nanobar which is obtained by introducing a hollow region to the solid nanobar enhances the ϕ_{Abs} significantly [279]. This manifests itself here by the darkening of the entire plot region in Figure 4.2, parts e and f, as the colormapped ϕ_{Abs} shifts to higher values with increasing contour size.

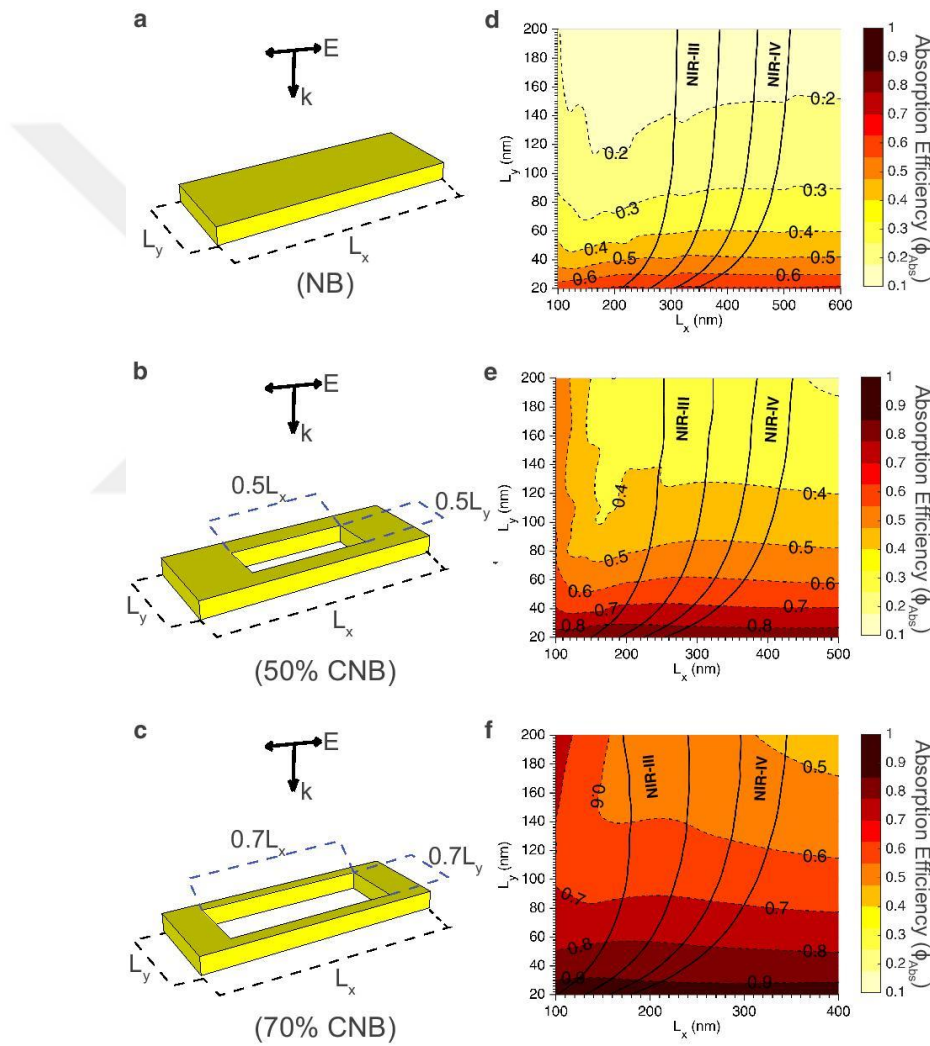


Figure 4.2: Schematic of (a) solid (NB), (b) 50% contour (50% CNB), and (c) 70% contour nanobars (70% CNB) and (d–f) their respective absorption efficiency (ϕ_{Abs}) as a function of the nanobar dimensions. Black lines border respectively the regions where the nanobar is resonant in NIR-III or NIR-IV.

Even though the current research on the cell intrusion mechanism for NPs is not conclusive, [280], [281] decreasing the dimensions of the NP would likely ease this process in addition to increasing the spatial resolution for thermal spot generation. A comparison among parts d–f of Figure 4.2 also shows that the NIR-III and -IV active regions shift toward smaller nanobar lengths with increasing contour size which is particularly noticeable for narrower designs (see where the NIR-III and -IV active regions cross the x-axis in Figure 4.2d–f). Thus, the contour nanobar design aids in eliminating both drawbacks at once.

Increasing the absorption efficiency (ϕ_{Abs}) is only one aspect as the absolute value of the absorption cross section (σ_{Abs}) is the key parameter in maximizing the heat generation. A recent experimental study of PTT in NIR-I employs small gold nanorods ($L = 16\text{--}45\text{ nm}$) that have almost 100% absorption efficiency and very high cellular uptake [282]. However, due to the very small σ_{Abs} , in order to generate enough heat for cell ablation, high laser intensities around 12 W/cm^2 were required which is well above the healthy limit ($1\text{--}2\text{ W/cm}^2$). The intensity could be reduced by increasing the NP concentration, but this causes further detrimental effects such as the elevated cytotoxicity.

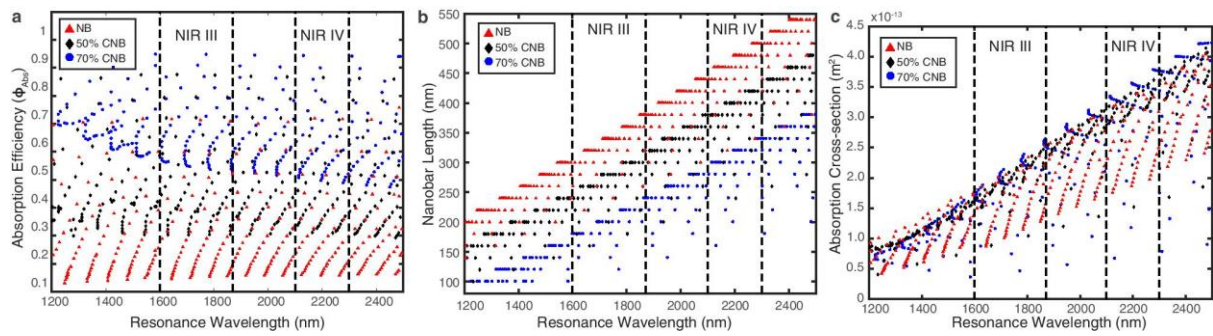


Figure 4.3: Benchmarking the solid nanobar (NB, triangle) and contour nanobars (CNB, star, circle) in terms of absorption efficiency (ϕ_{Abs}), nanobar length, and absorption cross section (σ_{Abs}) in NIR-III and NIR-IV. The distribution of data points due to a large number of solid and contour nanobars provides visual cues on the merits of contour design. Compared to the nanobars, most of the contour nanobars provide better ϕ_{Abs} (a) and smaller size (b) and accumulate more along the maximum σ_{Abs} trend (c). Note also that the maximum σ_{Abs} trend shows a universal behavior, independent of the nanobar design.

Evidently, designing a NP for PTT involves many trade-offs and requires a multidimensional optimization of absorption efficiency (ϕ_{Abs}), NP size and absorption cross section (σ_{Abs}). Figure 4.3 shows the scatter plot of a large number of solid and contour nanobars to benchmark these performance parameters and visually highlight the general strengths of the contour design. The contour nanobars resonant in NIR-III and -IV, on average, achieve 100–200% improvement in absorption efficiency ($\phi_{\text{Abs}} \sim 0.4\text{--}0.6$) depending on the contour percentage (Figure 4.3a). Furthermore, the contour nanobars provide 15–40% reduction in size compared to solid nanobars (Figure 4.3b).

Regarding the absorption cross section, Figure 4.3c shows that the contour nanobars crowd along the maximum σ_{Abs} trendline. This implies more freedom in design parameters while keeping the σ_{Abs} close to its maximum. Figure 4.3c also highlights the advantages of working in longer wavelength transparency windows (i.e., NIR-III and -IV) as the maximum of the σ_{Abs} linearly increases with resonance wavelength. Therefore, heat generation per particle is significantly higher in NIR-III (150%) and NIR-IV (250%) in comparison to NIR-II.

As stated before, the relation between the NP size and the cellular uptake is not clearly understood and varies significantly with the cell type and the NP geometry due to the differing mechanisms of endocytosis [283], [284]. The internalization of a NP is a 2-step process which starts with the adherence of the NP to the cell surface, followed by membrane wrapping and endocytosis. NPs of different shapes and sizes interact differently with the cell membrane. Findings of a recent study show that NPs with large flat surface areas generate stronger adhesion forces between the NP and the cell membrane. Additionally, membrane wrapping and accelerate cellular internalization [188]. In the light of these findings, regarding cellular internalization, nanobars have a favorable advantage over the commonly used nanorod design in PTT applications.

The internalization of gold NPs smaller than 100 nm for PTT in NIR-I and -II is well-known and reported by a number of studies [233], [273]–[275], [282]. However, there is need for further experimental evidence to support internalization of the gold nanobars in the dimensions analyzed in this study (300–500 nm). Evidently, size is a less stringent condition for nonmetallic (e.g., polymer) and organic NPs as internalization of such nanostructures up to 3000 nm is experimentally observed [284], [285]. One alternative solution to bypass the size limitation of monolithic nanobars is self-assembling NPs. These nanostructures are based on

disk/ring shaped NPs with diameter smaller than 100 nm which can first be transferred individually through the cell membrane and then assembled into a chain to construct a nanobar-like structure inside the cell. Next section is dedicated to the investigation of this approach.

4.3. Self-Assembling NPs: Nano-Disk Chains (NDCs) & Nano-Ring Chains (NRCs)

The self-assembly of nanodisks via DNA or protein assistance is well documented [243], [270], [286]–[288] and was also demonstrated in intracellular scale [289]. A nanodisk chain (NDC) is smaller than its monolithic nanobar counterpart but still resonates at the same wavelength [272]. Replacing nanodisks by nanorings would be a simple implementation of the contour design to the self-assembling NP chains. There are both top-down and bottom-up methods for fabricating these nanodisk and nanoring structures [290], [291]. Biological applications generally require vast number of NPs dispersed in solution and bottom-up fabrication techniques can provide low-cost solutions that can easily be scaled for mass production. Compared to nanospheres/shells, nanodisks/rings has the potential to increase the flat surface area for superior surface adhesion and to create high local curvature for better membrane wrapping, both of which contribute positively to their rate of cellular uptake.

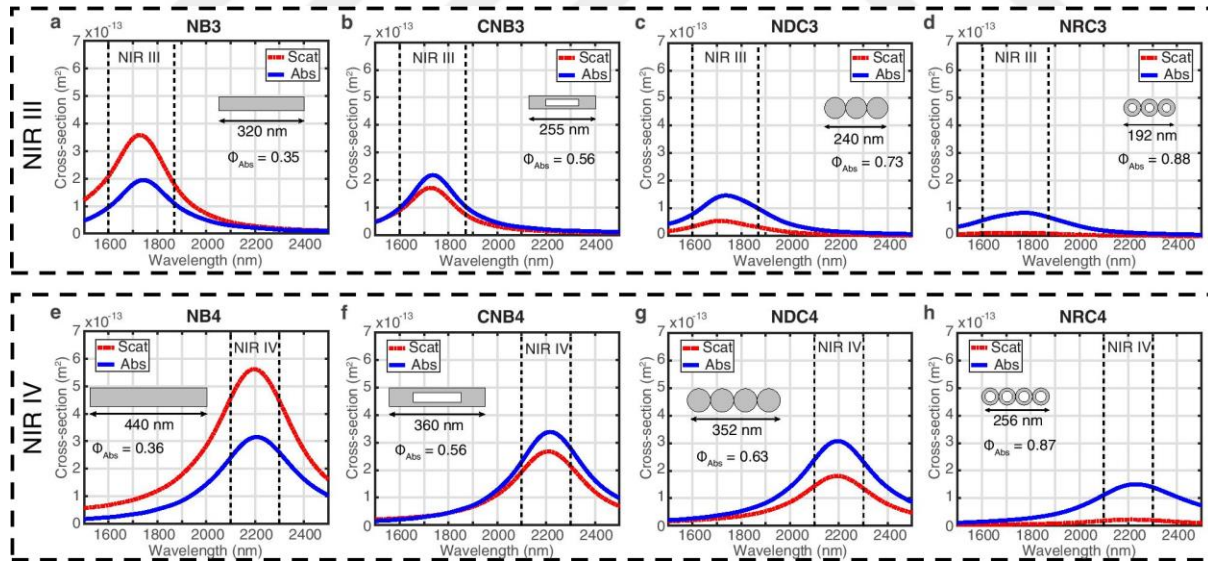


Figure 4.4: Comparison of the optical cross sections (absorption and scattering) of solid nanobar (NB), contour nanobar (CNB), nanodisk chain (NDC), nanoring chain (NRC), designed for NIR-III and NIR-IV, respectively. The change in the ordering of the cross section curves from part a to part b and from part e to part f indicates that the contour design transforms

the dominant response of the solid nanobar from scatterer to absorber in both NIR III and IV. For the nanoring chains (d, h), scattering is almost completely suppressed, rendering them as highly efficient absorber nanoparticles.

Figure 4.4 displays a comparison of the absorption properties of self-assembling NDCs/NRCs and monolithic solid/contour nanobars with samples picked from each design having the same resonance wavelength centered in the NIR-III and -IV. The scattering and absorption cross section spectra of these samples plotted respectively and signify that the NRC is the smallest in size and has the highest absorption efficiency both in NIR-III and -IV. Cellular internalization and size comparisons aside, the best performing NP candidate among these would be the contour nanobar with highest absorption cross section among all (7% larger than the solid nanobar) while also providing a moderate reduction in size (18% smaller than the solid nanobar) and in the amount of gold used per NP (40% less than solid nanobar).

Although cytotoxicity levels highly depend on particle morphology and targeted cell type, a generic metric used in measuring the toxicity level is the internalized mass of gold. Normalizing the absorption cross section with the mass of the NP produces a figure-of-merit (heating efficiency per mass) that approximately measures the heating efficiency of various NPs at a normalized toxicity level. Table 4.2 lists the heating efficiency per mass (HEPM) and the absorption cross section (σ_{Abs}) of NPs operating in NIR I–IV:

$$HEPM = \frac{\sigma_{Abs}}{m_{NP}}. \quad (4.4)$$

Overall, longer wavelength transparency windows (NIR-III and -IV) enhance the heat generation per particle (see Average σ_{Abs} in Table 4.2) by almost a full order of magnitude. On the other hand, HEPM is at its largest in NIR-I (see rightmost column in Table 4.2) partly due to an outlier data and partly because of the near 100% absorption efficiency of small NPs resonant in NIR-I. Nevertheless, it is remarkable that the contour NPs in NIR-IV (i.e., CNB 4 and NRC 4) provide an HEPM value on par with the other NPs listed in NIR-I. Moreover, a comparison of NPs, both in NIR-III and -IV, shows that the contour NPs (CNBs and NRCs) provide 50–90% improvement in HEPM over the noncontoured ones (NBs and NDCs).

Table 4.2: Comparison of the Absorption Cross Section (σ_{Abs}) and Heating Efficiency per Mass (HEPM) in All BTWs of Plasmonic Nanoparticles (RIS: rod-in-shell, NB: nanobar, CNB: contour NB, NDC: nanodisk chains, NRC: nanoring chains)

NIR Window	NP Type	σ_{Abs} (m ²)	Average σ_{Abs} (m ²)	HEPM (m ² .g ⁻¹)	Average HEPM (m ² .g ⁻¹)
NIR-IV	NB 4 ^a	3.15e-13	2.78e-13	17.6	25.9
	CNB 4 ^a	3.39e-13		30.9	
	NDC 4 ^a	3.08e-13		21.8	
	NRC 4 ^a	1.51e-13		33.2	
NIR-III	NB 3 ^a	1.93e-13	1.60e-13	14.9	19.9
	CNB 3 ^a	2.13e-13		27.5	
	NDC 3 ^a	1.48e-13		16.9	
	NRC 3 ^a	8.50e-14		20.3	
NIR-II	RIS ^b	2.00e-14	2.00e-14	21.4	21.4
NIR-I	RIS ^b	3.00e-14	1.29e-14	32.1	40.5
	Rod-I ^b	2.00e-14		61.8	
	Rod-II ^c	2.50e-16		32.7	
	Rod-III ^c	1.40e-15		35.4	
^a [292], ^b [293], ^c [282]					

4.4. Peripheral Heating & Selectivity Analysis of BTWs

PTT is applicable to a wide range of cancer types in different tissues. Each tissue type has its own set of restrictions, from the choice of the transparency window for optimum light penetration to the NP morphology for optimum cellular internalization. Because of these limitations, each treatment requires a tailored PTT strategy. For tissues that internalizes NPs under certain size limits (200/300 nm for NIR-III/-IV) self-assembling NP chains (NDCs and NRCs) propose a viable option. The self-assembling nanostructures such as NDCs and NRCs come at a cost of increased complexity due to the additional step of intracellular self-assembly. Besides, these self-assembling structures have lower heat generation per particle especially for the case of NRCs (see σ_{Abs} in Figure 4.4 and Table 4.2). However, in applications where the maximum absorption efficiency of the NP is of primary concern (e.g., photothermal imaging

[294]), NRCs perform better than NDCs in suppressing the scattering induced noise and interference. Additionally, from the perspective of heat generated per mass of gold, NRCs quite effectively replicate even surpass the efficiency of monolithic contour nanobars (Table 4.2).

Table 4.3: Peripheral Heating and Selectivity: Comparing the Absorption Coefficients of Rat Brain Tissue with and without NPs

NIR Window	NP Type	μ_{Brain} (mm^{-1}) ^a	μ_{NP} (mm^{-1})	Selectivity Contrast
NIR-IV	NB 4	1.44	73.5	51
	CNB 4		128.9	90
	NDC 4		91.0	63
	NRC 4		138.4	96
NIR-III	NB 3	0.54	62.1	114
	CNB 3		114.4	210
	NDC 3		70.6	130
	NRC 3		84.4	155
NIR-II	RIS ^b	0.07	89.0	1198
NIR-I	RIS ^b	0.004	133.6	36100
	Rod-I ^b		257.4	69576
	Rod-II ^c		136.2	36813
	Rod-III ^c		147.5	39852
^a [44], ^b [293], ^c [282]				

One concern in utilizing longer wavelength transparency windows in PTT applications is the absorbance of human tissue and its effects on the selectivity of heating and peripheral photothermal damage. Selectivity contrast ($\mu_{\text{NP}}/\mu_{\text{brain}}$) defined as the ratio of the absorption coefficient of the cell doped with NPs to that of the bare cell is a suitable metric for quantifying the selectivity of heating. The absorption coefficient is the inverse of the attenuation length presented in Eqn. (4.2) and represent the intensity attenuation of light passing through a medium due to absorptions. A large absorption coefficient signifies a short penetration of the light into the medium. The absorption coefficient of an ensemble of randomly oriented NPs are estimated at a concentration of 25 pg per cell is calculated as done similar by Cole et al. [295]:

$$\mu_{NP} = \langle \sigma_{Abs} \rangle \cdot N_{NP} . \quad (4.5)$$

N_{NP} is the number of AuNPs in a cell calculated by 25 pg/m_{NP} and $\langle \sigma_{Abs} \rangle$ is the average absorption cross section of a NP in random orientation. The selectivity contrast gives a rough factor by which the temperature in the tumor cell can be increased compared to the ambient heating generated by the irradiation (Table 4.3). The contour NPs proposed for NIR-III and -IV can provide about 2 orders of magnitude selectivity contrast, which is sufficiently large. The selectivity contrast of NIR-I is extremely high (in this case, due mostly to the very small absorption coefficient of brain at NIR-I wavelengths). Unfortunately, this does not imply an ultimate photothermal performance in practice due to other relevant factors discussed previously.

4.5. Fabrication and Potential Use Cases for Contour AuNPs

The chemical growth techniques for producing NPs provide several advantages compared to lithographic techniques. Chemical growth yields high morphological uniformity in mass production and produces single crystalline NPs which exhibit better plasmonic response. The sensitivity to growth conditions enables fine control on NP morphology, but also introduces a challenge to preserve uniformity across different growth batches. The clear advantages for commercialization such as lower cost and compatibility to industrial-scale production also introduce decisive factors in the layout [296]. The nanodisk and nanoring building blocks are well suited and presently achievable by chemical growth techniques [290], [291].

While the work in this chapter highlights the potential use of the proposed NPs in PTT, they can be implemented in other applications. The enhanced absorption efficiency and size reduction achieved by the contour and self-assembling NP designs can be utilized in chemistry [229], [230], [241] to improve localization of nanoscale heat generation in superheating and nanocavitation, [235], [297] plasmonic photocatalysis [298], [299] and plasmon-assisted phase separation [300].

Contour design can be exploited for more than increasing absorption efficiency of the NPs. The hollow regions of both the monolithic and the self-assembling nanostructures are utilized as light triggered drug [234] and gene [301] delivery vehicles into to the cancer cells. The hollow region can also be filled with a photosensitizer that uses the absorbed energy to produce

reactive oxygen species to kill cancer cells (photodynamic tumor therapy) [302]. Synergistic therapeutic strategies that use multimodal nanoplateforms (e.g., PTT + light-mediated chemotherapy, PTT + photo-dynamic tumor therapy) are shown to perform better than any single therapeutic approach [303]–[305]. Another perspective on the multi-modal approach is to utilize thermosensitive liposomes as drug delivery agents which are then triggered by the mild heating generated by the NPs [306].

4.6.Conclusion: Facilitating Deep Tissue PTT with Smart NP Designs

The NIR-III and -IV BTWs are promising candidates for the future of PTT applications in cancer treatment. These bands offer deeper tissue penetration (up to 2×) and, with well-engineered NP designs, more efficient heat generation. The contour nanobars and self-assembling nanodisk/ring chains provide both size reduction and enhanced absorption efficiency, which are two of the critical parameters in the optimization of NPs for PTT. Evidently, NP size, cellular uptake mechanisms, and cytotoxicity impose nonlinear and often nonintuitive constraints that require experimental data to assert the true potential of these NPs. The results reported here can open new opportunities in advancement of photothermal therapy applications by utilizing the newly discovered biological windows and also aid in development of nanoscale heat generation in general from nanocavitation and superheating to plasmonic photocatalysis and photothermal imaging applications.

Chapter 5:

NP DESIGN FRAMEWORK: A DATA SCIENTIFIC APPROACH

Research on gold nanoparticles (AuNPs) for cancer therapeutics and diagnosis shifted to building complex nano platforms that can simultaneously offers multiple modalities. Yet, commercialization of such platforms has been limited due to complicated fabrication and constraints in production costs, especially as the test subject's body mass scales up from a 20 g mouse to 75 kg human. Elementary AuNPs such as spheres, disks and cylinders are still the most viable candidates for large scale and feasible nanomedical tools in the fight against cancer. Therefore, establishing a fundamental understanding of elementary AuNP properties is an important challenge. The diversity of tumor types and the individuality of the patient requires dedicated AuNP designs tailored specifically for each patient paving the way towards personalized medicine. This chapter is a data scientific perspective on elucidating the relationship between the morphological features and the optical properties of elementary AuNPs.

The rapid evolution of nanomedicine as a field imposes continually changing constraints on engineering AuNPs while gradually making well-established designs obsolete. Each step of progress and the subsequent transformation in the desired optical properties necessitate a costly and slow process of reoptimization of AuNP morphology to find the best performing design. Adapting the AuNPs to the shifting demands requires a structured understanding on how to tailor NP morphology that best serves the target application while fulfilling the continuously updated constraints. The main objective of constructing a structured design framework is to empower researchers from all the contributing disciplines including medicine, biology, and chemistry with an essential and easy to use tool to identify the most appropriate AuNP matching the requirements for the target application.

5.1.Introduction: Constructing a Design Framework for Engineering AuNPs

Historically the efforts of understanding the relation between AuNP morphology and its optical properties was based on deductive analysis. Earlier models were built upon existing and well-understood physical theories such as harmonic oscillator with the addition of corrective terms to account for the underlying mechanics of LSPR including radiative and non-radiative damping. The proposed deductive models are consequently fitted to the experimentally and computationally generated optical response of the AuNPs to derive model parameters for each particular NP. The deductive models aim to establish a deep-rooted understanding of the mechanics governing the LSPR in a AuNP and draw conclusive insight about the relationship between the optical properties and NP morphology. The advanced deductive models feature several parameters to truly capture the intricate physics of the collective electron oscillations in AuNPs. The downside of large number of parameters is the difficulty of producing consistent and physically relevant fits to the experimental measurements. On the other hand, simple models with few parameters are considerably limited to capture all the nuances of the underlying physics but produces consistent fits to the generated NP optical response with diminishing success in capturing the distinguishing features.

Deductive models address the challenge of extending our understanding of AuNPs by leveraging existing theories of physics. Shifting the basis of the model to empirical observations such as data generated through computational studies brings an innovative approach to the NP engineering problem. An inductive model seeks patterns in the empirical data that will eventually form theories. The main objective of this chapter is to propose an inductive approach to expand our understanding of AuNPs that serves to ease the challenge of choosing the right morphology for accomplishing the ever-evolving task provided by the continually advancing cancer research.

5.2.Deconstructing the Framework: NP Geometries & Design Parameters

The initial constituent of a design framework is the systematic analysis of AuNP properties. Defining the elementary NP geometries, categorizing features to tune and targets to accomplish form the foundation of the framework that operates as an infrastructure layer for the entire AuNP design challenge.

5.2.1. Elementary Geometries for AuNPs & Degeneracy of the LSPR Modes

Geometry of a AuNP is an essential part of its design that determines the optical and pharmacokinetic properties in a large extent. Although wide variety of geometries and intricate designs are available thanks to the rapidly advancing research in chemistry of AuNP synthesis, the framework proposed here is founded on a systematic approach that reflects the perspective of physics and therefore centered around the fundamental attribute of AuNPs: LSPR. AuNPs support 3 fundamental LSPR modes corresponding to the 3 fundamental axes of its geometry. The degeneracy and the relative strength of these LSPR modes are strong identifying factors that can be used to classify the AuNP geometries. Degeneracy in the context of AuNPs represents the number of fundamental LSPR modes that can be induced at the same frequency. The level of anisotropy of a NP geometry determines the degeneracy of the LSPR modes. Spherical NP geometries are isotropic with 3 indistinguishable LSPR modes of equal strength, i.e. triply degenerate.

Cylindrical NP geometries support two distinct LSPR modes of differing strengths. The dominant mode confusingly referred to as Longitudinal Surface Plasmon Resonance (LSPR) and corresponds to the collective electron oscillations along the longer geometric dimension. On the other hand, Transverse Surface Plasmon Resonance (TSPR) is the weaker mode that occur along the shorter geometric axis. Doubly degenerate NPs are divided into two groups: gold nanodisks (AuNDs) with doubly degenerate LSPR and a singlet TSPR; and gold nanocylinders (AuNCs) with a singlet LSPR and doubly degenerate TSPR. The two topologically indistinguishable geometries exhibit significant differences in the case of AuNPs, especially in biological applications.

The cumulative response of a AuNP to the external stimulation by the electromagnetic radiation is determined by the contributions of each fundamental LSPR mode. For an individual AuNP, its presence in biological medium in a randomly oriented configuration introduces randomness to the contribution of each fundamental LSPR mode. In a large ensemble of AuNPs, as there is no favorable geometric orientation, the randomness averages out where each fundamental LSPR mode contributes equally to the cumulative response of the AuNPs ensemble. This subtle incidence highlights the importance of the distinction in AuNP design terminology for differentiating a AuND with diameter larger than thickness; from a AuNC with length dominating the diameter. The optical response of an ensemble of AuNDs (OR_{AuNDs}) is

composed of:

$$OR_{AuNDs} = \frac{2}{3}LSPR + \frac{1}{3}TSPR . \quad (5.1)$$

whereas in the case of an ensemble of AuNCs the optical response is:

$$OR_{AuNCs} = \frac{1}{3}LSPR + \frac{2}{3}TSPR . \quad (5.2)$$

The difference between the optical responses of the two NP ensembles is a critical factor with significant consequences to the NP performance. Identifying the parameter that controls this factor is an example to the kind of questions this framework aims to answer. Next section as well as the rest of this chapter is dedicated to identification of such influential parameters to the performance of AuNPs and the corresponding variables that control these parameters.

5.2.2. Taxonomy of NP Properties: Feature vs. Target Variables

A systematic approach to identifying and classifying NP properties is an essential part of the framework construction and offers an original challenge that benefits considerably from introduction of data scientific concepts. The data scientific perspective of AuNP design proposed in this chapter seeks to serve two key objectives. The first objective addresses practical concerns and aims to establish a framework to guide researchers for finding the most appropriate NP morphology to the target application. The second objective is what differentiates the approach proposed here from studies leveraging artificial intelligence for engineering AuNPs. By pushing the emphasis beyond pragmatic concerns and practical measures, the second objective of the data scientific approach is to develop the foundation for illuminating the mechanics governing the AuNP behavior in future studies. Thus, the scope of this chapter is limited to identifying patterns in engineering NPs rather than building machine learning algorithms to find the best performing NP design with restricted visibility on the underlying mechanics.

Figure 5.1 summarizes the proposed systematic analysis of elementary AuNPs and presents the framework to categorize the AuNP properties by introducing data scientific terminology starting with distinction of feature and target variables. Feature variables (features) are the parameters that can be controlled or manipulated in the production processes and primarily affect the AuNP properties. On the other hand, target variables (targets) are the key measurable

performance indicators of AuNPs relevant to the applications. Features and targets form the initial layer of classification. The second layer expands the taxonomy of AuNP properties to distinguish the directly and indirectly controlled/measured variables. Primary parameters represent directly measurable or controllable variables such as the resonance wavelength or the diameter of AuNP. Alternatively, there are equally important parameters that are widely accepted as key utility metrics especially for nanomedical applications in the literature, such variables are classified as derived parameters. The derived parameters are defined as a function of multiple primary parameters and cannot be measured/controlled directly.

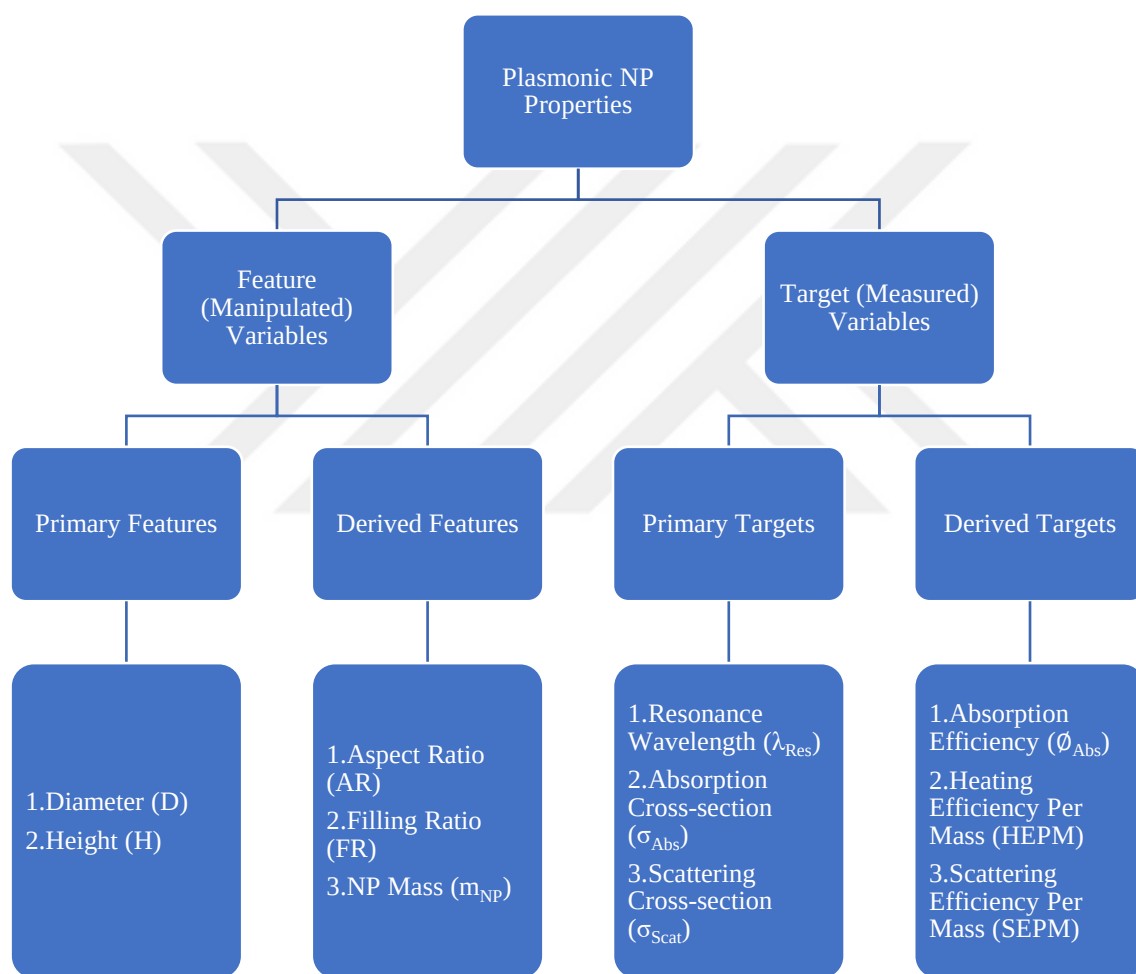


Figure 5.1: Schematic for Categorizing Plasmonic NP Properties

5.3.Expounding the Dataset: Spanning the Design Space

The deductive analysis of AuNPs commence with established theories of physics and aims to build a model by adjusting these theories. Contrarily, an inductive analysis originates from data

and by seeking patterns in the dataset aspires to develop a model that captures the interaction of AuNP feature and target variables.

The dataset studied in the following sections of this chapter is formed through simulations of elementary AuNP geometries, i.e. sphere, disk, and cylinder, using the MNPBEM package in MATLAB. The refractive index of the environment is set to 1.40 which is equivalent to that of a living cell. All three principal LSPR modes are exited for each AuNP along principal geometric axes. The resulting absorption and scattering cross sections are averaged with equal weight to portray the random orientation of AuNP in the biological medium. Both hollow and solid forms of elementary AuNPs are simulated and the generated data is assembled to construct a sizeable multidimensional database of the optical spectra of these AuNPs across the four near-infrared biological transparency windows within the 500-2500 nm range of the electromagnetic spectrum.

5.3.1. Exploring the Boundaries of the Feature Space

The term NP has a flexible definition, but the consensus is that the nomenclature applies to particles with at least one dimension of size around 100 nm or less. The dataset covers solid and hollow elementary AuNPs with the largest dimension (will be referred to as size) ranging from 15 to 900 nm while keeping at least one dimension in accordance with the limits defined above with the exception of few cases that are studied to highlight the behavior of edge cases and to explore overall continuance of the uncovered trends. Table 5.1 illustrates the resulting dataset of more than 300 distinct observations which provides an extensive representation of elementary AuNPs used in biological applications including photothermal cancer therapy and complementary diagnostic modalities.

Aspect ratio (AR) as a derived feature defines the proportional relation between the two primary features: diameter and height.

$$AR = \frac{\text{Height } (H)}{\text{Diameter } (D)}. \quad (5.3)$$

AR is the critical parameter that controls the relative strength of LSPR and TSPR in anisotropic AuNPs and significantly affects the optical response of a NP ensemble.

Analogously, filling ratio (FR) is defined as a metric to measure the thickness of the metallic

shell in proportion to the outer diameter of the NP:

$$FR = 1 - \frac{\text{Diameter (D) of the Hollow section}}{\text{Diameter (D) of the Entire NP}}. \quad (5.4)$$

A solid gold nanodisk (AuND) has a FR = 100% whereas a hollow counterpart, i.e. gold nanoring (AuNR) with the hollow region diameter half of the entire NP retains a FR = 50%.

Table 5.1: Feature Space of Elementary AuNP

	Solid	Hollow
Sphere	<u>Height</u> : 20 – 200 nm	<u>Height</u> : 20 – 200 nm
	<u>Diameter</u> : 20 – 200 nm	<u>Diameter</u> : 20 – 200 nm
	<u>AR</u> : 1	<u>AR</u> : 1
	<u>FR</u> : 100%	<u>FR</u> : 50%, 30%, 10%
Disk	<u>Height</u> : 5 – 150 nm	<u>Height</u> : 5 – 160 nm
	<u>Diameter</u> : 50 – 900 nm	<u>Diameter</u> : 50 – 800 nm
	<u>AR</u> : 1/5, 1/10, 1/15	<u>AR</u> : 1/5, 1/10
	<u>FR</u> : 100%	<u>FR</u> : 50%, 30%
Cylinder	<u>Height</u> : 15 – 650 nm	<u>Height</u> : 35 – 750 nm
	<u>Diameter</u> : 5 – 210 nm	<u>Diameter</u> : 5 – 125 nm
	<u>AR</u> : 3, 5, 10	<u>AR</u> : 5, 10
	<u>FR</u> : 100%	<u>FR</u> : 50%, 30%

5.3.2.Characteristics of the Target Space

The target space of the dataset exposes the potential capabilities of AuNPs. Figure 5.2 explores the distribution of primary and derived target variables over 25 bins of equal size to depicts the several key characteristics of elementary AuNPs. The feature space is expansively explored spanning the operational wavelength spectrum from visible (500 nm) to near-IR region (2500

nm) that covers the entire range of biological transparency windows (Figure 5.2a).

A typical elementary AuNP has an absorption cross-section (σ_{Abs}) in the order of 10^{-14} m^2 with rare examples achieving up to 4.10^{-13} m^2 per particle (Figure 5.2b). On the other hand, the scattering cross-section (σ_{Scat}) of an average elementary AuNP is an order of magnitude larger and displays a more spread out distribution centered around 10^{-13} m^2 with extreme examples ranging up to 1.10^{-12} m^2 (Figure 5.2c). An order of magnitude difference in the scattering and absorption cross-sections shows the tendency for scattering among AuNPs and attests to the comparative difficulty of producing absorber AuNPs for photothermal applications. As the later sections will demonstrate, increasing absorption and scattering cross-sections require extensions of the NP size and more importantly the dimensional growth favors scattering characteristics more than absorptive characteristic. Hence, this tendency verifies the well-established principle regarding the optical characteristics of AuNPs that small specimens constitute good absorbers and large ones act as good scatterers. The following sections will also elucidate on how to outperform such limitations building on top of the findings of Chapter 3 & Chapter 4 while simultaneously leveraging the proposed design framework.

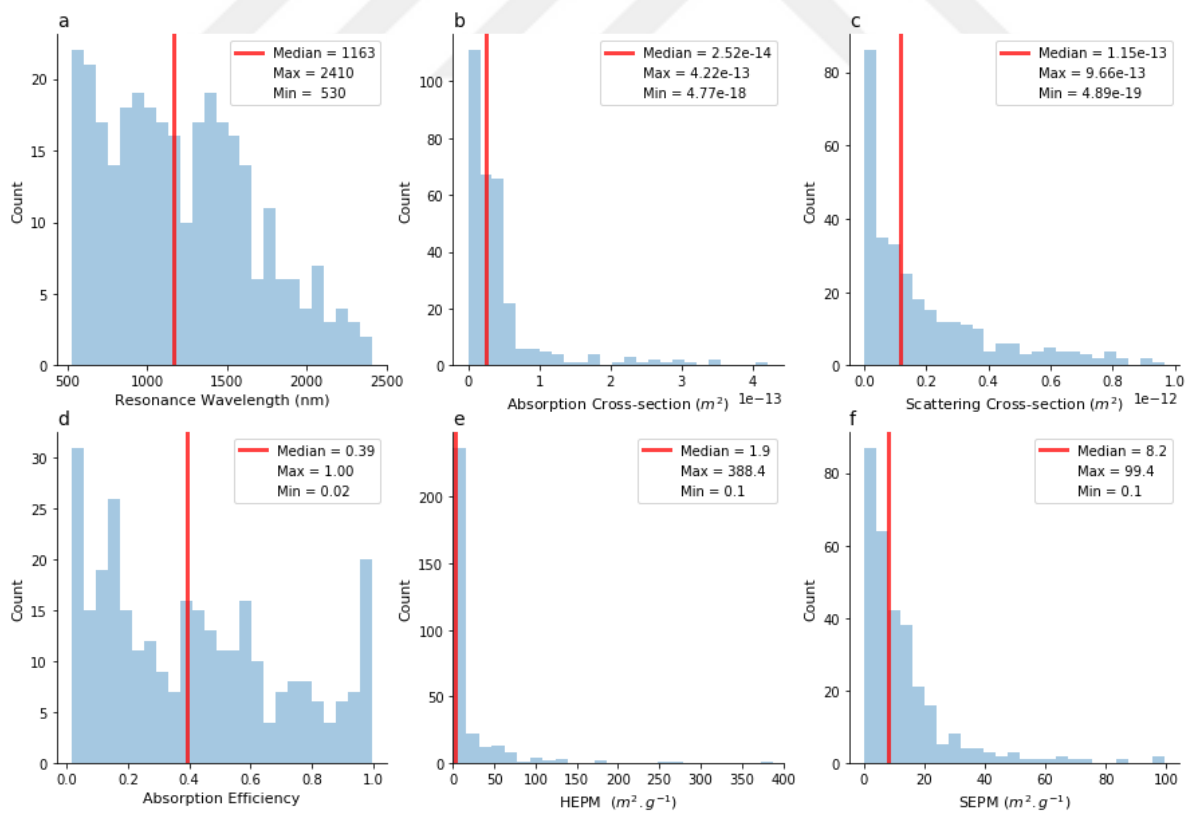


Figure 5.2: Primary and Derived Target Space of AuNP Dataset

Absorption efficiency (ϕ_{Abs}) is a derived target variable that commonly serves as a measure of the photothermal conversion efficiency of a AuNP in literature. The metric signifies the fraction of incident radiation that is converted to heat as defined in Eqn.(4.2). The distribution of absorption efficiency (ϕ_{Abs}) for elementary AuNPs (Figure 5.3d) covers the full range of from perfect absorbers ($\phi_{\text{Abs}} = 1$) to perfect scatterers ($\phi_{\text{Abs}} = 0$). The distribution also showcases the scattering tendency of AuNPs in general with 60% of the samples in the dataset dissipating more of the energy induced by the collective electron oscillations via scattering rather than heat generation.

The last two derived target variables are heating and scattering efficiency per mass (HEPM & SEPM) which are commonly used as a metric to evaluate the optical performance of AuNPs in nanomedical applications per potentially induced toxicity. The distributions of HEPM & SEPM (Figure 5.3e&f) reflect the observations of Figure 5.3b&c in an amplified manner especially in the case of HEPM (Figure 5.3e) due to higher concentration of data points at the left-hand tail. Several folds difference between the two metrics shows that engineering AuNPs for photothermal applications become even more challenging under the toxicity constraints and make the contributions of the design framework more valuable. A particular observation supporting the potential of the framework is the exceptionally high maximum attainable HEPM highlighting the scale of potential improvement.

5.4.A Dual-Perspective Design Approach: Fabrication vs. Clinical Applications

The framework for AuNPs provides the foundation for systematically exploring the optimization surface. Discovering optimum pathways for finding the physically most efficient morphologies among the biologically favorable structures are key to commercialization of AuNPs. Designing AuNPs for a wide range of applications is a highly interdisciplinary problem with contributors from various backgrounds. The proposed framework is constructed to provide easy to follow instructions to the researchers from all the contributing disciplines to attain the application-specific NP properties. Depending on the frame of reference of the researcher, the framework offers two distinct optimization paths for designing AuNPs.

The fabrication aspect of the NP research is accountable for the synthesis methods that determines the morphology of the AuNP to be produced. The initial question the researchers

working on the fabrication side, i.e. chemists, face is the choice of synthesis method which translates to engineering AuNPs as a geometry-centric optimization problem. Geometry-centric optimization approaches the NP design by initially fixing the geometry of the NP. In contrast, researchers working on the clinical application side simply act as operators of AuNPs as tools and in the reference frame of an operator the primary step in the design process is fixing the operational wavelength.

Wavelength-centric and geometry-centric optimizations appeal to distinct contributors of the AuNP research. Fixing the operational wavelength and the geometry are two different initial conditions that lead to distinct design paths. Therefore, this chapter provides two separate investigations of the AuNP design processes: Wavelength Centric Optimization for Utilization and Geometry Centric Optimization for Fabrication of the AuNPs (Figure 5.3).

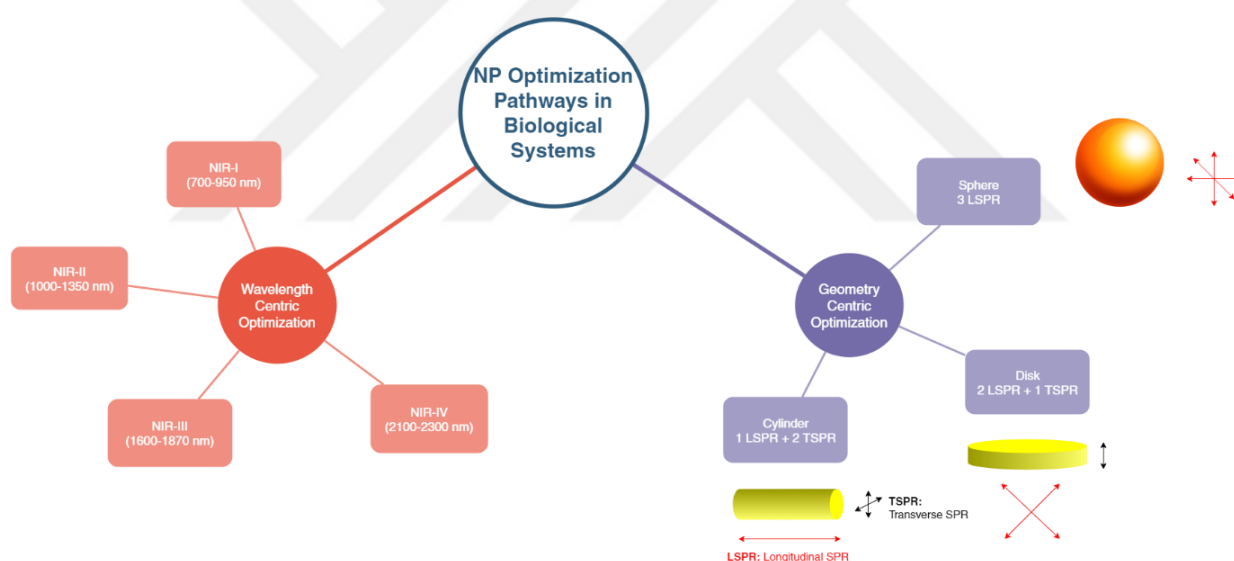


Figure 5.3: AuNP Optimization Pathways for the Manufacturer & the Operators

5.4.1. Fabricational Perspective: Geometry-Centric Optimization

Developing fabrication procedures initially starts with fixing the NP geometry and work towards producing NPs with desired target variables by tuning the procedure to adjust features such as diameter, height, and aspect ratio. Figure 5.4 presents an investigation of the dataset from the fabrication point of view centered around the NP geometry that highlights the strong influence of geometry as a determining factor on NP properties.

AuNP dataset pushes the limits of each elementary geometry to reveal the boundaries of the corresponding target space. Resonance wavelength is one of the key targets that verify the substantial influence of geometry in AuNP design as a strong determinant of the operational wavelength (Figure 5.4a). Cylindrical AuNPs (AuNCs) offer the greatest flexibility in operational wavelength and is the only elementary AuNP geometry that covers all 4 biological transparency windows. In comparison, disk-shaped (AuNDs) exhibit stronger inertia with regards to adjusting the operational wavelength as significant proportion of the samples in the dataset suited to operate NIR-II and few examples in NIR-I & -III. Spherical AuNPs (AuNSs) offer the most constraint range of operational wavelengths with most of the samples resonant in the short wavelength windows: NIR-I & -II.

Despite significant differences in the operational wavelengths, absorption efficiency remains relatively homogeneous across the elementary AuNP geometries. Perfectly absorber AuNPs ($\phi_{\text{Abs}} = 1$) are accessible by all geometries whereas perfectly scatterers ($\phi_{\text{Abs}} = 0$) are limited to AuNCs and AuNDs (Figure 5.4b).

Scattering and absorption cross-sections continue to be the most sought-after performance metrics for AuNP applications. In contrast to the absorption efficiency, the two primary target variables exhibit strong geometric dependency (Figure 5.4c&d). AuNDs show significant advantage in terms of the range of attainable absorption/scattering cross-sections, especially with specific examples outperforming the best of the other elementary geometries by up to 2-5 folds. The source of this curious observation lies in the doubly degenerate longitudinal surface plasmon resonance (LSPR). In a randomly oriented ensemble of NPs, the major contribution to the overall optical response of a NP originates from the highest degeneracy LSPR mode. As the strongest LSPR mode of AuNDs possesses the highest degeneracy, its impact is significantly amplified and leads to the outstandingly high per particle absorption/scattering cross-section in AuNDs. The scattering/absorption cross-section distributions also highlight the geometry independent scattering tendency of elementary AuNPs in general.

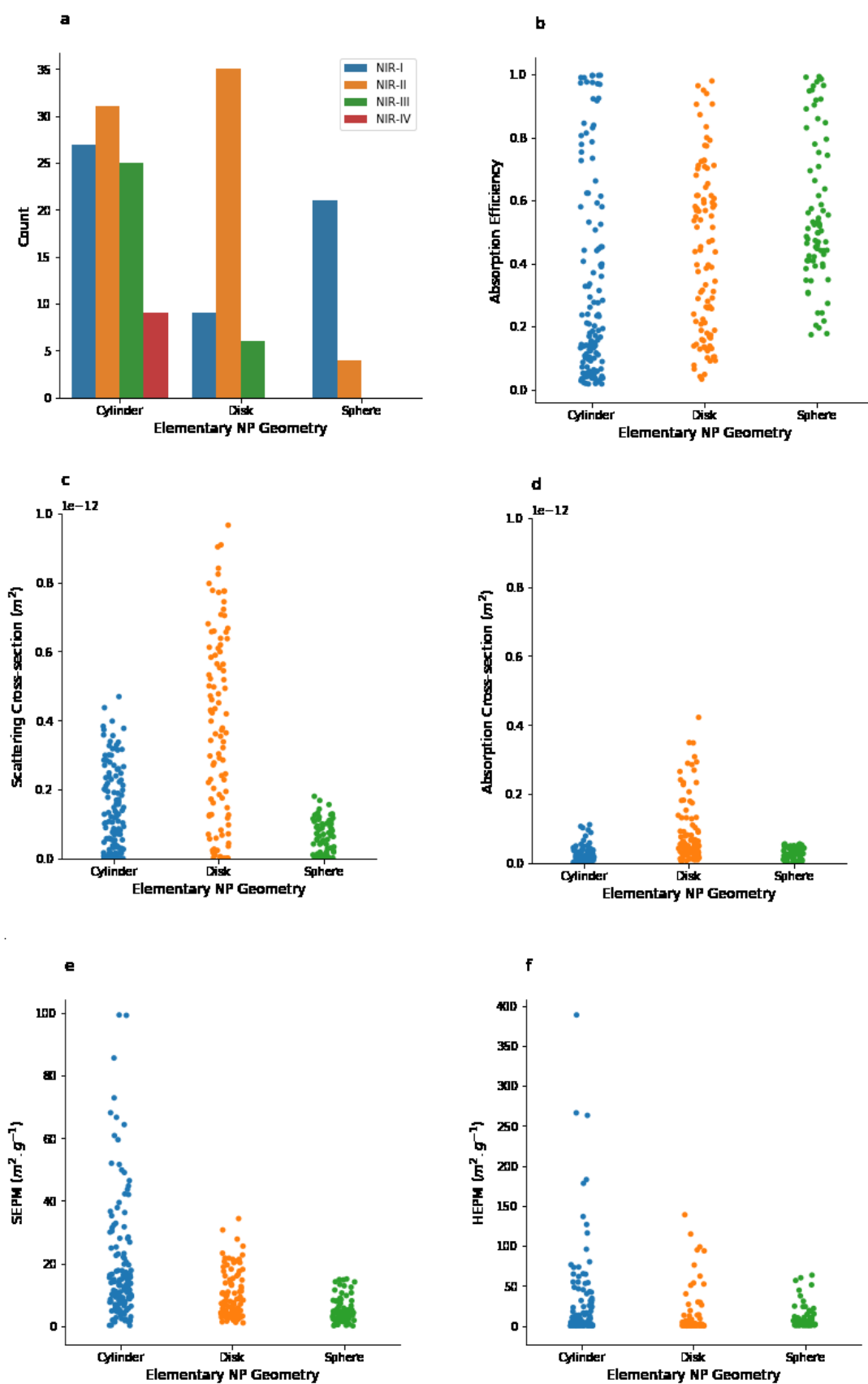


Figure 5.4: Geometry Centric Investigation of the AuNP Dataset

The per particle absorption/scattering metric disregards the NP mass which is an important constraint in nanomedical applications incorporating the toxicity concerns to the optimization process. HEPM/SEPM represents the normalized absorption/scattering per mass of gold and shows significantly different characteristics compared to the per particle absorption/scattering (Figure 5.4e&f). In contrast to the dominating per particle performance of AuNDs, the champion for the per gold mass optical performance metrics is AuNCs by a large margin. The substantial shift in the relative performance of the two anisotropic geometries is another attractive phenomenon that is caused by the interplay between the fundamental LSPR modes and the effect of the corresponding geometric dimension on the mass of the AuNP. The optical response due to the strong singlet LSPR mode of AuNCs has a much weaker influence on the NP mass (linear) compared to the strong doubly degenerate LSPR mode of the AuNDs (quadratic):

$$LSPR_{AuNCs} \sim L \text{ (NP Length)} . \quad (5.5)$$

$$LSPR_{AuNDs} \sim D \text{ (NP Diameter)} . \quad (5.6)$$

$$m_{NP} = \frac{\pi}{4} \cdot L \cdot D^2 \cdot FR \cdot (2 - FR) . \quad (5.7)$$

Besides particular inferences regarding individual design parameter, the geometry-centric analysis also provides insight pertaining to the overall performance of each elementary geometry. One such noteworthy corollary to this analysis is the relatively restrained tunability and the inferior performance of the isotropic AuNPs across most of the design parameters.

5.4.2.Operational Perspective: Wavelength-Centric Optimization

The operators working at the clinical side of the AuNP research bound by different constraints and consequently a distinct optimization process is required compared to the manufacturing side. The initial parameter that defines the AuNP design in the operator reference frame is the resonance wavelength. The core objective of this section is to outline the capabilities of elementary AuNPs in each biological transparency window (Figure 5.5).

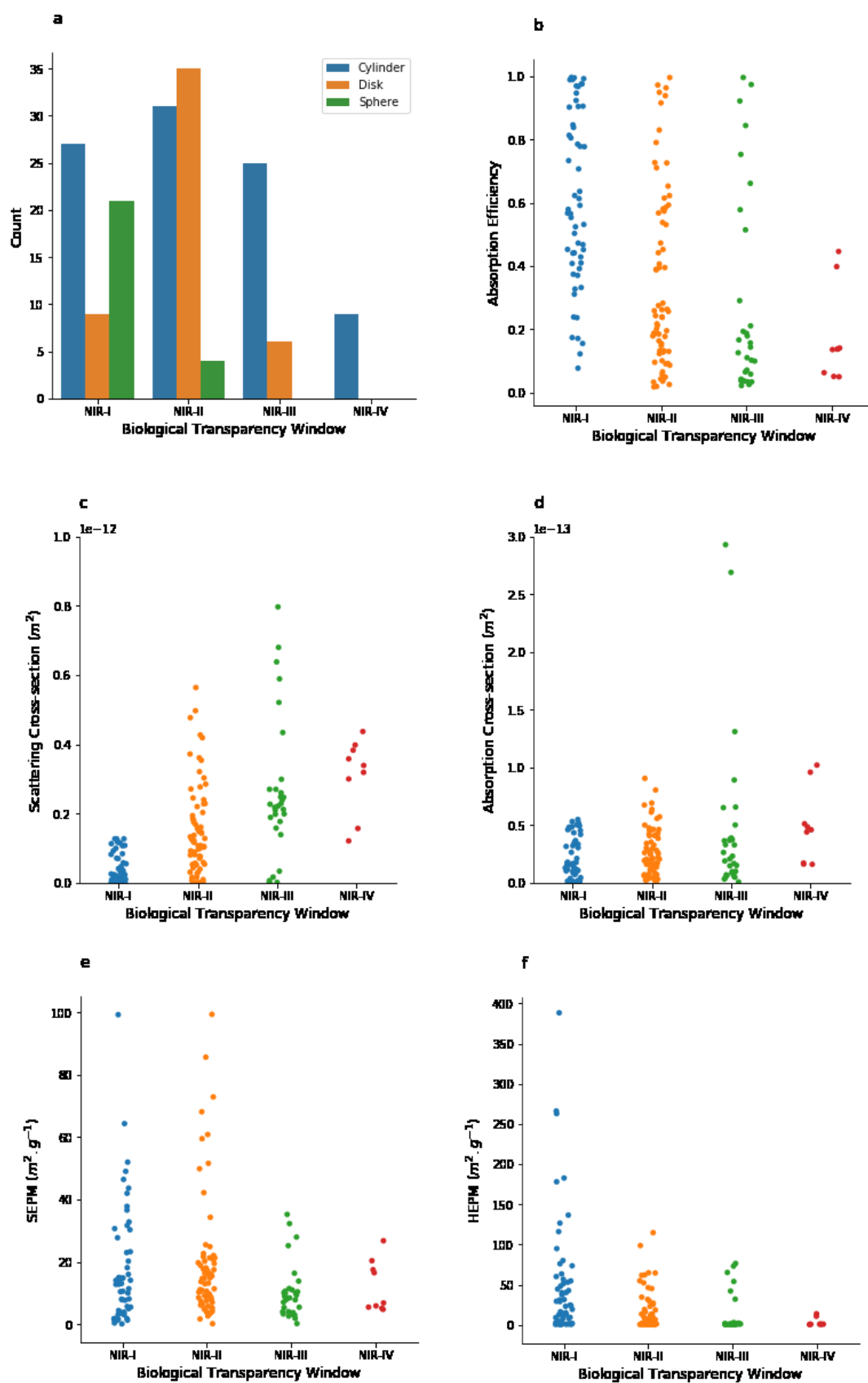


Figure 5.5: Wavelength Centric Investigation of the AuNP Dataset

In all BTWs with the exception of NIR-IV, elementary AuNPs provide samples in the full range of absorption efficiency from perfect scatterers to perfect absorbers. However, highly absorber AuNPs while easily achievable in shorter wavelength windows (NIR-I & -II) are difficult to come by in longer wavelength windows. NIR-IV and to some extent NIR-III remain underutilized due to the recency of their discovery and comparatively restrained concentration of research effort as a consequence of the practical limitations to experimentation. Producing absorber AuNPs operational in NIR-IV that convert greater extent of the incident radiation to heat remains an elusive challenge (Figure 5.5b). The primary factor limiting the absorption efficiency in NIR-IV is the larger NP size associated with long operational wavelengths (~2300 nm) and the consequent prevalence of scattering in large AuNPs.

Scattering and absorption cross-sections are reasonably homogeneously distributed across the biological transparency windows while favoring the longer wavelength windows slightly (Figure 5.5c&d). The homogeneity of the distributions is a distinguishing feature in contrast to the distributions of the geometry-centric approach indicating that the potentially maximum attainable levels of scattering/absorption per particle is relatively indifferent to the choice of operational wavelength window. Nonetheless, the order of magnitude difference between the two primary target variables is distinctly noticeable in the frame of reference of the operator as well, underlying the scattering tendency of AuNPs once more.

Mass normalization significantly disrupts the homogeneity of the per particle optical performance (Figure 5.5e&f). Shorter wavelength windows (NIR-I & -II) provide significantly more dosing flexibility for AuNPs usage as optical contrast agents and photothermal transducers by restraining the unintended toxicity effects induced in the biological medium. From an engineering perspective, the key observation is the clear trend reversal in transitioning from a per particle optical performance metric, i.e. absorption/scattering cross-section, to a per NP mass optical performance metric, i.e. HEPM/SEPM. Per mass metric strongly favors the shorter wavelength windows whereas per particle metric favors the longer wavelength windows slightly. The two contrasting trends indicate that sustaining a high level of absorption/scattering of a AuNP in longer wavelength windows requires significantly more amount of gold compared to the shorter wavelength windows. A similar turnaround is evident in the relative scale of absorption/scattering while shifting from a per particle to a per mass toxicity metric. Scattering per particle is almost an order of magnitude greater than absorption

per particle, in contrast as per mass, absorption dominates scattering by a similar extent. The shift provides valuable clues about the nature of AuNPs by highlighting the fact that scaling scattering to longer operational wavelengths is a more mass demanding process compared to that for absorption.

The following section will elaborate on the dual-perspective optimization approach to AuNP engineering presented in this section by incorporating the correlation of feature and target variables and paves the path to multi-functional AuNP designs to be utilized in advanced nanomedical applications (APPENDIX A contains the supplementary analyses).

5.5.Design Parameter Sensitivity Analysis: Tuning for Multiple Functionalities

Sensitivity analysis investigates the effects of changing specific feature variables on the overall optical performance of AuNPs. The primary objective of the sensitivity analysis conducted in this section is to answer the fundamental question: “What is the best way to control a specific NP property, i.e. certain target variable of an AuNP?” The intuitive choice for tuning a target variable is the major resonance axis (i.e. length for AuNCs and diameter for AuNDs & AuNSs) that is the geometric dimension in-line with the longitudinal surface plasmon resonance (LSPR). However, the potential of the minor resonance axis as a tuning feature variable is significantly underestimated. The minor resonance axis is the geometric dimension that corresponds to the transverse localized surface plasmon resonance (TSPR), i.e. weaker LSPR mode, and in certain cases exhibits significant control over a target variable. Exploring such anomalous cases is highly constructive for the AuNP design framework. In particular, the extreme values of correlation (close to ± 1 and near 0) assists the discovery of potentially useful relations between feature and target variables (Figure 5.6).

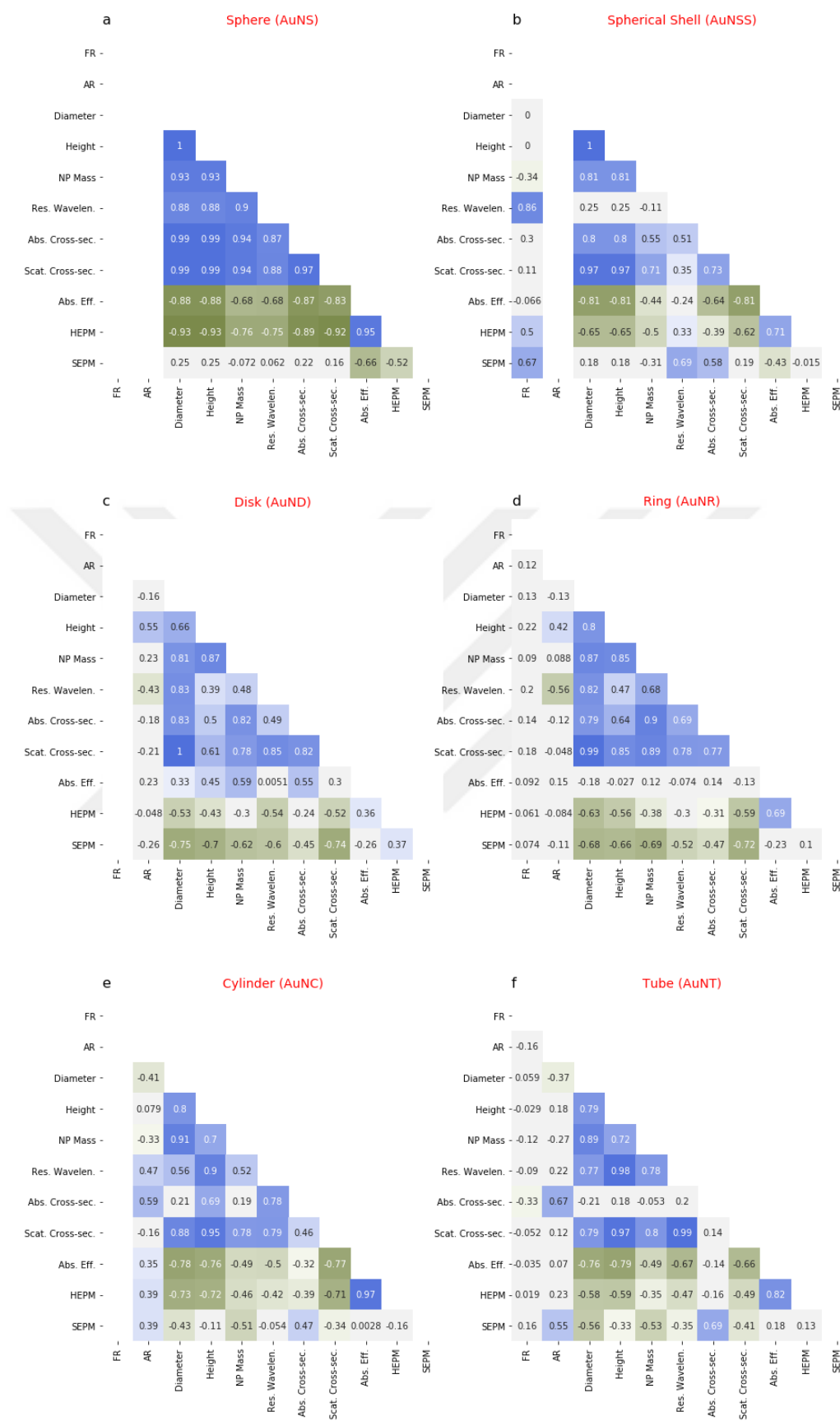


Figure 5.6: Correlation Matrices for Elementary AuNPs Properties

The preceding sections of this chapter explore the space formed by the feature and target variables of the elementary AuNP dataset together with the distribution of these variables from the fabrication and operational perspective of the AuNP research. The aim of this chapter is to scrutinize the correlations between the AuNP design parameters and develop an understanding of the relationship between individual feature and target variables which constitutes an extremely valuable tool for effectively tailoring AuNP properties to fit the application specific design criteria. Exploring the anomalies and extreme correlations are especially rewarding in devising pathways for a multistep design approach to engineer AuNPs with multiple functionalities optimized simultaneously.

5.5.1. Correlation Magnitude: Free vs. Tuning Feature Variables

The correlation matrices presented in Figure 5.6 contain large amount of valuable information for engineering AuNPs that could be made more digestible through postprocessing. The purpose of the postprocessing is to establish an indicative tool that provides guidance for identifying the most appropriate feature variable that controls each target variable of the AuNP. Defining a threshold level to classify the feature variables on an absolute magnitude basis is a practical initial step to simplify the feature-target correlation analysis. The threshold value for the classification is set to 0.5 and the choice of the threshold has limited impact as the analysis is simply intended for providing guidance.

The feature with the highest absolute correlation to a target variable that is above the threshold is defined as the tuning feature and represents the most appropriate parameter for adjusting a given target property. Distinguishing the feature that has the smallest impact on a target variable is also of equal importance. Analogous to the tuning feature, the free feature variable has the lowest absolute correlation to a given target variable while remaining below the threshold level. Identifying the free feature for a particular target variable allows the introduction of additional steps to the NP design process following the primary optimization conducted via the tuning feature. Each target variable has individually defined tuning and free features. Relying on the practical impartiality of the target variable being tuned, the free feature enables tuning of secondary features while preserving the initial optimization as the free feature of one target can be the tuning feature for another.

Table 5.2: Correlation Magnitude for Elementary AuNPs: Identification of Tuning & Free Feature Variables

Geometry	Feature	Primary Targets			Derived Targets		
		λ_{Res}	σ_{Abs}	σ_{Scat}	Φ_{Eff}	HEPM	SEPM
Sphere (AuNS)	Tuning	D	D	D	D	D	-
	Free	-	-	-	-	-	D, mNP
Disk (AuND)	Tuning	D	D	D	D, mNP	D	D
	Free	H, AR	AR	AR	AR	AR	AR
Cylinder (AuNC)	Tuning	H	H	D, H	D, H	D, H	D, mNP
	Free	AR	D, mNP	AR	AR	AR	H
Spherical Shell (AuNSS)	Tuning	FR	D	D	D	D	FR
	Free	D, mNP	FR	FR	FR	-	D, mNP
Ring (AuNR)	Tuning	D	D	D	mNP	D, H	D, H
	Free	FR	AR, FR	AR, FR	H, FR	AR, FR	AR, FR
Tube (AuNT)	Tuning	H	AR	H	D, H	D, H	D, AR
	Free	AR, FR	H, mNP	AR, FR	AR, FR	AR, FR	FR

The two subcategories of feature variables are designed to facilitate multi-objective AuNP designs and provide researchers the freedom to tune multiple target variables without disrupting the preceding optimizations. The findings resulting from the postprocessing of the correlation matrix analysis (Figure 5.6) are summarized in Table 5.2 and Table 5.3 with the aim to simplify the identification of the tuning and free features for both primary and derived target variables in all 3 elementary NP geometries, treating solid and hollow designs separately.

The prevailing pattern in Table 5.2 is the occurrence of the major resonance axis which is analogous to the largest physical dimension of the AuNP, i.e. diameter (D) for AuNS and AuND, height (H) for the AuNC as the dominant tuning feature across all elementary NP geometries. The intuitive observation is in line with the practices in the scientific community in utilizing major resonance axis to tune NP properties. The limited tunability of AuNS is another noticeable observation that justifies the underwhelming range of target values reported

in Section 5.4.

Table 5.2 also provides potential strategies for a multi-step optimization of AuNPs. The initial guidance is evident in the repeating pattern of AR as a free feature for many of the target variables and occasional manifestation as tuning feature for few. The observation indicates to the potential of AR for tuning a secondary target while preserving the optimization of the first target. Such instances will be investigated further in section 5.6 through two exemplary scenarios of designing AuNPs tailored for specific applications.

5.5.2. Direction of Correlation & The Law of Diminishing Marginal Returns

“It is not from the benevolence of the butcher, the brewer or the baker that we expect to eat our dinner, but from their regard to their own interest.” Adam Smith - The Wealth of Nations [307]

The categorization of the feature variable based on the magnitudes of correlation opens new frontiers in engineering AuNPs tailored to suit the needs of complex applications. The aim of this section is to advance the guidance provided in the previous chapter by incorporating the information carried in the sign (direction) of the correlations presented in the correlation matrices.

The directional information of the correlations is summarized in Table 5.3, correlations below the threshold of 0.4 are filtered out as the directional implications of such low correlations have little practical relevance. The sign of the correlations above the threshold are presented in a tabulated format.

The primary and derived targets exhibit a notable split where primary targets are predominantly positively correlated to feature variables and contrarily the derived targets mainly display negative correlation to the feature variables. The distinction between the primary and derived targets spans across all the elementary geometries signifying a universal trend in the AuNP design space that poses a peculiar conundrum.

The features sifted out by the correlation threshold are all representative of the NP size. The positive correlation highlighted by the table indicates that the primary target variables such as resonance wavelength, absorption and scattering cross sections, can be scaled up by increasing the AuNP size. Contrastingly, negative correlation of the derived target variables shows that

increasing AuNP size causes a decrease in absorption efficiency, HEPM and SEPM.

Table 5.3: Correlation Direction for Elementary AuNPs

Geometry	Feature	Primary Targets			Derived Targets		
		λ_{Res}	σ_{Abs}	σ_{Scat}	Φ_{Eff}	HEPM	SEPM
Sphere (AuNS)	D	(+)	(+)	(+)	(-)	(-)	
	mNP	(+)	(+)	(+)	(-)	(-)	
Disk (AuND)	D	(+)	(+)	(+)		(-)	(-)
	H	(+)	(+)	(+)	(+)	(-)	(-)
	mNP	(-)	(+)	(+)	(+)		(-)
	AR	(-)					
Cylinder (AuNC)	D	(+)		(+)	(-)	(-)	(-)
	H	(+)	(+)	(+)	(-)	(-)	
	mNP	(+)		(+)	(-)	(-)	(-)
	AR	(+)	(+)				
Spherical Shell (AuNSS)	D		(+)	(+)	(-)	(-)	
	mNP		(+)	(+)	(-)	(-)	
	FR	(+)				(+)	(+)
Ring (AuNR)	D	(+)	(+)	(+)		(-)	(-)
	H	(+)	(+)	(+)		(-)	(-)
	mNP	(+)	(+)	(+)	(+)		(-)
	AR	(-)					
	FR						
Tube (AuNT)	D	(+)		(+)	(-)	(-)	(-)
	H	(+)		(+)	(-)	(-)	
	mNP	(+)		(+)	(-)		(-)
	AR		(+)				(+)
	FR						

The peculiar conundrum presented here possibly resonates well with the economists, who are unlikely to be reading this thesis, reminiscing the earliest works of the forefathers of the discipline including Jacques Turgot, Johann Heinrich von Thünen, Thomas Robert Malthus, Adam Smith and David Ricardo. The law of diminishing marginal returns plays central role in production theory and states that *ceteris paribus*, i.e. keeping all other variables constant, adding more of one factor of production will yield lower incremental growth in the output after reaching an optimal level of capacity.

A classic example that captures the essence of the law of diminishing returns is adding more

workers to a factory floor past an optimum point where increasing production by one more unit requires increasingly greater number of workers as the last additional worker contribute in an ever decreasing efficiency.

It is a curious coincidence that a theory devised in 18th century for explaining a phenomenon prevailing factory worker also reverberates in the motion of sub-atomic particles through microscopic pieces of gold. The diminishing marginal return on productivity for an elementary AuNP signifies that each additional unit of gold yields a marginally decreasing contribution to the overall optical performance of a NP. One other critical point about the law of diminishing marginal returns is the presence of an optimum point and whether such a point exists for AuNPs is a stimulating question to end this section.

5.6.The Final Piece of the Framework & Demonstration on Hypothetical Scenarios

The final section of this chapter explores the presence of an optimum point, as observed in the production theory that comprises the law of diminishing returns. Bivariate analysis, a commonly employed tool of data science for establishing an empirical relation between two variables, provides evidence on the presence of an optimum point in engineering AuNPs while simultaneously revealing more exploitable insights. Conducting a bivariate analysis entails plotting of each target variable with respect to the primary features (diameter and height). The fabrication processes exercise comprehensive control over the primary features that constitute the strongest determining factors of the optical properties for a AuNP.

The presented analysis examines each elementary geometry separately, and part of the resulting information regarding AuNCs & AuNDs (Figure 5.7 & Figure 5.8) is portrayed in the subsequent parts of this section as two individual hypothetical case studies on engineering AuNPs upon demand in predetermined application scenarios. The remaining parts of the analysis comprising other elementary geometries such as AuNSs, AuNRs and AuNTs is reported in APPENDIX B for the purpose of conciseness (Figure B.1, Figure B.2, Figure B.3, Figure B.4 & Figure B.5). The key observations of the bivariate analysis on all elementary AuNPs are summarized in Table 5.4 highlighting the noticeable patterns. The main objective of the presented synopsis is to uncover noteworthy patterns in feature-target relations including identifying cardinal tuning features, exploring the existence of optimum points as expressed in

production theory, and recognizing the presence of consequential trends.

Cardinal tuning feature is a new concept introduced through the bivariate analysis and offers considerable flexibility in engineering AuNPs. The cardinal tuning feature represents the most suitable tuning feature for a target variable that simultaneously exposes a derived feature which can be used for tuning a secondary target variable without effecting the initial optimization. Cardinal tuning feature is one of the most prominent patterns noticeable in Table 5.4 occurring in half of the target variables studied, therefore constitutes as one of the most influential elements of the design framework with pronounced practical impact.

Among the two primary features, the intuitive preference for the cardinal tuning feature is the major geometric axis that corresponds to the strong LSPR mode. Intriguingly, as highlighted in Table 5.4 half of cardinal tuning variables correspond to the minor resonance axis which in general controls the TSPR, i.e. non-dominant LSPR mode.

Table 5.4: A synopsis of bivariate analysis of primary features and target variables

Geometry	Figure	Pattern	Primary Targets			Derived Targets		
			λ_{Res}	σ_{Abs}	σ_{Scat}	Φ_{Eff}	HEPM	SEPM
AuND	Figure 5.7	Cardinal Tuning Feature	x	x	x			x*
		Optimum Point	x					
		Trend		x	x		x	x
AuNC	Figure 5.8	Cardinal Tuning Feature			x	x*	x*	x*
		Optimum Point				x		x
		Trend	x		x		x	
AuNR	Figure B.2 Figure B.3	Cardinal Tuning Feature		x	x			
		Optimum Point		x				x
		Trend		x	x		x	
AuNT	Figure B.4 Figure B.5	Cardinal Tuning Feature	x*		x*			
		Optimum Point		x		x		x
		Trend	x		x	x	x	
AuNS & AuNSS	Figure B.1	Optimum Point						x
		Trend	x		x	x	x	

*: Cardinal Tuning Feature corresponds to the TSPR axis

A significant amount of the research effort that went into engineering AuNPs was focused on establishing the optimum NP morphology that satisfies the requirements of the proposed application to the greatest extent. Questioning the existence of such an optimum is one of the most valuable insights provided by the systematic analysis conducted throughout this chapter. Rigorous exploration of the landscape formed by the NP design parameters underlines the fact that such optimum points in AuNP engineering only prevail in less than 1/3 of the target variables (Table 5.4).

The presence of an optimum point for target variables with respect to one of the primary features, significantly simplifies the NP engineering process by setting the starting point of the optimization. Positioning the relevant feature variable to the optimum point for a target such as SEPM, sets the stage for identification of the free feature parameters that can be adjusted without disrupting the initial optimization. The associations of the free feature parameters to the remaining target variables is crucial and can be exploited to tune an additional target variable such as operational wavelength. Discovering such interactions establishes well-defined design paths for engineering AuNPs and will be elaborately demonstrated in the following case studies.

The absence of an optimum is complimented by identifying trends in the feature-target associations. The trending relations between primary features and target variables is the most frequently repeating pattern in the bivariate analysis of NP design parameters and provide information about the tuning direction for adjusting a certain variable. Universal observations such as the highest HEPM is always found among the smallest AuNP irrespective of geometry are the key contributions of trend identification to the AuNP design framework.

Table 5.4 constitutes the final piece of the AuNP design framework proposed in this thesis work with the aim of providing guidance on engineering AuNPs for specific applications. The following subsections demonstrate the practical utilization of the framework in finding the optimum AuNP morphology for two hypothetical scenarios.

5.6.1.Scenario 1: Transforming AuNDs to Longer Operational Wavelengths

Alice is leading a team of researchers composed of chemists and biologists. Her team is specialized in fabrication of disk-shaped AuNPs for nanomedical applications, she is in close collaboration with medical professionals who are conducting clinical studies of her prototypes.

Alice is trying to take advantage of the lately discovered BTWs in her research. She purchased a cutting-edge laser that operates in NIR-III to investigate the potential of the NPs she synthesizes in longer operational wavelengths. Alice's team has previously collaborated on a project that utilizes AuNDs for cancer imaging in NIR-I & NIR-II. Alice is wondering if she could synthesize larger versions of these NPs to use in her current experiments. She is concerned about the optical contrast that the new AuNDs can generate, but more importantly as she knows that the new particles will be larger, she is more concerned about the inadvertent dosing error that might cause unintended toxicity on her test subjects. She is also wondering if the large AuNDs she synthesis could be used in alternative applications.

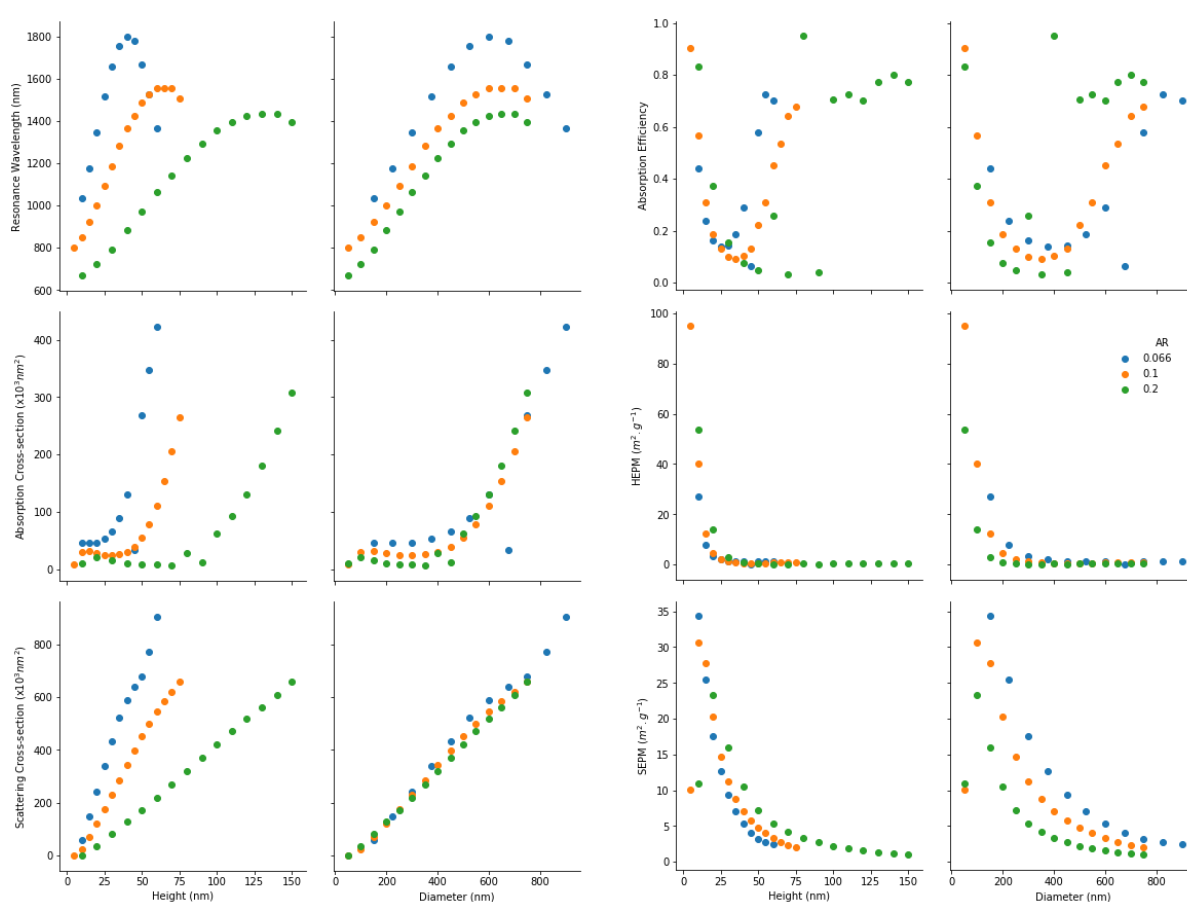


Figure 5.7: Bivariate Analysis of AuND Properties

The provided scenario portrays a researcher with a geometry-centric frame of reference trying to tune the operating wavelength of an elementary AuNP geometry while preserving or optimizing the scattering properties under the toxicity constraints and questioning alternative application potentials. Alice's case clearly warrants a NP design operating in NIR-III that

produces the largest amount of optical contrast while inducing minimum possible toxicity. The framework constructed gradually in the preceding sections of this chapter intends to approach such challenges exemplified by this scenario in a well-structured manner. The design framework provides guidance by progressively classifying elementary geometries, categorizing NP design parameters, and identifying pathways for strategic tuning of the features to achieve the desired AuNP properties suiting the targeted application.

Alice is following a geometry-centric optimization process as proposed in Section 5.4 where Figure 5.4 outlines the potential capabilities of the disk-shaped AuNPs she is working on. Alice notices that AuNDs have significant advantages in per particle absorption and scattering but overperformed by AuNC after mass normalization, verifying her concerns about the size and potential toxicity of her particles. She notes to explore applications that does not involve toxicity constraints for her particles, perhaps early cancer detection in urine or blood.

Following the framework, Alice observes that according to the sensitivity analysis conducted in Section 5.5, diameter of the nanodisks is the likely tuning feature for many of the NP properties and the aspect ratio represents the free feature that can be changed without affecting majority of the NP properties (Table 5.2). She tells her graduate students to identify the factors in their synthesis procedure that determines the diameter and the aspect ratio of the AuNDs they produce.

The final part of the framework presented in Section 5.6, informs Alice about the optimum points, cardinal tuning features and the prevailing trends in the nanoparticles she is working with (Table 5.4). Alice is primarily interested in SEPM and the resonance wavelength for the imaging application she is developing the AuNDs for. She notices both targets have a corresponding cardinal tuning feature that will give her extra freedom in tuning the properties of the AuNDs. Additionally, she notes that the resonance wavelength has an optimum point and SEPM is following a trend. The final bit of guidance is provided in Figure 5.7 for Alice to draw tangible conclusions. She observes that the trend in SEPM is sharply decreasing and predominantly controlled by the height of the disks and to achieve maximum SEPM, she needs to produce her nanodisks as thin as possible. She also notes that once the height is fixed due to the cardinality in SEPM she now has the AR as a free parameter. For adjusting the operational wavelength, Alice observes that the diameter corresponding to the optimum of the resonance wavelength is very large, but she can adjust the operational wavelength by tuning AR to the

desired range.

5.6.2.Scenario 2: Most Suitable Morphology at NIR-IV

Bob is a clinical researcher working on developing cancer theranostic techniques for deep tissue tumors. He previously conducted clinical trials in NIR-I using AuNPs for optical imaging and heat generated cancer therapy (PTT). In a recent online conference, he came across a presentation discussing the transparency of human tissue in deep NIR. After some preliminary research he decided to explore the potential of NIR-IV and ordered an appropriate laser that operates in that spectrum. He wants to incorporate AuNPs to his research, but he does not know which NP morphology would best suit his experimental setup, he is concerned that the size of the NPs can induce toxicity.

Bob's scenario clearly warrants a NP design operating in NIR-IV that produces the largest amount of scattering and absorption simultaneously while minimizing the potential for toxicity.

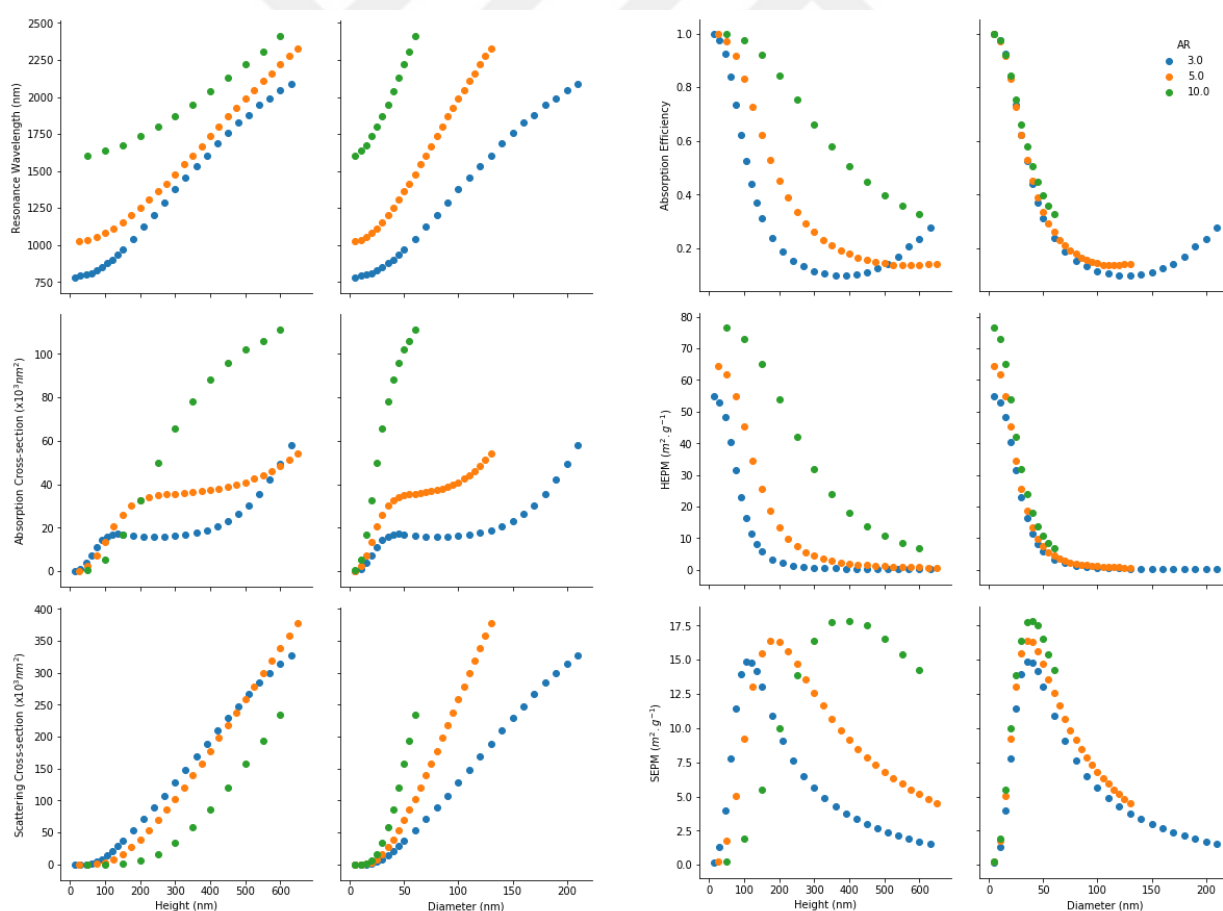


Figure 5.8: Bivariate Analysis of AuNC Properties

Bob follows the wavelength-centric approach of the framework, Figure 5.5 shows him that his options are in fact limited to AuNCs. He observes in Table 5.4 that SEPM has an optimum point. Checking Figure 5.8 Bob notices that he needs AuNCs with diameter of 50 nm, he also notes that for maximizing HEPM he needs to keep the diameter as small as possible. More importantly, he notices that both HEPM and SEPM are set by the diameter and he can freely adjust the AR to operating wavelength of the particles.



Chapter 6:

CONCLUSION

Feature-rich plasmonic nanoparticles have been attracting attention in numerous fields of science and engineering in the past decade. Properties such as biocompatibility, inertness and well-studied chemistry established gold as the de facto material for many of the plasmonic applications, especially in nanomedicine. As one of the leading causes of death worldwide, cancer stands at the epicenter of the interdisciplinary research efforts directed at developing gold nanoparticle (AuNP) mediated cancer diagnosis and therapy techniques such as plasmonic photothermal therapy (PPT). The ability of light-triggered heat generation at nanoscale is the key innovation of AuNPs and forms the foundation of the non-invasive and selective cancer therapy techniques that has been comprehensively presented in Chapter 2. The interdisciplinary field is driven by the constant innovations in chemistry, biology, and clinical studies. The continuous evolution of the nanomedical landscape demands adaptive engineering of AuNPs to satisfy the dynamic requirements of latest applications. This thesis work provides a physical perspective on advancing the boundaries of AuNPs for highly efficient and multi-functional implementations of cancer therapeutics and addressing the multifaceted challenges in commercialization of these applications.

The discovery of longer wavelength biological transparency windows (BTWs) is one of the critical advancements that has the potential to expand AuNP mediated cancer therapeutics such as PTT to deep tissue applications. Such implementations require large NPs that are specifically tailored for absorbing light to generate heat. Large absorbing NPs are hard to come by as the demand for such nanostructures was previously nonexistent. The longer wavelength use cases for AuNPs tend to fall into the research area of optics which emphasizes the scattering characteristics of NPs and treats absorption as an unintended loss mechanism that needs to be minimized. Chapter 3 validates the effects of the contour design approach on enhancing the absorption in large AuNPs and elucidates the underlying causes that originate from the

confinement of collective electron oscillations into significantly smaller cross-sectional area elicited by the contour.

Chapter 4 builds on the contour design approach for engineering AuNPs and portrays the first theoretical demonstration in literature of the applicability of PTT in long wavelength biological transparency windows (NIR-III & NIR-IV). Contour design has far reaching implications beyond absorption enhancement in large NPs and offers significant size reduction promoting deep wavelength light manipulation for AuNPs operating in any wavelength that potentially increases cellular internalization of NPs in NIR-I & NIR-II implementations. The effects of NP morphology and size on the cellular uptake of AuNPs is a growing area of research that is continuously providing new evidence on the viability of internalization for large AuNPs. In an effort to address cellular internalization concerns, Chapter 4 additionally explores self-assembly compatible AuNP designs that relies on the cellular uptake of small components that assemble through specifically designed binding molecules such as proteins and DNA strands to form large NP chains inside the cancer cell with operational wavelength in the long wavelength BTWs.

Advances in chemistry facilitates fabrication of wide variety of AuNPs with increasing complexity and diminishing cost of production. Choosing the most suitable NP design that satisfies the demands of a distinctive applications is a challenging task particularly for clinical researchers. Chapter 5 addresses this challenge by presenting a AuNP design framework to provide guidance for researchers from all contributing disciplines in identifying the optimum NP design suitable for the target application. The practicality of the framework is demonstrated through two hypothetical scenarios where starting with the requirements of the supposed application. The framework delineates a step-by-step design process that progressively distinguishes the existing optimum points of the potential design and highlights the routes for efficiently tailoring of supplementary NP properties.

Continuously evolving application landscape, driven by the progress in fabrication that enable production of increasingly complex NPs and in response to advancements of technical instrumentation which lead to the discovery of new BTWs expanding the operational range of AuNPs, creates a consistent demand for purposefully designed AuNPs. The inhomogeneous nature of cancer and the considerable variability of the state of the patients are the strongest proponents for the development of personalized cancer treatment strategies. The design

principles and the framework proposed as part of this thesis aims to form the foundation that supports the shift towards personalized AuNP implementations.

Exploration of the relationship between the optical properties and the NP morphology through a deductive analysis based on data scientific methods is an innovation contribution of this work to the scientific literature. The systematically presented findings that compose the design framework, jointly pose intriguing questions for future researchers, and stimulate the discovery of the underlying mechanics for the intricate patterns observed throughout the thesis. Exploration of fully anisotropic structures that supports 3 distinct LSPR modes constitutes a promising candidate for the next puzzle piece in expanding the AuNP framework.



BIBLIOGRAPHY

- [1] S. Szunerits and R. Boukherroub, “Near-infrared photothermal heating with gold nanostructures,” in *Encyclopedia of Interfacial Chemistry: Surface Science and Electrochemistry*, K. B. T.-E. of I. C. Wandelt, Ed. Oxford: Elsevier, 2018, pp. 500–510.
- [2] I. Freestone, N. Meeks, M. Sax, and C. Higgitt, “The Lycurgus Cup - A Roman nanotechnology,” *Gold Bull.*, vol. 40, no. 4, pp. 270–277, 2008, doi: 10.1007/BF03215599.
- [3] U. Leonhardt, “Optical metamaterials: Invisibility cup,” *Nat. Photonics*, vol. 1, no. 4, pp. 207–208, 2007, doi: 10.1038/nphoton.2007.38.
- [4] M. Faraday, “X. The Bakerian Lecture. —Experimental relations of gold (and other metals) to light,” *Philos. Trans. R. Soc. London*, vol. 147, no. 0, pp. 145–181, Jan. 1857, doi: 10.1098/rstl.1857.0011.
- [5] J. C. M. Garnett and J. Larmor, “XII. Colours in metal glasses and in metallic films,” *Philos. Trans. R. Soc. London. Ser. A, Contain. Pap. a Math. or Phys. Character*, vol. 203, no. 359–371, pp. 385–420, Jan. 1904, doi: 10.1098/rsta.1904.0024.
- [6] J. W. Strutt, “XV. On the light from the sky, its polarization and colour,” *London, Edinburgh, Dublin Philos. Mag. J. Sci.*, vol. 41, no. 271, pp. 107–120, Feb. 1871, doi: 10.1080/14786447108640452.
- [7] J. W. Strutt, “LVIII. On the scattering of light by small particles,” *London, Edinburgh, Dublin Philos. Mag. J. Sci.*, vol. 41, no. 275, pp. 447–454, Jun. 1871, doi: 10.1080/14786447108640507.
- [8] J. Tyndall, “IV. On the blue colour of the sky, the polarization of skylight, and on the

- polarization of light by cloudy matter generally,” *Proc. R. Soc. London*, vol. 17, pp. 223–233, Jan. 1869, doi: 10.1098/rspl.1868.0033.
- [9] Lord Rayleigh, “ XXXIV. On the transmission of light through an atmosphere containing small particles in suspension, and on the origin of the blue of the sky ,” *London, Edinburgh, Dublin Philos. Mag. J. Sci.*, vol. 47, no. 287, pp. 375–384, Apr. 1899, doi: 10.1080/14786449908621276.
- [10] G. Mie, “Beiträge zur Optik trüber Medien, speziell kolloidaler Metallösungen,” *Ann. Phys.*, vol. 330, no. 3, pp. 377–445, Jan. 1908, doi: 10.1002/andp.19083300302.
- [11] S. So, N. Park, H. J. Lee, and J. Rho, “New trends in nanophotonics,” *Nanophotonics*, vol. 9, no. 5, pp. 983–985, 2020, doi: 10.1515/nanoph-2020-0170.
- [12] I. S. Maksymov, “Magneto-plasmonic nanoantennas: Basics and applications,” *Rev. Phys.*, vol. 1, pp. 36–51, 2016, doi: 10.1016/j.revip.2016.03.002.
- [13] Y. Zhao and A. Alu, “Optical nanoantennas and their applications,” *IEEE Radio Wirel. Symp. RWS*, pp. 58–60, 2013, doi: 10.1109/RWS.2013.6486640.
- [14] M. I. Stockman, “Nanoplasmonics: past, present, and glimpse into future,” *Opt. Express*, vol. 19, no. 22, p. 22029, 2011, doi: 10.1364/oe.19.022029.
- [15] L. M. Liz-Marzán, C. J. Murphy, and J. Wang, “Nanoplasmonics,” *Chem. Soc. Rev.*, vol. 43, no. 11, pp. 3820–3822, 2014, doi: 10.1039/c4cs90026j.
- [16] S. V. Boriskina *et al.*, “Losses in plasmonics: from mitigating energy dissipation to embracing loss-enabled functionalities,” *Adv. Opt. Photonics*, vol. 9, no. 4, p. 775, 2017, doi: 10.1364/aop.9.000775.
- [17] G. Barbillon, “Plasmonics and its applications,” *Materials (Basel)*, vol. 12, no. 9, pp. 10–13, 2019, doi: 10.3390/ma12091502.
- [18] H. Yu, Y. Peng, Y. Yang, and Z. Y. Li, “Plasmon-enhanced light–matter interactions and applications,” *npj Comput. Mater.*, vol. 5, no. 1, pp. 1–14, 2019, doi: 10.1038/s41524-019-0184-1.

- [19] V. Giannini, A. I. Fernández-Domínguez, S. C. Heck, and S. A. Maier, “Plasmonic nanoantennas: Fundamentals and their use in controlling the radiative properties of nanoemitters,” *Chem. Rev.*, vol. 111, no. 6, pp. 3888–3912, 2011, doi: 10.1021/cr1002672.
- [20] G. Baffou, F. Cichos, and R. Quidant, “Applications and challenges of thermoplasmonics,” *Nat. Mater.*, vol. 19, no. September, 2020, doi: 10.1038/s41563-020-0740-6.
- [21] L. R. Hirsch *et al.*, “Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 100, no. 23, pp. 13549–13554, 2003, doi: 10.1073/pnas.2232479100.
- [22] C. M. Pitsillides, E. K. Joe, X. Wei, R. R. Anderson, and C. P. Lin, “Selective cell targeting with light-absorbing microparticles and nanoparticles,” *Biophys. J.*, vol. 84, no. 6, pp. 4023–4032, 2003, doi: 10.1016/S0006-3495(03)75128-5.
- [23] D. Pines and D. Bohm, “A collective description of electron interactions: II. Collective vs individual particle aspects of the interactions,” *Phys. Rev.*, vol. 85, no. 2, pp. 338–353, Jan. 1952, doi: 10.1103/PhysRev.85.338.
- [24] D. Bohm and D. Pines, “A collective description of electron interactions: III. Coulomb interactions in a degenerate electron gas,” *Phys. Rev.*, vol. 92, no. 3, pp. 609–625, 1953, doi: 10.1103/PhysRev.92.609.
- [25] K. M. Mayer and J. H. Hafner, “Localized surface plasmon resonance sensors,” *Chem. Rev.*, vol. 111, no. 6, pp. 3828–3857, Jun. 2011, doi: 10.1021/cr100313v.
- [26] R. E. Messersmith, G. J. Nusz, and S. M. Reed, “Using the localized surface plasmon resonance of gold nanoparticles to monitor lipid membrane assembly and protein binding,” *J. Phys. Chem. C*, vol. 117, no. 50, pp. 26725–26733, 2013, doi: 10.1021/jp406013q.
- [27] N. K. Grady, N. J. Halas, and P. Nordlander, “Influence of dielectric function properties on the optical response of plasmon resonant metallic nanoparticles,” *Chem. Phys. Lett.*,

- vol. 399, no. 1–3, pp. 167–171, 2004, doi: 10.1016/j.cplett.2004.09.154.
- [28] C. Burda, X. Chen, R. Narayanan, and M. A. El-Sayed, “Chemistry and properties of nanocrystals of different shapes,” *Chem. Rev.*, vol. 105, no. 4, pp. 1025–1102, Apr. 2005, doi: 10.1021/cr030063a.
- [29] B. Wiley, Y. Sun, and Y. Xia, “Synthesis of silver nanostructures with controlled shapes and properties,” *Acc. Chem. Res.*, vol. 40, no. 10, pp. 1067–1076, Oct. 2007, doi: 10.1021/ar7000974.
- [30] K. E. Fong and L. Y. L. Yung, “Localized surface plasmon resonance: A unique property of plasmonic nanoparticles for nucleic acid detection,” *Nanoscale*, vol. 5, no. 24, pp. 12043–12071, 2013, doi: 10.1039/c3nr02257a.
- [31] C. F. Bohren, *Absorption and scattering of light by small particles*. John Wiley & Sons, 1983.
- [32] J. J. Mock, M. Barbic, D. R. Smith, D. A. Schultz, and S. Schultz, “Shape effects in plasmon resonance of individual colloidal silver nanoparticles,” *J. Chem. Phys.*, vol. 116, no. 15, pp. 6755–6759, Apr. 2002, doi: 10.1063/1.1462610.
- [33] E. Hao and G. C. Schatz, “Electromagnetic fields around silver nanoparticles and dimers,” *J. Chem. Phys.*, vol. 120, no. 1, pp. 357–366, Dec. 2004, doi: 10.1063/1.1629280.
- [34] J. J. Xiao, J. P. Huang, and K. W. Yu, “Optical response of strongly coupled metal nanoparticles in dimer arrays,” *Phys. Rev. B - Condens. Matter Mater. Phys.*, vol. 71, no. 4, p. 45404, Jan. 2005, doi: 10.1103/PhysRevB.71.045404.
- [35] U. Kreibig, M. Gartz, and A. Hilger, “Mie resonances: Sensors for physical and chemical cluster interface properties,” *Berichte der Bunsengesellschaft/Physical Chem. Chem. Phys.*, vol. 101, no. 11, pp. 1593–1604, Nov. 1997, doi: 10.1002/bbpc.19971011107.
- [36] M. Sui, S. Kunwar, P. Pandey, and J. Lee, “Strongly confined localized surface plasmon resonance (LSPR) bands of Pt, AgPt, AgAuPt nanoparticles,” *Sci. Rep.*, vol. 9, no. 1, pp. 1–14, 2019, doi: 10.1038/s41598-019-53292-1.

- [37] K. L. Kelly, E. Coronado, L. L. Zhao, and G. C. Schatz, "The optical properties of metal nanoparticles: The influence of size, shape, and dielectric environment," *J. Phys. Chem. B*, vol. 107, no. 3, pp. 668–677, 2003, doi: 10.1021/jp026731y.
- [38] S. L. Jacques, "Optical properties of biological tissues: A review," *Phys. Med. Biol.*, vol. 58, no. 11, pp. R37–R61, 2013, doi: 10.1088/0031-9155/58/11/R37.
- [39] A. N. Bashkatov, E. A. Genina, V. I. Kochubey, and V. V. Tuchin, "Optical properties of human skin, subcutaneous and mucous tissues in the wavelength range from 400 to 2000 nm," *J. Phys. D. Appl. Phys.*, vol. 38, no. 15, pp. 2543–2555, 2005, doi: 10.1088/0022-3727/38/15/004.
- [40] H. Zhang, D. Salo, D. M. Kim, S. Komarov, Y.-C. Tai, and M. Y. Berezin, "Penetration depth of photons in biological tissues from hyperspectral imaging in shortwave infrared in transmission and reflection geometries," *J. Biomed. Opt.*, vol. 21, no. 12, p. 126006, 2016, doi: 10.1117/1.jbo.21.12.126006.
- [41] A. Alabugin, "Near-IR Photochemistry for Biology: Exploiting the Optical Window of Tissue," *Photochem. Photobiol.*, vol. 95, no. 3, pp. 722–732, May 2019, doi: 10.1111/php.13068.
- [42] R. Weissleder, "A clearer vision for in vivo imaging: Progress continues in the development of smaller, more penetrable probes for biological imaging," *Nat. Biotechnol.*, vol. 19, no. 4, pp. 316–317, 2001, doi: 10.1038/86684.
- [43] L. A. Sordillo *et al.*, "Third therapeutic spectral window for deep tissue imaging," *Opt. Biopsy XII*, vol. 8940, no. 212, p. 89400V, 2014, doi: 10.1117/12.2040604.
- [44] L. Shi, L. A. Sordillo, A. Rodríguez-Contreras, and R. Alfano, "Transmission in near-infrared optical windows for deep brain imaging," *J. Biophotonics*, vol. 9, no. 1–2, pp. 38–43, 2016, doi: 10.1002/jbio.201500192.
- [45] A. M. Smith, M. C. Mancini, and S. Nie, "NIH Public Access: Second window for in vivo imaging," *Nat. Nanotechnol.*, vol. 4, no. 11, pp. 710–711, 2009, doi: 10.1038/nnano.2009.326.Second.

- [46] T. L. Troy and S. N. Thennadil, "Optical properties of human skin in the near infrared wavelength range of 1000 to 2200 nm," *J. Biomed. Opt.*, vol. 6, no. 2, p. 167, Apr. 2001, doi: 10.1117/1.1344191.
- [47] D. R. Klaus, M. Keene, S. Silchenko, M. Berezin, and N. Gerasimchuk, "1D polymeric platinum cyanoximate: A strategy toward luminescence in the near-infrared region beyond 1000 nm," *Inorg. Chem.*, vol. 54, no. 4, pp. 1890–1900, Feb. 2015, doi: 10.1021/ic502805h.
- [48] Z. Tao *et al.*, "Biological imaging using nanoparticles of small organic molecules with fluorescence emission at wavelengths longer than 1000 nm," *Angew. Chemie - Int. Ed.*, vol. 52, no. 49, pp. 13002–13006, Dec. 2013, doi: 10.1002/anie.201307346.
- [49] K. Welsher, S. P. Sherlock, and H. Dai, "Deep-tissue anatomical imaging of mice using carbon nanotube fluorophores in the second near-infrared window," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 108, no. 22, pp. 8943–8948, May 2011, doi: 10.1073/pnas.1014501108.
- [50] Y. Jung *et al.*, "Quantum dot imaging in the second near-infrared optical window: studies on reflectance fluorescence imaging depths by effective fluence rate and multiple image acquisition," *J. Biomed. Opt.*, vol. 20, no. 4, p. 046012, Apr. 2015, doi: 10.1117/1.jbo.20.4.046012.
- [51] X. Wu *et al.*, "Deep-Tissue Photothermal Therapy Using Laser Illumination at NIR-IIa Window," *Nano-Micro Lett.*, vol. 12, no. 1, 2020, doi: 10.1007/s40820-020-0378-6.
- [52] R. P. Feynman, "There ' s Plenty of Room at the Bottom The Nanometer Scalescale," *Caltech's Eng. Sci.*, pp. 1–11, 1959, [Online]. Available: <http://www.zyvex.com/nanotech/feynman.html>.
- [53] M. Heron, "Deaths: Leading causes for 2016," *Natl. Vital Stat. Reports*, vol. 67, no. 6, pp. 1–77, Jul. 2018.
- [54] A. Kalbasi *et al.*, "Tumor-derived CCL2 mediates resistance to radiotherapy in pancreatic ductal adenocarcinoma," *Clin. Cancer Res.*, vol. 23, no. 1, pp. 137–148, Jan.

- 2017, doi: 10.1158/1078-0432.CCR-16-0870.
- [55] M. Baumann, M. Krause, and R. Hill, “Exploring the role of cancer stem cells in radioresistance,” *Nat. Rev. Cancer*, vol. 8, no. 7, pp. 545–554, 2008, doi: 10.1038/nrc2419.
- [56] J. B. Vines, J. H. Yoon, N. E. Ryu, D. J. Lim, and H. Park, “Gold nanoparticles for photothermal cancer therapy,” *Front. Chem.*, vol. 7, no. APR, p. 167, Apr. 2019, doi: 10.3389/fchem.2019.00167.
- [57] K. Kim and D. Khang, “<p>Past, Present, and Future of Anticancer Nanomedicine</p>,” *Int. J. Nanomedicine*, vol. Volume 15, pp. 5719–5743, Aug. 2020, doi: 10.2147/ijn.s254774.
- [58] Q. Ban, T. Bai, X. Duan, and J. Kong, “Noninvasive photothermal cancer therapy nanoplatforms: Via integrating nanomaterials and functional polymers,” *Biomater. Sci.*, vol. 5, no. 2, pp. 190–210, 2017, doi: 10.1039/c6bm00600k.
- [59] L. Zou *et al.*, “Current approaches of photothermal therapy in treating cancer metastasis with nanotherapeutics,” *Theranostics*, vol. 6, no. 6, pp. 762–772, 2016, doi: 10.7150/thno.14988.
- [60] A. Ribas and J. D. Wolchok, “Cancer immunotherapy using checkpoint blockade,” *Science (80-.)*, vol. 359, no. 6382, pp. 1350–1355, Mar. 2018, doi: 10.1126/science.aar4060.
- [61] C. H. June, R. S. O’Connor, O. U. Kawalekar, S. Ghassemi, and M. C. Milone, “CAR T cell immunotherapy for human cancer,” *Science (80-.)*, vol. 359, no. 6382, pp. 1361–1365, Mar. 2018, doi: 10.1126/science.aar6711.
- [62] J. Shen, W. Zhang, R. Qi, Z. W. Mao, and H. Shen, “Engineering functional inorganic-organic hybrid systems: Advances in siRNA therapeutics,” *Chem. Soc. Rev.*, vol. 47, no. 6, pp. 1969–1995, 2018, doi: 10.1039/c7cs00479f.
- [63] W. Fan, P. Huang, and X. Chen, “Overcoming the Achilles’ heel of photodynamic therapy,” *Chem. Soc. Rev.*, vol. 45, no. 23, pp. 6488–6519, 2016, doi:

- 10.1039/c6cs00616g.
- [64] B. W. Henderson and T. J. Dougherty, "How Does Photodynamic Therapy Work?," *Photochem. Photobiol.*, vol. 55, no. 1, pp. 145–157, Jan. 1992, doi: 10.1111/j.1751-1097.1992.tb04222.x.
- [65] S. Su, J. Wang, J. Wei, R. Martínez-Zaguilán, J. Qiu, and S. Wang, "Efficient photothermal therapy of brain cancer through porphyrin functionalized graphene oxide," *New J. Chem.*, vol. 39, no. 7, pp. 5743–5749, 2015, doi: 10.1039/c5nj00122f.
- [66] Z. Yang *et al.*, "Advances in nanomaterials for use in photothermal and photodynamic therapeutics (Review)," *Mol. Med. Rep.*, vol. 20, no. 1, pp. 5–15, Jul. 2019, doi: 10.3892/mmr.2019.10218.
- [67] H. Montaseri, C. A. Kruger, and H. Abrahamse, "Recent advances in porphyrin-based inorganic nanoparticles for cancer treatment," *Int. J. Mol. Sci.*, vol. 21, no. 9, p. 3358, May 2020, doi: 10.3390/ijms21093358.
- [68] P. Agostinis *et al.*, "Photodynamic therapy of cancer: An update," *CA. Cancer J. Clin.*, vol. 61, no. 4, pp. 250–281, 2011, doi: 10.3322/caac.20114.
- [69] X. Xue, A. Lindstrom, and Y. Li, "Porphyrin-Based Nanomedicines for Cancer Treatment," *Bioconjug. Chem.*, vol. 30, no. 6, pp. 1585–1603, Jun. 2019, doi: 10.1021/acs.bioconjchem.9b00231.
- [70] K. Wu *et al.*, "Endogenous oxygen generating multifunctional theranostic nanoplatform for enhanced photodynamic-photothermal therapy and multimodal imaging," *Theranostics*, vol. 9, no. 25, pp. 7697–7713, Oct. 2019, doi: 10.7150/thno.38565.
- [71] K. Szaciłowski, W. Macyk, A. Drzewiecka-Matuszek, M. Brindell, and G. Stochel, "Bioinorganic photochemistry: Frontiers and mechanisms," *Chem. Rev.*, vol. 105, no. 6, pp. 2647–2694, Jun. 2005, doi: 10.1021/cr030707e.
- [72] S. Link and M. A. El-Sayed, "Spectral Properties and Relaxation Dynamics of Surface Plasmon Electronic Oscillations in Gold and Silver Nanodots and Nanorods," *J. Phys. Chem. B*, vol. 103, no. 40, pp. 8410–8426, Oct. 1999, doi: 10.1021/jp9917648.

- [73] J. Yguerabide and E. E. Yguerabide, "Light-scattering submicroscopic particles as highly fluorescent analogs and their use as tracer labels in clinical and biological applications II. Experimental characterization," *Anal. Biochem.*, vol. 262, no. 2, pp. 157–176, 1998, doi: 10.1006/abio.1998.2760.
- [74] M. A. El-Sayed, "Some interesting properties of metals confined in time and nanometer space of different shapes," *Acc. Chem. Res.*, vol. 34, no. 4, pp. 257–264, Apr. 2001, doi: 10.1021/ar960016n.
- [75] E. E. Connor, J. Mwamuka, A. Gole, C. J. Murphy, and M. D. Wyatt, "Gold nanoparticles are taken up by human cells but do not cause acute cytotoxicity," *Small*, vol. 1, no. 3, pp. 325–327, Mar. 2005, doi: 10.1002/sml.200400093.
- [76] A. I. Sherman and M. Ter-Pogossian, "Lymph-node concentration of radioactive colloidal gold following interstitial injection," *Cancer*, vol. 6, no. 6, pp. 1238–1240, Nov. 1953, doi: 10.1002/1097-0142(195311)6:6<1238::AID-CNCR2820060618>3.0.CO;2-6.
- [77] S. P. Fricker, "Medical uses of gold compounds: Past, present and future," *Gold Bull.*, vol. 29, no. 2, pp. 53–60, 1996, doi: 10.1007/bf03215464.
- [78] S. Horikoshi and N. Serpone, "Introduction to Nanoparticles," *Microwaves in Nanoparticle Synthesis: Fundamentals and Applications*. pp. 1–24, Apr. 26, 2013, doi: 10.1002/9783527648122.ch1.
- [79] H. Chugh, D. Sood, I. Chandra, V. Tomar, G. Dhawan, and R. Chandra, "Role of gold and silver nanoparticles in cancer nano-medicine," *Artif. Cells, Nanomedicine Biotechnol.*, vol. 46, no. sup1, pp. 1210–1220, Oct. 2018, doi: 10.1080/21691401.2018.1449118.
- [80] S. S. Lucky, K. C. Soo, and Y. Zhang, "Nanoparticles in photodynamic therapy," *Chem. Rev.*, vol. 115, no. 4, pp. 1990–2042, Feb. 2015, doi: 10.1021/cr5004198.
- [81] A. Master, M. Livingston, and A. Sen Gupta, "Photodynamic nanomedicine in the treatment of solid tumors: Perspectives and challenges," *J. Control. Release*, vol. 168,

- no. 1, pp. 88–102, May 2013, doi: 10.1016/j.jconrel.2013.02.020.
- [82] R. R. Allison, V. S. Bagnato, and C. H. Sibata, “Future of oncologic photodynamic therapy,” *Future Oncol.*, vol. 6, no. 6, pp. 929–940, Jun. 2010, doi: 10.2217/fon.10.51.
- [83] A. C. V. Doughty, A. R. Hoover, E. Layton, C. K. Murray, E. W. Howard, and W. R. Chen, “Nanomaterial applications in photothermal therapy for cancer,” *Materials (Basel)*, vol. 12, no. 5, Mar. 2019, doi: 10.3390/ma12050779.
- [84] J. L. West and N. J. Halas, “Engineered nanomaterials for biophotonics applications: Improving sensing, imaging, and therapeutics,” *Annu. Rev. Biomed. Eng.*, vol. 5, no. 1, pp. 285–292, Aug. 2003, doi: 10.1146/annurev.bioeng.5.011303.120723.
- [85] G. F. Paciotti *et al.*, “Colloidal gold: A novel nanoparticle vector for tumor directed drug delivery,” *Drug Deliv. J. Deliv. Target. Ther. Agents*, vol. 11, no. 3, pp. 169–183, Jan. 2004, doi: 10.1080/10717540490433895.
- [86] K. K. Jain, “Nanotechnology-based drug delivery for cancer,” *Technol. Cancer Res. Treat.*, vol. 4, no. 4, pp. 407–416, Aug. 2005, doi: 10.1177/153303460500400408.
- [87] J. Kreuter, “Nanoparticles-a historical perspective,” *Int. J. Pharm.*, vol. 331, no. 1, pp. 1–10, 2007, doi: 10.1016/j.ijpharm.2006.10.021.
- [88] A. Z. Wilczewska, K. Niemirowicz, K. H. Markiewicz, and H. Car, “Nanoparticles as drug delivery systems,” *Pharmacol. Reports*, vol. 64, no. 5, pp. 1020–1037, 2012, doi: 10.1016/S1734-1140(12)70901-5.
- [89] P. N. Sudha, K. Sangeetha, K. Vijayalakshmi, and A. Barhoum, “Nanomaterials history, classification, unique properties, production and market,” in *Emerging Applications of Nanoparticles and Architectural Nanostructures: Current Prospects and Future Trends*, A. Barhoum and A. S. H. B. T.-E. A. of N. and A. N. Makhoul, Eds. Elsevier, 2018, pp. 341–384.
- [90] J. McMillan, E. Batrakova, and H. E. Gendelman, “Cell delivery of therapeutic nanoparticles,” in *Progress in Molecular Biology and Translational Science*, vol. 104, A. B. T.-P. in M. B. and T. S. Villaverde, Ed. Academic Press, 2011, pp. 563–601.

- [91] R. Halwani *et al.*, “A novel anti-IL4R α nanoparticle efficiently controls lung inflammation during asthma,” *Exp. Mol. Med.*, vol. 48, no. 10, p. e262, Oct. 2016, doi: 10.1038/emm.2016.89.
- [92] L. Treuel and G. Ulrich Nienhaus, *Nanoparticle interaction with plasma proteins as it relates to biodistribution*, vol. 2. World Scientific, 2016.
- [93] S. Schöttler *et al.*, “Protein adsorption is required for stealth effect of poly(ethylene glycol)- and poly(phosphoester)-coated nanocarriers,” *Nat. Nanotechnol.*, vol. 11, no. 4, pp. 372–377, Apr. 2016, doi: 10.1038/nnano.2015.330.
- [94] N. Doshi and S. Mitragotri, “Macrophages recognize size and shape of their targets,” *PLoS One*, vol. 5, no. 4, pp. e10051–e10051, Apr. 2010, doi: 10.1371/journal.pone.0010051.
- [95] Y. Liu, J. Hardie, X. Zhang, and V. M. Rotello, “Effects of engineered nanoparticles on the innate immune system,” *Semin. Immunol.*, vol. 34, pp. 25–32, Dec. 2017, doi: 10.1016/j.smim.2017.09.011.
- [96] F. M. Kievit and M. Zhang, “Cancer nanotheranostics: Improving imaging and therapy by targeted delivery across biological barriers,” *Adv. Mater.*, vol. 23, no. 36, pp. H217–H247, Sep. 2011, doi: 10.1002/adma.201102313.
- [97] P. Rodgers and J. Heath, “Nanoscience and technology: A collection of reviews from nature journals,” *Nanoscience and Technology: A Collection of Reviews from Nature Journals*. Co-Published with Macmillan Publishers Ltd, UK, pp. 1–346, Aug. 01, 2009, doi: 10.1142/7439.
- [98] F. Wang, C. Li, J. Cheng, and Z. Yuan, “Recent advances on inorganic nanoparticle-based cancer therapeutic agents,” *Int. J. Environ. Res. Public Health*, vol. 13, no. 12, Nov. 2016, doi: 10.3390/ijerph13121182.
- [99] J. Fang, H. Nakamura, and H. Maeda, “The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect,” *Adv. Drug Deliv. Rev.*, vol. 63, no. 3, pp. 136–151, Mar. 2011, doi:

- 10.1016/j.addr.2010.04.009.
- [100] H. Maeda, “The enhanced permeability and retention (EPR) effect in tumor vasculature: The key role of tumor-selective macromolecular drug targeting,” *Adv. Enzyme Regul.*, vol. 41, no. 1, pp. 189–207, 2001, doi: 10.1016/S0065-2571(00)00013-3.
- [101] K. Sokolov *et al.*, “Molecular Optical Imaging of Therapeutic Targets of Cancer,” *Adv. Cancer Res.*, vol. 96, pp. 299–344, 2006, doi: 10.1016/S0065-230X(06)96011-4.
- [102] M. C. Pierce, D. J. Javier, and R. Richards-Kortum, “Optical contrast agents and imaging systems for detection and diagnosis of cancer,” *Int. J. Cancer*, vol. 123, no. 9, pp. 1979–1990, Nov. 2008, doi: 10.1002/ijc.23858.
- [103] D. Yelin, D. Oron, S. Thiberge, E. Moses, and Y. Silberberg, “Multiphoton plasmon-resonance microscopy,” *Opt. Express*, vol. 11, no. 12, p. 1385, 2003, doi: 10.1364/oe.11.001385.
- [104] K. Sokolov *et al.*, “Real-time vital optical imaging of precancer using anti-epidermal growth factor receptor antibodies conjugated to gold nanoparticles,” *Cancer Res.*, vol. 63, no. 9, pp. 1999–2004, May 2003.
- [105] I. H. El-Sayed, X. Huang, and M. A. El-Sayed, “Surface plasmon resonance scattering and absorption of anti-EGFR antibody conjugated gold nanoparticles in cancer diagnostics: Applications in oral cancer,” *Nano Lett.*, vol. 5, no. 5, pp. 829–834, May 2005, doi: 10.1021/nl050074e.
- [106] K. Sokolov *et al.*, “Optical Systems for In Vivo Molecular Imaging of Cancer,” *Technol. Cancer Res. Treat.*, vol. 2, no. 6, pp. 491–504, Dec. 2003, doi: 10.1177/153303460300200602.
- [107] S. W. Tsai, Y. Y. Chen, and J. W. Liaw, “Compound cellular imaging of laser scanning confocal microscopy by using gold nanoparticles and dyes,” *Sensors*, vol. 8, no. 4, pp. 2306–2316, Apr. 2008, doi: 10.3390/s8042306.
- [108] X. J. Chen, X. Q. Zhang, Q. Liu, J. Zhang, and G. Zhou, “Nanotechnology: A promising method for oral cancer detection and diagnosis,” *J. Nanobiotechnology*, vol. 16, no. 1,

- p. 52, Jun. 2018, doi: 10.1186/s12951-018-0378-6.
- [109] T. Reuveni, M. Motiei, Z. Romman, A. Popovtzer, and R. Popovtzer, “Targeted gold nanoparticles enable molecular CT imaging of cancer: an in vivo study,” *Int. J. Nanomedicine*, vol. 6, pp. 2859–2864, 2011, doi: 10.2147/ijn.s25446.
- [110] R. Li, B. Liu, and J. Gao, “The application of nanoparticles in diagnosis and theranostics of gastric cancer,” *Cancer Lett.*, vol. 386, pp. 123–130, Feb. 2017, doi: 10.1016/j.canlet.2016.10.032.
- [111] S. W. Tsai, J. W. Liaw, F. Y. Hsu, Y. Y. Chen, M. J. Lyu, and M. H. Yeh, “Surface-modified gold nanoparticles with folic acid as optical probes for cellular imaging,” *Sensors*, vol. 8, no. 10, pp. 6660–6673, Oct. 2008, doi: 10.3390/s8106660.
- [112] X. Huang, I. H. El-Sayed, W. Qian, and M. A. El-Sayed, “Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods,” *J. Am. Chem. Soc.*, vol. 128, no. 6, pp. 2115–2120, Feb. 2006, doi: 10.1021/ja057254a.
- [113] M. Aioub, L. A. Austin, and M. A. El-Sayed, “Gold nanoparticles for cancer diagnostics, spectroscopic imaging, drug delivery, and plasmonic photothermal therapy,” in *Inorganic Frameworks as Smart Nanomedicines*, A. M. B. T.-I. F. as S. N. Grumezescu, Ed. William Andrew Publishing, 2018, pp. 41–91.
- [114] M. Blanco-Formoso and R. A. Alvarez-Puebla, “Cancer diagnosis through sers and other related techniques,” *Int. J. Mol. Sci.*, vol. 21, no. 6, p. 2253, Mar. 2020, doi: 10.3390/ijms21062253.
- [115] J. V. Jokerst, A. J. Cole, D. Van De Sompel, and S. S. Gambhir, “Gold nanorods for ovarian cancer detection with photoacoustic imaging and resection guidance via Raman imaging in living mice,” *ACS Nano*, vol. 6, no. 11, pp. 10366–10377, Nov. 2012, doi: 10.1021/nn304347g.
- [116] K. H. Song, C. Kim, C. M. Copley, Y. Xia, and L. V. Wang, “Near-infrared gold nanocages as a new class of tracers for photoacoustic sentinel lymph node mapping on a rat model,” *Nano Lett.*, vol. 9, no. 1, pp. 183–188, Jan. 2009, doi: 10.1021/nl802746w.

- [117] C. Kim *et al.*, “In vivo molecular photoacoustic tomography of melanomas targeted by bioconjugated gold nanocages,” *ACS Nano*, vol. 4, no. 8, pp. 4559–4564, Aug. 2010, doi: 10.1021/nn100736c.
- [118] Y. Wang *et al.*, “Photoacoustic tomography of a nanoshell contrast agent in the in vivo rat brain,” *Nano Lett.*, vol. 4, no. 9, pp. 1689–1692, Sep. 2004, doi: 10.1021/nl049126a.
- [119] H. J. Lee *et al.*, “In vitro and in vivo mapping of drug release after laser ablation thermal therapy with doxorubicin-loaded hollow gold nanoshells using fluorescence and photoacoustic imaging,” *J. Control. Release*, vol. 172, no. 1, pp. 152–158, 2013, doi: 10.1016/j.jconrel.2013.07.020.
- [120] L. Nie and X. Chen, “Structural and functional photoacoustic molecular tomography aided by emerging contrast agents,” *Chem. Soc. Rev.*, vol. 43, no. 20, pp. 7132–7170, 2014, doi: 10.1039/c4cs00086b.
- [121] M. R. K. Ali *et al.*, “Efficacy, long-term toxicity, and mechanistic studies of gold nanorods photothermal therapy of cancer in xenograft mice,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 114, no. 15, pp. E3110–E3118, Apr. 2017, doi: 10.1073/pnas.1619302114.
- [122] X. D. Wang, O. S. Wolfbeis, and R. J. Meier, “Luminescent probes and sensors for temperature,” *Chem. Soc. Rev.*, vol. 42, no. 19, pp. 7834–7869, Oct. 2013, doi: 10.1039/c3cs60102a.
- [123] P. Löw, B. Kim, N. Takama, and C. Bergaud, “High-spatial-resolution surface-temperature mapping using fluorescent thermometry,” *Small*, vol. 4, no. 7, pp. 908–914, Jul. 2008, doi: 10.1002/sml.200700581.
- [124] K. Okabe, N. Inada, C. Gota, Y. Harada, T. Funatsu, and S. Uchiyama, “Intracellular temperature mapping with a fluorescent polymeric thermometer and fluorescence lifetime imaging microscopy,” *Nat. Commun.*, vol. 3, p. 705, Feb. 2012, doi: 10.1038/ncomms1714.
- [125] V. A. Vlaskin, N. Janssen, J. Van Rijssel, R. Beaulac, and D. R. Gamelin, “Tunable dual emission in doped semiconductor nanocrystals,” *Nano Lett.*, vol. 10, no. 9, pp. 3670–

- 3674, Sep. 2010, doi: 10.1021/nl102135k.
- [126] A. Sedlmeier, D. E. Achatz, L. H. Fischer, H. H. Gorris, and O. S. Wolfbeis, “Photon upconverting nanoparticles for luminescent sensing of temperature,” *Nanoscale*, vol. 4, no. 22, pp. 7090–7096, Nov. 2012, doi: 10.1039/c2nr32314a.
- [127] J. Wang *et al.*, “Enhancing multiphoton upconversion through energy clustering at sublattice level,” *Nature Materials*, vol. 13, no. 2, England, pp. 157–162, Feb. 2014, doi: 10.1038/nmat3804.
- [128] J. C. G. Bünzli, “Lanthanide luminescence for biomedical analyses and imaging,” *Chem. Rev.*, vol. 110, no. 5, pp. 2729–2755, May 2010, doi: 10.1021/cr900362e.
- [129] X. Xie *et al.*, “Effect of hyperthermia on invasion ability and TGF- β 1 expression of breast carcinoma MCF-7 cells,” *Oncol. Rep.*, vol. 25, no. 6, pp. 1573–1579, Jun. 2011, doi: 10.3892/or.2011.1240.
- [130] Q. Chen, L. Xu, C. Liang, C. Wang, R. Peng, and Z. Liu, “Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy,” *Nat. Commun.*, vol. 7, p. 13193, Oct. 2016, doi: 10.1038/ncomms13193.
- [131] Q. Chen, J. Wen, H. Li, Y. Xu, F. Liu, and S. Sun, “Recent advances in different modal imaging-guided photothermal therapy,” *Biomaterials*, vol. 106, pp. 144–166, 2016, doi: 10.1016/j.biomaterials.2016.08.022.
- [132] Y. Liang *et al.*, “Integrated Hydrogel Platform for Programmed Antitumor Therapy Based on Near Infrared-Triggered Hyperthermia and Vascular Disruption,” *ACS Appl. Mater. Interfaces*, vol. 11, no. 24, pp. 21381–21390, Jun. 2019, doi: 10.1021/acsami.9b05536.
- [133] J. R. Melamed, R. S. Edelstein, and E. S. Day, “Elucidating the fundamental mechanisms of cell death triggered by photothermal therapy,” *ACS Nano*, vol. 9, no. 1, pp. 6–11, Jan. 2015, doi: 10.1021/acsnano.5b00021.
- [134] B. Yang, Y. Chen, and J. Shi, “Reactive oxygen species (ROS)-based nanomedicine,”

- Chem. Rev.*, vol. 119, no. 8, pp. 4881–4985, Apr. 2019, doi: 10.1021/acs.chemrev.8b00626.
- [135] H. Yan *et al.*, “Smart All-in-One Thermometer-Heater Nanoprobe Based on Postsynthetic Functionalization of a Eu(III)-Metal-Organic Framework,” *Anal. Chem.*, vol. 91, no. 8, pp. 5225–5234, Apr. 2019, doi: 10.1021/acs.analchem.8b05960.
- [136] Z. Wang *et al.*, “Redox-Activatable and Acid-Enhanced Nanotheranostics for Second Near-Infrared Photoacoustic Tomography and Combined Photothermal Tumor Therapy,” *ACS Nano*, vol. 13, no. 5, pp. 5816–5825, May 2019, doi: 10.1021/acsnano.9b01411.
- [137] S. B. Wang *et al.*, “A Versatile Carbon Monoxide Nanogenerator for Enhanced Tumor Therapy and Anti-Inflammation,” *ACS Nano*, vol. 13, no. 5, pp. 5523–5532, May 2019, doi: 10.1021/acsnano.9b00345.
- [138] Y. Liu, P. Bhattarai, Z. Dai, and X. Chen, “Photothermal therapy and photoacoustic imaging: Via nanotheranostics in fighting cancer,” *Chem. Soc. Rev.*, vol. 48, no. 7, pp. 2053–2108, 2019, doi: 10.1039/c8cs00618k.
- [139] S. Gai *et al.*, “Recent advances in functional nanomaterials for light-triggered cancer therapy,” *Nano Today*, vol. 19, pp. 146–187, 2018, doi: 10.1016/j.nantod.2018.02.010.
- [140] Z. Lin, N. A. Monteiro-Riviere, and J. E. Riviere, “Pharmacokinetics of metallic nanoparticles,” *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology*, vol. 7, no. 2, pp. 189–217, 2015, doi: 10.1002/wnan.1304.
- [141] A. L. Bailly *et al.*, “In vivo evaluation of safety, biodistribution and pharmacokinetics of laser-synthesized gold nanoparticles,” *Sci. Rep.*, vol. 9, no. 1, p. 12890, 2019, doi: 10.1038/s41598-019-48748-3.
- [142] J. Wang *et al.*, “Size- and surface chemistry-dependent pharmacokinetics and tumor accumulation of engineered gold nanoparticles after intravenous administration,” *Metallomics*, vol. 7, no. 3, pp. 516–524, Mar. 2015, doi: 10.1039/c4mt00340c.
- [143] M. A. Escudero-Francos *et al.*, “Cellular uptake and tissue biodistribution of

- functionalized gold nanoparticles and nanoclusters,” *J. Biomed. Nanotechnol.*, vol. 13, no. 2, pp. 167–179, Feb. 2017, doi: 10.1166/jbn.2017.2344.
- [144] T. Morais *et al.*, “Effect of surface coating on the biodistribution profile of gold nanoparticles in the rat,” *Eur. J. Pharm. Biopharm.*, vol. 80, no. 1, pp. 185–193, Jan. 2012, doi: 10.1016/j.ejpb.2011.09.005.
- [145] N. Khlebtsov and L. Dykmana, “Biodistribution and toxicity of engineered gold nanoparticles: A review of in vitro and in vivo studies,” *Chem. Soc. Rev.*, vol. 40, no. 3, pp. 1647–1671, Mar. 2011, doi: 10.1039/c0cs00018c.
- [146] H. Konoeda, H. Takizawa, A. Gower, M. Zhao, O. A. Adeyi, and M. Liu, “Pharmacokinetics, tissue distribution and safety of gold nanoparticle/PKC Delta inhibitor peptide hybrid in rats,” *Nanotoxicology*, vol. 14, no. 3, pp. 341–354, Apr. 2020, doi: 10.1080/17435390.2019.1702731.
- [147] J. Wang *et al.*, “In vivo pharmacokinetic features and biodistribution of star and rod shaped gold nanoparticles by multispectral optoacoustic tomography,” *RSC Adv.*, vol. 5, no. 10, pp. 7529–7538, 2015, doi: 10.1039/c4ra13228a.
- [148] O. E. Dictionary, “Tardis, n.” [Online]. Available: <https://www.oed.com/view/Entry/247369>.
- [149] M. Hlaing, B. Gebear-Eigzabher, A. Roa, A. Marcano, D. Radu, and C. Y. Lai, “Absorption and scattering cross-section extinction values of silver nanoparticles,” *Opt. Mater. (Amst.)*, vol. 58, pp. 439–444, 2016, doi: 10.1016/j.optmat.2016.06.013.
- [150] E. Huber and M. Frost, *Light scattering by small particles*, vol. 47, no. 2. Courier Corporation, 1998.
- [151] S. Marhaba, “Effect of Size, Shape and Environment on the Optical Response of Metallic Nanoparticles,” *Noble Precious Met. - Prop. Nanoscale Eff. Appl.*, 2018, doi: 10.5772/intechopen.71574.
- [152] J. Olson, S. Dominguez-Medina, A. Hoggard, L. Y. Wang, W. S. Chang, and S. Link, “Optical characterization of single plasmonic nanoparticles,” *Chem. Soc. Rev.*, vol. 44,

- no. 1, pp. 40–57, Jan. 2015, doi: 10.1039/c4cs00131a.
- [153] M. Yao *et al.*, “Enzyme Degradable Hyperbranched Polyphosphoester Micellar Nanomedicines for NIR Imaging-Guided Chemo-Photothermal Therapy of Drug-Resistant Cancers,” *Biomacromolecules*, vol. 19, no. 4, pp. 1130–1141, Apr. 2018, doi: 10.1021/acs.biomac.7b01793.
- [154] T. Wang *et al.*, “A cancer vaccine-mediated postoperative immunotherapy for recurrent and metastatic tumors,” *Nat. Commun.*, vol. 9, no. 1, p. 1532, Apr. 2018, doi: 10.1038/s41467-018-03915-4.
- [155] P. Wang *et al.*, “Thermo-triggered Release of CRISPR-Cas9 System by Lipid-Encapsulated Gold Nanoparticles for Tumor Therapy,” *Angew. Chemie - Int. Ed.*, vol. 57, no. 6, pp. 1491–1496, Feb. 2018, doi: 10.1002/anie.201708689.
- [156] W. Chen, M. Qin, X. Chen, Q. Wang, Z. Zhang, and X. Sun, “Combining photothermal therapy and immunotherapy against melanoma by polydopamine-coated Al₂O₃ nanoparticles,” *Theranostics*, vol. 8, no. 8, pp. 2229–2241, Mar. 2018, doi: 10.7150/thno.24073.
- [157] Z. Guo *et al.*, “Synthesis of BSA-Coated BiOI@Bi₂S₃ Semiconductor Heterojunction Nanoparticles and Their Applications for Radio/Photodynamic/Photothermal Synergistic Therapy of Tumor,” *Adv. Mater.*, vol. 29, no. 44, Nov. 2017, doi: 10.1002/adma.201704136.
- [158] J. Y. Zeng, M. K. Zhang, M. Y. Peng, D. Gong, and X. Z. Zhang, “Porphyrinic Metal–Organic Frameworks Coated Gold Nanorods as a Versatile Nanoplatfor for Combined Photodynamic/Photothermal/Chemotherapy of Tumor,” *Adv. Funct. Mater.*, vol. 28, no. 8, p. 1705451, Feb. 2018, doi: 10.1002/adfm.201705451.
- [159] N. Lu *et al.*, “Tri-stimuli-responsive biodegradable theranostics for mild hyperthermia enhanced chemotherapy,” *Biomaterials*, vol. 126, pp. 39–48, May 2017, doi: 10.1016/j.biomaterials.2017.02.025.
- [160] N. Rahoui, B. Jiang, N. Taloub, and Y. D. Huang, “Spatio-temporal control strategy of

- drug delivery systems based nano structures,” *J. Control. Release*, vol. 255, pp. 176–201, Jun. 2017, doi: 10.1016/j.jconrel.2017.04.003.
- [161] A. M. Goodman *et al.*, “Near-infrared remotely triggered drug-release strategies for cancer treatment,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 114, no. 47, pp. 12419–12424, Nov. 2017, doi: 10.1073/pnas.1713137114.
- [162] T. Vo-Dinh and B. A. Inman, “What potential does plasmonics-Amplified synergistic immuno photothermal nanotherapy have for treatment of cancer?,” *Nanomedicine*, vol. 13, no. 2, pp. 139–144, Dec. 2018, doi: 10.2217/nnm-2017-0356.
- [163] X. Dong *et al.*, “Intelligent MoS₂ Nanotheranostic for Targeted and Enzyme-/pH-/NIR-Responsive Drug Delivery to Overcome Cancer Chemotherapy Resistance Guided by PET Imaging,” *ACS Appl. Mater. Interfaces*, vol. 10, no. 4, pp. 4271–4284, Jan. 2018, doi: 10.1021/acsami.7b17506.
- [164] Y. Wang, L. Wang, M. Yan, A. Cai, S. Dong, and J. Hao, “Plasmonic microgels of Au nanorods: Self-assembly and applications in chemophotothermo-synergistic cancer therapy,” *J. Colloid Interface Sci.*, vol. 536, pp. 728–736, 2019, doi: 10.1016/j.jcis.2018.10.107.
- [165] J. Nam *et al.*, “PH-responsive assembly of gold nanoparticles and ‘spatiotemporally concerted’ Drug release for synergistic cancer therapy,” *ACS Nano*, vol. 7, no. 4, pp. 3388–3402, Apr. 2013, doi: 10.1021/nn400223a.
- [166] B. R. Smith and S. S. Gambhir, “Nanomaterials for in Vivo Imaging,” *Chem. Rev.*, vol. 117, no. 3, pp. 901–986, Feb. 2017, doi: 10.1021/acs.chemrev.6b00073.
- [167] X. Zhen, J. Zhang, J. Huang, C. Xie, Q. Miao, and K. Pu, “Macrotheranostic Probe with Disease-Activated Near-Infrared Fluorescence, Photoacoustic, and Photothermal Signals for Imaging-Guided Therapy,” *Angew. Chemie - Int. Ed.*, vol. 57, no. 26, pp. 7804–7808, Jun. 2018, doi: 10.1002/anie.201803321.
- [168] J. F. Borzelleca, “Paracelsus: Herald of modern toxicology,” *Toxicol. Sci.*, vol. 53, no. 1, pp. 2–4, Jan. 2000, doi: 10.1093/toxsci/53.1.2.

- [169] E. Fröhlich and E. Roblegg, “Models for oral uptake of nanoparticles in consumer products,” *Toxicology*, vol. 291, no. 1–3, pp. 10–17, 2012, doi: 10.1016/j.tox.2011.11.004.
- [170] D. Pissuwan, T. Niidome, and M. B. Cortie, “The forthcoming applications of gold nanoparticles in drug and gene delivery systems,” *J. Control. Release*, vol. 149, no. 1, pp. 65–71, 2011, doi: 10.1016/j.jconrel.2009.12.006.
- [171] S. Chaicherd, M. C. Killingsworth, and D. Pissuwan, “Toxicity of gold nanoparticles in a commercial dietary supplement drink on connective tissue fibroblast cells,” *SN Appl. Sci.*, vol. 1, no. 4, p. 336, 2019, doi: 10.1007/s42452-019-0354-2.
- [172] S. Sabella, A. Galeone, and G. Vecchio, “AuNPs are toxic in vitro and in vivo: a review,” *J. Nanosci. Lett.*, vol. 1, no. 3, pp. 145–165, 2011.
- [173] D. R. Lewinski N, Colvin V, “Cytotoxicity of nanoparticles. Smal,” *Small*, vol. 4, no. 1, pp. 26–49, 2008.
- [174] C. S. Yah, “The toxicity of gold nanoparticles in relation to their physiochemical properties,” *Biomed. Res.*, vol. 24, no. 3, pp. 400–413, 2013.
- [175] H. Chen, L. Shao, Q. Li, and J. Wang, “Gold nanorods and their plasmonic properties,” *Chem. Soc. Rev.*, vol. 42, no. 7, pp. 2679–2724, 2013, doi: 10.1039/c2cs35367a.
- [176] K. L. Aillon, Y. Xie, N. El-Gendy, C. J. Berkland, and M. L. Forrest, “Effects of nanomaterial physicochemical properties on in vivo toxicity,” *Adv. Drug Deliv. Rev.*, vol. 61, no. 6, pp. 457–466, 2009, doi: 10.1016/j.addr.2009.03.010.
- [177] J. L. Pelley, A. S. Daar, and M. A. Saner, “State of academic knowledge on toxicity and biological fate of quantum dots,” *Toxicol. Sci.*, vol. 112, no. 2, pp. 276–296, 2009, doi: 10.1093/toxsci/kfp188.
- [178] M. A. Maurer-Jones, K. C. Bantz, S. A. Love, B. J. Marquis, and C. L. Haynes, “Toxicity of therapeutic nanoparticles,” *Nanomedicine*, vol. 4, no. 2, pp. 219–241, 2009, doi: 10.2217/17435889.4.2.219.

- [179] S. M. Hussain *et al.*, “Toxicity evaluation for safe use of nanomaterials: Recent achievements and technical challenges,” *Adv. Mater.*, vol. 21, no. 16, pp. 1549–1559, 2009, doi: 10.1002/adma.200801395.
- [180] B. Fadeel and A. E. Garcia-Bennett, “Better safe than sorry: Understanding the toxicological properties of inorganic nanoparticles manufactured for biomedical applications,” *Adv. Drug Deliv. Rev.*, vol. 62, no. 3, pp. 362–374, 2010, doi: 10.1016/j.addr.2009.11.008.
- [181] H. J. Johnston, G. Hutchison, F. M. Christensen, S. Peters, S. Hankin, and V. Stone, “A review of the in vivo and in vitro toxicity of silver and gold particulates: Particle attributes and biological mechanisms responsible for the observed toxicity,” *Crit. Rev. Toxicol.*, vol. 40, no. 4, pp. 328–346, 2010, doi: 10.3109/10408440903453074.
- [182] Shuguang Wang, R. Lawson, P. C. Ray, and Hongtao Yu, “Toxic effects of gold nanoparticles on *Salmonella typhimurium* bacteria,” *Toxicol. Ind. Health*, vol. 27, no. 6, pp. 547–554, 2011, doi: 10.1177/0748233710393395.
- [183] I. Fratoddi, I. Venditti, C. Cametti, and M. V. Russo, “How toxic are gold nanoparticles? The state-of-the-art,” *Nano Res.*, vol. 8, no. 6, pp. 1771–1799, 2015, doi: 10.1007/s12274-014-0697-3.
- [184] G. Oberdörster *et al.*, “Principles for characterizing the potential human health effects from exposure to nanomaterials: Elements of a screening strategy,” *Part. Fibre Toxicol.*, vol. 2, no. 1, p. 8, 2005, doi: 10.1186/1743-8977-2-8.
- [185] G. Oberdörster, “Safety assessment for nanotechnology and nanomedicine: Concepts of nanotoxicology,” *J. Intern. Med.*, vol. 267, no. 1, pp. 89–105, Jan. 2010, doi: 10.1111/j.1365-2796.2009.02187.x.
- [186] M. Simkó, D. Nosske, and W. G. Kreyling, “Metrics, dose, and dose concept: The need for a proper dose concept in the risk assessment of nanoparticles,” *Int. J. Environ. Res. Public Health*, vol. 11, no. 4, pp. 4026–4048, Apr. 2014, doi: 10.3390/ijerph110404026.
- [187] W. Heisenberg, “Über den anschaulichen Inhalt der quantentheoretischen Kinematik

- und Mechanik,” *Zeitschrift für Phys.*, vol. 43, no. 3–4, pp. 172–198, 1927, doi: 10.1007/BF01397280.
- [188] K. Nambara *et al.*, “Reverse Size Dependences of the Cellular Uptake of Triangular and Spherical Gold Nanoparticles,” *Langmuir*, vol. 32, no. 47, pp. 12559–12567, 2016, doi: 10.1021/acs.langmuir.6b02064.
- [189] J. Noireaux *et al.*, “Gold nanoparticle uptake in tumor cells: Quantification and size distribution by sp-ICPMS,” *Separations*, vol. 6, no. 1, p. 3, 2019, doi: 10.3390/separations6010003.
- [190] D. B. Chithrani, “Intracellular uptake, transport, and processing of gold nanostructures,” *Mol. Membr. Biol.*, vol. 27, no. 7, pp. 299–311, Oct. 2010, doi: 10.3109/09687688.2010.507787.
- [191] J. Yue, T. J. Feliciano, W. Li, A. Lee, and T. W. Odom, “Gold Nanoparticle Size and Shape Effects on Cellular Uptake and Intracellular Distribution of siRNA Nanoconstructs,” *Bioconjug. Chem.*, vol. 28, no. 6, pp. 1791–1800, Jun. 2017, doi: 10.1021/acs.bioconjchem.7b00252.
- [192] P. Foroozandeh and A. A. Aziz, “Insight into Cellular Uptake and Intracellular Trafficking of Nanoparticles,” *Nanoscale Res. Lett.*, vol. 13, no. 1, p. 339, 2018, doi: 10.1186/s11671-018-2728-6.
- [193] M. A. K. Abdelhalim and M. Mady, “Liver uptake of gold nanoparticles after intraperitoneal administration in vivo: A fluorescence study,” *Lipids Health Dis.*, vol. 10, p. 195, Oct. 2011, doi: 10.1186/1476-511X-10-195.
- [194] I. Venditti, “Engineered gold-based nanomaterials: Morphologies and functionalities in biomedical applications. a mini review,” *Bioengineering*, vol. 6, no. 2, Jun. 2019, doi: 10.3390/bioengineering6020053.
- [195] Y. J. Lee, E. Y. Ahn, and Y. Park, “Shape-dependent cytotoxicity and cellular uptake of gold nanoparticles synthesized using green tea extract,” *Nanoscale Res. Lett.*, vol. 14, no. 1, p. 129, Apr. 2019, doi: 10.1186/s11671-019-2967-1.

- [196] X. Xie, J. Liao, X. Shao, Q. Li, and Y. Lin, “The Effect of shape on Cellular Uptake of Gold Nanoparticles in the forms of Stars, Rods, and Triangles,” *Sci. Rep.*, vol. 7, no. 1, p. 3827, Jun. 2017, doi: 10.1038/s41598-017-04229-z.
- [197] F. Moser *et al.*, “Cellular Uptake of Gold Nanoparticles and Their Behavior as Labels for Localization Microscopy,” *Biophys. J.*, vol. 110, no. 4, pp. 947–953, Feb. 2016, doi: 10.1016/j.bpj.2016.01.004.
- [198] A. Albanese and W. C. W. Chan, “Effect of gold nanoparticle aggregation on cell uptake and toxicity,” *ACS Nano*, vol. 5, no. 7, pp. 5478–5489, Jul. 2011, doi: 10.1021/nn2007496.
- [199] B. Drasler, D. Vanhecke, L. Rodriguez-Lorenzo, A. Petri-Fink, and B. Rothen-Rutishauser, “Quantifying nanoparticle cellular uptake: Which method is best?,” *Nanomedicine*, vol. 12, no. 10, pp. 1095–1099, Apr. 2017, doi: 10.2217/nnm-2017-0071.
- [200] C. Carnovale, G. Bryant, R. Shukla, and V. Bansal, “Identifying Trends in Gold Nanoparticle Toxicity and Uptake: Size, Shape, Capping Ligand, and Biological Corona,” *ACS Omega*, vol. 4, no. 1, pp. 242–256, Jan. 2019, doi: 10.1021/acsomega.8b03227.
- [201] N. Gunduz, H. Ceylan, M. O. Guler, and A. B. Tekinay, “Intracellular Accumulation of Gold Nanoparticles Leads to Inhibition of Macropinocytosis to Reduce the Endoplasmic Reticulum Stress,” *Sci. Rep.*, vol. 7, no. 1, p. 40493, 2017, doi: 10.1038/srep40493.
- [202] A. Cunningham and T. Bürgi, “Bottom-up Organisation of Metallic Nanoparticles,” C. Rockstuhl and T. Scharf, Eds. Berlin, Heidelberg: Springer Berlin Heidelberg, 2013, pp. 1–37.
- [203] T. J. Merkel, K. P. Herlihy, J. Nunes, R. M. Orgel, J. P. Rolland, and J. M. Desimone, “Scalable, shape-specific, top-down fabrication methods for the synthesis of engineered colloidal particles,” *Langmuir*, vol. 26, no. 16, pp. 13086–13096, Aug. 2010, doi: 10.1021/la903890h.

- [204] B. Van Eerdenbrugh, G. Van den Mooter, and P. Augustijns, “Top-down production of drug nanocrystals: Nanosuspension stabilization, miniaturization and transformation into solid products,” *Int. J. Pharm.*, vol. 364, no. 1, pp. 64–75, 2008, doi: 10.1016/j.ijpharm.2008.07.023.
- [205] S. Sant, S. L. Tao, O. Z. Fisher, Q. Xu, N. A. Peppas, and A. Khademhosseini, “Microfabrication technologies for oral drug delivery,” *Adv. Drug Deliv. Rev.*, vol. 64, no. 6, pp. 496–507, 2012, doi: 10.1016/j.addr.2011.11.013.
- [206] H. K. Chan and P. C. L. Kwok, “Production methods for nanodrug particles using the bottom-up approach,” *Adv. Drug Deliv. Rev.*, vol. 63, no. 6, pp. 406–416, 2011, doi: 10.1016/j.addr.2011.03.011.
- [207] X. Fu, J. Cai, X. Zhang, W. Di Li, H. Ge, and Y. Hu, “Top-down fabrication of shape-controlled, monodisperse nanoparticles for biomedical applications,” *Adv. Drug Deliv. Rev.*, vol. 132, pp. 169–187, 2018, doi: 10.1016/j.addr.2018.07.006.
- [208] T. Lednický and A. Bonyár, “Large Scale Fabrication of Ordered Gold Nanoparticle-Epoxy Surface Nanocomposites and Their Application as Label-Free Plasmonic DNA Biosensors,” *ACS Appl. Mater. Interfaces*, vol. 12, no. 4, pp. 4804–4814, Jan. 2020, doi: 10.1021/acsami.9b20907.
- [209] A. Klinkova, R. M. Choueiri, and E. Kumacheva, “Self-assembled plasmonic nanostructures,” *Chem. Soc. Rev.*, vol. 43, no. 11, pp. 3976–3991, 2014, doi: 10.1039/C3CS60341E.
- [210] B. Gallinet and O. J. F. Martin, “Refractive index sensing with subradiant modes: A framework to reduce losses in plasmonic nanostructures,” *ACS Nano*, vol. 7, no. 8, pp. 6978–6987, 2013, doi: 10.1021/nn4021967.
- [211] S. Mühligh *et al.*, “A self-assembled three-dimensional cloak in the visible,” *Sci. Rep.*, vol. 3, p. 2328, 2013, doi: 10.1038/srep02328.
- [212] J. Butet and O. J. F. Martin, “Refractive index sensing with Fano resonant plasmonic nanostructures: A symmetry based nonlinear approach,” *Nanoscale*, vol. 6, no. 24, pp.

- 15262–15270, 2014, doi: 10.1039/c4nr05623j.
- [213] M. Agio, “Optical antennas as nanoscale resonators,” *Nanoscale*, vol. 4, no. 3, pp. 692–706, 2012, doi: 10.1039/c1nr11116g.
- [214] I. S. Maksymov, I. Staude, A. E. Miroshnichenko, and Y. S. Kivshar, “Optical yagi-uda nanoantennas,” *Nanophotonics*, vol. 1, no. 1, pp. 65–81, 2012, doi: 10.1515/nanoph-2012-0005.
- [215] H. F. Hofmann, T. Kosako, and Y. Kadoya, “Design parameters for a nano-optical Yagi-Uda antenna,” *New J. Phys.*, vol. 9, no. 07, pp. 1–12, 2007, doi: 10.1088/1367-2630/9/7/217.
- [216] T. Kosako, Y. Kadoya, and H. F. Hofmann, “Directional control of light by a nano-optical Yagi-Uda antenna,” *Nat. Photonics*, vol. 4, no. 5, pp. 312–315, 2010, doi: 10.1038/nphoton.2010.34.
- [217] D. Dregely *et al.*, “Plasmonic antennas, positioning, and coupling of individual quantum systems,” *Phys. Status Solidi Basic Res.*, vol. 249, no. 4, pp. 666–677, 2012, doi: 10.1002/pssb.201100781.
- [218] P. Biagioni, J. S. Huang, and B. Hecht, “Nanoantennas for visible and infrared radiation,” *Reports Prog. Phys.*, vol. 75, no. 2, p. 24402, 2012, doi: 10.1088/0034-4885/75/2/024402.
- [219] L. Novotny, “Effective wavelength scaling for optical antennas,” *Phys. Rev. Lett.*, vol. 98, no. 26, pp. 1–4, 2007, doi: 10.1103/PhysRevLett.98.266802.
- [220] A. Boltasseva, “Empowering plasmonics and metamaterials technology with new material platforms,” *MRS Bull.*, vol. 39, no. 5, pp. 461–468, 2014, doi: 10.1557/mrs.2014.91.
- [221] U. Guler, V. M. Shalaev, and A. Boltasseva, “Nanoparticle plasmonics: Going practical with transition metal nitrides,” *Mater. Today*, vol. 18, no. 4, pp. 227–237, 2015, doi: 10.1016/j.mattod.2014.10.039.

- [222] G. V. Naik, V. M. Shalaev, and A. Boltasseva, “Alternative plasmonic materials: Beyond gold and silver,” *Adv. Mater.*, vol. 25, no. 24, pp. 3264–3294, 2013, doi: 10.1002/adma.201205076.
- [223] D. C. Adams *et al.*, “Funneling light through a subwavelength aperture with epsilon-near-zero materials,” *Phys. Rev. Lett.*, vol. 107, no. 13, pp. 1090–1099, 2011, doi: 10.1103/PhysRevLett.107.133901.
- [224] C. M. Soukoulis, T. Koschny, P. Tassin, N. H. Shen, and B. Dastmalchi, “What is a good conductor for metamaterials or plasmonics,” *Nanophotonics*, vol. 4, no. 1, pp. 69–74, 2015, doi: 10.1515/nanoph-2014-0013.
- [225] J. B. Khurgin, “How to deal with the loss in plasmonics and metamaterials,” *Nat. Nanotechnol.*, vol. 10, no. 1, pp. 2–6, 2015, doi: 10.1038/nnano.2014.310.
- [226] C. Wu *et al.*, “Metamaterial-based integrated plasmonic absorber/emitter for solar thermo-photovoltaic systems,” *J. Opt.*, vol. 14, no. 2, p. 24005, 2012, doi: 10.1088/2040-8978/14/2/024005.
- [227] J. Y. Rhee, Y. J. Yoo, K. W. Kim, Y. J. Kim, and Y. P. Lee, “Metamaterial-based perfect absorbers,” *J. Electromagn. Waves Appl.*, vol. 28, no. 13, pp. 1541–1580, 2014, doi: 10.1080/09205071.2014.944273.
- [228] L. W. Nien, S. C. Lin, B. K. Chao, M. J. Chen, J. H. Li, and C. H. Hsueh, “Giant electric field enhancement and localized surface plasmon resonance by optimizing contour bowtie nanoantennas,” *J. Phys. Chem. C*, vol. 117, no. 47, pp. 25004–25011, 2013, doi: 10.1021/jp408610q.
- [229] G. Baffou *et al.*, “Photoinduced heating of nanoparticle arrays,” *ACS Nano*, vol. 7, no. 8, pp. 6478–6488, 2013, doi: 10.1021/nn401924n.
- [230] G. Baffou and R. Quidant, “Thermo-plasmonics: Using metallic nanostructures as nano-sources of heat,” *Laser Photonics Rev.*, vol. 7, no. 2, pp. 171–187, 2013, doi: 10.1002/lpor.201200003.
- [231] J. Hao, L. Zhou, and M. Qiu, “Nearly total absorption of light and heat generation by

- plasmonic metamaterials,” *Phys. Rev. B - Condens. Matter Mater. Phys.*, vol. 83, no. 16, p. 165107, 2011, doi: 10.1103/PhysRevB.83.165107.
- [232] J. M. Stern, J. Stanfield, W. Kabbani, J. T. Hsieh, and J. A. Cadeddu, “Selective prostate cancer thermal ablation with laser activated gold nanoshells,” *J. Urol.*, vol. 179, no. 2, pp. 748–753, 2008, doi: 10.1016/j.juro.2007.09.018.
- [233] M. F. Tsai *et al.*, “Au nanorod design as light-absorber in the first and second biological near-infrared windows for in vivo photothermal therapy,” *ACS Nano*, vol. 7, no. 6, pp. 5330–5342, 2013, doi: 10.1021/nn401187c.
- [234] W. Xiong, R. Mazid, L. W. Yap, X. Li, and W. Cheng, “Plasmonic caged gold nanorods for near-infrared light controlled drug delivery,” *Nanoscale*, vol. 6, no. 23, pp. 14388–14393, 2014, doi: 10.1039/c4nr04400b.
- [235] G. Baffou, J. Polleux, H. Rigneault, and S. Monneret, “Super-heating and micro-bubble generation around plasmonic nanoparticles under cw illumination,” *J. Phys. Chem. C*, vol. 118, no. 9, pp. 4890–4898, 2014, doi: 10.1021/jp411519k.
- [236] Q. Jiang, S. Zhang, and M. Zhao, “Size-dependent melting point of noble metals,” *Mater. Chem. Phys.*, vol. 82, no. 1, pp. 225–227, 2003, doi: 10.1016/S0254-0584(03)00201-3.
- [237] W. Li *et al.*, “Refractory plasmonics with titanium nitride: Broadband,” *Adv. Mater.*, vol. 26, no. 47, pp. 7959–7965, 2014, doi: 10.1002/adma.201401874.
- [238] H. A. Atwater and A. Polman, “Erratum: Plasmonics for improved photovoltaic devices (Nature Materials (2010) 9 (205-213)),” *Nat. Mater.*, vol. 9, no. 10, p. 865, 2010, doi: 10.1038/nmat2866.
- [239] P. Bermel *et al.*, “Tailoring photonic metamaterial resonances for thermal radiation,” *Nanoscale Res. Lett.*, vol. 6, no. 1, pp. 1–5, 2011, doi: 10.1186/1556-276X-6-549.
- [240] G. Baffou, R. Quidant, and C. Girard, “Heat generation in plasmonic nanostructures: Influence of morphology,” *Appl. Phys. Lett.*, vol. 94, no. 15, pp. 1–3, 2009, doi: 10.1063/1.3116645.

- [241] G. Baffou and R. Quidant, “Nanoplasmonics for chemistry,” *Chem. Soc. Rev.*, vol. 43, no. 11, pp. 3898–3907, 2014, doi: 10.1039/c3cs60364d.
- [242] R. Adato and H. Altug, “In-situ ultra-sensitive infrared absorption spectroscopy of biomolecule interactions in real time with plasmonic nanoantennas,” *Nat. Commun.*, vol. 4, p. 2154, 2013, doi: 10.1038/ncomms3154.
- [243] S. J. Tan, M. J. Campolongo, D. Luo, and W. Cheng, “Building plasmonic nanostructures with DNA,” *Nat. Nanotechnol.*, vol. 6, no. 5, pp. 268–276, 2011, doi: 10.1038/nnano.2011.49.
- [244] A. E. Cetin *et al.*, “Handheld high-throughput plasmonic biosensor using computational on-chip imaging,” *Light Sci. Appl.*, vol. 3, no. 1, p. e122, 2014, doi: 10.1038/lsa.2014.3.
- [245] A. Alù and N. Engheta, “Cloaking a receiving antenna or a sensor with plasmonic metamaterials,” *Metamaterials*, vol. 4, no. 2–3, pp. 153–159, 2010, doi: 10.1016/j.metmat.2010.03.005.
- [246] F. Monticone and A. Alù, “Do cloaked objects really scatter less?,” *Phys. Rev. X*, vol. 3, no. 4, p. 41005, 2014, doi: 10.1103/PhysRevX.3.041005.
- [247] R. Fleury, J. Soric, and A. Alù, “Physical bounds on absorption and scattering for cloaked sensors,” *Phys. Rev. B - Condens. Matter Mater. Phys.*, vol. 89, no. 4, p. 45122, 2014, doi: 10.1103/PhysRevB.89.045122.
- [248] L. Novotny, “From near-field optics to optical antennas,” *Phys. Today*, vol. 64, no. 7, pp. 47–52, 2011, doi: 10.1063/PT.3.1167.
- [249] R. Fleury and A. Alù, “Cloaking and invisibility: A review,” in *Progress in Electromagnetics Research*, 2014, vol. 147, no. 7, pp. 171–202, doi: 10.2528/PIER15011403.
- [250] A. Alù and N. Engheta, “Cloaking a sensor,” *Phys. Rev. Lett.*, vol. 102, no. 23, p. 233901, 2009, doi: 10.1103/PhysRevLett.102.233901.
- [251] P. Y. Chen, J. Soric, and A. Alù, “Invisibility and cloaking based on scattering

- cancellation,” *Adv. Mater.*, vol. 24, no. 44, pp. OP281--OP304, 2012, doi: 10.1002/adma.201202624.
- [252] O. Lecarme, Q. Sun, K. Ueno, and H. Misawa, “Robust and Versatile Light Absorption at Near-Infrared Wavelengths by Plasmonic Aluminum Nanorods,” *ACS Photonics*, vol. 1, no. 6, pp. 538–546, 2014, doi: 10.1021/ph500096q.
- [253] Y. F. Chau, W. H. Lin, M. J. Sung, C. Y. Jheng, S. C. Jheng, and D. P. Tsai, “Numerical Investigation of a Castle-like Contour Plasmonic Nanoantenna with Operating Wavelengths Ranging in Ultraviolet-Visible, Visible Light, and Infrared Light,” *Plasmonics*, vol. 8, no. 2, pp. 755–761, 2013, doi: 10.1007/s11468-012-9469-7.
- [254] S. Sederberg and A. Y. Elezzabi, “Nanoscale plasmonic contour bowtie antenna operating in the mid-infrared,” *Opt. Express*, vol. 19, no. 16, p. 15532, 2011, doi: 10.1364/oe.19.015532.
- [255] M. Gharibi, H. Khoshshima, B. Olyaeefar, and S. Khorram, “Field enhancement by plasmonic contour H-shaped nano-antenna,” *Eur. Phys. J. D*, vol. 68, no. 5, pp. 2–6, 2014, doi: 10.1140/epjd/e2014-40543-7.
- [256] Lumerical Inc., “Lumerical.” <https://www.lumerical.com/products/> (accessed Sep. 05, 2020).
- [257] A. D. Rakić, A. B. Djurišić, J. M. Elazar, and M. L. Majewski, “Optical properties of metallic films for vertical-cavity optoelectronic devices,” *Appl. Opt.*, vol. 37, no. 22, p. 5271, 1998, doi: 10.1364/ao.37.005271.
- [258] P. Jahanshahi, M. Ghomeishi, and F. R. M. Adikan, “Study on dielectric function models for surface Plasmon resonance structure,” *Sci. World J.*, vol. 2014, p. 503749, 2014, doi: 10.1155/2014/503749.
- [259] R. Brendel and D. Bormann, “An infrared dielectric function model for amorphous solids,” *J. Appl. Phys.*, vol. 71, no. 1, pp. 1–6, 1992, doi: 10.1063/1.350737.
- [260] A. B. Dahlin, *Plasmonic biosensors: An integrated view of refractometric detection*, vol. 4. Amsterdam Washington DC: Ios Press, 2011.

- [261] D. Dregely, R. Taubert, J. Dorfmueller, R. Vogelgesang, K. Kern, and H. Giessen, “3D optical Yagi-Uda nanoantenna array,” *Nat. Commun.*, vol. 2, no. 1, p. 267, 2011, doi: 10.1038/ncomms1268.
- [262] B. Ng *et al.*, “Lattice resonances in antenna arrays for liquid sensing in the terahertz regime,” *Opt. Express*, vol. 19, no. 15, p. 14653, 2011, doi: 10.1364/oe.19.014653.
- [263] C. Simovski, D. Morits, P. Voroshilov, M. Guzhva, P. Belov, and Y. Kivshar, “Enhanced efficiency of light-trapping nanoantenna arrays for thin-film solar cells,” *Opt. Express*, vol. 21, no. S4, p. A714, 2013, doi: 10.1364/oe.21.00a714.
- [264] C. Feuillet-Palma, Y. Todorov, A. Vasanelli, and C. Sirtori, “Strong near field enhancement in THz nano-antenna arrays,” *Sci. Rep.*, vol. 3, p. 1361, 2013, doi: 10.1038/srep01361.
- [265] Y. Chen and O. J. F. Martin, “Periodicity-induced symmetry breaking in a Fano lattice: Hybridization and tight-binding regimes,” *ACS Nano*, vol. 8, no. 11, pp. 11860–11868, 2014, doi: 10.1021/nn505642n.
- [266] D. J. Griffiths and C. Ingelfield, *Introduction to Electrodynamics*, vol. 73, no. 6. Boston: Pearson, 2005.
- [267] A. Alù and N. Engheta, “Achieving transparency with plasmonic and metamaterial coatings,” *Phys. Rev. E - Stat. Nonlinear, Soft Matter Phys.*, vol. 72, no. 1, pp. 1–9, 2005, doi: 10.1103/PhysRevE.72.016623.
- [268] B. Gao, G. Arya, and A. R. Tao, “Self-orienting nanocubes for the assembly of plasmonic nanojunctions,” *Nat. Nanotechnol.*, vol. 7, no. 7, pp. 433–437, 2012, doi: 10.1038/nnano.2012.83.
- [269] A. Klinkova *et al.*, “Structural and optical properties of self-assembled chains of plasmonic nanocubes,” *Nano Lett.*, vol. 14, no. 11, pp. 6314–6321, 2014, doi: 10.1021/nl502746h.
- [270] L. S. Slaughter, B. A. Willingham, W. S. Chang, M. H. Chester, N. Ogden, and S. Link, “Toward plasmonic polymers,” *Nano Lett.*, vol. 12, no. 8, pp. 3967–3972, 2012, doi:

- 10.1021/nl3011512.
- [271] T. Atay, J. H. Song, and A. V. Nurmikko, “Strongly interacting plasmon nanoparticle pairs: From dipole-dipole interaction to conductively coupled regime,” *Nano Lett.*, vol. 4, no. 9, pp. 1627–1631, 2004, doi: 10.1021/nl049215n.
- [272] Z. Li, S. Butun, and K. Aydin, “Touching Gold Nanoparticle Chain Based Plasmonic Antenna Arrays and Optical Metamaterials,” *ACS Photonics*, vol. 1, no. 3, pp. 228–234, 2014, doi: 10.1021/ph4000828.
- [273] L. M. Maestro *et al.*, “Gold nanorods for optimized photothermal therapy: The influence of irradiating in the first and second biological windows,” *RSC Adv.*, vol. 4, no. 96, pp. 54122–54129, 2014, doi: 10.1039/c4ra08956a.
- [274] L. M. Maestro, P. Haro-González, A. Sánchez-Iglesias, L. M. Liz-Marzán, J. García Solé, and D. Jaque, “Quantum dot thermometry evaluation of geometry dependent heating efficiency in gold nanoparticles,” *Langmuir*, vol. 30, no. 6, pp. 1650–1658, 2014, doi: 10.1021/la403435v.
- [275] M. A. MacKey, M. R. K. Ali, L. A. Austin, R. D. Near, and M. A. El-Sayed, “The most effective gold nanorod size for plasmonic photothermal therapy: Theory and in vitro experiments,” *J. Phys. Chem. B*, vol. 118, no. 5, pp. 1319–1326, 2014, doi: 10.1021/jp409298f.
- [276] D. C. Sordillo, L. A. Sordillo, P. P. Sordillo, and R. R. Alfano, “Fourth near-infrared optical window for assessment of bone and other tissues,” *Photonic Ther. Diagnostics XII*, vol. 9689, p. 96894J, 2016, doi: 10.1117/12.2214320.
- [277] L. A. Sordillo, Y. Pu, S. Pratavieira, Y. Budansky, and R. R. Alfano, “Deep optical imaging of tissue using the second and third near-infrared spectral windows,” *J. Biomed. Opt.*, vol. 19, no. 5, p. 056004, 2014, doi: 10.1117/1.jbo.19.5.056004.
- [278] M. A. Calin, M. R. Calin, and C. Munteanu, “Determination of the complex refractive index of cell cultures by reflectance spectrometry,” *Eur. Phys. J. Plus*, vol. 129, no. 6, p. 116, 2014, doi: 10.1140/epjp/i2014-14116-1.

- [279] E. D. Onal and K. Guven, "Scattering Suppression and Absorption Enhancement in Contour Nanoantennas," *ArXiv e-prints*, p. 1511.01312, 2015, Accessed: Dec. 16, 2016. [Online]. Available: <http://arxiv.org/abs/1511.01312>.
- [280] A. M. Alkilany and C. J. Murphy, "Toxicity and cellular uptake of gold nanoparticles: What we have learned so far?," *J. Nanoparticle Res.*, vol. 12, no. 7, pp. 2313–2333, 2010, doi: 10.1007/s11051-010-9911-8.
- [281] A. M. Alkilany, L. B. Thompson, S. P. Boulos, P. N. Sisco, and C. J. Murphy, "Gold nanorods: Their potential for photothermal therapeutics and drug delivery, tempered by the complexity of their biological interactions," *Adv. Drug Deliv. Rev.*, vol. 64, no. 2, pp. 190–199, 2012, doi: 10.1016/j.addr.2011.03.005.
- [282] H. Jia, C. Fang, X. M. Zhu, Q. Ruan, Y. X. J. Wang, and J. Wang, "Synthesis of Absorption-Dominant Small Gold Nanorods and Their Plasmonic Properties," *Langmuir*, vol. 31, no. 26, pp. 7418–7426, 2015, doi: 10.1021/acs.langmuir.5b01444.
- [283] L. A. Dykman and N. G. Khlebtsov, "Uptake of engineered gold nanoparticles into mammalian cells," *Chem. Rev.*, vol. 114, no. 2, pp. 1258–1288, 2014, doi: 10.1021/cr300441a.
- [284] M. B. Fish, A. J. Thompson, C. A. Fromen, and O. Eniola-Adefeso, "Emergence and utility of nonspherical particles in biomedicine," *Ind. Eng. Chem. Res.*, vol. 54, no. 16, pp. 4043–4059, 2015, doi: 10.1021/ie504452j.
- [285] S. E. A. Gratton *et al.*, "The effect of particle design on cellular internalization pathways," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 105, no. 33, pp. 11613–11618, 2008, doi: 10.1073/pnas.0801763105.
- [286] K. L. Gurunatha *et al.*, "Nanoparticles Self-Assembly Driven by High Affinity Repeat Protein Pairing," *ACS Nano*, vol. 10, no. 3, pp. 3176–3185, 2016, doi: 10.1021/acsnano.5b04531.
- [287] H. J. Yin *et al.*, "Study of surface-enhanced Raman scattering activity of DNA-directed self-assembled gold nanoparticle dimers," *Appl. Phys. Lett.*, vol. 107, no. 19, pp. 10–15,

- 2015, doi: 10.1063/1.4935543.
- [288] B. Teschome, S. Facsko, K. V. Gothelf, and A. Keller, "Alignment of Gold Nanoparticle-Decorated DNA Origami Nanotubes: Substrate Prepatterning versus Molecular Combing," *Langmuir*, vol. 31, no. 46, pp. 12823–12829, 2015, doi: 10.1021/acs.langmuir.5b02569.
- [289] R. Ahijado-Guzmán *et al.*, "Intracellular pH-Induced Tip-to-Tip Assembly of Gold Nanorods for Enhanced Plasmonic Photothermal Therapy," *ACS Omega*, vol. 1, no. 3, pp. 388–395, 2016, doi: 10.1021/acsomega.6b00184.
- [290] T. Ozel, M. J. Ashley, G. R. Bourret, M. B. Ross, G. C. Schatz, and C. A. Mirkin, "Solution-Dispersible Metal Nanorings with Deliberately Controllable Compositions and Architectural Parameters for Tunable Plasmonic Response," *Nano Lett.*, vol. 15, no. 8, pp. 5273–5278, 2015, doi: 10.1021/acs.nanolett.5b01594.
- [291] H. J. Jang *et al.*, "Fabrication of 2D Au nanorings with Pt framework," *J. Am. Chem. Soc.*, vol. 136, no. 50, pp. 17674–17680, 2014, doi: 10.1021/ja510916y.
- [292] E. D. Onal and K. Guven, "Plasmonic photothermal therapy in third and fourth biological windows," *J. Phys. Chem. C*, vol. 121, no. 1, pp. 684–690, 2017, doi: 10.1021/acs.jpcc.6b10060.
- [293] S. Wang, H. Xu, and J. Ye, "Plasmonic rod-in-shell nanoparticles for photothermal therapy," *Phys. Chem. Chem. Phys.*, vol. 16, no. 24, pp. 12275–12281, 2014, doi: 10.1039/c4cp00902a.
- [294] J. M. Tucker-Schwartz, T. A. Meyer, C. A. Patil, C. L. Duvall, and M. C. Skala, "In vivo photothermal optical coherence tomography of gold nanorod contrast agents," *Biomed. Opt. Express*, vol. 3, no. 11, p. 2881, 2012, doi: 10.1364/boe.3.002881.
- [295] J. R. Cole, N. A. Mirin, M. W. Knight, G. P. Goodrich, and N. J. Halas, "Photothermal efficiencies of nanoshells and nanorods for clinical therapeutic applications," *J. Phys. Chem. C*, vol. 113, no. 28, pp. 12090–12094, 2009, doi: 10.1021/jp9003592.
- [296] L. Shao, Y. Tao, Q. Ruan, J. Wang, and H. Q. Lin, "Comparison of the plasmonic

- performances between lithographically fabricated and chemically grown gold nanorods,” *Phys. Chem. Chem. Phys.*, vol. 17, no. 16, pp. 10861–10870, 2015, doi: 10.1039/c5cp00715a.
- [297] R. Lachaine, É. Boulais, D. Rioux, C. Boutopoulos, and M. Meunier, “Computational Design of Durable Spherical Nanoparticles with Optimal Material, Shape, and Size for Ultrafast Plasmon-Enhanced Nanocavitation,” *ACS Photonics*, vol. 3, no. 11, pp. 2158–2169, 2016, doi: 10.1021/acsp Photonics.6b00652.
- [298] M. J. Kale, T. Avanesian, and P. Christopher, “Direct photocatalysis by plasmonic nanostructures,” *ACS Catal.*, vol. 4, no. 1, pp. 116–128, 2014, doi: 10.1021/cs400993w.
- [299] P. Wang, B. Huang, Y. Dai, and M. H. Whangbo, “Plasmonic photocatalysts: Harvesting visible light with noble metal nanoparticles,” *Phys. Chem. Chem. Phys.*, vol. 14, no. 28, pp. 9813–9825, 2012, doi: 10.1039/c2cp40823f.
- [300] O. Neumann *et al.*, “Nanoparticle-mediated, light-induced phase separations,” *Nano Lett.*, vol. 15, no. 12, pp. 7880–7885, 2015, doi: 10.1021/acs.nanolett.5b02804.
- [301] A. M. Goodman, N. J. Hogan, S. Gottheim, C. Li, S. E. Clare, and N. J. Halas, “Understanding Resonant Light-Triggered DNA Release from Plasmonic Nanoparticles,” *ACS Nano*, vol. 11, no. 1, pp. 171–179, 2017, doi: 10.1021/acsnano.6b06510.
- [302] Y. Li *et al.*, “Localized electric field of plasmonic nanoplatform enhanced photodynamic tumor therapy,” *ACS Nano*, vol. 8, no. 11, pp. 11529–11542, 2014, doi: 10.1021/nn5047647.
- [303] Y. Wang *et al.*, “Comparison study of gold nanohexapods, nanorods, and nanocages for photothermal cancer treatment,” *ACS Nano*, vol. 7, no. 3, pp. 2068–2077, 2013, doi: 10.1021/nn304332s.
- [304] S. Wang, X. Zhao, S. Wang, J. Qian, and S. He, “Biologically Inspired Polydopamine Capped Gold Nanorods for Drug Delivery and Light-Mediated Cancer Therapy,” *ACS Appl. Mater. Interfaces*, vol. 8, no. 37, pp. 24368–24384, 2016, doi:

- 10.1021/acsami.6b05907.
- [305] D. Zhang *et al.*, “Chlorin e6 conjugated poly(dopamine) nanospheres as PDT/PTT dual-modal therapeutic agents for enhanced cancer therapy,” *ACS Appl. Mater. Interfaces*, vol. 7, no. 15, pp. 8176–8187, 2015, doi: 10.1021/acsami.5b01027.
- [306] Y. C. Ou *et al.*, “Gold Nanoantenna-Mediated Photothermal Drug Delivery from Thermosensitive Liposomes in Breast Cancer,” *ACS Omega*, vol. 1, no. 2, pp. 234–243, 2016, doi: 10.1021/acsomega.6b00079.
- [307] A. Smith, *The wealth of nations*. W. Strahan and T. Cadell, London, 1776.



APPENDIX A:

DUAL-PERSPECTIVE DESIGN: SUPPLEMENT

A.1 Geometry-Centric Comparison of Solid vs. Hollow AuNPs

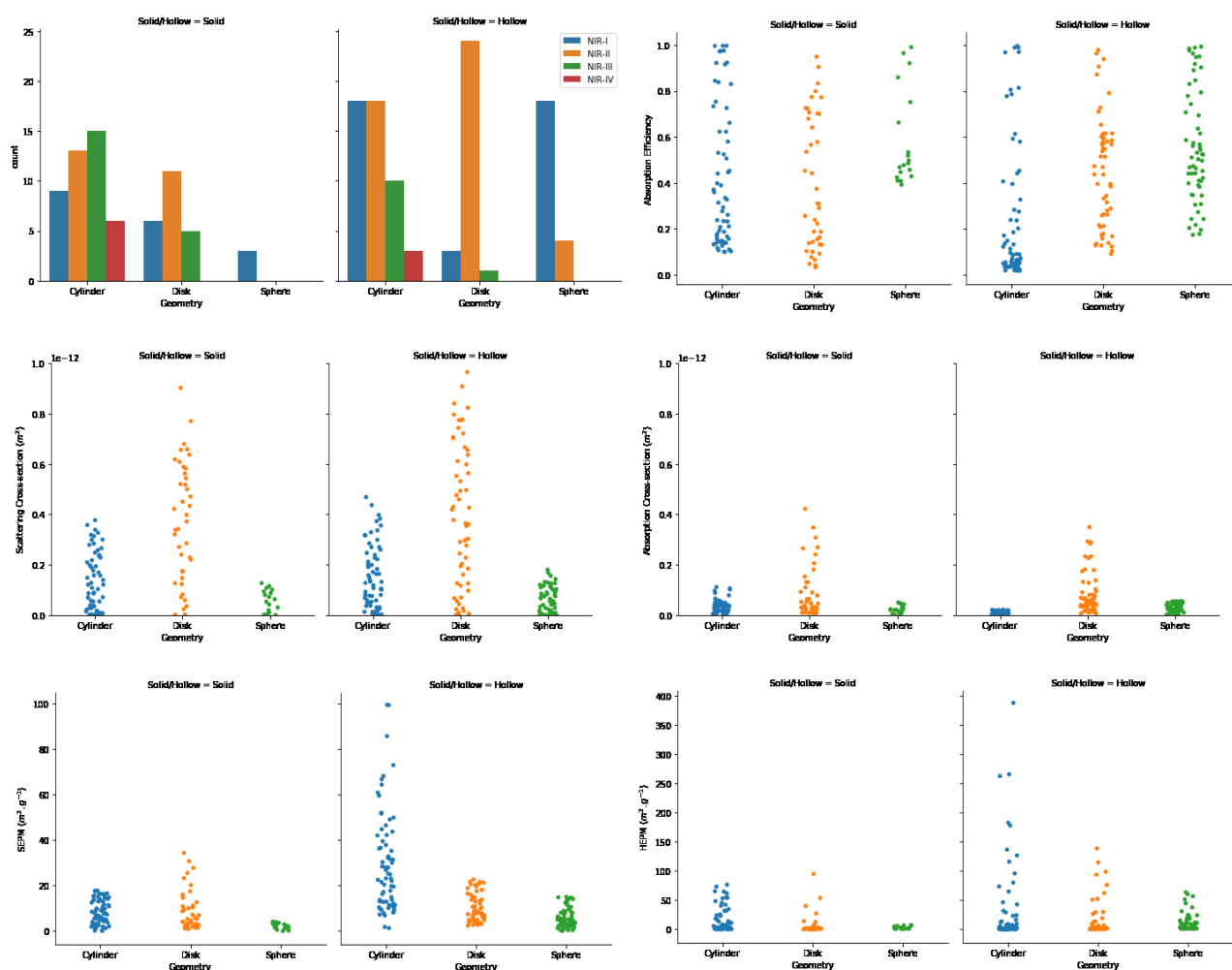


Figure A.1 Geometry Centric Investigation of the AuNP Dataset: Solid vs. Hollow Elementary Geometries

A.2 Wavelength-Centric Comparison of Solid vs. Hollow AuNPs

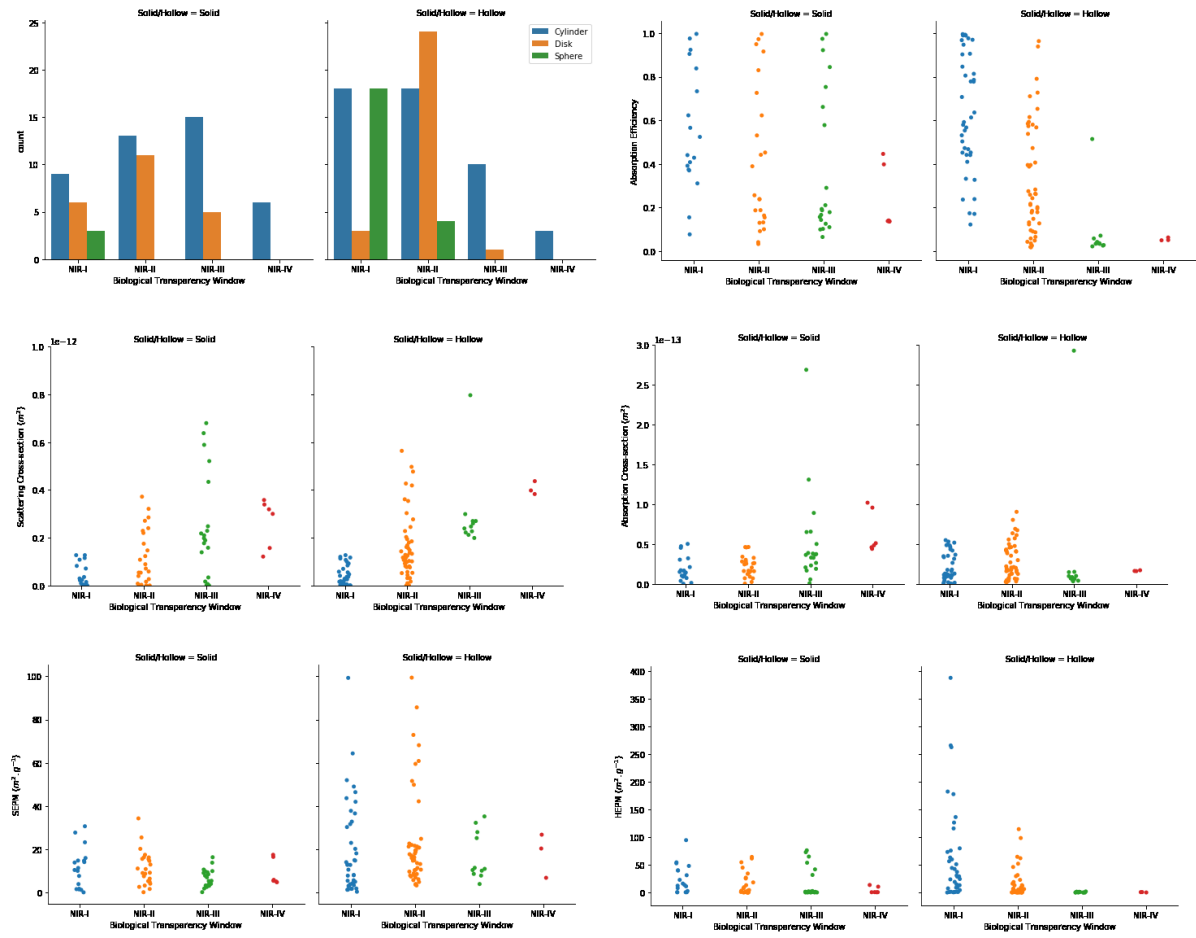


Figure A.2 Wavelength Centric Investigation of the AuNP Dataset: Solid vs. Hollow Elementary Geometries

APPENDIX B:

BIVARIATE ANALYSIS OF ELEMENTARY AuNPs

B.1 Gold Nanospheres & NanoSphericalShells: AuNSs & AuNSSs

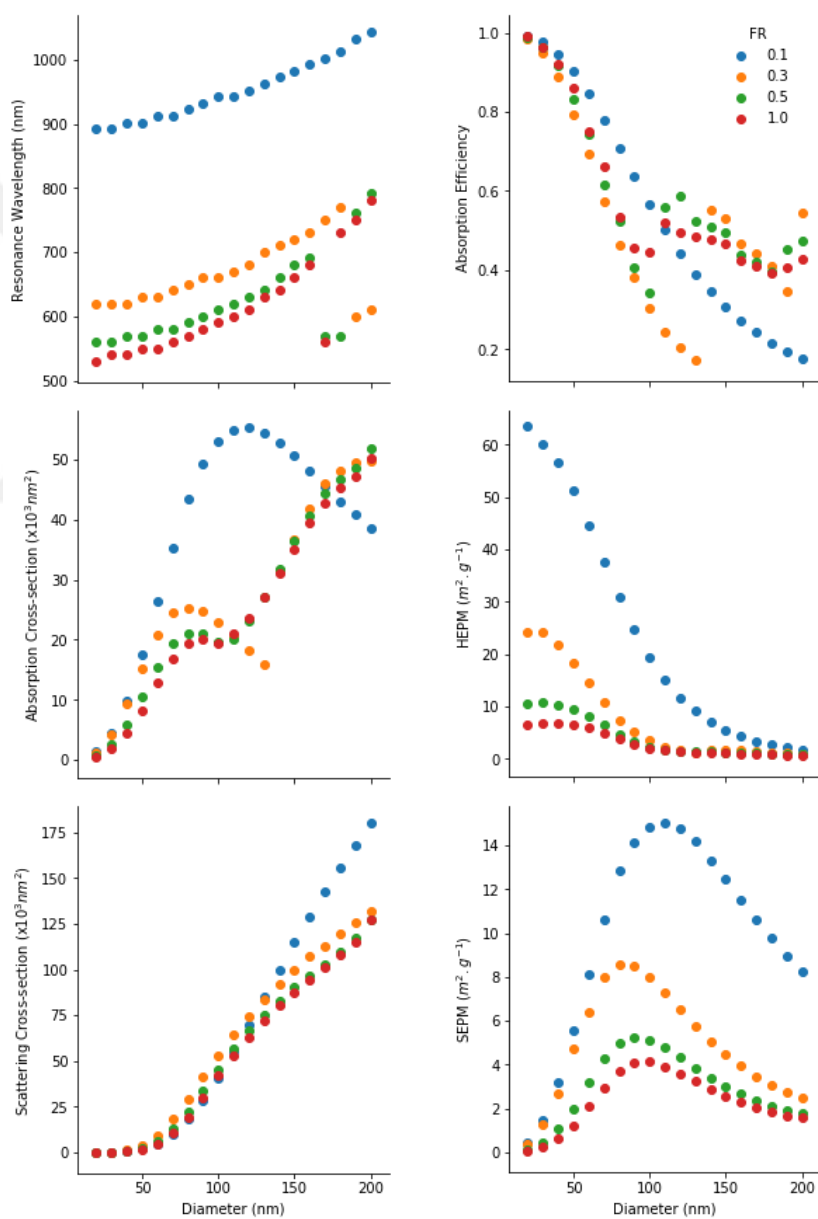


Figure B.1 Bivariate Analysis of AuNSs & AuNSSs Properties with respect to FR

B.2 Gold Nanorings: AuNRs

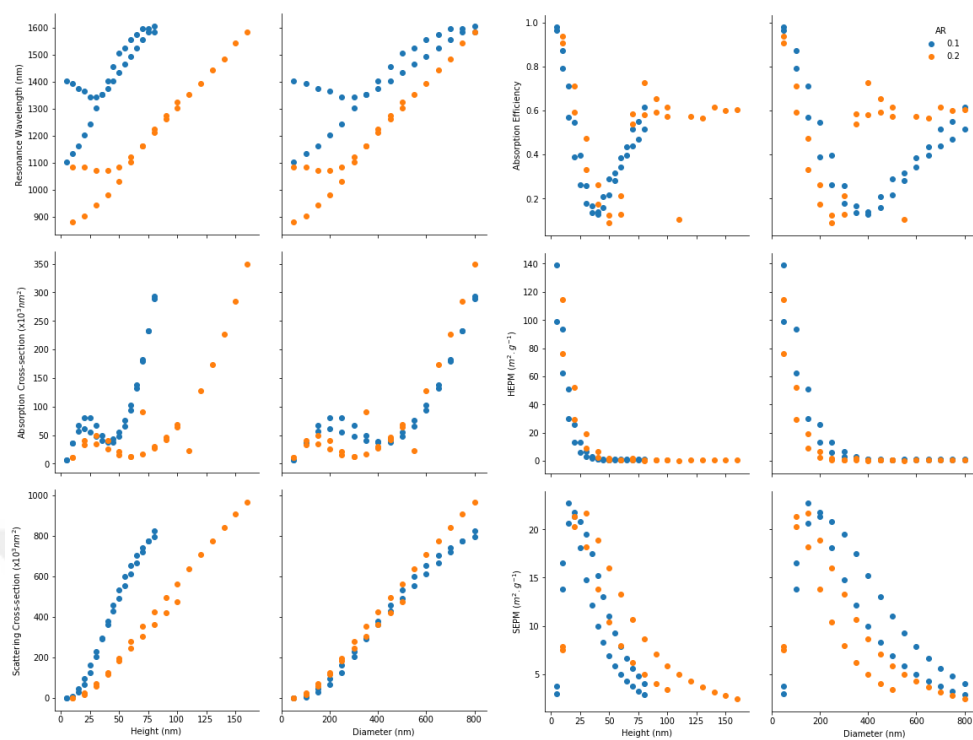


Figure B.2 Bivariate Analysis of AuNRs Properties with respect to AR

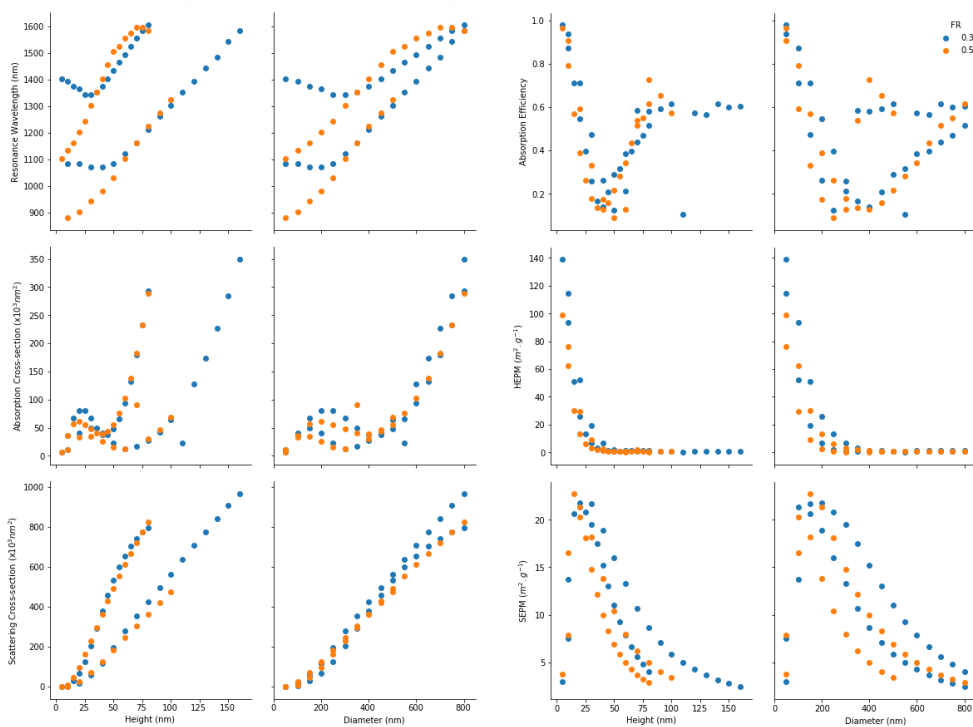


Figure B.3 Bivariate Analysis of AuNRs Properties with respect to FR

B.3 Gold Nanotubes: AuNTs

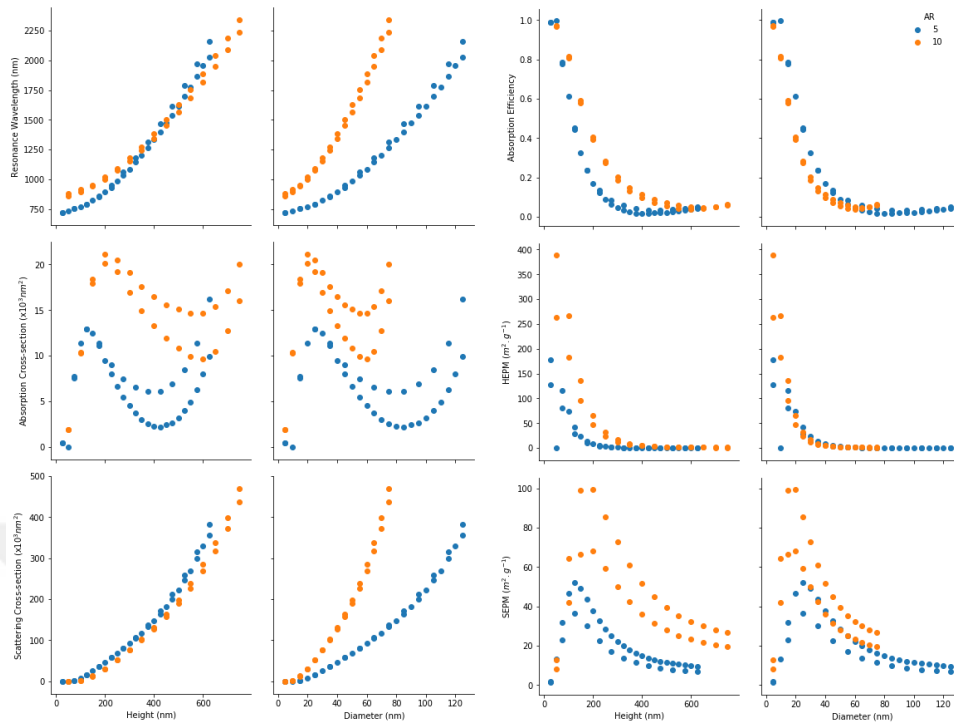


Figure B.4 Bivariate Analysis of AuNTs Properties with respect to AR

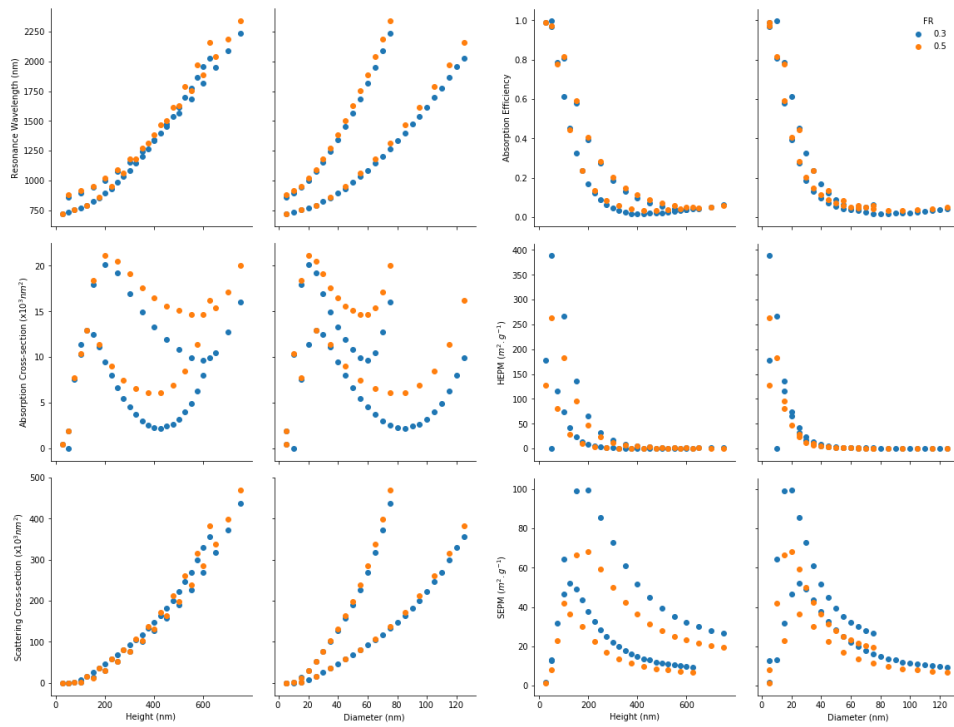


Figure B.5 Bivariate Analysis of AuNTs Properties with respect to FR