NANOANTENNA
Plasmon-Enhanced Spectroscopies for Biotechnological Applications

edited by
Marc Lamy de la Chapelle
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This book is closely related to the EU project Nanoantenna, which is focused on the development of a highly sensitive and specific nanobiosensor based on surface-enhanced vibrational spectroscopy dedicated to protein detection and disease diagnostics.

A. Examples of sensitive assays that biochemistry has developed on its own

1. Quantitative detection of target proteins by immunochemical procedures is very sensitive. The enzyme-linked immunosorbent assay (ELISA) uses an antibody against the protein of interest. The bound enzyme is, for instance, detected by bonding to a fluorescent dye.

2. As most proteins are negatively charged, they can be spatially separated by electrophoresis in, for instance, acrylamide gels by migration from the positive to the negative electrode according to their molecular weight and mobility, yielding characteristic stripes (so-called Western plot), which become visible by various techniques (e.g., by the antibody of a special protein, the antibody being tagged to a fluorophore).

B. Detection of proteins by a combination of optical plasma resonances at silver or gold surfaces and an immunoreaction

1. The oldest and as yet most successful pure optical method uses electromagnetic surface waves (called surface plasmon polaritons [SPPs]) at the interface of a silver film conditioned to bind special proteins or antibodies. The silver film is prepared on a prism. Under illumination from the prism side, the SPP becomes resonant in a small angular range. This resonance is slightly shifted by an immunoreaction, which can thus be recorded with high precision.

2. A promising method to detect immunoreactions are plasma resonances in small gold spheres. So-called reporter molecules with special Raman spectra are adsorbed on the spheres and protected by a very thin glass film. The spheres are conditioned
with a special antibody. A specific reporter molecule is employed for the specific antibody. Only those spheres that bond to the searched-for antisense stick to the assay and are characterized by the Raman spectrum of the special reporter molecule.

C. **Label-free detection of proteins**

The so-called label-free detection of proteins would observe directly the known specific vibrational spectra by infrared (IR) or Raman spectroscopy without any immunoreaction. Plasmon resonances at the “hot sides” of noble metal nanoparticles would enhance the IR or Raman spectra of small quantities of proteins adsorbed onto the “hot sides.” Such spectroscopy is called surface-enhanced infrared spectroscopy (SEIRS) or surface-enhanced Raman spectroscopy (SERS). Surface-enhanced coherent anti-Stokes Raman scattering (CARS) is discussed as a promising method. The goal of the above-mentioned project Nanoantenna is label-free detection of a small number of proteins. Nevertheless, functionalization of gold surfaces to achieve bonding of proteins is necessary.

The book is structured as follows.

C1. **Chapters centered on “bio-spectroscopy”**

Chapter 1 describes Raman spectroscopy in general and its wide use as a method for probing the structure and conformation of native proteins that play an important role in the body. Important structural information can be deduced from specific Raman vibrational bands such as amide I, amide II, and amide III bands. On the other hand, the influence of chemical reactions involving proteins (folding/unfolding, oxidation, reduction, phosphorylation, and polymerization) can be monitored by following the evolution over time of the Raman band related to disulphide bridge stretching, tryptophan and other aromatic ring vibrations, and protein side chain deformation. It is possible to determine reaction-free enthalpy and free enthalpies for the unfolding of protein structure and reaction kinetics in a biological environment.

Chapter 2 focuses on the analysis of biofluids by mid-infrared and Raman spectroscopy. Biological processes strongly depend on the fact that the relevant biochemistry takes place in water, which has a very strong absorption in the mid-infrared spectral range. The chapter describes strategies to mitigate the influence of water. Biomedical vibrational spectroscopy of serum is capable
of supporting medical diagnostics by, for instance, simultaneously
determining the concentration of multiple analytes or in the form
of a direct attribution of a sample's spectrum to a particular disease
under investigation. The need for independent validation is pointed
out.

Chapter 3 describes the functionalization of gold surfaces by self-
assembling films of various thiols. The functional groups attached
to the end opposite to the SH group (forming a strong Au–S bond)
control the surface properties of the monolayers formed. The
flexibility to design different head groups of monolayers using a large
number of functional groups makes this functionalization strategy
especially useful for the controlled fabrication of structurally ordered
assemblies of proteins on surfaces. Different types of thiols such as
mono-, di-, tri-, or mixed thiol molecules are discussed in view of their
benefits and disadvantages to immobilize special biomolecules.

C2. Chapters centered on surface plasmonic resonances

Chapter 6 discusses the resonant excitation of metallic nano-
structures by light. Dubbed nanoantennas, these structures
yield electromagnetic near-field enhancement, used for sensing
applications such as SEIRS and SERS. The interaction between
nanoparticles in multimers and arrays of nanoantennas affects the
optical properties of the system. These depend on the separation
distances, especially between nearest neighbor particles. The
interaction effects studied experimentally and theoretically in
dimers—consisting of ellipsoids, spheres, nanodisks, nanorods, or
nanoantennas—in linear arrays of nanocylinders or two-dimensional
nanoparticle arrays are discussed, especially concerning SEIRS.

Chapter 7 gives special attention to nanosculptured thin films,
which are assemblies of shaped, parallel, and tilted nanorods,
prepared using many variants of the basic oblique angle deposition
technique. Comparison is made between different materials such
as silver, gold, copper, and silicon and with various shapes such as
columns, screws, spheres, and helices that are deposited on different
substrates and with different porosities and orientations. Localized
surface plasmon resonances in the vis–NIR range lead to surface-
enhanced fluorescence and SEIRS.

Chapter 8 presents an extensive discussion of the excitation of
surface plasmon polaritons at plane metal surfaces by attenuated total
reflectivity. The self-organized templates of anodic porous alumina
allow patterning of noble metal structures with plasmon resonances over large areas. Arrays of square-like gold nanoparticles were fabricated by electron beam lithography. Au nanoaggregates were grown in a hole array. The SERS spectra of four different proteins on these samples were recorded. Large arrays of nanoantennas were achieved with reproducibility at the sub-10 nm scale. The sample topography was characterized by scanning electron microscopy and atomic force microscopy equipped with ultrasharp Si tips. Focussed ion beam milling was employed to produce a photonic crystal (PC) with a central cavity, on which a Pt nano-cone was grown by electron beam–induced chemical vapor deposition, and finally it was covered with gold. The adiabatic propagation of surface plasmon polaritons on this conical Au tip and field enhancement at the tip end was achieved by back illumination of the PC. The structure presented an extremely high electromagnetic enhancement at a very small radius of curvature of the tip end demonstrated by SERS of benzene thiol.

Chapter 9 is a general introduction to surface-enhanced infrared absorption (SEIRA) of adsorbates on metal island films at the percolation threshold and surface-enhanced infrared spectroscopy (SEIRS) using infrared resonances of nanoantennas. The metal island films at the percolation threshold have localized electromagnetic resonances throughout a wide spectral infrared range. Therefore, a complete IR spectrum of the adsorbed molecules may be obtained, including some microscopic surface–molecule “chemical” interactions. In SEIRS the resonances of tailored nanoantennas or antenna dimers and arrays are confined to narrow frequency ranges, overlapping only with some IR-active vibrations, directly adsorbed molecules, or molecules grafted by a functionalization layer on the antennas. Very strong enhancements have been observed in this case at the “hot spots” with atto-molar sensitivity. Also, the phonon-polaritons of the silica substrate confined to the hot spots of the antennas become observable.

Chapter 10 gives a short introduction to the history of SERS up to single molecule detection by SERS, followed by a general discussion of electromagnetic field enhancement and of the so-called first layer chemical mechanism. The chapter presents as example the measurement of the SERS enhancement of trans-1,2-bis(4-pyridil)ethylene (BPE) on different gold nanoparticle arrays. Various strategies to obtain SERS biosensors and the results achieved till now are described. The application of SERS substrates produced
by e-beam nanolithography to detect proteins is demonstrated, especially their conformation change with temperature.

Chapter 11 revisits the theory and experiments of surface plasmon resonance in Kretschmann configuration and the high sensitivity of the resonance that is shifted in angular distribution by very thin cover films. Only 2 nm of chromium and 5 nm of functionalization significantly shift plasmon resonance. Optimization methods may lead to more complex biosensors.

Chapter 12 covers coherent anti-Stokes Raman scattering. SERS requires the presence of a relatively large metal surface, and the intensity in surface plasmon resonances decays rapidly with distance away from the surface. Both linear (fluorescence, Raman, etc.) and nonlinear (second and third harmonic generation) physical processes can be generated from biological molecules near a metal surface. The final objective is to achieve single molecule detection. In the case of Raman processes, CARS generation is stronger than spontaneous Raman scattering. Since CARS is a four-wave mixing process in which the anti-Stokes signal results from the parametric coupling of an incident pump and a Stokes laser, a stronger local enhancement is expected for CARS than for conventional SERS, which would make surface-enhanced (SE-)CARS more challenging than SERS. However, strong field energies are needed in CARS generation, and CARS is not background free. This makes single molecule detection hard.

C3. Chapters centered on related subjects

Miniaturization of gold plasmonic antenna structures finally leads to atomic wires made of Au atoms. Chapter 5 discusses dimensionality and electronic correlation effects in relation to the atomic-scale confinement. Atomic wires are prospective materials for supporting plasmonic resonating modes. The dispersion relation of propagating plasmonic modes was measured by electron energy loss spectroscopy. It is quasi-linear with a wavevector (and was therefore named acoustic plasmon in former times). The first examples of measurements of plasmonic resonators in atomic wires are introduced together with nanoscale structure characterization by electron diffraction. The results clearly demonstrate that the frequency of the plasmon in an atomic wire can be fully tuned by controlling its width, separation, and length in the range of one to tens of nanometers.
The aim of chapter 4 is to summarize the recent advances in the field of nanoparticle surface functionalization, especially of magnetic nanoparticles. The intrinsic interaction of magnetic nanoparticles with applied magnetic field gradients makes these particles attractive for a large panel of biomedical applications such as magnetic separation systems for biomolecules and cells, for magnetic resonance imaging contrast enhancement, for therapy such as hyperthermia and drug delivery, as well as for multidetection systems based on biosensors.

Chapter 13 details multi-signal processing biosensors and bioactuators based on biocomputing. Molecular and biomolecular logic gates and their network-processing chemical input signals received high attention and were rapidly developed in the last decade. Networks with computational steps that solely involve biochemical processes are being researched for new technological capabilities: multi-input biosensors with new functionalities as well as approaches that allow removing the batteries from, and generally reducing the need for, inorganic leads and electrical power supply for those stages of information processing that occur during biomedical testing; implantable devices; and other fast decision-making steps in applications such as patient-tailored timely therapy. Most of the activity in such feedback-loop systems is currently being devoted toward the management of diabetes through integration of an electrochemical glucose-sensing element with an insulin-delivery feedback loop for optimal doses of insulin.

All in all, students and researchers in nanotechnology, physics, chemistry, biology, and medicine, especially those with an interest in biosensing technologies, will certainly benefit from this book.

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