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Novel Nanosensors for Health Monitoring and Environmental Control Based on Surface-Enhanced Raman Scattering (SERS)

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1. Identification and brief description of technology candidate that needs to be advanced from the concept to the system prototype level

When light interacts with molecules, in addition to fluorescence one can observe discrete spectral "lines", whose frequencies are uniquely shifted relative to the excitation frequency. This effect, called Raman scattering occurs due to the inelastic scattering of incident photons $h\nu_L$ at molecular vibrations.

Fluorescence

![Fluorescence Diagram]

Raman

![Raman Diagram]

Figure 1: Fluorescence and Raman scattering. Raman cross sections are between $10^{-30}$ cm$^2$ and $10^{-26}$ cm$^2$ per molecule, the larger values occurring only under favorable resonance Raman conditions, when excitation and/or scattered photons are in resonance with electronic transitions in the molecule. For comparison, effective fluorescence cross sections can reach about $10^{-16}$ cm$^2$ per molecule.
Figure 1 shows the schematics of fluorescence and Raman scattering in a molecular energy level diagram together with typical fluorescence and Raman spectra. Note, that in Raman scattering excitation and/or scattered photons do not need to be in resonance with any real molecular transition. The interaction with the molecule is not due to an absorption and emission process, but due to scattering.

In many cases, fluorescence spectra are relatively “broad bands” and do not provide so much structural information on the molecule. The Raman scattering signal is composed by many “sharp” lines. The frequency shift between the excitation light and the Raman lines is determined by the energy of the molecular vibrations $h\nu_M$, which in turn depends on the kinds of atoms and their bond strengths and arrangements in a specific molecule. Therefore, a Raman spectrum is something like a "fingerprint" of a molecule. The main advantage of Raman spectroscopy is its capability to provide rich information about the molecular structure of the sample. Recently, sophisticated data analysis techniques based on multivariate analysis have made it possible to exploit the full information content of Raman spectra, and to draw conclusions about the chemical structure and composition of very complex systems such as biological materials. In this sense, Raman spectroscopy has the potential to become a key tool for health monitoring based on molecular information. The high molecular specificity and high content of chemical information of the technique makes it also a very useful tool for environmental control. However, a great disadvantage in any application of Raman spectroscopy results from the extremely small cross section of the effect resulting in very weak spectroscopic signals.

Fortunately, the situation is dramatically improved when a new methodological approach is applied, which combines the interesting optical properties of metal nanostructures with modern laser spectroscopy [1]. Due to resonances between the optical fields and the collective motion of the conduction electrons (surface plasmons) in metallic nanostructures, strongly enhanced local optical fields can exist in the very close vicinity of these structures [2]. Exciting opportunities for enhancing spectroscopic signals exist, when spectroscopy takes place in these enhanced fields. Raman scattering signals from molecules attached to nanometer scaled silver and gold particles can be enhanced up to 14 orders of magnitude (see Figure 2).

The effect is called “surface-enhanced Raman scattering (SERS)”. SERS might be one of the most impressive effects for demonstrating the capabilities of this new spectroscopic direction, based on local optical fields. At present, SERS is the only way to detect a single molecule and simultaneously identify its chemical structure.

Figure 2 shows the principle of the technology approach for the new nanosensor based on surface-enhanced Raman spectroscopy [1]. Molecules (blue dots) are attached to a gold nanosphere (red ball). The molecules “feel” local optical fields, enhanced by factors $A(\nu)$ (see equation). In addition to this “electromagnetic field enhancement,” the electronic interaction between the Raman molecule and the metal can result in an increase of the Raman cross section itself, called "chemical or electronic enhancement." (The green dots represent atomic scale “active sites”, where this electronic or chemical interaction takes place.) In many experiments on nanometer scaled silver or gold structures, the "chemical effect" provides a contribution of 10-100 to the total SERS enhancement, the electromagnetic field enhancement can result in SERS enhancement factors up to 10 to 12 orders of magnitude resulting in up to 14 orders of magnitude total SERS enhancement [3-6].
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As a spectroscopic technology, SERS combines the advantages of fluorescence spectroscopy and Raman spectroscopy as it is illustrated in Figure 3. Additionally, since SERS spectroscopy takes place in the local optical fields, the lateral confinement is determined by the confinement of the local fields, allowing the collection of spectroscopic data from volumes below 5 nm dimensions [7].

Figure 2: Schematic of the technology approach for the new nanosensor based on surface-enhanced Raman spectroscopy [1].

\[ I_{SERS}(v_s) = N^* I(v_s) \cdot |A(v_s)|^2 \cdot |A(v_0)|^2 \cdot Q_{ads}^R. \]

Figure 3: SERS

We want to advance the concept of a SERS nanoprobe to a system prototype level for applications in health monitoring and environmental control. Both applications generate very similar needs for technological developments.

Advancing SERS technology includes the development of "SERS-active targets", e.g. silver and gold nanostructures optimized for a specific application in biomedicine or environmental analysis.

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For health monitoring, due to the chemical inactivity and good biocompatibility, gold nanostructures and – nanoparticles will be the favourite choice. For environmental control, cheap silver or gold targets for single use that can be stored for documentation should be developed.

The second component of the technology includes the “spectroscopic unit” for excitation the SERS signals, spectral dispersion and signal detection. Requirement for the spectroscopic unit will be very similar for environmental control and health monitoring.

In general, the spectroscopic part does not require new technological developments and can use technologies that are already well developed, such as stable lasers and detectors for field applications. Also, the mathematical tools for data analysis, which is based on multivariate analysis, is in principal developed.

Figure 4 Scheme of a portable SERS system and typical SERS-active substrates made from silver nanoparticles

The SERS technique allows operation by untrained personal and generates simple and relatively small data sets (spectra) suitable for transfer in short times.
2. Technology application areas; how technology is useful for aerospace or other industries

Molecular structural information including monitoring structural changes play an increasingly important role in health monitoring as this kind of information can provide a deeper insight into the development and treatment of diseases as well as advanced early diagnosis based on a "molecular understanding". Sensors, which provide high molecular structural information content together with high sensitivity, are of particular interest. There is also a strong interest in collecting spectroscopic information from small volumes, where biochemical modifications may start as precursor of the development of diseases.

SERS nanosensors can address most of these requirements. The potentials of the technique in the biophysical/biomedical field appear to be enormous.

![SERS spectra](image)

*Figure 5 SERS spectra collected from living cell using gold nanospheres as SERS sensors. The upper spectrum displays a typical DNA Raman lines, the lower spectrum was collected from the cytoplasm. The figure displays also the image of two typical Raman lines in a cell monolayer.*

The technology is potentially useful in astronaut health monitoring particularly in the following areas:

(i) Ultra sensitive Raman studies in the local optical fields of gold nanoparticles performed in single cells for monitoring and understanding molecular structural changes in cells and in the cell nucleus
(ii) Trace detection, identification and quantification of biomedically relevant molecules, such as neurotransmitters based on surface enhanced Raman scattering (SERS) signals. Such information can be of importance in case of emergency treatments.

**Figure 6** SERS spectra of two neurotransmitters dopamine and norepinephrine in nanomolar physiologically relevant concentrations. Despite of the very similar chemical structures, due to the high structural specificity of SERS sensors, both neurotransmitters show clearly different spectroscopic signatures.

(iii) Early diagnosis of diseases and health screening based on molecular information collected from cells and tissue in order to detect potential health problems before a space flight.

In addition to health care related applications, SERS opens up interesting opportunities for trace detection and chemical characterization of substances for environmental control. For example traces of the explosive TNT at the pg level have been detected in water using gold SERS sensors [10].
3. Benefits of the proposed MNT-based approach over existing solutions

Existing solutions for spectroscopic sensors in life sciences and environmental analysis are mostly based on fluorescence. The proposed approach based on SERS nanosensors provides the following benefits over other existing spectroscopic solutions:

**High molecular structural information content.** Fluorescence, which is widely used as sensor in the biomedical field and also for environmental control does not provide “chemical information” on the labeled molecule. At present, SERS is the only way to detect a single molecule and simultaneously identify its chemical structure.

**No labeling required.** To detect and to identify molecules of interest by fluorescence, particularly in the biomedical field, in many cases, they must be labeled by fluorescent dye molecules to achieve high enough fluorescence quantum yields and distinguishable spectral properties. The SERS approach does not require labeling and exploits the intrinsic spectroscopic Raman signature of the molecules of interest.

**High signal strength.** As outlined above, SERS can enhance Raman signals up to 14 orders of magnitude. This brings SERS signals to the level of “good” fluorescence signals.

**Very specific spectral signature.** Unlike fluorescence spectroscopy, which produces relatively broad bands, Raman scattering as a vibrational method yields a very specific spectrum composed of several narrow spectral lines, resulting in well distinguishable spectra even for similar molecules [1].

**Nonresonant excitation.** SERS is not a resonant process and therefore, the excitation wavelength is a “free parameter”, which can be selected depending on the specific application.

The nonresonant excitation also avoids photodecomposition.

Since spectroscopy takes place in the local optical fields, the lateral confinement is determined by the confinement of the local fields, which allows collection of spectroscopic data from volumes below 5 nm dimensions [7]. This is two orders of magnitude smaller than it can be achieved in other optical techniques, where the smallest probed dimensions are ~ half of the applied wavelength (Abbe diffraction limit)

A SERS sensor can be build from biocompatible components, such as gold nanoparticles.
4. Estimate of the potential market

The potential market for ultra sensitive sensors in life sciences and environmental analysis and control is enormous. Particularly because there is a strong need for structurally sensitive technologies, a field, which cannot be covered by existing spectroscopic or optics solutions.

Regarding Technology Readiness Level (TRL) descriptions in the three points, TRL is 4 for “Product”, and between 2 and 3 for “Analysis/Simulation”. In terms of “Process”, it is hard to apply criteria to the proposal, in “Process”; the project might be at a TRL level between 1 and 2. In a first step, over 2-3 years, levels 6-7 could be reached in all TRL criteria with a potential market of billions of USD.

5. Status of competing technologies and solutions

Fluorescence based technologies are well developed as ultra sensitive detection tools for more than one decade and are well established in the biomedical and environmental field. Recent developments of quantum dots as label provide additional perspectives for the further development of fluorescence-based sensors [11]. However there is still the problem with biocompatibility of the materials of quantum dots.

In general, in the moment, there is no competing technology, which could provide the high content of structural molecular information of a SERS sensor. Additionally, SERS sensor can be build from biocompatible components, such as gold nanoparticles.

6. International collaborations among organizations providing complementary core competencies, technical or financial

To our best knowledge, in the moment there are no international collaborations except informal scientific collaborations between Labs.

7. Implementation of the pilot project development

The development requires collaborative efforts between nanotechnology/material science and spectroscopy/optics teams and includes also questions of data handling and analysis. Feasibility tests require collaborations with biomedical groups and analytical chemists.

Milestones for assessing progress are (1) developing new SERS active substrates and building a spectroscopic system (parallel efforts), (2) test of the SERS substrates for molecules of interest in ex-situ experiments and optimize the SERS effect, (3) feasibility studies in biological systems and in field experiments.

Government funding can certainly contribute, but the project requires also other sources of funding [7].
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Appendices

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List of References