BIO-Ångström 2005

20th September 2005

Promoting cross-disciplinary meetings between life science researchers and material scientists.

Abstracts

UPPSALA BIO
THE LIFE SCIENCE INITIATIVE

BIO-Ångström 2005

Jonas Jarvius
Dept. of Genetics and Pathology, UU

Microfluidics and molecular tools, what can they do together?

Oral presentation only. For further information, please contact Jonas Jarvius.

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Kersti Hermansson
Materials Chemistry, The Ångström Laboratory

The making and breaking of Hydrogen bonds

Hydrogen bonds are quite special chemical bonds with remarkable versatility, as demonstrated by nature in numerous examples from Biology to Materials Science.

Hydrogen bonds are thus STRONG enough to significantly modify a molecule's properties and to hold it in place in a structure, yet WEAK enough to be distorted or broken fairly easily by an external stimulus, an incoming reactant or a by-passing molecule.

We are chemists and study the very fundamental properties of hydrogen bonding (using computational methods), such as:
* In a long water chain - how different is the middlemost molecule from the ends?
* How is a hydrogen bond affected if it is placed in an electric field?
* How important are the weak hydrogen bonds between C–H groups in organic molecules and heteroatoms (S, O etc.) in biological materials?
* How many water molecules surround K+ in solution?
* How much can IR/Raman tell us about the local molecular environment?
* Can we quantify these effects? (Answer: yes).

We have learnt (and keep learning) many intriguing facts, which I imagine might be useful to know also for the Uppsala Bio community! OR MAYBE YOU KNOW IT ALREADY?! I would like to discuss these issues with you and explore the possibilities for some interaction.

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Anders Isaksson
Dept. of Genetics and Pathology, UU

Molecular analysis and engineering skills are required for understanding and controlling cellular systems

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DNA microarrays can be used to measure the activity of all human genes in biological samples. Thereby a detailed picture of the state of the biological system is collected that can be used to try to explain biological differences between samples. In many cases the ultimate goal is to be able to manipulate the relevant molecular systems using small organic molecules suitable for therapy in humans.

In order to accomplish such goals biologists need to team up with engineers that can help with the identification of relevant molecular mechanisms.

There are several areas where engineering traditionally has excelled that could contribute to understanding and control of cellular systems:
i) Phenomenological modelling of complex systems using experimental data. Classical successful examples include modelling of radio channels and aircrafts
ii) Numerical optimisation of experiments, signals, controls, parameters, and complete systems.
iii) Statistical learning from experimental data.
iv) Information technology for organization of biological data in the literature and integration with experimental data for prediction of biological phenotypes.

In collaboration with Mats Gustafsson at the Department of Engineering Sciences UU, we have applied knowledge in some of these areas to the analysis of cellular systems. This has resulted in improved methods for estimating the uncertainty in predictions based on molecular data (in our case gene expression data).

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Peter Svedlindh
Dept. of Engineering Sciences, Uppsala Univ.

Nanomagnetic regulation of biological processes

Systems that enable controlled movement and positioning of single micron- or submicron-sized particles would open up new application possibilities. We have recently presented a novel method for programmable motion of single magnetic particles in contact with thin film micron-sized magnetic elements. The movement of magnetic particles is controlled by external magnetic fields. Arrays of elements are tailored in order to form transport lines for magnetic particles, with or without path junctions.

Our method has the potential of improving a number of existing applications in biotechnology as well as to generate new applications in life science. The high flexibility of the surface characteristics by this programmable method is suitable for high through-put screening of possible candidates for biocompatible materials. Programmable transport, adjustment of positions and delivery of materials make the method interesting for micro-surgery in connection with implants, nanodispension of ultra small volumes and micro- and nanoscale synthesis of substances, both in solid phase syntheses and in solution.

BIO-Ångström 2005

Anders Larsson
Akademiska Sjukhuset

Automated Interpretation of plasma protein electrophoreses.

Plasma protein electrophoresis is frequently used in health care. The sample is separated by agarose electrophoresis or capillary electrophoresis. The medical interpretation of protein electrophoresis is time consuming and it would thus be helpful to have an automated interpretation of the pattern. The results could then either be reported directly to the ward or scrutinised by a laboratory doctor before it is reported. Such automated evaluation could potentially replace a large number of the 2 million ESR that are performed per year in Sweden.

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Mats Boman
Dep. of Materials Chemistry

A nanostructured electroosmotic pump and a chromatography separation unit for biosensor applications

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In this research co-operation proposal we would like to interact with research groups around some newly developed nanoscale bio-devices. The devices are constructed using a template, nanoporous alumina, which will be used to make a very thin electro-osmotic pump combined with a chromatography separation unit. The devices can be made down to um in size with a pore aspect ratio of about 1000. The devices require therefore extremely small amounts of analyte, about 10-17 L/pore. The two devices can be combined with a third device, which could be some sort of sensor (or other device), which requires a liquid flow where the dissolved components are separated as a function of time. The electro-osmotic pump is characterized by a high flow and will deliver a high-pressure gradient. nm thin coatings using atomic layer deposition can change the properties of the pore walls of the template material comprising the pump. In this way the pump can be tailored for a wide variety of solutions. The nano-chromatography unit, also built around nanoporous alumina, will have unique properties with a resolution approaching the theoretical limit (as defined by the van Deemter's equation).

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Lars Bohlin
Department of Medicinal Chemistry

Antifouling potential in Swedish marine organisms

The appearance of biologically active metabolites in nature is determined by ecological needs and biosynthetic possibilities.The overall objective of our marine pharmacognosy research is to understand aspects of structure-activity relationships of chemical interactions in the marine environment. Our strategy is based on ecologically-guided search for compounds through studies of physiology and organism interactions coupled to identification of target molecules guided by in vivo assays followed by chemical characterization and new synthetic strategies. The marine sponge Geodia barretti produces a wide range of secondary metabolites.Two congenerous cyclopeptides, i.e. barettin and 8,9-dihydrobarettin were isolated and structurally elucidated guided by their ability to inhibit settlement of the larvae of the barnacle Balanus improvisus.

The recent successful total synthesis of the two cyclopeptides and a number of structural analogs are a further reason to making them interesting candidates in new antifouling applications. Resolving molecular targets of marine defence compounds is important for a sustainable bioprospecting of nature and can also contribute to an increased understanding of similarities between structure-activity relationships in invertabrates and humans.

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Anders Rydberg
Inst. för Teknikvetenskaper, Signaler och System

Towards a Biosensing Platform for In Vivo and In Vitro Measurement of Tissues at Microwave Frequencies

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Recently a digital camera has been integrated into a pill-sized package that can be swallowed by patients to enable nonsurgical imaging of the gastrointestinal tract, has been developed. However, the next challenging step needed in order to provide more information on the patient is to adopt impedance spectroscopy for the detection of physiological and pathological changes of biological tissues. It has been demonstrated that dielectrical properties of malignant tumors and normal tissues are different in e.g. breast, lung, colon, and liver. Based on the concept of backscatter, antennas for inclusion in pills using the technology of backscatter has been investigated to create a biosensing platform.

Using the same concept a probe – can *in vitro* be used for analysis biological materials.
For both of the applications the use of micromachined technology in combination with integration technology is essential in the development of the biosensing platform.

Conclusion and Bio-Ångström: We have access and knowledge to make very small sensors and are now looking for partners in medial diagnostics for collaboration on these new disruptive medical tools.

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Vadim Kessler
Department of Chemistry, SLU

New Sol-Gel Solutions for Bio-encapsulation and Bio-delivery

Oral presentation only. For further information, please contact Vadim Kessler.

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Stellan Hjertén
Department of Biochemistry, Uppsala University

Combination of New Approaches and Known Principles to Attack Biotechnical Problems in Life Sciences

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Artificial antibodies against proteins, viruses, cells (bacteria)
These antibodies are easy to prepare and more stable than protein antibodies, raised in experimental animals and probably more selective. We need more methods for the detection of the antigens (for instance, based on wave-guides, ultrasonics, confocal microscopy, QCM, different modes of fluorescence, microarrays, e.t.c.)

Microchips
We have experience in: monolithic beds for chromatography, electrochromatography and electrophoresis in microchips; UV-transparent hybrid microdevices with a supporting plate of ceramics; thermal and electroosmotic micropumps; how to create plug flow; isocratic separation of proteins, viruses and cells (bacteria), i.e. pumps are not required.

Nanoparticles
We need artificial antibodies in form of such particles for selective transport of a drug, for instance to a cancer cell. Nanoparticles are also of interest for different types of separation methods.

A new electrophoretic method to separate proteins, viruses and cells, according to their masses.
The method is based on pulsating direct current at a high frequency

Combination of electrical and magnetic fields
1.For centrifugation: The liquid rotates, but not the centrifuge tube
2.For pumping of liquid, for instance in microchips

Increase in the resolution in chromatography by decreasing the residence time, i.e., the time the analyte is in contact with the analyte. Hopefully, this may be accomplished by superimposing an alternating voltage on the hydrodynamic flow

Paramagnetic chromatography

New type of filters to remove viruses (HIV, SARS, Avian Flue, etc), bacteria…
These filters are designed to be used in aircrafts, hospitals, industries, and as mouth masks, etc

New class of antibacterial agents
The design is based on the knowledge about the structure of biological membranes we got in our chromatographic and electrophoretic studies of cells. This is a big area which requires cooperation with researchers from various disciplines and with support from pharmaceutical industry

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Alfonso E. Garcia-Bennett
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Mesoporous materials: Potential Opportunities in the Life Sciences

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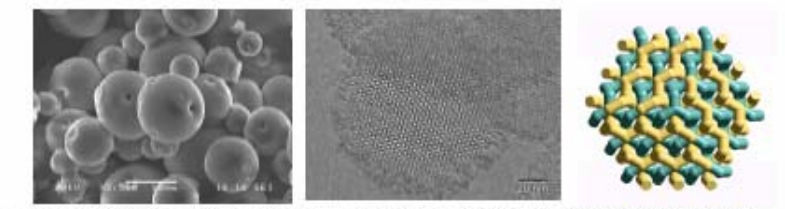
Mesoporous materials,[1] ordered porous structures with siloxane bridged amorphous walls, are a recently discovered family of nanoporous solids with several extremely attractive features for hosting molecules of various shapes, sizes and functionalities.[2] These features can be divided into three categories; structural, compositional and functional.

(1) The versatility of mesoporous materials is best represented in the numerous structure types that can be easily formed, including high surface area (above 600 and up to 1400 m2/g) 1, 2 and 3D networks of sharply distributed pores or cages of sizes varying from 1.5 to 30 nm.[3] Morphological (shape) control of particles has been developed through easy synthetic procedures to include, monodispersed particles as small as 5 nm to large monolithic solids and thin-films.

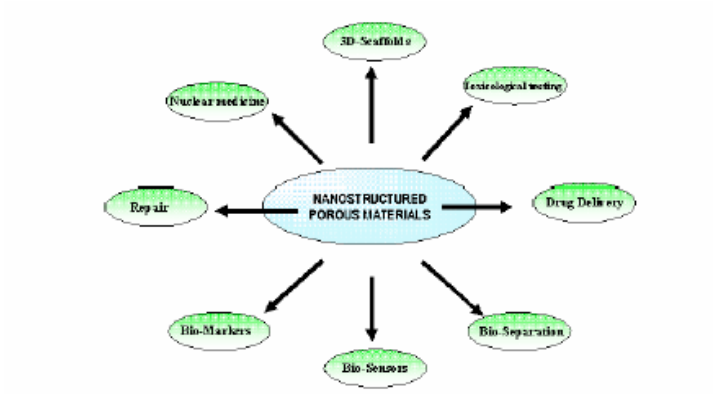
(2) The first mesoporous materials were made in their silicate form, however the family now extends to include carbons and metal oxide mesoporous solids through direct synthetic procedures or through post-synthetic replication of the silicate structure. This allows designing fundamental properties such as thermal, electronic, magnetic and optical properties.

(3) Functionalisation of the internal surface allows tailoring of the surface properties for specific applications, from hydrophobic surfaces for petrochemical catalysis to highly hydrophilic surfaces for gas/water adsorption.



SEM and TEM micrographs of silicate mesoporous material AMS-6 with cubic symmetry and pore model showing the chiral arrangement of pores.

A large number of applications are currently being explored in a variety of areas taking full advantage of the characteristics of mesostructures, as mentioned above. These include varied fields from supports for catalysts to low-*k* dielectric devices.[4] However, to date only a small amount of studies have been conducted to introduce mesoporous materials into the Life Sciences. Drug delivery is an area starting to be explored.[5] Conventional drug delivery systems consist of a polymeric matrix from which the drug is released under appropriate conditions. A wide number of materials have been employed, including mixtures of polymers and polymer based composites with different material such as bioactive glasses or ceramics.



Some Potential Applications of Mesoporous Materials in the Life Sciences

In these cases the drug is deposited by means of direct compression, wet granulation, or mechanical mixture of both matrix and drug. These methods have in general the disadvantage of heterogeneity of samples due to the difficulty of ensuring homogeneous distribution of the drug through the matrix, which can affect the release rate between different samples. Much improvement in this field is expected from the use of chemically homogeneous materials possessing well-defined porosity.[6] The adsorption of active pharmaceutical molecules into stabile, non-erosive mesoporous materials has been explored offering the potential to control (delay) drug release, enhance drug dissolution, promote drug permeation across the intestinal cell wall (bioavailability) and improve drug stability under the extreme environment of the gastro-intestinal tract when administered orally. Different types of drug molecules (including macromolecules) can be adsorbed into mesoporous microparticles by modifying the pore architecture and surface chemistry of the carrier material. [7]

Many other areas of the Life Sciences can be approached using mesoporous materials such as enzyme catalysis, bio-separation devices for the purification of proteins, biosensors, bio-markers and transfection devices in gene delivery. The possibility to combine properties of organic, bio and inorganic components in a unique material is fast becoming a reality through the use of mesoporous materials and related nanoporous solids. Our aim is to utilize our knowledge in the synthesis of these novel nanomaterials to fully realize their potential in the Life Sciences.

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BIO-Ångström 2005

Klaus Leifer
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Work and perspectives of the group of electron microscopy and nano-engineering

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Electron microscopy has been since its beginning connected to discoveries in both hard and biological materials. Number of dedicated electron microscopy methods for both types of objects have been developed and successfully used. In the last years, a fruitful exchange of biological and materials science analysis techniques has lead to new insight in both, soft and hard materials. This new evolution has been triggered by several needs: 1) for a growing number of structures in biology the characterisation of structure and elemental distribution on atomic or nanometric scale is necessary. 2) In materials science, nanoparticles are often distributed in 3-D structures. Both, their location and structure needs to be characterised. 3) Nanometer sized objects do not only have to be localised, but need to be manipulated in both hard and biological materials. We will present selected examples from elemental characterisation of soft matter as well as approaches to 3-D characterisation.

The understanding of water filtering in the soil systems is an important topics in environmental science. Electron microscopy has been employed to obtain the elemental distribution on organic aquatic particles using electron energy loss spectroscopy (Mondi, Leifer, Mavrocordatos and Perret, J.Microscopy 207, 2002). Chemical substructures inside these aquatic nanoparticles could be detected and quantified. Leapman and Rizzo (Ultramicroscopy 78, 1999) have used the same technique to analyse the distribution of phosphorous atoms in DNA.

3-D characterisation methods that have been developed for the assessment of the structure of biological molecules and cells, have been applied in materials science recently. We will show examples of the characterisation of nanometer sized objects such as semiconductor quantum dots. The case of QDs is particularly interesting since it shows that not only the characterisation, but also the localisation of these small entities becomes essential.

With the focussed ion beam device (FIB), we have available such instrument at the Ångström laboratory that can be used for localisation, manipulation and observation of sub-micrometer sized objects. Even more, it enables us to observe a sample with close to nanometer resolution while manipulating it on the sub-100nm level. When higher resolution in the observation of the object is needed, the FIB can also be used as a device for sample preparation for transmission electron microscopy. This nano-engineering capacity of the FIB can be used to create small structures and modify surfaces and subsequently attach nanometric objects such as molecules, nanoparticles and nanotubes.
As a new unit at the Ångström Laboratory, we actively search collaborations to use available and new techniques for the analysis of matter and nano-engineering at the interface between biology, chemistry and materials science.

BIO-Ångström 2005

Stefan Nygren
Ångström Microstructure Laboratory

The Ångström Microstructure Laboratory - Resource and Support

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Possibly the most powerful instrumentation resource at the Ångström Laboratory is the cleanroom facility, or the Ångström Microstructure Laboratory (MSL). This multidisciplinary laboratory provides fabrication as well as analytical capabilities and should, within the Swedish micro- and nanofabrication network (iFab), maintain a strong profile in life science. The lab is, and should be further developed as, a central playground for collaboration between researchers in life science and materials science.

Although collaboration across disciplinary borders should be encouraged, an even more important ambition should be to make the right resources available to any high quality project. For this reason, there is also a need to provide a working model for projects where the scientific qualities are restricted to life science and where the micro- / nanofabrication or analysis is merely a tool. In this case the MSL lab organisation is the right partner, with all competence needed to run the facility, use the equipment for the best possible results, educate new users and provide continuous support for the more experienced user. A limited lab utilization could be handled as a commission by MSL, whereas a long term project could motivate the introduction of a new user from the specific project organisation. A flexible access system makes it possible to adjust the level to specific needs. The laboratory is open to any university scientist or industrial developer.

BIO-Ångström 2005

Jan Eriksson
Department of Chemistry, SLU

Predicting the Success Rate of Proteome Analysis by Modelling Protein Abundance Distributions and Experimental Designs

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Proteome components are typically identified using mass spectrometry (MS) of peptides from digested proteins in combination with algorithms attempting to match the MS-data with protein sequences in a sequence collection. The peptide detection is challenging since MS has limited dynamic range and sensitivity, combined with the fact that protein amounts vary within a wide range in a proteome. Currently, results are reported without information on what proteome fraction was missed due to experimental limitations. Hence, results are difficult to evaluate and potentially misleading. We here report a solution to the problem of predicting the experimental success of proteomics experiments using a holistic experimental view and simulations [1,2]. Protein abundance distributions were modelled for biological samples (tissue and body fluid).

We studied the proteome analysis success rate as a function of sample type, mixture complexity, peptide loss, peptide separation, column size, and MS detection sensitivity and dynamic range. We show that the experimental design must be optimized for each type of biological sample and the results stress the importance of the right choice of technology. The prospect of using antibodies and/or nanometer scale probes as alternative experimental designs is discussed.

BIO-Ångström 2005

Fredrik Nikolajeff
Uppsala universitet, Ångströmlaboratoriet

Diamond micro- and nanostructures for biochemical sensing

Diamond has a whole set of unique materials properties; it is the hardest material found in Nature, diamond has a wide optical transparency window (from 220 nm and above), it is resistant against chemicals and has the highest thermal conductivity of all solids known. With recent advances in the fabrication of synthetic diamond the material cost has drastically dropped and scientists in such various fields as biochemistry, photonics, electronics, and environmental sensor technology are investigating the usefulness of diamond in their respective disciplines.

It has then become needed to find methods for structuring diamond as most applications typically demand some sort of microstructure. We have developed a method for rapid and accurate micro- or nanostructuring of diamond, using lithographic and plasma etching techniques. Our primary application has been space optics, since the environmental demands on such components are quite extreme.
What we now would like to pursue is how microstructured diamond can find relevance for biochemical sensing purposes. We have obtained very preliminary results for diamond microelectrodes used in electrochemical detection of DNA-fragments and proteins, but much more work is needed for elucidating the relevance of diamond surfaces. We would therefore like to come in contact with researchers/companies in the biotech field interested in exploiting this unique material.

BIO-Ångström 2005

Sima Valizadeh
Dept of Engineering Sciences, Uppsala University

Tools for High Resolution Imaging and Nanoprocessing of Advanced Materials

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Virtually all the spectacular advances now taking place during the life sciences are directly linked to the capability to resolve and work with nanoscale biologic structures. The materials with sizes below 100 nm can exhibit fundamentally new behavior when their sizes fall below the critical length scale associated with any given property. In this way, the scanning electron microscopies have become an indispensable tool for morphological observation in materials and biological sciences. Structural imaging of nanoscale biological material enables us to understand the atomic configurations at interfaces or in nanoparticles to be able to develop a rapid characterizations technique of DNA, smart drugs and delivery systems.

Biological samples having different characteristics were observed by environmental scanning electron microscopy (ESEM). The environmental conditions for untreated biological samples can be determined by optimizing sample temperature and chamber pressure using a Gaseous Secondary electron Detector (GSED). This is particularly suited to the study of the hydrated, live organisms, textiles and pharmaceutical products.

The ability to pattern nanometre scale structure in short timescales is of great importance in the fabrication of nanostructures and nanoscale devices.

Focused ion beam FIB/SEM, is essential tool to imaging, tailoring regular arrays of small magnets, creating contact structures linking a nanowire to microelectrodes. Another application is to prepare TEM cross-section samples in-situ with very high precision.

The presentations may intend to highlight current and future multidisciplinary research on advanced electron microscopy techniques with the focus on reinforce of connection between the materials and biological sciences.

BIO-Ångström 2005

Per I. Arvidsson
Organic Chemistry, Uppsala University

Artificial Biomimetic Peptides

We are interested in the design, synthesis, and detailed physical study of artificial oligomers capable of folding into defined secondary and tertiary structures, so-called foldamers. Thus, we are not only interested in learning more about the natural system, composed of ?-amino acids (in the case of proteins), but also focus our attention on other building blocks that may be assembled in a linear fashion and then be capable of adopting a folded conformation. Examples of molecules we are working on involve: b-peptides (i.e. peptides with one additional carbon atom in the backbone), peptoids (i.e. peptides with the side-chain positioned on the Nitrogen atom), and N-methylated peptides (a-peptides with an N-methyl group). Such oligomers have been shown to have various applications in the field of medicinal chemistry, as they are conformationally more rigid and metabolically more stable then normal a-peptides.

We believe that these unnatural biomimetic peptides could be of interest to, and find further applications by, many researchers involved in the Uppsala BIO programs.

BIO-Ångström 2005

Roman Zubarev
Laboratory for Biological & Medical Mass Spectrometry

Box of Mass Spectrometry Tools for Proteomics

Mass Spectrometry (MS) is one of the fastest-developing analytical methods, which recently outgrew in number of scientific publications such a well-recognized technique as NMR. Proteomics is the large-scale study of the proteome, and it has enormous potential in life sciences. In 2006, the total market of proteomics tools is expected to reach $3.3 bin, of which $2 bln due to MS. With most of the profit is invested back into R&D, there is an incredible competition in designing new MS tools for proteomics. Despite all the spectacular progress, MS is still three orders of magnitude away from its theoretical limits, which will take >20 years to reach even if the performance will double every two years.

An ideal box of MS tools for proteomics includes high-throughput technologies for protein identification, de novo sequencing and mapping the sites of posttranslational modifications. Fourier transform mass spectrometry (FTMS) is the most sophisticated type of MS that provides most accurate mass measurements as well as complementary fragmentation techniques.

This lecture will show how newly developed tools for FTMS, such as electron capture dissociation (ECD) and similar ion-electron reactions facilitate solving the above proteomics problems. These tools also provide solutions for previously impossible tasks, such as the quantitative, chromatography-scale analysis of chirality of individual amino acids and their isomeric states.

BIO-Ångström 2005

Claes G Granqvist
Department of Engineering Sciences, Uppsala university

Photo-Catalytic Self-Cleaning Surfaces

Nanocrystalline thin films of transition metal oxides--typically based on titanium oxide--are able to cause a breakdown of organic molecules and micro-organisms when irradiated by light. The division of solid state physics has unique competence on how to make such surface coatings by use of advanced gas evaporation as well as high-pressure reactive magnetron sputtering. We have also developed special materials that respond to visible light (not only ultraviolet, which is typically the case). Some work has been pursued in defence-related projects, but we believe that the applications of our work and general competence can be widened. Our photocatalytic surfaces are also able to exhibit super-hydrofilicity (ie, induce complete wetting). These and other aspects of today´s and tomorrow´s surface technology will be presented and discussed.

BIO-Ångström 2005

Emma Kristensen
Department of Physics, Uppsala University

Heparin coating durability on artificial heart valves studied by XPS and antithrombin binding capacity

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The durability and functionality of a heparin coating on artificial heart valve leaflets were evaluated with XPS and the antithrombin binding capacity of the coating. The coating is built upon a macromolecular conjugate of heparin in which heparin is covalently bonded to a carrier chain. The durability of the heparin coating was tested by pumping citrated plasma through a tube where the heart valve leaflets were attached. The leaflets were taken out after three different times: One hour, one week and three weeks. They were thereafter rinsed to remove attached proteins. With increasing test time the coating of the leaflets decayed, as found by XPS. These changes include an increased nitrogen signal and a slight increase in disulfide signal (present in plasma proteins and in the heparin conjugate) and a decrease of the sulfur signal from the heparin chains. This suggests that plasma is present on the leaflets after rinsing, or that the heparin chains were torn off from the conjugate. The substrate signal reveals that the heparin coating is getting thinner with time, confirming actual loss of heparin. We suggest that heparin chains from the upper layer of heparin have been torn off from the carrier chain, in combination with loss of heparin conjugate and plasma deposition in patches. It was found that the heparin coating had the same antithrombin uptake after three weeks of testing as non-tested coatings, indicating a biologically functional surface.

BIO-Ångström 2005

Gunnar A. Niklasson
Dept. of Engineering Sciences, Uppsala Univ.

Electrical and optical analysis techniques

The Division of Solid State Physics at the Ångström laboratory has achieved competence in a number of measurement and analysis techniques of potential significance to applications in biotechnological fields.

These include:
• electrical impedance spectroscopy, particularly on particulate and porous materials
• electrical noise (fluctuation) spectroscopy
• optical and infrared spectrophotometry
• optical scattering measurements, both wavelength and angle dependent
• simulations of optical scattering and extinction in particulate media

Apart from our basic physics work we have over the years participated in various cross-disciplinary projects, for example impedance spectroscopy of perforated polymer membranes, noise spectroscopy for sensitive gas detection, optical properties of biological specimen, such as leaves and butterflies, optical and infrared properties of bread and modeling of extinction from interstellar dust.

BIO-Ångström 2005

Göran Frenning
Department of Pharmacy, Uppsala University

Modelling and engineering principles for granular solids with special reference to pharmaceutical compaction technology

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In an attempt to meet the need addressed by the US Food and Drug Administration of a third type of research that will focus on creating effective products from new scientific discoveries, this research project is devoted to modelling and engineering principles for granular solids. Of safety and compliance reasons, the peroral route represents the major alternative for drug administration and tablets will be the dominating form of pharmaceutical preparations for a foreseeable future. A tablet is formed by compression of a powder, held in a confined space, by mechanical treatment. The physics and technology of mechanical powder processing have consequently evolved as an important part of formulation science.
In this project we intend to use continuum (finite element) and micromechanical (discrete element) modelling to describe powder compression and the evolution of compact structure and properties, and to use micromechanical modelling as a bridge between (local) single-particle properties and global properties of a powder bed or a compact. Striving to implement this program, we would be interested in cooperation with scientists working with similar questions, for instance in the fields of solid mechanics or scientific computing.

BIO-Ångström 2005

Göran Possnert
Uppsala University

Ultra-low exposure biomedical dosimetry

The unique sensitivity in accelerator mass spectrometry (AMS) has proven to offer an effective tool to quantify biomedical molecules at extremely low levels in studies of e.g. metabolism and pharmacokinetics. The advantages with this technique are 1) improved sensitivity over decay counting especially for long lived isotopes like 14C, 26Al, 36Cl and 129I ; 2) negligible radioactive exposure in human applications which means low radio-isotope concentrations; 3) very small sample sizes (µg range) and 4) extended time range compared to dynamic phenomenon studied by e.g. 11C and 18F with the PET-technique.
The AMS-method is since several years routinely used at the Uppsala tandem accelerator laboratory for application in environmental studies and general tracing techniques mainly aiming at geological and archaeological dating. All basic instrumental installations as well as chemical preparation techniques are therefore already well established for 10Be, 14C, 36Cl and 129I and small efforts are thus needed in order to initiate biomedical applications and collaborations within the Uppsala bio research community.

BIO-Ångström 2005

Göte Swedberg
Dept of Medical Biochemistry and Microbiology

Functional parts of hydroxymethylpteridine pyrophosphokinase-dihydropteroate synthase (HPPK-DHPS) from Plasmodium falciparum.

Folates are synthesised *de novo* in most bacteria, in many eukaryotic microorganims and in plants. The biosynthetic pathway starts from GTP and involves six enzyme activities leading to the synthesis of tetrahydrofolate (THF). The bifunctional enzyme hydroxymethylpteridine pyrophosphokinase-dihydropteroate synthase (HPPK-DHPS) is a target for sulfadoxine, which is a part of the combination drug Fansidar, used in antimalarial chemotherapy. HPPK and DHPS knock-outs of E. coli has been constructed to facilitate complementation studies of the HPPK part. The full length HPPK-DHPS as well as a separate HPPK part can complement the missing enzyme activity. The HPPK part of the plasmodial bifunctional enzyme is much larger than corresponding bacterial HPPK enzymes. The extra amino acids in the plasmodial enzymes are contained within two extensive insertions both of ca 100 amino acids. We are now generating deletions of these apparent insertions to define their role in the activities of HPPK and DHPS respectively. We want to develop studies of the enzyme activities to detect phenomena like domain interactions and substrate channelling, that can be used to interfere with the reaction and lead to new ways of inhibition. Further goals will include expression, purification and structural analysis of HPPK-DHPS. Studies should be extended to include other folate pathway enzymes to enable metabolic pathway modelling. Effects of inhibitors may be studied by proteomic and metabolomic analysis.

BIO-Ångström 2005

Johan Gråsjö
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Electron structure and hydrogen bonding in organic molecules

Hydrogen bonding in moderately sized molecules, e.g. drugs is studied, and especially how the electron structure around the hydrogen bonding is influenced by different inter- (e.g. crystal phase and aqueous solution) and intra- (different atoms or atom groups) molecular surroundings. The intention is to deepen the understanding of hydrogen bonding in order to apply it to the problem of solubility and development of predictive solubility models. Hydrogen bonding is also important in the understanding of other biological and medical phenomena such as cell membrane permeation, the drug receptor interaction and DNA and protein folding.

Soft X-ray spectroscopy (SXS) is used to study electron energy levels and electron distributions. The crucial feature of the method, which makes it suitable for our aims, is that it is atom specific, and in some cases also site specific. A newly developed flow-cell facilitates studies in liquids.
At the present this is a joint effort between Dept of Physics and Dept of Pharmacy at Uppsala University, and Dept of Theoretical Chemistry at KTH in Stockholm. As the problem of solubility stretches into the field of thermodynamics, collaboration with research groups with expertise in theoretical physics, physical chemistry, crystal structure determination, and molecular dynamics simulations could contribute to this project. As identified above we also see a potential for new projects including molecular biology and hydrogen bonding studies with SXS

BIO-Ångström 2005

Klas Hjort
Dept. Engineering Sciences

Rapid Prototyping of Microfluidic Systems to Solve Biological Problems Using Printed Fluidic Board Technologies

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We have developed a concept of printed fluidic board technology. The technology involves:
+ Rapid prototyping by Contact Liquid Photopolymerization (CliPP)
+ Paraffin based integrated active fluidics, allowing strong and long-stroke pumps, active valves and on-chip dispensers
+ Integration of advanced chips made of polymers, silicon, glass, diamond, etc… This allows the same low-cost advantage of unique small-scale systems as printed circuitboards allow electronics.
+ Integration of our unique ion track technology for on-chip through-the-film via fluidic or nanowire interconnects, ultrafiltration, small-size Coulter counting (particles below 0.5 mm in size), etc…

We are interested to learn of bio-applications we yet not have encountered, but believe there is a special strength in field studies for forestry and agriculture. Maybe these systems can enable more pathogens to be diagnosed on-site?

BIO-Ångström 2005

Klas Hjort
Dept. Engineering Sciences

Wireless sensor networks for Bio-applications

The consortium WISENET has today a full proposal to SSF Centre of Excellence and is invited to give a full proposal to a VINN-X centre on Wireless Sensor Networks. We are researchers from the Depts. of Engineering Sciences and of Information Technology, Uppsala University, and the Swedish Institute on Computer Science. Our expertise is in microsystem manufacturing, thin film bulk acoustic sensors for biochemical analytes, front end radio systems, radio communication, and software development for sensor networks.

Our focus will be on safe wireless networks with miniaturized sensor nodes – with special efforts on low-power consumption, power scavenging, and safe communication in the network and though gateways into the Internet.

We have industrial interest from companies like ABB, Ericsson, Hectronic, Biotage, and GE Healthcare and public organisations like FOI, FMV, and the Swedish Road Administration. However, we want to strengthen our coupling to more groups in bio-applications and medicine, especially forestry and agricultural researchers and companies.

BIO-Ångström 2005

Leif Hermansson and Håkan Engqvist
Doxa AB and Materials Science Department, Uppsala

Chemically Bonded Ceramics within the Biomaterials Field and Related Areas.

Leif Hermansson[1,2] Kajsa Björklund[1] and Håkan Engqvist[1,2]
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Chemically bonded ceramics include a group of room/body temperature formed biomaterials with excellent biocompatibility and bioactivity. The term bioactivity is used to describe the ability of a material to chemically bond to tissue. The materials are used within odontology (cements, restoratives and retrograde filllings) and orthopedics (coatings, injectable materials for vertebroplasty and as bone cements), and can be delivered as final components or as pastes or coatings in a un-reacted stage, meaning that the final implants are formed in vivo. Our activities comprehend Ca-based aluminates, silicates, phosphates and sulphates. Fillers are easily introduced in the material. The tailor-made materials open up for applications also within a number of other fields such as carriers for drug delivery, pastes for remodeling, and products for casting and replication. A specifically interesting feature is the possibility of maintaining the exact geometry during curing/hardening of the materials. Worth mentioning is a unique site-specific high resolution technique for studying interfaces - on the atomic level - between materials with different characteristics, e.g. metal-ceramic, ceramic-polymer and biomaterial-hard tissue interfaces.

BIO-Ångström 2005

Mats Gustafsson
Dept. Engineering Sciences (and Dept. Genetics and

Small Sample Analysis and Control of Biological, Chemical and Physical Signals

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In our research we are developing computer algorithms and statistical methods for small sample analysis and control of biological, chemical and physical signals. By signals, we mean any static or dynamic pattern that carries information about the underlying process of interest. Since most biological, chemical, and physical experiments are expensive and have limited access to independent samples, algorithms are needed to extract as much information as possible about the underlying processes of interest based on the small sets of samples and the prior knowledge available. Modern measurement techniques and computer simulations have made it possible to generate large amounts of data from and about individual samples, but it is important to note that many measurements on few samples cannot compensate for the lack of completely new independent samples. The information that can be gained from the small sample sets available seldom becomes detailed enough to understand any mechanistic details. However, from various systems engineering disciplines, it is well known that phenomenological models may be invaluable not only for useful monitoring and control of important signals, but also for gaining important insights about the main players in the underlying processes studied. Two classical systems engineering examples are modelling and control of aircraft and ship dynamics, and modelling and classification of speech, radar targets, and fingerprints.

BIO-Ångström 2005

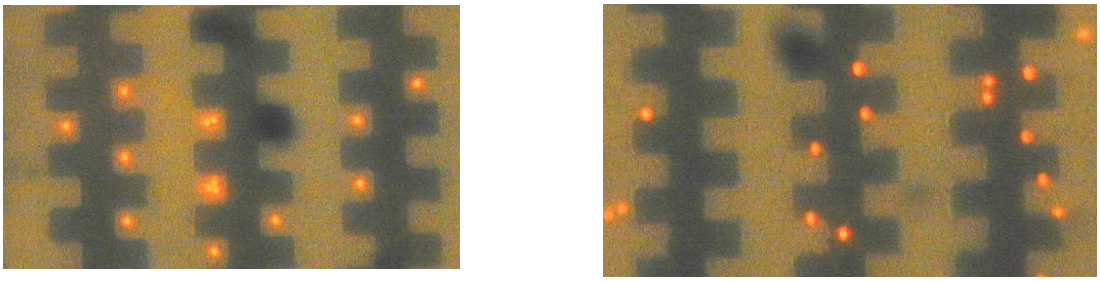
Mats Jönsson

Simple and Fast Positioning and Manipulation of Bioparticles using Dielectrophoresis

In many applications in biotechnology there is a need for positioning and manipulation of the sample of interest to be able to perform the analysis e.g. fluorescence investigation, confocal microscopy etc. This is conventionally achieved by a chemical treatment, modification and/or patterning of a glass slide surface. The surface treatment is a time consuming procedure and the glass slide can only be used once.

Dielectrophoretic (DEP) positioning is here presented as a simple and fast method for controlled manipulation of particles, cells, DNA, proteins etc on a surface as prepreparation before analysis and detection. It is a general method that can be used for all kind of biological particles and beads. For example 10 nm beads and DNA as well as 10 µm yeast cells have been studied successfully using DEP [1, 2.]

DEP was discovered by H. Pohl [3] in 1951. The phenomenon appears when an inhomogeneous electrical field (usually an AC-field) is applied on neutral particles (e.g. biological cell material). The field creates dipoles in the particle and they therefore starts to move towards increasing or decreasing field gradient. The DEP force exerted on the particles due to this field depends on factors such as: size of the particles, the permittivity of both the particles and the medium and the frequency of the applied electrical field. The DEP force could be attractive or repellent dependant on the applied frequency. DEP of 2 µm polystyrene beads using interdigitated electrodes is shown in fig 1.



a) *b)*

Figure 1. Fluorescence micrographs of repellent (a) and attractive (b) DEP of 2 µm polystyrene beads using interdigitated electrodes.

The DEP positioning is performed on standard microscope glass slides. Microelectrodes on the surface of the glass slide is used to create the positioning E-field. The sample is dispensed onto the slide and sealed with a cover glass. The geometry of the electrodes is designed for the specific sample and the desired pattern. The only peripheral equipment needed is a function generator. This opens for the integration of the positioning procedure into the existing analysis apparatus. During ongoing analysis the electrode slide is easily cleaned using ethanol and is ready for use again in 5 minutes. A new sample is dispensed and the positioning occurs immediately as the electric field is applied.

Ongoing work is done in a SSF project together with Mälardalen University and KTH and we see a potential that more applications can gain from using DEP positioning.

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BIO-Ångström 2005

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Acoustic Particle Trap for Microfluidic Systems

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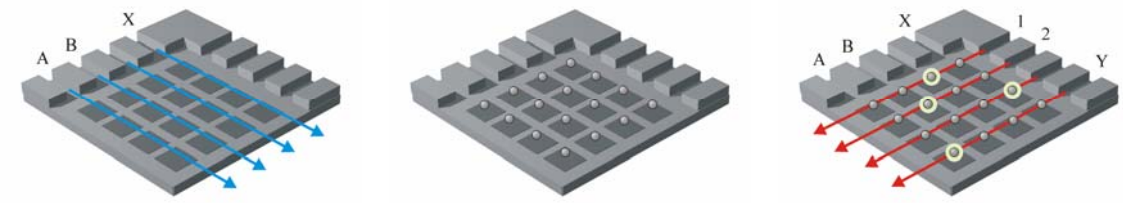
We have developed a technological platform, where microscopic particles (microbeads) or biological cells can be trapped at well-defined positions in a microfluidic system. The technology is based on ultrasonic manipulation and trapping of particles by means of acoustic forces. Particles in a fluid subjected to a standing acoustic wave are drawn to pressure minima in the acoustic field, thereby being trapped and confined laterally. It is anticipated that acoustic trapping using integrated transducers can be exploited in miniaturized total chemical analysis systems (μTAS), where e.g. microbeads with immobilised antibodies can be trapped in arrays and subjected to minute amounts of sample followed by a reaction, detected using e.g. fluorescence. The platform is ultimately aimed for parallel multistep bioassays performed on biochemically activated microbeads using submicrolitre sample volumes, as illustrated in the concept of a dynamic microarray (Fig. 1). It has also the prospect of becoming the basis for generic tools for scientists in the development of bioassays or in cell-based interaction studies.

A first set of devices with three individually controlled particle trapping sites, shown in Fig. 2, have been developed and evaluated. The acoustic traps are designed as acoustic microresonators, where integrated miniature piezoelectric ultrasonic transducers excite the local standing waves. The acoustic forces are very strong on a micro scale, keeping the material trapped in the centre of the channel at the position of the microtransducers. This allows the user to perform chemical or biological tests, perfusing sample, reagents etc. over the trapped material while studying the course of events in e.g. a fluorescent or confocal microscope. A fluorescence based avidin bioassay was performed on biotin-coated microbeads trapped in the flow-through device, providing a first proof of principle of the proposed dynamic arraying concept. By simply switching off the acoustic field, the solid material can be displaced, making the device ready for the next set of tests. The material can also be transported between different trapping sites in the device, see Fig. 3, to enable multistep assays.

The microfabricated multilayer piezoceramic transducers used in the evaluated devices are compatible with standard electronics, thus being prepared even for integration in portable devices. For future development of all-polymer microchips with integrated acoustic trapping, we have also developed process technology for the fabrication of efficient miniature ultrasonic transducers in piezoelectric polymers.



(a) *(b)* *(c)*

Figure 1: One embodiment of the technology is a dynamic array of microparticles in a flow through microfluidic cell. The illustrations show insertion of the solid phase (microbeads) of different antigen

specificity (a) through inlets (A, B…X), trapping of beads or bead clusters (b) and perfusion of sample (c) through inlets (1, 2…Y) followed by read-out of fluorescent response.

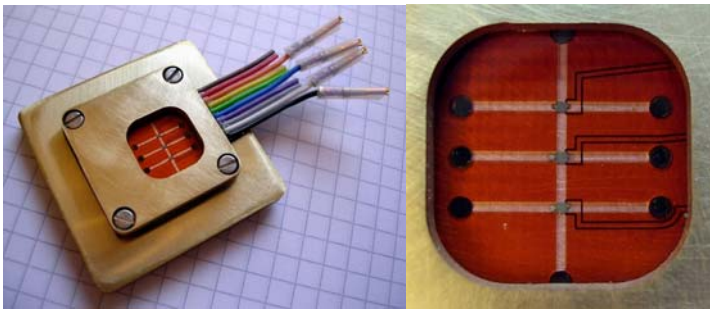


Figure 2: Assembled device showing the ultrasonic transducer array through the glass examination window, electrical connections on the side and fluidic connections on the backside. The ultrasonic transducers are about 600 µm wide.

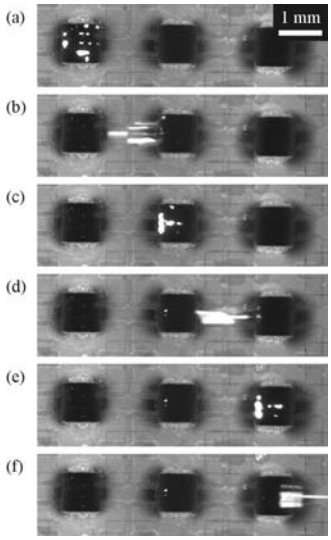


Figure 3: Trapping (a, c and e) and subsequent release (b, d and f) of fluorescent microbeads from left to right in three individually controlled array positions.

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BIO-Ångström 2005

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Heat- and moisture induced transformations in freeze-dried amorphous sucrose and Lactobacillus coryniformis Si3 formulations.

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Lb. coryniformis Si3 has broad antifungal activity and potential use as a food and feed bio-preservative. Lyophilisation (freeze-drying) is the preferred way of stabilising lactic acid bacteria (LAB). Generally, when stabilizing LAB in the dry state, an amorphous protective surrounding confers good survival. For stability reasons, it has been suggested that a lyoprotectant with a high glass transition temperature (Tg) should be selected and that crystallisation events, especially inside a cell are very harmful.

A drawback of amorphous solids is that they are generally less stable than their crystalline counterparts, and tend to transform during storage. Characterization of the dry state formulation is an important factor when predicting the stability.

In this study, we characterize a lyophilised powder consisting of Lb. coryniformis Si3 and sugar protectants. Moisture induced transformations at different humidities were evaluated by isothermal microcalorimetry (IMC-TAM, 2277 Thermal Activity Monitor, Thermometric AB, Sweden) and heat induced transformations by differential scanning calorimetry (DSC 220, SSC/5200H, Seiko, Japan). To our knowledge, there are no studies available on using these techniques to assess solid-state stability of LAB solid formulations.