



Setting the standard.

As 2005 gets underway, Q-Sense has much to be optimistic about. We have a loyal and growing customer base, the company has a world-wide distributor network, instruments used in more than 20 countries and an ever increasing portfolio of applications that demonstrate strong research results. In addition, we are backed by a parent group that sees a future in the business area in which we find ourselves and is committed to supporting us.

The launch of a new product is always an exciting occasion for any company. For the past few months, the preparations behind the scenes at Q-Sense have been reaching fever pitch. So now with the arrival of the E4, we pass a landmark in the company's history.

It marks us as a company whose technology has reached a new level of maturity, that we have a product range that can meet the diverse needs of our customers and that we are a company that has ambitions for the future. It will certainly give the competition something to think about.

If you didn't manage to see our new instrument, which was unveiled on February 28, 2005 at Pittcon in the US, you can read all about it in the pages of QNews. Details of the E4 are also available on the web and a full descriptive brochure can be ordered there.

As QNews enters its fifth year of publication, we confess that celebration is definitely in the air! We hope that 2005, brings success to all our customers and their ingenuity in the application of QCM-D continues.

*Elaine McClarence
Managing Editor*

Qsense®

P2 On the hunt for a killer

Sepsis is a disease that can kill most of its victims if not identified quickly. At McGill University in Montreal, Canada, Shawn Carrigan is working to improve the diagnosis of an infection which accounts for 120,000 deaths in the U.S. alone each year. Faster identification of systemic infection and better treatment regimes to reduce the high mortality rate is the key and QCM-D may have an important role to play.

P4 What goes on at the surface

Biomaterial engineering is a field that continues to grow in depth and breadth. Lars Renner is part of the Biomaterial group at the Leibniz Institute of Polymer Research Dresden at the Max Bergmann Centre of Biomaterials. Renner is using QCM-D as part of the characterisation of biomaterials.

P6 Publications Review

Four papers have been chosen for review in this issue covering paper making to proteins:

1. Surface Plasmon Resonance Spectroscopy and Quartz Crystal Microbalance Study of Streptavidin Film Structure Effects on Biotinylated DNA Assembly and Target DNA Hybridization.
2. Collapse and Swelling of Thermally Sensitive Poly(N-isopropylacrylamide) Brushes Monitored with a Quartz Crystal Microbalance.
3. Photo-Chemically Patterned Polymer Surfaces for Controlled PC-12 Adhesion and Neurite Guidance.
4. Viscoelastic Properties of Cationic Starch Adsorbed on Quartz Studied by QCM-D.

P7 Product and Company News

Heralding the launch of our new, flexible measuring instrument, the E4.



In the hunt for

Rapid Sepsis Diagnosis.



At McGill University in Montreal, Canada, work to improve the diagnosis of sepsis is underway. As a killer infection which accounts for 120,000 deaths in the U.S. alone each year, the hunt is on for faster identification of systemic infection and better treatment regimes to reduce the high mortality rate. Part of this work involves the design of biointerfaces that can

detect sepsis-related cytokines and Shawn Carrigan, within the university's Biomedical Engineering Department, is developing a system that employs QCM-D.

Shawn Carrigan is what you could call a renaissance researcher who started his career as a chemical engineer working with gas turbine technology, then moved on to biomechanics studies before settling into his Ph.D thesis on biointerface design, under the supervision of Maryam Tabrizian (McGill University) and George Scott (MDS Pharma Services). His research focus is the development of detection methodologies for sepsis related markers with the aim of producing an easy and rapid method of immobilising antibodies for real-time immunoassay. With sepsis, rapid diagnosis allows for prompt pharmaceutical intervention, ultimately improving patients' likelihood of survival.

Carrigan is trying to develop a real-time immunoassay system that could be applied in hospitals to the benefit of patients, as the

cost of present real-time immunoassays prevents their widespread application in clinical settings. He has been using the QCM-D system as an affordable transduction system for immunoassay to detect sepsis-related cytokines.

Working outside the box

Within his department Carrigan is the first to employ QCM-D and, in many respects, is taking the machine outside the boundaries of its original design. As he admits, the D300 model he uses from Q-Sense was not designed for the particular biomedical application he is working on. Though the QCM-D is being used outside its normal field, he notes, "The cost of the D300 was a major motivating factor in trying to develop alternatives capable of performing similar to an SPR real-time system."

Despite the fact that QCM-D is being pushed beyond its limits, Carrigan says that it has proved to be a promising technique. The D300 hasn't been designed for clinical applications; sample sizes are recommended to be 2 millilitres, while Carrigan's sample size tends to be 200 microlitres. This prevents adequate temperature stabilisation of the sample prior to entering the measurement chamber, causing large spikes in the frequency curves. "While I am very happy with the D300, it could benefit from some significant hardware modifications for biomedical applications."

The biointerfaces designed show strong initial immunoassay characteristics relative to other QCM-based assays (Biomaterials, accepted). By employing a combination of cross-linked polyethyleneimine and carboxymethylcellulose, direct immobilisation of antibodies produced a detection limit of 400 ng/mL for a 44 kDa cytokine. In addition to rapid biointerface preparation using non-toxic constituents, the biointerface demonstrates facile surface regeneration characteristics allowing repeat measurements at 1µg/mL and limited non-specific protein binding of human serum albumin. Additionally, the variability of the dissipation response is on par with the frequency response, providing a method of verification not possible with SPR systems (Fig. 1).

Modification increases sensitivity

Recent experiments indicate that modifications to the biointerface preparation can greatly increase the sensitivity of the immunoassay (manuscript in preparation). A new sur-

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face composition demonstrates measurement repeatability at 100 ng/mL for a 17 kDa cytokine, easily eclipsing previous repeatability while using a lighter antigen (Fig. 2). These measurements also clearly demonstrate that immunoassay detection levels similar to SPR are possible on a 5 MHz crystal.

Exploring the limits

Measurements have also employed 10 MHz crystals to explore the peak limit of detection possible with the current D300 system. With 10 MHz crystals for liquid measurements only one frequency can be measured reliably, which eliminates the benefits of overtones provided by the D300. While the response signal generated by a 10 MHz crystal is significantly higher than its 5 MHz counterpart, the measurement noise nullifies the potential benefit of higher frequency measurements. However, design changes to the measurement chamber to reduce noise have the potential to allow higher frequency crystals to exponentially increase the sensitivity of immunoassays using QCM-D.

Powerful potential

Given the widespread acceptance of SPR as an immunoassay method, it has been used for comparison using the same surface composition on a Biacore3000. While the detection limit was significantly higher using the SPR technology, Carrigan believes that it is not surprising given that the Biacore is a developed immunoassay platform and the D300 is not. Further, he postulates that QCM-D technology can surpass SPR detection sensitivity. "The major benefit of QCM for this type of work is cost and room for expansion. The system itself isn't really designed for medical samples or immunoassays, but modifications to the hardware in combination with smaller, higher frequency crystals could yield a very powerful tool," Carrigan suggests.

Aside from the cost advantage over other real-time mass detection systems, Carrigan was impressed by the sturdiness and adaptability the D300 provides. "Another major advantage of this system is its robustness. In all honesty, I'm surprised that it still works. I can't count the number of times that I've disassembled the system to clean it or modify it to suit my personal applications. I use the equipment every day, and the system works just fine. All the maintenance and modifications are free," says Carrigan. "Compare that to the maintenance contracts for some other systems and the advantages become apparent."

Fig. 1

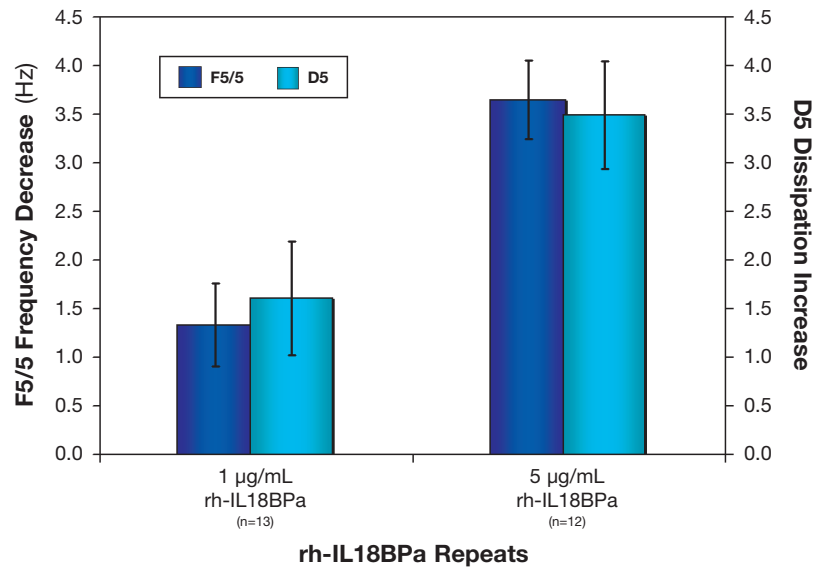


Fig. 2

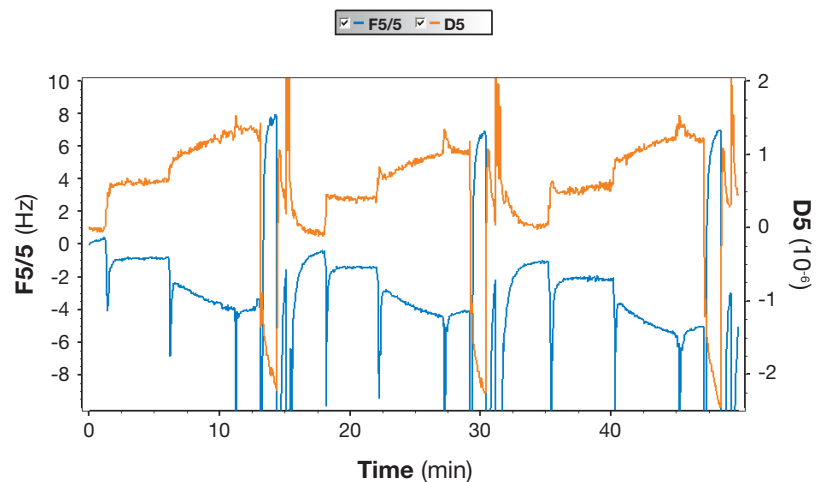


Fig. 1 Immunoassay repeatability in buffer by both frequency and dissipation monitoring for 44 kDa cytokine IL-18BPα.

Fig. 2 Frequency and dissipation monitoring of 100 ng/mL repeat measurements of a 17 kDa cytokine. Each of the three measurements indicated includes injection of the antigen, followed by a secondary antibody, buffer rinse, and surface regeneration.



Protein Adsorption on polymer surfaces reveals potential of biomaterials.

There is an increasing focus within the research community on molecular bioengineering applications. As part of this work researchers need a deeper understanding of materials' physicochemistry, the implications of modifying such materials and the subsequent behaviour of biomolecules as they impinge upon those surfaces. Lars Renner, part of the Biomaterial group at the Leibniz Institute of Polymer Research Dresden at the Max Bergmann Centre of Biomaterials, is using QCM-D as part of the characterisation of biomaterials.

Headed by Dr. Carsten Werner, this group comprises 44 members. The Max Bergmann Centre of Biomaterials Dresden is a relatively young organisation established in 2002 as a joint initiative by scientists of the University of Technology Dresden and the Leibniz Institute of Polymer Research Dresden. The institute's work covers the broad sweep of molecular engineering applications. This ranges, for example, from the design, preparation and development of materials to establish the compatibility of biomolecules (e.g. proteins, DNA, polysaccharides) to biomaterial surfaces modification to adjust the physicochemical properties of materials (wettability, surface charge, topography). By putting constraints on bio-interfacial phenomena (molecular binding of proteins, cell matrix reorganisation) and the immobilisation of bioactive molecules onto 2D and 3D artificial scaffolds, they aim to achieve specific interactions with components of bio-systems. Additionally, the group works with the synthesis of biomimetic molecular architectures (inhibitors of blood coagulation, for example) in order to develop pharmacological biomaterials.

Special interests involve:

- in vitro determination of the haemocompatibility of biomaterials
- proliferation and vascularisation of cells in matrix
- protein-protein interactions
- analysis of biodegradable scaffolds
- surface modifications to alter the physicochemical properties of materials (plasma treatment, graft polymerization)
- controlled drug release from hydrogels

Lars Renner, Dr. Tilo Pompe, Dr. Toshihisa Osaki and Dr. Carsten Werner are the workers mainly involved with the research related to the QCM-D application. They have been using QCM-D since December 2003 to study protein adsorption (stem cell factor, fibronectin (Fn), human serum albumin (HSA)), subsequent protein displacement (HSA and fibronectin) and surface characterisation of polymer thin films (dynamics of swelling and chemical reactions). QCM-D is used alongside other techniques – such as electrokinetic measurements, ellipsometry, confocal laser scanning microscopy, atomic force microscopy and X-ray photoelectron spectroscopy.

Versatile materials for research

Renner explains, “Maleic anhydride (MA) copolymers are used as a versatile platform for biomaterial research, because they provide a wide reactivity range, especially for the reaction with amino groups. Biopolymers can be attached either covalently or physically, which are adjusted by the chemical conversion of the anhydride group to carboxylic acid groups.” A general sketch of the MA surfaces is shown in Figure 1. By varying the kind of monomer, the physicochemical properties of the surfaces can be adjusted (hydrophobicity, surface charge, grafting density). The hydrophobic character increases with the chain length of the comonomer.

Measurements of the swelling behaviour of maleic anhydride polymers have been carried out using QCM-D. “From the results we can attribute a huge water uptake, and swelling of hydrophilic polymer films poly(propylene-alt-maleic anhydride) (PPMA), poly(ethylene-alt-maleic anhydride) (PEMA), and

poly(styrene-alt-maleic anhydride) (PSMA),” notes Renner. “For very hydrophobic polymers poly(octadecene-alt-maleic anhydride) (POMA) only insignificant swelling was detected.” Frequency changes are shown in Figure 2. “We observed the in-situ dynamics for physical swelling as well as the chemical hydrolysis of maleic anhydride groups to carboxylic acid groups, which induced an acceleration in the swelling process.”

Dynamic stages

The dynamics can be divided into three stages with different scaling laws, says Renner. Figure 3 illustrates the dynamics of swelling with scaling laws demonstrating the three different regimes of swelling. By the maximum of the first derivative of the swelling dynamics a characteristic time constant was obtained which showed a dependence on the size of the comonomers of the applied copolymers. “As it was hypothesised that this special swelling process is determined by the hydrolysis of the anhydride groups, a verification of the data by XPS revealed a decrease of 60% of the total anhydride groups after the characteristic time constant. After 24h all anhydride groups have been transformed into carboxylic acid groups,” says Renner. Hence, the QCM-D allowed a quantification of the scaling behaviour of the swelling process and revealed a comonomer dependent dynamics of the anhydride hydrolysis.

Fibronectin adsorption experiments

On POMA and PPMA polymer surfaces, fibronectin (Fn) adsorption experiments have been performed which involved exposing different amounts of Fn in bulk solution (2.5, 5, 10, 50 g/ml). “We found smaller frequency

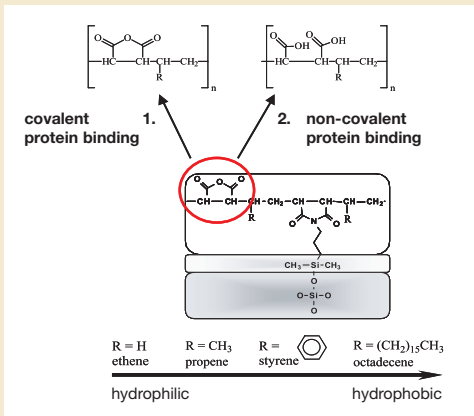


Fig. 1

Structure of maleic anhydride copolymers. As substrate platform SiO₂ surfaces are used, Aminosilane is used as a crosslinker to covalently bind the polymer to the surface. Strategies for further analysis of

biocompatibility of the surfaces are: (1.) annealing to achieve covalent binding, (2.) hydrolysis of anhydride groups to achieve non-covalent binding of biopolymers (for example proteins, polysaccharides).

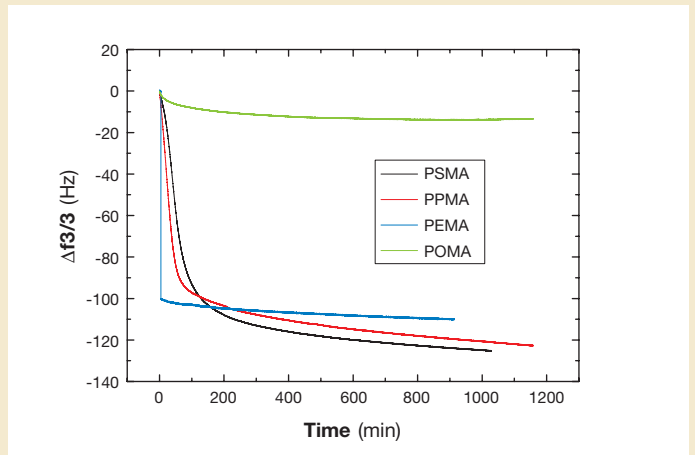


Fig. 2 Typical frequency response of polymer swelling.

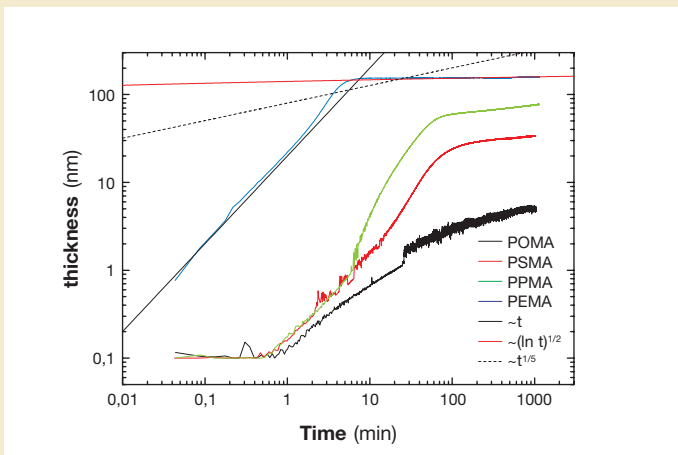


Fig. 3 Dynamic of swelling of copolymer layers at pH 7.4.

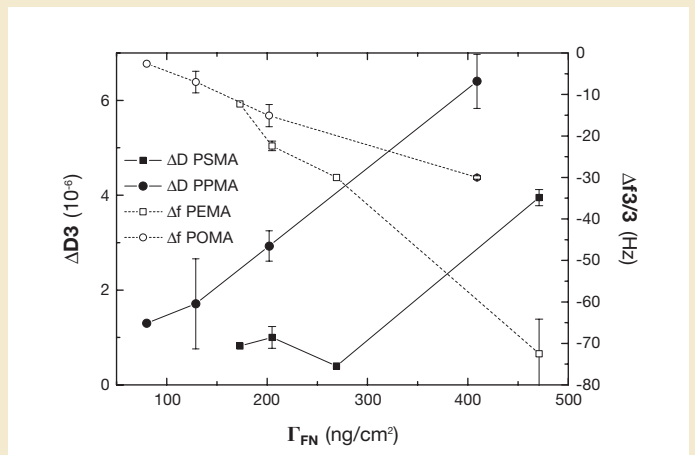


Fig. 4 Dissipation and frequency change upon Fn surface coverage.

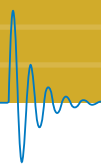
changes and higher dissipation changes on PPMA,” says Renner (illustrated in Figure 4). This can be attributed to higher adsorbed mass on POMA and the formation of a more rigid layer of Fn molecules. “On PPMA we found less protein attached to the polymer surfaces, accompanied by a higher flexibility of the adsorbed Fn. The hypothesized lower adsorption strength was verified by a higher displacement during a protein heteroexchange experiment by human serum albumin (HSA) at 50 $\mu\text{g/ml}$. Fluorescence confocal laser scanning microscopy of fluorescent labelled Fn was applied to measure the protein heteroexchange,” explains Renner.

Furthermore, the QCM-D data revealed differences in the frequency-dissipation changes with an increasing surface coverage of Fn protein. This is caused by a higher quantity of entrapped water as well as the higher adsorbed protein mass. “We could conclude that a variation of the adsorbed protein film characteristic was dependent upon the surface coverage, which was verified by the protein heteroexchange experiments and the immuno-fluorescence studies probing Fn conformation,” concludes Renner.

Renner notes that QCM-D is unique in its ability to detect adsorbed absolute amounts

and information about the viscoelastic properties of very thin films. Other advantages, he noted were the easy set up, fast sample in situ measurements, and the ability to use only small amounts for expensive samples.

The group is now using QCM-D to observe protein adsorption of molecules of special interest in its applications. Renner says, “We are especially interested in the amount and conformation of adsorbed proteins. In future work we will perform measurements controlling cell interactions, and blood compatibility tests.”



Publications File.

Surface Plasmon Resonance Spectroscopy and Quartz Crystal Microbalance Study of Streptavidin Film Structure Effects on Biotinylated DNA Assembly and Target DNA Hybridization.

Authors: Xiaodi Su, Ying-Ju Wu, Rudolf Robelek and Wolfgang Knoll

Publication: Langmuir. 2005 Jan 4;21(1):348-53

Disease diagnosis and biomedical research has become increasingly dependent on the ability to hybridise oligo-nucleotides with surface-immobilised DNA in a reproducible and efficient way. In this study, surface plasmon resonance (SPR) spectroscopy is used for the study of biotinylated DNA assembly on streptavidin modified gold surfaces for target DNA hybridization.

Researchers have chosen two immobilization strategies to construct streptavidin films, namely, (1) physical adsorption on biotin-containing thiol treated surfaces through biotin-streptavidin links and (2) covalent attachment to 11-mercaptopundecanoic acid (MUA) treated surfaces through amine coupling. To investigate the structural properties of the streptavidin films, QCM-D is used to monitor the streptavidin immobilization procedures. The simultaneously measured frequency (Δf) and dissipation factor (ΔD) changes, together with the SPR angle shifts ($\Delta\theta$),

suggest that the streptavidin film assembled on the biotin-containing surface is highly rigid with a well-ordered structure while the streptavidin film formed through amine coupling is highly dissipative and less structured. The subsequent biotinylated DNA (biotin-DNA) assembly and target hybridization results show that the streptavidin film structure has distinct effects on the biotin-DNA binding amount.

The researchers say they have demonstrated that, for biotin-DNA assembly on streptavidin modified surfaces, not only the probe density but also the probe orientation influenced by the streptavidin films has distinct effects on the hybridization efficiencies, and, in turn, the sensitivity of the hybridization analysis.

Photo-Chemically Patterned Polymer Surfaces for Controlled PC-12 Adhesion and Neurite Guidance.

Authors: Alexander Welle, Siegfried Horn, Jutta Schimmelpfeng and Dorothee Kalka

Publication: J Neurosci Methods. 2005 Mar 30;142(2):243-50

The researchers present work used in neuroscience research and other applications in cell biology. The group has developed a versatile technique based on polymer surface modification which allows the patterning of different cell lines for advanced tissue engineering; among them are Pheochromocytoma cells (PC-12). In contrast to other techniques applied for surface patterning, the presented photo patterning by deep UV irradiation is applicable to the widely used cell culture substrate material polystyrene (PS) and should be easily performed in most laboratories.

It involves irradiation of polystyrene with UV radiation and yields mainly carboxyl groups at the polymer surface which can be used to control the spontaneous competitive protein adsorption from serum containing culture media or to serve as defined coupling sites for controlled protein/-

peptide immobilization. This is an extension to previous studies on patterning hepatoma cells and fibroblasts via spatially defined plasma protein adsorption. Here the group describe an advanced application to produce patterns of cell repellent albumin domains and cell attractive laminin regions for the patterning of Pheochromocytoma cells.

QCM-D was used within the experiments with PS surfaces that were freshly prepared by spin coating of the polymer solutions onto the quartz sensor crystals. The researchers noted that QCM-D opens a new route in biomaterial examination and cell culture substrate development for tissue engineering. QCM-D has proven its ability to follow several processes, like folding, cross linking, denaturation, water uptake and release within protein adsorbates and surface-bound extracellular matrices.

**Collapse and Swelling of Thermally Sensitive
Poly(N-isopropylacrylamide) Brushes
Monitored with a Quartz Crystal Microbalance.**

Authors: Guangming Liu and Guangzhao Zhang

Publication: J. Phys. Chem. B, 109 (2), 743 -747, 2005

Polymer brushes, which are polymer chains grafted onto a surface, are of interest in such diverse fields as tribology, colloidal stabilisation and self-assembly of polymers. In this study, researchers were looking at the transition of chains and factors which affect the formation and collapse of brushes. Polymer brushes are formed on a surface when the grafting density is so high that the chains have to stretch outwards from the surface without any overlapping.

The researchers grafted thermally sensitive poly(N-isopropylacrylamide) (PNIPAM) brushes onto SiO₂-coated quartz crystal surfaces that were prepared with a surface-immobilised initiator. QCM-D was used to investigate, in real-time, the collapse and swelling of the brushes in water. The frequency and dissipation of the PNIPAM brushes gradually changed over a temperature range of 20-38°C. This indicates that PNIPAM brushes undergo a continuous collapsed transition in contrast to PNIPAM chains free in dilute solution that exhibit a sharp coil-to-globule transition. This coincides with previous theoretical work and the study also reveals that there is a hysteresis in the swelling of the collapsed chains, attributed to intrachain and interchain interactions formed in the collapsed state at higher temperatures and the non-uniformity of the brushes.

**Viscoelastic Properties of Cationic Starch
Adsorbed on Quartz Studied by QCM-D.**

Authors: Tekla Tammelin, Juha Merta, Leena-Sisko

Johansson and Per Stenius

Publication: Langmuir. 2004 Dec 7;20(25):10900-9

In this paper, QCM-D is the principal method of investigation for cationically modified starch (CS). This substance has widespread use as a paper-making chemical for improving retention and the dry strength of paper. Researchers are seeking a better understanding of how adsorption and the properties of the adsorbed layers of CS at the solid/liquid interface are affected by parameters such as ionic strength, surface charge density, and the molecular weight and degree of substitution (charge density) of the CS.

The QCM-D instrument, say the researchers, offers new possibilities of in situ investigation of not only adsorption kinetics and adsorbed mass but also the time dependence of viscous and elastic properties of adsorbed polymer layers at the solid/liquid interface.

Korean Distributor adds strength.

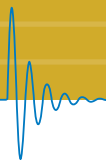
D.I. Biotech Ltd based in Seoul, Korea is now part of the Q-Sense distributor network. This is a very experienced company that represents some other Swedish instrument companies and has a broad, relevant product portfolio. It opens up new markets for QCM-D and support our company's ambitions to grow in this geographic area.

Tips and Tricks 6

Reality check

In any modelling activity, you need to have certain expectations about the results you are likely to get.

When modelling QSoft data, it is always necessary to ask the fundamental question, "Is the outcome reasonable?" One way to confirm if the modelled results are the optimal ones with respect to the input parameters, is to start the calculations with only the overtones number 3 and 5, and then compare the results obtained with a second calculation using overtones number 5 and 7 (or 3 and 7). By using different f and D sources for the same measurement, it is possible to get an indication about the stability of the model results.



Enter the E4.



The E4 is the complete system for real-time characterisation of molecular interactions and molecular adsorption to many different surfaces. It is the next phase in the evolution of instruments based on the Quartz Crystal Microbalance with Dissipation monitoring technique, QCM-D. It has been designed for real-time, label free, in situ measurements of molecular interaction and adsorption to surfaces.

“For all applications, the E4 can track events in real time; be used with a large selection of substrate materials, provide information about structural changes, measure the mass change and operate with non-labelled molecules,” says Michael Rodahl, head of R&D.

Broad applications

The instrument has a broad range of research applications to characterise molecular binding events on surfaces of all kinds. It includes, for example the study of material properties, thin film technology, functionalised surfaces, electrochemistry, biomaterials, drug development, biocompatibility and biofouling. This means that it can support the development and evaluation of biomaterials with specific properties, sensor platforms for bio recognition studies, research on the interaction between molecules such as protein interaction, study the build-up of polyelectrolyte multilayers for example and, fundamental research on thin films/properties of surfaces. Substances that can be studied include proteins, lipids, polyelectrolytes, polymers and cells/bacteria interacting with surfaces or with previously bound molecular layers.

Technical advancements

The E4, being the latest development, benefits from a number of technical advancements including upgraded electronics for faster data acquisition and higher sensitivity as well as a new measurement chamber design to increase the flexibility in the type of measurements that can be carried out. The mass of molecular layers forming on the surface with nanogram sensitivity and a 1% or less of a protein monolayer can be detected. It is a complete turnkey instru-

ment and includes everything needed to quickly get started and produce high quality data. The chamber has been specifically designed for flow measurements in a temperature-controlled environment. The chamber holds four removable flow modules, each holding one sensor. The flow modules can be used in any serial or parallel configuration to suit different measurements needs. This also allows higher throughput and makes reproducibility easier. It also includes software that allows the system to extract the thickness, viscosity and elasticity of adsorbed layers as well as kinetic constants. Structural changes can be measured simultaneously so as to distinguish between two similar binding events or observe a phase transition in bound layers. It is also possible to study electrochemical reactions simultaneously by using an optional electrochemistry cell. In all, the E4 marks a significant advance in QCM-D technology and gives users a flexible investigation tool that can be used across a broad range of applications.

Upcoming Events

March 28-30, 2005. Sapporo, Japan
Annual Meeting of JSBBA 2005

March 28 - April 1, 2005. San Francisco, USA
Materials Research Society 2005 Spring Meeting

April 14-16, 2005. Yokohama, Japan
The 94th Annual Meeting of The Japanese Society of Pathology

May 18-20, 2005. Tokyo, Japan
4th International Bio Expo Japan

May 31 - June 3, 2005. Strasburg, France
EMRS Spring meeting 2005

June 12-15, 2005. Potsdam, NY, USA
79th ACS Colloid and Surface Science Symposium

June 18-23, 2005. Sant Feliu, Spain
ESF Conference Biological Surfaces and Interfaces

September 19-23, 2005. Brighton, UK
Bionanotechnology 2005

October, 2005. Japan
The 64th annual meeting of the Japanese Cancer Association

October 31 - November 4, 2005. Boston, USA
AVS 52nd International Symposium and Exhibition

November 28 - December 2, 2005. Boston, USA
2005 MRS Fall Meeting

December 7-10, 2005. Fukuoka, Japan
28th Annual Meeting of the Molecular Biology Society of Japan