Nanostructured Sensors



Materials Nanoarchitectonics for Mechanical Tools in Chemical and Biological Sensing

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Abstract: In this Focus Review, nanoarchitectonic approaches for mechanical-action-based chemical and biological sensors are briefly discussed. In particular, recent examples of piezoelectric devices, such as quartz crystal microbalances (QCM and QCM-D) and a membrane-type surface stress sensor (MSS), are introduced. Sensors need well-designed nanostructured sensing materials for the sensitive and selective detection of specific targets. Nanoarchitectonic approaches for sensing materials, such as mesoporous mate-

Introduction

In recent research, considerable efforts have been made to develop efficient and effective methodologies in various scientific and technological fields, such as energy and environmental science,^[1] chemical conversion and catalysis,^[2] materials development,^[3] nanotechnology,^[4] biological and biomedical applications^[5] and many other fields.^[6] In numerous cases, the recognition and discrimination of particular molecules and substances are key processes to initiate appropriate responses. These recognition processes are often supported by supramolecular

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rials, 2D materials, fullerene assemblies, supported lipid bilayers, and layer-by-layer assemblies, are highlighted. Based on these sensing approaches, examples of bioanalytical applications are presented for toxic gas detection, cell membrane interactions, label-free biomolecular assays, anticancer drug evaluation, complement activation-related multiprotein membrane attack complexes, and daily biodiagnosis, which are partially supported by data analysis, such as machine learning and principal component analysis.

chemistry, as seen in molecular recognition^[7] and specific selfassembly.^[8] In addition, chemistry-based efforts have played crucial roles in the design and synthesis of functional molecules and their assemblies for responsive systems.^[9]

The designed and synthesized molecules are examined by using spectral methods, such as NMR-spectroscopy-based chiral discrimination,^[10] fluorescence-based ion/molecular detection,^[11] and other optical-based methods.^[12] These approaches can be regarded as chemistry-based tools. In many cases, these molecular and supramolecular sensing systems are coupled with various device-based tools, such as electrodes, transistors, and advanced nanotechnology devices.^[13] In addition to conventional chemical approaches, nanoscience tools based on the nanostructure-driven fabrication of sensing materials have been explored for advanced sensors, as seen in layered nanomaterials,^[14] polymer-based structural platforms,^[15] gel assemblies,^[16] nano-optode structures,^[17] hybrid architectures with nanocarbons,^[18] DNA arrays on surfaces,^[19] and nanoporous materials.^[20]

Representing an advanced conceptual paradigm for the design and synthesis of functional materials with nanosized structural features, the novel term "nanoarchitectonics" was coined by Masakazu Aono, who first proposed this concept in the conference titled "1st International Symposium on Nanoarchitectonics Using Suprainteractions" in 2000.^[21] The nanoarchitectonics strategy combines advanced nanotechnology with other scientific disciplines, such as supramolecular chemistry and materials processing.^[22] Functional materials and structures are architecturally designed with atomic/molecular/ nanoscopic elements through various processes, for example, atom-/molecular-level manipulations, chemical modification, self-assembly/self-organization, and structural regulation by external stimuli; uncertainties and unexpected disturbances are accommodated through statistic distributions and thermal fluctuations in the nanoscale regime (Figure 1).^[23] The nanoarchitectonics concept has been recently introduced in various research fields, such as the fabrication of functional materials,^[24] energy and environmental science,^[25] and biological and biomedical applications.^[26] In these fields, sensing applications represent one of the most promising areas that can benefit from the nanoarchitectonics approach.^[27]

In this Focus Review, nanoarchitectonics approaches for mechanical-based chemical and biological sensors are highlighted. Although optical and electrical responses require specific struc-

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Figure 1. Outline of the nanoarchitectonics concept.

tural features that display optical and/or electrical activity, mechanical responses, such as mass changes, viscoelastic properties, and various types of motion, can be applied universally to a wide range of materials. Therefore, mechanical sensing tools are an excellent class of measurement devices to realize the potential of nanoarchitectonic approaches for a wide range of applications.

Of the various classes of mechanical sensors, recent examples of piezoelectric sensors, such as the quartz crystal microbalance (QCM) and the quartz crystal microbalance with dissipation monitoring (QCM-D), are introduced herein. Although

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the sensing capabilities of QCMs for molecular detection,^[28] biomolecular interaction,^[29] viscoelastic phase transitions of ordered materials,^[30] and evaluation of thin-film fabrication^[31] were first demonstrated in the 1980s and early 1990s, recent progress in nanoarchitectonic-inspired structural fabrication and model membrane assemblies have created huge possibilities for new bioanalytical applications. In addition, as an emerging tool for mechanical sensing, a membrane-type surface stress sensor (MSS)^[32] is briefly described in the final section. With versatile abilities and broad applicability, application of the nanoarchitectonics concept to mechanical sensors creates a lot of possibilities for the future development of cutting-edge sensing tools.

Materials Nanoarchitectonics with QCM

Because QCM-based measurement tools are often coupled with various surface coatings to introduce sensing specificity for particular targets and to promote sensitivity, nanoarchitectonics approaches for the fabrication of sensing structures on electrode surfaces have been researched extensively. One successful strategy to enhance sensitivity involves immobilization of high-surface-area nanostructured materials to increase the potential for contact between target analytes and sensing materials. As seen in the following examples, nanoarchitecturebased mesoporous (nanoporous) materials on QCM electrodes have demonstrated strong promise.

In the example in Figure 2A,^[33] a partially oxidized mesoporous carbon material, CMK-3, was immobilized through layerby-layer (LbL) techniques^[34] with polyelectrolyte interlayers on a QCM plate. This designed system was used for the in situ sensing of nonionic aqueous guest molecules, such as catechin and tannic acid. Tannic acid showed particularly high affinity for the sensing system, likely due to a strong interaction with the carbon surfaces of the mesoporous material due to size matching with the pores. The measurement sensitivity was enhanced by using high-surface-area materials composed of mesoporous structures. Interestingly, a sigmoidal trend in the adsorption behavior of tannic acid was observed as a function of guest-molecule concentration in the mesoporous carbon. QCM sensor responses indicated cooperative adsorption of the guest molecules within the nanochannels. Enhanced guestguest and/or guest-carbon interactions within the confined nanopore space due to effective π - π interactions and hydrophobic effects are plausible reasons for the observed, highly cooperative adsorption.

In another attempt with nanoporous carbon materials, carbon cage-in-fiber structures were fabricated on a QCM electrode for the facile detection of aniline vapor (Figure 2B).^[35] In this sensing design, carbon nanocages (cage-type mesoporous carbon)^[36] were dispersed within electrospun polymer fibers and immobilized on the QCM electrode surface. This hierarchical nanoarchitecture design offers larger opportunities for contact with gas molecule analytes for rapid sensing. Based on the QCM response, detection of aniline down to ppm levels was repeatedly demonstrated, whereas other chemical compounds, such as water, ammonia, and benzene, showed negligible



Figure 2. QCM sensors with mesoporous carbon materials: A) LbL assembly of mesoporous carbon and polyelectrolytes. B) Cage-in-fiber structures of carbon nanocages with electrospun polymer fiber.

QCM responses. Aromatic amines, such as aniline, are often found in nonsmoking lung-cancer patients and the detection of volatile aromatic amines in a patient's breath could be an effective method for lung-cancer diagnosis.

Hollow carbon nanofibers prepared from nanostructured silica nanofibers on a QCM plate exhibited selective sensitivity to volatile organic compounds, such as pyridine and toluene, probably due to promoted interactions with sp² carbon atoms on the fiber surface.^[37] In particular, pyridine is known to be a hazardous chemical that potentially reduces male fertility and is carcinogenic. Compared with responses for benzene (77 Hz) and toluene (83 Hz), exposure of the fabricated QCM sensor to pyridine gas induced a significantly larger response (186 Hz), which was also much larger than those for aliphatic molecules, such as hexane (5 Hz) and cyclohexane (51 Hz). Selectivity for pyridine gas likely originates from the sp² nature of the fabricated carbon materials and the presence of Brønsted acid surface sites, such as OH and COOH groups, as confirmed by using XPS. A biomass-derived material, namely bamboo-derived nanoporous carbon, was also subjected to QCM-based gas sensing.^[38] The fabricated sensing platform exhibited excel-



lent sensitivity to acetic acid and, interestingly, could discriminate between C_1/C_2 alcohols (methanol and ethanol).

2D materials, such as graphene, have been used for a wide range of applications on the basis of their excellent electronic and electrochemical properties.^[39] Their structural features, such as wide-area flat structures and sp² carbon orbitals, are also useful in nanoarchitectonics for sensing applications. As illustrated in Figure 3, graphene nanosheets can be assembled



Figure 3. LbL assembly of graphene nanosheets with ionic liquid to form a π -rich nanospace.

into LbL structures with aromatic ionic liquid interlayers on a QCM electrode with the aid of an ionic polyelectrolyte.^[40] The interlayers of ionic liquid formed between the graphene planes comprise nanospaces rich in π electrons. Therefore, adsorption of toxic aromatic gas molecules into a LbL structure composed of graphene nanosheets and ionic liquid is more favorable than the adsorption of aliphatic carbons. In the QCM sensing system, a significantly higher sensitivity (more than 10 times) for benzene vapor was achieved compared with cyclohexane vapor, although they have similar molecular sizes, molecular weights, and vapor pressures.

As advanced hierarchical structures of mesoporous carbon capsule sensors, LbL structures of mesoporous carbon capsules were also fabricated on a QCM electrode surface (Figure 4).^[41] Similar to the responses observed in the aforementioned graphene-based QCM sensors, the hierarchical mesoporous carbon sensors showed higher sensitivity to aromatic carbons, such as benzene, toluene, aniline, and pyridine. Interestingly, unlike the previous examples, impregnation of a second sens-



Figure 4. LbL assembly of mesoporous carbon capsules on a QCM electrode doped with a second type of recognition component.

ing element into the mesoporous capsules could modify sensor selectivity. Doping of the mesoporous carbon capsules with an acidic second component, lauric acid, changed the best affinity to nonaromatic amines. In contrast, alteration of the affinity for acetic acid was confirmed through impregnation with dodecyl amine as the second sensing component. Very recently, it has been also found that covering the mesoporous carbon capsules with appropriate polymers is another effective way to modify the sensing capability.^[42]

As a versatile method to design nanostructured materials, the liquid-liquid interfacial precipitation method has been used for the fabrication of shape- and structure-defined assemblies from molecular nanocarbons and fullerene families.^[43] Gentle addition of poor solvents (low-solubility solvents) to a solution of fullerene results in variously shaped supramolecular fullerene assemblies. Depending on the modification conditions, that is, concentration, temperature, solvent combinations, additional chemicals, and external stimuli (agitation and sonication), assemblies in rod and tube,^[44] sheet,^[45] cube,^[46] and tadpole-like^[47] shapes can be spontaneously precipitated, and sometimes can be converted into graphitized carbon materials.^[48] Some have been used as sensing materials in QCM devices.^[49] Recently, hierarchically structured cubes, microcube structures with many small antenna rods, were successfully fabricated through the liquid-liquid interfacial precipitation of C_{70} and post-solvent treatment (Figure 5). $^{\left[50\right] }$ As an analogy to insects with sensitive antennae, QCM electrodes with antennadecorated C70 cubes showed more sensitive responses to aromatic solvent vapors, such as toluene and pyridine, than those with antenna-free C70 cubes. Because each antenna rod has a nanoporous structure, the resulting high contact area promotes the diffusion of gas molecules towards the carbon surface for detection.

In contrast with the former example with nanopores in antenna structures, the next example (Figure 6) shows how mi-



Figure 5. Fabrication of C₇₀ microcubes with sensing antennae.



Figure 6. C_{70} hole-in-cube structures for the selective incorporation of carbon particles.

croscopic holes can be manipulated at the faces of the C₇₀ cubes.^[51] The microscopic holes become a medium that is appropriate for the discrimination and sensing of microparticle objects. The liquid–liquid interfacial precipitation process for C₇₀ synthesis involves mesitylene and *tert*-butyl alcohol treatment with appropriate agitation to promote the spontaneous formation of cube-shaped crystals of C₇₀ molecules with a

single open microscale hole structure on each face. These microscale holes can be intentionally closed through the addition of excess C₇₀ molecules and can be reopened by local electron beam irradiation at the faces of the cubes. Interestingly, the trapping of microparticles into the holes supports discrimination of graphitic carbon compositions over polymeric resin particles of similar size. The more favored trapping of graphitic carbon particles likely results from π - π interactions between the sp²-carbon-rich open holes of C₇₀ and the graphitic carbon particles. Therefore, C₇₀ hole-in-cube structures in QCM systems are highly useful for the detection of pollutant particles in the atmosphere and exhaust gases.

QCM and QCM-D have been used for the sensing and analysis of various bioprocesses, and changes in the mass, mechanical properties, and viscoelasticity of adsorbates can be detected in many processes. Jin et al. reported a real-time evaluation of the molecular recognition process of cisplatin-damaged DNA with a cellular responsive protein by coupling a QCM detection system with flow-injection analysis.^[52] Such sensing systems would be useful for real-time screening and evaluation of DNA-targeting anticancer drugs. A demonstration of a sensitive flow-based immuno-QCM-sensor was proposed by Filipe, Hoare, and co-workers through surface modification by using a graphene oxide-biotin-avidin complex strategy.[53] The proposed immobilization scheme is versatile and can be applied to a wide range of biotinylated capture antibodies. Tufenkji and co-workers reported an evaluation system for bacterial capture behavior by bacteriophages immobilized on a QCM-D plate.^[54] The measurement response appears to occur mainly due to elastic coupling of the bacteria, which suggests that surface nanoarchitectonics controls, such as optimization of bacteriophage surface densities, are crucial. Preininger and coworkers used a surface imprinting strategy with polyurethanes^[55] because the molecular imprinting technique is a powerful method to detect specific molecules and materials.^[56] Their QCM strategy successfully demonstrated the detection of large biological particulates, specifically E. coli bacterial cells.

Bio-Membrane Nanoarchitectonics with QCM-D

In this section, approaches that use model membranes as detection platforms to track biological processes based on the QCM-D technique are introduced. In addition to detecting shifts in the resonance frequency upon mass uptake or release at the electrode surface, as in conventional QCMs, viscoelastic changes can be evaluated through the energy dissipation factor in QCM-D. The QCM-D technique has played an important role in characterizing the viscoelastic steps involved in supported lipid bilayer (SLB) formation. SLBs represent an important model membrane tool that is widely used in biosensing, surface functionalization, and cellular interface applications.^[57] Here, we introduce several promising sensing examples based on bio-membrane nanoarchitectonics.

Membrane-peptide interactions

QCM-D measurements have played an important role in the study of membrane-peptide interactions and led to the development of new strategies for SLB fabrication. When an amphipathic, α -helical (AH) peptide is added to surface-adsorbed vesicles on gold and titanium oxide surfaces, the peptide can induce vesicle rupture and lead to SLB formation.^[58] This achievement is significant because SLB formation was previously limited to silica-based materials, and gold and titanium oxide possess attractive properties for surface science applications. QCM-D experiments provided key insights that revealed how peptide molecules adsorb onto the lipid membrane surface before inducing vesicle rupture, and the resulting vesicle-to-bilayer structural transformation provided a model system to study changes in thin-film behavior.^[59] From a biosensing perspective, it was observed that the QCM-D kinetics of the AHpeptide-mediated vesicle rupture process depend on the material composition of the sensor surface.^[60]

However, this AH peptide only ruptures adsorbed vesicles below a certain diameter, and QCM-D measurements identified that the efficiency of vesicle rupture was inversely related to vesicle size.^[61] Kinetic analysis of the QCM-D measurement data indicated that cooperative peptide binding leads to pore formation and vesicle rupture, whereas noncooperative binding does not cause vesicle rupture. Combined measurement approaches involving QCM-D and ellipsometry experiments have further identified that a critical density of peptide-induced pores form in a lipid vesicle before rupture occurs.^[62] Figure 7 illustrates the experimental strategy to measure the peptide (P)/lipid (L) ratio. In particular, a lipid-based model system composed of substrate-supported adsorbed vesicles was monitored by using simultaneous QCM-D and ellipsometry measurements to investigate the membrane-peptide interaction. The combined measurement approach, together with biophysical models, enabled us to determine that membrane lysis occurs at a critical peptide/lipid ratio.

Antimicrobial lipid evaluation

Antimicrobial lipids are a promising class of antibacterial compounds that destabilize bacterial cell membranes.^[63] Historically, antimicrobial lipids have been studied by microbiological methods that determine the potency and scope of a test compound to inhibit the growth of or kill a bacterial species. Past studies have identified that medium-chain fatty acids and monoglycerides have particularly high antibacterial activity, although in vitro methods provide limited insight into how these compounds destabilize lipid bilayer targets. To address this measurement gap, SLB platforms have been employed to characterize the concentration-dependent membrane interactions of antimicrobial lipids.^[64] QCM-D experiments identified that lauric acid and glycerol monolaurate (a fatty acid and a monoglyceride molecule, respectively) can trigger three-dimensional remodeling of SLBs. The membrane morphological changes occur only above the corresponding critical micelle concentration value of the tested antimicrobial lipid, and the



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Figure 7. Schematic illustration of a measurement strategy to calculate the peptide-to-lipid ratio for the AH peptide case. The interaction of the AH peptide with surface-adsorbed lipid vesicles was monitored by using simultaneous QCM-D and ellipsometry measurements. These measurements were applied to evaluate the AH peptide's potential as an antiviral drug candidate. Reprinted with permission from Ref. [62]. Copyright 2016 American Chemical Society.

specific type of morphological response depended on the particular compound that was added. Lauric acid induced relatively small frequency shifts and moderate energy dissipation shifts, whereas glycerol monolaurate induced appreciably larger frequency and energy dissipation shifts. These measurement shifts were consistent with time-lapsed fluorescence microscopy imaging that showed lauric acid induced tubule formation whereas glycerol monoglyceride caused membrane budding. The distinct membrane morphological responses were explained by taking into account the different membrane translocation rates of anionic fatty acids and nonionic monoglycerides and, therefore, their variable effects on membrane strain. The results provided the first evidence that different classes of antimicrobial lipids exhibit unique membrane interaction profiles. It was further identified that additional fatty acids and monoglycerides exhibit similar trends in membrane morphological responses,^[65] which demonstrated the broadly applicable utility of QCM-D measurements to profile the activity of different classes of membrane-active compounds.

Within this scope, a particularly interesting measurement example was reported when the QCM-D technique was applied to characterize how sterols affect the interaction between antimicrobial lipids and SLBs.^[66] The three-dimensional remodeling of confined lipid membranes is a passive means to regulate stress,^[67] and understanding the role of sterols is highly relevant because they function as biological mediators of stress relaxation.[68] To this end, cholesterol-rich SLBs were prepared by using the aforementioned solvent-assisted lipid bilayer (SALB) method, and then lauric acid or glycerol monolaurate was added to induce membrane morphological responses. For all tested compositions, the addition of lauric acid to SLBs led to tubule formation, and QCM-D monitoring revealed that the extent of membrane remodeling (as interpreted by the magnitude of the measurement responses) was greater for SLBs with larger cholesterol fractions (Figure 8). In contrast, the addition of glycerol monolaurate caused membrane budding in all cases, but the extent of membrane remodeling was smaller for SLBs with larger cholesterol fractions. Thus, the QCM-D results provided strong evidence to indicate that cholesterol can either inhibit or promote membrane remodeling, and the trends could be understood by taking into account how cholesterol affects the elastic (stiffness) and viscous (stress relaxation) properties of lipid membranes. These insights confirm that the membrane morphological responses that occur in simplified SLB platforms provide a useful model system to characterize the activity of antimicrobial lipids that may occur in more complex biological systems, and these compounds are being incorporated into nanotechnology formulations to treat bacterial infections.[69]



Figure 8. Schematic illustration of cholesterol-dependent membrane remodeling behavior of a SLB in response to treatment with lauric acid (LA) or glycerol monolaurate (GML). Ref. [66]. Copyright 2018 American Chemical Society.

Complement-activation monitoring and drug development

Over the past few decades, nanomedicines and protein-based biologicals have become key components of pharmacotherapy, and there is growing recognition that intravenous administration of these modern therapeutics can cause complement-activation-related pseudoallergy (CARPA).^[70] CARPA is a form of acute immune toxicity, and there is an outstanding need to establish measurement platforms that can predict the CARPA potential of drug candidates.^[71] Towards real-time CARPA detection, an SLB platform was developed to monitor the formation of the multiprotein membrane attack complex (MAC) that is implicated in complement activation.^[72] QCM-D measurements tracked complement protein adsorption that led to MAC formation, and it was identified that membrane surface charge is a key parameter that influences protein adsorption. The basic sensing principles could be translated into the detection of MAC formation as a predictive marker of complement activation on the target surface, and the sequential addition of different proteins facilitated stoichiometric analysis. By using the same measurement approach, it was also noted that other pattern-recognition proteins involved in complement activation exhibit preferential binding to negatively charged membrane surfaces.^[73] The tested proteins can function as opsonins, which aid immune clearance, and the observed trend in the amount of adsorbed proteins correlated with known patterns in immune clearance. Therefore, the findings provide guidance for the design of synthetic lipid bilayer platforms with immunocompetent features.

Another advantage of the SLB platform is the possibility to evaluate drug inhibitors that prevent MAC formation and thus mitigate complement activation. Compared with conventional measurement approaches, such as red blood cell assays, the QCM-D technique has competitive advantages in characterizing the mechanism of action of drug candidates, and it was determined that two MAC inhibitors, vitronectin and clusterin, differentially interfere with MAC assembly at lipid membrane interfaces.^[74] For example, vitronectin inhibits complement protein adsorption by binding directly to particular complement proteins and also by competitive adsorption onto the lipid bilayer (Figure 9). Conversely, clusterin binds to particular complement proteins but does not inhibit membrane association. Rather, clusterin prevents critical protein-protein interactions that are necessary for MAC assembly. The aforementioned examples involve noncovalent protein adsorption, and it has also been possible to attach complement proteins covalently to functionalized SLB platforms.^[75] In some cases, the covalent immobilization scheme was necessary to facilitate self-assembly of functional, multiprotein complexes, and the efficacy of a peptide inhibitor, compstatin, was tested. In all these cases, the key benefit of the QCM-D measurement approach is the label-free quantification of step-by-step protein adsorption, and the corresponding results provide guidance for the study of complement assemblies across fundamental and translational applications. Furthermore, the measurement tools can be applied to study other drug inhibitors, such as complement

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Figure 9. Effect of vitronectin protein on adsorption of the C5b-7 protein complex onto an SLB platform. A) Schematic illustration of the experimental steps: C5b-7 complex was preincubated with vitronectin, then the mixture was added to the SLB platform. B) A corresponding schematic illustration of the addition of vitronectin to the SLB platform, followed by addition of the C5b-7 protein complex. Reprinted with permission from Ref. [74]. Copyright 2015 American Chemical Society.

factor H, and could lead to the development of new therapies to treat complement-related diseases.^[76]

Within this scope, there is a significant push towards establishing validated models to predict the CARPA potential of a drug candidate. The porcine model is highly sensitive to CARPA-reactive drugs, and is currently being explored as a suitable animal model.^[77] Recently, it has been experimentally demonstrated that the miniature pig is useful as a CARPA model and could be the favored species for regulatory testing because it is already a popular porcine model for toxicological studies.^[78] QCM-D measurement platforms to detect complement activation would provide a complementary in vitro assay that benefits from rapid response time, label-free readout, and detailed quantification. Looking forward, these measurements tools can be utilized to test CARPA-reactive agents, such as superparamagnetic iron oxide nanoparticles,^[79] and also to design new strategies to inhibit nanomaterial-induced complement activation, as recently demonstrated by graphene oxide sheets coated with factor H protein.^[80] Ultimately, such abilities will be useful for regulatory testing and in the development of nanomedicines and biologicals with improved safety profiles.

Membrane-Type Surface Stress Sensor (MSS)

Mechanical sensing tools are not limited to QCM and QCM-D, and there are many other exciting examples of recent developments. Motivated in part by the need for more advanced mechanical tools for the versatile and sensitive detection of gas molecules, an MSS was recently developed by Yoshikawa and co-workers. This MSS can work as a nanomechanical sensor to detect biomolecules and gas molecules (Figure 10).^[81] In contrast to a conventional cantilever-type nanomechanical sensor, the MSS involves the integration of a center membrane and supporting bridges with embedded piezoresistors. The isotropic surface stress on the membrane is efficiently measured by the piezoresistors as an amplified uniaxial stress. The sensitivity of the MSS is a factor of more than 100 higher than that of a standard cantilever-type piezoresistive sensor.



Figure 10. An MSS as a nanomechanical sensor for gas molecules.

Adsorption of target substances, including gas molecules and biomolecules, alters the mechanical properties of a membrane with sensing films, resulting in an MSS response. Therefore, the coating of sensing films is a critical step for successful sensing performance. To establish an analytical guideline for effective coating materials, the deformation of a nanomechanical sensor coated with various films was investigated.^[82] An analytical model was developed for the dependence of the deflection on mechanical properties, such as the thickness and the Young's modulus of the coating film. For more practical requirements, double-side and single-side coating features in MSS devices have been compared.^[83] The working mechanism was also supported by both experimental results and finite element analysis (FEA). Basically, the symmetric double-side coating has inferior sensitivity as compared with the asymmetric single-side coating. However, the double-coating strategy has other advantages, such as a wider range of applicable materials with easier possible coating techniques, for example, dip coating and self-assembled monolayers involving silane chemistry and gold-thiol interactions.

To specify additional advantages of MSS, the signal reproducibility of MSS and conventional cantilever-type sensors were compared.^[84] First, the smaller standard deviation of the distribution of the output for humidity sensing with MSS compared with that of cantilever sensors was confirmed. Another important advantage of the MSS system is a high tolerance to coating inhomogeneity. In many cases, the homogeneous coating of sensing films to obtain reliable and reproducible responses is technically difficult to achieve. The poor reproducibility and significant fluctuations of the sensing output of cantileverbased sensors with functionalized films were unfortunately confirmed by experimental facts and theoretical considerations aided by FEA. In contrast, the MSS system is appreciably more robust against inhomogeneous surface coating and functionalization effects, as demonstrated by simulations and experiments. In fact, the reproducibility of the MSS system has been reported to be around five times higher than that of similarly coated piezoresistive cantilevers. This excellent reproducibility, together with the intrinsically high sensitivity of MSS systems, points to the development of a promising bio/chemical sensor platform for the accurate measurement of various molecules.

To test the utility of MSS systems in practical applications, the discrimination of scents, such as cinnamon, oregano, parsley, garlic, nutmeg, rosemary, yuzu, and peppers, has been

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demonstrated by using an MSS system with four channels that were coated with poly(vinyl pyrrolidone) (PVP), poly(allylamine hydrochloride) (PAH), poly(methyl methacrylate) (PMMA), and a PVP/PMMA hybrid (1:1 by weight).^[85] Although these aroma substances are complex mixtures of various odorous molecules, evaluation of the data sets by using principal component analysis (PCA) successfully discriminated each smell.

Because the adsorption and interaction of guest substances typically occur at material surfaces, the nanoarchitectonics of the sensing platform is an important design element. One successful example was demonstrated in which novel hybrid network silica particles conjugated with functional organic molecules, tetraphenylporphyrins, and metal complexes were used as sensing components.^[86] The porphyrin was introduced by triethoxysilane substituents, which are moieties for binding to silica. Metal complexes comprised of Co, Ni, Cu, and Zn with porphyrin rings were also employed. The organic molecules, including metal complexes, were reacted with silica flake-shell capsules. Each material in solution was deposited onto each MSS membrane arranged on a chip. Repeated exposure of the chip to target gases, such as 50 ppm acetone and nitrogen gas flow, showed a reproducible electric output. The use of highsurface-area integrated nanostructures as the sensing platform improves the sensitivity of MSS systems. In fact, the possibility of sub-ppm detection of acetone vapor was demonstrated by using this approach. Because acetone is known to be an important metabolite in lipid metabolism, the developed MSS system could be also used as a portable, easy-to-use device for analyzing local acetone levels for daily bio-monitoring applications.

The realization of MSS nanomechanical sensing with machine-learning analysis has also been reported.^[87] By using an MSS system together with machine learning, specific information was extracted from multiple output signals. The surfaces of the MSS channels were coated with functional nanoparticles and 35 liquid samples, such as water, teas, liquors, and water/ EtOH mixtures, were measured by using the MSS array. The MSS signals were processed by using kernel ridge regression, which led to quantitative prediction of the alcohol content with high accuracy.

In another unique application of mechanical gas measurements, the direct evaluation of a compound's molecular weight without ionization has been achieved through the nanoarchitectonic integration of aerodynamics, thermodynamics, and mechanics.^[88] This aero-thermo-dynamic mass analysis (AMA) approach transduces microscopic events into measurable macroscopic phenomena. The flow of gas molecules, such as carbon dioxide, argon, air, nitrogen, and helium, can be converted into detectable mechanical deformation, such as cantilever deflection. It should be noted that this approach is not limited to a microsize sensing platform but applicable to a macroscopic object, as demonstrated by a hand-held business card, and provides an accurate molecular weight that agrees well with results given by a newly developed analytical model and finite element analysis. This AMA approach can be integrated into various devices and could be useful for consumer mobile platforms.

Conclusions and Outlook

Herein, we have presented several examples of mechanical sensing systems, such as the QCM, the QCM-D, and the MSS. The responses of these sensors are based on general physical parameters, such as changes in mass, mechanical properties, and viscoelasticity of the attached materials. As a general principle, all kinds of materials have mass and certain mechanical characteristics. Thus, the application of stimuli to attached materials on the sensor surface can cause changes in the mechanical properties of the material that can be detected by sensor responses in many cases. As such, mechanical sensors can respond to a wide range of stimuli, such as temperature changes, pH shifts, and the addition of chemicals and biomaterials. Because useful sensing tools require high sensitivity and selectivity, the design of application-driven sensing materials to recognize and/or respond to particular targets is crucial. Therefore, fabrication of materials based on the nanoarchitectonics concept is an important step towards the development of high-performance sensors. For example, a conventional ATcut 9 MHz QCM sensor can ideally sense mass changes at the nanogram level. After modification of the QCM surface with appropriate nanomaterials, nanogram-level adsorption can be attained at a much lower concentration of target guests, which results in much higher sensitivity.

As exemplified herein, the control of nanostructured architectures is one of the most promising ways to achieve high levels of sensor performance. The higher surface area conferred by nanostructured material designs enhances the effective contact area between target molecules and the sensing materials. Regularly organized nanostructures may be advantageous for barrier-free diffusions of target molecules into sensing materials. Additionally, biomimetic structures, such as SLBs, on sensor surfaces offer excellent the ability to translate delicate biological events into sensing signals. For the development of mechanical sensors as effective bioanalytical tools, biomaterialbased and bioconcept-oriented nanoarchitectonics^[89] becomes critically important. The coupling of nanostructures and biomaterials has been actively seen in recent research examples, such as mesoporous materials composed of cytochrome C protein molecules^[90] and alternately layered structures of 2D nanomaterials and DNA,^[91] which have already been used for sensing and biomaterial delivery applications. In addition, so-called biofilms^[92] could offer good contributions to this field. Both the development of mechanical sensors themselves and biomaterials nanoarchitectonics integrated together with highperformance sensors could create powerful analytical tools to support bio-related science and technology.

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Conflict of interest

The authors declare no conflict of interest.

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