Quartz Crystal Microbalance with Dissipation Monitoring: Enabling Real-Time Characterization of Biological Materials and Their Interactions

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In recent years, there has been a rapid growth in the number of scientific reports in which the quartz crystal microbalance (QCM) technique has played a key role in elucidating various aspects of biological materials and their interactions. This article illustrates some key advances in the development of a special variation of this technique called quartz crystal microbalance with dissipation monitoring (QCM-D). The main feature and advantage of QCM-D, compared with the conventional QCM, is that it in addition to measuring changes in resonant frequency (Δf), a simultaneous parameter related to the energy loss or dissipation (ΔD) of the system is also measured. Δf essentially measures changes in the mass attached to the sensor surface, while ΔD measures properties related to the viscoelastic properties of the adlayer. Thus, QCM-D measures two totally independent properties of the adlayer. The focus of this review is an overview of the QCM-D technology and highlights of recent applications. Specifically, recent applications dealing with DNA, proteins, lipids, and cells will be detailed. This is not intended as a comprehensive review of all possible applications of the QCM-D technology, but rather a glimpse into a few highlighted application areas in the biomolecular field that were published in 2007.

KEY WORDS: QCM-D, quartz, DNA, proteins, lipids, cells.

A BRIEF BACKGROUND AND HISTORY OF QCM

The quartz crystal microbalance (QCM) is a nanogram sensitive technique that utilizes acoustic waves generated by oscillating a piezoelectric, single crystal quartz plate to measure mass. The basis of QCM operation relates to quartz's inherent property of piezoelectricity. Piezoelectricity stems from the Greek word piezin which means to press and the electricity that is generated by the pressure.[1] By applying alternating electric fields to quartz an alternating expansion and contraction of the crystal lattice is induced. In today's most common QCMs a circular piece of quartz is sandwiched between two metal electrodes. The quartz is generally processed using the so called "AT-cut" to give favorable properties relating to stability (low temperature coefficients and a purely shear mode of oscillation). Resonance is excited when a sufficient AC voltage is applied with a frequency close to the resonant frequency (f_0) of the particular crystal. The resonant condition of the QCM occurs when the standing wave produced by the alternating expansion and contraction is an odd integer of the thickness of the quartz plate. Resonant frequencies of typical QCMs are on the order of MHz and the tradeoff between the frequency (relating to sensitivity) and the thickness (relating to usability) of QCMs is that the higher the resonant frequency the thinner the crystal. The common frequency (f_0) of 5 MHz has a corresponding thickness of ~ 330 μm.

QCMs became widely used as mass balances only after the theory and experiments relating a frequency change of the oscillating crystal to the mass adsorbed on the surface was demonstrated by Sauerbrey in 1959.[2] This linear relationship between frequency change (Δf) and mass adsorbed (Δm) is given by:

$$\Delta m = \frac{C}{n}\Delta f,$$

where n is the harmonic number and

$$C = \frac{t_q \rho_q}{f_0},$$

with t_q being the thickness of quartz, and ρ_q being the density of quartz and equals ~ –17.7 Hz ng/cm^2 for a 5-MHz crystal. There are three assumptions that must be fulfilled for the Sauerbrey relationship to hold. First, the adsorbed mass must be small relative to the mass of the quartz crystal; second, the mass adsorbed is rigidly

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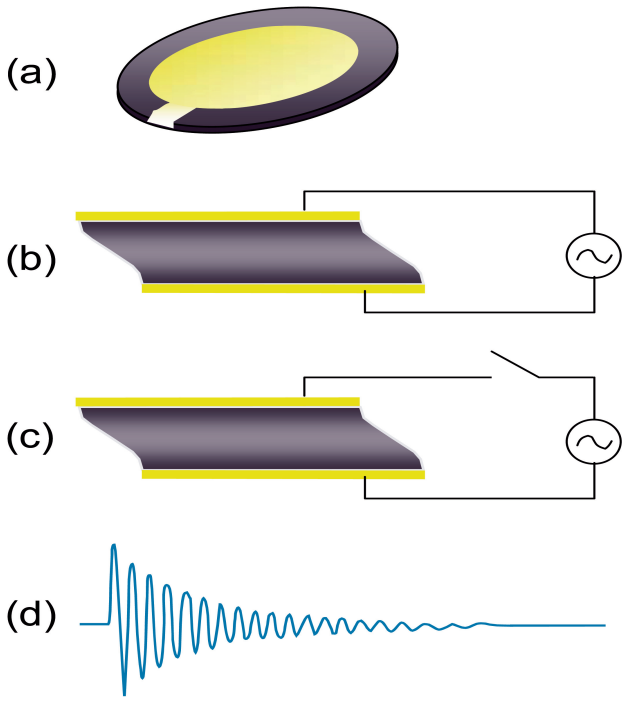

FIGURE 1

Description of the main components in QCM-D. **a:** Typical QCM-D sensor with Au electrodes. **b:** Quartz crystal with alternating current applied across electrodes. **c:** Short circuiting the alternating current. **d:** The oscillatory decay as the quartz disk comes to rest. The frequency of the oscillating crystal, shown in b, is related to the total oscillating mass adsorbed on the surface, while the energy dissipation, shown in c, is related to the viscoelastic properties of the oscillating mass. Thus, changes in adsorbed mass of, for example, a rigid protein provide a change in frequency, but for viscoelastic masses such as biomacromolecules, there is a change both in frequency and dissipation.

adsorbed; and third, the mass adsorbed is evenly distributed over the active area of the crystal. This frequency/mass relationship was, in the early days of QCM, almost exclusively used in vacuum or gas phase monitoring of metal plating in vacuum deposition systems. Later, other applications such as measuring dry etch rates, oxidation rates of metal surfaces, and various gas adsorption and desorption processes were demonstrated.[3] Each of these applications takes advantage of the submonolayer sensitivity of a QCM.

Even more widespread use of QCMs began when they were shown to be applicable in liquid environments around 1980.[4,5] Liquid application of QCM technology expanded the number of potential applications dramatically including biotechnology applications and in particular biosensor applications.[6] The drawback of applying the QCM to many liquid applications was that the liquid phase often incorporated viscous and elastic contributions to the frequency change and thus violated the assumption of the Sauerbrey relation stating that the mass adsorbed must be rigidly adsorbed. This prompted new approaches for characterizing mass deposits with frictional dissipative losses due to their viscoelastic character, and the theory for interpreting this new data.

UTILIZING QCM WITH DISSIPATION MONITORING

The two main approaches for addressing dissipation (D) due to viscoelastic film adsorption are monitoring the decay of a crystal's oscillation after a rapid excitation close to the resonant frequency[7] (since the decay rate is proportional to the energy dissipation of the oscillator) or impedance analysis.[8] The former will be addressed in this work. QCM with dissipation monitoring (QCM-D) fits the voltage of oscillatory decay after a driving power is switched off in such a way as to ensure that the quartz decays close to the series resonant mode.[9] The amplitude decays over time depending on the properties of the oscillator and the contact medium. The decay voltage, i.e., the output voltage amplitude as a function of time, with a frequency given by the resonant frequency of the quartz crystal (f_0), is mixed with a reference frequency (f_R) and filtered with a low pass band filter. This gives an output frequency (f) based on the difference between f_R and f_0. This difference frequency is fit to an exponentially damped sinusoidal, $A(t)$, according to:

$$A(t) = A_0 e^{t/\tau} \sin(2\pi f t + \alpha),$$

where $f = f_0 - f_R$. The dissipation parameter is given by

$$D = \frac{1}{\pi f \tau}$$

and is dimensionless, defined as

$$D = \frac{1}{Q} = \frac{E_{Dissipated}}{2\pi E_{Stored}},$$

with Q being the quality factor, $E_{dissipated}$ being the energy dissipated during one oscillatory cycle and E_{stored} being the energy stored in the oscillating system. This technology was commercialized by Q-Sense in 1996. Currently, there are two different versions of QCM-D instruments available from Q-Sense; a single channel version and a four channel version. Figure 1 depicts the main components of the QCM-D principle used with this instrumentation.

Resolution of frequency and dissipation in liquids is on the order of ± 0.1 Hz and 1 × 10^{-7}, respectively, with approximately one order of magnitude better in air or vacuum. Typical f and D responses for protein, vesicle, or cell

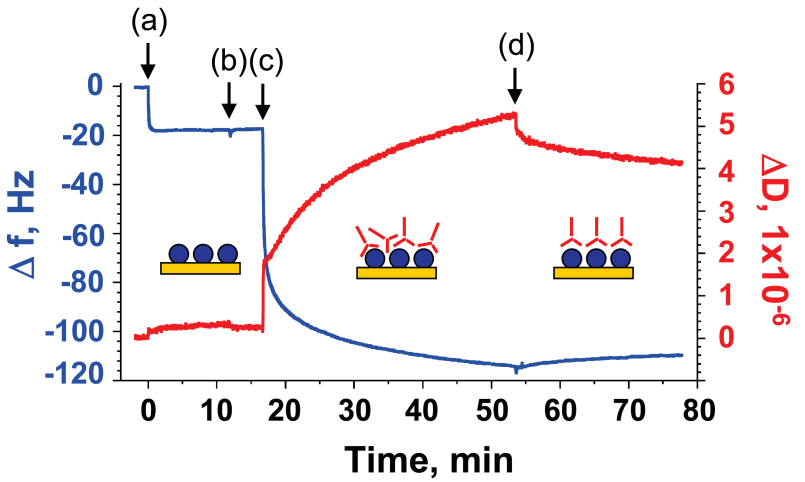

FIGURE 2

Example of raw data from a QCM-D experiment. This particular example demonstrates the adsorption of human serum albumin (**a**) and an antibody for human serum albumin (**c**). Steps **b** and **d** correspond to buffer rinses. Frequency changes (Δf) are shown in blue on the left axis and dissipation changes (ΔD) are shown in red on the right axis. Note the frequency change of step **a** and lack of dissipation change indicating the rigid characteristics of the human serum albumin film as it adsorbs on the surface. In contrast, the adsorption of the antibody at **c** gives a large frequency and dissipation change, indicating both mass adsorbed and increased viscoelastic characteristics due to the incorporation of water. Also, the rinsing step at **d** shows how a conformational change of the antibody can be detected as the physisorbed antibody molecules are rinsed away. For more information see reference 14.

adsorption are on the order of tens to hundreds of Hz and single to tens ($\times 10^{-6}$) of dissipation units. For viscoelastic films greater than 100-nm thick, these responses are typically an order of magnitude higher.

The QCM-D approach allows for probing f and D values at multiple harmonics (n = 3, 5, . . .) of a resonant frequency in succession on the millisecond time scale. The multiple harmonic data permits modeling the experimental data with theory to extract meaningful parameters such as mass, thickness, density, viscosity, or storage modulus.[10–13] The viscoelastic data allows broader characterization of systems that fall outside of the scope of the linear Sauerbrey relationship between Δf and Δm and makes QCM-D more than a simple mass balance. Additionally, associated solvent or water content of adsorbed films can be measured by comparing the mass measured using QCM-D with that of complementary techniques such as ellipsometry or surface plasmon resonance.[6]

APPLYING THE QCM-D TECHNIQUE TO BIOMOLECULAR STUDIES

In practical biomolecular applications the dissipation parameter and the subsequently extracted viscoelastic parameters are critical for many applications. In cellular adsorption applications, the simple QCM frequency and Sauerbrey relationship would greatly underestimate the adsorbed mass of cells, since the shear wave of the oscillating quartz is dampened out before even reaching the middle of the cell. The frequency penetration depth (in the z direction away from the sensor surface) depends on the material in question and typically is on the order of 250 nm in water[14] (rigid materials may strongly couple to the sensor surface and thus permit monitoring thicker films, but viscoelastic materials will be limited to within this range). When the adsorbed mass is viscous and sufficiently soft that it does not follow the sensor oscillation perfectly (such as in the case of cell adsorption), this leads to internal friction (due to the deformation) in the adlayer and thus to dissipation. This mass is the dynamic mass (incorporating associated water) and not the rest mass. The more viscous the adsorbate the more the oscillation will induce deformation, and thus the coupled mass will deviate more and more from the rest mass. Therefore, monitoring cell adsorption requires using the dissipation parameter to fully characterize the adsorption of a viscoelastic cellular structure. On the other hand, the adsorption of a small, rigid protein may be accurately measured by monitoring only frequency changes and fitting these to the Sauerbrey relation, although associated coupled water may again give an underestimation of the adsorbed mass. For an example of typical f and D data versus time for both a rigid protein and a viscoelastic protein that incorporates water, see Figure 2.[15] Generally speaking, as the size and structural flexibility of the adsorbed molecules increases the importance of measuring the dissipation also increases. Combined f

and *D* measurements along with the appropriate theory can provide a way to test for a linear relationship of the simple Sauerbrey model. Furthermore, by plotting Δf versus ΔD information about conformation of the adsorbed materials may be extracted and a so-called reaction fingerprint described (i.e., how the mass adsorbed changes, approximated by Δf, with the viscoelastic characteristics, approximated by ΔD). Also, by monitoring both Δf and ΔD it is possible to quantify and separate the viscoelastic variables relating to the shear viscosity and storage modulus of the adsorbed materials.

In addition to being able to measure both mass and viscoelastic properties of adsorbed films, one of the major advantages of QCM-D as an analytical technique is the flexibility in the choice of substrate. Essentially any material that can be evaporated or deposited within a sufficiently thin regime (~ nm to μm range) is capable of being coated on the QCM-D surface. This means that specialized surfaces may be prepared and monitored stepwise during preparation and that these same surfaces can be used as sensor platforms for studying further biomolecular interactions. This provides a huge development platform for biological-based studies. This review will illustrate a number of important, biologically relevant applications of the QCM-D ranging from DNA, the basic building blocks of life, to in vitro studies of living cells, which were described in 2007.

DNA

Recently, DNA studies using the QCM-D technology have featured a wide range of applications. This includes investigating the effects of ligands on estrogen transcription factors. In particular, the conformational effects of ligand binding on an estrogen receptor and DNA complex to elucidate details regarding the mechanism of how these receptors bind to specific gene sequences was monitored.[16] Also, the adsorption of linear and supercoiled plasmid DNA onto "natural organic matter" under a variety of salt conditions was measured in the context of better understanding DNA adsorption onto solid surfaces from aquatic and soil environments relevant to DNA sensors, gene delivery, DNA hybridization, and DNA–protein interactions.[17–19] Additionally, development of surface scaffolds using single- and double-stranded DNA surfaces for potential array applications was carried out.[20] DNA itself was also used as a tool to investigate other biologically relevant areas such as being a tag for phospholipid vesicles to determine binding dynamics in the context of coagulation studies[21] and using complementary strands to build up 3-D networks of proteoliposomes to study membrane proteins.[22]

PROTEINS

Protein adsorption to biomaterial surfaces often plays a role in biocompatibility and can affect whether adverse effects are triggered by the biomaterial leading ultimately to the body rejecting the implant. One of the major applications of the QCM-D is to measure the amount of protein adsorbed onto different surfaces to determine if a material resists or promotes protein adsorption. This initial protein adsorption step can later mediate the cellular response. Therefore, adsorption of extracellular matrix proteins that can promote cell attachment, and subsequent compliance of the biomaterial are very important areas of consideration. Fibronectin, an extracellular matrix protein, was adsorbed onto layer-by-layer polymer films in the context of developing new biomaterial coatings and then used for subsequent cell spreading measurements.[23] In this case[24] fibronectin was precoated onto the surface and then the subsequent interaction with proteins from saliva was measured in the context of tissue integration for dental biomaterials. Adsorption of laminin, another cell adhesive protein, was adsorbed onto surfaces with varying surface chemistries in the context of biomaterial development, drug delivery and diagnostics.[25] Collagen, an additional extracellular matrix protein, adsorption was also measured on different polyester surfaces that were hydrolyzed.[26] Three studies looked at the blood plasma protein bovine serum albumin (BSA) and additional serum proteins from fetal calf serum in the context of promoting cellular adhesion onto either biodegradable 3-D polycarbonate scaffolds,[27] polystyrene- and UV-exposed polystyrene,[28] or in the context of resisting cellular adhesion onto polyethylene glycol coatings on nanostructured SiO_2 surfaces.[29] Ion beam modifications were made to polymer surfaces such that adsorption characteristics of various proteins found in a common cell incubation medium either inhibited or enhanced cell colonization.[30] In this case[31] cellulose film properties were modified with a peptide to promote protein adsorption from a cell culture medium for adhesion and proliferation of endothelial cells. Protein coatings of BSA and mucin were tested to determine the effectiveness as a protective overcoat for biomaterials in terms of preventing unwanted interactions, but also promoting cellular adhesion.[32] Biomaterial coatings for anti-inflammatory activity were developed using an embedded protein in a layer-by-layer architecture that allowed the protein to keep its activity.[33]

On the other hand, unwanted protein adsorption, such as that responsible for blood clotting in stents, must be reduced so that biomaterials do not induce clotting. Secondary screening of polymeric biomaterial candidates for fibrinogen adsorption (a protein involved in blood

clotting) was carried out to determine which material had the lowest amount adsorbed and was therefore the best candidate for potential blood contacting medical devices.[34] A similar study[35] measured fibrinogen adsorption onto surfaces coated with heparin using a varied spacer length in order to determine the biological performance of these coatings.

A wide variety of properties related to biosensor development by QCM-D were investigated in 2007. When developing microelectrode arrays for neuronal network investigation, cell coupling to the array surface is very important, and neurite promoting proteins govern this interface and, therefore, were thoroughly characterized in this study.[36] Developing magnetic-based labeling material for biosensors of a specific serum protein was accomplished using magnetic particles and assay performance was analyzed by QCM-D and optical microscopy.[37] Surface development of polyethylene oxide modified surfaces and their protein resistance was shown by QCM-D for potential use in nanostructured biosensors.[38] Adsorption of lactoferrin onto polyacrylic acid surfaces was measured in the context of developing potential biosensor surfaces and a new theory to interpret data for inhomogeneous protein layers.[39] A new approach for immobilizing transmembrane proteins onto surfaces for potential surface biosensor development using a proteoliposome multilayer structure was described.[22] Similarly, these examples[40,41] demonstrate a way to selectively orient a membrane protein onto a functional membrane. Bioassay development typically requires understanding the physical processes associated between the analyte to be sensed and the sensor itself and was why Au nanoparticle–protein interactions were characterized in this application.[42] Also, antibody–antigen interactions in the context of potential diagnostic autoimmune assays were studied with QCM-D in this example.[43]

Fundamental studies of protein adsorption phenomena in order to better understand protein–surface interactions was another area with numerous publications. Here, adsorption of R-lactalbumin (types I and III), BSA, hemoglobin, myoglobin, cytochrome c, R-casein, and lysozyme onto model anionic citrate surfaces as a function of salt, pH, solvent, and surface conditions was studied.[44] Fundamental investigation of the surface activity of hydrophobins versus solution phase hydrophobins was performed.[45] Formation of layer-by-layer structures using proteins both as a building block of the architecture and then later as an adsorbate was measured.[46] For the first time, amyloid fibrillation formation was monitored in real-time leading to realistic models for development of amyloid plaque formation in vitro.[47] Fouling of membrane filters for the purification of whey proteins was studied by testing the adsorption characteristics of the most common whey proteins, β-lactoglobulin, onto the most common filter material, polyethersulfone.[48] Besides just looking at fundamental adsorption processes of proteins, conformational changes of adsorbed proteins can be studied after formation including processes such as swelling and hydration.[49]

Small molecule–protein interactions were measured by QCM-D in a number of different studies. In this example,[16] QCM-D was used to elucidate the details about how estrogen receptors can play a role in differentially regulating genes by examining the conformation of estrogen receptor–DNA complexes. Other studies examined polyphenol adsorption from different components in tea to BSA surfaces in the context of better understanding thearubigin–protein interactions[50] and (-)-epigallocatechin gallate–protein interactions.[51] Protein-polysaccharide interactions (important due to their implications to many biological processes) are another area that was studied by QCM-D; specifically, details about the interaction between the polysaccharide pectin and BSA at varying ionic strengths were investigated.[52]

There has been renewed interest in enzymatic surfaces since the surfaces often have benefits over enzymes in solution, and there have been recent developments in coating procedures for enzyme immobilization and entrapment. Often new advances in technology allow revisiting old problems and such was the case in the development of enzymatic surfaces prepared using layer-by-layer assembly and the activity measurement of these surfaces.[53] A different study[54] measured the adsorption and activity of lipase onto hydrophobic and hydrophilic surfaces.

LIPIDS

The majority of QCM-D applications relating to phospholipids in 2007 describe forming supported lipid bilayers (SLBs) and using these scaffolds to investigate additional systems of interest. This arises since QCM-D offers a unique fingerprint detection for SLBs by sensing trapped water inside intact lipid vesicles when they adsorb on the surface, and then when they rupture to form bilayers the dissipation decreases, indicating loss of water and formation of a rigid structure.[55] Formation of SLBs onto new substrates including TiO_2 and Au has the potential to increase the applications of the technology to surfaces that we have previously been unable to study.[56] In this example,[57] a novel coating was created on a SLB by hyaluronan immobilization to form a model system of a glycoconjugate cell coat. A 3-D scaffold of proteoliposomes for investigating transmembrane proteins was built upon an SLB in this study.[22] Here,[40,41] an SLB was

used to reconstitute a membrane protein and then create a platform for subsequent binding of this protein with a constituent in an efflux pump. Further studies[58] probed the reactivity of SLBs with fatty acids to learn more about the underlying processes of cell membrane associated functions. The simplicity, ease of preparation, and current knowledge about SLBs has led to their use in better understanding of theoretical models for interpreting QCM-D data.[59] Lateral mobility phenomena within an SLB has been studied by peptide inhibition[60] and by using an anchored polymer film/SLB architecture.[61] SLBs have also been used as scaffolds to investigate bilirubin–model cell membrane interactions in the context of learning more about the adsorption mechanism for preventing diseases such as jaundice or kernicterus.[62] An exception to using the SLB form of the lipid is the previously mentioned example of using a lipid vesicle in combination with cholesterol–DNA for binding dynamics measurements.[21]

CELLS

Often the adsorption characteristics of a particular type of cell on a surface are measured in order to better understand the underlying mechanisms of cellular adhesion. With QCM-D, there is the ability to monitor the stepwise development of a biological platform and then to directly monitor the adsorption of cells onto these surfaces. Such was the case when studying fibronectin adsorption and the subsequent adsorption of human umbilical vein endothelial cells.[23] A similar approach was taken to monitor in situ living cell attachment and growth of biofilms.[63]

The majority of cellular applications using QCM-D relate to developing coating architectures for subsequent cellular adsorption studies and then using traditional methods such as assays or fluorescence imaging to monitor the actual cell adsorption process. These applications typically involve building up a bioactive surface consisting of either a bioactive material or a protein layer. In this example,[33] QCM-D was used to test the buildup of bioactive polyelectrolyte multilayer coatings, and subsequent cell adsorption was measured by an ELISA assay. Fibroblast adsorption was studied using standard assay procedures on surfaces prepared by layer-by-layer deposition of hyaluronan, whose buildup was monitored by QCM-D.[64] Heparin-based biosensor coatings for detecting $CD4^+$ T-lymphocytes (the biological marker for determining the clinical stage of HIV infection) were characterized by QCM-D, while cell detection was monitored by fluorescence.[65] Also, supported lipid bilayers that were previously mentioned[61] have been developed for cellular-based adsorption that in turn was monitored by optical microscopy.

Building up intermediate protein architectures for the specific purpose of cell attachment is often measured, since proteins can mediate the cellular response. Implant materials have garnered much attention recently and QCM-D can help to test the biomaterial's response to typical physiological conditions. In this example,[24] keratinocyte and platelet adhesion were measured by scanning electron microscopy and immunological assays after QCM-D were used to probe the adsorption of pellicle proteins. To avoid rejection of biomaterials by the body, cell adhesion must be promoted, and in this particular application hydrolysis of polyester polymers was carried out to promote collagen adsorption and subsequent cell attachment with cellular adsorption monitored by a standard assay.[26] Understanding serum protein adsorption onto polymer or modified polymer surfaces with the underlying assumption that these proteins will drastically influence cellular adhesion was measured in these studies.[27–30] Protein adsorption in the context of promoting endothelial cell attachment was studied while the actual cell adsorption was measured by confocal fluorescence microscopy.[31] In this study,[36] after neuron-promoting protein adsorption was monitored by QCM-D, neuron adsorption was probed by scanning electron microscopy and transmission electron microscopy.

CONCLUSION

This review outlined the background principles of QCM-D and highlighted recent applications regarding DNA, proteins, lipids, and cells published in 2007. It showed that the technology has reached a point where commercially available instruments exist as well as associated theoretical models required for interpreting data in terms of meaningful physical parameters such as mass, thickness, density, viscosity, or storage modulus. These achievements, plus the various publications using the instrument, of which only a small number are described in this text, help lay the groundwork for the QCM-D technology transitioning into a standardized approach for addressing questions about biological materials and their interactions.

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