Special Article

Quartz Crystal Microbalance Biosensors: Prospects for Point-of-Care Diagnostics

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Background: *A QCM is a label-free and extremely mass-sensitive device, which allows the detection of the binding event between trace medical analytes and bio-receptors on its surface. QCM, the most promising type of biosensors, has attracted much interest due to the inherent benefits over other transducers, including better sensitivity, ease-of-use, integration with compact analytical devices, and economy, and also involving relatively simple technology in its production. Thus, they have great potential with regard to point-of-care (POC) testing for early detection of diseases.*

Material and Method: *Retrievable articles that related to acoustic type sensing of Pubmed and Science direct database were included. Additionally, abstracts presented at Biosensor World Congress held between 2008 and 2012 were searching to identify relevant clinical trials.*

Results: *All studies demonstrated the opportunity in the use of QCM as a novel diagnostic method. Several attempts have been made to construct integrated systems that show promising application for POC tests.*

Conclusion: *This review represents another step to meet challenges, especially in the improved minimization and sensitivity of biosensors. As this work continues, new bioreceptor and biomarkers emerging from the could make it an ideal candidate for cheap POC diagnostic.*

Keywords: *Quartz crystal microbalance, Biosensor, Point-of-care testing*

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Biosensors are analytical devices, which convert biological responses into measurable signals. They consist of two main components: a bio-receptor, which recognizes the target, and a transducer, which converts this recognition into an electrical signal (Fig. 1). Biosensors can be classified by their bio-receptor or transducer type (Fig. 2). There is a large variety of biosensor types; this review focuses on the use of mass-sensitive transducers as promising biosensors.

Mass-sensitive biosensors are suitable for very sensitive detection in which the transduction is based on small changes in mass[1]. The principal means of mass analysis depends on the use of piezoelectric crystals that can be made to vibrate at specific frequencies. The frequency of oscillation of the crystals is therefore dependent on the electricity applied to the crystals. When the mass increases due to the binding between the bio-receptor and target, the frequency of oscillation of the crystals changes and can be

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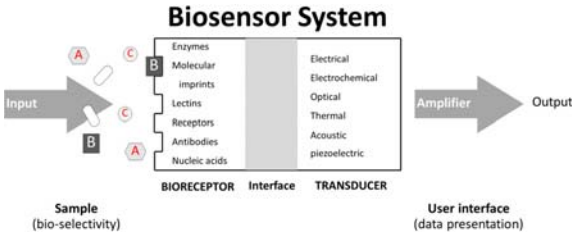

Fig. 1 The basic configuration of biosensor.

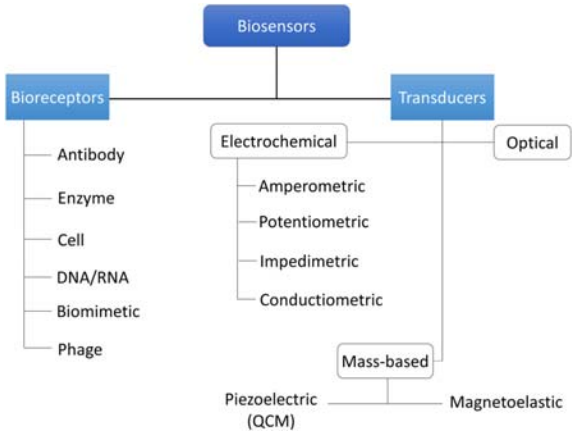

Fig. 2 Classification of different biosensor based on their elements.

measured. The two main types of mass-based sensors are (1) quartz crystal microbalance (QCM) and (2) surface acoustic wave (SAW). QCM-based detection is relatively easy to use, cost-effective, and offers direct label-free analysis with increased sensitivity and specificity.

Basic principle of quartz crystal microbalance

Basically, a QCM disc is covered by a metallic deposit on the top and bottom sides (Fig. 3A and 3B). A QCM disc is coupled to an oscillating circuit that applies an alternating electrical field to the crystals with the purpose of inducing an oscillation in the center of the piezoelectric crystals. The application of electrical potential induces change in the QCM oscillation frequency and is directly monitored by the frequency counter. As a result, a displacement of the crystal atoms parallel to the surface occurs. Sauerbrey[2] was the first who recognized the potential usefulness of the QCM technology and demonstrated the relationship between mass and resonant frequency. The change in frequency (Δf) resulting from added mass (Δm) is described as follows:

$$\Delta f = -2.3 \times 10^6 f_0 \frac{\Delta m}{A}$$

In this way, a reduction in oscillating frequency (Δf) occurs if a material is deposited on the surface of the crystal resulting in a decrease in its oscillating frequency (where f_0: original oscillation frequency, A: area covered by electrode on the QCM surface). When the QCM surface is coated with a bio-receptor, such as a DNA probe or antibody, the binding event results in an increase of crystal mass (Δm) and a proportionate decrease in frequency oscillation (Fig. 3C).

Quartz crystal microbalance and its clinical advantages

The number of research articles and reviews that involve QCM in the analysis of biological systems continues to increase each year, with a near-linear growth. QCM-based biosensors have been shown to be potential and efficient tools for clinical diagnosis that makes them promising candidates for POC applications. A QCM is an extremely sensitive mass sensor, capable of measuring sub-nanogram levels by detecting changes in the frequency of a quartz crystal. This review evaluates QCM applications concerned with medically related topics such as bacteria, viruses, and tumor biomarkers, and highlights the versatility of QCM in the detection of a wide range of analytes with diverse biological targets. The developing trend of QCM applications in POC testing is also discussed.

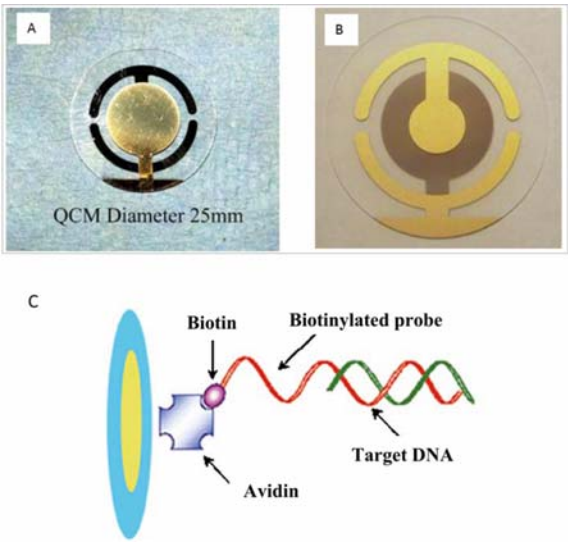

Fig. 3 Photograph of a typical QCM: (A) Front or contact side; (B) back or electrode side; (C) basic concept for a QCM-DNA biosensor[26].

Bacteria

Several papers revealed the detection of bacteria by QCM was achieved using either antibody binding (immunosensor) or novel methods. Table 1 lists the comparison of the limit of detection (LOD) for medical analytes detection obtained by various QCM techniques. The live pathogenic bacteria *Escherichia coli* were successfully detected using antibodies immobilized on a long chain organo-silicon self-assembled monolayer[3]. In addition to antibody binding, *E. coli* was also detected on imprinted oil polystyrene coated crystals[4]. Compared to the culture method as gold standard, sensitivity and specificity of this sensor were 96.4% and 99.2%, respectively. Besides *E. coli* detection, a clinical QCM application was demonstrated by the detection of volatile organic compounds from six different pathogenic bacteria in the exhaled breath of a patient using an electronic nose system where the patient had an infection due to a single bacterial species. The successful classification rate was 98%[5].

In an immunosensor which has been used to detect *Mycobacterium tuberculosis* (MTB), a QCM was constructed by using a multi-channel series piezoelectric quartz crystal (MSPQC) sensor system[6]. The silver-coated oscillator played a key role in detection and it was sensitive to changes in frequency.

Table 1. Limit of detection in measuring biological analytes using QCM sensor compared with their reference methods

Target	Disease	Assay principle	LOD of QCM sensor	LOD of reference method	References
E. coli (O157:H7)	enteropathogen	Immunosensor	10^3 CFU/mL	10^4 CFU/mL[a]	Kim et al[36]
		DNA sensor: gold nanoparticle amplification	2.6x10^2 CFU/mL		Mao et al[37]
		DNA sensor: gold nanoparticle amplification	2.0x10^3 CFU/mL		Wang et al[38]
MTB bacilli	Tuberculosis	Volatile metabolic product QCM sensor	10 CFU/mL	10^3 CFU/mL[b]	Ren et al[6]
HCV	Hepatitis C	DNA sensor: biotinylated DNA probe	38 IU/mL	50 IU/mL[c]	Skladal et al[14]
HPV-16	Cervical cancer	DNA sensor: DNA probe	250 copies/mL	600 copies/mL[d]	Dell'Atti et al[15]
HPV-58	Cervical cancer	DNA sensor: isothermal amplification with DNA probe	100 copies/mL	600 copies/mL[d]	Prakrankamanant et al[17]
DENV	Dengue fever	Immunosensor: anti-Dengue antigen	0.05 mg/mL	5 mg/mL[e]	Su et al[19]
CEA	Colon cancer	Immunosensor: His-tagged antibody	0.1 mg/mL	1.6 mg/mL[f]	Shen and Lu[23]

[a]multiplex-PCR, [b]culture technique, [c]Cobas HCV amplicor, [d]Cobas 4800 system, [e]sandwich ELISA, [f]chemiluminescence
MTB = Mycobacterium tuberculosis; HCV = hepatitis C virus; HPV = human papillomavirus; DENV = dengue virus; CEA = carcinoembryonic antigen

The system was designed to detect volatile metabolic products such as NH_3 and CO_2 produced as a result of MTB growth. This assay had a wide linearity range from 10^2 to 10^7 CFU/mL and a detection limit of 10 CFU/mL. Also in food-borne poisoning, Lui et al[7] recently developed a 2D molecularly imprinted film-coated QCM by in situ immobilization using sol-gel imprinting for the rapid detection of staphylococcal endotoxins. By using this film as the bio-receptor material, a novel QCM sensor with short response time, wide linearity, low cost, and relatively high selectivity was developed and compared with previous works[8-11]. Reports of reusable QCM-based sensors for detection staphylococcal enterotoxin A were established[12]. There were similar reports of endotoxin detection using QCM with a lower limit of detection of 0.01 pg/mL[13].

Viruses

Rapid detection of viruses has important implications for medical healthcare. Current methods for virus identification and quantification are time-consuming and often expensive. Therefore, demand for sensitive and accurate viral biosensors with rapid detection systems is increasing. QCM is well established as a fast and sensitive method for virus detection. Skladal et al[14] reported the use of QCM to detect HCV virus DNA in serum using biotinylated DNA probes, immobilizing onto a biotin-tagged QCM surface. Meanwhile, Dell'Atti et al[15] detected HPV using QCM in combination with a PCR product, again using a DNA probe. Work was also conducted by Yao et al[16] which detected HBV genomic DNA using peptide nucleic acids specific to HBV immobilized on the biosensor with a detection limit of 8.6 pg/L. A recent study by Prakrankamanant et al demonstrated the novel integration of QCM for HPV-58 detection with 10 times greater sensitivity than the nested-PCR and conventional LAMP methods[17]. Modification of the QCM sensor with single-wall carbon nanotubes with conjugated antibody allowed the detection of Cymbidium mosaic potexvirus[18]. The sensor was used to quantify the potexvirus particles. In dengue QCM biosensors, multi-antibody coating allows the capture of several different antigens, which increase the overall mass and the detection signal. This exhibited 100-fold higher sensitivity than conventional EIA in a short response time (30-60 min)[19]. In another work, instead of conventional antibody immobilization on QCM surface for antigen detection, a thin film of molecularly imprinted polymers (MIPs) specific of the dengue viral NS1 protein was formed by polymerization of monomers

onto a QCM chip surface[20]. In this work, the researchers claimed the first application of MIPs for early clinical diagnosis of dengue-infected biological samples. More recently, QCM geno-sensor for detection of DENV2 oligonucleotide sequence obtained by RT-PCR was developed through specific hybridization with the complementary oligonucleotide[21].

Tumor biomarkers

Cancer is a life-threatening disease and its early detection is a challenging goal. New and emerging molecular methods are being used to study the disease and these are resulting in a better understanding as well as the discovery of potential biomarkers. Analysis based on POC devices are needed to overcome the challenges in cancer diagnosis. In clinical applications, a number of papers regarding QCM that related to cancer were published and developments in almost all of them were based on immunosensors in which the specific antibody is immobilized on the sensor chip. Cancer biomarkers were detected using His-tagged antibody fragments that were immobilized on a nickel nano-particle before deposition on the quartz surface[22]. Antibodies were immobilized on a mixed self-assembled monolayer containing cysteamine and 6-mercapto-1-hexanol with glutaraldehyde cross-linking in an attempt to reduce non-specific adsorption and detect a carcino-embryonic antigen (CEA) in a QCM immunosensor[23]. The detection of glycolytic enzyme, α-enolase, (up-regulated in pancreatic ductal carcinoma), was successfully setup by a QCM sensor. The results of the experiment could be applied to the development of specific protocols for detecting tumor biomarkers with non-labeled biosensors[24]. QCM-based biosensors are also suitable for p53 point mutation detection of lung cancer using DNA hybridization on gold QCM electrodes[25]. These platforms show the very high sensitivity and specificity in serum samples. Apart from genetic alternation cancers, epigenetic changes, which affect gene expression without altering DNA sequences, were also demonstrated by QCM sensor. Aberrant cytosine methylation, the most common epigenetic modification, of p16 tumor suppressor gene was evaluated in clinical cholangiocarcinoma tissues by using gold electrode QCM sensors. It was able to differentially diagnose between the methylation and unmethylation statuses of p16 gene, presenting a promising molecular screening point-of-care with sensitive, specific, accurate, and cost-effective testing[26]. Uludag and Tothill[27] demonstrated the high sensitivity for PSA with LOD of 0.29 ng/mL by performing a sandwich assay using antibody-modified nano-particles in QCM platforms. This platform exhibited higher sensitivity compared to 4.0 ng/mL of the gold standard method[28]. The clinical applicability of the developed immunoassay can be applied to patients' serum samples, revealing the high potential for prostate cancer diagnosis and prognosis.

Future perspectives

Integrations

To date, QCM has become one of the most promising types of non-labeling biosensors in terms of sensitivity and fast assay. The principle of detection is monitored by frequency changes of the quartz vibration caused by specific DNA biding or DNA hybridization on the QCM surface. Unfortunately, piezoelectric biosensors cannot be directly used with a target amplification technique, such as PCR, because dramatic changes in temperature and solution viscosity create an unstable signal. To address this pitfall, loop-mediated isothermal amplification (LAMP) was successfully combined with QCM (so called LAMP-QCM). The LAMP-QCM assay comprised the frequency counter, a temperature control device, and housing of the quartz crystal was setup as shown in Fig. 4. The developed prototype reduced analysis time with good diagnostic performance and improved the positive rate of HPV-58 detection. There is potential for real-time quantitative assay applicable to a variety of interested targets[17].

Beside the target amplification as discussed above, future research also looks to the use of nano-particles and novel nano-materials for alternate signal amplification. Nano-technology offers many great advantages for pathogen detection. The use of nano-particles as labels in combination with current detection

Fig. 4 In-house temperature control box with QCM detection system. The QCM sensor was inserted into the flow cell inside the temperature control box and connected with the frequency counter[17].

technologies led to improvement in sensitivity and multiplex capabilities[29-33]. Chen et al[34] reported that amplification of the detection signal is achieved through interconnected oligonucleotide-attached gold nanoparticles (AuNPs) hybridized on a stepwise, layer-by-layer process with the gold surface-grafted oligonucleotide duplex. Since each primary binding event is amplified through successive hybridization events between complementary oligonucleotides (probe and target), not only the detection sensitivity but also the specificity are greatly increased. This QCM was able to detect DENV2-specific RNA plaque titers as low as 2 PFU/mL and exhibited a linear concentration range up to $2x10^6$ PFU/mL. Salam et al[35] also demonstrated the application of QCM developed with goldnano-particles for the detection of contamination of *Salmonellas* spp. in raw and processed foods. The performance of this sensor gave the highest sensitivity with a limit of detection of about 10-20 CFU/mL compared to direct and sandwich assay ($1.83x10^2$ CFU/mL and $1.01x10^2$ CFU/mL, respectively) which demonstrates the potential of technology for rapid and sensitive microbial analysis. Additionally, the method is label-free and does not require expensive equipment, valuable features for in-the-field applications.

Moving quartz crystal microbalance to point-of-care testing

POC testing is diagnostic assessment performed on site that might significantly improve healthcare and healthcare delivery. As discussed above, POC testing may permit rapid and less costly diagnosis. At present, QCM-based POC testing for various diseases is being practiced in clinical settings of developed countries where current clinical diagnostic systems are relatively complex and expensive. Integrated devices with sample preparation and detection in a robust, cheaper, and user-friendly manner remain challenging. Various types of QCM-based POC diagnostic tools against several diseases are listed in Table 2.

When using POC in real clinical diagnosis, QCM has to overcome several challenges. One of these is multiplex or multi-parametric analysis, as most diseases have more than one marker associated with their incidence. Another challenge is system integration that eventually realizes the POC diagnostic with a hand-held analyzer. Until now, most research efforts have focused on the methodology rather than the application of QCM, and more and more researchers show concern for fabrication of QCM-based POC systems.

Table 2. QCM-based POC testing in the clinical diagnostic of various diseases

Disease	Target	Assay principle	LOD	References
Lung cancer	TP53	DNA sensor: DNA probe	2 mM	Altintas and Tothil[39]
Burkitt's lymphoma	EBNA-1	DNA sensor: signal amplification	50 ng/mL	Garai-Ibabe et al[40]
Cervical cancer	HPV	DNA sensor: direct detection	1.21 pg/L	Wang et al[41]
Tuberculosis	IFN-g	DNA sensor: DNA aptamer	1-10 pM depending on buffer	Min et al[42]
	IS6110 gene	DNA sensor: DNA probe	10 fM	Kaewphinit et al[43]
	Whole bacilli	Immunosensor	10^5 CFU/mL	He and Zhang[44]
Coagulation disorder	Platelet aggregation	Electrochemical QCM	N.A.	Sinn et al[45]

TP53: tumor protein p53, EBNA-1: Epstein-Barr nuclear antigen 1, N.A.: not addressed

Thus, experts in the field of microelectronic systems are encouraged to participate. It can be expected that POC systems are going to speed up diagnosis of disease and make analytical results readily available at the patient's bedside or in the physician's office.

At this time, there is growth in the industry with some commercial products available on the market (Table 3). Commercial biosensors principally address two key markets. The first is scientific research in which sensors are used to study biological interactions and surface characterization. The second is in detection systems for medical POC applications and chemical detections.

Conclusion

This article represents a step in meeting a number of challenges, especially in the improved minimization and sensitivity of biosensors, and in the development of an integrated instrument. As this work continues, new bio-receptors and biomarkers emerging from laboratories could make them ideal candidates for cheap POC diagnostics.

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Potential conflicts of interest

None.

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Table 3. Commercially available QCM biosensors on the market

Manufacturer	Website	Model	Application
ANT Technology	www.anttech.com.tw	ADS Plus ANTQ300PSS	Life sciences
Attana	www.attana.com	CellA100CellA200	Life sciences
Bioscale	www.bioscale.com	ViBE Bio Analyzer ViBE workstation	Diagnostics, Biomarker
CH Instruments	www.chinstruments.com	400B	Materials & life sciences
Q-sense	www.qsense.com	Q-Sense E4 AutoQ-Sense E4Q-Sense E1	Materials & life sciences
Resonant Probes GmbH	www.resonant-probes.de	IQCM	Materials & life sciences
Sierra Sensors	www.sierrasensors.com	QCMA-1	Life sciences

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Quartz Crystal Microbalance: การพัฒนาเพื่อมุ่งสู่การวินิจฉัยแบบ Point-of-care Testing

ปรีดา ปราการกมานันท์

ภูมิหลัง: *Quartz crystal microbalance (QCM) เป็นระบบไบโอเซนเซอร์ที่มีความไวในการตรวจจับการเปลี่ยนแปลง ของมวลบนพื้นผิวที่เกิดจากการจับกันระหว่างสารชีวโมเลกุลจับไบโอรีเซปเตอร์โดยไม่จำเป็นต้องมีกระบวนการติดฉลาก ในขั้นตอนการตรวจสามารถตรวจวัดแม้มีปริมาณสารเล็กน้อย ปัจจุบัน QCM เป็นระบบไบโอเซนเซอร์ชนิดหนึ่ง ซึ่งได้รับความสนใจจากนักวิจัยอย่างแพร่หลาย เนื่องจากเป็นระบบที่มีความไวสูง ขั้นตอนการเตรียมไม่ยุ่งยากและมีแนวโน้มที่จะสามารถลดระดับขนาดของเครื่องมือให้เล็กลงได้ หากมีการผลิตเป็นปริมาณมากก็จะมีต้นทุนการผลิตที่ถูกลง*

วัสดุและวิธีการ: *ทำการสืบค้นวารสารจากฐานข้อมูล Pubmed และ Sciencedirect ที่เกี่ยวข้องกับการประยุกต์ใช้ QCM ในระบบ acoustic sensing นอกจากนี้ยังได้สืบค้นจากบทคัดย่อที่นำเสนอในงาน Biosensor World Congress ในช่วงปี พ.ศ. 2551-2555 เพื่อดูถึงแนวทางการนำ QCM ไปใช้ในงานการตรวจทางคลินิก*

ผลการศึกษา: *ในทุกการศึกษาแสดงให้เห็นชัดเจนถึงโอกาสในการพัฒนาเพื่อนำ QCM ไปใช้เป็นวิธีการตรวจวัดใหม่ที่มีความไวและหลายการศึกษาได้แสดงการพยายามลดขนาดเครื่องมือเพื่อมุ่งไปสู่การตรวจ ณ จุดผู้ป่วย (point-of-care testing)*

สรุป: *ในหลายการทดลองได้แสดงให้ถึงการพยายามที่จะพัฒนา QCM เพื่อตอบโจทย์การใช้งานจริงทางคลินิก โดยเฉพาะการเพิ่มความไวและลดขนาดของตัวเซนเซอร์ โดยงานวิจัยจากทางห้องปฏิบัติการถือได้ว่าเป็นส่วนผลักดันให้มีการพัฒนาเพื่อใช้ QCM ในเชิง point-of-care testing ต่อไป*