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Precise detection of single particles and bio-sensing applications on quartz crystal microbalance using non-linear resonance behavior

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Abstract
Ultrasensitive mass detection is essential across various fields, including environmental monitoring, biosensing, and medical diagnostics. Quartz crystal microbalance (QCM) and nanoelectromechanical system (NEMS) sensors are widely utilized, yet NEMS approaches are hindered by issues of stability and reproducibility, whereas QCMs face fundamental physical limitations in enhancing sensitivity. To address the limitations of current sensing technologies, we demonstrate that increasing the driving force applied to the QCM induces non-linear resonance, and that utilizing the abrupt amplitude drop occurring at this non-linear resonance enables mass detection down to 100 fg. Unlike conventional linear QCM operation, our method significantly enhances mass sensitivity by exploiting amplitude-drop behavior in the non-linear regime, without requiring additional surface functionalization or device modification. We validated this sensing strategy through the detection of micro/nanoparticles and protein-antibody interactions, successfully achieving single micro/nanoparticle detection and reaching a detection limit of 100 fg. Notably, this method enables reliable single micro/nanoparticle detection with high reproducibility. This sensing approach provides a simple yet powerful platform that overcomes key limitations of traditional QCM systems. With the potential for real-time biomolecular diagnostics in aqueous environments and future integration with microfluidic chips, our approach represents a promising strategy for ultra-sensitive mass detection.

Coupling between electrical and mechanical degrees of freedom enables the precise measurement of physical quantities and has led to the development of various sensor technologies that transduce mechanical responses into electrical signals. Such coupling has been applied to mass detection, leading to the development of microelectromechanical systems (MEMS)-, nanoelectromechanical (NEMS)-based mass sensors[1–4] and piezoelectric mass sensors[5,6]. Among these technologies, recent advances in NEMS based on two-dimensional (2D) materials such as graphene, MoS_2, and carbon nanotubes (CNTs) have demonstrated ultra-high mass sensitivity in the attogram (ag) to yoctogram (yg) range. For instance, Ekinci et al.[2] reported a silicon carbide (SiC)-based resonator achieving a sensitivity of 2.53 ag, while Chaste et al.[3] demonstrated 1.7 yg sensitivity using a CNT resonator. However, despite their exceptional performance, these NEMS sensors face limitations in practical applications due to their mass loading position dependency, environmental instability, and poor reproducibility. On the other hand, quartz crystal microbalance (QCM), which leverages the piezoelectric effect of quartz crystals, has been widely employed as a representative mass sensor capable of detecting minute mass variations by correlating applied voltage-induced mechanical oscillation with mass change. QCMs are known for their scalability, consistent performance, and environmental robustness, and are commonly used in industrial applications such as monitoring gold film thickness in physical vapor deposition[7], air pollution level[8,9] and biomolecular interactions[10–12]. Conventional QCMs typically offer mass sensitivity in the

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Table 1 Comparison of our non-linear amplitude-drop mass sensor with previously reported resonant sensing approaches

Reference	Sensor type	Key mechanism	Limit of detection/ sensitivity	Linear/non-linear regime	Surface treatment
Yao et al.[38]	High-Q QCM	GO film → high stiffness → suppress damping → high Q-factor	Humidity sensing, not optimized for mass	Linear regime	QCM/GO film (graphene oxide)
Chen et al.[39]	Ultra-high-Q QCM	Resonance $f_0\uparrow$ → High sensitivity	5.33×10^{17} Hz/kg	Linear regime	Quartz inverted-mesa/no coating (bare)
Kumar et al.[40]	Micro-cantilever	Saddle-node bifurcation: Amplitude jump caused by collapse of upper stable branch	Proof-of-concept	Non-linear regime	Silicon cantilever/Poly-4-vinylpyridine functionalization
Qiao et al.[41]	Coupled MEMS	1:3 internal resonance: mode-ratio-instability-induced unlocking jump	0.137 fC	Non-linear regime	MEMS coupled beams/no mass film
Li et al.[42]	Dual micro-resonator	1:1 internal resonance: mode-coupling-induced amplitude jump	Proof-of-concept	Non-linear regime	Dual MEMS beam/no coating
Our study	Commercial QCM	Abrupt amplitude drop	~100 fg	Non-linear regime	QCM/no coating

nanogram range, which limits their ability to detect mass changes at lower mass scales. To overcome this sensitivity limitation, various strategies have been explored[13–16], such as surface functionalization[12,17], molecular recognition layers[18,19], and nanomaterial integration[20], which aim to enhance effective mass sensitivity. However, these approaches often involve complex fabrication processes, high-cost bio/functional materials, and limitations in long-term stability and reproducibility. Therefore, a new approach utilizing the intrinsic dynamic properties of the sensor is highly desirable. As a promising alternative, the use of non-linear resonance characteristics has been investigated. By increasing the driving force applied to a resonator, non-linear oscillation regimes can be induced, leading to abrupt changes in mechanical resonance behavior, which can improve both sensitivity and resolution. In particular, non-linear resonators can exhibit amplitude drop responses under specific conditions. Although previous studies have not directly exploited abrupt amplitude-drop phenomena, several have demonstrated that non-linear dynamic features can significantly improve sensing performance. For example, Buks and Yurke[21] theoretically demonstrated that the steep response slope in the non-linear regime of a Duffing resonator can surpass the thermodynamic noise limit of conventional sensors. Venstra et al.[22] applied the bistability-induced bit-switching behavior of a micro-cantilever to mass sensing applications. Zhao et al.[23] experimentally verified that a compressed bistable resonator structure can achieve more than three times the sensitivity of its linear counterpart. QCM is particularly promising for non-linear resonance-based mass sensing due to its inherent robustness, reusability, and scalability. Incorporating non-linear resonance mechanisms into QCMs enables the development of next-generation mass sensors with both high sensitivity and practical applicability. While previous studies on non-linear resonators have demonstrated the potential of non-linear dynamics to enhance sensing performance, the explicit exploitation of abrupt amplitude-drop phenomena in QCM-based practical mass sensing remains largely unexplored. Compared to prior high-Q or bifurcation-based resonant mass sensors, our approach offers practical advantages. High-Q QCM sensors require special quartz geometries or additional fabrication steps to enhance the quality factor, while bifurcation-based mass sensing has mainly been explored at the theoretical or proof-of-concept level, and practical demonstrations remain relatively limited. In contrast, our method achieves sensitivity enhancement simply by increasing the drive amplitude without any surface functionalization or structural modification. A comparative summary of these differences is provided in Table 1. In this study, we propose a non-linear QCM-based sensing platform, which exploits abrupt amplitude-drop phenomena in the non-linear regime of QCMs (Fig. 1a). Here, we define the “amplitude-drop frequency” as the specific frequency at which the vibration amplitude of the non-linear QCM abruptly

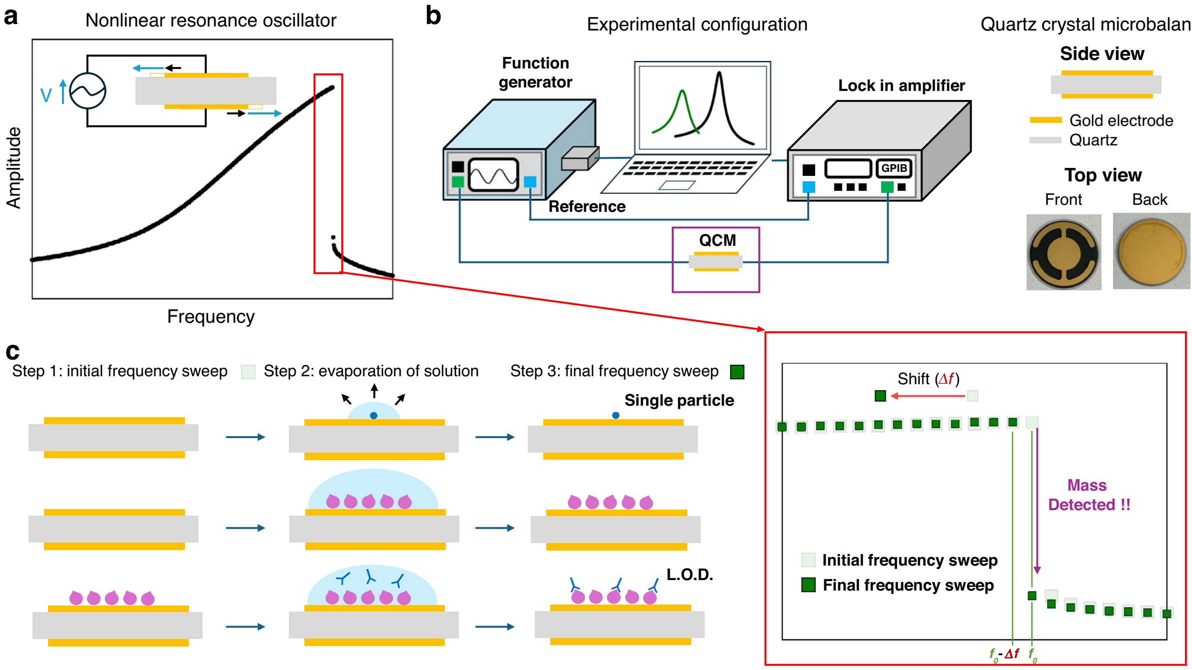

Fig. 1 Schematic illustration of a non-linear QCM-based sensing platform. a A non-linear QCM-based sensing platform schematic illustrating the working principle: when mass is detected, abrupt amplitude drops. **b** Experimental configuration consisting of a lock-in amplifier, function generator, and QCM, along with side and top views of the QCM. **c** Schematic illustration of the mass detection process. Three different targets were detected: (1st row) micro/nanoparticles, (2nd row) BSA, and (3rd row) anti-BSA. In Step 1, the initial frequency–amplitude sweep was performed. In Step 2, the sample solution was dropped and allowed to evaporate. In Step 3, the final frequency–amplitude sweep was conducted to detect the mass-induced frequency shift

transitions from the high-amplitude state to the low-amplitude state due to bistability. An experimental system composed of a function generator, lock-in amplifier (LIA), and QCM was used to confirm high-sensitivity measurements under ambient temperature and pressure conditions (Fig. 1b). The simplicity of this experimental configuration enhances the potential for practical deployment and commercialization of the proposed sensing approach. Comparative analyses between linear and non-linear states were conducted using micro/nanoparticles and protein molecules (Fig. 1c). We demonstrate that the non-linear regime enables single-particle mass detection at the micro/nano scale and supports repeated measurements without device replacement, due to the reversible and stable non-linear vibration characteristics of the QCM. Furthermore, we performed antigen–antibody-based single-molecule detection experiments to demonstrate the practical applicability of the platform. By leveraging the enhanced transduction sensitivity of the non-linear QCM regime, a sensitivity level of 100 fg was achieved. Our non-linear QCM operation-based mass sensing platform offers significant potential for precision sensing and medical diagnostics, including nano-plastics and fine dust monitoring, and single-molecule biomarker detection.

Results

Verification of dynamic stability at non-linear resonance mode

To ensure that the system exhibited sufficient dynamic stability for reliable mass sensing, we conducted repeated forward (up-sweep) frequency sweeps while incrementally increasing the driving voltage from 0.1 to 6 V in the non-linear QCM sensing system (Fig. 2a, b). At low voltages (0.1–2 V), the resonance response maintained a symmetric Lorentzian shape, indicating that the system remained in the linear regime. However, when the voltage exceeded 3 V, an asymmetric resonance curve appeared, and above 5 V, a sudden amplitude change occurred near the resonance frequency, exhibiting an abrupt amplitude drop. This indicates that the system entered a region with multiple amplitude solutions due to the influence of non-linear stiffness, consistent with the typical foldover effect[24,25]. Although the amplitude-drop behavior first emerged at approximately 5 V, the drop region exhibited several small discontinuities and insufficient amplitude contrast between adjacent frequency points (Fig. 2b), making 5 V unsuitable as a reliable sensing point. Furthermore, drive amplitudes exceeding 9 V resulted in unstable and inconsistent amplitude-drop points (Supplementary Fig. 1). Accordingly, we selected 6 V as the

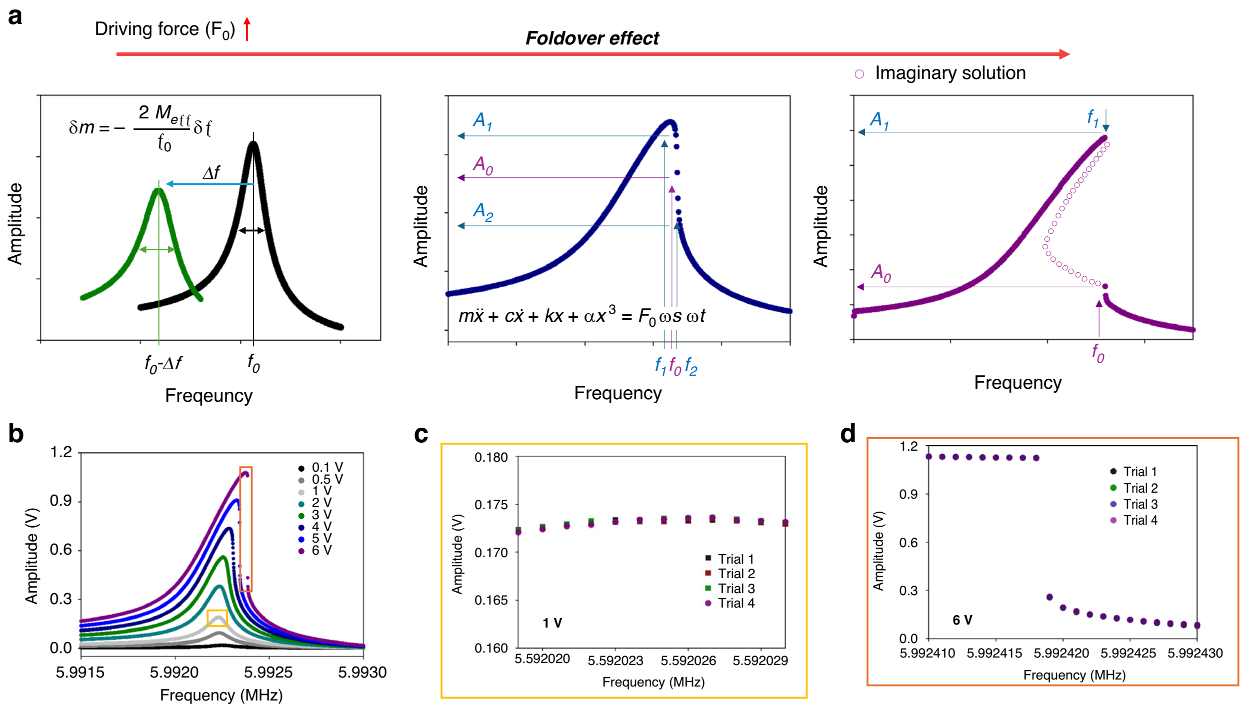

Fig. 2 Verification of the stability and reproducibility of the non-linear QCM-based sensing platform in both linear and non-linear regimes. **a** Comparison of frequency–amplitude in linear and non-linear regimes. Left: frequency shift (Δ*f*) due to added mass based on the Sauerbrey equation, with calculated mass change (δm). Middle: non-linear Duffing oscillator model showing multiple amplitude solutions (A_0, A_1, A_2) corresponding to frequencies f_1, f_0, and f_2. Right: abrupt amplitude-drop phenomenon in non-linear regime. **b** Frequency–amplitude under different driving voltages. Resonance responses of the QCM were measured as the driving voltage was incrementally increased from 0.1 V to 6 V. **c** Repeated measurements at 1 V (linear regime). Nearly identical amplitude profiles demonstrate high stability in the linear regime. **d** Repeated measurements at 6 V (non-linear regime). Consistent drop positions validate reproducibility and stability under a non-linear regime

operating condition for non-linear sensing. At 6 V, the resonance curve exhibited a single, well-defined amplitude-drop point, a large and clearly distinguishable amplitude change, and high repeatability across multiple sweeps, thereby providing a stable non-linear operating point for mass detection. To verify the stability of the system, frequency sweeps at 1 V and 6 V were repeatedly performed under controlled temperature and humidity conditions (22.5 ± 1 °C and 40 ± 5% RH). As shown in Fig. 2c, d, there were no significant differences in the frequency and amplitude graphs, confirming the reliability and reproducibility of both the linear and non-linear sensing regions for subsequent mass measurements. The corresponding standard deviation values are provided in Supplementary Fig. 2.

Measurement of BSA and micro/nanoparticles

To validate the sensitivity advantage of the non-linear regime utilized in the non-linear QCM sensing system, we compared mass measurements of particles and bovine serum albumin (BSA) in both linear and non-linear regimes. Measurements were performed by dropping 1 µl of suspended nanoparticles at concentrations of 100 ng/ml, 200 ng/ml, 10 µg/ml, and 1 mg/ml. Starting with the bare QCM, samples were incrementally concentrated and measured sequentially. Compared to the resonance frequency of the unloaded crystal, shifts of 9 Hz, 10 Hz, 15 Hz, and 97 Hz were observed, respectively (Fig. 3a). In the linear regime, the peak amplitude is not clearly defined, making it difficult to reliably detect small mass changes.

Single micro/nanoparticle and anti-BSA measurement and reusability

In the next step, we attempted to measure a single 1 µm particle. To collect individual particles for QCM measurement, a small droplet was dispensed onto the slide glass to resuspend the remaining particles, which were then aspirated and transferred onto the QCM surface (Fig. 4a–c). After evaporation, a frequency–amplitude measurement was performed. Compared to the unloaded state, a frequency shift of 1 Hz was observed as shown in Fig. 4d. To further verify the repeatability and reproducibility, repeated measurements were performed by sequentially depositing particles onto the QCM, showing consistent 1 Hz shifts (Fig. 4e). This result confirms the

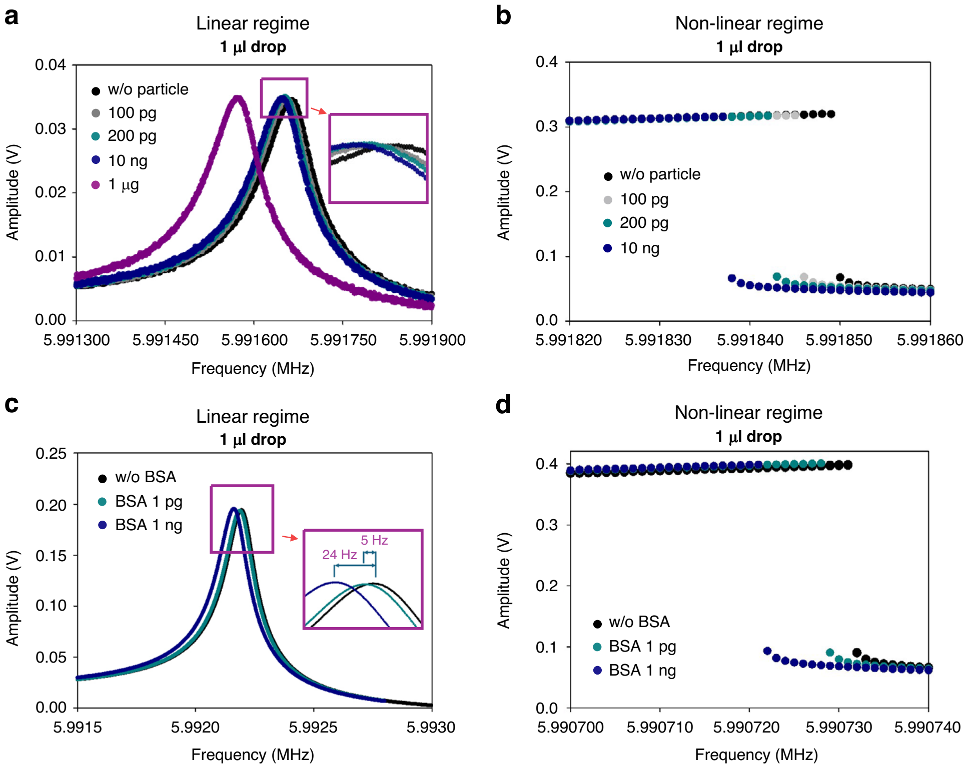

Fig. 3 Comparison of linear and non-linear regimes for mass detection using the non-linear QCM-based sensing platform. **a** Frequency–amplitude in the linear regime for micro/nanoparticles at various concentrations. **b** Frequency shifts of abrupt amplitude drop in the non-linear regime, showing enhanced resolution for the same micro/nanoparticle samples. **c** Frequency–amplitude in the linear regime after loading BSA. **d** Frequency shifts of abrupt amplitude drop in the non-linear regime after BSA loading

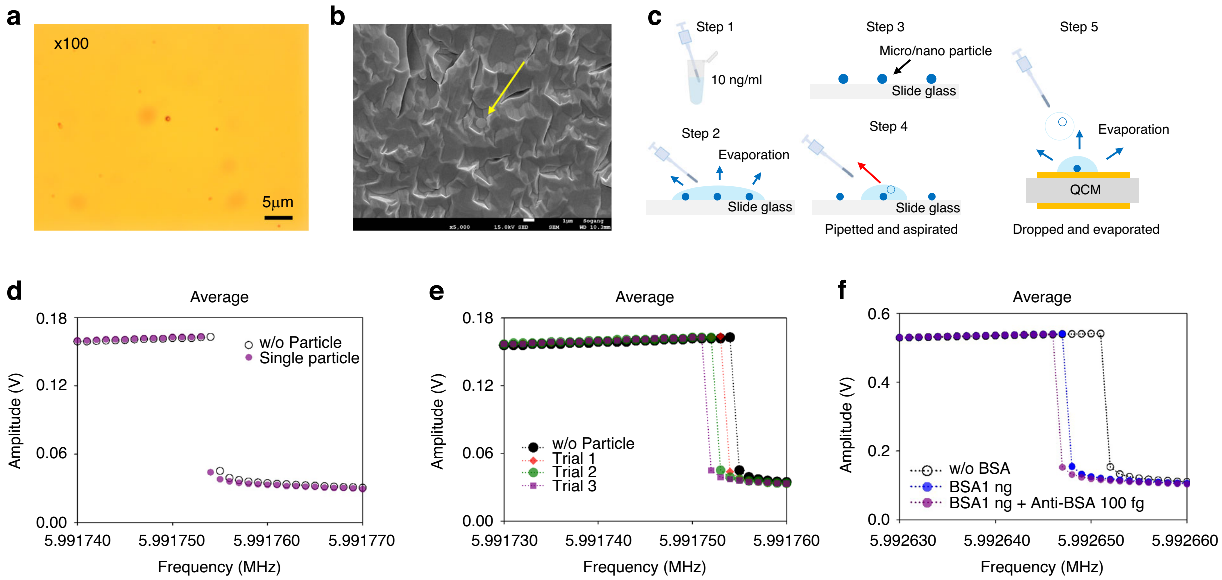

Fig. 4 Single microparticle mass detection using the non-linear QCM-based sensing platform. **a** Optical microscopy image of micro/nanoparticle after solvent evaporation on a glass slide. **b** Field Emission Scanning Electron Microscope (FE-SEM) of micro/nanoparticle after solvent evaporation on the QCM. **c** Schematic illustration of the particle transfer method. A droplet containing a particle is dispensed onto a glass slide, then pipetted and aspirated back into the pipette before being dropped onto the QCM surface. **d** Frequency–amplitude before and after loading a single micro/nanoparticle, showing a 1 Hz shift from the unloaded state. **e** Repeated single-particle measurements confirm consistent 1 Hz shifts, demonstrating the reliability and reproducibility of the detection method. **f** Frequency–amplitude response showing stepwise mass loading from BSA 1 pg and anti-BSA 100 fg, resulting in successive resonance shifts

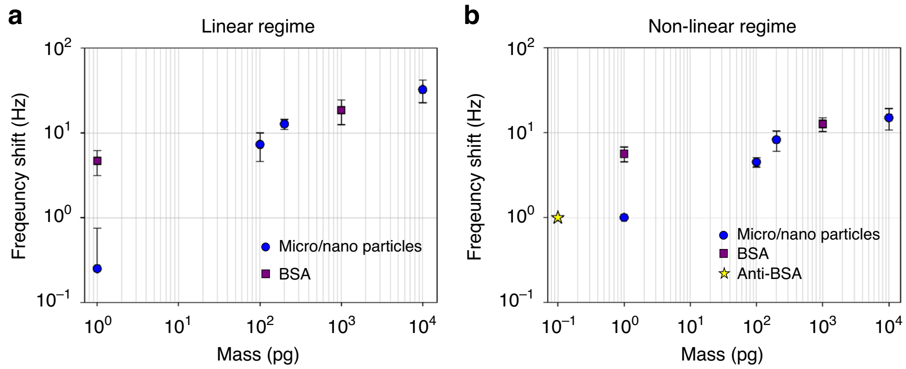

Fig. 5 Application of the non-linear QCM-based sensing platform for antibody detection. a Frequency shift measured in the linear regime across different concentrations for micro/nanoparticles and BSA. (mean ± SD, $n = 3$–5 per data point). **b** Frequency shift measured in the linear regime across different concentrations for micro/nanoparticles, BSA, and Anti-BSA. (mean ± SD, $n = 3$–5 per data point)

reliability of single-particle mass measurement and demonstrates reusability. Finally, an experiment was conducted to bind an antibody to its antigen. BSA is known to adsorb well onto gold surfaces[26,27], so anti-BSA detection was performed on BSA-adsorbed QCM. Comparing the frequency sweep before and after adsorption of 1 pg BSA, a 4 Hz frequency shift was observed (Fig. 4f). Anti-BSA solution was then dropped onto the BSA-coated QCM and incubated for 20 minutes. After rinsing five times with DI water, frequency and amplitude were measured, and a 1 Hz shift was observed due to the 100 fg anti-BSA (Fig. 4f)

To evaluate the quantitative sensing performance across different mass ranges, frequency shift was compared under both linear and non-linear regimes (Fig. 5a, b). In the linear regime, frequency shifts showed a relatively shallow slope at low concentrations, making it difficult to resolve mass measurements below ~10 pg. In contrast, the non-linear regime exhibited significantly enhanced responsiveness even in the low-mass region, including clear frequency shifts for samples with masses as low as ~100 fg. Notably, single micro/nanoparticle and ~100 fg protein mass were resolved with distinct frequency shifts in the non-linear regime. These results confirm that the non-linear QCM sensing strategy effectively expands the detectable mass range and improves resolution, especially for low-mass analytes.

Discussion

This study clearly demonstrates the high sensitivity and reliability of a non-linear QCM-based sensing platform that exploits amplitude-drop behavior for detecting minute mass changes. Under low driving voltage (~ 2 V), the QCM system stably measured microparticles and BSA, achieving a Q-factor of ~39,000. However, as shown in Fig. 3a, c, the resolution in the linear regime was limited under low concentration conditions, making it difficult to distinguish mass changes below 10 ng/ml. Additionally, the large effective mass of the QCM inherently limits the overall mass detection resolution. In contrast, when the driving voltage exceeded ~6 V, due to the occurrence of a sudden amplitude drop, the system exhibited a significantly higher effective Q-factor near the resonance frequency. Under this non-linear condition, we successfully measured a 1 pg mass change corresponding to a single silica particle. This enhanced sensitivity fundamentally stems from the non-linear resonance characteristics of the QCM. As the driving force increases beyond the linear regime, the system follows a Duffing-type non-linear response, where the cubic stiffness term (αx^3) distorts the resonance curve and induces a foldover effect. (see Materials & Methods) This deformation generates a multi-solution region near the resonance frequency, in which the oscillator becomes dynamically unstable and exhibits an abrupt amplitude drop. By fixing the driving frequency immediately before this amplitude-drop point, even a minute added mass shifts the non-linear resonance curve leftward and forces the system to transition to the lower-amplitude branch, resulting in an instantaneous amplitude drop. This mechanism provides an intrinsic amplification effect for detecting small mass loading. In addition, this enhanced sensitivity is closely related to the intrinsic stability of the non-linear operating point. In the non-linear regime, the QCM exhibits a maximum-amplitude point where no noticeable frequency fluctuation is observed under controlled temperature and humidity conditions (22.5 ± 1 °C and 40 ± 5% RH), allowing the resonator to maintain a highly stable operating state. This stability arises from the inherently large mass of the QCM, which makes its dynamic response relatively insensitive to external disturbances. Such a stable non-linear operating condition enables clear amplitude transitions in response to minute mass loading, thereby providing superior mass detection performance

Table 2 Comparison of QCM sensing methods and reported L.O.D. values

Reference	Target/sample type	Surface functionalization	Operating mode	L.O.D.
Cakir et al.[28]	2,4-D (pesticide)	Molecularly imprinted polymer film	Liquid-phase QCM	20.17 ng/L
Ding et al.[29]	2,4-D (pesticide)	Self-assembled monolayer + Glutaraldehyde + BSA conjugate + gold nanoparticles	Immuno-QCM	19.82 mg/mL
Zhou et al.[30]	DNA sequence	Probe DNA + Ag nanoclusters	Flow-injection QCM	0.1 nM
Waiwijit et al.[31]	IgG/HAS	Antibody immobilization	Flow-based multi-channel QCM	4.3 mg/L
Wabnitz et al.[32]	Complex organic matrices	None	High-performance liquid chromatography + dry-mass QCM	16 mg/L
Our study	Single-particle/ protein	None	non-linear amplitude-drop	100 fg

that is difficult to achieve in the linear regime. Also, experiments with BSA and anti-BSA proteins confirmed amplitude-drop frequency shifts corresponding to 100 fg level mass changes, demonstrating a sensitivity surpassing that of conventional QCM systems (Fig. 5a, b). The limit of detection (L.O.D.) performance was also excellent. While previous QCM-based studies have primarily reported detection limits in terms of solution concentration (e.g., ~20 ng/L)[28–32], our approach enables direct detection of surface-bound analytes at the single-particle level, with detectable protein masses down to ~100 fg. (See Table 2) The present method targets event-level mass measurement rather than concentration-based detection, establishing a distinct sensing regime without surface functionalization. One notable point is that the applied detection condition involved depositing 1 µL of a 0.1 pg/ml protein solution, which theoretically corresponds to 100 fg of total mass. However, considering the number of molecules adsorbed onto the QCM and the adsorption efficiency, the detected mass may be significantly higher, indicating that the reported sensitivity is conservatively estimated. However, the current system has limitations in accurately quantifying the mass and is not suitable for real-time detection under fluidic conditions. As shown in Supplementary Fig. 3, when the abrupt amplitude drop (just before f_0) in the non-linear regime was used as a fixed frequency, a sharp amplitude drop was immediately observed upon the arrival of a 1 µl droplet on the QCM surface. This indicates the potential of the non-linear QCM-based micro-resonator platform for real-time mass detection. Although real-time detection of biomarkers or molecular interactions in aqueous environments is generally challenging due to strong damping effects, this study experimentally demonstrated the feasibility of the concept by inducing non-linear resonance. Specifically, even though the Q-factor decreased to ~1600 in water, clear amplitude drops were still observed when the driving force increased (Supplementary Fig. 4). These results significantly expand the potential of a non-linear QCM-based sensing platform to detect not only single microparticles but also mass changes at the single-molecule level.

From a microsystem integration perspective, the non-linear amplitude-drop sensing scheme presented here offers several advantages for future continuous-flow and microfluidic applications. Unlike conventional frequency-sweep-based QCM sensing, the non-linear operating mode enables event-based detection by fixing the driving frequency near the non-linear critical point. Under this condition, a minute mass loading immediately induces an abrupt amplitude decrease, suggesting that the effective detection speed is governed by the mechanical response time of the resonator and mass transport dynamics rather than by frequency scanning. This characteristic indicates the potential for rapid, sub-second detection when combined with controlled flow delivery. Operation in liquid environments inevitably reduces the Q-factor due to viscous damping; however, our experimental results demonstrate that the non-linear amplitude-drop behavior remains clearly observable even when the Q-factor decreases to ~1600 in water (Supplementary Fig. 4). This indicates that the sensing mechanism does not rely solely on ultra-high-Q operation, but instead exploits the existence of a robust non-linear regime, which can persist under strong damping conditions when sufficient driving force is applied. Furthermore, the proposed approach does not require surface functionalization, electrode miniaturization, or structural modification of the QCM, which significantly simplifies integration with micro- or nanofluidic platforms. By confining the active sensing area and minimizing the effective fluid volume interacting with the resonator surface, hydrodynamic damping can be further reduced while maintaining sensitivity.

These features suggest that the non-linear QCM-based sensing platform is well-suited for future implementation in integrated microsystems, including real-time biomolecular detection, continuous-flow mass sensing, and multiplexed QCM array architectures.

Thus, this non-linear QCM-based sensing platform offers a high-sensitivity mass detection platform that surpasses conventional Sauerbrey-based QCM sensing. By minimizing the sensing area of the resonator and limiting the volume of fluid in contact with this active region, hydrodynamic damping can be reduced. When integrated with micro- or nanofluidic systems, the platform holds strong potential for future applications such as protein characterization[33,34], single-molecule detection, and multiplexed QCM arrays capable of monitoring multiple targets simultaneously. In addition, the simplicity of the experimental setup and the reusability of the device offer important practical advantages for real-world applications and commercialization.

Conclusion

In this study, we developed a non-linear QCM-based sensing platform capable of detecting femtogram-level analytes without additional functionalization or complex nanofabrication on the QCM. By exploiting the abrupt amplitude-drop phenomenon induced by non-linear behavior, this platform achieved a detection limit of ~100 fg and enabled single-particle measurement. By fixing the driving frequency at the maximum-amplitude point in the non-linear regime, even a minute added mass shifts the resonance curve and immediately induces an amplitude drop, providing a simple and intuitive measurement principle that differs fundamentally from conventional frequency shift-based QCM sensing. Through comparative analysis of linear and non-linear regimes, we found that non-linear regime conditions are advantageous for low-mass detection. Furthermore, the reusability of the system and its compatibility with both ambient and liquid environments expand its practical applicability. This approach can be expected to enable real-time biological sensing, protein interaction monitoring, and integration with microfluidic systems, providing a simple yet powerful alternative to traditional QCM sensing methods.

Materials & methods

Mass sensing strategy based on non-linear resonance

To develop a mass sensing strategy based on non-linear resonance behavior, we utilized the abrupt amplitude drop that emerges in QCM systems operating beyond the linear regime. In the linear regime, a harmonic oscillator exhibits a symmetric resonance characterized by a Lorentzian[35] (Fig. 2a). If the driving force (F_0) is increased beyond a certain limit, the system transitions into a non-linear regime described by the Duffing equation:

$$m\ddot{x} + c\dot{x} + kx + \alpha x^3 = F_0 cos\omega t \tag{1}$$

where m, c, k, and α represent the mass, damping coefficient, linear stiffness, and non-linear stiffness, respectively. The cubic stiffness term (αx^3) introduces non-linear stiffness, which modifies the system's restoring force and contributes to the resonance non-linearity[36]. In this non-linear regime, the resonance curve becomes asymmetric due to the influence of α, resulting in a foldover effect[24,25] and the coexistence of multiple amplitude solutions near the resonance frequency. These non-linear responses are influenced by damping and energy dissipation and are well understood by the Duffing model[37]. An abrupt amplitude drop occurs as the system undergoes a dynamic instability arising from the multi-solution structure induced by the foldover effect. Our sensing strategy involves fixing the driving frequency (f_0) at the point of maximum amplitude just before the amplitude of the oscillator drops down in the non-linear regime. When a small amount of mass is added to the QCM, the resonance curve shifts leftward due to the added inertia, causing a sudden drop in amplitude at f_0 (Fig. 1a, inset). This effect enables highly sensitive detection of even extremely small mass changes. We verified this behavior by measuring frequency-dependent amplitude responses of QCMs under different surface conditions: a bare QCM, and QCMs loaded with micro/nanoparticles, BSA, and anti-BSA antibody (Fig. 1a, c).

Measurement system

The experimental setup consists of a lock-in amplifier (SR844, Stanford Research Systems, USA), an arbitrary function generator (AFG320, Tektronix, USA), and a QCM (OT6US-14AE, OTWOCOM, Korea) with a nominal resonance frequency of 6 MHz. During the experiments, the actual resonance peaks appeared between 5.990 MHz and 5.994 MHz. As we typically observed non-linearity at the driving voltage above 5 V in our experimental condition, all the measurements in this study were conducted at a driving voltage in the range of 5–6 V (Fig. 2B). The resonance peak was repeatedly measured with a frequency measurement resolution of 1 Hz.

Materials, sample preparation, and SEM image

Three types of test materials were used: Silica micro/nanoparticles (1 μm, Sicasatr®-redF, micromod, Germany), BSA (A8549-10MG, ThermoFisher, USA), Anti-BSA antibody (A11133, ThermoFisher, USA). Each material was dispersed as follows: Silica nanoparticles were dispersed in DI water; BSA was diluted in T50 buffer (10 mM Tris-HCl, 50 mM NaCl, pH 7.5); Anti-BSA antibody was diluted in PBS (pH 7.3), each to a concentration.

Then, 1 μL of each suspension was drop-cast onto the QCM surface. After solvent evaporation (which was completed within minutes), frequency–amplitude measurements were repeated across the same frequency range.

QCM surfaces after loading with micro/nanoparticles, BSA, and anti-BSA were imaged using FE-SEM (JSM-7100F, JEOL Ltd., Japan), and the results are provided in the Supplementary Information. (Supplementary Figs. 5 and 6).

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Author contributions
S.W.L. and D.H.S. conceptualized the study. J.K., S.W.L., and D.H.S. designed the experiment. J.K. conducted experiments and analysis. Y.J. contributed to conducting experiments. S.H.K. contributed to the design of experiments. S.W.L. supervised and led the research. All authors discussed the results and contributed to the manuscript.

Data availability
The data sources that support the findings of this study are available from the corresponding author upon reasonable request. Supplementary information is available for this paper at http://doi.org/.

Conflict of interest
The authors declare no competing interests.

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