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HIGH-Q NANOELECTROMECHANICAL RESONATOR FOR DYNAMIC BIOMOLECULAR INTERACTION MONITORING

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ABSTRACT

Nanoscale resonators can also be implemented as Nanoelectromechanical Systems (NEMS) that will offer a powerful label-free way to monitor biomolecular interactions in real time because resonance frequency, linewidth, phase, the Quality factor and dissipation will all change due to molecular binding, adsorptions, hydration and mechanical changes at interfaces. A review manuscript based on research is provided for NEMS Biomolecular Interaction Analysis Platform and contains resonant nanobeams, suspended microchannel resonators, film bulk acoustic resonators, hypersonic acoustic resonators and integrated photonic-mechanical NEMS. A thorough literature survey is presented starting from the basics and the more recent contributions to mass sensitivity, cross-compatibility in liquids, surface functionalization, noise, signal processing, kinetic interpretation of data and contributions. The conceptual NEMS platform features microfluidic closed-loop sample delivery along with a functionalized nanoresonator, and closed-loop frequency tracking. The paper stresses the importance of not only high responsivity, but also on optimal designing of the surface chemistry, mass transport, thermal stabilization, damping control, readout precision, and data modelling on the analytical performance of NEMS. Nanobeam and cantilever NEMS are ideal for measuring the mass of a single particle or single protein in their respective applications, but suspended microchannel resonators are ideal for continuous liquid phase applications. Several architectures based on acoustics and photonic-mechanics, offering interesting properties for the diagnostics of multiplexed, transportation enhanced diagnostics systems and miniatur scale diagnostics systems. The manuscript concludes that NEMS biosensing is progressing from a proof-of-concept mass detection to systems-integration for continuous and kinetic protein and nucleic acid analysis, as well as vesicles, pathogens and cells.

keywords: nanoelectromechanical systems as a new category of microelectronic devices, NEMS, biomolecular interactions, nanomechanical resonators and biosensors, real-time monitoring, suspended microchannel resonators and label-free detection.

1. Introduction

Molecular diagnostics, drug discovery, analysis of biomolecular interactions in place – for environment monitoring and also in systems biology – is required. Non-spectroscopic optical measurement methods like enzyme-linked assays, fluorescence imaging etc., can be very sensitive, but may necessitate the requirement for labels, amplification, washing or delayed measurement. To overcome this, there is a high demand for solutions that have real-time measurement capabilities for binding, which biosensors that are “label-free” kinetic can do. These are sensors like surface plasmon resonance, quartz crystal microbalance with dissipation and optical microcavity sensors. Yet, added mechanical modes of transduction (mass binding, surface stress, stiffness changes and dissipation of energy) have been added to these systems because of the nanoscale dimensions of a nanoscale resonator, which can either be physically deformed or dissipate energy when receiving an added mass (Arlett et al., 2011; Eom et al., 2011; Tamayo et al., 2013).

The resonance of a NEMS biosensor, which is typically a nanomembrane, nanowire, membrane, cantilever or acoustic resonator, is typically measured continuously. However, it will change when biomolecules are functionalized after binding with the functionalized surfaces of the device resonance. However, there are biomolecular interactions which

are not ‘rigid mass loading events' and hence the simple rigid mass model predicts a negative frequency shift that is proportional to the overall and added effective mass. Proteins and Nucleic acids may be conformationally changed; can sequester water in hydration shells in interior; can alter surface stress; can cause viscoelastic losses to system. With the advent of modern NEMS biosensors, the number of observables has grown over time and a large number of these observables are simultaneously reported, including resonance frequency, amplitude, phase, quality factor, linewidth and mode-dependent shifts (Eom et al., 2007; Gil-Santos et al., 2010; Hanay et al., 2012).
This manuscript is written in the form of Research paper & conceptual platform for Review. The purpose of its presentation is to elucidate on possible applications of NEMS in real time monitoring of biomolecular interactions, discuss important device architectures, define methodological needs and present future research potential. This main idea implies that miniaturization is not sufficient to make useful NEMS bio-sensing devices. To achieve nanoscale sensitivity to forces, one must be able to read out a given force in an accurate and stable manner, but also have excellent surface chemistry, microfluidic transport, thermal control, noise suppression, and the ability to interpret the kinetic data.

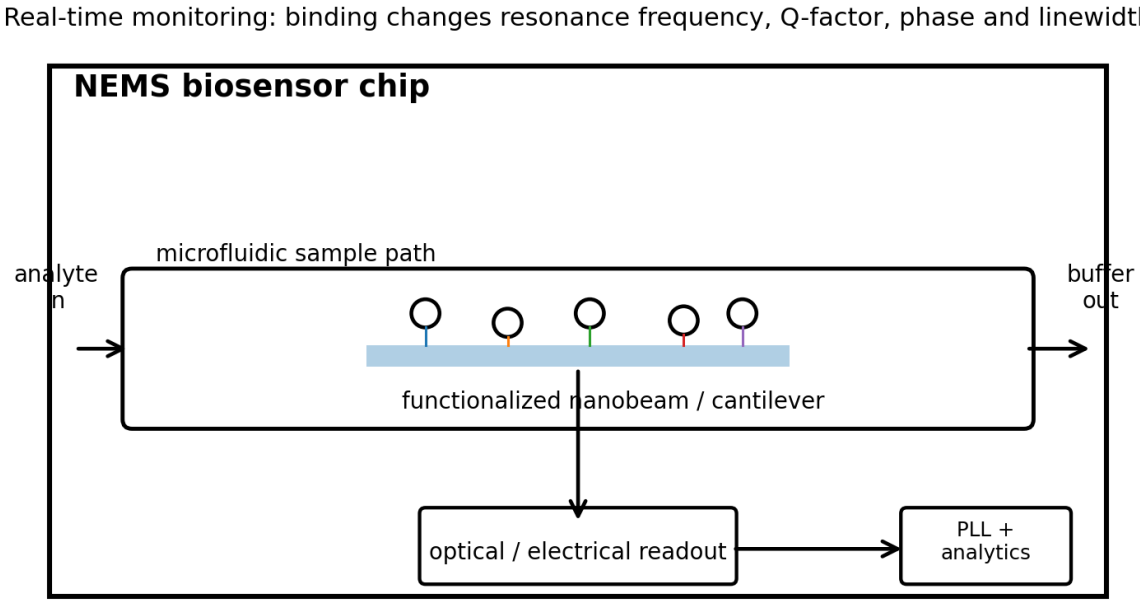

Figure 1. Conceptual architecture of a functionalized NEMS biosensor integrated with sample flow and optical/electrical readout.

2. Background and Operating Principles
The work and concepts of this system are described.
NEMS devices are those that combine electrical, optical, piezoelectric, piezoresistive, or capacitive transduction with mechanical motion all in a nanoscale device. Resonant biosensing would be a device that is operating at a resonant frequency for mechanical systems. The natural frequency is dependent on the effective stiffness/effective mass ratio. The fundamental equation for an idealized resonator is: f0 = (1/2π)(keff/meff)½. This equilibrium is changed by molecular binding. The effect of small effective mass will be to shift the resonant frequency down, the effect of changing effective stiffness (surface stress) will be either up or down, depending on the geometry and boundary conditions (Eom et al., 2007; Yang et al., 2006; Ekinci et al., 2004).
According to the classical mass-loading approximation, Δf/f0≈ − (1/2)(Δmeff/meff) (see the other abbreviations for their definition). This equation is thus indicative of why NEMS are attractive: the smaller the mass the smaller the molecule, the larger (relatively) the fractional frequency shift is where the mass is much smaller. Initial ultrasensitive NEMS mass detection experiments have shown that sensitivity of $attogram$ and $zeptogram$ ranges is achievable, and single protein and single particle detection has been demonstrated (Ekinci et al., 2004; Yang et al., 2006; Hanay et al., 2012). However, for soft/hydrated biomolecules the approximation is not complete especially for liquids. Other elements aiding its functionality are mass, stiffness, internal friction, surface stress and fluid coupling, as well as the receptor / antigen layer, DNA film or extracellular vesicles or membrane fragments. Thus, it appears that the best way

to view a physically meaningful NEMS signal is as a perturbation of the entire resonator-environment system and not simply as a simple weighing event.
The other basic measurement is called quality factor or Q. It is an indicator of how sharp the resonance is and is a factor related to the energy loss per vibration cycle. The large the Q – the more accurate the frequency precision, but high Q is difficult in the liquid, because the viscous damping removes mechanical energy. To solve this issue, a novel type of microchannel resonators in which the liquid to be analyzed is inside the microchannel resonator and air or vacuum exists outside the resonator is proposed to obtain a relatively high mechanical resonance quality factor (Burg et al., 2007; Lee et al., 2011). The real-time biosensing of liquid can be also made by acoustic resonators and film bulk acoustic resonators, but one must take into account acoustic coupling, surface loading and fluid losses (Nirschl et al., 2010; Pan et al., 2017).

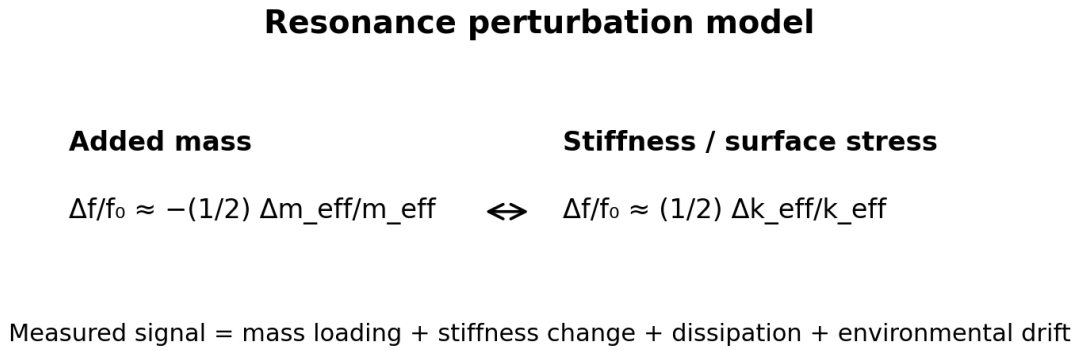

Figure 2. Simplified measurement model showing why biomolecular NEMS signals can reflect mass, stiffness, dissipation, and environmental drift.

3. LITERATURE REVIEW

3.1 Nanocantilever and Nanobeam NEMS:

Among the most studied NEMS biosensors are nanocantilevers and nanobeams. The strength of their team is that they have a low effective mass, high resonance frequency and that they can be functionalized on surfaces. Ultrasensitive NEMS cantonies for sensing and scanning probe applications were demonstrated by Li et al. (2007) and zeptogram scale mass sensing was demonstrated by Yang et al. (2006). The results of these studies have given rise to the scaling argument that mass shifts which could be detected on a smaller resonator are considerably smaller. It was then further developed to single particle and single molecule mass spectrometry. Naik, et al., (2009) proposed a route for SMnMS, while Hanay, et al., (2012) demonstrated the real time measurement of mass of a single protein using multimode NEMS. These were especially interesting experiments for the unknown landing position problem: the recognition of the induced frequency shift is depending on the landing position of the particle on the mode shape. Multiple modes can enable multiple pieces of information to be found about a particle, such as its mass and position.
The identical architecture also can be employed in interactions studies, but is a real challenge in aqueous biosensing. If a nanobeam is just immersed in a liquid, resonance can be damped by viscosity and the frequency resolution can be reduced because of that damping. However, the direct-liquid nanobeam sensing often involves special geometries, short integration times and/or careful design of the fluidic system or operation in amplitude or phase response regimes that are stable. According to literature, nanobeams are ideally suited for realization of extremely high mass responsivity, single particle detection in dry/vacuum, aerosol/particle analysis and hybrid configuration, where the sample preparation process does not affect the operation of the resonator (Chaste et al., 2012; Jensen et al., 2008; Sage et al., 2018).

3.2 Suspended Microchannel Resonators

An SMR can be a very interesting solution for biomolecules real-time monitoring in liquid. To avoid liquid immersion of the resonator, SMRs contain the liquid in a hollow microfluidic channel, which is etched into a resonating structure. This setting has less external viscous damping and provides the possibility to pass analytes thither the resonator. Burg

et al. [2] (2007) used this theory for weighing of biomolecules, nanoparticles and cells in fluid. The group of Godin et al. (2007) has demonstrated the ability to use SMRs to measure particle mass density and size in fluids, as well as in single-cell growth (Godin et al., 2010) and cell biophysical measurements. Not necessarily nanoscale in all dimensions, SMRs are central to the NEMS/MEMS biosensing landscape because they address the most demanding practical challenge—maintaining the resonance stability—and yet it is necessary when considering the analysis of a native liquid sample.

Signal of SMRs is based on the buoyant mass of the analytes and therefore dependent on the difference in density between the analytes and carrier fluid unlike dry mass measurements. Because of binding with biomolecules on channel walls, there will be a change in resonator mass and hence resonator frequency. Transient events manifest themselves as either a peak or dip in the high cell particle sensitivity regime, when the analytes are moving through this regime. The benefits are good liquid compatibility, on-line flow-through analysis and compatibility with microfluidic functions. The drawbacks include sensitivity to pressure, need to be calibrated, complexity of the packaging, bio fouling and clogging within the small channels (Burg, 2005; Lee et al., 2011; Martin-Perez et al., 2021).

3. 3 In this tutorial, acoustic, FBAR and hypersonic resonators are discussed.

A possible alternative to real-time biomolecular analysis is by utilizing an acoustic NEMS or microacoustic resonator. Film bulk acoustic resonators (FBARs), solidly mounted resonators and hypersonic resonators also have high frequencies and their resonance can be interrogated electrically, thus their use is interesting for integrated arrays of biosensors. The connection between acoustic resonance and scalable electronics was emphasised, by example of implementation of CMOS integrated FBARs for label-free biomolecular interaction analysis (Nirschl et al., 2010). As a way of modulating the biointerface, acoustic energy also has been demonstrated to remove biofouling and detect proteins at the same time by Bïntz et al. (2012) by using a hypersonic resonator. Recently an acoustic resonator based NEMS device was developed to act as biomolecular concentrator to enhance biomolecular binding to the surface (Liu et. al, 2018), and tunable acoustic streaming was explored for biomolecular surface interactions control (Pan et. al, 2023).

This body of work is important in that many affinity biosensors that are packaged into miniaturised form are transport limited. In a small channel, molecules of interest could have been diffusing slowly to the surface of the sensor and could have been causing rates of association to be pegged as diffusion rates. The effects of these restrictions can be reduced through the use of acoustic streaming which can enhance convective transport, elevate the convective flux of analytes and diminish nonspecific accumulation. Hence, acoustic NEMs are considered as not just transducers but also active microfluidic actuators which can tailor the space of interaction (Liu et al., 2018; Pan et al., 2023).

3.4 Photonic-Mechanical and Hybrid NEMS

A hybrid approach to photonics-mechanics (photonic-mechanical NEMS) can benefit from optical fields that can be integrated onto the silicon photonic platforms and also can provide sensitive displacement readout. The principles of monolithic actuation and transduction using optical approaches has been demonstrated with the all nanophotonic NEMS biosensor-on-chip proposed by Fedyanin et al. (2015). Label-free refractive index sensing and interferometry in general have a strong precedent and moreover in the case of the phonic biosensors (Luan et al., 2018; Vollmer & Arnold, 2008). Hybrid NEMS using mechanical mass sensitivity and optical readout precision is possible, but issues of optical heating, damping, fabrication tolerance and fluidic access need to be considered.

In the biosensors field, hybridization will probably be involved in the Next Generation of NEMS Biosensors. Mass, stiffness, changes of refractive index of the optical resonator, and charge transfer or catalytic events from the electrochemical sensor, for example, can be measured by the mechanical resonator. In summary, a multi-transducer platform may be more successful than a single transduction channel to distinguish among binding, nonspecific adsorption, conformational change and environmental drift.

Table 1. Comparison of major NEMS platform classes for biomolecular interaction monitoring.

Platform	Main observable	Strength	Primary limitation
Nanobeam / nanocantilever	Frequency shift, mode shifts, linewidth	Extreme mass responsivity and single-particle capability	Strong damping in liquid and small capture area
Suspended microchannel resonator	Buoyant mass and flow-through frequency events	Native liquid analysis with preserved resonance	Complex packaging, pressure effects, possible clogging
FBAR / solidly mounted resonator	High-frequency acoustic resonance shift	Electrical readout and array integration	Surface and liquid acoustic losses

Hypersonic acoustic NEMS	Resonance plus acoustic streaming effects	Improves mass transport and can reduce fouling	Thermal/acoustic mode management
Photonic-mechanical NEMS	Optomechanical displacement and resonance shift	Chip-scale optical sensitivity	Heating, alignment, and liquid operation challenges

4. METHODOLOGY

In the present paper the methodological approach is that of a narrative review and conceptual engineering. Articles that satisfied five criteria were selected for consideration: (a) basic demonstrations of NEMS mass sensing and biomolecular detection, (b) articles explicitly addressing issues related to the real-time monitoring, (c) articles pertaining to an acoustic or hybrid platform which supported better transport of analytes or integration, (d) articles in which understanding the origin of the noises was a major goal, and (e) articles which addressed functionalization of the surface and interpretation of the signals. The evidence base was organized according to platform and compared based upon performance characteristics useful for real-time biosensing including sensitivity, frequency stability, compatibility within liquids, surface chemistry, control of transport, the ability to multiplex and practical manufacturability.

The findings on the review were then used to design a conceptual NEMS biosensor architecture. A platform consisting of four modules is proposed below. The first is a sample module where buffer to the microfluidic network is injected as well as the analyte and regeneration solution. The second is a biointerface module where the molecules immobilized on the surface of the resonator are antibodies, aptamers, nucleic acid probes or peptides or receptor proteins. The third one is the mechanical transducer module which would consist of a nanobeam, cantilever, SMR and/or acoustic resonator depending on the application. The fourth one is the readout/analysis module that can operate the resonance frequency estimation, Q-factor estimation and kinetic parameter estimation based on the phase-locked loop tracking method, ring down analysis or the frequency-response fitting method.

The time dependence of the real time response obtained in the simple affinity assay, can be written as $d\Gamma/dt = ka\, C(\Gamma max - \gamma) - kd\, \gamma$ where γ represents the surface coverage and c is the analytes concentration, ka is the association rate constant and kd is the dissociation rate constant. Apparent kinetic parameters can be estimated by fitting to $\Delta f(t)$ if the response of NEMS is linearly proportional to surface coverage. But, this model can be only valid under the conditions where mass transport, rebinding, surface heterogeneity, and conformational change phenomena are controlled, or explicitly modeled. An elegant model could consist of a mass term, a stiffness term and a dissipation (damping) term such that: $\Delta f = Sm\Delta m + Sk\Delta k + Sd\Delta D + \varepsilon(t)$, where Sm, Sk and Sd are sensitivity parameters and $\varepsilon(t)$ is noise and drift. It requires multimodal measurements where they are motivated as compared to a single frequency only read out.

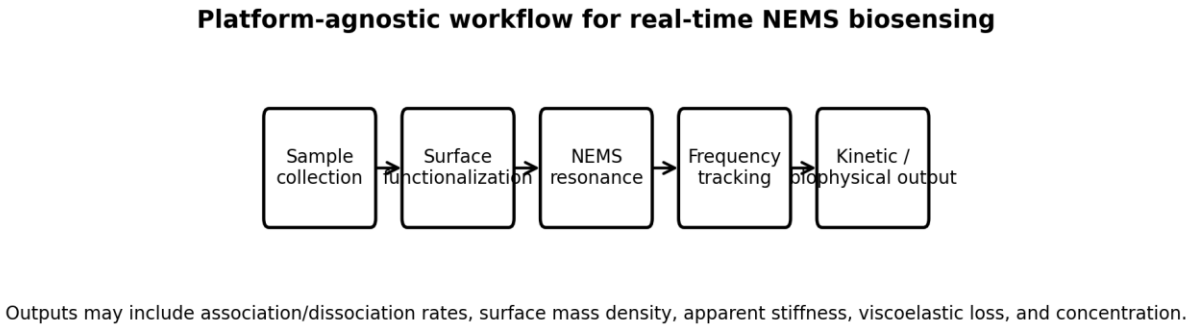

Figure 3. Workflow used in the conceptual methodology for real-time NEMS biomolecular monitoring.

5. Proposed Platform Design

Requirements for a NEMS-platform for real-time monitoring of biomolecular interactions should be determined by the targeted application(s). A nanobeam or SMR can be used to provide good mass sensitivity for extracellular vesicles, viral particles and nanoparticles which are of high molecular weight. Small molecules or weakly bound ligands may have a more significant surface chemistry and kinetic model than the raw mass sensitivity because of small mass shifts from small molecules. If continuous liquid monitoring is required, architectures used should be given

preference to SMR or acoustic resonator. With portable diagnostics, there is a need for electrical readout, low power electronics, multiplexed arrays and strong packaging.

The idea is to use a suspended microchannel or acoustic NEMS resonator as a basis for the liquid-phase biomolecular assay, with a microfluidic cartridge as the second component. Chemistry matching the resonator surface is provided with a capture probe that modifies the resonator surface. Thiol self-assembled monolayers (SAMs) and carbodiimide linking or affinity linkers can be used for functionalization of gold-coated areas. Silane chemistry is one way to modify the SiO2 and SiN surfaces. Nonspecific adsorption needs to be reduced with the help of blocking agents: polyethylene glycol (PEG), bovine serum albumin (BSA), zwitterionic coating, dynamic antifouling flows (Bhakta et al., 2015; Lichtenberg et al., 2019; Rusmini et al., 2007).

This readout system should keep the resonator in a stable tracking regime. Often PLL is used to track the resonance frequency in real time, but if speed and accuracy are not critical open-loop frequency sweeps and ring-downs may be another option. Thermal control is needed as changes in temperature affect material stiffness, the viscosity of fluids, and their electronic readout. Common mode drift should be eliminated by adding a reference resonator (no receptor chemistry) on the same chip. Several resonators can be functionalized with different probes, which can be detected with separate resonance frequencies or channels of the readout electronics when multiplexed detection is used.

All of the above (baseline correction, event detection, kinetic fit and confidence estimation) can be included in data analysis. For ensemble surface binding, association and dissociation phases can be fit to give an apparent ka, kd and KD. Note if this is used for the single particle detection, each landing event would result in a step in modal frequency; multimode could rationalize estimation of particle mass and position. Transit signatures for cells (and vesicles) flowing through channels yield buoyant mass distributions. With an appropriate fluidic and readout architecture, both molecular affinity assays and particle/cell biophysical analysis can then be implemented on the same platform.

6. RESULTS AND DISCUSSION

This manuscript is a review-based design paper, so the results presented here are in the form of a structured synthesis and conceptual analysis and NOT new experimental measurements. In three cases, which occur consistently, the literature results in three outcomes. First, the mass sensitivity of NEMS may be able to enter a regime that is not possible with conventional microscale resonators. At the nanoscale, mechanical resonators have also been successfully demonstrated for detection of very small mass changes in an experiment from Attogram and zeptogram (Ekinci et al., 2004; Yang et al., 2006). Subsequent single-particle, and single-protein, studies demonstrated that NEMS can be used for measuring frequency shifts of individual analytes if frequency shifts are tracked with sufficient precision and mode-shape effects suitably modeled (Hanay et al., 2012; Naik et al., 2009; Sage et al., 2018).

Second, there is the central engineering problem of performing the operation of the liquid phase in real time. Biological interactions typically take place in aqueous buffer, serum, cell culture media or saliva or similar complex fluids. These environments affect specifically by adding viscous damping, nonspecific adsorption and mass transport limitations. So it is not necessarily the smallest beam that has the best architecture for liquid monitoring, rather it is one that maintains frequency stability, whilst enabling controlled delivery of the analyte. In this regard, SMRs can boast very high values, as the fluid is contained within a resonator whose external damping can be separated from the fluid. (Burg et al., 2007, Lee et al., 2011). A second type, acoustic platforms, also deals with liquid issues, by modifying flow with mechanical waves and streaming in the vicinity of the surface (Liu et al., 2018; Pan et al., 2023).

Thirdly, the interpretation of NEMS signals is shifting towards multi-parametric. A mental model of the very first NEMS biosensing was a very small balance – one molecule lands on the balance and the resonant frequency drops. Although this model is useful, biomolecular interactions may also alter surface stress and/or stiffness, hydration and dissipation. Eom et al. (2007) noted that biomolecular interactions can cause shifts of resonance due to the molecular interaction effects, and the trend of mass-stiffness deconvolution studies further continues. It is therefore desirable for a good NEMS biosensor to measure as many observables as possible. Combination of frequency and Q-factor provide suggestion of whether a signal is dominated by rigid mass, soft film formation or damping. Multimode tracking can also help to distinguish the position/mass effects.X

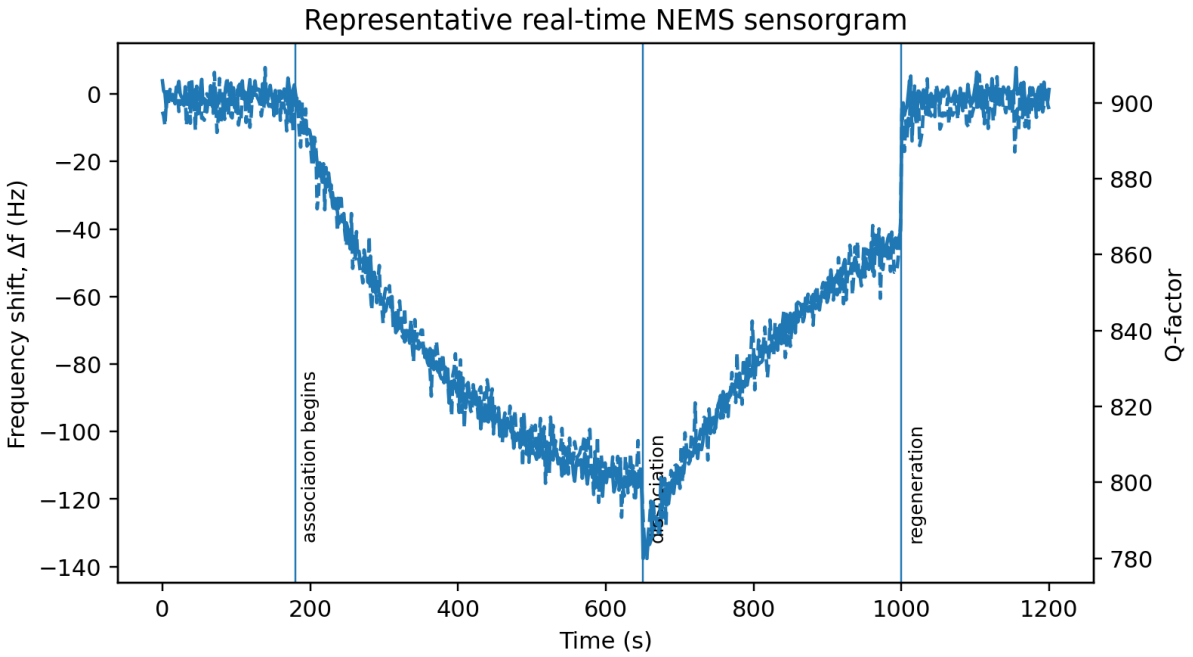

Figure 4. Representative simulated sensorgram showing baseline, association, dissociation, and regeneration phases in a real-time NEMS assay.

A simulated sensorgram is shown in Figure 4 that represents the kind of sensorgram that can be expected from a real time affinity assay. The resonator frequency is stable during the baseline. As the analyte approaches the functionalized surface, binding causes the surface to be more covered and results in the negative frequency shift. In the dissociation, buffer flow sweeps the weakly bound analytes away and the signal starts to recover to some extent. Regeneration brings the surface back to the original condition. In practice, it is possible to obtain important information from deviations from this ideal behavior. Slow baseline drift can be due to thermal instability or nonspecific adsorption. If the regeneration is not complete, it could be a sign of irreversible binding or surface degradation. If the Q-factor drop is large, this might indicate some soft-film formation, enhanced fluidic loss, or fouling, but not necessarily simple addition of mass.

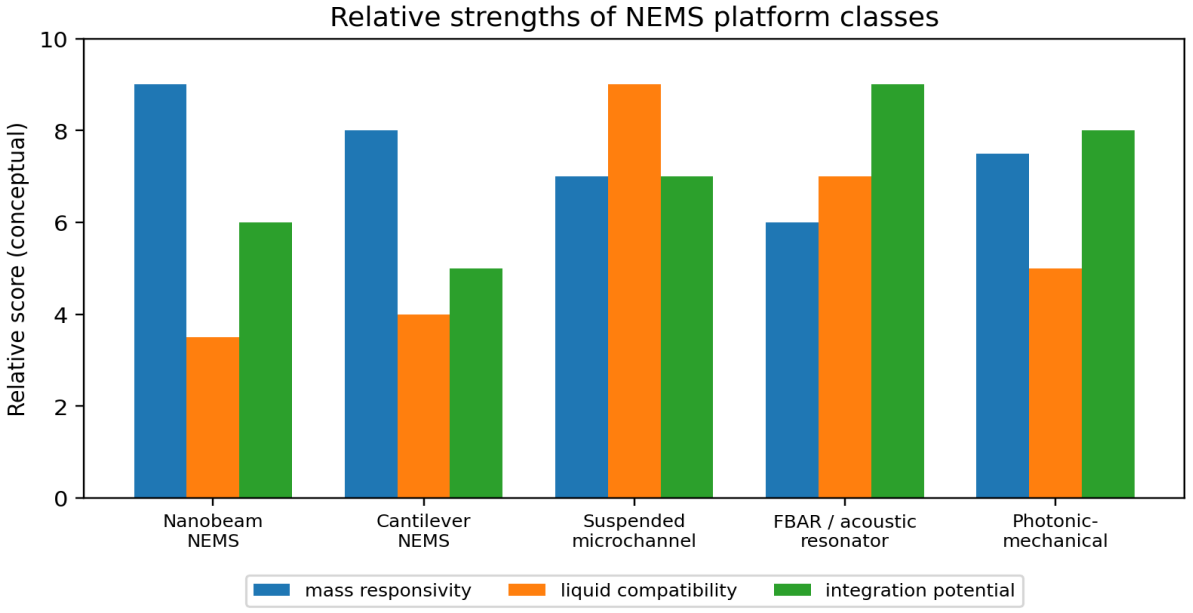

Figure 5. Conceptual comparison of relative strengths across platform classes. Scores are illustrative and literature-informed, not experimental measurements.

Figure 5 is an example of a design trade-off. Nanobeam and cantilever NEMS can have the highest intrinsic mass responsivity, but pose greater challenge for operation in the liquid directly. SMRs possess increased liquid compatibility and are ideal for biomolecular assays, single-cell growth analysis and buoyant mass measurements. Acoustic resonators are interesting when a high frequency electrical readout and active mass transfer are desired. Photonic-mechanical platforms exhibit a high integration potential, yet still have to overcome practical challenges related to fluidic packaging and optical heating. Thus, it is important to consider the sample environment and analytical question when selecting a platform, not just a single "headline sensitivity number".

Table 2. Engineering factors governing real-time analytical performance.

Design factor	Why it matters	Practical recommendation
Effective resonator mass	Lower mass increases fractional response to molecular loading	Use nanobeams or optimized thin membranes for dry single-particle studies
Quality factor	Higher Q improves frequency precision and phase stability	Use vacuum packaging, SMRs, or acoustic modes when liquid damping is limiting
Surface chemistry	Determines selectivity, fouling, and regeneration	Use covalent probe immobilization, PEG/zwitterionic blocking, and reference channels
Mass transport	Controls apparent binding rates in micro/nanoscale assays	Use optimized flow, acoustic streaming, or mixing structures
Temperature stability	Drives frequency drift through stiffness and fluid property changes	Use on-chip reference resonators and active thermal control
Readout bandwidth	Determines whether fast binding or single-particle events are resolved	Match PLL/filter bandwidth to event duration and noise floor

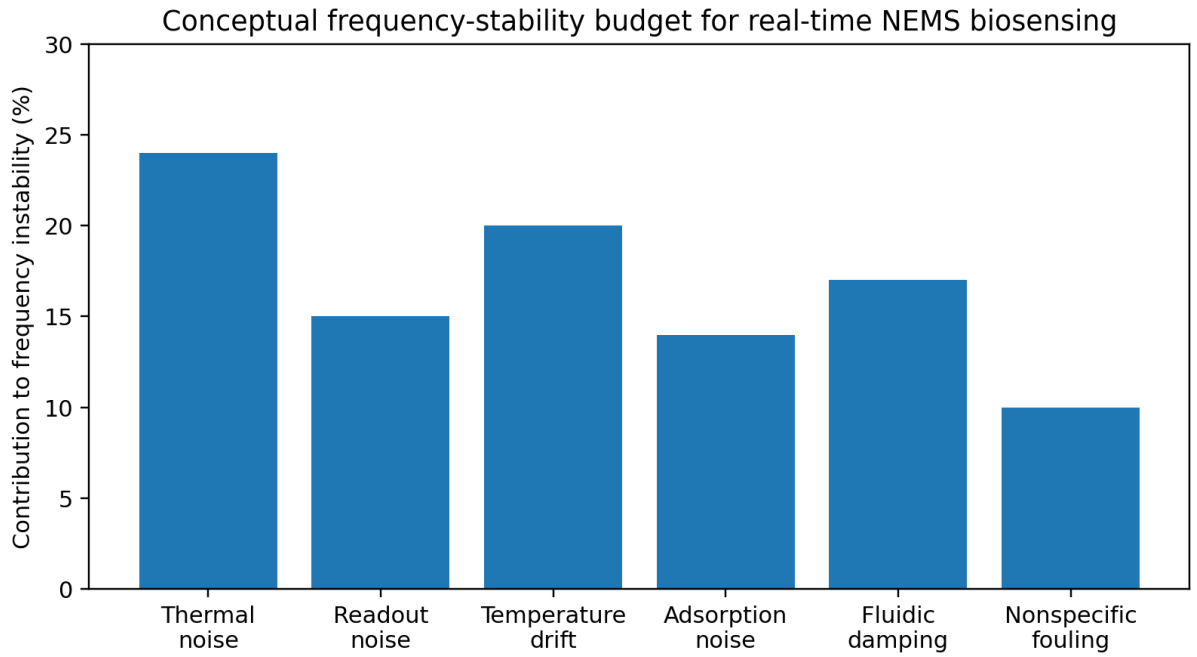

Figure 6. Conceptual noise budget for real-time NEMS biosensing.

7. Challenges and Limitations

It is the conditions in the actual biological fluids one big challenge. Nanoscale surfaces can be nonspecific absorbers of proteins, salts, lipids, vesicles and particulates in serum and saliva, plasma, wastewater or cell media. Even non-specific adsorption to a small extent can have the appearance of binding of target. This potential is minimised with chemistries that block, but can't be avoided. To monitor for longer periods, surfaces have to be non-fouling and maintain receptor activity.

The second one is the calibration. The changes in frequency depend on the mode shape, the position of the analyte, on the density of the fluid, on surface coatings and on the environmental parameters and are unique to the device. In the case of biomolecular NEMS, standards are required to be based on known particles/molecular layers, but are not as standardized as in optical/ electrochemical assays. It will be interesting to see how these differences in binding kinetics and mass transport can be distinguished. A small channel may not allow analytes to move fast enough to reach the sensing surface and kinetic effects of the molecular binding may be under measured. This is a concern for targets directed towards low exposure levels.

The fourth challenge is in the packing and production. The nanofabrication of NEMS, as well as thin film control, stable transduction, and protection from contamination are all required. Optical tables, vacuum systems or custom-made electronics are required for demonstrations; clinical or field devices should incorporate low cost cartridges and be automatically operated. Lastly, interpretation of data is complicated. A signal may include mass, stiffness and damping and the kinetic parameters from simple models may give false clues if the model assumptions of physics are not fulfilled.

8. Future Directions

The future of NEMS biosensors will involve taking this concept towards more integrated, multiplexed and data rich sensors. One direction is the resonator arrays turned into various resonators to detect specified biomolecules or target them with various frequencies. Arrays increase the area captured, throughput and internal controls. Frequency-addressed arrays for particle mass spectrometry has proven to be beneficial, just like Sage et al. (2018) did.

The other direction is called multimodal transduction. Resonance refers to any mechanical effect; in addition to using optical or acoustic/electrical sensing, one can distinguish between mass loading and conformational/environmental effects using mechanical resonance. Machine learning can also be useful for even more complicated classification of sensorgrams, for fouling detection, drift correction and single particle event pattern analyses; however these will need to be explainable for clinical and regulatory applications.

The third is that of an active creation of the biointerface. Nonspecific adsorption can be reduced and delivery of analytes improved through use of acoustic streaming, electrokinetic focusing, and temperature control and responsive surface coatings. Not only will molecules need to diffuse to the surface of a future NEMS device, they will be able to control the interaction environment that's in which particles move. This is especially true of biomolecules occurring at low concentrations, time-sensitive measurements and for compact point-of-care devices.

Lastly, a no-brainer will be making it normal. Of course, sensitivity is not the only parameter that should be reported, but many other ones such as Allan deviation, Q-factor in medium, Drift rate and limit of detection, surface regeneration and validation in complex matrices. The absence of these parameters will make it difficult to compare NEMS platforms and/or convert them to working assays.

9. CONCLUSION

NEMS platforms provide a very sensitive, label-free way of real-time biomolecular interaction monitoring. The transduction of molecular binding into physical/mechanical signal in very small mass & length scale constitutes their strength. But the concept of a nanobalance is getting past. Biomolecular NEMS signals quantify the mass, stiffness, hydration, surface stress, dissipation and drift. Thus, the necessities for a good platform include construction over the resonator mechanics, the floor chemistry, the fluidics and the processing of the sign.

The amazing mass responsivity and single particle analysis continue to be the top contenders for the use of nanobeam and nanocantilever NEMS. The suspended microchannel resonator that has value for liquid phase monitoring and acoustic or photonic-mechanical systems which have the potential to solve problems of transport enhanced and integrated biosensing have two additional takes that are very important. It is anticipated that the most important developments in the future will be multiplexed arrays and active fluidic control as well as development of antifouling interfaces and multimodal readout and standardized reporting. These transmutations can lead to the potential use of NEMS biosensors as real-time sensors for protein, nucleic acid, vesicles, as well as detecting pathogens and cells in biomedicine and the environment.

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