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Review Article

MEMS-Based Biosensors for Mass Detection in Single Cells-Review of Techniques and Approaches

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Abstract *- The significance of early detection and diagnosis in medicine is widely acknowledged, whereas clinicopathological methods, which are more effective after diseases have progressed, tend to receive less attention. With hematological diseases, the chances of cure or extension of life span are higher with early-onset diagnosis. Early detection of the disease onset and progression is vital and challenging for reasons of minuscule changes in molecular or cellular behaviors. Cells are the basic building block, so understanding the changes at the cellular level is crucial to estimating the ecological and biogeochemical models. In the case of single-cell studies, sensitivity and resolution are the key challenges that the scientific community addresses as the key focus areas. With traditional label-free sensing techniques, though these challenges are addressed, the sample preparation, handling, and characterization are setbacks for making their gold standards. With emerging technologies incidental to micro/nanofabrication processes, MEMS-based resonant sensors emerged as a paradigm technique for the detection of bio-physical changes in a single-cell study due to their good sensitivity and resolution. This paper focuses on the review of techniques and methods to detect the mass of biological cells and compares their results with the MEMS Resonating mass sensors. It also focuses on the technique of resonant frequency shift and approaches for improving the sensitivity of the resonators by focusing on reported structures.*

Keywords *- Cell behaviour studies, Label-free sensing, Micro/nano-fabrication, Micro-electro mechanical system, Resonant sensors.*

1. Introduction

During the recent pandemic, the need for early diagnosis and care has played a pivotal role in the field of medical sciences. The need for and urge for diagnosis are addressed through laboratory tests using conventional systems, such as imaging and biosensors [1]. However, conventional systems face numerous challenges that need to be addressed, such as sensitivity, swift detection, sample sizes, and energy demands. These challenges are addressed by the incorporation of Micro-Electromechanical Systems (MEMS). With the advent of this technology, diversified fields of medicine, bio-systems, etc., have been observed to have profound applications. Conventional diagnostic techniques have been dependent upon clinical-pathological tests within laboratories upon onset of disease symptoms, minimising the chances of cure due to rapid disease progression over therapy management. So, the prominence of early detection and diagnosis is always credited to the field of medicine. Over the decades, early detection techniques and technologies have progressed very minimally, creating challenges in early diagnosis. To accomplish the purpose of developing early detection mechanisms, the cell is the basic functional unit of the living entity that is the motive for targeted study. Molecular changes in bio-functional operations are the reasons for disease prognosis, which leads to physical changes in the cell. For understanding this molecular behaviour, cell functions have critical checkpoints that are crucial for understanding and detection and can be well established with single-cell analysis[2, 3]. These understandings not only provide implications for diagnosis but also give insights into estimating the ecological and bio-geochemical models[4].

However, the paucity of literature on mammalian cell growth models hinders the technical evaluation process. This is because most of the reported studies are with population-based models and size homeostasis [5, 6] making single-cell analysis a quest for research. In population-based studies, experiments on cell cycle analysis are implicated with the mean of the population parameters that emanate poor resolutions. This results in the shortcoming of establishing the growth relationship of the cell cycle. To a greater extent, anticrafts generated during the diagnosis process add to further downgrading the resolution. All these factors result in daunting challenges, creating the urge to pursue single-cell studies and research [6, 7].

Among the contemporary techniques for single-cell studies, label-free detectors (Fluorescent and radioactive labelling) gained eminence for their high throughput. However, these devices were hindered due to sample preparation and complicated characterizations, resulting in less interest[5], [9]. Though the challenge of sample preparation is overwhelmed by the Quartz Crystal Microbalance (QCM) and Surface Plasmon Resonance (SPR), these devices endure with sensitivity. As label-free devices endure with appealing factors for single-cell studies, expediting emerging technologies like micro/nanodevices (optical sensors, microdevices and micro-mechanical sensors) have the potential to scale down devices according to sensitivity systemization[9, 11].

With equally poised pros and cons of these techniques, where resolution is common is taken by scale-down prerogatives. On the contrary, Micro-Electromechanical Systems (MEMS), resonant sensors have the technique to detect the bio-physical properties of single cells. With the principle of frequency shift, MEMS resonant sensors detect the frequency difference between load and no-load conditions.

Having the advantage of scaling down approaches from MEMS to NEMS, higher sensitivity and better resolutions are achieved with techniques discussed above, making them most viable for chemical and bio-sensing[12-17]. This paper focuses on the techniques that are intended for mass sensing mechanisms at the nano to femtogram level. The challenges of existing techniques and the scope of micro-electromechanical resonators are discussed.

2. Biological Cell Cytometry

The miniature and basic building block of the living entity is referred to as a cell. With varying living organisms in terms of physical (size, shape, and type) and geophysical habitations (aquatic, non-aquatic amphibian, etc.), the size and volume of the cell differ and also have differentiation with the type of cell within the body, but the architecture remains unchanged except in regard of prokaryotic and eukaryotic. An outer membrane, nucleus, chromosomes (DNA/RNA source), and cytoplasm are the major constituents of a cell. A major contributor to cell volume is the cytoplasm- a semi-fluidic membrane that is the source for cellular and chemical functionalities (inter-cellular and extracellular) and communications. Other constituents of cells include mitochondria, organelles, Golgi complex, lysosomes, microbodies, and Vacuoles. The constituents of cells and the typical cell sizes in the nano-to-micro regime are shown in Figure 1.

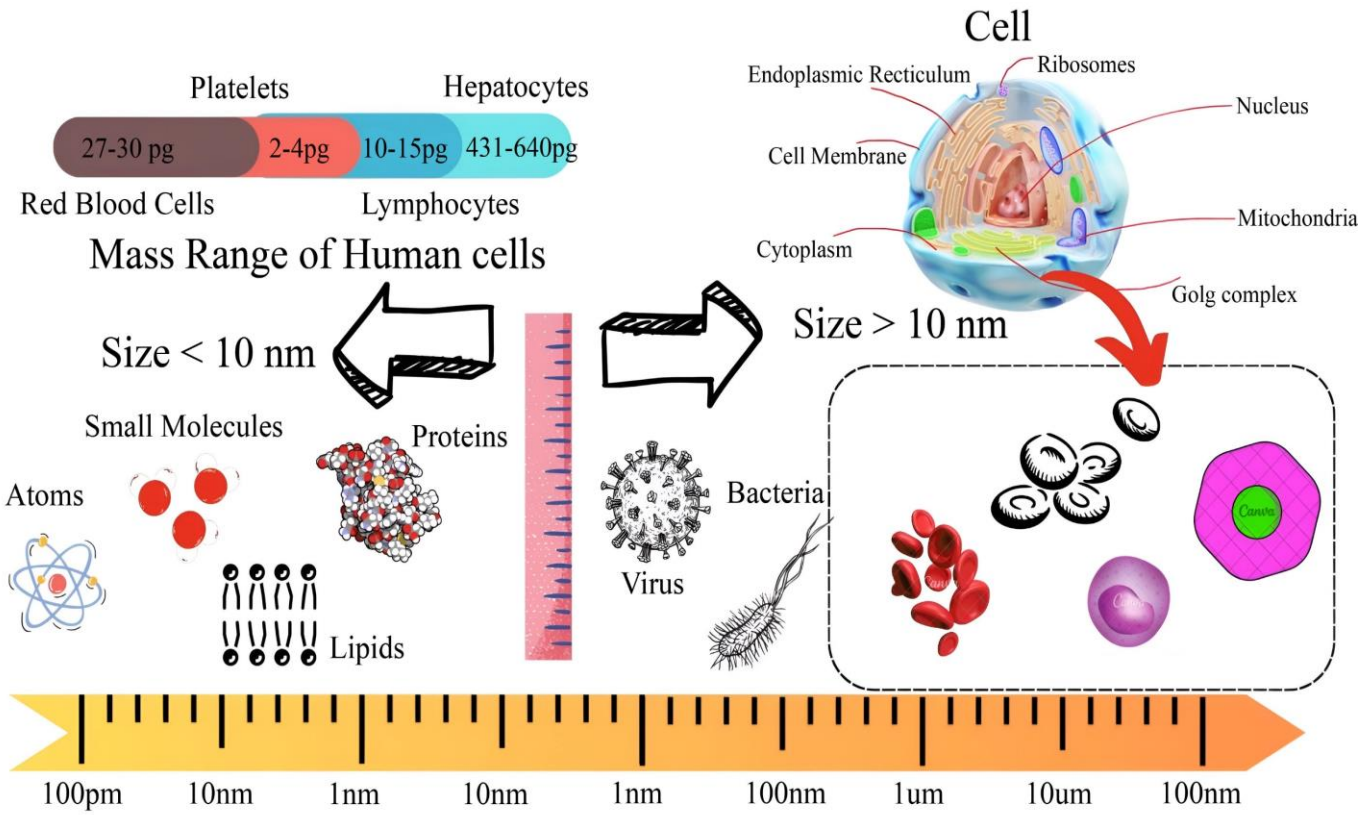

Fig. 1 Scale of different particles and human cells ranging from 100pm to 100 um

2.1. Mass and Volume in the Cell Cycle-Biomarkers for Homeostatic Processes

The cell cycle incorporates cell division (proliferation) and apoptosis (natural death)- where proliferation includes the development of cell multiplication. Upon multiple proliferation phases, the cell triggers the natural death process referred to as apoptosis. During the growth phase, DNA replication is a major change that happens to form daughter cells. During this process, the cytoplasm increases in size; thus, its volume is altered as most of the cytoplasm contains water.

The process of DNA synthesis and daughter cell formation time is considered to double rate, which spans mostly to within 24 hours timeframe. However, this rate differs from cell types and organisms; for example, yeast has a doubling rate of 90 min [18]. During this process, the concentration of regulatory proteins plays a major role in cell division, through which volume and mass are controlled. So, each phase of cell division is adapted with specific mass and volume growth projected with cell cycle physical checkpoints. As a result of this, these checkpoints, with specific mass and volume changes, can be biomarkers for Homeostatic disease detection at the very early stages. These checkpoints refer to the growth and division of cells, which are not uniform over the population of them, irrespective of ambient environments.

The mean deviation of cell proliferation over a population of cells is not constant due to ambient conditions. Due to this, the study of single cells has gained prominence, and the study of any deviated cell behavioral patterns correlates to disease conditions and oncogenesis, resulting in early detection. However, during the population-based studies, the behavioral patterns of cells are determined to be not attributed to single cells for their uncertainty of growth patterns. On the other hand, behavioral patterns of a single cell can be depicted in a population of cells. The study of single-cell behavior under disease conditions is correlated with deviating checkpoints and has greater applications in the field of omics.

In literature, most of the studies and models emphasized population-based studies with cell count and doubling rate as crucial parameters [18-25]. During cell growth, cyclic kinases play a major role in depicting the checkpoints[26, 27] and grow to critical size in mass and volume for undergoing DNA replication [20]. The cell cycle can be expressed in two phases- at the start of the cell cycle (time of birth), the mass of the cell is comparable less than that of its critical size (proliferation time). During the start of this proliferation point, the mass increases over time, which is considered a time-dependent phase. The second phase is the independent phase, where mass incremental is very minimal, and size remains independent of time, which is expressed with examples of yeast and eukaryotic cells[28, 29].

2.2. Cell Cycle Model

In order for the cell to initiate the growth model (division), an external parameter is vital as a trigger point, which can be ambient temperature change or the environment of the cell. In most instances, Insulin (IGF- Insulin Growth factor) is the triggering point that stimulates the kinases and ribosomes. These actions initiate the S6 protein, which is the basis for protein synthesis, which is the genesis of cell growth. For this reason, the growth of the cell is directly proportional to [S6] and the total ribosomal quantity of R.

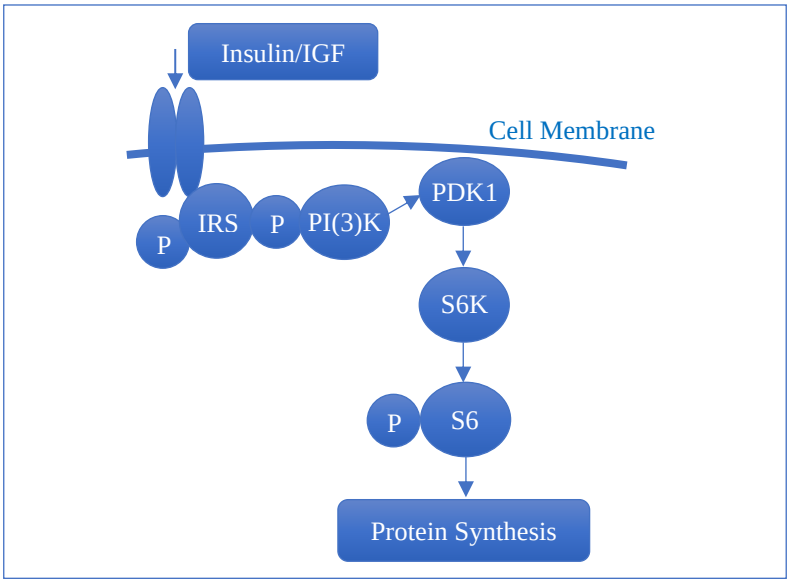

Fig. 2 Growth model of cell-signalling pathways (Ahmadian et al., 2020)

$$\frac{dm}{dt} = k_1[S6]R - k_2 \qquad \text{(a)} \qquad [19]$$

From Equation (a), the m is total mass, k_1 and k_2 are arbitrary constants that define the rate at which the cell grows, and R is total ribosomal content. This $\frac{dm}{dt}$ is considered the rate of change mass with time. From Figure 2, the process of protein synthesis is rational to the concentration of the S6 protein transfer from the cell wall to the inner cytoplasm. The transfusion of this protein concentration so depends upon the surface area of a cell.

$$\frac{d[S6]}{dt} = k_3 A/V - k_4[S6] \qquad \text{(b)}$$

From Equation. (b), k_3 and k_4 are considered to be rate constants, A is surface area, and V is volume. But under steady-state conditions, the rate of change of concentration remains constant means $\frac{d[S6]}{dt} = 0$, which means equation (b) is modified as

$$\frac{k_3 A}{k_4 V} = [S6] \qquad \text{(c)}$$

From Equation. (c), The equation can be expressed as

$$\frac{dm}{dt} = k_1 \frac{k_3 A}{k_4 V} R - k_2 \qquad \text{(d)}$$

The negative sign of ($-k_2 m$)is protein decay (loss), which is minimal during the process of the cell cycle and results in constant volume throughout the growth phase. The number of ribosomes is also unaltered, making R/V = R_1(constant). As a result, cell growth depends upon the surface area; in contrast, the larger the surface area of a cell, the higher the rate of change of mass.

$$\frac{dm}{dt} = \frac{k_1 k_3 R\prime}{k_4} A \qquad \text{(e)}$$

$$\frac{dm}{dt} = KA \qquad \text{(f)}$$

K is constant, and A is the cell surface area.

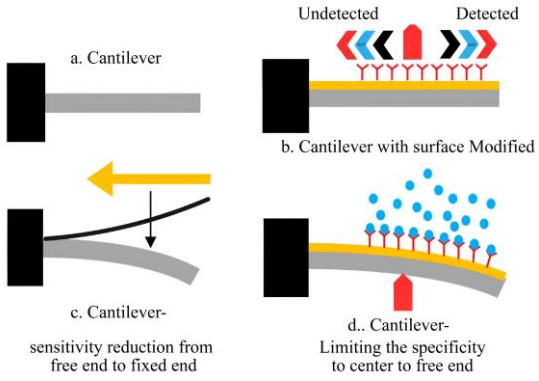

Fig. 3 Spatial sensitivity variation in traditional cantilevers for mass sensing applications

2.3. Challenges with Cell Population-Based Studies

Considering the population of cells, each set of cells has the potential to grow and divide or go to apoptosis. Estimating or evaluating population dynamics is possible with knowledge of single-cell characteristics and mechanisms that drive the cell cycle. Conversely, sufficient and accurate prediction of population dynamics with time helps in inferring single-cell characteristics (lifespan/growth rate). The correlation between the growth versus division phase of the cell cycle is tenuous due to the dynamics of ambient environments, making it difficult to understand the cardinal properties of the cell cycle. So, having a persistent feedback mechanism between population and single-cell studies is essential to understanding cell growth dynamics. And this can be possible with emphasized studies on single-cell studies. Another challenge with population-based studies is about cell volume, as it substantiates static measurements because of its simplicity while being accurate. However, the volume doesn't depict the synthesis rates of the cell as it is associated with cytoplasmic content (the volume of the cell is due to the cytoplasm). Studies on the hydration of the cell during its birth have shown a doubling of its volume than average volume for a small interval of time, affecting growth rates due to these variable hydration levels, which is reported by Terasima and Tolmach (1963) and Sandritter, Schieder, Kraus, and Dorrien (1960). With this uncertainty, a measure of volume could not be an ample statistic for metamorphosing the relation between linear and exponential growth models. Studies by Bell and Anderson in 1967[20] estimated that the largest deviation between the linear and exponential models is 6%. So, the alternate measure can be the mass of the cell, which includes the cytoplasmic content and other ribosomes, etc.

2.4. Cell Growth Modelling Tools and Approaches

Cell models that investigate processes such as cell proliferation, growth, and death frequently employ proteins that exhibit stoichiometric relationships. This is because proteins are the main drivers of cellular activity, and being able to study the stoichiometric relationships between them can help researchers better understand how cells grow, divide, and die [26]. And these reactions are explicated by CDK (Cyclin-Dependent Kinases) induced kinetic equations. However, these equations result in more inconsistent behaviour due to intractable and random patterns of parameters -necessitating the need for improved formulation perpetually.

Through the comparison of cell modeling with continuous advancements over time, the complexity of cell behavioral systems remains the same. This daunted the researchers and made them focus more on cell dynamics. In 2020, Gillespie introduced the Stochastic Simulation Algorithm (SSA), which is considered the most effective in expressing molecular interactions within the cell by considering their dynamics in nature (as shown in Equation. 1-3)) [30].

$$\frac{dx}{dt} = \frac{(k_3' + k_3'' A)(1-x)}{J_3 + 1 - x} - \frac{K_4 myx}{J_4 + x} \quad (1)$$

$$n\frac{dy}{dt} = k_1 - (k_2' + k_2'' x)y \quad (2)$$

$$\frac{dm}{dt} = \mu m(1 - \frac{m}{m_*}) \quad (3)$$

Population-based dynamics were explained by Bell and Anderson in 1967, which considered volume to be a vital parameter.

$$N(V) = N(\frac{V_O}{V}^2) \quad \text{(h) [20]}$$

From the above equation, Vo – cell volume and V – volume are before the cell division.

3. Methods for Detecting Biophysical Properties of the Cell

3.1. Techniques Involved in Cell Cytometry

Within this last decade, the devices for measuring cell mass have been unfolded because of micro/nanofabrication and optical techniques. Before the quest for these advanced devices, fluorescence-based immunoassay and bio-chemiluminescence techniques are widely used because of their standardization in commercial applications in single-cell analysis. However, these techniques are efficient in extracting cellular function in correlation with chemical compositions. These techniques tend to cause damage to cells, and during high throughput scenarios, extracting non-polluting measurements is highly challenging due to biochemical process flows. With such challenging aspects, these techniques tend to give a specific characteristic of the cell within its structure but do not yield any synthesis parameters of the cell as a whole.

Thus, fails in explaining the cell proliferation and cycle parameters with these techniques. However, measuring the physical properties, especially mass, is challenging due to the miniature size of eukaryotic cells, typically between 10 to 20 microns in diameter, making it difficult to design tools and devices that can measure mass precisely.

The growth models- the volumetric approach of the cells is measured with coulter counter and flow cytometry. But recent research has brought forward a few techniques like single-cell cytometry, Micromechanical Methods (MEMS), Magnetic Levitational Image Cytometry (MLIC), and Optical/Opto-Electrokinetic (OEK) are widely in practice and research. All of these can be categorized as label-free and labeled sensors.

3.1.1. Labelled Sensors

Label detection has the reagent or assay that binds to the target detection is possible by identifying the shape, colour or any other physical presence. This method of detection facilitates the target's binding for the labels, which could give a measure of them. Though label detection methods are precise, they are difficult in sample preparation and complex. This method is prone to alternation of biomolecules, impacting negatively for detection.

3.1.2. Label-Free Sensor

Label-free sensing is a mechanism that does not utilize any detection labels or chemical essays. In this method, the ligand or target molecule is directly immobilized onto the surface of the substrate without any alterations to the biological molecule. This technique has a major edge in eliminating the background noise during the detection due to the non-specificity binding of conjugated enzymes, antibodies, and labeled proteins.

This allows the biological samples to be unaltered in their physio-cystic nature, yielding better sensing results. The basic pros and cons of label-free and labeled detection schemes are shown in Table. 1 highlighting the feasible parameters. Industries for various separation and toxicity studies. A few of the adherent and suspended cells are listed in Table 2.

Table 1. Differentiating labelled and label-free detection schemes

Type of Sensing	Principle of Operation	Sample Preparation	Sample Handling	Quantitative	High Throughput	Equipment cost	Examples
Labelled Sensors	Sensing/detection using labelled molecules.	It is required, in most cases; it is difficult to medium	Yes Required	Limited to few techniques	Yes	Inexpensive	Fluorescent Probe, Radioisotope, chemiluminescent, ELISA
Label-Free Sensors	Labelling is not required.	Minimal	Minimal	Yes	Specific to a type of label-free	Expensive	SPR, QCM, MS, MEMS.

3.2. Cell Types

3.2.1. Adherent Cells

Cell lines that adhere to the external layer of a cell culture vessel proliferate. Due to the adherent character of the cells, enzymes such as trypsin are necessary for harvesting or subculturing the cells from the cell culture vessel. Adherent cell culture is essential in the disciplines of the biology of cells, biochemistry, and cancer studies due to the presence of numerous adherent cancer cell lines.

3.2.2. Suspended Cells

When cells are suspended, they are made to float without any binding, but in media for proliferation, they are regarded as suspended cells. Mostly used in pharma and bio-medical

3.3. Coulter Counter

This device can be referred to as a resistive pulse sensor due to its detection mechanism of identifying the shift in resistance of a conductive channel when the particles transverse through it. A series of pulses of voltage/current is subjected to application on these selective microchannels, where the measure of conductivity is taken as a reference for detection. CC devices are limited to suspended cells/particles where bio-physical properties like size, shape, mobility, surface charge density and concentration are detected. The sensitivity of the device is built upon the channel diameter, as throughput is proportional to the cube of diameter (channel).

For sub-micron particles like single cells, the diameter design is scaled down to have a better detection range and achieve significant sensitivity. So this renders the throughput of the devices, especially for biomolecular detection, having greater volume ranges (>100ml) [31], and to avoid this, multichannel CC devices have been brought forward [32] where high throughput is achieved. Overall, these devices are limited for the suspended cells, lack considerable throughput, and are also subjected to analyte differences, resulting in deviating results.

3.4. Fluorescent Techniques

Most widely used and commercially available method for cellular observations and examination. For larger cell volumes, the fluorescent technique is combined with flow cytometry for single-cell observation, which has recently been researched and is available [33].

Over some time, this technique has evolved with digital fluorescent imaging [34], micromachining [34], and understanding the kinetics of fluorescent molecules diffusion in aqueous solution at room temperatures [35] have brought micro and nano fluorescent devices that can detect minimal particle concentration limiting to single cells. But, being a labeled sensing mechanism, the bio-compatibility and forced stress on cells leading to cell death or alteration are major setbacks in implementing this system to understand the single-cell behaviors [33].

Table 2. List of suspended cells and adherent cells with functionalities in the human body

	Suspended Cells	**Function**
1	Erythrocytes	Oxygen transportation
	Leukocytes	Antibodies, Immune
	Thrombocytes	Clotting agent
	Monocytes	Immune system
	Neutrophils	Immune system
	Eosinophils	Anti-allergic, Immune system
	Basophils	Immune system
	Mast cells	Immune system, anti-inflammatory.
2	**Adherent cells**	**Function**
	Epithelial Cells	Skin
	Endothelial Cells	Blood Vessels
	Fibroblasts	Tissue Repair
	Adipocytes	Fat storage
	Osteoblasts	Bone
	Myocytes	Muscle
	Hepatocytes	Liver
	Neurons	Brain

3.5. Flow Cytometry

In conventional flow cytometry, particles are subjected to pass through an illuminating channel where light scattered is determined to detect the particle characteristics. With Flow cytometry, identification, sorting, and separation of biological particles can be achieved. But detection sensitivity of the FC depends upon the angle of scattered light and fluorophores.

Advanced techniques like single-cell mass cytometry inherit flow cytometry to achieve high flow rates for better throughputs, making flow cytometry undesirable in single-cell studies.

3.6. Mass Spectrometry

Mass cytometry is derived from the MS technique to understand the cell properties when coagulated with the antibodies.

For its sensitivity, selectivity and high throughput, mass cytometry is a hand-picked technique for most scientific domains from forensics, food certifications, pharmaceutical and biological studies [36-41].

The structural information of the analyte is determined by mass to the to-charge ratio (m/z) of the charged particle and the time of flight. With a wide variety of configurations from high to low resolution, complex cell base studies need a series of instruments concurrently employed to address them.

Moreover, the metamorphosis of the analyte from liquid to solid and then to ionised, regardless of the configuration of MS, causes denaturing of the cells that deviate from the single-cell studies [42].

3.7. Optical Methods

The physical cytometric parameters like dry mass, size, volume, and shape of cells are related to their Refractive Index (RI) for detection using optical methods. These techniques are considered to be non-invasive and non-contact techniques for continuous monitoring. The best attribute of this technique is that it is independent of cell type. A group of techniques that fall in the Quantitative Phase Contrast Microscopy (QPCM) for providing single-cell parameters are approached with interferometric and non-interferometric methods.

3.7.1. Interferometric Methods

The technique of separation of light into two different optical paths and recombining to form fringes is used for quantifying the phase shift. When one of the source beams is passed through the cell, the phase obtained is a measure of the refractive index of the cell through its volume. From this, the dry mass is calibrated using the refractive index and density of the cell. Techniques like Phase-Shifting Microscopy/Imaging (PSM/PSI) and Diffraction-Phase Microscopy (DPM) use the interferometry method using lasers that result in artifacts resulting in lower sensitivity[43]. On the contrary, Spatial Light Interference Microscopy (SLIM) is a type of PSI that has the capability of calibrating nanoscale structures, pushing the limits of sensitivity to higher levels to 0.1- 1 fg/μm^{-2}[43]. However, these techniques are limited to the measurement of the dry mass of the cell when they are altered for compatibility with detection mechanisms. For live cell measurement, Quantitative Phase Microscopy (QPM) is used in single-cell studies[43]. This technique uses four-wave transverse shear interferometry for observing phase change in real-time, allowing labelling cells in real time, yielding live cell mass calculation and, upon developments made, increasing the throughput and volume detection. Further enhanced techniques like Digital Holography Microscopy (DHM) in which rather than phase, the intensity is also considered and compared with phase. Due to this, it is most effective in identifying organelles and also tracks intracellular transportation [71]. Indeed, this technique is less preferable due to complex data processing and the use of a laser that has complicated optical paths. The above techniques discussed perform the detection of cellular parameters in 2D whereas Quantitative Phase Tomography (QPT) can perform a 3D scan by obtaining phase transition in 3D space[44]. Due to this advantage, it can detect sub-cellular regions and can even detect certain thickness regions of cells in clusters. However, this device has limitations with mammalian embryos and involves complex data processing systems.

3.7.2. Surfaced Plasmon Resonance

SPR was originally used for sensing purposes in 1980 [27], followed by probing procedures on metal layers [45]. SPR is well-known for measuring immobilized biological analytes in real time. In the early 1990s, the first SPR biosensors were produced and applied to the investigation of bio-molecular interactions [46]. Traditional SPR biosensors provide real-time measurements of interactions between biological objects immobilized on the surface of a metal-supporting plasmon and their liquid counterparts. Surface Plasmon Resonance imaging (SPR) and microscopes are techniques that aim to isolate this relationship by imaging the surface of metal [47]. The combined oscillations of free electrons close to the interface metal-dielectric contact are known as surface plasmons, which are a type of electromagnetic field. Surface plasmons have a confined electromagnetic field that decays into the metal-dielectric interface[47]. Because of this property, surface plasmons are valuable for studying activities on metal surfaces [27], [48]. There are multiple distinct SP modes on different metal/dielectric configurations [49]. The Propagating Surface Plasmon (P-SP) mode is commonly used in SPR imaging/microscopy and is supported by a continuous metallic sheet. Although SPR imaging and microscopy are commonly used to identify a wide range of biological entities, this study focused solely on reporting cells.

Argoul's team reported on their research of adhering cells using a High Resolution (HR) SPR microscope[50]. They investigated the adhesion and motility of C2C12 mouse myoblasts cultured on an SPR chip. The morphologies of the adhering cells were tracked, and the dynamics of filopodia and lamellipodia marks were seen locally. They also observed how C2C12 mice myoblast cells migrated, adhered, disengaged, and connected to a gold substrate. Tu et al. investigated the mechanism by which individual cells adhere [27], [47]. They employed SPR microscopy on a nano-porous array system that was integrated with microfluidic devices such as single-cell traps. The growth of Human cancer cells (HeLa) and mouse foetal stem cells (C3H10) was seen, and it is demonstrated that the individual-cell binding approach adheres to Tao's team investigated the movement of mitochondria along significant rat hippocampal neurons [47].

4. Physical Cytometry Using MEMS Resonant Sensors

With the ability to measure physical parameters down to the attogram level using MEMS/NEMS devices [51], the physical characteristics of cells are monitored for minute dynamic changes that happen during the proliferation phase. The foremost advantage of MEMS resonators is that they facilitate detecting the physical cytometry of cells by avoiding antibodies or fluorescent markers[52]. As mentioned in previous sections about efficient label-free detection using SPR and Quartz Crystal Microbalance (QCM), with applications spanning from basic biological system laboratory to advanced drug-based studies, these techniques have setbacks in scaling down and mass fabrications [6], [53], [54], [55]. Though various types of micro-fabricated devices like mechanical, electronic, chemical and optical are reported in the literature, they have challenges when it comes to single cell cytometry due to charge screen, optical alignment of

components, and surface adhesion and modifications, respectively. However, with the use of resonant mass sensors, challenges are addressed when compared with the devices mentioned above [52]. With mass variation at femtogram to atto-gram level in cell proliferation studies, device complexities are comprehensively high. Though the quest for proliferation studies lasts from 50 years for a population of cells to single cells, still, there is a tremendous interest in interpreting the relationship between physical cytometry to cell cycle [57-61]. The major quest is to understand growth rate versus cell size over the cell cycle and whether it is constant or proportionate [53], [15]. The cell cycle is explained with both linear and exponential models, where the linear model is due to the 'gene dosage' that is because of DNA growth for the transcription process, and the exponential growth model is due to mass growth of cytoplasmic and ribosome of the cell. Due to this, the cell grows heavier by accelerating its rate of mass. So this explains the exponential model size-dependent model whereas the linear model depicts size-independent [63], [64]. So to understand this behavior of cells, extensive research is carried out, and various researchers make progress in identifying the dry cell mass [65], buoyant mass [53], [66], [67], and volume [68].

4.1. Principle of Resonant MEMS Mass Sensor

The principle of a resonant sensor is that it works on the shift in resonant frequency with cells isolated on the device to that of time when a cell changes its morphology [69]. Using this principle, Thomas P Burg (2006) modified the cantilever with nanopatterns for mass sensing applications [52], and Kafri measured the mass of yeast and bacteria in 2016 [71], [72].

$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m^{*}+\propto \Delta m}} \qquad \text{(i)}$$

Where f is the frequency of the beam, k refers to the spring constant, and m* is the mass of the device. The change in mass (Δm) is the loading of the cell, and α represents the constant [69]. The sensitivity and resolution of the cantilevers depend upon the effective surface area, as it is the governing parameter for absorbed mass. To improve this absorbed mass, considerable progress was made by Lee et al. and Datar in 2009 with perforations and nanopatterns. On the other hand, the sensing in fluidic mediums has considerably poor sensitivities, resulting in a bottleneck in employing resonant mass sensors. For such environments, the alternatives are the detection of surface stress and Suspended Micro-channel Resonators (SMR) [53].

With the wide scalability of structural dimensions, these traditional structures are influenced by the challenges of stiction, S/V ratio, and surface modification techniques, which will be discussed in detail in later sections. Besides these challenges, they also have quality factors and sensitivity bottlenecks. To address these challenges of traditional structures, pedestal mass sensors and SMR are reported in the literature, and they overcome most of them.

4.1.1. MEMS Resonant Sensors for Adherent Cell Detection

The rectangular cantilevers are modelled according to sensitivity requirements for mass sensing applications by scaling down the dimensions. On the other hand, it is widely reported that the mass sensitivity of resonant mass sensors (rectangular cantilevers) is spatially uneven[73]. With adherent cells, the need for immobilization onto the surface of the cantilever is essential, which limits the sensing area due to downsizing and spatial non-uniformity of the sensor, as shown in Figure 3. Suppose there are going to be a large number of connected target entities that are significantly smaller than the sensor[62]. In that case, it is reasonable to assume that their masses are all roughly the same and to use an average mass sensitivity that can be easily calculated analytically. No one can presume that the target mass is uniformly distributed if only a few or a single target entity needs to be linked to the sensor, and if an attachment site other than the end of the cantilever is used, the extracted mass must be adjusted to account for the cantilever's mass dispersion from optical images [52].

However, these techniques reduce the mass sensor's sensitivity and functionality. The structure of the sensor is shown in the form of a platform in the center suspended by four-legged springs. The sensor platform is considered for sensing and has a homogeneous vibrational amplitude for the attached mass (irrespective of position on the platform) due to the transformation of flexural bending to torsional bending at the angle of the spring (each leg). With this pedestal mass sensor, the mean variation of vibrational amplitude is confined to 2% for its maximum resulting error margin of 4.1% in mass sensing to least to the maximum value [10, 56].

4.1.2. MEMS Resonant Sensors for Suspended Cell Detection

As we have discussed the behavior and characteristics of suspended cells in previous sections, where the mass sensing of suspended cells needs medium, traditional methods of immobilization on MEMS cantilevers yield a dry mass of the cell rather than the actual mass. To address this challenge, Buoyant mass detection using Suspended Micro resonating Channels (SMR) is introduced [52]. The initial suspended channel walls are immobilized for the deposition of mass, which makes up the effective mass of the cells. If the S/V ratio of the channel is significant, then the mass deposited on the walls of the channel contributes substantially. Proteins in aqueous solutions have a bulk density roughly equivalent to that of purified solutions, allowing them to be detected using this method[4], [6], [8], [9], [66], [69]. The resonant frequency shift of the SMR is directly related to the mass of the particle it travels through, and successive repetitive measurements define the particle propagation phase.

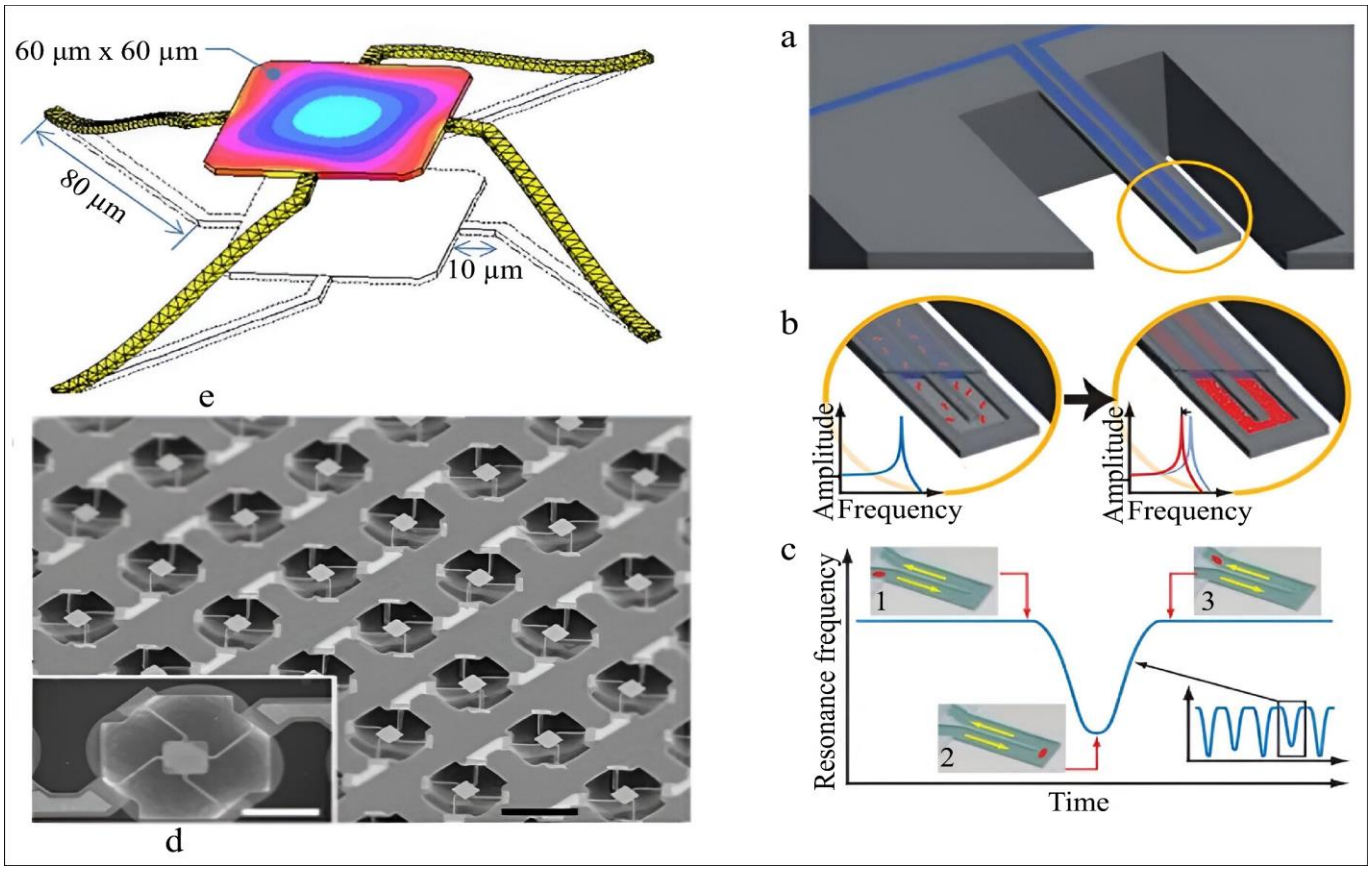

Fig. 4 From right to left a) Suspended micro-resonating channel for particle mass sensing b) Frequency shift when the particle travelling from free tip back to outlet [70] c) Graph showing frequency and deflection change during the particle at free end d) Uniform pedestal mass sensor for adherent cells fabricated cell [62] e) Showing uniform mass sensing of Pedestal mass sensor

Though these devices have proven highly efficient and can detect up to 1pg/Hz sensitivity, they lack compatibility with the size of the particles. When the density of a particle is higher than that of the background solution, its differential mass Md is not zero (it is positive). If a nanoparticle floats in the background solution, the mass difference M_d is negative. When nanoparticles are fed through the channel, the mean frequency shift for the solution is between 25 and 3 mHz, indicating that gold and polystyrene particles possess a non-zero differential mass of 1.0 g/cm3 in PBS solution [52], [66]. Although the masses of polystyrene (195.6fg) and gold (9.8fg) particles are vastly different, their divergent masses during transport in fluid PBS are close to 9fg [52]. So, re-engineering for particle dimensional range is essential for SMR technology insight into their effective device's capabilities in mass sensing.

5. Conclusion

The emerging technologies incidental to micro/nanofabrication processes, such as MEMS base resonant sensors, have emerged as promising techniques for detecting biophysical changes in a single-cell study due to their high sensitivity and resolution. With further evaluation of the process flows, MEMS/NEM's scale dimensional dynamics, and improved surface modification methods, the limitation of mass sensitivity has crossed the barrier from cellular detection to protein molecule detection.

The mass limitation from picogram detection is pushed to the attogram and Zeptogram level using MEMS resonant sensors, which has facilitated this possibility. Despite the challenges of single-cell isolation, spatial adhesion of particles on the sensor, engineering with materials, and cost-effective devices, resonant sensors are potentially viable sensors for mass detections with ultra-low sensitivity.

This paper reviewed the techniques that are used in mass sensing and cell cytometry along with the MEMS resonant Sensors. The challenges and the progressions in this field are reported.

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