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Chapter 1

Emergence of analytical techniques

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The impact of nanotechnology and the development of micro/nano sensors has significantly enhanced the discovery of new therapeutic and diagnostic approaches. The emergence of precision medicine towards developing personalized healthcare systems have been achieved by high throughput analytical systems. Current analytical systems are the integration of multiple fields like material science, biology, electronics, MEMS, physics, computer, chemical science, etc towards developing a better diagnostic system. There are many versatile techniques available that have transformed the healthcare sector in many ways. Some of the well-known techniques are electrochemical, Raman, mass spectroscopy, SEM/TEM, fluorescence, NMR, MEMS, artificial intelligence (AI), etc. These systems are highly sensitive and accurate; however, an ideal analytical system would consist of multiple characterization tools providing more scientific information for rapid diagnostics and quicker analysis. These innovative biosensing platforms need to be cost-effective, user friendly and allow real time monitoring, particularly for point-of-care applications. The emergence of nanotechnology and nanobiotechnology along with the significant advancements in material science (nanomaterials, nanomedicine) has provided reliable, ultra-high sensitivity, high selectivity and efficient portable sensors to screen, monitor and treatment of diseases in real time. Current researchers are looking ahead to build a multidisciplinary system for developing advanced diagnostics systems for all in one chip technology for personalized healthcare management.

1.1 Introduction

The rapid developments and innovations in nanotechnology/nanomaterials have opened up several opportunities in all technological fields such as electronics, energy, agriculture, and the healthcare sector [1]. Further, the unique properties of the nanomaterials like larger active surface atoms, tunable optical and chemical properties, variable size and shape have provided significant advances in biomedical applications [2–4]. Recent years have witnessed significant progress in precision

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medicine for developing more efficient and multi-analysis immunoassay/biomedical systems by combining nanotechnology with nanomaterials [2, 5, 6]. These newly decorated and advanced systems have revolutionized the healthcare systems from developing ultrasensitive medical devices to point-of-care tools for clinical practice in hospitals/houses [7, 8].

Immunoassay/biomedical tools are one of the most advanced tools for the quantitative detection of biochemical targets (e.g., pathogens, bacteria, cells, nucleic acids, proteins, etc) [8, 9]. Most of these analytes are extracted from body fluids like saliva, urine, blood/plasma, etc for clinical investigation. There are various assays/tools that have progressed from the traditional ones performed on tubes/glass plates/microplates to sophisticated miniaturized platforms using various kinds of readout signals. The current technique for detection and analysis of analytes which include electrochemistry, Raman, electronics, magnetic, UV, FTIR, optical microscopy, surface plasmon resonance, fluorescence and mass spectroscopy, etc are the frontiers of the traditional disciplines in science and engineering [10, 11]. These amazing analytical techniques allow better characterization to be achieved, providing more accurate clinical information, rapid diagnostics, cost-effective, user friendly approaches, and state-of-the-art facilities for personalized health management [12–14].

This chapter discusses different emerging and existing techniques to prepare nanostructures and the benefits/limitations of each type along with their application. Next, various approaches to prepare different types of systems, their characteristics in generating nanomaterials with desired properties are presented. The chapter also focuses on existing and new tools combined with nanostructures for development of ultrasensitive instruments for health management. Further, current immunoassay/tools like ELISA (the enzyme-linked immunosorbent assay), PCR (polymerase chain reaction), FACS (fluorescence-activated cell sorting), clustered regularly interspaced short palindromic repeats (CRISPR) as sophisticated analyte-detecting tools composed of biological, chemical, electrical, optical, computational or combination techniques have provided a rapid diagnostic system in hospitals and medical research facilities [8, 15–17]. However, the human effort in improving the diagnostic system is a continuous process and many factors contribute to achieving these milestones. Now, we will summarize some of the factors that have contributed immensely for developing advanced healthcare systems.

1.2 Nanomaterials

We will discuss some of the well-known characteristics of nanostructures that led to the development of better healthcare systems [18]. Some of the characteristics of nanostructures are unique in nature that can be controlled or tuned as per the requirement. (i) The shape and size of nanomaterial: the better control over the size and shape of nanomaterials leads to various novel properties [19]. The size tuneability has control over the color of the quantum dots such as CdSe emits multiple color over a nanometer range of particle size. Also, different shapes of gold nanomaterials (rod, dumbbell, triangle, flower, etc) provide their unique surface resonance plasmonic effect. (ii) Non-toxic and biocompatibility: these unique characteristics of nanoparticles are an important factor in the biomedical sector for *in vitro* usage as well as drug development. (iii) Stability: stable nanoparticles are a necessity to avoid aggregation and provide the same characteristics every time for sophisticated tool development. (iv) Versatility: this factor is important as nanomaterials can be used for multipurpose utilities like coating, drug delivery, magnetic separation, imaging, etc. Iron oxide is one such nanomaterial which can serve all the above purposes for developing biomedical devices. Hence this versatile nanomaterial was approved by the FDA for human usage.

1.2.1 Analyte/biomarker

An analyte/biomarker is a substance which may or may not be present in human fluids (blood, saliva, urine, etc) and can be measured/quantified for the detection of disease [20, 21]. Consequently, the outcome of these investigations leads to proper prognostic or diagnostic steps for the precise management of the disease. For example, cancer biomarkers which are present in blood or other body fluids can be traced through the detection of cells, proteins, nucleic acids, enzymes, exosomes, lipids, etc [22]. The purpose of tracing the cancer biomarker is to develop a reliable, highly sensitive and selective sensor for early cancer detection, monitoring and treatment strategy. Various promising detection methods based on the specific recognition of biomarkers or analytes have been developed to manage various diseases. Figure 1.1 depicts some of the recently developed techniques like artificial intelligence, lab on chip, nanomedicine, smart nanomaterials, bioimaging tools, etc have revolutionized the personal healthcare system for investigation of diseases by integrating multiple analytical systems (optical, electrochemical, microscopy, MEMS, etc).

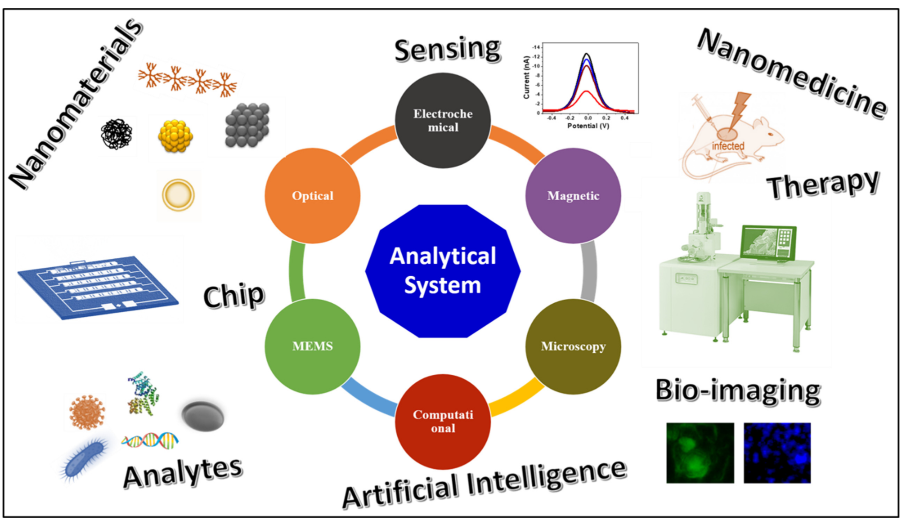

Figure 1.1. Schematic illustration of analytical system integrating multiple platforms for biomedical application.

1.3 Electrochemical system

One of the earliest analyte detection systems (or immunoassays) developed by researchers and scientists was electrochemical techniques which can quantify the analytes by measuring the changes in electrical signals such as potential, current, resistance, and capacitance and has gained a wide variety of applications in biosensor arena [23]. Electrochemical assay has been prevalent in the market for its simplicity and high sensitivity for providing quick diagnostics to millions of people. The sensitivity of amperometric immunoassays is significantly affected by the conductivity and specific area of the sensing interface as well as the electrochemical activity of redox species [23]. The large specific area, good electron conductivity, biocompatibility, and catalytic performance of the redox species led to excellent electrochemical activity. Some of the well-known devices available in the market are glucose sensors, cholesterol sensors, tumor markers etc [24]. It offers quick, simple and sensitive detection but has some clinical limitation of interference, long-term stability and non-specific adsorption.

1.3.1 Optical systems (fluorescence, SPR, Raman, mass spectroscopy)

The optical properties of nanomaterials such as fluorescence spectra, colorimetry, and Raman scattering properties are being developed to construct medical devices. Depending on the type of optical material used, color-based fluorescent (dye, quantum dots) and non-fluorescent nanomaterials (gold, silver, graphene, etc) are being continuously explored in order to design ultrasensitive higher resolution imaging systems [25].

In the last few decades, the invention of the laser and extensive research on optical nanomaterials have led to many optical sensors. Hence, the optical detection technique has become one of the most popular methods for immunoassay development. Popular simple colorimetric assay like pregnancy test strips have been employed in various hospitals and maternity centers for initial screening. Similarly, UV–visible spectroscopy, FTIR techniques and chemiluminescence immunosensors are being utilized in clinical diagnosis for its simplicity and ease of handling [26].

Recently, fluorescence immunoassays have revolutionized the health industry for improved sensitivity and fast readout process. Molecular fluorescence imaging has achieved a new height of success as they can image a single molecule with high precision [27, 28]. Fluorescence microscopy utilizes an imaging agent known as fluorescent dye tagged with target antibodies (proteins) that binds with target analyte to capture the highlighted image. For example, they can image protein agglomeration present on human cell surface through a fluorescence dye tagged antibody [4]. One of the pioneering works performed by Koller *et al* demonstrated the first clinical trials of investigating fluorescence-guided surgery in humans [29]. They reported the clinical translation and evaluation of tumor-targeted fluorescent tracers for molecular fluorescence imaging of tumors in breast cancer.

Surface plasmon resonance (SPR) immunoassays provides a label-free optical sensing platform [30]. The working principle for measuring the analyte is to measure the absorption index and the specific interactions between antibodies and antigens can be determined by the changes in reflective index. This system provides *in situ* monitoring of analyte through the adsorption of analyte onto a gold or silver metal surface for various biosensor applications.

Raman spectroscopy has significantly changed the vibrational spectroscopic techniques for its versatile application like materials characterization, material detection, diagnostics system, etc [31, 32]. Among the various Raman spectroscopy variants, surface enhanced Raman spectroscopy (SERS) has been a promising tool development as a result of significant progress of nanomaterial as it provide single molecule sensitivity in molecular diagnostics [4, 33]. Some of the technical benefits of SERS as a clinical assay are minimal sample preparation and the ability to detect target molecules in aqueous samples, as water exhibits very weak Raman scattering due to its small Raman cross-section. These qualities have enabled Raman spectroscopy to construct multiplex detection platforms for point-of-care application [34].

Mass spectroscopy (MS) is another powerful analytical technique to quantify biomolecules and to identify unknown samples [35]. Under the influence of external electric and magnet field, MS disintegrates compounds or molecules into charged species and categorized them according to their mass and charge ratio. They are extensively used in lipid and protein analysis for understanding the basic human metabolic system. It provides precise determination of the molecular mass of target molecule for various proteins/peptides identification.

1.3.2 Electron microscope (SEM, TEM, AFM, EDX, XPS)

The most advanced imaging system such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), energy-dispersive x-ray spectroscopy (EDX), and are more frequently used for imaging as well as disease evaluation [36, 37]. They offer qualitative, quantitative and/or structural information regarding changes that occur in nanomaterials/biomaterials/thin film sensors/interfacial areas of devices. SEM/TEM/AFM provide micro- and nanoscale characterization of nanomaterials/biological structures, internal shape and size, surface topology for in-depth analysis. The compositional and elemental analysis of nanostructures are facilitated by EDX. These highly sensitive imaging techniques have found application in biomolecule (cells, proteins, bacteria, etc) structure evaluation, nano biomaterial-interface determination, nano-enabled drug delivery systems, targeted therapy, nanomedicine, etc [38]. Another useful photoelectron based system known as x-ray photoelectron spectroscopy (XPS) has been widely used for measuring surface chemistry of a few nanometers width of solid surface to extract information about the chemical state of the nanostructures.

1.3.3 Magnetic systems (NMR, VSM)

Nuclear magnetic resonance (NMR) and vibrating sample magnetometer (VSM) techniques are based on magnetic properties of nanomaterials. NMR is a physical phenomenon where the nuclei of nanomaterial oscillates with external weak magnetic field to determine the structure of organic molecules whereas VSM measures magnetic moment as a function of an applied magnetic field in solid and liquid samples. They are utilized to explore magnetic properties of nanomaterials/micro-nano systems to understand molecular dynamics, determining purity of sample, understanding biomolecule structures, probing magnetic activity at drug target sites. Recently, the microfabrication technique has enabled miniaturization of the NMR system using immuno-magnetic labeling as well as label-free biomolecule detection [39]. Magnetic systems have wide applications in medical diagnostics as magnetic sensors, magnetic material as probes, brain mapping in nanomedicine, etc. Another lesser known technique electron paramagnetic resonance (EPR) spectroscopy is used to study the free radicals and paramagnetic species in nano-biomaterials when the spin states of an electron oscillate under an applied magnetic field. One of the interesting areas that has changed the biomedical sector is nanomedicine due to significant progression of magnetic nanoparticles and their diagnostic applications in human organ imaging (liver, lymph node, inflammation and vascular imaging, etc) [40, 41]. Iron oxide nanoparticles are one of the most sought nanomaterials as image-guided drug delivery, magnetic particle imaging, image-guided and microbubble-mediated opening of the blood–brain barrier, and theranostic tissue engineering [42].

1.3.4 Microfluidic system

Microfluidic chip-based point-of-care assays are gaining popularity for the concept of developing a lab-on-a-chip device [43]. These platforms can perform multitasks in one assay procedure for rapid diagnosis and quicker decision making. It consumes a minute quantity of reagents and analytes to perform quantitative, rapid, automated and high-yield measurement [44]. These novel prototypes have revolutionized the clinical settings in hospitals, diagnostics centers as well as personalized medicine development. Further, microfluidics can be easily integrated within standard detection systems and opened new possibilities for multiplexed detection of diseases with minimal requirement of essential reagents for constructing a cost-effective and portable device. For example, Trau *et al* fabricated a gold electrode-based lab-on-a-chip devices combining hydrodynamic microfluidic flow with multiple detection systems for various disease screening, monitoring, detection and quantification (pathogens, bacteria, cancer biomarkers, etc) [8, 45–47]. This versatile nanoshearing chip has evolved as a lab-on-a- chip multifunctional platform. They have integrated this chip successfully with electrochemical systems, colorimetric assay, fluorescence technique and SERS instrument for biomolecule identification, immunoassays development, drug monitoring tool, and individual analyte imaging.

1.4 Conclusion and future direction

The future of the biomedical sector is very promising. This chapter has summarized the existing technologies and has reported the potential of nano-enabled multidisciplinary smart platforms for personalized healthcare management. The immediate future in clinical pathology is to build multiple detection of analytes in a single run of assay. This will have myriad advantages over single assay systems. A multiplexed system provides simultaneous measurement of multiple analytes and provides valuable information to reduce false positive results and is able to design a more accurate system for better disease diagnosis. This single platform for multiple assay performance would reduce medical expenses and analysis time. This would be a valuable step forward for constructing a point-of-care system.

The imaging applications of nanostructures in the health sector is immense. The imaging systems have great advantages due to their nanoscale dimensions suitable for biomolecule labelling and monitoring. The imaging applications depend on several factors such as shape, biocompatibility, biodegradability, and stability of nanostructures. One of the key areas in developments would be high-resolution imaging of biomolecules for targeted drug delivery. This would allow specific drug delivery treatments to be safer and more accessible to all patients [48].

Dr Francis Collins, a renowned American scientist who led the 'Human Genome Project' shared his vision about the precision medicine initiative and remarked that the next generation of scientists would create new approaches for detecting, measuring, and analyzing a wide range of biomedical information—including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters [49]. Based on that concept many opportunities have evolved and AI is one of the prodigies in this area to achieve this feat. AI is the future of smart healthcare system. Medical technology will revolutionize as AI can assimilate billions of data related to health including patient data such as medical imaging, drug data, treatment procedure, electronic records, etc. In this way, AI with the help of human intelligence can create a predictable algorithm to manage and combat deadly diseases for better health management.

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