Analytical Techniques for Biomedical Nanotechnology

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Edited by
Ajeet Kaushik
NanoBioTech Laboratory, Department of Environmental Engineering, Florida Polytechnic University, Lakeland, FL 33805, USA

Sesha S Srinivasan
Department of Engineering Physics, Florida Polytechnic University, Lakeland, FL 33805, USA

Yogendra Kumar Mishra
Mads Clausen Institute, NanoSYD, University of Southern Denmark, Alison 2, 6400 Sønderborg, Denmark

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The authors dedicate this book to every analytical technology making the science of spatial impact by providing information and knowledge to understand the existing state-of-the-art technology and explore future technology for a sustainable society.

Contents

Preface

This book is an effort to explore 'analytical techniques', at both, the fundamental as well as the applied level, for biomedical applications. It aims to provide a broad perspective about the development of analytical methods involved in materials science and electronics, especially in the field of nano-enabled biomedical sciences. It will highlight the fundamentals and systematic developments in analytical techniques to achieve better characterization, providing more scientific information, rapid diagnostics, cost-effective, user-friendly approaches, and most importantly the *state-of-art* developing methodologies for personalized health management. Moreover, it will give an adequate understanding of the imposed limitations and propose the future perspectives and challenges associated with analytical methods to achieve the desired performance in targeted biomedical applications.

Recently, nanotechnology has emerged as a necessary vehicle for the development of advanced technologies for healthcare and wellness. Such developments require advanced surface functionalized hybrid materials for targeted biomedical applications. Nano-biotechnology assisted methodologies are gaining attention due to desired performance, which can be useful to detect, monitor, and manage targeted diseases. Moreover, the significant advancements in developing 'holy grail' materials for biomedical applications often demand the availability of advanced analytical techniques, which are the key factors to understanding the followings aspects.

1. To identify the fundamental knowledge of the various analytical techniques and procedures with reference to targeted biomedical applications.
2. To explore alteration in properties of materials, bio-systems, and involved interfaces in the nano–bio-systems.
3. To demonstrate whether the as-developed nano-system and devices are useful for health and wellness or otherwise need more developments.
4. To develop the miniaturized, reliable, and efficient systems of high sensitivity and selectivity needed for complex disease managements.
5. To discover the knowledge of the nano–bio interface to assess the potential of techniques and the corresponding developed prototypes.

As objectives, it has been noted that on-going nano-biotechnology related research involves multidisciplinary science and simultaneous expertize from various fields on a single platform. The role of analytical science has improved the performance of devices, which have been developed for biomedical applications. Despite significant advances, there is a gap between chemists, biologists, physicists, mathematicians, engineers, and information technologists (internet of things) and bridging that gap is essential for adequate realizations of advanced biomedical technological breakthroughs. To develop the next generation technologies, this book is crucial to bridge the gap and connect experts. The major objectives of this book will be:

(a) to investigate the analytical techniques for targeted biomedical applications,
(b) to introduce the fundamental insights and mechanisms for conceptual understanding,
(c) to identify the prospects and perspectives of analytical tools and techniques,
(d) to demonstrate the challenges and involve experts of different disciplines to develop innovative and precise measurement systems, and
(e) to explore the multidisciplinary research for developing advanced systems for improved performance with respect to targeted nanomaterials-based biomedical applications.

This book will educate the scholars (students, researchers, post-docs, scientists, academicians, industrialists, government) and experts who belong to different disciplines and conducting multidisciplinary research. The knowledge of this book will be useful to translate fundamental research to applied nano-enabled biomedical research. In addition to fundamental knowledge at deep levels, this book will be an ideal platform to explore appropriate single or combinational techniques to improve the system's performance as per requirements, i.e., point-of-care health wellness.

Ajeet Kaushik
Sesha S Srinivasan
Yogendra K Mishra

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Editor biographies

Ajeet Kaushik

Ajeet Kaushik is an assistant professor of Chemistry at the Department of Environmental Engineering of Florida Polytechnic University. He has over 15 years of experience in exploring analytical techniques for the characterisation of nanostructures, bio/chemical sensors fabrication confirmation, and nanomedicine optimization. Prior to joining Florida Polytechnic University in 2019, he worked as a faculty member at the Medical College of Florida International University.

Sesha S Srinivasan

Sesha Srinivasan is an assistant professor of Engineering Physics at Florida Polytechnic University. He has more than two decades of research and project management experience with expertise in the analytical characterization and synthesis of novel materials for emerging applications in hydrogen storage, catalysis, thermochemical and thermal energy, thermochromic coatings, advanced oxidation and biofuel generation. Srinivasan was a Postdoc (2002–2004) at the University of Hawaii, Research Assistant Professor (2004–2009) at the University of South Florida, and on the Faculty of Physics (2009–2014) at Tuskegee University.

Yogendra K Mishra

Yogendra Mishra is a professor and leader of Smart Materials at University of Southern Denmark. He was an Alexander von Humboldt Fellow and later a Group Leader at Kiel University, Germany, from 2009 to 2019. He joined University of Southern Denmark as a professor in 2019. He is known world-wide for tetrapod-based 3D materials engineering and translational materials-based research activities.

List of contributors

Tansir Ahamad
Department of Chemistry, College of Science, King Saud University, PO Box 2455, Riyadh 11451, Saudi Arabia

Md. Mottahir Alam
Department of Electrical and Computer Engineering, Faculty of Engineering, King Abdulaziz University, PO Box 80204, Jeddah 21589, Saudi Arabia

Radheka Bhaduri
St. Xaviers College, Kolkata (Autonomous), West Bengal, India

Shilpa Bhatkande
Arts and Science Department, University of Houston-Victoria Katy Campus, 22400 Grand Cir Blvd Suite 206, Katy, TX 77449, USA

Rahul Bhattacharjee
KIIT School of Biotechnology, Kalinga Institute of Industrial Technology (KIIT-DU), Bhubaneswar, Odisha, India

Hima Sree Buddhiraju
Department of Biomedical Engineering, Indian Institute of Technology Hyderabad, Kandi 502 284, India

Srija Chakrabarty
St. Xaviers College, Kolkata (Autonomous), West Bengal, India

Soumalya Chakraborty
Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, S.A.S. Nagar, Mohali 160062, Punjab, India

Sanjoy Kumar Das
Institute of Pharmacy, Jalpaiguri, West Bengal 735101, India

Abhijit Dey
Department of Life Sciences Presidency University 86/1 College Street, Kolkata 700073, West Bengal, India

Swapnil Dharaskar
Nano-Research Group, Department of Chemical Engineering, School of Technology, Pandit Deendayal Energy University, Raisan, Gandhinagar, Gujarat 382426, India

Jaspreet Dhau
Research and Development, Molekule Inc, 3802 Spectrum BLVD, Tampa, FL 33612, USA

Neeraj Dilbaghi
Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar-Haryana 125001, India

Shraddha Dorlikar
Department of Microbiology, Rashtrasant Tukadoji Maharaj Nagpur University, India

Hardik Gohel
Arts and Science Department, University of Houston-Victoria Katy Campus, 22400 Grand Cir Blvd Suite 206, Katy, TX 77449, USA

Akhilesh Kumar Gupta
Department of Physics, University of Nebraska Omaha, NE 68182, USA

Gaurav Hitkaric
School of Applied Sciences, Shri Venkateshwara University, Rajabpur Gajraula Amroha 244236, India

Mohd Imran
Department of Chemical Engineering, Faculty of Engineering, Jazan University, PO Box 706, Jazan 45142, Saudi Arabia

Sulagna Kar
KIIT School of Biotechnology, Kalinga Institute of Industrial Technology (KIIT-DU), Bhubaneswar, Odisha, India

Sandeep Kaushik
Department of Environmental Science, Indira Gandhi National Tribal University, Amarkantak, MP 484887, India

Afzal Khan
State Key Laboratory of Silicon Materials, School of Materials Science and Engineering, Zhejiang University, Hangzhou 310027, China

Kamil Reza Khondakar
School of Health Sciences and Technology, University of Petroleum and Energy Studies, Dehradun 248007, Uttarakhand, India

N Y Kim
RFIC Center, Kwangwoon University, Seoul 139-701, Republic of Korea

Rajeev Kumar
Department of Environment Studies, Panjab University, Chandigarh 160014, India

Sandeep Kumar
Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar-Haryana 125001, India

Saurabh Kumar
Centre for Nano Science and Engineering (CeNSE), Indian Institute of Science, Bengaluru, India
Department of Medical Devices, National Institute of Pharmaceutical Education and Research, Guwahati, India

Vijay Kumar
Department of Physics, National Institute of Technology Srinagar, Jammu and Kashmir 190006, India

Chinmaya Mahapatra
Department of Biotechnology, National Institute of Technology Raipur, Raipur, Chhattisgarh 492010, India

Vidhu Malik
Department of Chemistry, DCRUST Murthal, Sonipat, Haryana, India

Priyanka Mankotia
Institute of Forensic Science & Criminology, Panjab University, Chandigarh 160014, India

Hirak Mazumdar
Woxsen University, Hyderabad 502345, India

Bhaskar Mazumder
Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh 786004, Assam, India

Jyotsana Mehta
Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar-Haryana 125001, India

Priya Mitra
KIIT School of Biotechnology, Kalinga Institute of Industrial Technology (KIIT-DU), Bhubaneswar, Odisha, India

Sayan Mukherjee
School of Medical Sciences and Technology, Indian Institute of Technology, Kharagpur, India

Vivek Kumar Nautiyal
Department of Physics, Gaya College Gaya, a constituent unit of Magadh University, BodhGaya, Bihar 823001, India

Vanya Nayak
Department of Chemistry, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India

Karishma Niveria
Nanobiotech Lab, Department of Zoology, Kirori Mal College, University of Delhi, Delhi 110007, India

Ritesh Palkar
Department of Chemical Engineering, Faculty of Technology, Marwadi University, Rajkot, Gujarat 360003, India

Shashank S Pawitwar
Department of Cellular Biology and Pharmacology, Herbert-Wertheim College of Medicine, Florida International University, Miami, FL, USA

G Qiao
School of Materials Science and Engineering, Jiangsu University, Zhenjiang 212013, China

Rajan Rajabalaya
PAPRSB Institute of Health Sciences, University Brunei Darussalam, Brunei Darussalam

Pooja Rawat
Department of Applied Physics and Institute of Natural Sciences, Kyung Hee University, Yong-in 17104, Republic of Korea

Syed S Razia
Department of Chemistry, Gaya College Gaya, a constituent unit of Magadh University, BodhGaya, Bihar 823001, India

Aravind Kumar Rengan
Department of Biomedical Engineering, Indian Institute of Technology Hyderabad, Kandi 502 284, India

Jong Soo Rhyee
Department of Applied Physics and Institute of Natural Sciences, Kyung Hee University, Yong-in 17104, Republic of Korea

Nitish Sagar
Centre for Nano Science and Engineering (CeNSE), Indian Institute of Science, Bengaluru, India

Ishwar Prasad Sahu
Department of Physics, Indira Gandhi National Tribal University, Amarkantak, MP 484887, India

K Saremi
Institute of Biological Science, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia

S V Satya Prasad
Department of Production and Industrial Engineering, National Institute of Technology Jamshedpur, Jharkhand 831014, India

Rakesh Sehgal
Department of Mechanical Engineering, National Institute of Technology Srinagar, Jammu and Kashmir 190006, India

Prosenjit Sen
Centre for Nano Science and Engineering (CeNSE), Indian Institute of Science, Bengaluru, India

Z Shahnavaz
School of Materials Science and Engineering, Jiangsu University, Zhenjiang 212013, China

Kashma Sharma
Institute of Forensic Science & Criminology, Panjab University, Chandigarh 160014, India

Parshant Kumar Sharma
RFIC Bio Centre, Kwangwoon University, 20 Kwangwoon-ro, Nowon-gu, Seoul 01897, South Korea
Department of Electronics Engineering, Kwangwoon University, 20 Kwangwoon-ro, Nowon-gu, Seoul 01897, South Korea

Vishal Sharma
Institute of Forensic Science & Criminology, Panjab University, Chandigarh 160014, India

Poonam Shashidhar
TERI-Deakin Nanobiotechnology Centre, The Energy and Resource Institute, Gurugram, Haryana 122001, India
Deakin University, Geelong, Waurn Ponds, VIC, Australia

M J A Shiddiky
School of Environment and Science (ESC) and Queensland Micro- and Nanotechnology Centre (QMNC), Griffith University, Nathan, QLD 4111, Australia

Ravikumar B Shinde
Department of Zoology, Shri Pundlik Maharaj Mahavidyalaya, Nandura, MS, India

Vikas Shukla
Nanobiotech Lab, Department of Zoology, Kirori Mal College, University of Delhi, Delhi 110007, India

S Shweta
Department of Botany, Guru Ghasidas University, Bilasur, Chattisgarh 495009, India

Amritpal Singh
Department of Chemistry, Mata Gujri College, Fatehgarh Sahib 140406, India

Avtar Singh
Research and Development, Molekule Inc, 3802 Spectrum BLVD, Tampa, FL 33612, USA
Department of Chemistry, Sri Guru Teg Bahadur Khalsa College, Anandpur Sahib, Punjab 140118, India

Kirandeep Singh
Physical and Material Chemistry Divison, CSIR-National Chemical Laboratory, Pune 411008, India

Kshitij RB Singh
Department of Chemistry, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India

Poonam Singh
Department of Applied Chemistry, Delhi Technological University, Delhi, India

Ravindra Pratap Singh
Department of Biotechnology, Indira Gandhi National Tribal University, Amarkantak, MP 484887, India

Subhash Singh
Department of Production and Industrial Engineering, National Institute of Technology Jamshedpur, Jharkhand 831014, India

Anindita Tarafdar
Department of Biomedical Engineering, Indian Institute of Technology Hyderabad, Kandi, 502 284 India

Yash Thakare
Department of Chemical Engineering, Sinhgad College of Engineering, Pune, Maharashtra, India

Anita Kamra Verma
Nanobiotech Lab, Department of Zoology, Kirori Mal College, University of Delhi, Delhi 110007, India

Kartikey Verma
Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur 208016, Uttar Pradesh, India

Chapter 1

Emergence of analytical techniques

Kamil Reza Khondakar

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).

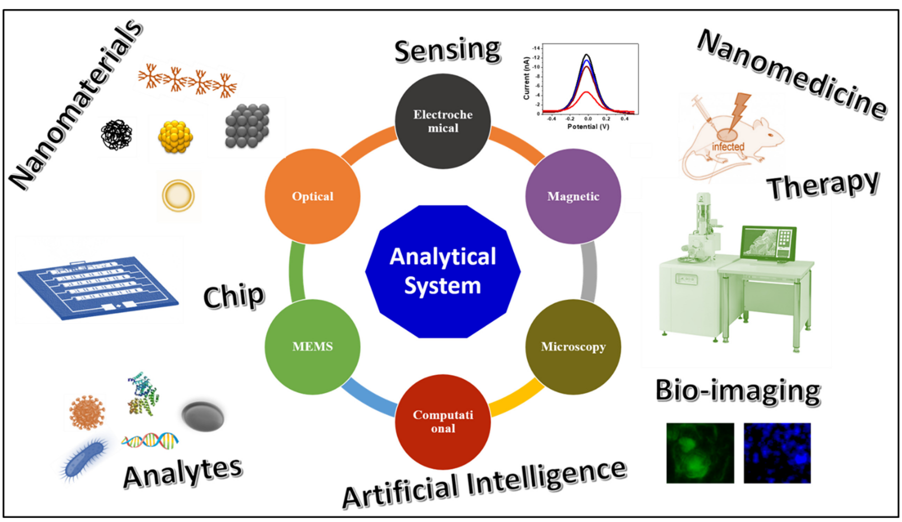

Figure 1.1. Schematic illustration of analytical system integrating multiple platforms for biomedical application.

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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Chapter 3

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Chapter 11

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