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Advancing Modern Healthcare With Nanotechnology, Nanobiosensors, and Internet of Nano Things: Taxonomies, Applications, Architecture, and Challenges

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ABSTRACT Healthcare sector is probably the most benefited from the applications of nanotechnology. The nanotechnology, in the forms of nanomedicine, nanoimplants, nanobiosensors along with the internet of nano things (IoNT), has the potential to bring a revolutionizing advancement in the field of medicine and healthcare services. The primary aim of this paper is to explore the clinical and medical possibilities of these different implementations of nanotechnology. This paper provides a comprehensive overview of nanotechnology, biosensors, nanobiosensors, and IoNT. Furthermore, multilevel taxonomies of nanotechnology, nanoparticles, biosensors, nanobiosensors, and nanozymes are presented. The potential medical and clinical applications of these technologies are discussed in details with several examples. This paper specifically focuses on IoNT and its role in healthcare. In addition to describing a general architecture of IoNT for healthcare, the communication architecture of the IoNT is also explained. The challenges in the successful realization of IoNT are also discussed critically, along with a special discussion on internet of bio-nano things (IoBNT) and its potential in making IoNT more compatible to human body.

INDEX TERMS Nanoparticle, nanobionics, nanomedicine, nanosensor, biosensor, IoNT, IoBNT, taxonomy, WBAN, medical implants, bio-nanochip, protocols, data management.

I. INTRODUCTION

The smaller entities in the world have always enticed the imagination of humans, which led to discovering the magnifying lens, following the basic microscopes. The invention of electron microscopes in the mid-20th century had opened a new world to the scientists, which allowed us experiencing the unseen face of the biodiversity and the biogenesis of this universe. The continuous development towards this direction enabled scientists and researchers to make images of molecules and their bonds, which ultimately led to the field of study which we know as nanotechnology [1]. Nanotechnology refers to the study and application of tiny things, typically measured in nanoscale. It has enormous potential to provide technological solutions in a diverse range of application areas employing multidisciplinary fields of study such as chemistry, biology, physics, electronic sciences, and materials sciences. However, the applications of nanotechnology in biomedical and medicine probably have the most significant impact on the wellbeing of humans. The medical use of nanotechnology in different modes such as nanomedicine, nanoimplants, and nanosensors

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(or biosensors) has revolutionized the practice of diagnosis and treatment.

In another light, a new revolutionizing technological paradigm known as IoT (Internet of Things) is set to change the way we interact with our surroundings and the physical entities in our daily life. Initially, the Internet was started as the interconnection of computers, providing a global network with WWW services. Then it moved towards the interconnection of people in which social web came into existence where people could connect with each other via the internet. It gradually inclined towards connecting not only computers and people but every physical entity in the world emerging the vision of IoT. The traditional Internet has been transformed into IoT with the focus of connecting every physical object, building a global interconnection of 'things' [2]. The objective of IoT is to connect everything to the internet that is connectable so that every connected thing can interact with each other and of course, with human [3]. The IoT describes a vision where each object has its existence in a global network by becoming a part of the Internet; each object is uniquely identified and accessible to the network available with services related to it. IoT aims to access and possibly control every object remotely, be it an electronic device or kitchen appliance or smart building equipment or apparatus in a production house or automobile or any other device. These objects are stuffed with small sensors and actuators, which helps the object in which they are embedded to sense the condition within or outside of it. Several these types of interconnected objects or 'things' exchange the generated data for sharing their state information which is used by applications to inferring knowledge about a particular system and its neighbourhood and acquaintances [4]. This knowledge is used to automate the systems and associated processes. In short, IoT promises to transform the digital world and human life radically, bringing with its new possibilities in diverse applications.

Lately, researchers are implementing the idea of IoT at the nano level, referring it as IoNT (Internet of Nano Things). IoNT is the interconnection of nanoscale devices to the existing communication networks. These nanoscale devices must be able to perform simple tasks like sensing, actuation, and transmission via electromagnetic radiations. The most profound use of IoNT has been found in healthcare, and it has been significantly instrumental in providing flexible and pervasive healthcare [5]. In the context of healthcare, nanothings refer to the miniaturization of the biosensors and medical implants in nanoscale. The nanoscale size of the nanomachines enables them to be deployed inside the human body in a non-invasive way [6]. Smart drug administration and nanoscale surgeries are some of the examples where IoNT can be really useful.

Significant advances in wireless communication and networking technologies have paved the way to envisage and design innovative healthcare services that could not be thought of before. Technologies such as WBAN (wireless body area network) [7], mHealth (mobile health) [8], and wearable health systems can support provisions of health services through smartphones. As the cost and size of sensor devices are decreasing fast, the applications of IoNT in affordable healthcare are set to expand rapidly.

In this paper, we shall explore the possibilities, advantages, and challenges of using nanotechnology, by means of nanobiosensors and IoNT, in modern healthcare. The highlights and the organisation of the paper are shown in Figure 1.

II. NANOTECHNOLOGY

The concept of nanotechnology was proposed in 1965 by Richard Feynman, a Physicist, and Nobel Laureate. The main idea behind nanotechnology was to exploit the advantages of miniaturization of materials and explore the future of creating compelling and tinier devices [9]. Nanotechnology involves the study and applications of matter on an atomic or molecular scale and often incorporates knowledge from multiple scientific disciplines like biology, physics, chemistry, medicine, and engineering in order to design, synthesis, characterization, and application of nanomaterials and nanodevices [10] [11]–[13]. The standard working range of nanotechnology is 1 to 100 nanometers (nm), often referred as nanoscale. Particles of this tiny size can control individual atoms and molecules. Materials exhibit better cell functionality at the nanoscale as compared to at micro or macro scale [14]. The matter changes its behaviour as its size reduced to nanoscale due to quantum size effects [15] which states that specific behaviour of the individual atoms or molecules gets prominent at the nanoscale level of a particle in compared to the atomic or molecular behaviour of the particle as a whole [16]. Because of the ability to work in molecular scales, nanotechnology promises to produce novel materials and devices with special and improved chemical-physical features [11]. For instance, mass silver is nontoxic, whereas silver nanoparticles are capable of killing viruses upon contact.

The advancement in nanotechnology is resulting in nanomanufacturing revolution and is making a significant impact, especially on healthcare and medical field along with other sectors such as the economy, social, environmental, and military-based real-time applications. In the last decade, nanomaterials have been widely used in the fields of disease diagnostics, imaging, and therapeutics. The nanomaterials are widely accepted due to their size, shape, composition, structure, and other physical/chemical properties that can be used to produce the desired materials with specific absorptive, emissive, and light-scattering properties. The size constraint of nanomaterials makes them widely accepted as most of their constituent atoms are located at or near the surface.

A. CLASSIFICATION OF NANOTECHNOLOGY AND NANOMATERIALS

According to the evolution of nanotechnology in terms of structural and dynamic complexity, nanotechnology is divided into four generations of products:

FIGURE 1. Highlights and organisation of the paper.

i) **Passive nanostructures:** The first one, which began in 2000, was passive nanostructures, i.e., materials designed to perform one job. First-generation nanomaterials were used in the manufacturing of coatings, nanoparticles, nanostructured metals, polymers, ceramics, etc.

TABLE 1. **Dimensions of Nanomaterials [17].**

Nanomaterial dimensions	Scale	Movement of electrons	Key representative	Examples
Zero-dimensional (0-D)	All three dimensions (i.e., x, y, and z) are confined to the nanoscale range.	Confined in all three dimensions.	Quantum dots	Molecules, fullerenes, metal carbides, powders, rings, clusters, grains, etc.
One-dimensional (1-D)	Only two dimensions are confined to the nanoscale range.	Move only in the X-direction.	Quantum wires	Nanotubes, filaments, springs, columns, whiskers, spirals, fibres, belts, needles, etc.
Two-dimensional (2-D)	Only one dimension is confined to the nanoscale range.	Move in the X-Y plane.	Thin films	Layers, graphene, graphene oxide (GO), etc.
Three-dimensional (3-D)	No dimension is confined to the nanoscale range.	Move in all three directions.	Nanostructured material (built of nanoparticles)	Small nanoclusters, nanoporous membranes, etc.

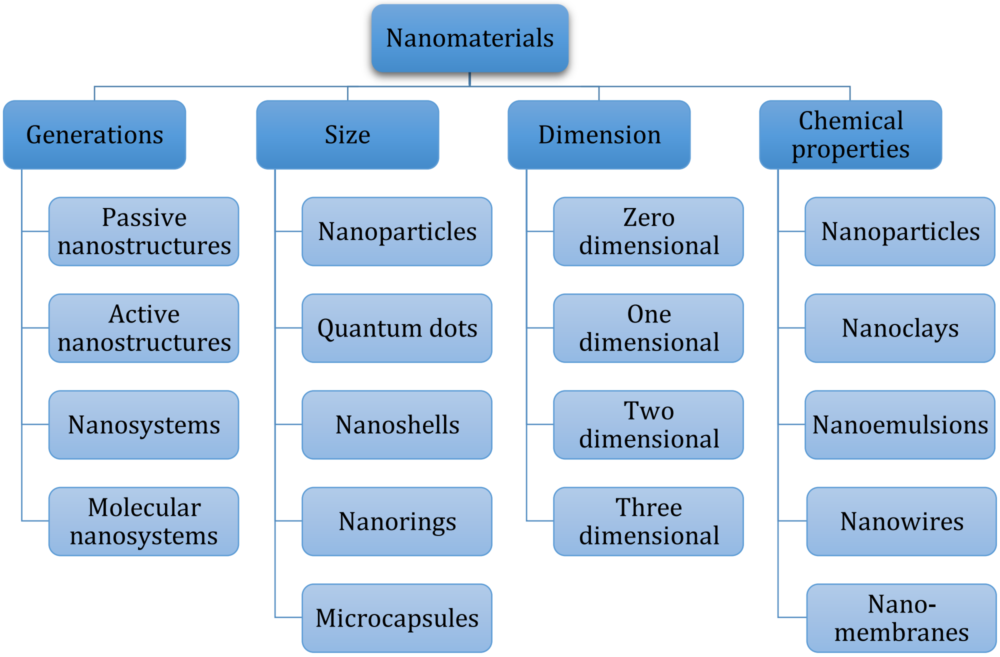

FIGURE 2. **Classification of nanomaterials.**

ii) **Active nanostructures:** The second generation includes active nanostructures for multitasking, which involves the development of very competent sensors, actuators, 3D transistors, and medicine delivery (e.g., targeted drugs) devices.

iii) **Nanosystems:** The third generation that emerged around 2010 includes systems of nanosystems that comprise of thousands of interacting gears. Guided assembling; 3D networking, robotics are the examples of third generation nanomaterials applications.

iv) **Molecular nanosystems:** 2015 onwards is considered the fourth generation of nanomaterials. Implementation of molecular devices 'by design' and atomic design are examples of fourth-generation nanomaterials applications.

Besides based on evolution, nanomaterials can be classified based on a) size and b) the number of dimensions that are beyond the nanoscale range (<100nm). Nanomaterials of different dimensions are shown in Table 1. If two dimensions are less than 100nm, the type of nanomaterials are nanotubes and nanowires. If one dimension is less than 100nm, the type of nanomaterials is thin films. Classification of nanomaterials based on different parameters is shown in Figure 2.

B. NANOPARTICLES

There are different types of nanomaterials, as shown in Figure 2. Among them, the most commonly used nanomaterials, especially in healthcare, are nanoparticles. Nanoparticles are naturally found in the environment (e.g., proteins, virus, volcanic eruptions, etc.). They may also be produced as a result of human activities [18]. These are microscopic particles which have at least one dimension that is sized between 1 and 100 nm, having a surrounding interfacial layer. The half-life and distribution of the nanoparticles are determined by their size. For that reason, in biomedical applications, specifically, the ideal nanoscale range should be 10 to 100 nm so that therapeutic nanoparticles can be distributed throughout the circulatory system and penetrate through small capillaries [19]. Materials beyond this range either do not serve the desired purpose or they induce adverse effects. For example, the materials with size more than 100 nm may induce embolism and are typically phagocytosed and are removed by the spleen. On the other hand, materials with a size of less than 10 nm can pass through the reticuloendothelial system and kidneys. Also, because of higher surface density and additional surface reactive electrons, the materials of less than 10 nm are more toxic and reactive [14].

Nanoparticles share the following three key physical properties [20]:

a. Highly mobile in the free state (i.e. in the absence of some other additional influence).
b. Have very large specific surface areas.
c. Capable of exhibiting quantum effects.

Based on different parameters, nanoparticles may be of various types. A taxonomy of nanoparticles is presented in Figure 3.

C. NANOZYMES

Enzymes are the key elements of a biosensor and are used as sensing elements of the sensors. Though enzymes are found naturally, artificial enzymes (also known as synthetic enzymes) are being developed to address the limitations (such as cost, low stability, unavailability, delicate to manipulate, etc.) of natural enzymes [21]. The artificial enzymes simulate the organism behaviour in the biosensors.

Nanozymes are special types of nanomaterials which exhibit enzyme-like characteristics and are used as artificial enzymes in the nanobiosensors [22], [23]. With mimetic enzyme activities (e.g., oxidase, peroxidase, catalase, etc.), nanozymes offer greater advantages than the conventional artificial enzymes and are potentially being used in the applications of biosensing, immunoassays, therapeutics, in recent times [24]–[26]. Nanozymes-based immunoassays are not only accurate and effective but also more robust even in harsh environments, in comparison to natural and other artificial enzymes [25]. Figure 4 lists, though not extensively, various aspects of typical nanozymes.

III. BIOSENSORS AND NANOBIOSENSORS

One of the most practical applications of nanotechnology in healthcare is realized using nanosensors and nanobiosensors. The advancement of microfabrication platforms and nanotechnology has enabled the nanosensors to be used in a wide range of biosensing applications which require to tap the events at the molecular level [30]. Since biosensors are the foundation of nanobiosensors, it is worth to have a look at the basics of biosensors before jumping to nanobiosensors.

A. BIOSENSORS

A Biosensor is an analytical device and is capable of sensing the chemical and electrochemical events occurring at different biological extents, including tissues, cells, and molecules [31]. International Union of Pure and Applied Chemistry (IUPAC) defines biosensor as:

A device that uses specific biochemical reactions mediated by isolated enzymes, immune systems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals.

The widely accepted definition of biosensor is [32]–[36]:

An analytical device which incorporates a biologically active element with an appropriate physical transducer to generate a measurable signal proportional to the concentration of chemical species in any type of sample.

The biosensor research was started with the generation of glucose oxidase (GOx) biosensor in 1962 by Clark and Lyons [37]. Nowadays, biosensors are used in diverse applications areas such as healthcare, food safety, environment observing, home security, etc. [38]–[42].

1) COMPONENTS AND WORKING OF BIOSENSORS

Biosensors utilise the basic principles of the signal, which is transduction and biorecognition elements. The biorecognition element responds to the target compound, and a physiochemical transducer converts the biological response to a detectable electrical signal so that it can be easily measured and qualified. These signals are then processed, and the results are presented in a user-friendly format. The instrument which is having biosensors is called an affinity sensor when it detects an event. The instrument is called a metabolism sensor when biological elements like enzymes, antibodies, etc. are analysed with a chemical change.

The key components of a biosensor are as following:

- **Bioelements:** The biological elements, also known as bioanalytes, which are required to analyse and fed as input to the biosensor.
- **Bioreceptors:** A biological element (e.g. enzymes, antibodies, DNA, synthetic molecules, etc.) which specifically recognizes and captures the analyte [43].
- **Transducer:** This module converts the biochemical signals generated by the interaction between the bioelement and bioreceptor into a measurable electrical signal which can be used for the quantification of the analyte [44].
- **Electronic system:** The electrical signal generated by the transducer is sent to this module which amplifies the signal and processes it for further utilisation such as displaying, storing, or transmitting through network.

The components and the workflow of a typical biosensor are shown in Figure 5 and Figure 6, respectively.

2) CLASSIFICATIONS OF BIOSENSORS

Depending on different parameters, biosensors can be classified in various categories, as mentioned below. Figure 7 presents a taxonomy of biosensors.

- **Based on biorecognition principles:** Depending on materials and mechanisms, biosensors are broadly categorized into the following three groups [45]:
  a. Biocatalytic group (enzymes)

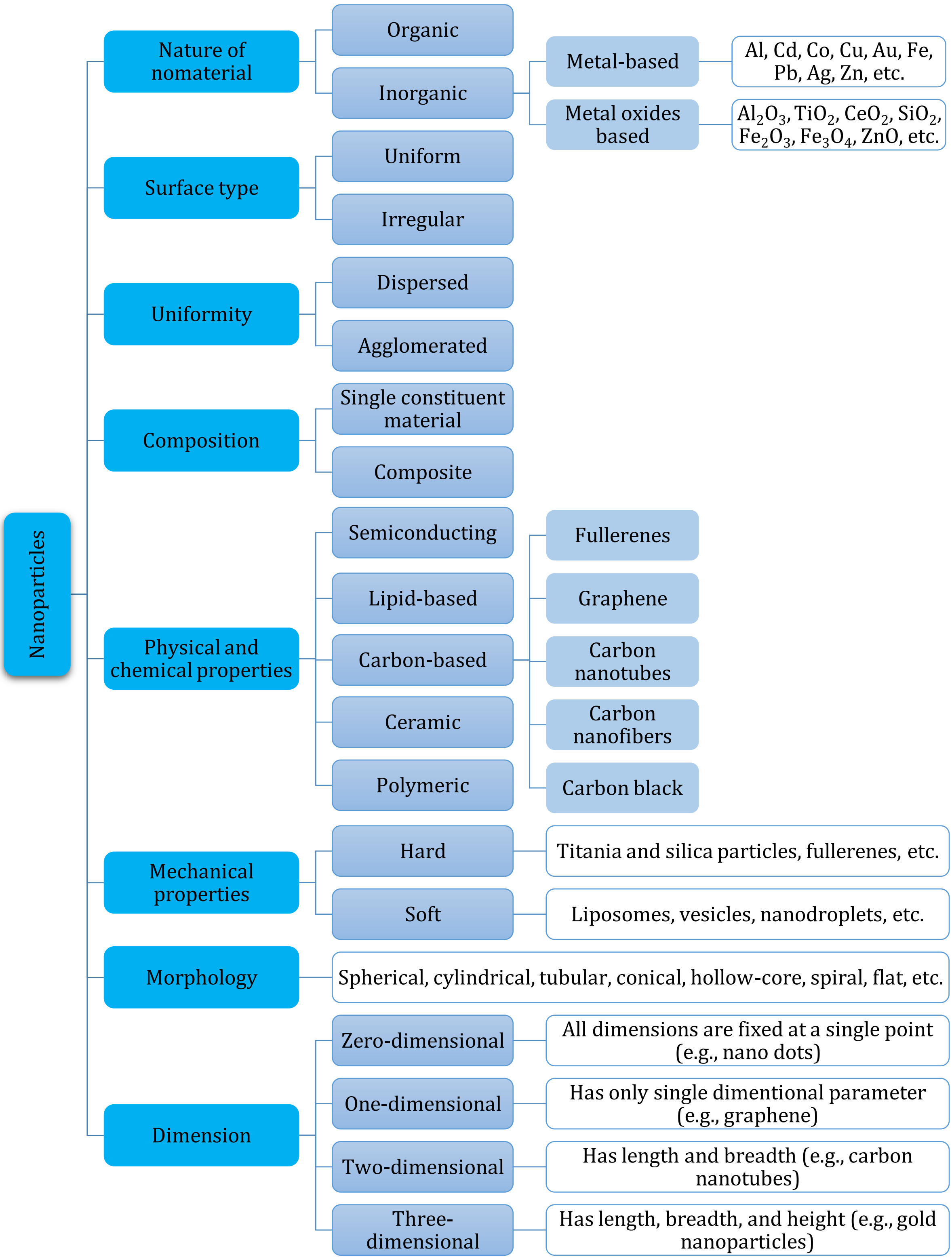

FIGURE 3. Taxonomy of nanoparticles [27], [28].

b. Bioaffinity group (antibodies, antigen, DNA)
c. Microorganisms-based (microbes)

- **Based on the sensing mechanism:** Based on the sensing mechanisms, biosensors can be of various types. The most common among them are [46], [47]:

a. **Electrochemical biosensor:** These are the most commonly used biosensors and are generally comprised of immobilized enzyme and a transducer, which measure the changes in electronic current, ionic, or conductance on the medium,

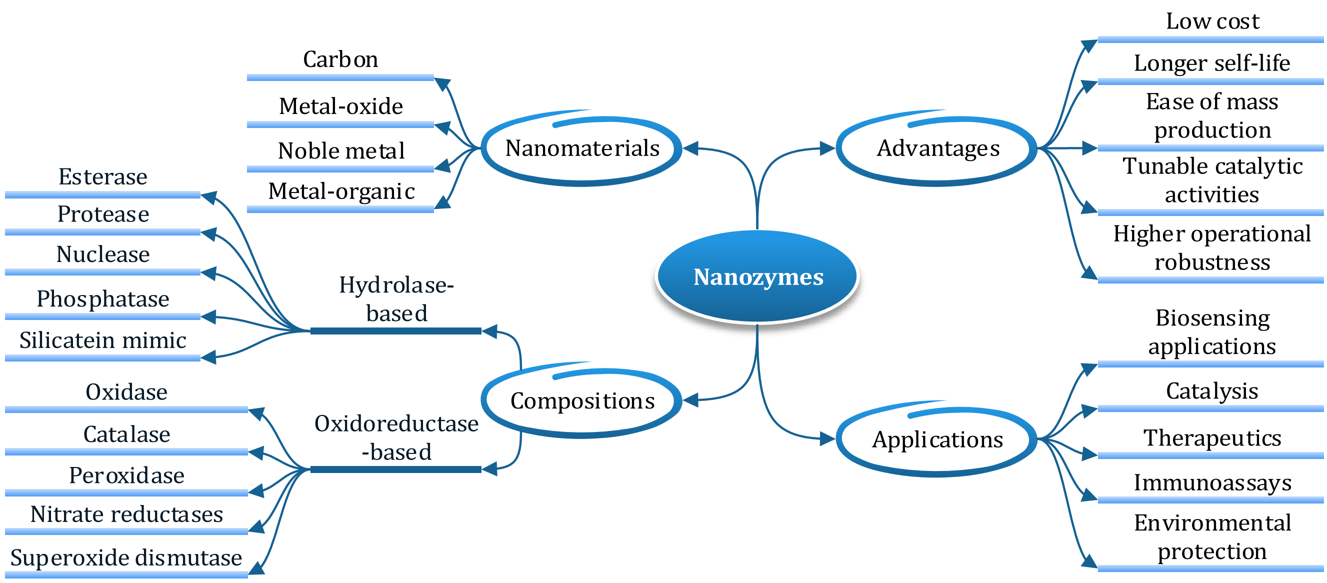

FIGURE 4. Various aspects of nanozymes [25], [29].

carried by bio-electrodes [48], [49]. Depending on the change in properties, based on which the molecular recognition events are transduced, an electrochemical biosensor can further be categorised as followings:

- **Amperometric biosensor:** An amperometric biosensor measures the change in current between a working and a reference electrode, caused by the presence of an analyte leading to an oxidation-reduction (redox) reaction.
- **Potentiometric biosensor:** A potentiometric biosensor gages the charge accretion (potential) between an ion-selective electrode and a reference electrode.
- **Conductometric biosensor:** A conductometric biosensor measures the change in the electrically conductive properties of the medium, triggered by the entry of an analyte that changes the ionic species concentration.
- **Impedance biosensor:** An impedance biosensor measures the change in resistivity or conductivity of the medium, caused by a biorecognition event.

b. **Thermometric biosensor:** These types of biosensors measure the change in enthalpy or thermal on biochemical recognition. The change in heat is measured by sensitive thermistors.

c. **Optical biosensors:** The optical biosensors work on the principle of optical measurements of the light absorbed or emitted instigated by a biochemical reaction. Different optical techniques such as fluorescence, absorbance, luminescence, etc. are used for sensing in optical biosensors. Enzymes and antibodies are the primary elements of the transducers in an optical biosensor.

d. **Piezoelectric/acoustic biosensors:** Piezoelectric biosensors measure the change of mass due to a biomolecular interaction by correlating with the variation in the oscillation frequency of the piezoelectric crystal. Since these biosensors use the sound vibrations, they are also called acoustic biosensors.

- **Based on bioreceptor types used:** Subject to the bioreceptor type used, biosensors can be classified into the following four broad categories [45]:
  a. Nucleic acid/DNA [50]
  b. Enzymes [51], [52]
  c. Antibody/antigen [53], [54]
  d. Cells [55]
  e. Artificial receptors such as molecularly imprinted polymers, biomimetics, aptamers, etc. [56], [57]
- **Based on the immobilization method of the receptor layer:** Depending on the receptor layer's immobilization method, biosensors can be categorized as [56]:
  a. Physical sorption
  b. Immobilization in a polymer matrix
  c. Covalent binding
  d. Affinity immobilization

B. MICRO-BIOSENSORS

The micro-transducers devices are manufactured with organic sensing factors that have changed the arena of sensors. These devices have a complete understanding of the metabolism of human biology. In the modern development of micro-biosensor covers the detection of cancer with the aid of tracking the awareness of precise antigens present inside the

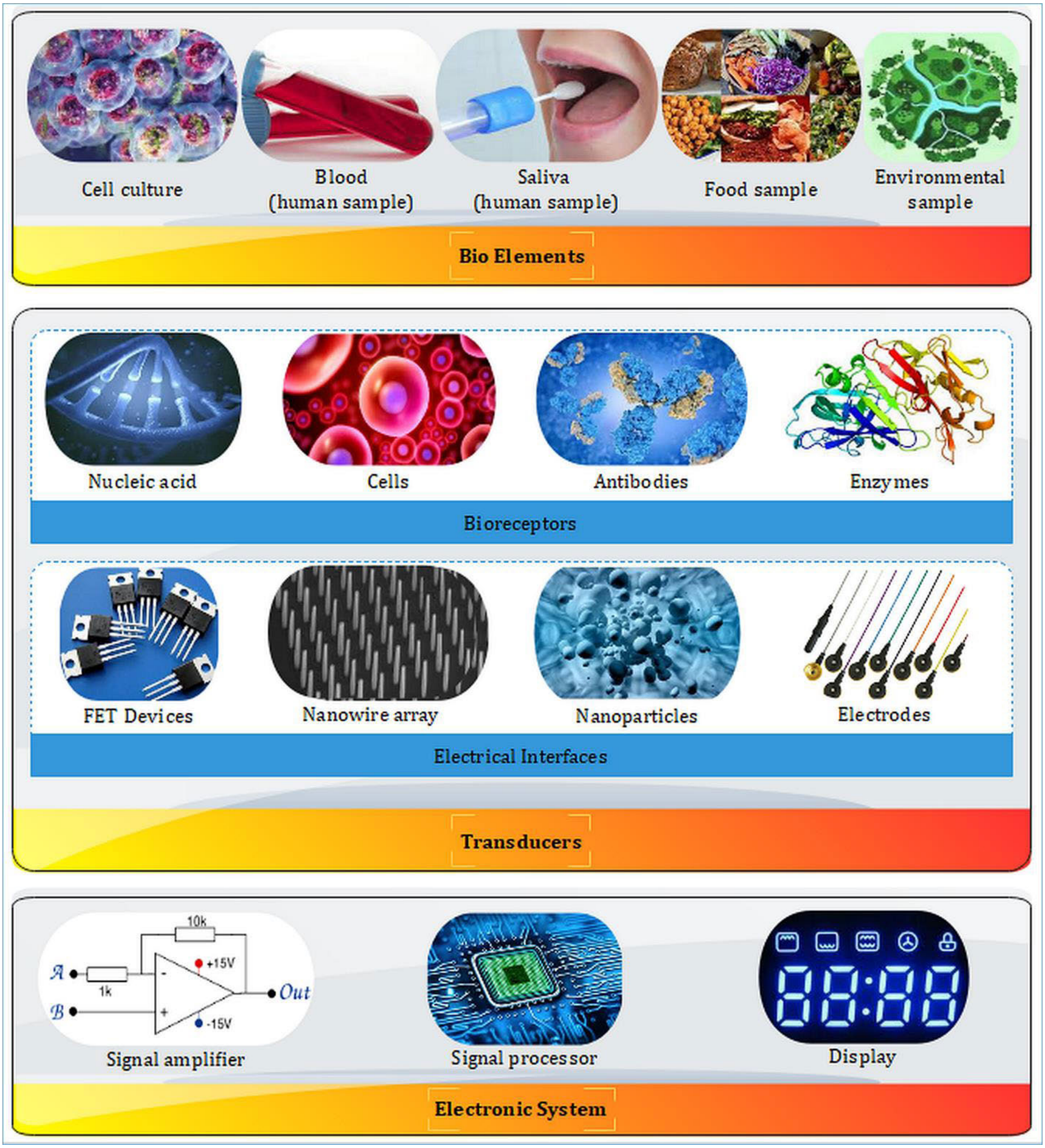

FIGURE 5. Elements of a biosensor.

bloodstream or other physical fluids, or via tissue examinations [42]. There are different types of micro-biosensor used in the detection of different type of diseases.

C. NANOBIOSENSORS

Nanobiosensors are the product of merging biosensors and nanotechnology. The huge potential of nanomaterials and excellent prospects of using it in designing innovative sensing systems and augmenting the working of the biosensors have fuelled the research interests as well as the practical use of different nanomaterials in biosensors, developing nanobiosensors [58]. Using nanomaterials for fabricating biosensors can improve the sensitivity and other vital attributes of a biosensor. Nanotechnology makes nanobiosensors portable, wearable, and implantable in our body or in any medical device. Nanobiosensors detect diseases in the early stages and at the molecule level or single-cell level with the help of a biochemical and biophysical signal. Nanobiosensors are very

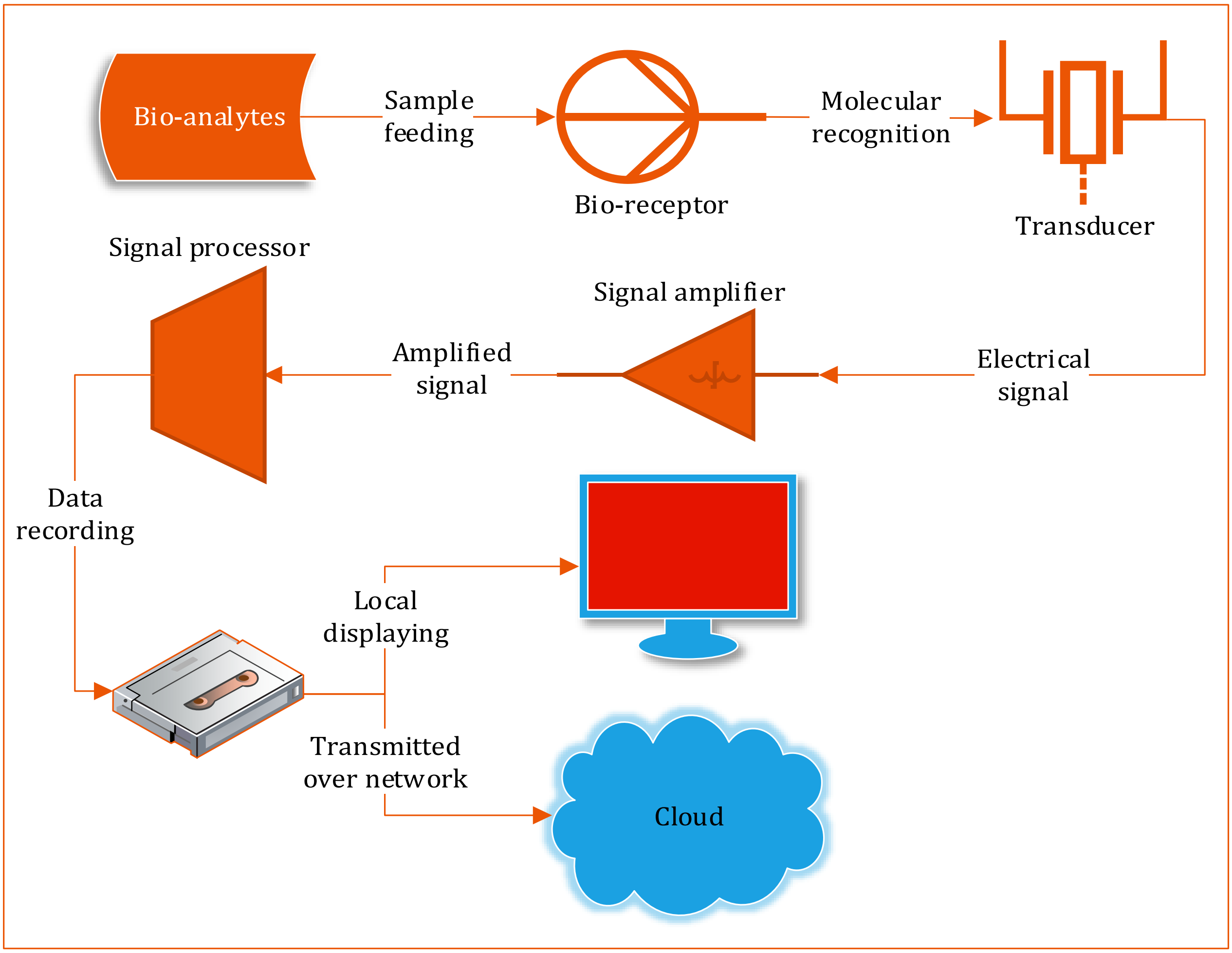

FIGURE 6. **General workflow of a biosensor.**

useful in the detection of diseases like cancer using tissue pathology.

The advancement of sensor technology has paved the development of nanoscale biosensors. These nanoscale health sensors have been instrumental in modern diagnostic technologies, providing access to data from places that were previously unreachable and impossible to sense, and also from instruments that were previously inaccessible due to sensor size. As a result, new medical and environmental data are being able to be collected, allowing augmentation of existing knowledge, new findings and better medical diagnostics, which opens the door of the emerging medical fields and improves the overall healthcare sector.

In this section, nanobiosensors are generally discussed in terms of classifications (based on various parameters), advantages, and issues.

1) CLASSIFICATIONS OF NANOBIOSENSORS

Like biosensors, depending on different parameters, nanobiosensors also can be classified in various categories, as mentioned below. Figure 8 presents a taxonomy of nanobiosensors. As nanobiosensors are the extension of biosensors, most of the categories are overlapped.

- **Based on the type of nanomaterial:** Different nanomaterials used in nanobiosensors:
  a. **Inorganic:** Nanopowders, surface-functionalized nanoparticles, quantum dots, gold nanoparticles, fullerenes, etc.
  b. **Organic:** Carbon nanotubes, graphene, dendrimers, dendrons, hyperbranched polymers, liposomes, micelles, ferritin, etc.
  c. **Composite:** Nanoclays, core-shell inorganic-organic hybrids, etc.
- **Based on the materials used:** Based on the materials used to craft, the nanobiosensors may be of the following three types [24]:
  a. **Biological nanosensors:** DNA and proteins are used for recognising the chemical target and storing its information.
  b. **Synthetic biological nanosensors:** These types of biosensors are made by modifying single-cell

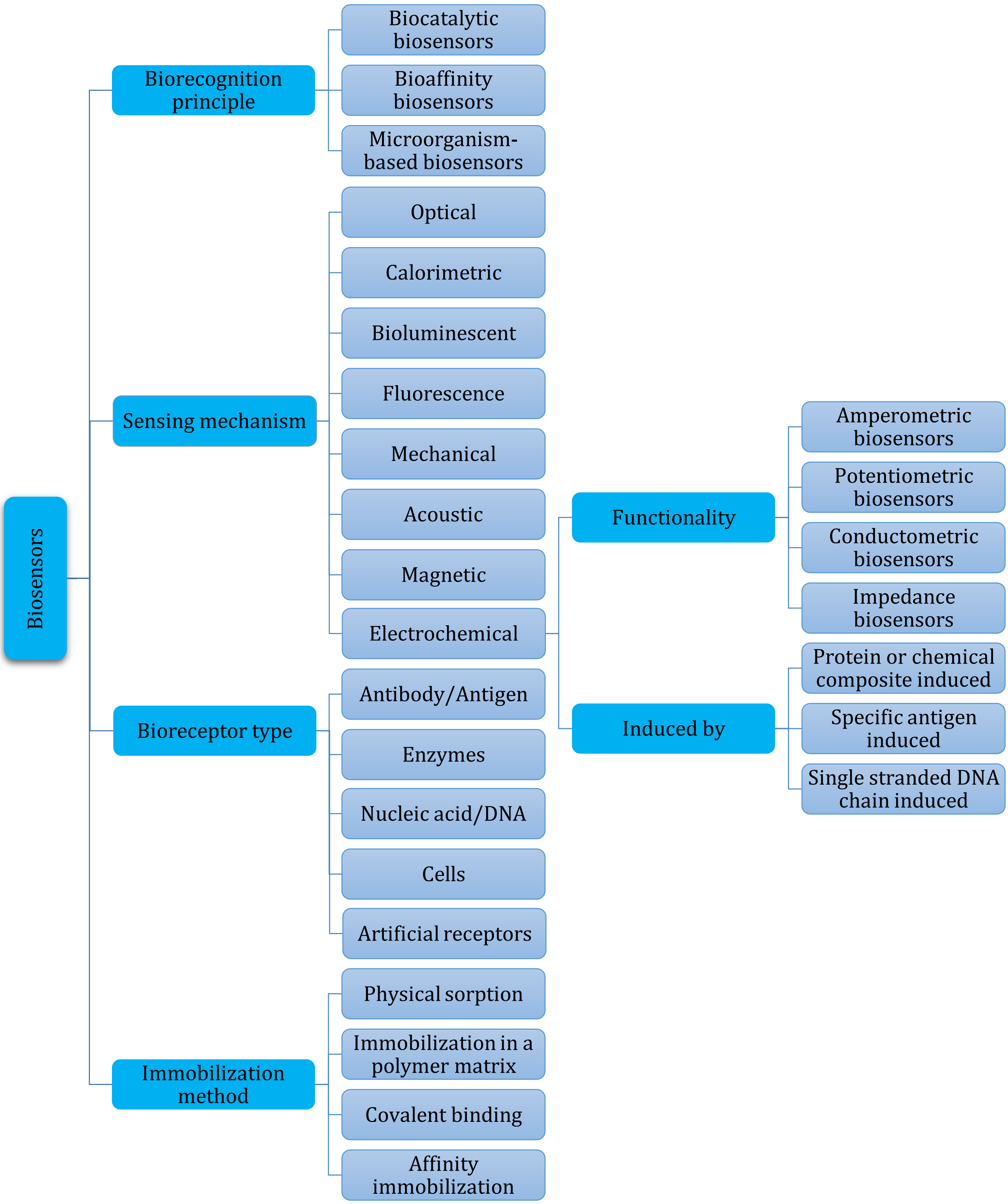

FIGURE 7. Taxonomy of biosensors.

organisms (e.g., bacteria) and using molecular imprinting techniques. These biosensors are limited to targets of lower molecular weight.

c. **Biomimetic nanosensors:** Biomimetic sensors mimic or borrow the concepts and methodologies from the biological or cellular systems, and also include innovative components from other disciplines to build synthetic enzymes [59]. In biomimetic nanosensors, metallic nanoparticles (e.g., gold, silver, iron, etc.) and nanocomposites are used to create the synthetic enzymes [60], [61].

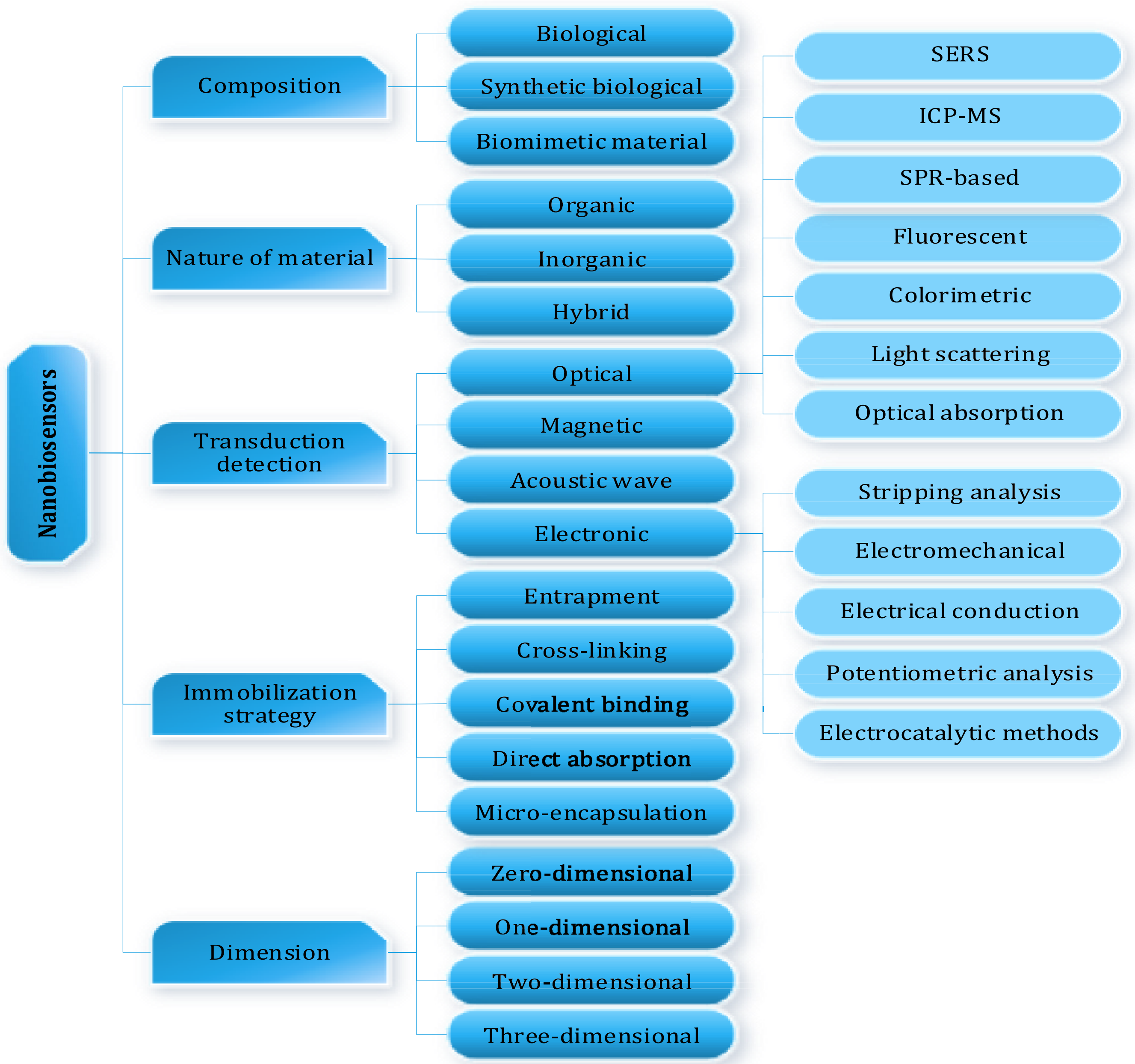

FIGURE 8. Taxonomy of nanobiosensors.

- **Based on the dimension:** The nanobiosensor products can be classified into three categories based on the dimensions which are pushed to the nanometer scale:
  a. **Zero-dimensional:** Nanoparticles like quantum dots are used in zero-dimensional nanobiosensors.
  b. **One-dimensional:** Thin films have only one dimension of few tens to hundreds of nanometers, while the other two dimensions scale to millimetres.
  c. **Two-dimensional:** Nanomaterials, such as carbon nanotubes, silicon nanowires, nanorods, and fibres, have two dimensions that are of the nanometer scale.
  d. **Three-dimensional:** Nanomaterials, such as quantum dots, gold, magnetic and polymeric nanoparticles, and liposomes, have all the three dimensions of nanometer scale.
- **Based on transduction detection:** Subject to the transduction detection schemes and techniques, nanobiosensors may be categorised as follows [62]:
  a. **Optical nanobiosensor:** Optical systems are used as a detector in nanobiosensor. Depending on the optical detection methods, the optical nanobiosensors may be of different types, as mentioned below:
     - Colorimetric nanobiosensors [63], [64]
     - Optical absorption-based nanobiosensors [65]

- Fluorescent nanobiosensors [66], [67]
- Light scattering nanobiosensors [68], [69]
- Surface plasmon resonance (SPR) based nanobiosensors [70], [71]
- Surface-enhanced Raman scattering (SERS) nanobiosensors [72], [73]
- Inductively coupled plasma mass spectroscopy (ICP-MS) nanobiosensors [74], [75]

b. **Electronic nanobiosensor:** The electronic properties of nanomaterials are applied in electronic nanobiosensors. In other words, electronic systems are used as a detector. Depending on the electronic property, electronic nanobiosensors may of different types, as mentioned below:
- **Electromechanical detection:** Microgravimetric quartz crystal microbalance is used to transduce.
- **Conductivity:** Changes in conductivity of the analytes are detected.
- **Stripping analysis:** Coupling of the amplification feature of stripping voltammetry is applied when quantum dots are used as labels for DNA hybridization, which allows detecting multitarget.
- **Potentiometric analysis:** Potentiometric sensors are based on polymer membrane electrodes and provide measurement capability in small volumes in detecting protein and other biomolecules.
- **Electrocatalytic methods:** Nanomaterials like palladium (Pd), gold (Au), etc. are used to create an electrocatalytic antibody for electrochemical immunoassay sensing.

c. **Magnetic nanobiosensors:** Magnetic nanoparticles are used in magnetic nanobiosensors as immobilization platforms for isolating, purifying, and detecting in protein and DNA detection systems [76], [77].

d. **Acoustic wave nanobiosensors:** Acoustic wave sensors monitor the change in the physical properties (e.g., mass, pressure, temperature, etc.), of acoustic waves to obtain information about the entity being measured (measurand) [78]. The acoustic waves can be generated and received by different means such as piezoelectric, magnetostrictive, optical, thermal, etc. [79].

- **Based on immobilisation strategies:** Biosensors, transducers get into contact with the analytes through a process called immobilisation. Nanobiosensors are categorised according to the immobilisation strategies they adopt, as following [80]:

a. **Adsorption:** The biomaterials adsorb enzymes on their surfaces.
b. **Microencapsulation:** Biomaterials are encapsulated by an inert membrane, and kept in close contact with the transducer.
c. **Entrapment:** Biomolecules are physically enclosed in a small space, entrapped within a polymeric gel matrix.
d. **Cross-linking:** *Bifunctional agents* are used to binding the biomaterial to solid supports.
e. **Covalent bonding:** *Nucleophilic* groups (e.g., NH_2, COOH, OH, C_6H_5OH) are used for coupling.

2) ADVANTAGES AND ISSUES OF NANOBIOSENSORS

The boons of nanomaterials have benefitted nanobiosensors as compared to their non-nano counterparts (biosensors). The key advantages of nanobiosensors are as follows [81]:

- Ultrahigh sensitivity: Use of nanotechnology has made biosensors more adept in terms of detection capability and sensitivity.
- Large surface area: A superior surface area to volume ratio of nanomaterials allows the nanobiosensors to use the surface in a better and far more diversely functional manner, which leads to special properties of these sensors that cannot be achieved using the bulk materials.
- Signal enhancement: The bioanalytical platforms of the nanobiosensors, empowered with the nanoscale features, tender better assay sensitivity and signal enhancement.
- Miniaturised platforms: The miniaturization electrochemical platforms of the nanomaterials used in nanobiosensors have allowed the development of the innovative and sophisticated implantable clinical devices.
- Minimal sample volume: By utilizing nanomaterials, nanobiosensors have been able to achieve lower or reduced detection limits, enabling even single-molecule detection.
- Rapid and high throughput detection: Nanobiosensors exhibits much lower response times and high throughput detection than conventionally used sensor systems.
- Label-free transduction of biorecognition reactions: Nanobiosensors offer label-free transduction which enables rapid point-of-care diagnostics, in comparison to the label-based detection, which is time-consuming.
- Long-term nanomaterial stability: Nanomaterials make nanobiosensors more stable as compared to the conventional biosensors that are more susceptible to ambient disturbances. This improves the precision and accuracy of the nanobiosensors.
- Multi-functioned platforms: Sophisticated nanobiosensors allow to integrate multiple sensors made of different nanomaterials, which not only gives nanobiosensors a very high efficiency and specificity but also allows to accommodate all the sensing components of a nanobiosensor such as software, reagents, nanoscale fluid volume plumbing, and sample processing.
- Low-power consumption: Due to their tiny size, nanobiosensors consume considerably low power,

which is crucial for battery-powered non-rechargeable devices.

- Multiplex analysis: Nanobiosensors allow to detect a number of analytes in the same sample.
- Early-stage disease diagnosis: Early detection is very crucial for diseases like cancer and AIDS. Nanobiosensors allows early detection of target molecules.
- Mycotoxins analysis: As the use of nanotechnology has enabled developing ultrasensitive devices, mycotoxins analysis has been improved by adopting nanomaterial-based sensors.
- Simple detection processes: The detection process using nanobiosensors are simple, user-friendly, fast, and cost-effective.
- Environment-friendly: Due to their small size, nanobiosensors require less material to fabricate and are easier to recycle and dispose off.

Undoubtedly, nanobiosensors have shown the potential to revolutionising healthcare. But like any other systems, nanobiosensors also faces some hurdles which should be taken care of. In addition to the usual issues with nanomaterials, some of the other issues with nanobiosensors are:

- Variability
- Increased cost
- Toxicity
- Lack of consensus on toxicity analysis
- Lack of international nanomaterial safety guidelines
- Public concerns

IV. INTERNET OF NANO THINGS

Nanotechnology not only provides excellent opportunities to make improved and advanced materials for industrial and medical uses but also makes possible creating new ''smart'' devices and technologies [82]. The advances in nanotechnology have introduced nanodevices, which are composed of nano components and can perform simple tasks such as sensing or actuation and also can be connected to the Internet through seamless nanoscale communication technologies for information sharing. Basically, the concept of IoNT is derived by merging IoT and nanotechnology, in other words, by bringing IoT down to the nanoscale. In IoNT, the nanosensors, termed as nano things, are connected through a nanoscale network and exchange information using nanocommunication technologies. Ian F. Akyildiz and Josep Miguel Jornet, the proposer of the concept, defined IoNT as follows:

The Interconnection of nanoscale devices with existing communication networks and ultimately the Internet, define a new networking paradigm called "Internet of Nano-Things".

The basic functionalities of the nano things are to sense and transmit the sensed data. Practically, the nanosensors are embedded in different objects. One object might incorporate multiple nanosensors which communicate internally with each other through nanonetworks. The incorporating object communicates with other objects or the outer world through wireless sensor networks (WSNs). The data produced by the nanosensors are transferred through these networks to suitable sinks for appropriate actions. The complex applications involve multiple nano things, and the effectiveness of the application depends on the efficient coordination and information sharing among several nano things. Deployment of IoNT is complemented by other allied technologies like IoT [83], sensor networks [84], pervasive computing [5], cloud computing [85], fog computing [4], big data analytics [86], etc.

V. APPLICATION AREAS OF NANOTECHNOLOGY, NANOSENSORS, AND IoNT

Some examples of general applications of nanotechnology (including nanosensors and nanobiosensors) and IoNT are mentioned in this section, as follows [87]:

Energy: Nanotechnology can improve the existing technology of fuel cells by growing their lifecycle and decreasing the cost of catalysts, leading to sustainable energy [88], [89].

Industry: Vehicle producers can utilize light and solid materials like carbon nanotubes to make quicker and more secure autos. The material producers can profit by the advancement of nanofibers, which is stain-repellent and can be washed at a shallow temperature. Nanotechnology could likewise modernize the nourishment business by improving the protection, handling, and bundling process. Different applications incorporate microscopic organisms revelation and nanoencapsulation of bioactive food compounds to keep them in secure anti-microbial environments.

Electronics and communication: The advances in nanotechnology have reduced the weight and power utilization of on-body gadgets, which are used for sensing the data from the human body. To carry these gadgets with the human body has become easier due to its tiny size and low weight. As power increased, the information handling speed also increased, which has transformed the scenario of data transport.

Consumer goods: Other products that could be created include anti-reflective shades, easy-to-use ceramics, and glasses that may be carrying nanodevices. These devices can further send human data which can be monitored at a remote site.

Oil and gas field: Nanosensors can go through the pores of the rocks and can help in making a decision about the oil limited to the rocks. Abundant magnetic source and recipient are utilized to outline nanoparticles that are infused utilizing reused water for distinguishing the situation of oil [90], [91]. IoNT permits the nanosensors to communicate with one another utilizing sub-atomic correspondence, and the data can be transmitted progressively utilizing an opening set in closeness. The oil well can be effectively mapped.

Civil engineering: Any development with time should be observed to guarantee wellbeing. Graphene-based nanocomposites are utilized to screen strain [92]. Multiwalled carbon nanotubes are utilized to screen strain in FRP bridge decks [93]. The nanocomposite shell at the base of the sheet goes about as a self-detecting component to screen the effect of traffic and the quality of the structure.

Smart cities: Nanodevices monitor the different component of the smart city like smart sanitation, smart and sustainable environment, and smart public health and hygiene. For example, when an item is found littered, the nearby nanosensors can frame a grid-like structure and spot in the trash canister. Nanosensors can detect harmful particles in the environment, and when the alarming pollution level is measured in the surroundings, IoNT can generate a trigger to the concerned authority.

Agriculture: Nanotechnology has huge potential in high-tech and advanced agriculture. Nanoparticles, along with nanosensors and nanobiosensors, have enabled direct and targeted material (e.g., fertilizers, pesticides, herbicides, etc.) delivery to plants, allowing precision farming [94] [95]. Nanomaterials-enabled precision farming not only helps in quick disease diagnostic but also helps to reduce the spreading of chemicals and fertilization's nutrient loss while boosting harvest through pest and nutrient management. Use of nanotechnology-yielded specific agriculture products like nanofertilizers and nanopesticides increase productivity without (or less) contaminating the soil and waters and also protecting against harmful insects, pests, and microbial diseases [96]. Several kinds of nanoparticles and their composites have been found useful in pest management. These particles can be implanted into a nanosensor, and the utilization of these particles can be controlled and observed through IoNT. The fertilizer can be discharged to the plant on an on-request premise utilizing IoNT. IoNT underpins the precision farming, where the administrations of satellite correspondence, remote detecting, and geographic data frameworks can be utilized.

Remediation of groundwater: Currently, carbon nanotubes are utilized for this work, using the portability of the nanoparticle in the stained water and by following the particles utilizing IoNT and filtering them through.

Food and water quality control: Nanotechnology might be helpful in monitoring and controlling of the quality of food and fluid. The toxic elements and the small bacteria in the food and water can be detected using the nanosensors, which otherwise remain undetected using traditional sensing technologies [97].

Food packaging: Nanosensors can give the continuous status of the food freshness, which helps in acquiring the right expiry date [98] [99]. The packaging can be made intuitive, where the thing will make an impression on the private gadget on the off chance that it is not put away or set in appropriate condition. To stay away from wastage, a message can be sent to the cell phone in a range showing its expiry date. Likewise, in the conveyance chain, the item can be followed continuously with no association of the messenger administration.

Health monitoring applications: Various parameters like glucose, cholesterol, and sodium can be observed utilizing nanosensors. Nanosensors can likewise be utilized to spot disease-causing tumours and different damaging specialists. The present application is the brilliant conveyance of medications inside the human body wherein atomic correspondence is utilized for the most part.

Medicine: Nanoparticles are created so as to ship medications to unhealthy cells. New bio-compatible materials are created that can be utilized to make medicinal implants. Stents are additionally created to counteract supply route blockage.

VI. MEDICAL APPLICATIONS OF NANOTECHNOLOGY

As mentioned in the previous section, nanotechnology has a wide range of application areas. However, its medical applications probably are the most imperative that benefit human lives directly. Nanotechnology brings some truly game-changing possibilities in medical practice. Table 2 lists the pharmaceutical and clinical applications of nanomaterials. This section discusses the four broad medical application categories of nanotechnology, especially, the nanomaterials and the nanoparticles.

A. NANOMEDICINE

Nanomedicine is the application of nanotechnology in the field of medicine for the prevention and treatment of diseases. Nanomedicine is a term which has wide-ranging aspects. It refers to diagnosing, curing, and preventing diseases. Nanoscale health services are generally categorized into three broad categories, as shown in Figure 9.

Nanoparticles are a significant component of nanomedicine. They are increasingly used for different medical purposes. The biocompatible nanoparticles and nanorobots are potentially used for diagnosis, drug delivery, and sensing purposes in a human body. They are also being used to improve drug accumulation, internalization, and therapeutic efficacy. One of the primary reasons behind the considerable potential of employing nanoparticles medically, is that the physicochemical and biological properties of the nanoparticles can be adjusted and tailormade for specific purposes by altering their chemical properties, sizes, shapes, structures, morphologies, surface properties, etc., as per the need. Some of the examples of the medical use of nanoparticles and nanomaterials are:

- Applications of nanoparticles are proposed for building nanorobots which are supposed to perform the task of repairing or healing at the cellular level.
- Polymer nanoparticles coated with a red blood cell membrane, known as *nanosponges*, are used to clean bloodstream by removing the toxin from it.
- Silver nanoparticles have been used in *silverware* which contain antimicrobial agents and are used for preventative wound care.
- A specialized nanoparticle, known as *nanoflare*, is used to locate genetic targets in cancer cells. They are mapped to a particular genetic target and generate light when that target is found.
- In combination with radiotherapy, nanoparticles are being used to control tumours locally.

TABLE 2. **The appliance of Nanomaterials in Clinical and Pharmaceutical Applications.**

Nanomaterials	Pharmaceutical and clinical applications	Comments	References
Carbon nanotubes	Drug carrier to target cancer cells	Properties like high carrying capacity, Cell specificity, and biocompatibility, carbon nanotubes are used for drug delivery in tumour cells and also to explore the cancer cells to evaluate pharmacokinetic parameters, cell viability, and cytotoxicity.	[100] [101]
	Vaccine, gene, and drug delivery	CNT will be used as non-viral delivery vectors. CNT are internalized by cells and by binding with macromolecules like proteins and oligosaccharides, they can be potentially used as a vehicle for delivery of different antigens or drugs.	[102] [103] [104]
	Toxicity reduction and effective drug delivery	After systemic administration, CNTs can be readily eliminated from our body. Excretion and concentration of CNTs in different organs and reactivity to various immune cells in our body will determine the CNT safety profile.	[105]
	Gene silencing	CNTs complexed with siRNA (small interfering RNA) enters into the malignant cell and silence the targeted gene releasing siRNA.	[106]
	Efficient diagnosis	Pressure sensing technology using CNTs can be used in blood pressure measurement, intradialytic blood pressure monitoring and in different portable respiratory devices.	[107]
Fullerenes	Diagnostic purposes	Fullerenes used for allergies, asthma, and arthritis diseases.	[108]
	Cancer therapy	By inducing apoptosis, monocationic fullerene can be very effective photosensitizer for killing tumour cells.	[109]
	Free-radical scavenging	Fullerenes have a high electron affinity (ca.2.7–2.8 eV) and are therefore capable of acting as radical scavengers.	[110]
	Photosensitizing	Fullerenes can effectively photoinactivate either or both pathogenic microbial cells and malignant cancer cells.	[111]
	Antimicrobial therapy	The fullerene can be reduced by biological reductant NADH and produce superoxide radicals by electron transfer to oxygen. This can act as an antimicrobial.	[112]
Quantum dots	Cancer therapy	Quantum dots conjugated with antibody target a specific membrane protein. Due to tumour associated neovasculature and lack of effective lymphatic drainage, macromolecule or nanoparticle accumulate.	[113]
Nanoshells	Cancer therapy	Nanoshells have thermoablative properties, and they absorb infrared on exposure to a source external to the body. The nanoshells become heated and cause tissue destruction. This phenomenon is studied in carcinoma cells.	[114] [115]
	Diagnostic purposes	Nanoshells have a wide optical scattering, and they are used in photonics-based imaging. With the help of confocal microscopy and optical coherence, tomography cancer can be detected in early stages.	[116]
	Hydrogel mediated delivery	Gold nanoparticles that can absorb infra-red can be incorporated into a drug-coated polymeric hydrogel. After implantation, drug release is initiated by laser, which is transmitted through tissue with no local damage.	[117] [118]
	Micro metastasis and diabetes	Optical imaging with nanoshells offers the detection of Micro metastasis and diabetes very easily.	[118]
Nanobubbles	Ultrasound imaging	Compared to the larger bubbles, the nanobubbles, have the quality to become a superior ultrasound contrast agent. The ability to perfuse into the capillaries easily makes nanobubbles capable of capturing detailed images of biological tissues.	[119] [120]
	Drug delivery	Ultrasound-facilitated drug delivery has been significantly enhanced using nanobubbles. Near a tumour cell, triggered by ultrasound, the nanobubbles burst, loosening the tumour cell, which makes the penetrations of the drug capsule to the targeted tumour cell easy.	[121] [122]
	Cancerous tumour treatment	Solid tumours are in the hypoxic stage, and it is responsible for reduced response to therapy. Micro/nanobubbles reverse hypoxic conditions and increase the tissue oxygen level.	[123]
	Sonothrombolysis	Nanobubbles (with ultrasound) have shown efficacy in blood clot lysis (sonothrombolysis) acceleration.	[124] [125] [126]
	Gene therapy	Nanobubbles can be used as the non-viral strategy for the site-specific gene delivery, i.e., the genes are delivered to the targeted cells, selectively and effectively, without too many side-effects, which is the key to successful gene therapy.	[127] [128]
Paramagnetic nanoparticles	Protein identification	The synthesized magnetic nanoparticles are considered beneficial in identifying target proteins, which is necessary for biomedical research as well as imperative in daily medical laboratory diagnostics.	[129] [130] [131]
	Drug delivery and cancer therapy	Due to the ability of efficient bioelement (e.g., protein) detection, magnetic nanoparticles have been potentially used to detect cancer cells. They are also popularly used to deliver drugs to the tumour/cancer sites. Magnetite cationic liposomes are used to introduce magnetite nanoparticles into targeted cancer cells.	[132] [133] [134] [135]
	Eliminating plasma opsonins	Paramagnetic nanoparticles mark an antigen for an immune response or marking dead cells for recycling.	[136]
	MRI imaging	Magnetic nanoparticles nowadays are popularly being used in diagnostic scans. Magnetic nanoparticles can be used as contrast media for magnetic resonance imaging.	[137] [138] [139]
Nanosomes	Treatment of tumour cells	Nanosomes are the exosome-gold nanoparticle-based therapeutic delivery system. Exosomes can transport therapeutic complexes without any immune reaction.	[140]
Dendrimers	Drug and gene delivery	Thanks to its structural configuration, a large amount of drug (anti-HIV, anti-cancer and brain-specific drugs) can be transported.	[141]
	Disease diagnosis	Used in gene therapy and chemotherapy.	[142]
	Cell targeting	A dendrimer is a nanoparticle, and so has advantages over microparticles or others due to its small size, easy uptake by cells.	[142]

TABLE 2. ***(Continued.)*** **The appliance of Nanomaterials in Clinical and Pharmaceutical Applications.**

Nanopores	DNA sequencing	Nanopores are able to sequence long single strands of DNA and have the potential for ultrafast genome sequencing.	[143]
	Pharmacogenomics in the drug development process	Pharmacogenetic research has identified a multitude of gene-drug response associations, which have resulted in genetically guided treatment and dosing decisions to yield a higher success rate of pharmacological treatment.	[144]
	Treatment for insulin-dependent diabetes mellitus	Nanopore size material surrounds a tiny silicon box (can be implanted under the skin) with pancreatic beta cells. These pores allow glucose and insulin to pass, but not larger molecules of the immune system.	[145]
Nanocrystals and nanosuspension	Drug delivery	The drug nanocrystals can be used for poorly soluble drugs.	[146]
Solid lipid nanoparticles	Non-viral transfection	Enhance gene delivery to cancer cell line by utilizing different non-viral transfection procedures.	[147] [148]
	Drug delivery	Controlled and targeted drug release with better stability and excellent biocompatibility.	[149] [150]
Silicon-based nanoparticles	Delivery of antitumor agent, antibody, DNA, antibiotics, and enzymes	Protein encapsulation is used to protect from intracellular destructive environment, and final release of the nanoparticle is triggered by acidic organelles.	[151] [152] [153]
Metallic nanoparticles	Drug delivery	Noble metal-based nanoparticles, especially gold and silver-based nanoparticles, have huge potential as drug delivery systems, supporting compounds with bactericidal, fungicidal, and anti-viral properties.	[154] [155]
	Cancer therapy	Improves the quality of radiation-based anticancer therapy.	[156] [157]
	Bioassays applications	Metal nanoparticles can initiate various liquid-phase chemiluminescence bioassays.	[158] [159]
Liposomes	Cancer therapy	Preclinical applications in different tumour models for cancer therapy.	[160] [161]
	Immune enhancement	By reconstitution of antigens into the liposomal membrane to increase antibody production and macrophage activation.	[162]
	Drug delivery	Liposomal preparations of amphotericin B, which is less toxic, is used in the treatment of leishmaniasis. Liposomal formulations of drugs can cross the blood-brain barrier and can be used in the treatment of brain tumour - glioma.	[163] [164] [165]
	Carrying antigens	Liposomes have been widely used as carriers of protein or peptide antigens.	[162] [166]
Polymeric nanoparticles	Drug delivery	Polymer nanoparticles (NPs) represent one of the most innovative non-invasive approaches for drug delivery applications.	[167] [168] [169] [170]
	Imaging	Supports molecular imaging.	[171] [172] [173]

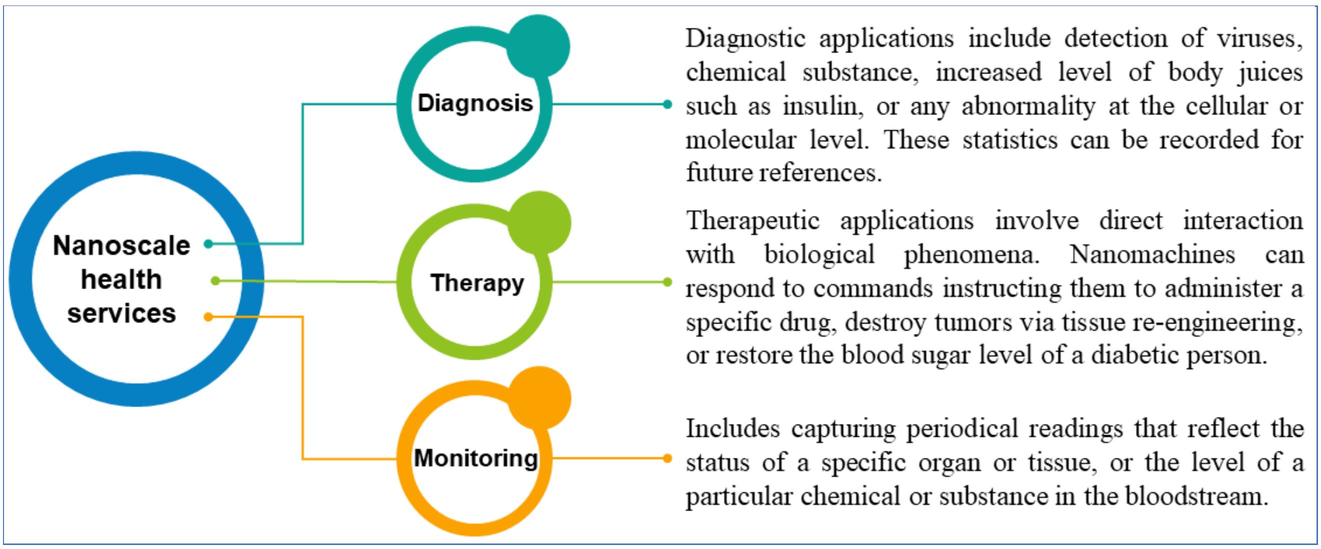

FIGURE 9. **Categories of nanoscale health services.**

- Researches are going on to develop *nanoformulations* solutions with a triggered release for tailor-made pharmacokinetics.
- Researchers have proposed using functionalized nanoparticles for targeted in-vivo activation of stem cell production.
- Nanomaterials comprising of peptide-based nanotubes offers an innovative approach for controlling disease progression where the vascular endothelial growth factor receptor and cell adhesion molecules like integrins, cadherins, and selectins are specifically targeted.

Nanomedicine involves implanting nanodevices and nanostructured materials into the human body. The core concept of nanomedicine is to provide an interface between biological systems and nanodevices. Nanosensors and nanoactuators are under research for providing such interfaces. Nanomedicine can create another paradigm or dimension of healthcare. It is a technology that can finally give health administrators (physicians) a prominent and efficient tool to cure and detect traumatic diseases.

Three major nanomedicine domains are taking advantages of nanotechnology, as shown in Figure 10 and discussed in the following subsections.

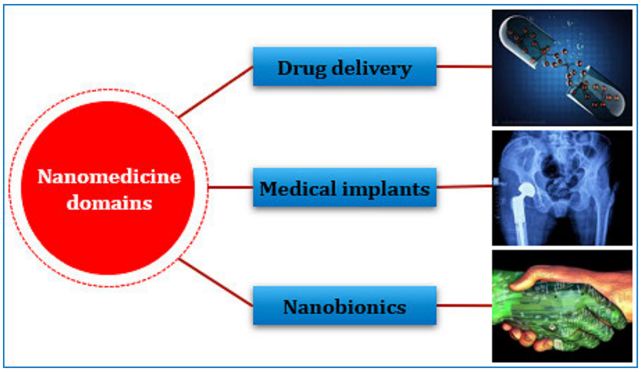

FIGURE 10. Major nanomedicine domains that are taking advantages of nanotechnology.

B. DRUG DELIVERY SYSTEMS

Nanoparticles have a massive potential in effective drug delivery. Drug delivery system refers to methods and technologies that provide efficient transportation of pharmaceutical compounds in the body as required in achieving desired results. The present drug delivery system in most of the pharmaceutical companies is still centred around the conventional methods such as oral (pills and liquids) or injectable. In the past years, the focus of these companies has been on developing methods to synthesize fast-acting chemicals that can be dispensed through conventional methods. However, due to the complex formation of the human body, formulations to control the rate and period of drug delivery has come into focus. Pharmaceutical compounds in the conventional delivery system take a longer time to reach the targeted area, which reduces the effectiveness of the drug. Also, these compounds, while travelling through the body are a potential threat to the healthy cells and henceforth can weaken the body's immune system.

1) IMPACT OF NANOTECHNOLOGY IN DRUG DELIVERY SYSTEM

Nanotechnology, as mentioned above, is the manufacturing of materials at an atomic or molecular level. The application of nanotechnology in the field of pharmaceuticals and biotechnology holds enormous promises for an efficient and effective drug delivery system. Nanotechnology, if applied effectively can add a different dimension to drug delivery, which provides methods and techniques to improve the existing therapeutics or drugs, and at the same time, pave the path for new ones that are only possible with the advanced and nanoparticles incorporated drug delivery system.

The recent development of drugs that have the ability to affect the cellular processes directly demands a more intelligent drug delivery system that can sense and provide the appropriate drug to the targeted tissue or cells. Nanoscale devices incorporated systems are termed as intelligent systems as they increase the efficiency of therapeutic drugs. The main reasons are supporting the above premise being that these intelligent systems are capable of detecting and responding to the site of the disease, thereby sparing the healthy cells and tissues [174].

The use of nanotechnology in drug delivery deploys nanoparticles as the 'delivery vehicle' to reduce the side effects on the body. These nanoparticle carriers transport the drugs to the target cell, exactly, thus maximizing the drug effectivity, without harming other cells. A typical targeted drug delivery scenario is depicted in Figure 11. Some advantages of using nanoparticles in drug delivery systems are shown in Figure 12 [176]. Organic nanoparticles are most widely used in the targeted drug delivery system due to their advantageous properties such as biodegradable, non-toxic, efficient and also can be injected on specific parts of the body [27].

The use of iron nanoparticles and gold shells in cancer therapy is under clinical trial. Nanoparticles are also finding its relevance in the effective medication of therapy of diabetes (nanosponges), dissolving clots and also in the field of vaccination. Researchers are also developing nanoparticles that can be taken orally, and these particles then pass through the digestive system and the intestines to the blood. Apart from developing different nanoparticles for different therapeutic challenges, another concern is to engineer various efficient methods for drug release from the nanoparticles, once the targeted site is identified. One of the most popular methods in the research field today is *triggered response* method of drug release [177]. It is important to know that the nanocarrier design is greatly influenced by the mechanism by which it releases the drug.

Nanocarrier systems that respond to the physiological changes are generally made with materials that are responsive to pH, oxidation potential, or enzymes [177]. These physiological stimuli cause some physical and chemical change to the material which causes the material to degrade and therefore release the required drug.

The size of nanoparticles ranges typically from 1 to 100 nm. In reference to nanotechnology, nanoparticles can be assumed as a whole unit in terms of individual properties and transportation. The size of nanoparticles varies from 1-100 to 100-2500 nm, depending upon the type of nanoparticle, whether it is ultrafine (1-100 nm) or fine (100-2500 nm). Some specific types of nanoparticles are:

- Polymeric biodegradable nanoparticles (10-1000 nm): Used in brain tumours, vaccine therapy, etc.

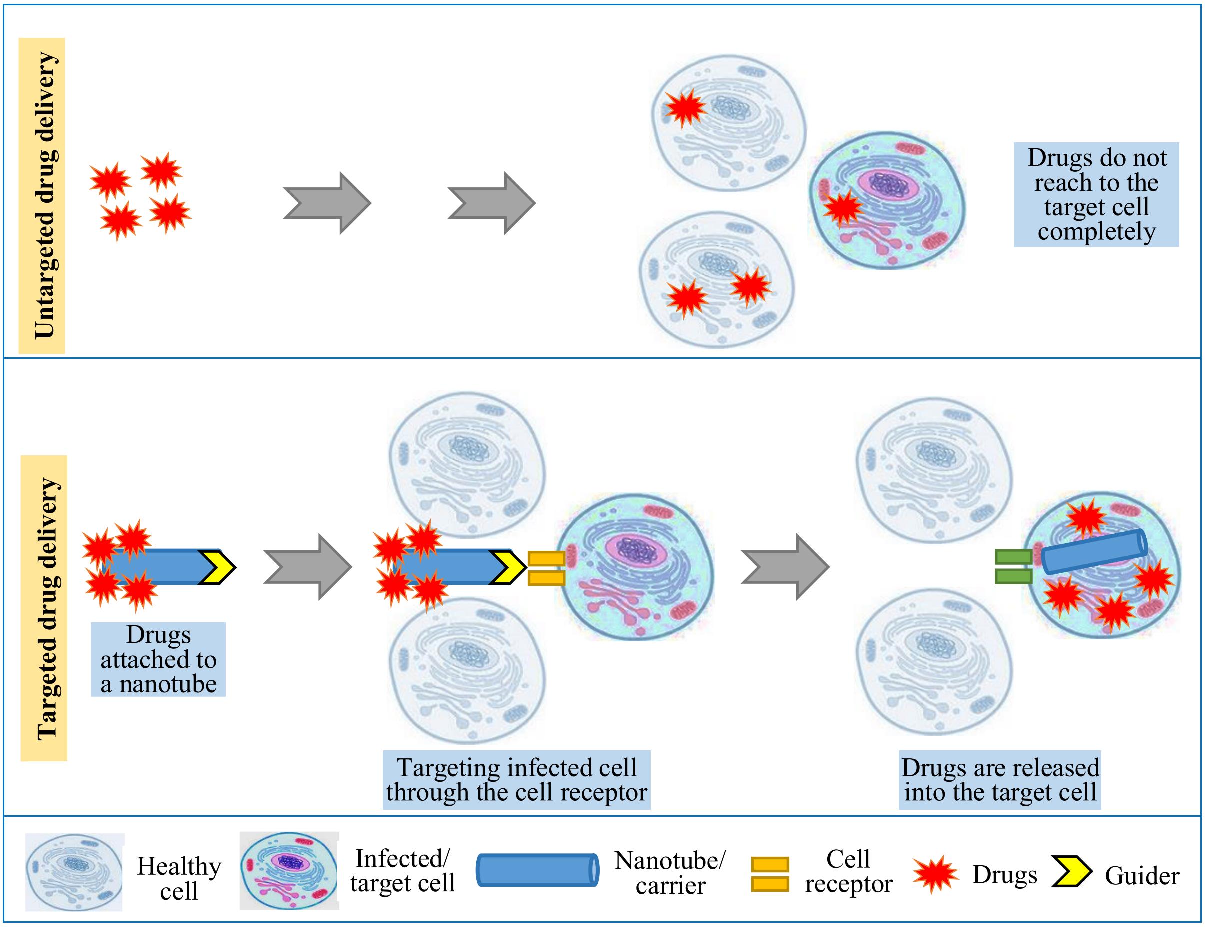

FIGURE 11. Targeted drug delivery directly affects the diseased site [175].

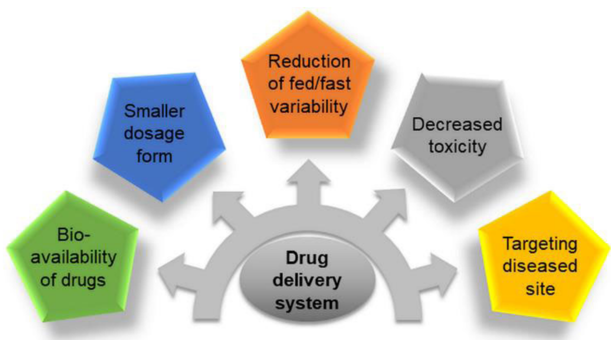

FIGURE 12. Advantages of using nanoparticles in drug delivery systems.

- Ceramic nanoparticles (less than 100 nm): Used in liver and diabetes therapy.
- Metallic nanoparticles (less than 50 nm): Used in cancer therapies.
- Dendrimers (less than 10 nm): Used in HIV and cancer therapy.

2) NANOPARTICLE APPLICATION IN CANCER

Nanoparticles and nanotechnology have found their use in the treatment of cancer. It is evident today that cancer treatment (chemotherapy) has many side effects, such as hair loss, nausea, weakness, etc. Therefore, it is essential that the drugs used in chemotherapy directly attack the cancer cells.

Many nanoparticles have been devised by the researchers for this purpose [178]:

- Ethylene glycol molecules are attached to the nanoparticles carrying drugs. The ethylene glycol molecules prevent the white blood cells from spotting the nanoparticles as external substances.
- Researchers at MIT are working on the concept of using two nanoparticles for the dual purpose of detecting the cancer cells and releasing the drug. One nanoparticle detects the target and the other nanoparticle containing the drug acts on the signal received from the other.
- Another development is being made to treat skin cancer. Gold nanoparticles are attached to RNA molecules. This mixture is made in the form of an ointment, which is applied to the patient's skin. The RNA molecules penetrate the skin and prevent the cancer genes from growing the cancer tumour.
- Apart from the drug release mechanisms, some thoughts are also being put into the efficient shape and structure of the nanoparticles. Disk-shaped nanoparticles (nanodisks) and rod-shaped structures are taken into consideration for chemotherapy for breast cancer.

3) NANOPARTICLE APPLICATION IN DIABETES

Another use of nanotechnology is in providing insulin for diabetic persons. Researchers have developed a triggered response-based drug delivery technique in which sponge-like material surrounds the insulin core. The sponge-like matrix is made up of Chitosan, a material found in shrimp or crab shells. Multiple numbers of small nanocapsules, containing glucose oxidase, are scattered in this matrix. This technique responds to the blood sugar level of the patient. When the glucose level in the patient's body increases, it triggers a reaction that invokes the nanocapsules to release hydrogen ions. These hydrogen ions attach to the sponge molecules and make them repel each other. The sponge matrix gets wide open and causes insulin to release.

Once the glucose level decreases, the molecules lose their charge and come back to their original shape, thereby trapping the rest of the insulin [179]. These sponges usually are 250 micrometres in diameter and can be injected into the patient's body.

C. MEDICAL IMPLANTS

The primary goal of an implant is to allow patients to enjoy active lives and live more. Nanoparticles are increasingly being used in manufacturing implantable devices. The market of the medical implant devices is expected to grow vastly using nanotechnology and nanomaterials. Implantable cardiac resynchronization therapy devices, pacemakers, orthopaedic spinal implants [180], hip replacements [181], breast implant [182], [183], and cosmetic implants [184] are among the most demanded implants. The continuous research in this area has led researchers finding further positive attributes of using nanomaterials to improve the quality of implants. Soft tissue implants, bone substitute materials, dental implants, hard tissue implants, and orthopaedic implants are also some major application fields. However, the study and applications of nanomaterials in medical implants is in its very early stage, but it boasts a huge potential in developing novel and improved biomedical implants. A few applications of biomedical implants using nanomaterials are discussed below.

1) SOFT TISSUE IMPLANTS: REPAIR AND HEALING

Nanotechnology is increasingly used in tissue engineering (construct and repair various tissues) required for plastic surgery. Utilization of enhanced biomaterials, developed using nanomaterials, can provide safe, reliable, and reproducible reconstruction with aesthetic appearance after surgery [185].

Wound and burn are another two scopes of soft tissue clinical care [11]. Construction of wound dressing using nanoscale fabrication techniques can improve wound healing considerably [186], [187]. Some of the essential properties for tissue repair that can be obtained from nanofiber scaffolds are [185]:

- Temperature control
- Mechanical integrity
- Fluid absorption
- Gas exchange

Among others, nanocrystalline silver dressing is an emerging and promising solution for wound healing [188]. Silver is already known for its antimicrobial and anti-inflammatory properties and also been effective against multi-drug resistant organisms [189]. The clinical utility of silver is magnified by applying nanoscale fabrication techniques to manufacture silver-based nanoparticles. The silver nanocrystalline dressing is found to be effective in diminishing the surface bacterial counts in the wounds [190].

Utilization of nanotechnology is getting popular in cosmetic and topical skincare. For example, the nanoscale fabrication in zinc oxide (ZnO_2) and titanium dioxide (TiO_2), used in sunscreen manufacturing, not only make the layer on the skin more transparent but also increases the refractive index, which is supposed to make the sunscreen more effective [11].

2) BONE GRAFTING AND IMPLANTS

Nanotechnology can be used for standard bone replacement implant to increase tissue ingrowth [191]. Use of nanotechnology can be effective in making bone, joint, and tooth implants and is nearly comparable to the original one. The host organisms, reacts more favourably, at the protein and cellular level, to nanomaterials compared to the materials used conventionally [192]. The surface nanocharacteristics of biomaterials are the vital beneficial factors towards this favourable tissue acceptance and cell behaviours. Researchers have tried applying different nanocomposites, materials, and particles to achieve bone tissue growth as naturally possible, which should diminish the autoimmune reactions and microbial infections [14]. The microbial infections are checked by applying anti-friction coating with the nanobiomaterials on the prosthesis surface, which can be loaded with various antimicrobials. The nanoscale structures and coating of various prosthetic implants have another huge advantage in orthopaedic surgeries that they produce and deposit less debris in the articular joints.

3) DENTAL IMPLANTS

Nanotechnology, in the form of nanorobotics and nanomaterials, has shown great potential in the field of dentistry [193]. Besides dental fillers and dental restorative materials, nanomaterials are potentially used in dental and prosthetic implants also [194]. Dental implants are used as interfaces with the jaw bone and skull to support a dental prosthesis. The basis for modern dental implants is a biologic process called *osseointegration* where materials, such as titanium, form an intimate bond to the bone. Use of nanomaterials makes these materials strong, deformable, and corrosion-resistant with a well-finished surface.

4) BREAST IMPLANTS

Nanofibers and nanoparticles have great advantages in breast implants and have the potential to revolutionize cancer diagnosis and treatment [183]. For tumour-specific anticancer drugs delivery, nanofiber coated breast implants are being considered. This has the advantage of facilitating area-specific (targeted) chemotherapy to the tumour bed, which allows avoiding the adverse effects of existing chemotherapy procedures. Utilizing nanoscale technology to manufacture breast implants can improve their strength. The silicon rubber is enforced with SiO_2 and then used as the main component in a breast implant.

D. NANOBIONICS

Nanotechnology is finding its broad use in the field of *nanobionics*. Nano bionics is considered as a technology that finds the convergence between biology and electronics [82]. *Bionics,* in the term nanobionics, means the study of mechanical systems that are capable of acting like a normal human body part. The previously used traditional methods of implant or body part replacement included implanting an artificial wooden leg or limb, or a glass eyeball. These parts had no function and were implanted just to support the bearer.

Nanobionics swoops in with a more efficient and promising technology of creating or engineering such as artificial implants using nanoscale devices that act just like a normal human body part. The primary challenge faced by the researchers in implementing this concept is to make the electronic device (artificial organ) adapt to the biology of the patient.

VII. CLINICAL APPLICATIONS OF NANOBIOSENSORS

Though clinical science is the heart of modern medicine, in the present era, medical sciences are predominantly dependent on technology. Multidisciplinary researches are going on in various fields like physics, chemistry, biology, and engineering. Depending on these, medical technologies are developing continuously. These technologies are important, as with the help of them the minor changes in our body at a biochemical level can be detected, even before any significant clinical manifestations. So, this can be helpful in primordial prevention.

In this section, we will focus on the development of nanobiosensors in the medical field. A nanobiosensor can be of great use in the screening of disease, health monitoring, and accurate diagnosis. With the help of nanobiosensors, we can avoid many invasive procedures in critically ill patients, which eases the process of monitoring, and that is cost-effective too. Figure 13 shows a few examples of nanobiosensors used for in vitro diagnostics. Some of the most prominent clinical applications of nanobiosensors are discussed in the following.

Microfluidic biochip for blood cell counts: The chip is basically a nanosensor that is fed with a single blood drop and uses microfluidic channels to count the blood cells electrically. When individual cells passed through the electrode, voltages are generated. The amplitude of voltages shows the distinct populations of different cell lines. Using a microfluidic device, we can count different blood cells separately. It depends on membrane properties and the size of different cells. WBCs can be counted individually when RBCs are lysed selectively. Diluting only one microL of blood on-chip, we can count RBCs and platelets electrically within twenty minutes [195]. In clinical practice, the blood cell count is a frequently asked investigation. Approaching any infection, chronic disease, or malignancy, it is the initial investigation of choice. The patient will be able to use this at home and cost will be very less, though validation of this technique is yet to be done.

Measurement of electrolytes: In a critically ill patient, electrolytes like sodium, potassium values are frequently changing, so we need proactive monitoring. If we can develop a technique that will continuously monitor these values and display on the screen, will be beneficiary to patients. Electrolytes are measured by potentiometry. By measuring the voltage between two surfaces of the ion-selective electrode, it is compared with reference electrode potential. If we can generate a microsensor with the above mechanism, it will be able to measure different electrolytes periodically. This will break off the need for frequent blood sampling.

Programmable bio-nanochips for cardiovascular disease: Cardiovascular diseases are more common in the population. In detecting early cardiovascular disease, more advanced non-invasive technology is needed, which can detect biochemical changes in our body very early. P-BNC can detect different cardiac bioelements from saliva even before disease manifestation. The concept of P-BNC is based on Luminex and ELISA methodologies. Due to 3D sensor P-BNCs provide a thousand-fold increase in surface area, whereas the 2D planar surface area in ELISA is limited [196].

Biosensor-based diagnosis of infectious diseases: This can be a novel sensitive and cost-effective approach to detect the different infectious pathogenic organism. It can also diagnose infectious biological weapon. Though there are diversities in microbes, they share some standard features in their genomes. Using highly conserved sequences of the bacterial ribosome, we can use a large-range priming target for the largest possible groups of organisms for PCR and mass spectrometry to detect different nucleotide composition.

Continuous assessment of epileptic seizures with biosensors: A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain. People with a seizure disorder are at higher risk of sudden death. Though till date, the pathophysiology of the sudden unexpected death in epilepsy (SUDEP) is not obvious [197]. With the help of wearable electrodermal activity (EDA) and biosensor, we can show its clinical utility in the assessment of epileptic seizures. The wearable biosensors can be used as an ambulatory seizure alarm. It can detect autonomic alterations and heart rate variability during an epileptic attack. In the post-ictal period, we can assess SUDEP risk by analysing autonomic bioelements (increased sympathetic surge and cardiac activity along with impaired vagal reactivation).

Microelectromechanical systems (MEMS) in nephrology: MEMS [198] is the use of fabrication

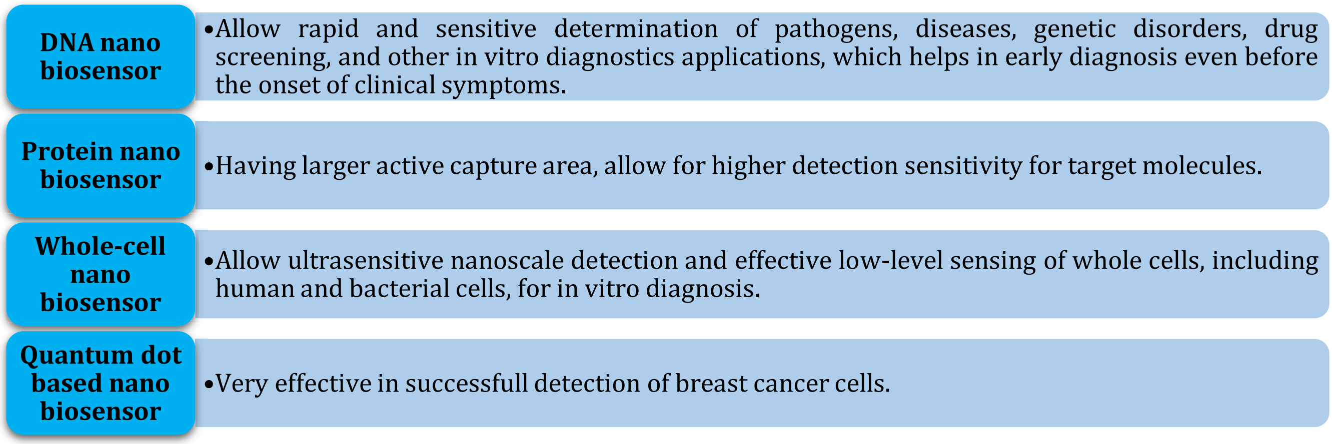

FIGURE 13. Use of nanobiosensors for in vitro diagnostics [62].

techniques from the microelectronics industry. MEMS is a generalized term for miniaturized modified devices adapted from the microelectronics industry. It can be very small (few nanometers) and both fluidic channels and optical sensors can be used in a single device with a high precision rate. Blood and urinary bioelements can be integrated with microfluidic devices for rapid point of care testing in the emergency room. Vascular access plays a crucial role in any ESRD (end-stage renal disease) patient and extreme vigilance are required to maintain a well-functioning fistula. MEMS-based pressure sensor for monitoring blood flow can be used here. Alteration of an electrochemical microsensor (detects pH change after enzymatic reaction by urease) can be used for on-line monitoring of urea during haemodialysis. This MEMS technology can also be used in the volume status monitoring of haemodialysis patients.

VIII. ROLE OF IoNT IN HEALTHCARE

IoNT provides nanonetworking between different nanobiosensors implanted in and/or on the body. Individual nanobiosensors work isolatedly. IoNT provides networked healthcare, which allows these isolated devices working together, providing more comprehensive information. The collective information from different parts of the body help in more accurate clinical decision making. Through IoNT, the health information, perceived by the biosensors, are accessible to the stakeholders such as doctors, medical service providers, the patient and his/her relatives, etc. Thus, IoNT actually provides a ubiquitous healthcare system, which enables continuous and real-time monitoring of the patient's health status, from anywhere and anytime. This not only allows immediate attention but also enables early disease detection and diagnosis. This also bestows cost-effective, precise, and effective treatment and rehabilitation tailored to the patient [82]. The primary advantages of IoNT in healthcare are listed in Figure 14. Considering the advantages, several IoNT-based real-time healthcare applications are coming up [199].

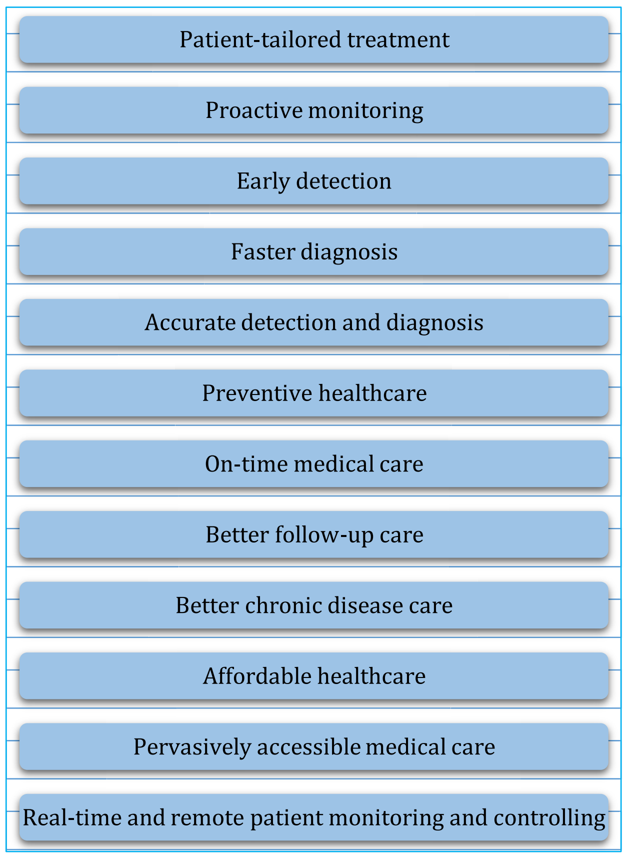

FIGURE 14. Advantages of IoNT in healthcare [7], [82], [200].

IX. IoNT ARCHITECTURE

In order to offer a complete and dynamic set of services, diverse and heterogeneous technologies that carry health services are required to bring jointly in a single system, i.e., IoNT enabled system. In IoNT enabled healthcare system, many systems can work together to offer a healthcare facility at a single site.

Nanotechnology-enabled healthcare system provides the monitoring of the specific organ of the human body. This type

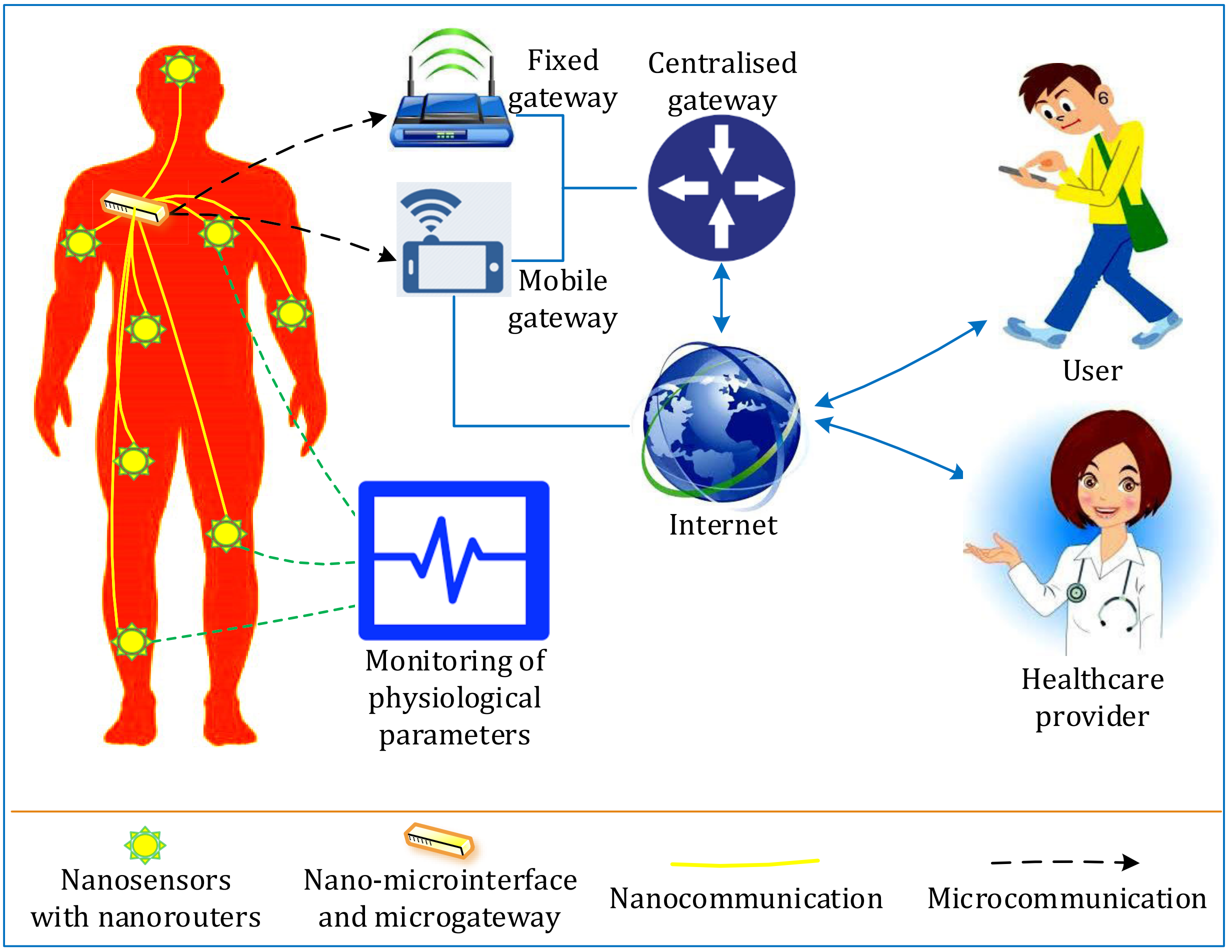

FIGURE 15. Typical architecture and common components of IoNT.

of healthcare system is also used as a smart drug delivery system. The nanodevices may be deployed in the human body or the external environment. There are several nanodevices available in the market which can be used as wearable garments or maybe monitored through mobile phones. The architecture of the IoNT enabled healthcare system has a set of sensors and smart devices that are deployed in/on/off the human body and connected to the gateway to the internet, as shown in Figure 15. Depending on the deployment location of the nano-medical device on/within the body, IoNT is categorised in following three dominant nanonetworks [201]:

- **Off-body systems:** Deployed from an individual's point of view, house, engine vehicle, road, or sanatorium. Off-body systems can offer wide health monitoring services.
- **On-body systems:** Deployed remotely on the patient's body. Exhibit WBANs and wearable gadgets that permit the mass customization of health monitoring and convey health services speedier to the patient's private space.
- **Intra-body systems:** Deployed at different areas inside the individual's body, either as joined or implanted in savvy checking gadgets or as internetworked nanodevices.

The carbon nanotubes in the biosensors (especially, in the Non-biological nanosensors) are used as wireless antennas which act as a sensor and send the collected data to the integrating module. The gateways are Wi-Fi access points that provide a definite position in which a patient is positioned, or the position of a patient's smartphone. By using nanonetworks, data can be collected from all parts of the body, so there is a need for the nano router. This nano router has the table of existing routes that can be used to collect the human body information. These nano routers have a restricted correspondence range; thus, IoNT keeps up a multi-layered, dynamic, and various levelled design [202]. In IoNT framework, the nanodevices are in the group, and each group has a group head. This cluster head handles data propagation to the nano router. The route of data propagation is completely dynamic, and it changes according to setting and accessibility. Nanorouters are craftily associated with the closest gateway to send information. The nanodevices are connected through the networks and physically disconnected to one another. There is a little seamless integration on the communication and on the information level, which prompts repetition and irregularity while accepting the information. To make it an omnipresent network, health services are needed to be integrated on different levels [203]:

- **Connectivity level:** Nanotechnology-empowered systems share their gateways as their setting changes. A BAN utilizes the patient's cell phone to report any undesirable health conditions, yet in the event that the patient is driving his vehicle which is associated with a cell phone; at that point, the information will be transmitted by means of the vehicle's handset.
- **Data level:** The information ought to be interestingly connected to the individual patient regardless of its configuration, granularity, and setting. The repetition and irregularity of information are kept least utilizing standardization. The data integration strategies are conveyed in this level for further analysis. The information can be put away at the patient's gadgets or the healthcare services supplier's servers.
- **Services level:** It should be conceivable to execute administration services and these services must be given by the diverse systems administration frameworks so as to set up further complex services, rather than structuring new services from the beginning.

X. COMMUNICATION SYSTEM OF IoNT

IoNT utilizes Terahertz (THz) band (0.1THz – 10THz) for correspondence among sensors for health management of a patient. This band gives high transfer speed and high information rates. With the help of THz points of interest, the highspeed information move can be made conceivable by remembering nanodevices for the cutting-edge cell systems and real-time applications. IoNT utilizes two broad areas of communication of correspondence, as pursues:

- **Electromagnetic nano correspondence:** It is viewed as transmission and accepting of electromagnetic radiation from segments dependent on nanomaterials.
- **Molecular correspondence:** It is viewed as transmission and accepting of data encoded in molecules 204].

However, the molecular correspondence gives off an impression of being superior to electromagnetic correspondence since it gives bio-similarity, ability to work in fluid medium and universality [204]. Particles trek from transmitter to collector either utilizing active transport (molecular motors) or passive transport (diffusion) [204]. Data is encoded either as a concentration or a kind of messenger molecules. Messenger molecules might be utilized to hold data through the medium, like air or fluid. In any case, these atoms are suitable for exceptionally short-run correspondence, for instance, correspondence in BANs [205].

A. NETWORK ARCHITECTURE OF IoNT

The interconnection of nanomachines with dynamic communication systems requires the development of system models [206]. Figure 15 portrays a run of the design of IoNT, demonstrating the intrabody nanonetworks for remote healthcare. In intrabody systems, nanomachines, for example, nanosensors and nano actuators injected to individuals and remotely controlled over the web by an outer client. The next part is coming up with the fundamental segments in the system design of the IoNT [207]:

- **Nano nodes:** These are the littlest and least difficult nanomachines. Nano nodes can do the protected calculation, have confined memory, and can just communicate over negligible separations, by and large in view of their decreased vitality and limited correspondence capacities.
- **Nanorouters:** These nanodevices generally have more noteworthy computational assets than nanonodes, and are appropriate for accumulating data originating from limited nanomachines.
- **Nano-micro interface devices:** These can combine the data originating from nanorouters, to pass on it to the microscale, and the other way around.
- **Gateway:** This device empowers the remote control of the entire framework over the web.

B. IoNT NETWORK LAYERS AND THEIR REQUIREMENTS

Nano communication is used by the nano network to exchange information among physical objects. In this section, we pursue a layered systems approach to examine the necessities and difficulties of IoNT human services applications and services utilizing a nano correspondence network.

Application layer: The main designing features of a healthcare application should cover real-time, reliable, and context-aware operation. However, due to the transmission medium, network overhead, and other unavoidable reasons, a delay is expected. The heterogeneity of nanodevices inside the body will bring about various information in different formats. Accordingly, information integration ought to be ideal, dynamic, and delay-tolerant [87]. Information integration is not always reasonable for the medicinal services domain since continuous applications required fine-grained data without any varieties. The context-awareness is another challenging piece of the application layer of the nanonetworks. The systems outside of the body can be geographically labelled and can communicate with the outer condition, to decide and refresh their specific context. The nanonetworks inside the human body need a non-invasive system to perceive their specific context, particularly for arrangements that rely upon node mobility.

Transport layer: There is a significant level of biological noise, which brings about unreliable transmission [87]. As there are a few nanodevices that can send similar information, henceforth packet loss is less. The information is received by the group head and circulated among the units. This makes it conceivable to address a group of nodes dependent on the health usefulness they perform or the biological organ [208].

Network layer: In IoNT frameworks, the THz-based correspondence range is between 1 cm and 1 m, and for subatomic correspondence, the range is 1 nm to 1 cm [208].

This implies that the transmission range is very limited, which makes multi-hop communication and routing a critical perspective for nanonetworks. The nanodevices float inside the body and lead to correspondence delay. The mobility of nanodevices is used for routing to reduce the delay incurred due to biological propagation limitations. This will require proficient plans for multi-hop route creation and management [87].

MAC/PHY layer: The MAC/PHY layer ensures guaranteed information delivery to the goal. Since the transmission range for nanodevices is restricted; thus, the thick arrangement of nanodevices is required. These gadgets are combined with multi-hop correspondence to support reliable data delivery [209]. Channel models with path loss, thermal noise, and channel limit with regards to both molecular and electromagnetic nano correspondence are needed [210]. The channel medium is the molecules for molecular communication. Molecular correspondence propagates through organic tissue and is liable to Brownian motion [209]. Since the body is made out of 65% water, this makes it trying to foresee how the information will spread through the organic channel. Ultrasonic correspondence fills in as a dependable channel to accomplish the internetworking of the nanomachines for intra-body communication [211].

Wireless MAC protocol cannot catch the individual attributes of THz band correspondence and nano nodes specifications; therefore it cannot be used in IoNT. The THz band correspondence gives huge data transfer capacity and altogether short transmission time [212], which prompts fewer impacts and obstruction than in customary systems. In past work, various scientists proposed straightforward MAC conventions that were actualized in IoNT. The straightforward MAC convention gets the packets from the network layer and transmit it to the physical interface without taking care of any flow control, error control or adding any headers to the packet [209]. The high path-loss and low vitality of nanodevices advance the requirement for packet control MAC conventions that address the need for controlling access to the THz-band channel to diminish packets retransmissions. Packet retransmissions may present an unavoidable delay that renders packet retransmission pointless. Past researchers have proposed energy harvesting aware MAC convention used by CSMA/CA-CD called RIH-MAC. In RIH-MAC, the recipient sends an RTR sign to every single intrigued source once it has adequate collected vitality to get a packet and interested source answers with a data packet sent to the beneficiary.

XI. IoNT CHALLENGES

Although IoNT is a strong concept with massive potential in the medical field, there are many challenges to be met for the real-life implementation, as discussed in the following.

A. LIMITED COMPUTATIONAL CAPABILITIES

Installed nano processors use tiny transistors. The smallest transistor that has been experimentally succeeded till date is based on a graphene strip, which is made of only ten by one carbon iotas. These transistors are minor as well as ready to work at much-raised frequencies. In any case, the intricacy of the tasks that a nano processor will have the option to hold relies upon the number of transistors in the chip, hence, on its absolute size.

B. LIMITED MEMORY SPACE

The biological data that are procured by the nanosensors and the nanodevices ought to be buffered inside the device itself before it is transmitted to an external system. However, considering that the total size of a nanodevice is in the request for a couple of cubic micrometres, all things considered, it is impossible for a nanothing to have the option to store more than one data packet at an instance. Consequently, the nanosensors may battle to store the sensed information, even temporarily. Nevertheless, luckily, nanomaterials and new assembling procedures are empowering the development of much denser recollections, in which the capacity of one bit of the data may, in the long run, need only a few atoms. The entire amount of data storable in a nano memory relies upon its size.

C. CONSTRAINTS IN DATA COMMUNICATIONS

Planning and usage of effective, error-free, and secure information correspondence in IoNT are not insignificant. A portion of the critical requirements in IoNT information correspondences are:

- Unpredictable transmission medium because of the high level of biological noise.
- The nanoscale of the parts of nanonetwork makes it trying to give an individual address to every component in the system. Consequently, they must be clustered in groups.
- Congestion control in the high data traffic cannot be handled by nanodevices.

In this section, the primary challenges in IoNT information correspondences are briefly examined.

1) COMMUNICATION RANGE

Due to the intra-body nanoscale gadgets, communication is a lot smaller than expected. Difficulties looked by IoNT in such a manner are as follows:

- Limited correspondence range, 1 nm to 1 cm (for sub-atomic transmission) and 1 cm to 1 m (for electromagnetic transmission).
- Short-extended intra-body correspondence can prompt postponement if there should arise an occurrence of crises.

2) COMMUNICATION STANDARDS

As the usefulness of BAN is not the same as conventional systems, the correspondence norms additionally pursue a somewhat distinctive model. i.e., only a couple of functionalities of OSI/TCP model can be taken into consideration.

WBAN is incorporated with IoT, and it requires a separate addressing mechanism for IoT networks;

however, when we are managing addresses of sensor nodes in WBAN, it's not a significant issue. Since information communication is an imperative segment of nanocommunication for in-body networks, the foundation of standards for improvement and arrangement of the correspondence organize is extremely necessary. Till now, we know essential benchmarks that are practically precise for conventional models (OSI/TCP). Yet, for in-body networks, which utilize molecular correspondence in an aqueous medium, another convention stack should be structured. The basal layers (information connection, system, and application) can be propelled by TCP/OSI models.

3) BANDWIDTH

For data transmission assignment, FDMA (frequency division multiple access) and CDMA (code division multiple access) are not a savvy decision since they require sophisticated equipment alongside high vitality requirements for their execution. The sensor nodes in WBANs are required to work with the least conceivable power utilization. Along these lines, we go to CSMA/CD and TDMA. Further, in the event that the WBAN is not dynamic in nature, at that point, CSMA/CD would not be adequate. This situation leaves us with the decision of TDMA (time division multiple access) that has high throughput and least deferral in any event, when the heap is expanded. In this manner, the usage of TDMA when we are receiving an atomic correspondence approach can be a tricky task.

4) DESIGNING LIGHTWEIGHT PROTOCOLS

As IoNT requires nanonetworks, the functionalities related to it are additionally constrained to the nanoscale. This implies it is not attainable to utilize a conventional protocol. Designing precise and lightweight protocols are the main alternative to keep away from the complexity of communication norms.

5) INTERFERENCES OF OTHER WIRELESS SIGNALS

At the point when nanodevices are in the biological system, the network is known as *nanobionetwork*, and in this system, different transmitter-receiver operate in a similar medium. The inter-symbol interference (ISI) and multi-user interference (MUI) cause immersion at the receiver side, and this impact may cause a blackout [213]. The answer to this issue is using various molecules for various transmitter-receiver sets. This is an extremely far-fetched process, in light of the fact that there are numerous nanodevices working at a relative volume. Subsequently, it has been accepted that the transmitters will utilize a similar atom to impart each time. The ISI and MUI make critical breaking points in the communication network.

D. SENSOR FUSION

Sensor fusion is a strategy wherein factual information accumulated from single or different sensors are fused or combined. In this strategy, received data is better when these sources were utilized individually. The nanodevices are utilized in the human body with various uses; so the information got from various gadgets are heterogeneous in nature. Sensor combination in human healthcare domain will be ideal, dynamic, and delay-tolerant for applications that depend on the joining of different information sources as utilized continuously in healthcare applications. In any case, aggregation and fusion are not always reasonable for healthcare applications, on account of the continuous prerequisites, and since a significant number of those applications rely upon fine-grained varieties in the temporal domain that are lost in the aggregation/fusion process. A physical sensor estimation, for the most part, suffers from the following accompanying issues:

- **Context loss:** The glitch of a sensor component causes loss of the context of the desired object.
- **Limited coverage:** Usually, an individual sensor just covers a restricted piece of the patient body. A few sensors need a particular set-up time to execute and to send a calculation.
- **Lack of accuracy:** Computation from singular sensors are restricted to the precision of the utilized detecting component.
- **Lack of certainty:** Lack of certainty, as opposed to the absence of accuracy, relies upon the item being watched instead of the watching gadget. Vulnerability emerges when highlights are missing when the sensor cannot measure every single significant quality of the percept, or when the perception is vague 214].

E. SENSOR VALIDITY

The data is received from the sensors at a time interval or in real-time as stream data. The validity of the sensed data plays the most crucial role in the accuracy and reliability of the IoNT based WSN healthcare applications to assure data quality for sound decision making. Researchers have proposed various procedures for sensor information validation. One of the procedures for sensor information validation, which depends on an adaptive threshold for real-time IoT/WSN sensor node level. The proposed methodology thought about the recognition of different kinds of detected information errors and tended to a straightforward mechanism to classify between error and event [215].

F. TEMPERATURE CONTROL

Continuous operation of embedded health sensors is likely to generate heat. The temperature might vary depending on various factors. For the embedded sensor, the heat cannot disappear in the air. The accumulated heat might hamper the operation of the sensor and make it consume more energy. If the generated heat is beyond normal, it might have adverse side effects to the adjacent cells or other internal body parts. Hence, it is very crucial for the sensors to have automatic temperature control. Designing this type of sensor, considering the other factor required for an embedded health sensor, is not trivial.

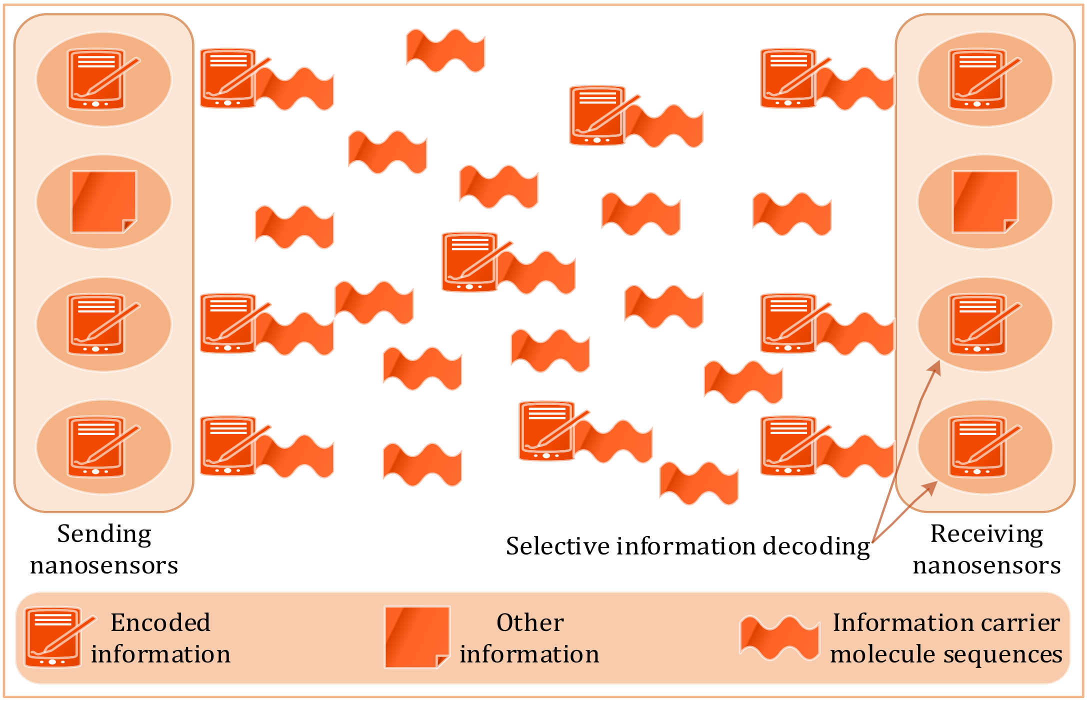

FIGURE 16. Nano communication in an aqueous medium.

G. DATA MANAGEMENT

Monitoring and diagnosis of the human body on a regular basis and in minute detail, as done by nanodevices, are bound to create and accumulate an enormous amount of data. The data collected may include relevant health-related information from different body parts. Therefore, another challenge in nanotechnology implementation is the issue of collecting large-scale data and storing it in highly functional and efficient databases. Along with the storage, also comes the overhead of mining of the collected data to find disease patterns or to find out the probability of disease to occur to an individual. The following subsections explain some predefined and technically perfectioned steps to manage data transmitted by nanomachines that reside in in-body networks and BANs.

1) ACQUISITION AND COLLECTION

For communication among the nanomachines, molecular communication is considered, which is a new interdisciplinary research area that spans the nanotechnology, biotechnology, and communication technology. Molecular communication allows nanomachines to communicate using molecules as a communication carrier. It uses chemical signals and an aqueous medium to propagate and transfer information. The data collection process in such a communication paradigm is much more complex as compared to traditional communication that involves electromagnetic devices and waves propagating in the airborne medium.

The sender nanodevice sends encoded information which is mainly in the form of proteins, ions or DNA, etc. in the form of molecular sequences, as shown in Figure 16. These data atoms are then stacked on transporter particles that are made of synapses or hormones and transmitted to the receiver nanomachine. As such, the data is gathered by nanodevices that can be then transmitted over the web to an outside healthcare supplier utilizing a nano-small scale interface.

2) STORING

Storing the gathered information inside the body is a complex and an unattainable task as of now. But storing the data collected externally is a viable option. It is evident that although nanotechnology has changed today's healthcare scenario, it has also put forward the issue of an extensive repository of data, its storage, and management. Since a large number of nanodevices will be implanted inside the human body, therefore, a considerable amount of data will be generated on a daily basis that needs to be stored and processed. A scenario as such requires storing devices with large storage capacity that can store data for a more extended period of time. The conventional storage devices such as disks or tapes are bound to wear out because of the nature of large data. Recent advancements in technology have led to the development of a new era of storage devices. These devices can prove to be an aid for nanotechnology. These devices are assumed to have a comparatively higher and enhanced storage, along with better and faster data processing.

At this point, it is necessary to establish a vital fact that storage for nanomachines implanted inside the human body may have two aspects. First, a temporary data storage that stores all the immediate data for a specified time. Second, large storage to keep data records for analysis, such as a server. The first aspect of this storage may have a time duration of 24 hours, for example. The storage will be cleared after the time bound for new data arrival. At this point, the need for the second aspect of data storage arises, to keep data record permanently. All the processing and notification tasks can be performed on the temporal data, as it is easily accessible and most updated data. All the devices that have been fashioned for such temporal data storage are customarily designed for short ranges as nanodevices can transmit over a very short commute. For example, nanodevice inside the body for diabetes check can send a message for a dip in insulin level. This information can be transferred to the device for storage, and the health provider then uses this information to communicate with the device to release the insulin required in the body. The collected data can be sent over the internet for permanent storages where analysis of the medical history of a particular patient can be done effortlessly.

Some of the existing and emerging technologies for data storage are mentioned below:

- **Cloud storage:** Cloud storage is a model of data storage in which digital data is stored in logical pools. A hosting company, a cloud storage provider, manages this data which spans over several physical servers. This data can be accessed through a web API (application programming interface), or co-located cloud computer service. The ubiquitous feature of the IoT is further enhanced by integration with cloud storage. Therefore, cloud storage can be comparatively more helpful than on-premise storage of data generated during the process of nanomachine operations. It is a much-preferred approach as the devices can directly communicate and store data in the cloud without worrying about space and storage capacity. Another advantage of using cloud storage is that it reduces the computational overhead that is required for data storage as that would now be the cloud service provider's responsibility to manage data.
- **Holographic storage:** Holographic data storage is an underdevelopment technology with a potential of high capacity data storage which is currently dominated by magnetic data storage. The concept has arisen from the small hologram that we observe in the front cover of published books. The hologram supports the idea of storing a large amount of data in a relatively small space. This approach uses laser beam generating optical patterns of dark and light pixels. The information is stored in photosensitive optical material. If developed, this technology can provide a revolutionizing and positive spin to the data storage problem that computer experts face today.
- **Electronic skin:** Electronic skin is a new advancement in data storage which is a type of wearable sensor that is as thin as skin or a tattoo that is capable of monitoring a person's movement and store diagnosis information. Electronic skin is also capable of delivering drugs through the skin to the body. It is constructed by forming multiple layers of stretchable nanomaterials and resistive RAM to store data. The trade-off for such a construct is that this device works only if supported by the power supply and data transmitter.
- **5D data storage:** 5D data storage is the most awaited data storage technique, which has the potential to transform today's method of data storage and manipulation completely. Scientists at the University of Southampton have developed a 5D glass disc that can store 360 terabytes of data for 13.8 billion years. The discs are made of nanostructured materials, and data can be retrieved by using femtosecond laser writing.

3) PROCESSING

In customary sensor systems, information assortment normally happens by means of an information structure like a static tree. Every node along the tree detects the information and afterwards passes it along the tree to the sink node at the root. Information handling in the healthcare services framework utilizing nanodevices alludes to the way toward performing explicit activities on tangible information. To manage the colossal information of the framework, proficient information preparing techniques must be embraced. The preparing of the information is made known in the accompanying steps:

i) **Protocol conversion:** The information gathered from the physical layer is made out of various protocols, and it will intensify the multifaceted nature of the process, the management, and upkeep for the online healthcare framework. A savvy passage is added to the framework to move the information in assorted conventions into an information-dependent TCP convention. The applications in the application layer can be in contact with the sensor node in the physical layer and device layer through the smart gateway by sending the messages.

ii) **Congestion control:** Due to substantial volume of information in the nanonetwork, there might be a blockage in the traffic. If the framework does not choose a productive calculation to deal with this issue, it will prompt an endless loop, which will exacerbate the Congestion. Researchers have embraced the RED (random early detection) calculation to control the blockage in the human services domain [216]. The hypothesis of this calculation is to watch the length of the data packet queuing in the router. Before the cache is flooding, the information packet will be disposed of at a specific likelihood once found congestion approaches.

iii) **Data filtering:** The amount of data received from the various equipment is enormous, but only part of them are significant for processing. In the event that the framework does not sift through the superfluous information, it will bring the following issues:

- Increase a heap of system transfer speed since the framework needs to communicate a lot of information.
- Increase the heap of the information processor on the grounds that the processor needs to process gigantic information.
- Increase the heap of the information stockpiling on the grounds that the database needs to store a tremendous measure of extra information.

To dispose of these issues, researchers have proposed duplicate data filtering and event filtering process [217].

4) EVENT NOTIFICATION

An event notification is a system in which, based on certain state, alarms or other kinds of information is sent to the stakeholders. Depending on the healthcare application, the sensed data or the processed results need to be sent to appropriate entities. For example, different biosensors regularly observe the different biological parameters (like blood pressure, glucose level, sugar level, etc.) of a patient's body on a different level and if any of these parameters cross its threshold limit, an emergency notification is sent to the authorized person [218]. The notifications are generally delivered to devices, such as smartphones and desktop PCs, which work as service providers. Most often, these notifications are critical and need to be accessed in real-time. Upholding a hard-real-time constraint in a networked setup for a critical and sensitive application like healthcare is challenging.

H. ENERGY EFFICIENCY

One of the significant challenges of implementing IoNT in any area is to tackle the problem of battery life of the devices. As per the current scenario, the majority of connecting devices work on battery, and according to a certain estimation, there will be 24 billion connected devices by the year 2020. But given current energy availability, powering so many devices will be an impossible task. So, there is an urgent need to find energy alternatives and also to fashion connecting devices that do not depend on a battery.

Another considerable constraint is the risk of wearing out the battery when the nanodevices inside the body are functioning. To replace the devices from time to time just for the reason of battery life is an expensive trade-off. To mitigate this problem, temporary solutions such as using rechargeable batteries, solid-state batteries that are thin and flexible and easy to integrate with ICs are used. But for long-term and permanent solutions, advancements such as energy harvesting or designing power-aware protocols that determine an energy-efficient route to transfer information are being made.

Recent studies suggest that in not so distant future, we shall have lithium-ion batteries that will last much longer [219]. Also, other technologies are coming up that will allow devices to be charged by various means, not depending on a rechargeable battery [220].

I. SECURITY AND PRIVACY

As advanced as the whole nanomachines working on molecular communication concept be, the fact that it exposes very detailed and personal information related to a person to the whole world, is a matter of concern. Considering its pervasive usage, it is straightforward to access one's medical records by hacking into the core and extended IoNT network. This can impose catastrophic repercussions in context with securing a person's privacy and health interests [221]. However, nanotechnology uses a different protocol stack for internal communication, so, the traditional hacking resisting techniques may be inefficient in the nano communication levels. But when the information travels longer distance over the Internet, the risk remains as usual. To tackle potential data theft, the best-available preventive and security measures and standards should be opted at every stage of IoNT systems, as shown in Figure 17.

J. COMPATIBILITY AND INTEGRATION

IoNT paradigm is going to imbue in the healthcare sector at lightning speed. Hence, a lot of architectures, frameworks, guidelines, platforms, and standards are being proposed and marketed very regularly. These solutions may vary in different parameters. The two most important of these are discussed below.

1) DEVICE COMPATIBILITY

The nanodevices and other devices used by IoNT in healthcare applications are made by different vendors of different standards and functionalities. To make the nanotechnology-enabled healthcare truly pervasive, the nanodevices need to be compatible with other nanodevices, existing micro-devices, and traditional medical and healthcare devices.

2) COMMUNICATION MEDIA COMPATIBILITY

As discussed in Section 10, IoNT involves different types of communications with dissimilar communication media requirements. For example, the medium of in-body and off-body communications will be completely different. For error-free and communication, the IoNT applications and data should be compatible with different communication media.

3) COMMUNICATION PROTOCOL COMPATIBILITY

Compatibility and integration of various atomic correspondence standards between different IoNT gadgets have two following aspects:

- The external mix of artificially designed convention protocol stack with a sub-atomic communication physical layer.
- The interconnection between various layers of the protocol stack.

These two perspectives are effectively reachable if there should arise an occurrence of homogeneous nature of electromagnetic-based correspondence systems. However,

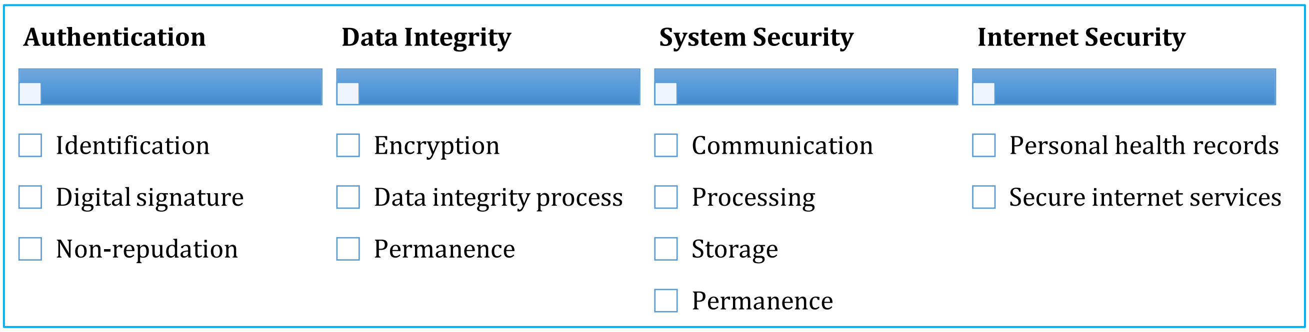

FIGURE 17. **Healthcare specific security standard [222].**

on account of the heterogeneous nature of organic procedures, similarity and mix of various layers of the convention stack is a complicated task.

Researchers are in persistent effort in creating IoT systems and protocols that are unequivocally perfect on various stages. For instance, the authors in [223] proposed a negligible rule for IoT-empowered devices that can be utilized by different creators as a kind of perspective to construct their very own IoT-empowered gadget on various stages. However, there is a need for a further investigation concentrated particularly on the IoNT that includes expertise fields in biomedical, electronics, and communications. For example, significant moves should be tended towards nano communication.

K. BIOLOGICAL COMPONENT CHARACTERISTICS

The making of sub-atomic correspondence arrange is profoundly dependent on the repurposing of biological components and procedure so they can impart and collaborate with the system. Likewise, it is essential for the components to adjust and get to know the atomic successions engaged with data move. For instance, infections and DNA have a specific decay or half-life that influences the communication challenge. In this way, a course of action should be made for replicating nodes.

XII. HEALTH RISKS AND CLINICAL CHALLENGES

The intra-body biosensors are the foreign entities to the human body. So, there is a strong likelihood that the human body might react unfavourably. For on-body and off-body devices also there is a possibility of adverse effects of the radio signals, used in communication, on human health. In the following, the health hazards and the clinical challenges of using nanotechnology in healthcare are briefly discussed.

A. HEALTH CONSEQUENCES

Although nanotechnology has a promising future and the potential to solve many healthcare issues such as cancer diagnosis and regular check-ups and providing medicines as and when required by the body without delay, implanting electronic devices with radiating signals inside the human body is still a concern for the scientists and medical experts. Many experts have been sceptical about the nanodevice implants is due to the probability of damages it may cause to the human body. Some of the health hazards imposed by nanotechnology are:

- Every human body reacts differently to the nanodevices implanted inside it. The risk of nanodevices and the signals emitted by them damaging the soft and delicate tissues and organs is persistent. Moreover, prolonged exposure to such devices made of materials like silicon, silver, etc. can alter the functionality of many body organs and cells.
- Nanodevices can slowly accumulate inside organs and block the blood flow and oxygen reachability.
- There is a fair chance that the body will consider nanodevices as a foreign body and generate pathogen cells to develop a strong immunity. Such repeated actions of the body may possibly weaken the immunity system of the body.
- Some scientists believe that making the human body a hub of electronic devices in an attempt to interfere with the nature that may have devastating repercussions.

The sensitivity of the nanodevices and their effects on the human body should be precisely analysed [224]. Biocompatibility of these devices should be of high priority consideration. One probable solution is to cover the intra-body nanodevices with an antimicrobial or protective coating, which can prevent the potential toxicity of nanomaterials from harming the human body [225].

B. CLINICAL CHALLENGES

Though research works on biosensors are going on, there are lots of difficulties in practical implementation. First thing how to use it and when to use it, is a big question. Will it be acceptable to use it under the skin or any other particular body parts will be preferred for different biosensors. But this should be the least invasive process when putting biosensor on someone. The best location for a biosensor will be subcutaneous tissue or superficial mucosa. In these areas, we can implant the sensors with non-invasive technique, rather than in other deeper body areas like aorta or another vascular system, a heart where more invasive technique is required.

In the case of subcutaneous biosensors, the immune response may disrupt the sensing power by generating fibrous tissue between the sensor and the body. The formation of this tissue matrix may lead to a device failure. Works are going on to reduce this inflammation by using an anti-inflammatory system - Titania nanotubes, Chitosan hydrogel, and drug-releasing nanoparticles. They reduce macrophage activity and subsequently, fibrotic changes.

The next question is, can we use in every person. It would be better to select a particular population, to whom it can be used. We have to select a high-risk group population who will be benefited from intense monitoring through the biosensors. Using it in all populations will be not wise, as it will be not cost-effective and may not be fruitful.

Next important thing is biosensors should be lighter, and materials of biosensors should be nonreactive to our body's immune system. Among different metal nanoparticles, gold nanoparticles are mostly used for their optical and electronic properties. Others are quantum dots based on cadmium which provide a broad absorption spectrum, nano-sized magnetic nanoparticles, ferromagnetic materials - iron oxide, carbon nanostructures, different DNA and enzyme biosensors. After coming in contact with their substances, they can be modified to express different fluorescent proteins. But which material will be more acceptable by our body is a matter of debate, as limited data are available on it?

Few obvious questions arise regarding biosensors such as:

- Can we use a biosensor for a long duration?
- Are these biosensors auto degradable or we have to remove it from our body separately?

The answers are not very clear. Recent research efforts are going on for resorbable magnesium alloy-based biosensors. The answer to a crucial question, "how the people of different socioeconomic status will accept these biosensors?", is not known. We need to conduct a trial on a large-scale basis to see the response of different biosensors on population.

XIII. IoBNT: THE NATURAL DESCENDANT OF IoNT

As discussed in the previous section, one of the major implementational issue of IoNT with nanobiosensor is the compatibility with human body because typically these sensors are made artificially. The artificialness of the nanodevices may result in unwanted effects on health [226]. To mitigate this issue, the concept of internet of bio-nano things (IoBNT) has been proposed [227]. The fusion of nanotechnology, IoNT and synthetic biology [228], [229] has materialised IoBNT with the aim of controlling, modifying, re-engineering and reusing the biological cells in IoT enabled computing device [97]. IoBNT involves networking and communication via nanoscale and biological entities, where cells are based on organic molecules rather than electronics.

IoBNT is envisioned to have strong potential in diverse applications such as communications, network engineering, environment sustainability, industrial applications, military applications and healthcare. Some of the prominent applications of IoBNT, specific to healthcare are [97]:

- Bio-hybrid implants: All human body organs, nervous tracks and lost tissues can be replaced.
- Immune system support: Various foreign and pathogen elements are controlled in body and nanodevices can be collaborated with smart sensors to protect against diseases and will lead revolutionize medical field especially in cancer cells detection.
- Health monitoring: Biological nanosensor networks can provide precision information of patients about Oxygen, Cholesterol and other hormonal disorders for early diagnosis.

DNA-based infrastructure, data processing via biochemical, chemical energy transformation and information exchange via molecules (known as *molecular communication*) will lay the base for applications enabled by IoBNT [227]. Different aspects of molecular communication are shown in Figure 18.

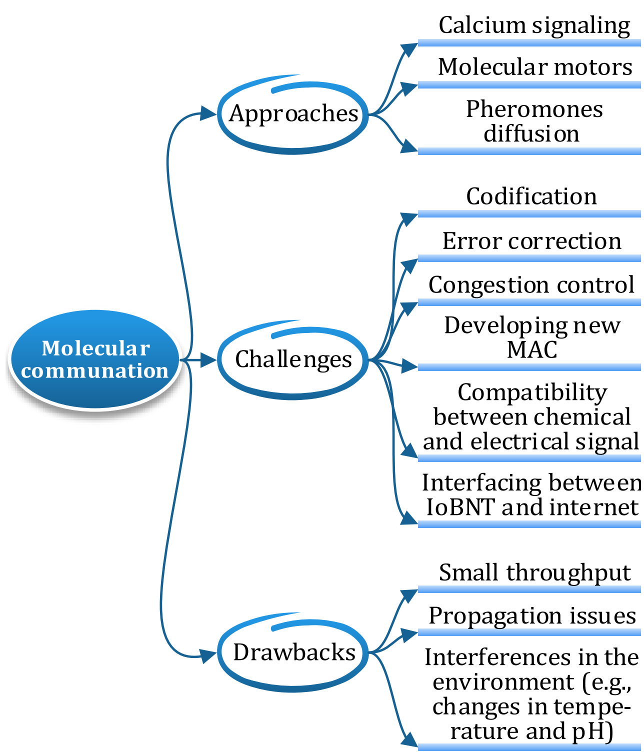

FIGURE 18. Different aspects of molecular communications [213], [230].

With recent advances in nanotechnology and biotechnology, bacteria are receiving substantial attention towards scientific research as a potential activator for IoBNT. Researchers believe that bacteria could allow the development of a biological version of the IoNT. According to the researchers, this new concept could be well supported by the *do-it-yourself* biology [231]. As of now, IoBNT is still in the very early stages of research. However, in the near future, microbes could eventually replace the electronic sensors of IoT devices. Scientists are still looking into the similarities between bacteria and computing devices as well as how these similarities could be exploited. Despite being in the early stages of research, they say that initial findings are intriguing; and hopefully the realisation of the very goal of IoNT is not so far-off.

XIV. CONCLUSIONS

Nowadays, nanoscale device technology has been a hot research area. Nanotechnology is the fast-emerging science that intends to revolutionize every aspect of human life, healthcare being one of the central areas. The concept, now under development, of implanting nanoscale devices inside the human body has the potential to transform the whole health and medicine paradigm that exists today. The deployment of internetworked nanodevices constitutes the system, known as IoNT. Nanotechnology has led to the development of the IoNT. Information sharing and coordination between nanodevices and internet devices will expand the application of IoNT. The advancement and extensive implementation of nanotechnology-based systems will have a tremendous positive impact on various aspects of our daily life and society. The IoNT vision could be realized by incorporating nano-communication capabilities with the nanodevices, and enabling them to communicate with existing micro- and macro-devices seamlessly, along with overcoming several other technological hurdles. IoNT possesses a bright future in the ubiquitous healthcare field. Due to its nanoscale and efficient network paradigm, healthcare and medical science can grow to levels that were thought as impossible a few years ago.

Although nanotechnology has a promising future in the coming years, there are certain issues and challenges that need to be taken care of. Apart from implementation issues, characteristics of nanodevices, communication protocols, and the impact on the human body are some of the broad areas that create a hindrance for this technology to propagate. Recognising and handling the issues related to toxicity and health effect of nanoscale materials are valid concerns for using nanotechnology in healthcare. The major challenge of IoNT scheme is to design proper information and data reservoir and routes to pass that information in the network. There is a need for designing efficient information and routing schemes. Another challenge is to integrate IoNT with current healthcare systems as well as other related IoT applications in a heterogeneous networking environment and data domains.

If these challenges are overcome, healthcare would be able to reach another dimension in terms of prevention, protection, and accessibility. Many diseases could be diagnosed beforehand at their early stages. Medicines will be provided as and when required by the body in exact amounts. Side effects from medicines can be avoided as the drugs would now target the desired body part. If to be quoted in a single line, health monitoring and disease curing will be comparatively an easy task, and expensive healthcare could be provided to anyone anywhere without constraints such as availability of doctor and drugs. The time is to develop a genuinely persistent computing atmosphere that can serve humanity better.

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