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Computational Approaches in Biomedical Nanoengineering: An Overview

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1.1 Introduction

Nanobiotechnology – a revolution in "biomedical engineering," "nanomaterials synthesis," and characterization activities – rules the subfield of biomedicine. One nanometer, or meters, is the length of a single sugar molecule. A cubic nanometer provides only enough room for a few hundred carbon atoms. Since it may never be possible to create novel arrangements of subatomic particles, a nanometer represents the approximate lower limit on the size of technology. The dream of nanoscale computing was first brought to prominence by Richard Feynman in his 1959 speech to the American Physical Society. As he put it, "there's plenty of room at the bottom."

This emerging technology will usher in new possibilities in computation: molecular electronics, DNA computing, disease diagnosis, target-specific drug delivery, molecular imaging, and more. Nanoscale architectures must function correctly even when individual devices fail.

In a layman's terminology, applying nanotechnology for treatment, diagnosis, monitoring, and control of diseases is usually referred to as "nanomedicine." Nanobiotechnology deals with the construction and application of various nanomaterials particular to pharmacy and medicine; it has enormous potential to solve critical issues of important human diseases. For example, the advanced drug delivery, imaging/diagnosis, theranostics and biosensors, and their application to cure patients with cancer, diabetes, cardiovascular disease, and other diseases reflect the advancement in the field of nanotechnology.

Nanotherapeutics and nanodevices, since explored, have proved to shed enormous positive impacts on human health. Examples include nanoparticles (NPs) for the delivery of small molecule drugs, proteins, DNAs, siRNAs, and messenger RNA (mRNAs) for different kinds of therapy (e.g. chemotherapy, gene therapy, immunotherapy, etc.) via different administration pathways (e.g. oral administration, intravenous injection, inhalation, etc.), brand-new nanomaterials for novel

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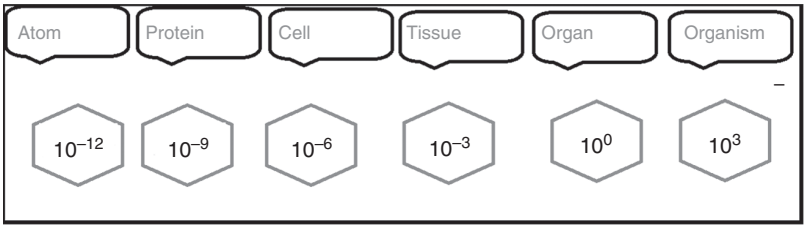

Figure 1.1 Organ/tissue/cell/subcell levels.

treatment approaches (e.g. photothermal therapy, photodynamic therapy, radiotherapy, etc.), and multifunctionalized nanoagents for imaging (e.g. photoacoustic tomography, fluorescent imaging, computed tomography, magnetic resonance imaging, etc.), as well as the development of novel nanotechnology-based diagnosis/detection approaches.

Implementation of nanobiotechnology in pharmacology means that "nanoformulations and nanodevices" are technically designed to interact with organ/tissue/cell/subcell levels (see Figure 1.1) of the body with special multistage and multiscale properties, achieving maximum efficacy with minimal side effects.

The superparamagnetic NPs are used in the field of biomedicine for multiple applications. These magnetic nanoparticles (MNP) when manipulated by magnetic fields can be used for the hyperthermia treatment of cancerous cells and for the purification and separation of biomolecules and whole cells. Lee et al. (2010) verified through laboratory experiments that the composite NPs can be used for the separation and sensing of template molecules (the human serum albumin in urine). Some routes to NP synthesis are presented in Figure 1.2. Thus the MNPs

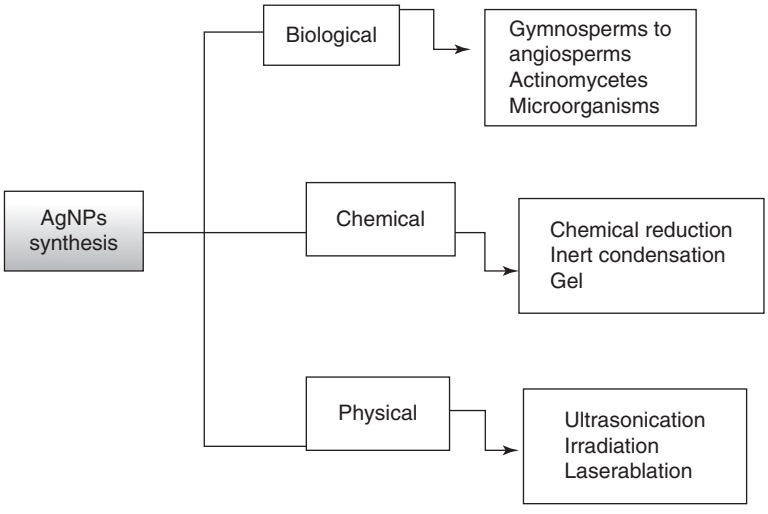

Figure 1.2 Nanoparticle synthesis routes. Source: Sohail et al. (2017). Reproduced with permission of Elsevier.

Figure 1.3 Time scales for biological processes.

are used in a variety of ways in the field of biomedicine and therapeutics, and their successful application in all such fields requires detailed understanding of their pre- and post-application requirements.

Computational approaches, when interfaced, allow the modeling and simulation of complex nanometer-scale structures. The predictive and logical power of computation is essential to success since the insight provided by computation should allow us to reduce the development time of a working "dry" nanotechnology (derived from surface science and physical chemistry) to a few decades and it will have a major impact on the "wet" (study of biological systems that exist primarily in a water environment) side as well.

Computational nanobiotechnology encompasses not only research into these exciting new approaches but also how to interface them. Theoretical, computational, and experimental investigations of target-specific drug therapy and methods for early diagnosis and treatment of diseases are all a part of the paradigm, breaking set of concepts we call "computational nanobiotechnology." Development of computational approaches to deal with noise at nanoscale is challenging. For example, computational nanotechnology can deal with the stochastic assembly and fault-tolerant (two fundamental and complex challenges, not specific to a particular type of manufacturing process) issues more swiftly. One important feature of computational research is that it can not only analyze the physical problems in temporal and spatial frames and different levels (see Figures 1.1 and 1.3) separately but also can further analyze the different molecular, cellular, and subcellular interactions and dynamics using multiscale and multiphase approaches.

In this chapter, we have made an attempt to summarize elementary as well as recent advances in the field of computational nanobiotechnology. This chapter is divided into five sections: Section 1.1 provides an overview of the concept, and the rest (Sections 1.2, 1.3, and 1.4) provide an overview of the subfields of nanobiotechnology, i.e. the disease diagnosis, treatment and drug delivery, and corresponding computational approaches. In Section 1.5, some traditional as well as some novel computational techniques are summarized.

1.2 Nanobiotechnology in Disease Diagnosis

Currently, physical properties such as cell stiffness (cell mechanobiology) are being used in different fields of biomedicine, such as in the field of oncology, and Young's modulus is used to distinguish malignant cancerous cells from

benign cells (Suresh 2007; Guo et al. 2018). The peptide self-assembly, which relates structures to molecular activities and mechanical properties, has also been studied recently. As reported by Knowles et al. (2014), there are now approximately 50 disorders, with a multitude of disparate symptoms. The pathological protein components inside the cerebral spinal fluid (CSF) and blood undergo macro- to nanolevel physical changes. Such changes include the formation of protein aggregates that reflect disease advancement. The nanoscale characterization may help to detect these components and their physical changes during the aggregation. Such approach(es) may be termed as new class of "physical biomarkers" for disease diagnosis.

Nanosphere (Northbrook, Illinois) is one of the companies that developed techniques to optically detect the genetic compositions of biological specimens. Nanogold particles studded with short segments of DNA form the basis of the easy-to-read test for the presence of any given genetic sequence. The engineering of nonlinear nanoplasmonic materials for biological applications requires detailed understanding of their physical properties. Recently, Lachaine et al. (2016) provided important physical insights on the influence of materials on nanocavitation and simulation-based design. Recently, Yue et al. (2017) presented their results and proposed that this approach may provide a potential measure to determine how alterations to the nanomechanics and nanomorphology of proteins in patients' CSF and blood reflect and affect Alzheimerâ€™s disease onset and pathogenesis. Similarly, Wong (2006) discussed the role of nanotechnology in salivary diagnostics.

1.2.1 Application of Nanoparticles for Discovery of Biomarkers

Biomarkers are combined with NPs (Chinen et al. 2015; Lin et al. 2016; Howes et al. 2014) for the medical diagnostic applications. Such biomarkers are usually based on proteins, antibody fragments, and DNA and RNA molecules. This technology is promising in a sense that it will make the early detection and treatment of cancer possible in the near future, as reported by Altintas (2017). Similarly, the modeling and characterization of kinetic regulatory mechanisms in human metabolism with response to external perturbations by physical activity is reported by Breit et al. (2015). Their presented modeling approach demonstrates high potential for dynamic biomarker identification and the investigation of kinetic mechanisms in disease or pharmacodynamics studies using multiple sclerosis (MS) data from longitudinal cohort studies.

The quantitative structure–activity relationship (QSAR) is another emerging subfield of nanobiotechnology. It uses the relationships to predict various biological responses after exposure to nanomaterials for the purposes of risk analysis. This risk analysis is applicable to manufacturers of nanomaterials in an effort to determine potential hazards. Because metal oxide materials are some of the most widely applicable and studied NP types for incorporation into cosmetics, food packaging, and paints and coatings, we focused on comparing different approaches for establishing QSARs for this class of materials. Metal oxide NPs are believed, by some, to cause alterations in cellular function due to their size and/or surface area. Others have said that these nanomaterials,

because of the oxidized state of the metal, do not induce stress in biological tests systems (Sayes and Ivanov 2010).

Another computational approach, by utilizing the density functional theory (DFT) and time-dependent DFT, has been utilized by Michos and Sigalas (2018) to explore the energy levels and absorption spectra of defected ZnS NPs. In general, this type of defect moves the absorption spectra in lower energies, thus bringing the absorption edge into the visible spectrum, while the unperturbed NPs have absorption edges in the UV region. In addition, ZnS NPs are made from more abundant and less toxic elements than the more commonly used CdSe NPs. For that reason, these are used in biosensing applications as biomarkers.

1.2.2 Nanotechnology-based Biochips and Microarrays

The biochip is a microarray (a collection of miniaturized test sites) arranged on a solid substrate that permits many simultaneous tests to be performed, allowing higher-throughput volume and speed. One of the more promising uses of biochips is isolation and analysis of individual biomolecules, such as DNA. This capability could lead to new detection schemes for cancer. The construction of silicon nanowires on a substrate, or chip, using standard photolithographic and etching techniques, followed by a chemical oxidation step that converts the nanowires into hollow nanotubes, is an example of this subfield of research. Protein microarrays for the study of protein function are a developing field of research since the proteins to spot on the arrays are a challenging task. Protein nanobiochips utilize nanotechnology-based biochips and microarrays. Extensive literature review equipped with recent advancement in this field may be obtained from Altintas (2017). It is emphasized that robust computational research may lead to successful development of the sensing technology.

1.2.3 Detection via Semiconductor Nanocrystals

Enzymes are essential in the human body, and the disorder of enzymatic activities has been associated with many different diseases and stages of disease. Luminescent semiconductor nanocrystals, also known as quantum dots (QDs), have garnered great attention in molecular diagnostics. Owing to their superior optical properties, tunable and narrow emissions, stable brightness, and long lifetime, QD-based enzyme activity measurement has demonstrated improved detection sensitivity, which is considered particularly valuable for early disease diagnosis. Recent studies have also shown that QD-based nanosensors are capable of probing multiple enzyme activities simultaneously. The review provided by Knudsen et al. (2013) highlights the current development of QD-based nanosensors for enzyme detection.

The synthesis and multifunctionalization of upconversion nanocrystals with controlled size, shape, and dissolution properties is really challenging. On the other hand, the nonspecific binding and loss of biological activities at multiscales requires serious attention. It is anticipated that advancement in bioconjugate techniques will certainly lead to enhanced long-term performance. The nanocrystals impact on living systems is discussed by Gnach et al. (2015).

Though highly informative, the results that have confirmed low levels of cellular cytotoxicity in short-term assays may not be applicable to normal physiological conditions.

It is believed that the surface impacts emissive behavior (Klimov 2003). The computational techniques can help to improve the yield. Recently, Krause and Kambhampati (2015) reported the developments in ligand chemistry and spectroscopic and computational approaches used for advancing the poorly understood electronic structure of the surface.

1.2.4 Nanoscale Sensor Technologies for Disease Detection via Volatolomics

Many infections may remain undiagnosed due to the inefficiency of available treatments or due to other reasons. Inexpensive, efficient, and minimally invasive technologies are thus desired (i) to allow early detection of diseases, (ii) to stratify the population for personalized treatment and therapy, and (iii) to improve the usefulness of swift bedside evaluation of treatment. Some recent techniques have been reported, based on the chemical processes involved in highly volatile organic compounds (VOCs). The VOCs are emitted from body fluids, such as breath, skin, urine, and blood. A compact name of this field of research is "volatolomics." It is believed that the human breath contains two hundred plus VOCs, which can be detected at the trace level down to the part-per-trillion (ppt) range.

Quantitative analysis and classification of potential disease biomarkers can be seen as the driving force for the analysis of exhaled breath. The ingestion of isotopically labeled precursors producing isotopically labeled carbon dioxide and potentially many other metabolites is used in breath tests. The exogenous VOCs, penetrating the body as a result of environmental exposure, can be used to measure body burden. Details of environmental exposure and the health risk assessment may be obtained from the book authored by Asante-Duah (2017).

Several experimental and computational tools have been used in the literature (Vishinkin and Haick 2015 and the references therein) (i) to choose nanomaterial-based sensors for the correct targeting of volatile markers and (ii) to identify the specific limitations on the application of the sensing approach. The computational techniques used in this field of research include both the numerical and statistical approaches. More precisely, algorithm-based techniques (Koç et al. 2011; Nakhleh et al. 2017; Vishinkin and Haick 2015) have been adopted in the recent literature. For example, artificially intelligent nanoarrays have been used in the literature to analyze the targeted VOCs. The schematic diagram (Figures 1.4 and 1.5) is designed to interpret the multicomponent nature of the samples. During the first step, the key compounds of the unknown sample are identified through spectrometry and spectroscopy methods. These classifications help out in a quick selection of sensor array components according to the polarity, dielectric constant, size, and steric effect of the key compounds.

Another example of computational analysis of VOCs is the accurate detection and monitoring of disease with volatolomics. Once again, artificially intelligent sensing arrays have been used by Nakhleh et al. (2017) (Figures 1.6 and 1.7 schematically describe the different stages of artificially intelligent olfaction analysis).

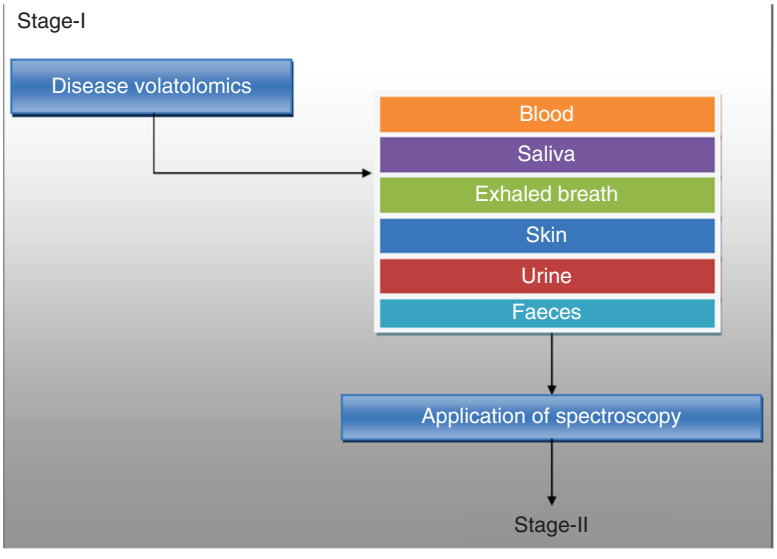

Figure 1.4 Schematic for the volatolomics detection.

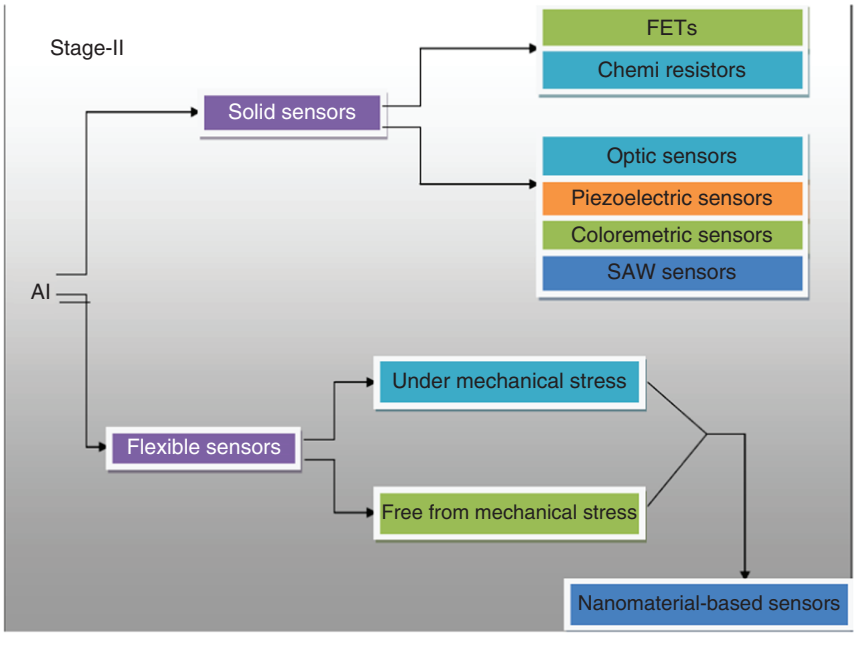

Figure 1.5 Spectrometry results as depicted in Figure 1.4, when processed via artificially intelligent (AI) nanoarrays, lead to decision of solid or flexible sensors and other steps involved in decision making.

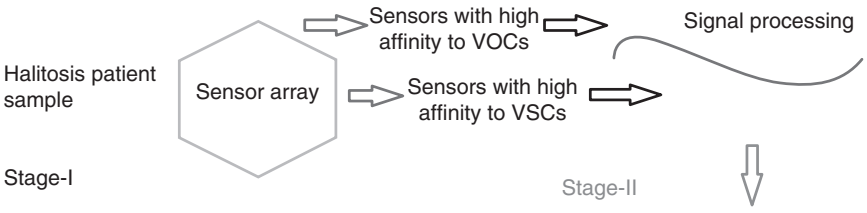

Figure 1.6 The pattern recognition step-by-step process.

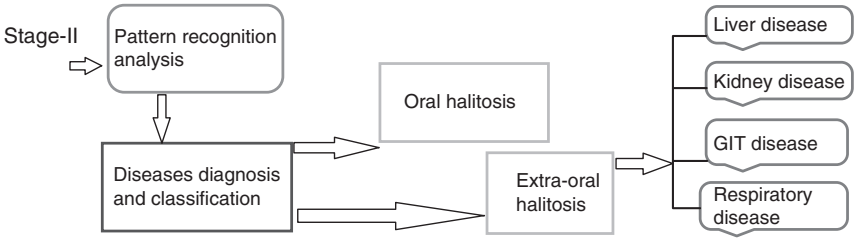

Figure 1.7 Comparison of the patterns calculated from the different sets of sensors.

1.3 Nanobiotechnology in Treatment

Nanobiotechnology is serving the clinicians in treating different diseases including cancer. A consequence of this field is the advancement in the field of green nanotechnology with minimum side effects. Green nanotechnology has fascinated the nanotechnologists since it is composed of processes with reduced toxicity. The biosynthesis of metallic NPs by plants is currently under improvement. The biological methods of NP preparation include the usage of microorganisms, enzymes, fungi, and plants or plant extracts. Recently Sohail et al. (2017) discussed the important features of nanotechnology and specifically the advancement in hyperthermia treatment.

1.4 Nanobiotechnology in Target-specific Drug Delivery

The absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the drug and its target-specific delivery require detailed analysis. The *in silico* computational approaches have been reported by Bunker et al. (2016), Sohail et al. (2018). In addition, the multifunctionality, complexity, and emergent properties of NP-based systems create additional and unique challenges. In this section, some recent techniques are summarized.

1.4.1 Future of Giant Magnetoresistance (GMR) Sensors: An Alternative to the Traditional Use of Enzymes, Radioisotopes, or Fluorescent Tagging

Giant magnetoresistance (GMR) sensors have been applied to biological devices to detect magnetic labels. These sensors are used primarily in the read heads of

magnetic hard drives and in magnetoelectronic components such as magnetic isolators. Their growing demand in the field of bionanotechnology cannot be denied. It has remained a challenge to expand the application of GMR sensor technology to be a robust tool for biomedical applications such as immunoassays and filtration processes.

The use of GMR sensors in this context may provide an alternative to the traditional use of enzymes, radioisotopes, or fluorescent tagging. There are several open problems in this field of research, such as how to evaluate the capability of this technology to achieve novel biomedical targets, how to develop advanced designs of such sensors for practical applications, and how to simulate their efficiency using robust solvers.

Different research groups over the past decade evaluated the use of GMR sensors to trap and count small concentrations of MNPs (Beveridge et al. 2011; Serrate et al. 2012). Microfabricated GMR sensor arrays have the potential to detect low concentrations of MNPs in macroscale sample volumes ($10\,\mathrm{MNP\,ml^{-1}}$) at macroscale processing rates ($1\,\hat{\mathrm{I}}\,¼\mathrm{l\,min^{-1}}$). Microfluidic channels allow for continuous flow within the sensors' limited detection range. GMR sensor elements and microfluidic channels can be arrayed to increase the processing rate of the device. Such devices would make magnetic detection of magnetic labels more feasible for robust "immunoassays" and "filtration studies."

1.4.2 Drug Delivery via Hyperthermia

Recently, Sohail et al. (2017) discussed the importance of hyperthermia treatment in the field of drug delivery. The effective dose delivery of chemotherapeutics to the interior of tumor is hampered by ill-developed perforated vasculature. Hyperthermia improves blood flow and oxygenation to the tumor core, instigating an escalated drug uptake by the deep seated regions without affecting the healthy cells. Therapeutic efficacy is further fortified by direct cytotoxic effect of hyperthermia that includes many extracellular and intracellular degradation processes. High thermal dose results in elevated expression of heat shock proteins (HSP) in malignant cells at the temperature range of 41–45 °C. Moreover, membrane permeability and cytoskeleton structure of the cancer cells is changed, resulting in degradation processes such as protein folding, denaturation, aggregation, and DNA cross-linking. This apoptotic signaling cascade of events induces programmed demise of malignant cells. Thus combined approach eliminates most of the cancer cells while leaving resistant cells more susceptible to adjuvant therapies. Synergistic application of hyperthermia with radiation increases the vulnerability of cancerous cells. Thermal shocks result in aggregation of nuclear proteins. Consequently sensitized and already denatured cells are easily killed by radiation, leading to highest thermal enhancement ratio (TER). TER is defined as "ratio of radiation sensitivity at 37.5 °C to the sensitivity at elevated temperatures."

In recent years term hyperthermia has got broadened meaning involving therapy along with magnetically modulated drug delivery by heating. Increased interstitial pressure and impaired blood supply are the main reasons of sporadic drug delivery to solid tumors. Specially tailored multifunctional MNPs for

hyperthermia provide an opportunity for spatiotemporal control release of drug at specific target. Studies have shown that MNP-based hyperthermia can also be employed as potentially useful magnetothermally triggered drug delivery system. Review of the current literature shows that most of the investigation studies utilized iron oxide MNPs for hyperthermia-based drug delivery. Experimental results revealed that major ongoing challenges of this strategy for preclinical trials include optimization of MNP properties along with elimination of toxicity, biocompatibility and clearance, induction and maintenance of therapeutic temperature, thermal tolerance, and self-regulation (Sohail et al. 2017).

1.5 Computational Approaches

The traditional experimental techniques, when interfaced with the computational methods, help to validate the hypotheses more swiftly. The recent biotechnology news includes many amazing facts such as "Gene therapy can potentially correct genetic disorders by directly editing defective genes" (Nakajima et al. 2018), "Green nanotechnology and the anti-cancer effect of a daffodil extract" (Pellegrino et al. 2018), and "New Bioartefacts and Their Ethical and Societal Consequences," which has been recently reported by Salgado (2018). "Metrology and nano-mechanical tests for nano-manufacturing and nano-bio interface: Challenges & future perspectives" has been discussed by Koumoulos et al. (2018). In all such disciplines of bionanotechnology, the advanced computational techniques, such as the deterministic, stochastic, and statistical techniques, have played a vital role. Additionally, computer simulations allow for theory to propose areas of interest to which experimental techniques may be applied.

Knowledge representation/reasoning, machine learning, statistical pattern recognition, and natural computing or soft computing contribute as imperative elements in the fields of science and engineering. With some modifications in nanotechnology characteristics, these techniques can be implemented to control the "nanoformulations and nanodevices" interacting with organ–tissue–cell–subcell levels and kilo, milli, micro, or other temporal scales (Figures 1.1 and 1.3). Soft computing methods are believed to overcome concerns about harmful implications of nanotechnology and are thus trusted to provide benchmarks in the field of designing biomaterials and application of nanotechnology and nanostructured surfaces for biophysics, cell biology research, and other subdisciplines of bionanotechnology.

Different probabilistic approaches have been used in the literature to model the disease diagnostics. Heckerman (1990) provided a probabilistic model for the diagnosis of multiple diseases. In the model, diseases and findings were represented as binary variables. An algorithm for computing the posterior probability of each disease, given a set of observed findings, called QuickScore, was presented. The order for the time complexity of the algorithm was obtained.

1.5.1 Computational Model of Drug Targeting

Current research on methods to target chemotherapy drugs in the human body includes the investigation of biocompatible magnetic nanocarrier systems. For example, magnetic liquids such as ferrofluids can play an important role as drug carriers in the human body (Altintas 2017). As such, they can be used for drug targeting in modern locoregional cancer treatment. A remaining challenge for this medical application is the choice of clinical setting. Important parameters are optimal adjustment of the external magnetic field and the choice of ferrofluid properties.

Avoiding damage to healthy human cells from chemotherapy drugs imposes an upper limit in the treatment dose. This limit impedes the chances of successful treatment of the tumor cells. One objective of modern cancer research is therefore to concentrate chemotherapy drugs locally on tumor tissue and to weaken the global exposure to the organism.

Consider a computational model of the blood ferrohydrodynamics. This model demonstrates a simple setup for investigating an external magnetic field and its interaction with blood flow containing a magnetic carrier substance. The liquid will be treated as continuum during the simulations. The model can further be interfaced with the particle tracing model to interface it with the current challenges of drug-targeting approaches. The equations and theory are based on Maxwell's equations and the Navier–Stokes equations. The coupled solver first solves Maxwell's equations in the full modeling domain. It consists of permanent magnet, blood-vessel, tissue, and air domains. A magnetic volume force then couples the resulting magnetic field to a fluid flow problem in the blood-vessel domain described by the Navier–Stokes equations. In Figure 1.8, the top panel describes the schematic and the mesh discretization, whereas bottom panel shows the magnetic potential and surface velocity.

1.5.2 Computational Model of Electrical Activity in Cardiac Tissue

Cardiac tissue engineering has rapidly progressed during the past decade, as reported by Hirt et al. (2014) and later on by Fleischer et al. (2017). The threshold values, for the fabrication of biomaterials in cellular microenvironments, can be recognized with the aid of computational techniques. The use of inorganic NPs and nanodevices for improved performance of engineered tissues and the main challenges and prospects of applying nanotechnology in tissue engineering is discussed by Fleischer and Dvir (2013). It is anticipated that the integrated tissue engineering with complex electronics will provide the therapeutic control of cardiac function. A detailed study has been provided by the research group (Feiner et al. 2016).

There has been a growing trend toward applying conducting polymers for electrically excitable cells to increase electrical signal propagation within the cell-loaded substrates. A novel approach was presented by Baheiraei et al. (2014). The potential application of bioelectroactive polyurethane was discussed (as a platform substrate to study the effect of electrical signals on cell activities).

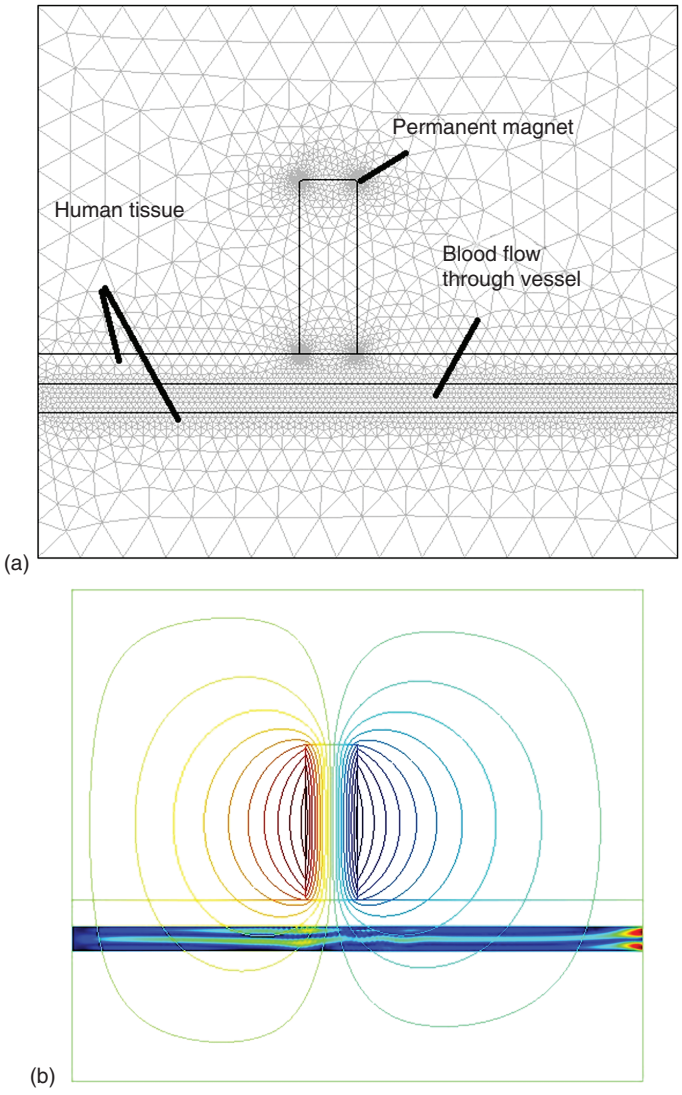

Figure 1.8 Finite element modeling of blood ferrohydrodynamics.

Let us consider a computational model of electrical activity in cardiac tissue. This model will provide a helpful tool in understanding the patterns of contractions and dilations in the heart. We will now consider two models to describe different aspects of electrical signal propagation in cardiac tissue: (i) the FitzHugh–Nagumo equations and (ii) the complex Ginzburg–Landau equations, both of which are solved on the same geometry using COMSOL Multiphysics finite element solver (Dickinson et al. 2014). Interesting patterns emerging from these types of models are, for example, spiral waves, which, in the context of cardiac electrical signals, can produce effects similar to those observed in cardiac arrhythmia. In Figure 1.9, panel (a) shows the discretization

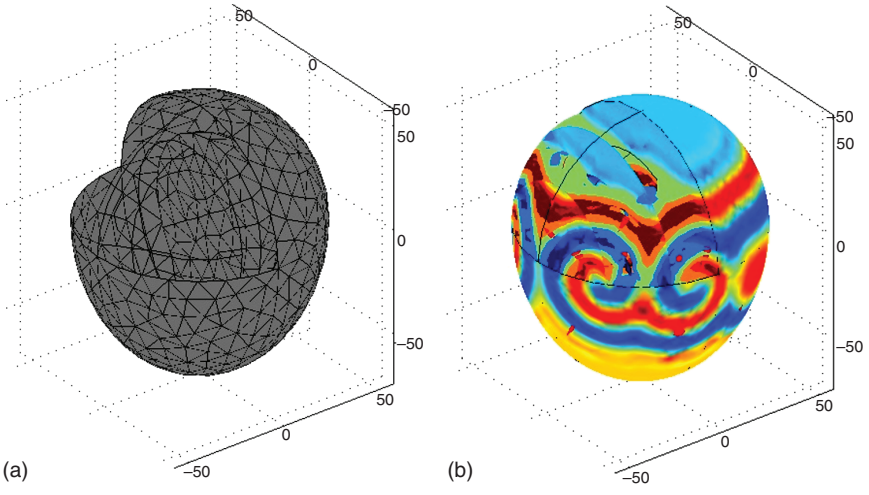

Figure 1.9 Finite element modeling of electrical activity in cardiac tissue.

of the domain, whereas panel (b) shows the diffusing species, displaying the characteristic spiral patterns. This model can be extended to incorporate with the complex electronics as anticipated by Feiner et al. (2016).

1.5.3 Computational Model of Fringe Field Effect

As communicated in Section 1.4.1, the GMR sensors can be used, while modeling biological devices, to detect magnetic labels. When it comes to computational approach, an inverse method can be used to utilize the effect of fringe fields present on the periphery of the GMR elements, thus changing the GMR response per MNP. The study of a solution containing MNPs, flowing through microfluidic channels parallel to the GMR sensor's edge, under Poiseuille flow, can demonstrate such approach. In Figure 1.10, a schematic of the fringe field effect between

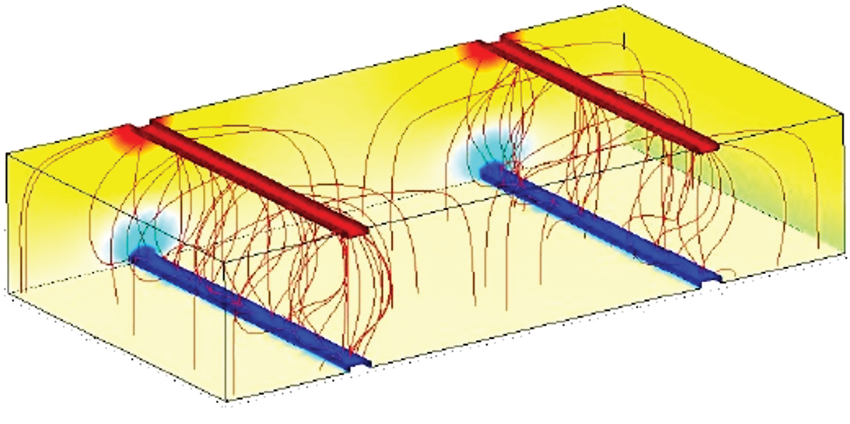

Figure 1.10 Finite element modelling of fringe field effect in a micro device.

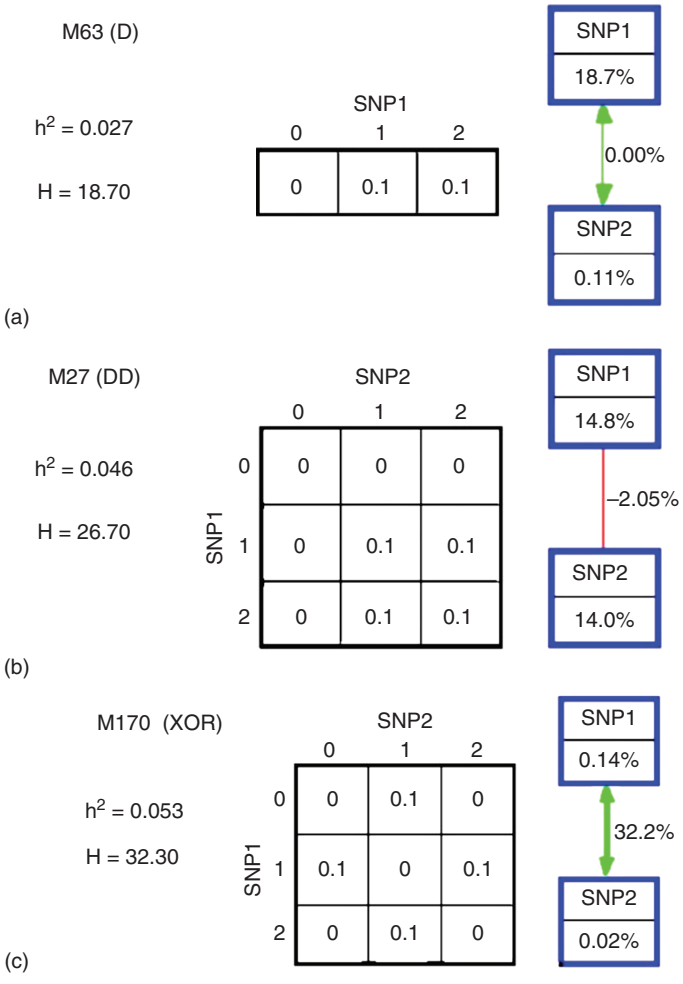

Figure 1.11 Penetrance functions (tables), broad-sense heritability (*h*), total entropy (*H*), and interaction graphs for a dominant main effect model (a), a dominant-by-dominant interaction model (b), and a nonlinear interaction model based on the XOR function (c). Note that the entropy estimates in the interaction maps recapitulate the genetic models. Source: Moore et al. (2006). Reproduced with permission of Elsevier.

two sensors is presented. For further information on the device design concept, modeling, and computations, some useful sources may be accessed (Pankhurst et al. 2003; Hamdi and Ferreira 2008; Rani 2014). With the passage of time, and with the advancement in the field of nanotechnology, more advanced and accurate algorithms (e.g. Figure 1.11) and computational models have commercially launched.

1.5.4 Computational Model of Nanoparticle Hyperthermia

The nanofluid infusion and the subsequent thermal activation of the infused NPs are two critical stages during the hyperthermia treatment. A computational model can demonstrate such stages in a noninvasive and time-efficient manner.

A simplified analytical technique was adopted by Pizzichelli et al. (2016) to predict the NP concentration profile during the infusion process. The concentration profile was then exploited to depict the steady-state temperature profile. The important features such as the tissue heterogeneity, poroelasticity, blood perfusion, and NPs absorption onto tissue were taken into account. Such mathematical models can be used for planning real procedures. The work can further be extended by taking into account the NP synthesis and relevant parametric values.

Recent advances in the field of computational nanobiotechnology can be utilized to model and predict the nanofluid infusion, thermal activation, and drug therapy during NP hyperthermia treatment. The discrete and hybrid mathematical models such as the models presented by Sohail et al. (2017) and Tang et al. (2018) can be extended to optimize such factors.

1.5.5 Hybrid Models in Computational Nanobiotechnology

The field of nanobiotechnology has become an important ingredient while manufacturing the devices for the drug discovery, disease diagnosis, and treatment. Nanoscale studies are not limited to single-scale ideology due to their applied nature. The variation in scale is a natural requirement and is somehow really challenging while optimizing the parametric values associated with such studies. Computational nanobiotechnology helps to analyze the multiscale, multidimensional, and multiphase dynamics of each problem in novel way. Recently, the research group Valverde and Orozco (2016) discussed the hybrid techniques, such as the ultrasequencing techniques (NGS) and the cheaper options of genome reading techniques. Such techniques depend on the "metabolic interrelations" and "unstable biological circuits." They discussed some examples of DNA nanotechnology (molecular structure of insulin), which provide rapid translational (bioinformatics) services for the diagnosis and prognosis. Similarly Kim et al. (2013) discussed the recent advances and limitations in the analysis and control of mechanical, biochemical, fluidic, and optical interactions in the interface areas of nanotechnology-based materials and living cells in both in vitro and in vivo settings. Biological applications using hybrids of nucleic acids and CNTs were discussed by Umemura (2015). In the recent literature, several hybrid models are presented to detect complex stages of the cancer invasion and to design treatment strategies accordingly. Thus hybrid models are required at nano-, micro-, and mesoscales in the field of computational nanobiology and biotechnology, for example, the models presented by He et al. (2015), Belkahla et al. (2017), and Zhang et al. (2017a).

1.5.6 Machine Learning for Detection and Diagnosis of Diseases

Machine learning is basically an algorithm-based field of research, consists of powerful tools that can extract relevant information from massive and noisy data sets, and is thus serving successfully in the field of science and engineering. Such algorithms are capable of adapting their structure (e.g. parameters) based on a set of observed data, with adaptation done by optimizing over an objective or cost function. It is thus a rapidly growing technical field, lying at the intersection

of computer science and statistics and at the core of artificial intelligence and data science.

Understanding of the physical properties of the assemblies of atoms of various sizes is desired at different stages such as manufacturing and application of nanosystems. Continuous mathematical models are used at several occasions, under limitations, such as the Schrödinger equation that is used for the hydrogen atom and ions with only one electron. For larger atoms and molecules, robust numerical solvers are required. Machine learning can be an efficient alternative to numerical computations. During the recent era, this technique has been used to accelerate the drug discovery techniques. As compared with the traditional approaches, the computer-aided techniques may swiftly provide a range of possible compositions. Recently Durrant and Amaro (2015) discussed the feasibility of machine learning in identifying the experimentally validated antibiotics.

Machine learning is also used to propose increasingly accurate and low-cost drug target methods. Simultaneous use of systems biology and machine learning has been used in the literature to access gene and protein druggability. Kandoi et al. (2015) discussed the open challenges and recent advances in this field of research.

Bayesian and probabilistic techniques are adopted in machine learning domains, where uncertainty is a necessary consideration. The well-developed Bayesian inference methods are well suited for incorporating sources of noisy measurements and uncertain prior knowledge into the diagnostic process. A relatively popular application of Gaussian processes is the hyperparameter optimization for machine learning algorithms. The choice of technique depends on the type of the data set. Some frequently used techniques are listed in Table 1.1.

1.5.6.1 Machine Learning and Recent Bioinformatics: Case Studies

In vivo magnetic resonance spectroscopy imaging (MRSI) is a noninvasive approach. It allows characterization and quantification of molecular markers for improving disease detection and treatment. MR spectra across a volume of tissue with common nuclei are acquired from MRSI. Machine learning approaches help to integrate MRSI with structural MRI and are thus promising to improve the assessment of soft tissue tumors (i.e. brain). Similarly, MS, which is an inflammatory disorder of the brain and spinal cord (affecting approximately 2.5 million people worldwide), can be detected and treated with the utility of MRSI interfaced with machine learning. For example, Ion-Mărgineanu et al. (2017) classified the MS courses, using "features extracted from MRSI" combined with "brain tissue segmentations of gray matter, white matter, and lesions." Different classifiers were used, and results were obtained after training "support vector machines (SVMs)" with Gaussian kernel on the stated problem.

Machine learning has successfully progressed in the field of genomic medicine. As stated by Leung et al. (2016), "one of the goals of genomic medicine is to determine how variations in the DNA of individuals can affect the risk of different diseases, and to find causal explanations so that targeted therapies can be designed." The relationship between the cell variables and with the disease risk can be modeled with the help of machine learning. Such cell variables

Table 1.1 Recent machine learning approaches with applications.

Technique	Recommended for	Application
MRSI		
Linear discriminant analysis (a linear classification technique)	For more than two classes	Classification of MS courses (Ion-Mărgineanu et al. 2017)
Random forest regression	Ensembled learning method for classification and regression	For measuring brain tissue metabolite levels in vivo (Das et al. 2017)
Uncertainty sampling	Active learning approach	For efficient labeling in automatic quality control (de Barros et al. 2017)
Hu moment invariants (HMI) and TSVM	Rapid computer-aided diagnosis system	Pathological brain detection (Zhang et al. 2017b)
Random forest classifier	For quality control of the spectra	Pedrosa de Barros et al. (2016)
Weighted-type fractional	Spectrum extraction	To classify brain images
Fourier transform		Zhang et al. (2015)
mRNA		
Perturbation theory	For the management of ruminant growth yield	Ran et al. (2016)
MutPred Splice	For the identification of coding region substitutions that disrupt pre-mRNA splicing	Mort et al. (2014)

include gene expression, splicing, and proteins binding to nucleic acids, which can all be treated as training targets for predictive models. Thus it is anticipated that machine learning can prove to be an imperative tool to explore intracellular networks and dynamics.

Another example is the SVM, which has been used as a machine learning tool to analyze the gene expressions measured via microarrays. Microarrays measure mRNA in a sample through the use of probes, which are known affixed strands of DNA. mRNA is fluorescently labeled and those that match the probes will bind. Concentration is measured via the fluorescence. The signals can thus be seen as a set of intensities within a known probe matrix. Some applications of machine learning to explore mRNA are discussed in Table 1.1. In this chapter, we have outlined some of the applications of machine learning in the field of nanobiotechnology. The field is diverse and is rapidly growing; thus the readers are encouraged the most state-of-the-art literature for further details.

1.5.6.2 Current Challenges

Clear understanding of the mechanical properties of materials, such as cell interaction with surfaces, nanopatterns, and NPs, and electrical and optical effects (such as electrical stimulation, energy storage, absorption, luminescence,

and fluorescence) is necessary, and their computing via chemical wet computers and DNA computing is getting tremendous attention in the current era. In this chapter we have outlined some important studies. The computational design of chemical nanosensors, the stochastic dynamics of bionanosystems, the in vitro anti-hydroxyl radical activity using spectroscopic and computational approaches (as reported by Pejin et al. (2014) and Forrestal et al. (2017)), and the advanced imaging options all require robust computational tools. Such tools are rapidly developing as discussed in this chapter.

Improved detection and diagnosis of disease, while at the same time increasing objectivity of the decision-making process, is highly desired. Although computational approaches such as the machine learning can work in this domain (i.e. the use of machine learning for mammographic screening), there are certain limitations. It is anticipated that the *in silico* studies can provide new tools for interpreting the high-dimensional and complex medical data sets.

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