

Computational Approaches in Bioengineering

Volume 2: Computational Approaches in Biomaterials and Biomedical Engineering Applications



Edited by Pranav Deepak Pathak, Roshani Raut,
Sebastian Jaramillo-Isaza, Pradnya Borkar, and Rutvij H. Jhaveri



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Computational Approaches in Biomaterials and Biomedical Engineering Applications

Computational Approaches in Bioengineering, Volume 2—Computational Approaches in Biomaterials and Biomedical Engineering Applications is a comprehensive and up-to-date resource that provides a broad overview of the use of computational methods in the fields of biomaterials and biomedical engineering. Written by a team of experts in the field of biomaterials and biomedical engineering, it provides a wealth of information on the use of computational methods in these fields. Furthermore, it explores emerging trends and discusses future directions and associated limitations in the field. Through thorough exploration and explanation, it showcases the latest research and advancements, offering valuable insights into how computational methods are utilized to design and optimize biomaterials, simulate biological processes, and develop innovative medical devices.

FEATURES

- Provides practical guidance and real-world examples to help readers apply computational approaches effectively in their work.
- Explores the diverse computational approaches employed in biomaterials and biomedical engineering applications, offering a comprehensive view of the field.
- Introduces emerging topics and cutting-edge techniques, keeping wide range of readers at the forefront of advancements in computational bioengineering.
- Discusses the integration of computational methods in biomaterials and biomedical engineering, fostering a deeper understanding of their synergistic potential.
- Provides a valuable resource for researchers, practitioners, and students alike, serving as a comprehensive guide to computational approaches in biomaterials and biomedical engineering applications.

The book is well-organized and easy to read. The chapters are written in a clear and concise style, and they provide a comprehensive overview of the topics covered. The book is also well-illustrated with figures and tables that help to explain the concepts discussed in the text. With its comprehensive coverage, practical examples, and expert insights, this book serves as a valuable resource for researchers, students, and professionals in the fields of biomaterials and biomedical engineering.

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Preface

This book, *Computational Approaches in Biomaterials and Biomedical Engineering Applications*, is a comprehensive guide to understanding and exploring the cutting-edge applications of computational methods in these interdisciplinary domains. This book is Volume 2 of the *Computational Approaches in Bioengineering* set.

Biomaterials and biomedical engineering are undergoing a profound transformation due to the integration of computational approaches and techniques. This book, *Computational Approaches in Biomaterials and Biomedical Engineering Applications*, aims to give a thorough overview of the most recent developments and applications of computational methods in these dynamic and interdisciplinary domains.

In order to offer their expertise and ideas on various themes, this book brings together eminent experts and researchers from academia, business, and healthcare facilities. The chapters covered in this book discuss a variety of topics like drug delivery, challenges of biomaterials in ophthalmology, machine learning for cancer diagnosis, genetic diagnosis, etc.

The book chapters include theoretical and real-world examples to give readers a thorough and current understanding of the subject. This book brings together leading experts and researchers from academia, industry, and healthcare institutions to share their knowledge and insights on various topics.

This book comprises twelve chapters.

Chapter 1 presents current trends, challenges, and opportunities in biomaterial implementations in biomedical engineering. Metals are favoured in almost all constant stream applications due to their greater structural rigidity and high flexibility. The requirement for advanced implanted biomaterials that can manage unique problems in the cardiovascular system, orthotics, shock, backbone, dental, and wound care has developed into a common concern. Enzymes and proteases can change most natural biomaterials and are biodegradable. Using this characteristic, unique medical devices and therapies can be created that only temporarily change the implant site or are resorbable. Future research projects may be possible to integrate supramolecular, injectable, and immunomodulation biomaterials and develop a self-sufficient power source. This chapter also explains modern set trends and opportunities in biomedical engineering with their novel applications in the biomedical field and other imperative domains.

Chapter 2 explains the applications of biomaterials in advanced drug delivery systems. It explains how the best strategy to reduce the adverse effects of medications is to increase the effectiveness of drug nano-carriers in delivering drugs to the targeted areas. The medication administration process becomes more challenging due to high activation barriers for drug adsorption and unfavourable thermodynamic properties. In this regard, the use of advanced biomaterials, such as synthetic polymeric and self-assembled materials, for the implementation of drug transportation systems has been expanding quickly due to their increased biocompatibility, ability to cross biological membranes easily, and ability to deliver controlled and sustainable drug

release to the target sites. Regarding applications of cutting-edge drug transportation networks and the rehabilitation of health-related concerns, this chapter also discusses the synthesis and properties of relevant biomaterials.

Chapter 3 explains the advantages and challenges of biomaterials in ophthalmology. Biomaterials are polymers (synthetic or modified) or other substances (metals, glasses, and ceramics) used to prepare implants or other medical devices to interact with biological systems. The use of synthetic polymers as biomaterials has been pioneered by ophthalmology more than by other medical specialties. Biomaterials are used in or around the eye for various applications. Applications of biomaterials in ophthalmology include several eye implants used to repair and restore the function of the cornea, lens, vitreous fluid, etc., when they are diseased or damaged. Different biomaterials are available to manufacture intraocular and contact lenses to correct vision. Biomaterials are applied during surgical operations, allowing for corneal curvature correction and a detached retina indentation. Biomaterial solutions are used as replacements in tears and vitreous liquids. Corneal tissue engineering uses silk as a biomaterial and collagen in eye shields for corneal protection, opening the application of biomaterial in ocular drug delivery systems to treat various microbial infections.

Chapter 4 explains using artificial intelligence and machine learning to analyse cellular images in breast cancer. By enabling early diagnosis and treatment, using artificial intelligence and machine learning efficiently in identifying and treating numerous fatal diseases has raised patient survival rates. Deep knowledge has been developed to explore the critical factors affecting the diagnosis and treatment of serious illnesses. It will be covered in detail how previous studies have examined the early detection and treatment of breast cancer using genetic sequencing or histopathological imaging. Convolutional neural networks (CNNs), support vector machines (SVMs), Bayesian techniques, and other semisupervised and unsupervised techniques have been used to categorise breast images.

Chapter 5 presents genetic diagnosis, classification, and risk prediction in cancer using next-generation sequencing in oncology. Identifying and extracting these biomarkers and genetic signs of various cancers from among the thousands of genes appears complex and challenging. This research aims to create an algorithm to assist with next-generation sequencing data gene extraction, identification, and prediction. Three folds compose the proposed technique: a filtering fold using minimum redundancy maximum relevance (mRMR), a wrapper fold using the Boruta algorithm, and a final fold using deep learning (DL). Using five RNA-seq datasets from a cancer patient, a comparative assessment between the suggested algorithm and the current approaches has been carried out. The final results show that the proposed algorithm significantly outperformed the existing techniques.

Chapter 6 covers how artificial intelligence and machine learning treat cardiovascular diseases. Various applications in cardiovascular risk assessment, imaging, and emerging therapeutic targets in cardiovascular therapy are based on AI. This chapter aims to discuss various AI applications, such as ML and DL, and how they are used in cardiovascular care. AI-based solutions have improved knowledge of heart failure and congenital heart disease phenotypes. These applications have produced newer approaches to cardiovascular drug therapy, more unique treatment techniques for

various types of cardiovascular illnesses, and post-marketing analyses of pharmaceuticals. Data privacy, poorly chosen/outdated data, selection bias, and inadvertent perpetuation of historical biases/stereotypes in the data are some of the difficulties in the clinical application of AI-based applications and interpretation of the results, which might result in incorrect conclusions. However, AI is a revolutionary technology with enormous potential for the healthcare industry.

Chapter 7 explains the role of big data, AI, and machine learning in decision making for disease diagnosis and treatment. This chapter describes the emerging field of big data analytics in healthcare, provides an overview of artificial intelligence (AI) and machine learning (ML), discusses the subsets of AI, outlines the benefits of AI and ML in disease diagnosis, describes examples reported in the literature, briefly discusses the challenges, provides few open-source distributed data analytics software platform, and offers conclusions and future directions. The chapter makes it easy for readers to recognise potential technologies like big data, AI, and ML that provide creative solutions for processing patient data. It generates patient reports, helps grade patient illness conditions based on molecular changes in their bodies, and allows immediate medication actions for revolutionary AI-based precision medicine for all patients.

The application of artificial intelligence to drug research is discussed in Chapter 8. This chapter demonstrates current and historical data interactions, including access to new or enhanced biological and chemical processes, higher success rates, and more efficient and cost-effective discovery techniques. Identifying specific known genes associated with diseases and selecting new therapy targets is feasible based on analysing databases with gene–disease correlations. This chapter presents a complete overview of network pharmacology based on current research, highlighting numerous active ingredients, accompanying techniques, tools, databases, and use in efficient drug development and discovery.

The importance of artificial intelligence is discussed in Chapter 9, which present the identification, classification, and prognosis of hepatocellular carcinoma. The relevance of artificial intelligence to hepatocellular carcinoma (HCC) research is updated in this chapter. For the detection of HCC, AI algorithms that analyse and incorporate massive datasets are used. AI can help interconnect various data variables to predict survival chances after HCC treatment. Benign tumours, malignant tumours, and HCC can now be classified or recognised better by using AI.

Artificial intelligence for neuromotor rehabilitation engineering is discussed in Chapter 10. This chapter discusses the developments and issues that currently affect the field of rehabilitation engineering for neuromotor disabilities from the perspective of artificial intelligence and how this allows for improving the performance of systems for adequate accessibility of this population in daily activities. In light of the planned 2030 Sustainable Development Goals for Health and Welfare, it is possible to highlight specific solutions and future work that will benefit people with disabilities.

Chapter 11 discusses innovative computational techniques for recovering motor functions in brain–computer interface (BCI) systems. Electroencephalogram (EEG)-based BCI systems use EEG data to determine the user's intention, which requires different computational methods to interpret the electrical activity of the EEG. The

number of mental states that can be classified, the interference from other signals (artefacts) that contaminate the EEG, the effectiveness of the EEG in generating commands, and the slow rate of information transfer are some of the significant restrictions that still apply to using EEG signals for BCI applications at the moment. Several processes are involved in processing EEG signals, including trial/artefact rejection, eye tracking, filtering, feature extraction, and classification/regression. This chapter explains the EEG signal processing pipelines utilised in the scientific literature and introduces novel methods for analysing EEG data utilising advanced computing techniques used in BCI applications.

Using wearable sensors and AI-based machine learning methods, Chapter 12 describes how to improve telerehabilitation. In addition to highlighting potential applications of AI to enhance the delivery of telerehabilitation, this chapter gives an overview of the obstacles, facilitators, and challenges associated with telerehabilitation. Also included are cutting-edge technologies that can provide pertinent information during rehabilitation, such as wearable sensors, the Internet of Things, sensor-based devices, and video applications.

The material collected in this book has been edited to provide knowledge about the current research achievements and challenges in biomaterial and biomedical engineering applications. The book targets senior and junior engineers, undergraduate and postgraduate students, researchers, and anyone interested in these concept trends, development, and opportunities.

The editors would like to acknowledge and appreciate the contributions of all the authors who have submitted the chapter manuscripts to this book.

Editors

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1 Use of Biomaterials in the Field of Biomedical Engineering

Current Trends, Challenges, and Opportunities in Implementations

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ABBREVIATIONS

3D	Three-dimensional
Ag	Argentum (silver)
Au	Arum (gold)
BMG	Bulk metallic glass
CAR-T	Chimeric antigen receptor T-cells
Ce	Cerium
CRT	Cardiac resynchronization therapy
Cu	Copper
DB	Droplet-based
DBS	Deep brain stimulation
EB	Extrusion-based
EBM	Electron beam melting
ECM	Extracellular matrix

EM	Electromechanical
FDM	Fused deposition modelling
Fe⁺³	Ferric cation
GF	Growth factor
ICD	Implantable cardioverter defibrillator
iPSCs	Induced pluripotent stem cell
LB	Laser-based
m	Metre
Mb	Methylene blue
MESW	Melt electrospinning writing
Mg	Magnesium
Mn	Manganese
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant staphylococci
N	Nitrogen
Ni	Nickel
NK	Natural killer cell
O	Oxygen
P	Phosphorus
PCL	Polycaprolactone
PGA	Poly glycolic acid
PHA	Polyhydroxy alkenoate
PHB	Polyhydroxy butyrate
PLA	Polylactic acid
PLGA	Poly lactic-co-glycolic acid
PVA	Polyvinyl alcohol
S	Sulphur
SLA	Stereolithography
SLM	Selective laser melting
SLS	Selective laser sintering
TE	Tissue engineering
Ti	Titanium
Zn	Zinc

1.1 INTRODUCTION

Biomaterials play an important role in modern medicine since they aid in patients' recuperation from disease or injury by restoring function. According to National Institute of Health (NIH),

any substance or association of chemical compounds, other than drugs, that maybe exploited for any event momentary and that can improve or entirely supplant any tissue, organ, or bodily function so that preserve or embellish an individual's value of life are refer to as biomaterials.

(Frag, 2023)

In therapeutic applications, biomaterials may be either organic or synthetic and are intended to sustain, enhance, or replace damaged tissue or a biological function.

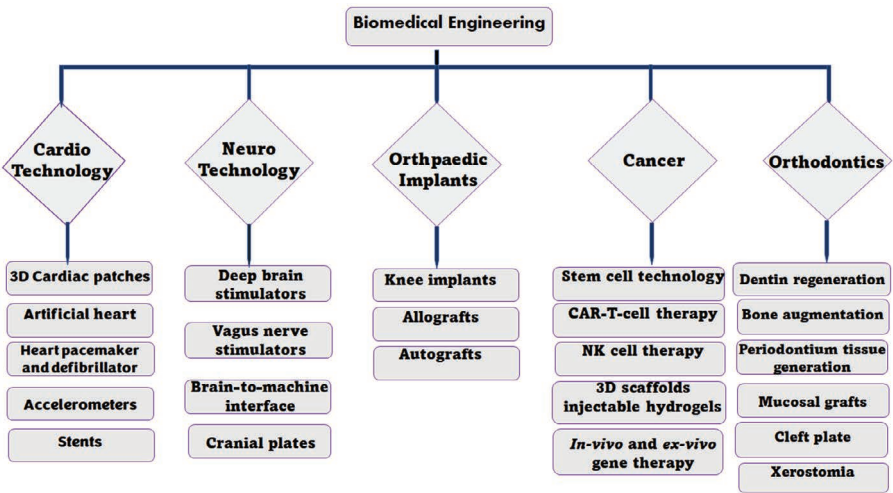


FIGURE 1.1 Subdisciplines of biomedical engineering.

Biomaterials were first employed historically by ancient Egyptians, who used sutures constructed from animal tendons. The modern field of biomaterials integrates medicine, any branch of natural science, physics, chemistry, and recent influences from tissue manufacturing and material technologies. The discipline has extended considerably over the past decade on account of advancements in constructive medication, tissue design, and additional areas (Figure 1.1). Biomedical engineering is a much broader field, despite the fact that biomaterials can also be considered a larger field than materials used in medical applications (Ha et al., 2013). The discipline of bioengineering has made numerous strides, these developments are directly reliant on the availability of biomaterials, or suitable materials, without which bioengineering would be severely constrained. Biomaterials, for instance, are used in disposable plastics and other things. From a medical perspective, biomaterials are substances found in therapeutic or diagnostic systems that come into contact with biological fluids but are not foods or medications (Zargar et al., 2015). Biomaterials have had, and will continue to have, a significant influence on biomedical engineering. Studying materials for use in medicine is the specific emphasis of this chapter (Ahsan et al., 2018). Despite the fact that numerous synthetic polymers are used in biomaterials, many polymers that are naturally generated are also in use. Naturally derived polymers have the possibility to be used in drug delivery systems and medical devices because they can help cells function more efficiently than many synthetic alternatives for adhesion, migration, proliferation, and differentiation (Gutiérrez, 2017). The development and improvement of biomaterials are primarily motivated by the need to satisfy the physical and biological needs of injured tissues (Firdous et al., 2013; Ali and Ahmed, 2018).

This, in turn, increases the demand for biomaterial qualities such as biocompatibility, biodegradability, non-antigenicity, and cost-effectiveness. The development of biomaterials such films, foams, gels, scaffolds for implants, and microporous particles has been made possible by the capacity to improve the aforementioned qualities. However, problems with biocompatibility limit the use of biomaterials manufactured

from synthetic polymers; this is driving research into biomaterials made from naturally occurring polymers. This chapter focuses on the uses of naturally occurring polymers as biomaterials in cutting-edge research, including chitosan, collagen, hyaluronic acid, and silk fibroin (Rodrigues et al., 2012).

1.2 MULTI-FUNCTIONAL BIOMATERIALS FOR ADVANCED THERAPIES

The interaction of engineered tissues and materials with their surroundings and cells is critical to their success. Various levels of material integration and interaction with their environment are required depending on the application (Figure 1.2). Bioinert substances should merge with the tissue as little as possible, whereas materials that are bioactive or biomimetic are intended to directly interact with their organic environment by altering, encouraging, and stimulating cellular reactions (Pacelli et al., 2016; Kyziol et al., 2017). Materials with active or preliminary characteristics can be surface-altered to produce bio interfaces that must be specifically functionalized for the intended tissue or use in the body (Aamodt et al., 2016; Hinderer et al., 2016; Zhang et al., 2018; Ganeshkar et al., 2022). The majority of tissues is composed of gradients or various distributions rather than containing an established extracellular matrix (ECM) and growth factor composition, a single topographical feature, or a distinct mechanical value. It is well known that cellular migration and differentiation are led by biophysical and biochemical gradients during organogenesis, tissue renovation and conversion, inflammation, and diseases (Hale et al., 2010).

The surface coarseness (bulk and size of conferred geological surface patterns) of biomaterials also considerably influences the cell behaviour (Fiedler et al., 2013). A complex interaction of biochemical and mechanobiological processes manages how cells communicate with the ECM. Transmembrane proteins (integrins), for instance, arbitrate adhesion to ECM proteins by identifying particular amino acid sequences (adhesion peptides) (Kim et al., 2011; Xiang et al., 2022). Tissues make up intricate and incredibly vital systems. The multi-functional microenvironments coordinate cellular behaviour through a dynamic interplay of biochemical and material patterns from the ECM accompanying soluble determinants like tumour factors, cell–cell contacts, and hydrostatic pressure.

1.2.1 BIOMATERIALS FOR 3D SCAFFOLDS

Implantable three-dimensional (3D) scaffolds are designed to repair and reorganize anatomical imperfections in intricate organs and functional tissues. These scaffolds represent a model for the restoration and reconstruction of defects while advancing cell connection, expansion, ECM creation, and the reestablishment of vessels, nerves, muscles, cartilage, etc. Scaffolds with the least amount of toxicity and inflammation, stringy, or penetrable biomaterials created to elevate ECM deposition, cell synergy, and viability. Moreover, they biodegrade steadily as well. At the same time, 3D scaffolds may be used to form tissue models that mimic the sophisticated skeletal structure of living tissues (Chen et al., 2022). The macro-, micro-, and nano-architecture of the scaffolds, in addition to the biomaterial employed, are therefore crucial (Nikolova and Chavali, 2019).

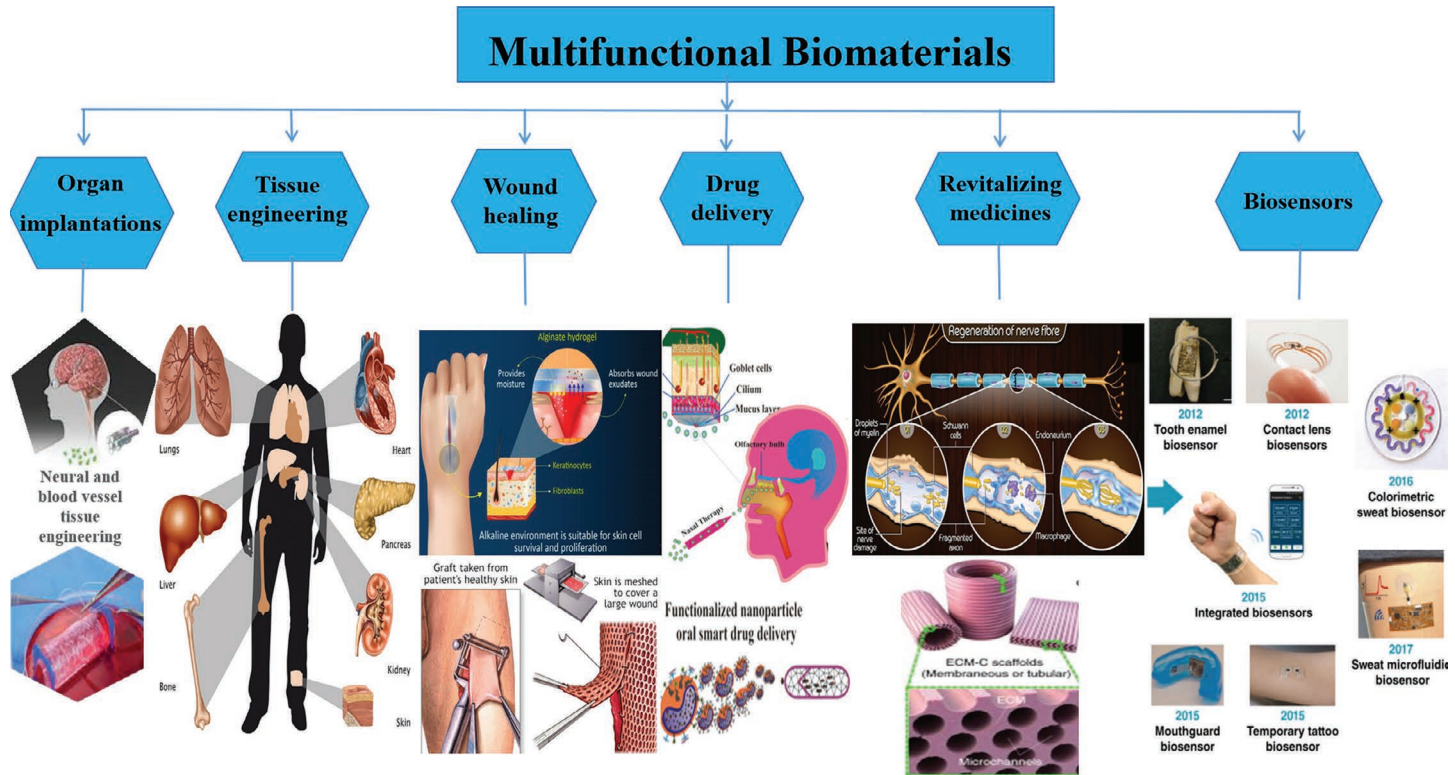


FIGURE 1.2 Applications of multi-functional biomaterials.

Biomaterials may degrade in bulk or on the surface. Bulk deterioration devastates the material's internal structure rather than the surface, maintaining the majority of the structure. Without the partition of lethal byproducts, the rate of degradation is presumed to be effectively equal to the rate of tissue progress. Physical, chemical, organic, or connected processes may be used to degrade a biomaterial, facilitating the biocompatibility of the 3D platform. Permanent (nondegradable) or semi-constant scaffolds, for instance, may be used to repair articular cartilage when it is not essential for the scaffolds to degrade entirely. Nanostructured surfaces have a greater surface energy than refined substances, which improves hydrophilicity and, thus, improves protein adhesiveness and cell attachment. Not merely because it boosts mechanical strength, the smaller grain size was found to be more beneficial for osteogenic cell adhesion and proliferation in metal and ceramic scaffolds (Saiz et al., 2013).

1.2.2 SPONGE OR FOAM POROUS SCAFFOLDS

In order to promote cartilage regrowth, arterialization, and ECM deposition, sponge scaffolds often have an inter-linked pore construction (either organized or random). These scaffolds increase the flow of nutrients and gas across the channel network on account of the extreme physical surface, improving external nerve and artery development. However, the automated properties of the scaffold must be maintained while increasing pore interconnectivity. If not, nourishment flow and cell in-growth will be restricted. Cellular penetration, ECM deposition, and neovascularization might not occur if the pores are extremely narrow. The interconnected porous structure should ideally have 90% porosity (Feng and others, 2015), which could have a serious influence the final mechanical properties. But various cells and tissues have diverse optimum pore sizes (Marrella et al., 2018).

1.2.3 FIBROUS SCAFFOLDS

An assortment of environmentally friendly polymers made up of polylactic acid (PLA) (Rampichová et al., 2014), polycaprolactone (PCL) (Ren et al., 2013), polylactic-co-glycolic acid (PLGA) (Wang et al., 2011), gelatine (Loordhuswamy et al., 2014), cellulose (Xu et al., 2016), and silk fibroin (Melke et al., 2016) has been employed to build fibrous scaffolds. The standard characteristics of these fibres make them exemplary carriers of drugs, DNA, and proteins in addition to scaffolds for skin, cartilage, ligaments, bone, tissue, and veins (Vasita et al., 2006). Nanofibres as scaffolds are demonstrated to be more promising biomaterials than microfibrils because the nanosize encourages cells to gain a normal form *in vivo*. By demonstrating topographical signifiers impacting cell differentiation and fate, nanofibres have the competence to offer leading arrangements for neurite formation (Xia et al., 2014). These nanofibres are more successful at inducing basic affinity than microfibrils cause they closely simulate the makeup and aspects of the ECM (Hejazian et al., 2012). They also have a more advanced feature arrangement, greater porosity, and higher surface-to-volume arrangement. When compared to the features of individual scaffolds, assorted fibre-mesh scaffolds offer the chance to build structures with

upgraded biomechanical, physico-synthetic, and biological traits (Wade et al., 2014). The management of nanofibre reinforced composites, for instance, shall result in substances with higher mechanical energy than typical unfilled composites (Subbiah et al., 2005). But there are various drawbacks to emblematic fibre scaffolds, including their restricted width and tiny pore capacity. These scaffolds exhibit a definite level of site-specific targeting while being widely used in splitting applications including DNA therapy, regulated medication, and tumour growth factor administration (Cai et al., 2018).

The bioactive moiety release refers to a scaffold's capacity to prudently regulate and switch on the element release by interacting with bio-microscopic cues (Yin et al., 2015). High-molecular-weight microspheres produce a more sluggish release of the medication than low molecular weight polymers (Frohbergh et al., 2012). Microspheres are capable of release optimized bioactive compounds gradually when included in 3D scaffolds as construction blocks (Repanas et al., 2016). Oil-in-water dispersion, solvent/non-solvent sintering, solvent vapour analysis, and selective laser sintering (SLS) are a few of the methods created utilizing microspheres and microsphere based 3D scaffolds (Christopherson et al., 2009).

1.2.4 CELLULAR 3D PRINTING

Selective laser melting (SLM), electron beam melting (EBM), fused deposition modelling (FDM), and melt electrospinning writing (MESW) are subcategories of acellular distribution, and extrusion-based (EB), droplet-based (DB), laser-based (LB), and stereolithographic approaches are subcategories of cellular 3D printing (Datta et al., 2017; Deng et al., 2019). A photoreactive adhesive is selectively treated at the same time as the stereolithography (SLA), or vat polymerization process, which shifts the scaffold following the establishment of each new layer. With tremendous preciseness and resolution, the approach is utilized to amalgamate polymer, ceramic, and polymer-ceramic composite scaffolds (Algardh et al., 2016; Yang et al., 2019).

1.2.5 RESORBABLE BIOMATERIALS

Bioresorbable materials have advantages over permanent biostable implants due to the latter's risk of immunological reactions and biocompatible issues. Natural qualities like mechanical strength and steady growth are restored as the bioresorbable material degrades over time (Ulery et al., 2011). The non-toxic, non-inflammatory, non-carcinogenic, and non-immunogenic properties of biocompatible resorbable materials make them suitable for bone graft alternatives and other biomedical applications.

Chitosan is a flexible biopolymer that has been widely used in tissue architecture due to its biocompatibility, biodegradability, and antibacterial characteristics. When combined with different natural components like calcium hydroxide, hydroxyapatite, etc., chitosan scaffolds' bioresorbability and mechanical energy increase, making them the ideal material for cartilage implants (Chaya et al., 2015). Moreover, chitosan's reciprocal action with DNA fragments reinforces its potential for use in genetic code remedy for orthopaedic anomalies. Bioresorbable biomaterials'

chemical, material, mechanical, and biological traits change as they diminish gradually. In comparison to the source material, these alterations bring about distinct host responses (Bhatnagar et al., 2013).

The number of artificial bioresorbable polymers that are realistic for use is constrained on account of the complicatedness of the criteria. Given the complications and restraints of shaped bioresorbable polymers, individuals may favour normal polymers that share structural correspondences with components in host tissues. Natural polymers have many basic benefits, including bioactivity, the ability to administer receptor binding ligands to cells, susceptibility to cell-prompted proteolytic breakdown, and unrefined renovation (Avila et al., 2010). The critical deep-rooted bioactivity of these natural polymers does, however, have drawbacks, in conjunction with a harsh immune response and the chance of rejection. External drawbacks involve missing mechanical substance, trouble obtaining compatible features, the need for purification, and the chance of disease transmission (Balani et al., 2015). In contrast, artificial biomaterials typically lack biological action and have more consistent features from cluster to cluster in addition to certain properties. Their traits maybe modified for certain uses (Bender et al., 2012).

1.3 SUSTAINABLE APPROACH TO BIOPOLYMERS

Biopolymers are characterized as polymers that can degrade biologically (Yadav et al., 2015; Bala et al., 2017; Udayakumar et al., 2021) and are produced by living things. A thriving interest in promoting tangible sustainability make them potential replacements for fabricated plastics (Pattanashetti et al., 2017). Biopolymers are effortlessly environmentally safe because of their fundamental basis of carbon, oxygen, and nitrogen atoms. Biodegradation converts these components into carbon dioxide, water, humic matter (organic macromolecular material), biomass, and different instinctive compounds, allowing them to be consistently reused (Rendón-Villalobos et al., 2016). The natural biological origins of biopolymers include plants, animals, microorganisms, and land waste. Rice, maize, wheat (Kumar et al., 2017), sorghum (Nath et al., 2020), yams (Arora, 2018), cassava (Díez-Pascual, 2019), potatoes (Qasim et al., 2021), banana (Hamouda, 2021), tapioca (Shivam, 2016), corn (Chen, Xie et al., 2019), cotton (Swain et al., 2018), and barley (Varma and Gopi, 2021) biopolymers can be chemically synthesised from monomeric components such as oils, sugars, and amino acids. Cattle are the common animal origin, whereas corals, sponges, fish, invertebrates, and shrimp are the most frequent aquatic sources. Algae, fungi, and yeasts constitute the majority of microbiological origins (Baranwal et al., 2022). Table 1.1 depicts the source, types, extraction methods, advantages, and disadvantages of natural and synthetic biopolymers.

1.3.1 APPLICATIONS OF BIOPOLYMERS

Studies from several fields have explained the potential of using biopolymers as elements in the production of medical instruments (Wróblewska-Krepsztul et al., 2019). Other enterprises that utilize biopolymers involve those in the foodstuff industry (edible film wrap and emulsifiers), pharmaceuticals (encapsulation), the cosmetic

TABLE 1.1
Advantages and Disadvantages of Natural and Synthetic Biopolymers

Bio-Derived Polymers	Polymers	Extracted From	Advantages	Disadvantages	References
Synthetic biodegradable polymers	Biomass	Polylactic acid (PLA)	Improved cell viability	High water solubility; low tensile strength	Wu, 2016; Singh et al., 2020
	Petrochemicals	Polycaprolactone (PCL)	Biodegradable, non-toxic, low melting point	Hydrophobicity, slow degradation	Asti and Gioglio, 2014
		Polyvinyl alcohol (PVA)	Good architectural accuracy, desired drug loading, and quick melting	Random shapes and sizes of pores, generating in homogeneity and low structural strength	Diaz et al., 2018; Cernencu et al., 2019; Musazzi et al., 2018
		Poly (glycolic acid) (PGA)	Biocompatible, non-toxic, biodegradable, low solubility in organic solvents	High degradation rate, poor solubility	Sanko et al., 2019
Natural biopolymers extracted from biomass	Polysaccharides	Starch	Shear-thinning behaviour; good geometries, structural homogeneity, and deposition; high gelation temperature; thixotropic behaviour	Low structural strength, adhesion between layers, spreading after printing, and some of thermal instability	Lille et al., 2018; Zheng et al., 2019; Maniglia et al., 2020; Theagarajan et al., 2020; Liu, Bhandari et al., 2019; Paggi et al., 2019; Chen et al., 2019
		Cellulose	Good printing accuracy and resolution, shear-thinning behaviour, high yield stress	Spreading after printing, limitation of layer number, continuous deformation until spreading	Lille et al., 2018; Holland et al., 2018
		Alginate	Biocompatible, non-toxic, biodegradable, non-thrombogenic, non-antigenic, cost effective	High hydrophilicity, low protein adsorption	Sun and Tan, 2013; Ruvinov and Cohen, 2016

(Continued)

TABLE 1.1 (Continued)**Advantages and Disadvantages of Natural and Synthetic Biopolymers**

Bio-Derived Polymers	Polymers	Extracted From	Advantages	Disadvantages	References
		Carrageenan	Desired rheological parameters, increased gelling temperature, enhanced mechanical performance	Poor structural strength	Warner et al., 2019; Caroway et al., 2020
		Chitosan	Non-toxic, non-immunogenic, biocompatible, biodegradable, mucoadhesive, antimicrobial, haemostatic, good cytocompatibility, processability, and renewability,	Too fragile, limited solubility at physiological pH	Sivashankari and Prabakaran, 2017; Jing et al., 2017
	Lipids	Glycerides/Waxes	Absorbable, soft, malleable, provides sealing capacity	Inherent haemostatic quality, promotes infection and induces thrombosis	Zhou et al., 2019
	Proteins	Gelatine	Excellent biocompatibility and biodegradability, non-toxic, fully absorbable	Lower melting temperature, rapid dissolution in water, lack of 3D structural integrity	Yang et al., 2016; Feyen et al., 2016; Nikkhah et al., 2016
		Casein	Thermally stable gels improve thixotropy, high-fidelity parts	Some extent of aggregation, low printability due to low gelation temperature, somewhat heterogeneous matrix	Daffner et al., 2021; Schutyser et al., 2018; Liu et al., 2019
		Whey protein	Desired shape fidelity inducing a homogeneous matrix, shear-thinning behaviour, high fidelity	Low hardness and solid-gel structure due to the increase in particle size	Liu and Ciftci, 2021; Oliveira et al., 2020; Liu et al., 2018

Polymers produced by microorganisms	Microbial products	Soy protein	Enhanced geometric accuracy, shear-thinning behaviour, proper flow properties	Limited cell proliferation, low hardness, and low cohesiveness	Chen et al., 2019; Phuhongsung et al., 2020; Chien et al., 2013
		Zein	Improved printability, enhanced mechanical strength, improved convexity index	Lower mechanical properties, some extent of macroscopic contraction, slow sintering kinetics	Jing et al., 2018; Chaunier et al., 2017; Chaunier et al., 2019
		Wheat flour	Improved printability, enhanced flow properties	Collapsing the uppermost layer	Pulatsu et al., 2020; Fahmy et al., 2020
		Gluten	Improved rheological properties	Poor mechanical strength	Liu et al., 2020
		Bacterial cellulose	Versatility, moldability <i>in situ</i> , biocompatibility, used as a wound dressing composite, in the production of scaffolds, transdermal applications, as a pharmaceutical excipient	Bacterial cellulose production requires efficient and stable bacterial strains	Gorgieva and Trcek, 2019
		Polyhydroxyalkanoates (PHA)/ Polyhydroxybutyrate (PHB)	Biocompatible and biodegradable, potentially ideal alternatives to synthetic polymers, degradation products can be excluded from the body	Degradation by bulk erosion, poor mechanical properties, hydrophobic polymer surface	McAdam et al., 2020
		Poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)	Supports cell growth, delivery of drugs or growth factors	Lacks mechanical strength, water sorption and diffusion	Rivera-Briso, and Serrano-Aroca, 2018

industry (especially hydrogels), water treatment, biosensor manufacturing, and even data storage (Ezeoha and Ezenwanne, 2013). Biopolymer composites are galvanized biopolymers. They can be supported with fillers that considerably reinforce these features to make them more acceptable for particular applications. In order to maximize the influence of bioactive particles, drug delivery approaches are still passed down, and progress in this field has significant advancements have been made in this field. Natural and semi-artificial polymers are repeatedly employed in the incorporation of drug delivery methods in this framework (Redondo-Gómez et al., 2020). Bio-based polymers still account for a very small percentage of the global plastic market. Due to their unusual conditions, biopolymer-based nanocomposites are suitable to be accepted to a greater extent. An appropriate matrices were preferred, such as aliphatic polyesters, polypeptides, proteins, polysaccharides, and polynucleic acids, and their chemistry and design were altered to match the target field in order to produce bionanocomposite. Due to their extraordinary eco-friendly properties, biopolymers like polyhydroxyalkanoates (PHAs) and polyhydroxybutyrates (PHBs) are common in a variety of enterprises. PHAs are compelling biopolymers with a growing manufacturing demand. PHAs are a class of polyesters that may be constructed through bacterial fermentation and have the potential to replace usual hydrocarbon-based polymers (Nezakati et al., 2018). They are found naturally in many species, but bacteria may be used to manage their fabrication in cells. Biomedical implants commonly use PHA and its copolymers as their material. These include tissue repair patches, cardiovascular patches, arched repair gadgets, rivets, bone plates, surgical mesh, and stem cell growth. PHAs' controlled degradability and biocompatibility make them suitable for use in drug delivery. PHBs are biopolymers with short chains of polyhydroxyalkanoates (3–5 carbons) and are created naturally by microorganisms fermenting sugars and lipids. These polyesters are hoarded as carbon and energy sources inside microbial cells and are produced in ecosystems with reduced nutrient availability (P, S, N, and O).

PHBs are mostly present in *Alcaligenes eutrophus*, and they build up inside of cells as granules. Biomedical applications include sutures, bond substitution, wound dressings, medication delivery, and tissue engineering (Martão et al., 2019). A growing class of biomaterials, chitosan-based nanocomposites, has the potential to support and promote cell development for the controlled administration of drugs in addition to forming a part of biosensors to label levels of glucose in the blood. Sensors are important in diagnosing molecular changes and may be used to check ailments such as carcinogenic epigenetic changes (Gonçalves et al., 2022). Biopolymers' internal structure-dependent are dependent functional qualities such as microstructure, permeability, and chargeability and can be obtained by modifying the composition and matrix of the polymer. The ability of particles to aggregate and form bonds inside the biopolymer matrix is influenced by their electrical properties. The biopolymer fractions with a high electrical charge are those that inhibit aggregation (Wróblewska-Krepsztul et al., 2019). The class of biopolymers called polysaccharides is the one that is most frequently used to supplement or replace synthetic materials, either alone or in combination with other biopolymers. Biopolymers are propitiously used to constitute nanoparticles, nanoemulsions, nanogels, or hydrogels that are recycled as carrier structures in the biomedical field (Severino et al., 2019).

1.3.2 BIOCOMPATIBILITY AND BIODEGRADABILITY OF BIOPOLYMERS

Polymeric components for medical equipment that may come into contact with blood should be able to withstand protein adsorption and blood cell adhesion without setting off the body's defensive mechanisms. The term "biocompatibility" is used broadly and emphasized to describe the property of materials to not cause harm when they come in contact with biological cells, tissues, or proteins. Three distinct types of biocompatible polymer surfaces have been devised, including hydrophilic surfaces, surfaces with micro-point-separated realms, and surfaces with zwitter ionic groups that resemble biomembranes. Physical and synthetic characteristics include moistening, texture, stiffness, flexibility, and strength. Extrusion, electrospinning, grafting, diversified shape techniques (Velu et al., 2019), solvent casting, liquefied mixing, intercalation, filament bending, stage separation (Chaitanya and Singh, 2017), radiation printing, and film stacking (Udayakumar et al., 2021) are just some of the approaches that can be used to design biopolymer composites. In order to improve physical, chemical, electrical, and mechanical properties and increase resistance to humid, warm, or cold storage conditions, biopolymers are currently being constructed and optimized using mathematical models. This is advantageous for applications that call for specialized features (Ncube et al., 2020). Even though plenty of research has been performed on the use of an array of biopolymers, the majority of studies have been hinged on polysaccharides due to their superior features when compared to different materials like proteins or lipids.

Therefore, a research focus is on biopolymers' potential for efficient encapsulating agents in pharmaceutical manufacturing, especially for the transfer of pharmaceuticals and probiotics. By uncovering their benefits over chemically produced polymers, the use of cellulose, starch, agar, chitosan, and alginate makes them viable options for product distribution (Idumah, 2016).

Natural polymers exhibit a number of advantages and disadvantages. Similarity to the host tissue, interaction with biological systems, compatibility with host metabolism, lack of toxicity and inflammation, enzyme degradability, and use of their degradation products in cellular metabolism are a few potential benefits (Tiwari et al., 2023). However, due to their sensitivity to temperature, natural polymers are destroyed before they melt, and their intricate structure makes processing them challenging. One of the known drawbacks of these polymers is the potential for disease transfer from other species to humans as a result of the production of various natural polymers using plant and animal resources (Sonia and Sharma, 2012). The biopolymers are made to be biocompatible and biodegradable, which helps them in a variety of utilizations, such as edible films, emulsions, packing materials, and therapeutic implants for organs, wounds, tissue scaffolds, and dressing materials in the pharmaceutical industry (Abraham and Venkatesan, 2023). The most accepted macromolecules are biopolymers, which comprise large, non-polymeric particles like macrocycles and lipids in addition to nucleic acids, proteins, carbohydrates, and lipids. Plastics, artificial fibres, and scientific necessities like carbon nanotubes are few examples of fabricated macromolecules. PHA and polylactic acid (PLA) are two types of biopolymers that have been discovered in bacteria or genetically mutated organisms utilizing traditional synthetic procedures. These are made up

of hydrogen-derivative carbohydrates and milk or collagen proteins (Rouchi and Mahdavi-Mazdeh, 2015). Microorganisms could be genetically altered to produce biopolymers with distinguishing characteristics that are suitable for extremely valuable medicinal uses like tissue design and drug release. The supramolecular methods used to produce innovative biocompatible polymers are advancing towards highly efficient methods. All grading levels of cell behaviour are significantly influenced by surfaces constructed of biocompatible and biodegradable polymers. A few scientific articles have illustrated that biopolymers derived from plant-based and organic materials are superior for packaging products. Biopolymers are more biocompatible and biodegradable than plastics, which benefits both human health and the conservation of ecosystems. These precisely designed polymeric biomaterials might be useful in the era of customized medicine (Fang et al., 2013).

1.4 TISSUE ENGINEERING IN BIOMEDICINE

The first line of treatment for maintaining or restoring an organ or tissue's function is transplantation (Tonelli et al., 2012). The classical implants used for organ or tissue transplantation are autografts, allografts, and xenografts. Even though autografts are more commonly employed to treat tissue abnormalities, donor sites are frequently limited. As a result, a new remedy that can get around the drawbacks of traditional therapy is required.

Biomedicine is the scientific application of biology and physiology. A possible biomedical engineering field of tissue engineering (TE) combines biology and engineering for treating damaged tissues or replacing them with healthy tissue or organs (Figure 1.3). The three critical fundamentals of TE are cells, scaffolds (3D polymeric models), and growth determinants (signalling molecules). The scaffold is the most influential of these three units because it accommodates the cells and creates an environment where they can reproduce and differentiate into a particular tissue by discharging nutrients and development components (Krishnan et al., 2012; Li et al., 2013). TE primarily entails performing the *ex vivo* culture of living human cells, usually in a biocompatible polymer scaffold, and then allowing them to grow into a 3D tissue. TE could thereby avoid the issues related to tissue deterioration, which are currently managed *via* transplants, mechanical devices, or surgical reconstruction (De Peppo et al., 2013).

1.4.1 USE OF SCAFFOLDS AND CELLS FOR TISSUE ENGINEERING

The development of scaffolds that can mimic the *in vivo* microenvironment, which is primarily provided by the ECM, is a fundamental aim of TE. Therefore, these structures should include the appropriate biophysical, biomechanical, and pharmacological inputs that control cell proliferation, differentiation, maintenance, and function (Sah and Pramanik, 2012). Scaffolds must be mechanically consistent with natural tissue and must be biocompatible, non-immunogenic, biodegradable, and non-toxic. Additionally, they must be simple to produce, sterilize, and implant (Bhardwaj and Kundu, 2010). Most significantly, scaffolds should rarely or never result in immunological or foreign-body reactions. Cells should be guided by scaffolds as they

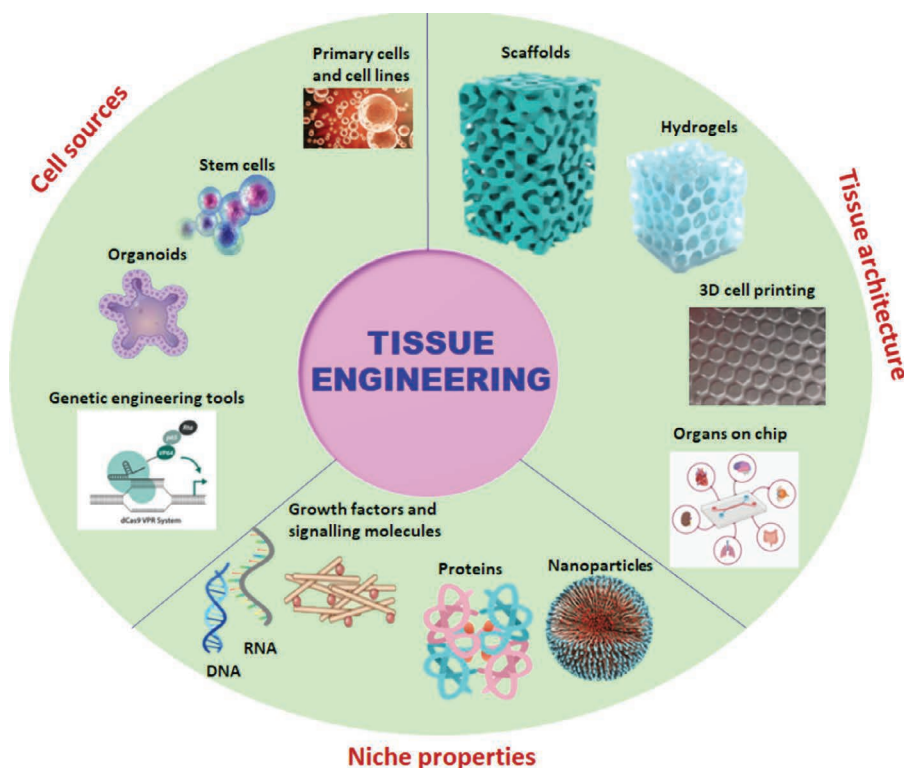


FIGURE 1.3 Tissue engineering in biomedicine.

develop into 3D tissues. Cell adherence, endurance, proliferation, differentiation, movement, and organization should be likely under both *in vitro* and *in vivo* conditions. Additionally, they should result in optimal cell shape and ECM composition by cells. Cell arrangement and adjustment are particularly important in the architecture of neuronal, cardiac, and ocular tissues because exact cell alignment is necessary for active tissue function (Ranakoti et al., 2023). The separation, expansion, and neurite offshoot of cells are necessary for productive nerve regeneration in neurological fabric design. Many recent studies have focused on the use of scaffolds to specify contact guidance for better cell adjustment. By electrospinning, a coordinated PLA nanofibrous scaffold was generated that addresses cell extension and neurite projection *in vitro* along the scaffold's fibre aspect (Zarekhalili et al., 2017).

The positioning of rooted cells and the regeneration of exterior nerves were supported in an investigation by adapting collagen-based nerve guide channels (Yang et al., 2018). An imperative capacity of the ECM in biophysical communication is to determine anchoring for cells. They are given a suitable 3D environment by the highly porous ECM nanostructure, which also transmits biochemical signalling *via* two mechanisms: (i) the binding of diverse dissolved growth factors (GF) and enzymes, which manages their local concentrations and dissipation; and (ii) the

identification of particular patterns that cellular attachment receptors can perceive. Therefore, the intracellular signalling pathways that control gene verbalization and influence cell phenotypes are dynamically integrated amidst the ECM (Khorshidi et al., 2016; Wu et al., 2017). According to their source, scaffolds for TE can be classified as natural or synthetic. Natural scaffolds are easily accessible and offer a wide variety of signals that assist various cell types in their morphogenesis and function *in vivo*. The *in vivo* assay's reliability is jeopardized since the composition of the substance is highly dependent on the animal origin, isolation, and purification methods (Yang et al., 2018). Synthetic scaffolds, on the other hand, can be specifically designed to imitate particular ECM properties and offer regulated cellular settings.

It is important that the cells used to regenerate new tissue have the ability to adapt to their surroundings, differentiate into new tissue, and integrate with the existing tissue. Cells are obtained from the same patient or another person to heal damaged tissues or regenerate new tissue. The choice of the cell source is crucial when developing methods for TE (Ma et al., 2023). If tissue engineering technique was to be used in a therapeutic setting, selecting the right cell would be a significant challenge. Integration into the target tissue and the release of numerous growth factors and cytokines that promote the body's natural tissue regeneration process are two important requirements that cells must fulfil. The use of native precursor cells constitutes the first cell-occupying order procedure. In the last decade, both adult stem cells and immature stem cells have been considered as potential sources to rejuvenate or repair damaged tissues (Kaur et al., 2017; Sharma and Sinha, 2018).

Pre-implantation embryonic stem cells are the origin of immature stem cells and can eventually become tissue or organ cells (Logith Kumar et al., 2016). Adult stem cells, like mesenchymal stem cells (MSCs), are very attractive and a promising origin for TE applications, as they can differentiate into a variety of tissues, including osseous matter, cartilage, muscle, ligaments, fat, and connective tissue. Similarly, these cells present fewer ethical challenges (Kadner et al., 2012). Induced pluripotent stem cells (iPSCs) are another cell type being studied for their applicability in TE that were first obtained from rodent fibroblasts (Zhu and Huangfu, 2013) and thereafter derived from adult human cells (Alves et al., 2014). In general, iPSCs are somatic cells that have been treated with a specific set of transcription factors to retrain them into a pluripotent state. These cells' primary benefits include their autologous nature, ability to differentiate, robustness, and ease of reprogramming (Bose et al., 2012).

1.4.2 TISSUE ENGINEERING IN REGENERATIVE MEDICINE

Regenerative medicine is a multidisciplinary field of research that offers novel methods for preserving healthy human tissues and organs, particularly when some form of impairment occurs in them (Stoltz et al., 2015). An example of this includes tissue loss followed by injury, which necessitates support to enable tissue regeneration in order to return to normal function. In addition to regenerating damaged or ill tissue, TE also influences the mechanisms that determine cell fate and looks for promising diagnostic tools (Sallustio et al., 2015). The terms "tissue engineering" and "regenerative medicine" have been broadly used in opposition to one another in

an attempt to concentrate on remedies rather than therapies for complex and chronic ailments (Diez-Pascual and Rahdar, 2022). By studying how individual cells respond to signals, engage with their environment, and arrange into tissues and organisms, researchers have endeavored to control these processes to replace damaged tissues or even produce new ones (Jayarama et al., 2013). The construction of a scaffold from an array of potential sources, including proteins and polymers, is a prevailing beginning in the procedure. Cells may expand the scaffolds either with or without a “cocktail” of development forces. In some instances, the growth determinants, scaffolds, and cells are all linked directly, enabling the tissue to “self-assemble”. Making convenience of an existing scaffold is another approach to produce new tissue (Linh and Lee, 2012). The collagen scaffold that is left behind after discarding the cells from a donor organ is therefore used to develop new tissue. A tissue can evolve if the circumstances are conducive.

The bioengineering of internal organs like kidney, alveolus, liver, and heart tissue has been performed by applying this arrangement. By utilizing scaffolds from human tissue that was left over after abscission and merging it with a patient’s own cells, this approach has the potential to produce made-to-order organs that will not be refused by the immune system. Figure 1.4 provides a diagrammatic summary of

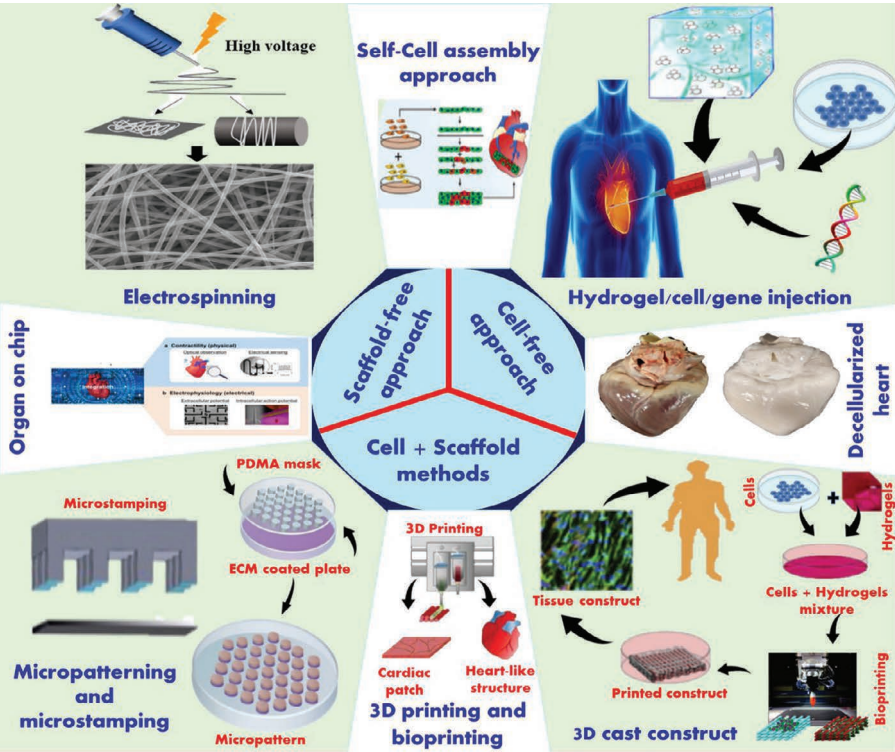


FIGURE 1.4 Schematic summary of cardiovascular tissue engineering.

cardiovascular tissue design. Tissue architecture is currently used to treat patients, even though its impact continues to be restricted. In patients, extra bladders, miniature arteries, skin grafts, osseous, and even an entire oesophagus have been implanted, but the medications are still in the exploratory stage and are very expensive (Huang et al., 2012). Although more complex organ tissues, for instance heart, lung, and liver tissues, have been strongly reconstructed in the laboratory, they are still far from being completely reproducible and ready for implantation into a patient. However, these tissues have enough potential for research, specifically in the area of drug advancement.

Utilizing active human tissue for drug screening research could expedite development, provide critical and essential tools for facilitating individualized care, save money, and minimize the need for animal testing (Zhang et al., 2012).

1.5 BIOMEDICAL DEVICES

A device with combined mechanical and electronic functions is referred to as a biomedical device. Typically, the device uses a charged signal to drive an automated motion or a mechanical motion to propel an electrical signal (Khakbaz et al., 2014). The essential fields of biomedical equipment experimental approach include gene therapeutics (Pattar et al., 2020; Pattar et al., 2021) and regenerative therapy. Electromechanical (EM) systems can be used in medical devices to improve control over the device's operation, support sustainable energy use, produce clean and hygienic equipment, develop compact and potent tools, reduce costs for all parties involved, and adhere to regulatory requirements. Few EM devices are being designed with a tendency towards miniaturization in order to make them as small as possible, whether for use in healthcare or as wearable units (Lyndon et al., 2014). Healthcare practitioners would benefit from having a system that can identify even the smallest actuation of a medication delivery mechanism, for instance, as drug delivery systems are indeed a major focus (Saharan et al., 2017). The various beneficial devices contain micro actuators for cochlear stimulation, microelectrodes for deep brain stimulation (DBS) and nerve reclamation, ocular micro prosthetic devices, and microneedles. These technologies limit the instability and inefficiency of human processes, providing the patient with better serenity and a greater opportunity for an outstanding medical procedure. Transducers are low-cost, lightweight, and reliable sensors that sense the acceleration of the body parts causing tremors, so they can be used in place of accelerometers, piezoelectric, piezoresistive, or capacitive sensors (Figure 1.5) that regulate tremor limits by feeling the stimulation of the vibration-causing body part (Sutton et al., 2016; Sharma et al., 2017).

1.6 FUTURE PROSPECTS AND LIMITATIONS OF EMERGING BIOMATERIALS

Due to the ageing populations in developed countries and patients' desire to maintain their standard of health and wellbeing, the use of implants has increased considerably over the past few years. The need for high-performance implantable biomaterials that can deal with unique difficulties in cardiology, vascular therapy,

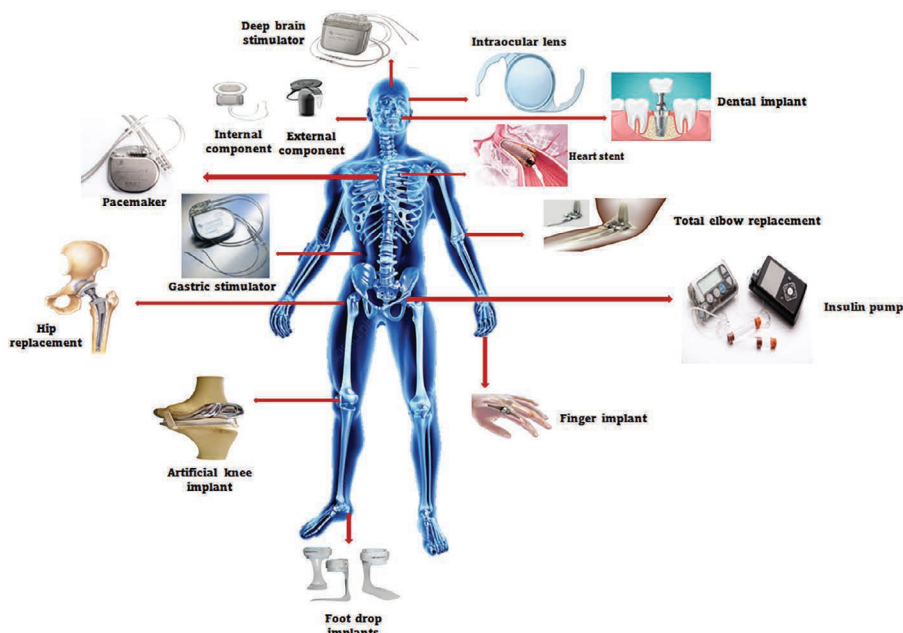


FIGURE 1.5 Various biomedical devices for implantation in different body parts.

orthopaedics, trauma, spine (vertebrae), dentistry, and wound care has thus been steadily increasing. According to Wang et al. (2022), advancements in the study of biomaterials have been used in contraception, TE, prosthetic ovaries, and follicle culture (Peng et al., 2023). The most accepted resorbable biomaterials are presumably sutures for intramural stitching, which use biopolymers like PLA/PGA with regulated deterioration rates (Bhat and Kumar, 2013). The key benefit of utilizing resorbable components is that it removes the need for additional surgery to eliminate the material. Apart from compositional differences, porosity plays an important role in the achievement of these structures since tissue in-development and scaffold disruption are critical components. Although $100\text{ }\mu\text{m}$ is the minimum hole size required for vascularization, $300\text{--}600\text{ }\mu\text{m}$ size have been shown to be more effective in these scaffolds. However, there are still great challenges in devising absorbent scaffolds with interconnected porosity that are potent enough automatically *in vivo* for tissue assimilation and growth with healing. An even more challenging task is making compositional changes to the demands of the patient. Although resorbable materials are attractive and have full potential for treating cartilage complications, some challenges include: product degradation, automated strength, processing competence, and tissue component intercommunication. To date, the majority of medical apparatuses are inactive, favouring persons being treated for medical problems to live more healthily (Henkel et al., 2013).

Controlling infections is one of the main limitations of bone condition treatments. Frequently used procedures that typically have a high success rate can still cause infection and seriously traumatize the patients. The majority of treatment methods

include using antibiotics, which is effective for the first 12 weeks. One such example is MRSA, which can lay dormant for several months but then, even after three or six months, still develop into a biofilm. Unfortunately, the only course of action if a biofilm develops is to remove the implant and clean the area to stop infection before another implant is placed (Hallab and Jacobs, 2017). Better and more dependable therapy solutions, however, remain elusive and require invention. A key challenge that must be addressed in the use of naturally derived materials for implantable medical devices is the consistency and integrity of the materials' features and properties. It is possible to anticipate a natural variation in the qualities and traits of such materials due to the sources' uniqueness. When it comes to collagen made from animals (e.g., bovine or porcine), the procedures used to manufacture animal-derived biomaterials for use in medical devices and treatments must, therefore, be continually improved (Wang et al., 2016). The fact that the human body is typically ready to detect these biomaterials and to respond negatively to their implantation presents a significant challenge for the development of biomaterials derived from natural sources. While some biomaterials, like collagen, exhibit immunogenic tolerance, the majority of natural materials need to be customized to reduce the host response after implantation. Combining with other, more tolerable biomaterials is one approach that might be taken to address this problem.

Certainly, the use of computer-assisted design and modelling is responsible for 3D printing to ensure the high-quality 3D representation of the fundamental results procured from the patient utilizing computer tomography (CT) and produce a model that portrays the anatomic surfaces and corrects any disparities (Ortolani et al., 2016). Nevertheless, the improvement of 3D printing is still impeded by a variety of technological concerns. The integration of a vascular network is the biggest biological barrier in 3D printing because without it, the built 3D tissue or organ will not receive enough nutrients, undergo the right amount of gas exchange, or exhibit the right amount of waste elimination, all of which are crucial for maturation during perfusion (Zhao et al., 2017) and would have a direct impact on cell viability and artificial organ performance. Economic concerns regarding 3D-printed parts must likewise be taken into account. Currently, printing customized surgical implements and implants is substantially more expensive than using standard equivalents, and there are supplementary costs, including the supplementary scans required to amass the essential facts. Stainless steel used in biomedical appeals is usually categorized as either conventional stainless steels or Ni-free stainless steel. As the name implies, Ni-free stainless steels are free of Ni, as Ni not only increases oxidation resistance but also lowers stress corrosion and biocompatibility (Vaithilingam et al., 2015). An exemplification of a typical hypersensitivity connected to the use of Ni-containing gird implants is shown in Figure 1.2. In order to ensure low Ni aggregation, nitrogen is repeatedly alloyed with Ni-free stainless steel. Nitrogen's nonmagnetic property has no influence on the MRI technology that is widely used in the biomedical field. In contrast to ecological ceramics and polymers, dormant golden scaffolds cannot be easily introduced *in situ* with bioactive chemicals or cells, restricting their application for thorough tissue transformation.

The functionalization of pharmaceutically relevant biomolecules, like paracetamol (Kruzic, 2016), coupled onto phosphonic acid-based self-assembled monolayers is

therefore necessary to control surface chemistry. Thus, there is a chance that metal ions from stainless steel, Ti, and Co–Cr, and Ti alloys will be extracted into the peri-implant environment on the grounds that the significantly heightened surface-to-quantity ratio causes the individual inclusion of filling pores. Given that surface oxide films are known to restrict ion release *in vivo*, this may be especially important when applied to environments with low levels of dissolved oxygen. Ion release could be hastened even more by inorganic ions, proteins, and cells found in bodily fluids. The plethora of unknown natural biomaterials that can play a significant part in cutting-edge biomedical applications and therapies is one of the most obvious potentials in investigating natural biomaterials for biomedical applications. The biomaterials starch and silk fibroin, which have previously demonstrated a variety of desirable qualities for the biomedical industry, are two notable examples. Utilizing high-throughput approaches to screen biomaterial libraries and assess biological performance in a subject newly designated materiomics is a prominent area of study in this regard. These procedures appear to influence an extending body of research specifically proclaimed in the literature, providing a more deeper understanding of the real design intercommunication between living things and organic biomaterials. Bulk metallic glass (BMG) alloys may utilize bioinert metals like Ti and bioresorbable metals like Zn and Fe. These alloys have better characteristics than current biometals, including high strength, reduced deformability, and an extreme flexural strain limit when compared to traditional alloys. When selected in hard-tissue prosthetic devices, these qualities offer a better fit to cortical osseous matter and, thus, a decrease in stress guarding.

Devices made of bioinert BMG offer controlled surface topography and resistance to corrosion. They could be utilized in flexible vascular stents, surgical scalpels, and orthopaedic prostheses (Kim et al., 2017; Shen et al., 2017). Stress shielding is weaker because the strength degradation has an inverse relationship with bone formation and fracture healing. These actions result in the release of non-toxic ions. Once the procedure is finished, no surgery is required to remove the device because it has been absorbed. Bioresorbable BMGs have the potential to be employed as temporary vascular stents, intramedullary nails, bone screws, or surgical plates. A biomaterial with a Ti basis and 50% atomic Ni concentration is called nitinol. Nitinol possesses mechanical resistance, decreased rigidity, thermal resilience, and biodegradation and corrosion resistance, making it one of the most anticipated shape-memory alloys. Materials based on titanium have these characteristics. The promising properties of nitinol allow it to potentially replace stainless steel implants. In addition to these, wires, palatal arches, intramedullary nails, staples, intraspinal implants, and scoliosis therapy devices like self-augmenting vascular stents and spinal vertebrae spacers all contain nitinol (Moghaddam et al., 2016).

Advanced-age implant patients frequently exhibit functional dependency, systemic health issues (comorbidities), and frailty. Additionally, immunosenescence, the term for the ageing immune system, may lead to a weakened host defence against a bacterial challenge at dental implants, which is harmful to the health of the surrounding tissue. In comparison to younger patients, older recipients of conventional and cardiac resynchronization therapy (CRT) defibrillators experience higher mortality but require fewer cardioverter defibrillator (ICD) shocks and/or therapies.

There may be a need to conduct randomized controlled studies to assess the role of defibrillator therapy in elderly individuals. Despite the fact that other technological challenges remain to be solved, innumerable opportunities exist for researchers and industries to augment biomedical devices with the ideal conductivity and strength for widespread use.

1.7 CONCLUSION

Demand for environmentally friendly biomaterials has increased amidst concerns over the usage of non-renewable resources. The biomedical and pharmaceutical industries have been completely transformed by this research, but there is still a lot of work to be done if we want to focus on making changes that affect not only the individual but also the environment and are environmentally sustainable and approachable. The mechanical, thermodynamic, environmental, and biocompatible properties of the biomaterials have been significantly improved. However, there are still challenges in developing carriers that are specific to the target and biocompatible with different transfer patterns in order to offer a maintained release at the target site. Applications that are based on biomaterials are extremely advantageous for transferring small compounds that are highly efficient, biopotent, and secure.

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Significance of Artificial Intelligence in the Recognition, Characterization, and Prediction of Hepatocellular Carcinoma

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Artificial Intelligence Applied to Neuromotor Rehabilitation Engineering

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