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REVIEW / DERLEME

A Review of Biomedical Engineering Research in Turkey During the Period 2008-2018

Türkiye'de 2008-2018 Döneminde Yapılan Biyomedikal Mühendisliğindeki Araştırmaların Derlemesi

Mehlika KARAMANLIOGLU [1]

[1] *Istanbul Gelisim University, Faculty of Engineering and Architecture, Biomedical Engineering, 34310, Istanbul, Turkey*

Abstract

Biomedical engineering is one of the fastest developing research disciplines in the past 60 years with the aid of rapid advances in technology. Biomedical engineering has emerged in Turkey in late 1970s but the research conducted in this area has been developing only in the past 15 years. The aim of this review is to summarize the problems regarding biomedical engineering in Turkey; to present the main subjects that are conducted in biomedical field in Turkey; and to summarize the prominent research papers conducted by Turkish Institutes published during the period 2008-2018 that contribute and/or have a potential to contribute to research and development (R&D) in biomedical engineering field in Turkey. These studies were divided into categories of tissue engineering, biosensors and biomedical devices; and summarized in this review.

Keywords: Biomedical engineering, tissue engineering, biosensors, biomedical devices, research and development, Turkey

Öz

Biyomedikal mühendisliği, teknolojideki hızlı gelişmelerin yardımıyla son 60 yılda en hızlı gelişen araştırma disiplinlerinden biri olmuştur. Biyomedikal mühendisliği Türkiye'de 1970'lerin sonunda ortaya çıkmış, ancak bu alanda yapılan araştırmalar sadece son 15 yılda gelişmeye başlamıştır. Bu derlemenin amacı, Türkiye'de biyomedikal mühendisliği ile ilgili sorunları özetlemek; Türkiye'de biyomedikal alanında yürütülen ana konuları sunmak; ve 2008-2018 yılları arasında yayınlanan ve Türkiye'de biyomedikal mühendisliği alanında araştırma ve geliştirmeye (AR-GE) katkıda bulunan/bulunma potansiyeline sahip olan ve Türk Enstitüleri tarafından yürütülen önde gelen araştırma makalelerini özetlemektir. Bu araştırmalar doku mühendisliği, biyosensörler ve biyomedikal cihazlar konularına ayrılarak incelenmiştir.

Anahtar Kelimeler: Biyomedikal mühendisliği, doku mühendisliği, biyosensörler, biyomedikal cihazlar, araştırma ve geliştirme, Türkiye

I. INTRODUCTION

Biomedical engineering is the application of engineering principles to biology and medicine for mainly diagnosis and treatment of patients [1, 2]. Therefore, biomedical engineering aims to use technologies to design and develop instruments to improve human life and to be used for research purposes.

1.1. A Brief History of Biomedical Engineering in the World

The field of biomedical engineering emerged in the 1950s mainly in the United States of America (USA), however, the foundation of biomedical engineering was established during the late 1700s when Luigi Galvani initiated his research on electrophysiology [1, 3]. Galvani studied the 'animal electricity' by observing electricity in living organisms. Galvani observed that frog muscle fibers contracted with electrical discharge and he stated that the source of animal electricity was muscle tissues or

Sorumlu yazar/Corresponding Author: Mehlika KARAMANLIOGLU, **Tel:** +902124227000-286, **e-posta:** mkaramanlioglu@gelisim.edu.tr,
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nerve fibers [3, 4]. Engineering was initially associated with biology and medicine through only instrumentation [5]. At the end of 19th century, Wilhelm Roentgen invented X-Ray machine and in early 20th century, Willem Einthoven built the foundation of two medical instruments, the electrocardiograph and the electroencephalograph, via string galvanometer invention [5]. Therefore, initially biomedical engineering was mainly concerned with manufacturing of medical devices during 1950s and 1960s [1, 2] Engineers were introduced to hospitals in 1960s to protect patients from electrocution from medical devices during treatment by maintaining electrical safety of these instruments in hospitals [1]. The rapid growth of science and technology enhanced development of new techniques and methods in biomedical engineering as well [5]. Moreover, the research area of biomedical engineering has expanded from medical and laboratory instrumentation to artificial organs, biomaterials, biomechanics, medical imagining, computer analysis of medical research data, etc. mainly in the last 20 years [1–3]. As an academic field, biomedical engineering began to appear in the late 1950s [2]. At Drexel University in the USA, graduate biomedical engineering programs were taught and shortly after that PhD programs were taught at Johns Hopkins University and University of Pennsylvania [6–8]

1.2. A Brief History of Biomedical Engineering in Turkey

In Turkey, biomedical engineering first emerged in late 1970s as research on medical devices at Middle East Technical University (METU) [8]. Initially, biomedical engineering field was primarily concerned with the limited production of medical devices in Turkey [8, 9]. Biomedical engineering was introduced as a graduate program and then as PhD programs [9]. During the late 1970s and beginning of the 1980s, Boğaziçi University started teaching biomedical engineering as an elective course and opened graduate programs [8, 9]. METU opened graduate programs in 1985 and then Marmara University trained the first biomedical device technology technicians during the late 80s [8]. Junior technical colleges have been teaching biomedical device technology since 1980s [9]. The undergraduate studies of biomedical engineering began in the beginning of 2000s. As of 2018, approximately 51 universities have biomedical engineering undergraduate programmes in Turkey [10]. Since there are 175 universities in Turkey officially recognized by Turkish higher-education institutions [11], less than half of these universities have biomedical engineering undergraduate programs. In this paper, some of the challenges of biomedical engineering encountered in Turkey is presented and the prominent researches on biomedical engineering conducted in Turkey during the period 2008-2018 is summarized.

II. CHALLENGES REGARDING BIOMEDICAL ENGINEERING IN TURKEY

Biomedical engineering trainings began in 1980s, however, the number of graduates could not meet the number of biomedical engineers required especially in the hospitals [8, 9]. Due to this, the main problem in biomedical engineering during the 80’s and 90’s in Turkey was that many expensive biomedical devices were imported but none of them were used effectively due to the lack of trained biomedical technicians and researchers [8, 9]. Not only in biomedical engineering but in general, the number of researchers is reported to be 57% lower than EU average in 2014 according to European Research Area Progress Report [12]. Therefore, the lack of number of researchers in biomedical engineering still has not been completely resolved as biomedical engineering still is not being taught as undergraduate programs in many universities in Turkey [13]. Another problem is that the number of medical devices manufactured is very low and they do not have the advanced technology [13–15]. Therefore, most medical devices i.e. imaging and dialysis devices are imported from other countries which costs more than manufacturing of these devices [13]. According to a report 85% of the medical devices in the sector is imported from other countries [16]. Moreover, maintenance of these devices cost a lot more since they are imported from other countries [13]. Although the number of medical devices have been increasing over the years in Turkey, ultrasound machine being the most common, MR being the least common medical device, the total number of medical devices in Turkey compared to Organization for Economic Cooperation and Development (OECD) countries, is not sufficient [14, 16, 17]. Moreover, the distribution of medical devices is reported to be uneven throughout the country as big cities contain the most number of medical devices and small cities and generally south east of Turkey has the least number of medical devices [16]. Health expenditure has been increasing especially in the last 10 years in Turkey. As of 2016, total health expenditure was approximately 120 million Turkish Liras in general total which is almost 25 times more than the expenditure reported in 1999 [18]. Not only medical devices but also other medical supplies are also imported to great extent [19]. Therefore, there is an increasing need of biomedical supplies, efficient biomedical instruments, researchers and technicians to operate them. According to European Research Area Progress Report, 2016, Turkey still needs to improve national research systems as it falls behind EU [12].

Therefore, as in biomedical perspective, considering a 20-year gap between the USA and Turkey, today there is still need for development on this research area and proper use of medical devices.

In general, Turkey has been making progress in R&D projects as some university laboratories, research institutions and technology development zones have been associated to European Union (EU) Framework Programs (FP) since 2003 [20, 21]. Framework Programs are the European Community research and technological development activities and have been undertaken since 1984 [22]. Turkey has been participating in multi – annual FP series since FP6, which took place between 2002-2006. Turkey also participated in FP7, which was during 2007-2013; and currently to Horizon 2020 (2014-2020) which has a funding of about 80 billion Euros [23]. In FP7, more than 1000 participants with about 950 projects received approximately 200 million Euros in EU funding [23].Turkey's investment on R&D is reported to be below EU average, which is less than 1% of gross domestic product (GDP) [23]. Although there is an increase in R&D in biomedical engineering with participation to these EU FP, valorization and industrializing remain to be one of the main challenges in this research area [20]. Also Turkey only publishes 1,5% of scientific literature globally [24], therefore there is still need to do more scientific publishing including biomedical engineering.

There is still insufficient research on some research areas of biomedical engineering such as biotelemetry, bioimaging, bioinformatics in biomedical engineering in Turkey [13, 25]. Biotelemetry is the remote detection of a living organism's physiological functions and has been developing due to fast growing technology of smart phones specifically to trace elderly as it is estimated that by 2050, there will be a 70% increase in the number of people in the EU aged over 65 [26]. Biotelemetry is also important specifically for medical emergencies, however, there has not been any tangible research on this area in Turkey yet [13]. Bioinformatics is the analysis of biological data especially used in molecular biology and likewise, bioinformatics has not been taught or studied effectively in Turkey [13]. Biomedical tools used in sports medicine are also still insufficient [13].

III. MAIN BIOMEDICAL ENGINEERING RESEARCH AREAS IN TURKEY

According to data retrieved from Scopus, research and development in biomedical engineering has been increasing in Turkey since 1970 especially after 2000 (Figure 1) [20, 25]. In general, number of publications have increased in Turkey [24] and in accordance with this, there is a steady increase in the number of documents published in biomedical engineering area specifically after mid 90s (Figure 1) [25]. During the period 1970 – 2018, in total 4802 documents related to biomedical engineering were retrieved [25]. According to Scopus database, most of these studies were conducted at Hacettepe University (11%) and then at METU (9%), then at Ege University (8%), Gazi University (6%) and Istanbul University (5%) [25].

During 2008 – 2018, 3655 research documents were published [25]. When compared with the number of publications between 1970-2018 with the same search criteria except for the publication years, 76% of the publications were published during the period 2008-2018.

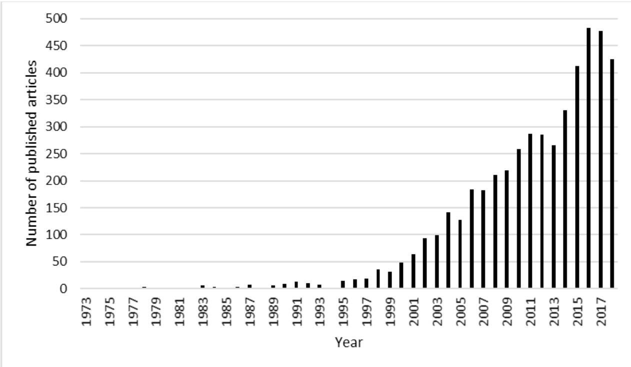

Figure 1. The number of published articles regarding biomedical engineering during 1970-2018 in Turkey. Data retrieved from *Scopus*; last accessed January 22, 2019 [25].

Scopus is an international citation database where peer-reviewed literature can be accessed [25] and since citation numbers show the scientific respectability of a specific research [24], first 100 most cited papers out of 3655 research documents published in between 2008-2018 regarding biomedical engineering on Scopus database were analyzed and the ones with significant results that would contribute to R&D in Turkey were summarized. Also the papers which were not in the first 100 most cited list but would and/or have a potential to contribute to R&D sector in Turkey were selected and summarized as well. Reviews and conference papers were excluded. The selected researches were mainly conducted in Turkey and some of them were collaborated with international institutions. As of 2018, The USA and Germany are the two countries collaborating with Turkey for biomedical engineering research according to Scopus database. The United Kingdom, The Netherlands and Italy were the other countries that were collaborated to publish articles related to biomedical engineering [25]. Most of the studies in biomedical engineering in Turkey have been conducted as an interdisciplinary branch relating to the field of medicine, engineering, materials science, molecular biology, chemistry and dentistry [25]. Therefore, the studies published during the period 2008-2018 in biomedical engineering research area were divided into categories of tissue engineering, biomaterials and nanomaterials, biosensors and biomedical devices; and summarized for this review.

3.1. Tissue Engineering, Biomaterials and Nanoparticles

Tissue engineering is a new branch of engineering and has rapidly been growing since 1980s [2, 3]. It is an interdisciplinary field combining biological sciences (cell biology, histology) with engineering methods and materials sciences [2]. Tissue engineering mainly develops new therapeutic strategies, designs biocompatible artificial tissues and devices. Therefore it aims to regenerate impaired tissues, to provide function to organs that lost their ability and to treat wounds [2, 3, 27, 28]. Tissue engineering research areas include production of new biocompatible devices made of materials like polymers, ceramics and metals; and scaffold matrix materials to grow cells on; therefore academic and industrial communities have an increasing number of research and development projects on this subject [3, 28]. Tissue engineers treat the materials beforehand so that these materials are biocompatible and in case they are biodegradable, tissue engineers make sure biomaterials and their by-products do not have any side effects and toxicity [3].

Tissue engineering is increasingly becoming a popular research area in Turkey as well, especially the design and development of scaffold materials. Scaffolds are derived from native extracellular matrices (ECM) to offer three-dimensional support for regeneration of tissues and organs [29] and various studies have been conducted on scaffolds and improvement of their materials.

In materials sciences, biomaterials are widely used in tissue engineering applications and have many applications [30]. Biomaterials are mainly classified as metals, ceramics, polymers [29]. Biopolymers are polymers from natural sources which can either be synthetic or natural such as collagen, chitosan, etc.

Biomaterials can be used as scaffolds, implants, orthopedic devices and drug delivery systems [30]. Biodegradable biomaterials are mainly used as bioresorbable sutures, wound dressing materials, orthopedic devices since they slowly hydrolyze in the body and they do not need to be removed with an operation [31–34]. Function of biomaterials can be classified either as passive (e.g. a heart valve biomaterial) or bio active (e.g. hydroxyapatite-coated hip implants) [35].

Biomaterials research area in Turkey is mostly based on scaffold synthesis, tissue implants and drug delivery applications with the use of natural and synthetic polymers and also nano sized particles [21].

In scaffold synthesis studies involving biomaterials, polyhydroxybutyrates, PHB, as a polymeric scaffold, was synthesized from a bacterium strain and nanofibrilar scaffold of PHB was produced by electrospining technique [36]. Also when surface of PHB scaffold was modified, it improved cell attachment and proliferation which are necessary for optimal tissue engineering applications [36]. Developing scaffold materials with favourable mechanical qualities has also been studied. For instance, gelatin fibre-based scaffolds were mechanically improved with boron nitride nanotubes (BNNTs), which has a potential to improve mechanical properties of scaffolds for tissue engineering applications [37]. Auxetic PCL, polycaprolactone, nanofiber membranes were fabricated to be used as scaffolds with improved mechanical properties used in tissue engineering [38].

Scaffold synthesis for bone tissue applications, chitosan based scaffolds with sequential growth factor delivery system were constructed to increase bone cell proliferation for bone tissues [39]. A 3-D scaffold capable of releasing two bone morphogenetic proteins (BMP) was also designed [40]. New biomimetic scaffold materials were demonstrated to increase osteoblastic differentiation to form new bone tissue when electrospun polycaprolactone (PCL) nanofiber mats were synthesized in calcium phosphate solutions [41]. To repair bone deffects, scaffolds were obtained from strontium doped bioactive glass and these scaffolds were shown to release strontium for bone tissue regeneration [42].

In bone tissue engineering studies other than scaffold synthesis, biomaterials are used such as cerium oxide-bovine hydroxyapatite composites were prepared with improved mechanical properties [43]. Apatites are widely used in implants and Raman spectroscopy was used to analyze the effect of coating hydroxylapatite [44]. Bioactive glass fibers were prepared to be used in bone and soft tissue regeneration [45]. To treat bone, cartilage and adipose tissue defects in regenerative medicine, a synthetic polymeric agent, F68, was shown to enhance cell differentiation [46]. This particular study also employed human tooth germ stem cells (hTGSCs) isolated from wisdom teeth as stem cells to differentiate into bony tissues for skeletal repair [46]. In dental procedures zirconia, a ceramic material, is widely used and in a study Er:YAG laser irradiation was shown to improve mechanical properties i.e. shear bond strength of yttrium-stabilized tetragonal zirconia (Y-TZP) ceramics [47]. Additionally, roughening the surface of Y-TZP ceramic by laser treatment was shown to decrease microleakage in the adhesive-ceramic interface [47]. Also PHB membranes were treated with NaOH for antimicrobial purposes to be used in orthopedic and dental tissue engineering applications [48].

Since chitin and chitosan have a wide range of applications in medicine as biomaterials, they were extracted for the first time from six different aquatic invertebrates [49]. Tannic Acid molecules were turned into poly(tannic acid) particles in a single step to be used as a biomaterial since poly(tannic acid) particles are determined to be more biocompatible than tannic acid molecules [50]. Sodium alginate was used in a drug delivery system to synthesize pH and temperature responsive beads to deliver an anti-inflammatory drug, indomethacine (IM) [51].

In other applications of biomaterials, a biodegradable nerve conduit was synthesized using polyesters which can be effective in nerve injury regeneration [52].

Environmentally friendly and biocompatible materials for organic field-effect transistors were developed to have wide range of applications including biomedical implants [53].

Mechanically improved hydrogels were produced from Poly(N,N-dimethylacrylamide; PDMA) for autonomous self-healing purpose of the tissue [54]. A promising wound dressing material with favourable properties was also fabricated using a silk protein, sericin, is also added to wound dressing material [55].

In order to heal tendon injuries, adipose-derived stem cells (ASC) were used instead of using mesenchymal stem cells which is commonly used in the literature [56]. ASCs were shown to increase primary tendon healing in this study collaborated with Japan [56]. Self healing hydrogel with strong adhesion and good self-healing properties to be applied in tissue engineering was produced with a poly(acrylic acid) having 30% catechol appendants on its backbone [57]. Adipose derived stem cells were used to synthesize hydrogels which were also UV crosslinked to increase vascularization in wounded tissues [58].

Peptide nanofibers were designed to interact with growth factors by mimicing heparin which is necessary for formation of new blood vessels in case of injuries [59]. This is an important study for tissue regeneration as there is no need to add growth factors exogenously to form new blood vessels [59]. In a follow up study, nanofiber gel which is again mimicking heparin was synthesized and shown to enhance scar free wound reperations [60].

Nanoparticles are also applied in clinical diagnostics and in therapeutic methods as they are suitable to be used in cancer therapy and bioimaging of specific cell targeting. In bioimaging applications of nanoparticles, gold–magnetite ($Au–Fe_3O_4$) hybrid nanoparticles (HNPs) were synthesized to be used in magnetic resonance imaging (MRI) as contrast agents (CAs) to enhance imaging quality for diagnosis [61]. These novel $Au–Fe_3O_4$ hybrid nanoparticles (HNPs) were found to be good candidates as MRI CAs [61].

Collagen is a natural biomaterial and recently its nanofibers are synthesized to be used in biomedical applications [62]. Collagen nanofibers were synthesized using electrospinning to be used in drug delivery systems since collagen is a highly biocompatible biomaterial [63]. Furthermore, structural properties of collagen nanofibers were observed [62] and different preparation parameters were tested when its nanofibers were synthesized by electrospinning [64].

Magnetic nanoparticles (MNPs) have been used in tissue engineering as new nanobiomaterials. The chitosan-coated magnetic nanoparticles (CS MNPs) were fabricated and characterized to be used in different biomedical applications such as drug delivery and magnetic resonance imaging (MRI) [65]. As another application of MNPs, they were encapsulated within cell-encapsulating hydrogels [66]. Since these hydrogels were degradable, the release of encapsulated MNPs were studied to be applied in tissue regenerative medicine and drug delivery systems [66].

Iron oxide particles were coated with PHB polymer and this magnetic carrier system was used as a drug delivery system for cancer treatment [67]. A new method to coat magnetic iron oxide nanoparticles (MIONPs) with polyethylene glycol (PEG) hydrogel was designed [68]. MIONPs are used in early tumor or cancer detection and in targeted therapies, this new method to coat MIONPs allowed specific tissues to be targeted and also enhanced viability and drug uptake of HeLA cell [68]. Gold-coated iron oxide magnetic nanoparticles were also synthesized to isolate bacteria in a biological sample facilitating bioassay studies [69].

Poly(acrylonitrile) (p(AN))-based materials such poly(acrylonitrile-co-(3-acrylamidopropyl)-trimethylammonium chloride (p(AN-co-APTMACl)), poly(acrylonitrile-co-4-viniyl pyridine)(p(AN-co-4-VP)) and poly(acrylonitrile-co-N-isopropylacrylamide) (p(AN-co-NIPAM)) were prepared, chemically modified and succesfully used in drug delivery systems [70]. Also some of the particles were shown to have antimicrobial activities [70].

Apart from drug delivery and bioimaging, nanoparticles can be used for antimicrobial purposes. For instance, to prevent bacterial infection of medical devices, instead of using antibiotics, adhesion of bacteria on medical devices were reduced through controlling surface properties of titanium nanotubes [71]. Four types of xeolites, the nanoporous alumina silicates, with different cation contents were synthesized and their antimicrobial properties were tested [72]. Xeolite with silver Ag^+ was shown to have more antimicrobial property than other xeolites containing copper (Cu^{+2}) and zinc (Zn^{+2}) [72]. This study suggests that zeolites with synthesized various materials can be used to manufacture antimicrobial surfaces, textiles, medical devices or household items [72].

3.2. Biosensors

Sensors are widely used in bioinstrumentation systems to monitor physiological variables and also non-physiological variables such as environment, agriculture and bioprocessing [1, 73]. Sensors mainly convert physical parameters to electrical signals [73]. Sensors with a biological sensing component i.e. enzyme, anti-body, etc. that can detect the presence of a specific agent such as a chemical group or a compound are classified as biosensors [2, 74]. Biomedical sensors are designed to detect and measure physiological variables and provide diagnostic information [1]. Research related to biosensors have been steadily increasing since 1980s [74].

Biosensors are studied substantially in Turkey as well. Biomedical engineering research in Turkey is mostly related to biosensor synthesis with a wide range of applications. The most prominent study in biosensor research in Turkey is a study collaborated with the USA and it involves graphene nanosheets as novel biosensor materials [75]. In that particular study, graphene nanosheets were chemically developed to detect some neurotransmitters such as dopamine and were shown to be more effective than single-walled carbon nanotubes [75].

Carbon nanotubes, a novel class of nanomaterial, can also be used in biosensor design to detect various molecules. In vivo detection of the marker and signalling molecule nitric oxide concentration was achieved by development of near-infrared-fluorescent single-walled carbon nanotubes sensors [76]. This optical sensor study would allow to detect tissue inflammation and cancer activity as well as to study cell signalling [76]. Multiwall carbon nanotubes (MWCNTs) and gelatin were employed in an amperometric biosensor detecting hydrogen peroxide in disinfector solutions biosensor [77]. Amperometric hydrogen peroxide biosensor was synthesized with myoglobin (Mb) on multi-walled carbon nanotube (MWCNT) –Nafion–nanobiocomposite film with gold electrode [78]. In order to detect phenol and its derivatives which are toxic to environment, an amperometric biosensor was developed by incorporating horseradish peroxidase (HRP) to carbon nanotube (CNT)/polypyrrole (PPy) nanobiocomposite film [79]. More recently, a new amperometric biosensor based on HRP immobilized on poly(glycidylmethacrylate)-grafted iron oxide nanoparticles was synthesized to detect phenol's and its derivatives' their presence in the environment [80].

A xanthine biosensor was fabricated with chitosan, Co_3O_4 nanoparticles and using multiwall carbon nanotubes (MWCNTs) [81]. A sensitive urea biosensor was also synthesized when urease enzyme was immobilized on polyamidoamine grafted multiwalled carbon nanotube (MWCNT-PAMAM) dendrimers [82].

A DNA biosensor was presented to determine anticancer drug, 6-mercaptopurine (6-MP) [83]. For this purpose, DNA was immobilized on a pencil graphite electrode which was modified with polypyrrole and functionalized multiwalled carbon nanotubes (MWCNT/COOH) [83].

A new DNA biosensor with cysteamine and gold nanoparticles was also fabricated to detect aflatoxin M1 in milk samples which provided good analytical results and in that particular study interaction of aflatoxin and DNA on gold nanoparticles were shown [84]. In a prominent study in 2014 by Yola et al, an electrochemical DNA bioensor with better stability and higher selectivity to certain DNA samples was prepared with iron-gold nanoparticles (Fe@AuNPs) using n-graphene oxide [85]. In relation to this study, an electrochemical biosensor with Fe@AuNPs was developed to detect cefexime in biological samples, i.e. human plasma [86]. This biosensor has potential to enable new β-lactam antibiotics recovery [86].

Since pathogen detection with biosensors have been becoming popular, a new quartz crystal microbalance (QCM) biosensor was developed to detect *Salmonella* pathogen that causes gastroenteritis in humans [87]. This QCM biosensor was based on DNA aptamers which are the bio-recognition molecules [87].

Glucose biosensors have wide range of applications such as in medical diagnosis, therefore, in the last decade many studies using different approaches and materials to be used as glucose biosensors were fabricated. A sensitive electrochemical glucose biosensor was synthesized using gold (Au) nanoparticles on a semiconductor, molybdenum disulfide (MoS_2) nanosheet in a single step reaction [88]. A new sensitive glucose sensor was fabricated using activated carbon (AC) and monodisperse nickel and palladium alloy nanocomposites by an in-situ reduction technique [89]. A highly sensitive amperometric glucose biosensor was designed with the immobilization of glucose oxidase (GOx) on poly(pyrrole propylic acid)/Au nanocomposite for diagnosis of diabetes [90].

microRNAs, miRNAs, are the small non-coding ribonucleic acids (RNAs) and have recently been gaining attention in biomedical research due to its potential to be used as biomarkers in diagnosis and treatment of cancer [91, 92]. An enzyme biosensor for the early detection of breast cancer was developed by detection of mir21 which forms in cancer cells during the early stages of breast cancer [91]. A very sensitive and rapid electrochemical biosensor was also developed to detect mir21 using protein 19 [92].

Myocotoxins are found in meat and dairy products due to fungal infection of crops and cause serious health problems. Citrinin (CIT) is one of the most harmful mycotoxins and in order to detect mycotoxins in food, a sensitive molecular CIT imprinted surface plasmon resonance (SPR) biosensor was designed for the first time and was shown to successfully detect CIT in red yeast rice [93].

Biosensors using different materials to detect various molecules were also designed. For instance, a new approach to synthesize an ethanol biosensor, an amperometric biosensor was reported [94]. This amperometric biosensor containing polypeptide and ferrocene side was reported to detect ethanol content in alcoholic beverages [94]. Chitosan–ferrocene (CHIT–Fc) hybrid, a redox biopolymer, was synthesized to be used as an immobilization matrix for biomolecules in biosensor systems [95].

3.3. Biomedical Devices

Biomedical engineers have been contributing to modern health care by developing instruments for diagnosis, treatment and follow up of patients and also for prevention of diseases [2, 14]. Nowadays, these devices are engineered to use non – invasive methods and to provide rapid results with more information specific to each patient's requirements [2]. Biomedical devices can mainly be classified as diagnostic devices, which provide information about the condition of the patient (electrocardiography, X-ray, etc); and as therapeutic devices , which aim to cure a disease or a condition (defibrillators, heart pacemakers, etc.) [3].

A new effective biomedical instrument for kidney stone destruction was developed by using hydrodynamic cavitation where fluid pressure is used to trigger inception, growth, and implosion of cavities [96]. A new device named soft tissue stiffness meter (STSM) was also designed to assess soft tissue stiffness to diagnose dermatological pathologies [97]. This study has significance on on diagnosis of skin cancer since cancerous tissues are stiffer than healthy tissues [97, 98].

Data analysis techniques are very important for efficiency of biomedical devices. In a study, electroencephalogram (EEG) signal processing and analysis framework were developed to classify EEG data in order to determine the presence of epileptic seizure [99]. In EEG results, data can be incomplete due to electrode disconnections. For this purpose, an algorithm called CP-WOPT (CP Weighted OPTimization) was developed for incomplete data to factorize tensors which can be applied for EEG [100]. ECG signal classification system was initially developed [101]. Further on, a new fast electrocardiogram (ECG) data classification and monitoring specific to a patient has also been developed by using 1-D convolutional neural networks (CNNs) [102]. Therefore, long ECG data of a patient, such as a Holter device output which records ECG of a patient for more than 24 hours, can be processed rapidly and accurately. For this purpose, CNNs are used for ECG classification in this study for the first time [102]. Another signal classification for EEG was developed using a new deep learning approach [103]. A classification system for electromyography (EMG) was also developed for arm prosthesis control studies and for this purpose discriminant analysis and support vector machine (SVM) classifier were used to identify and classify EMG signals at a good accuracy [104].

Metamaterial absorbers (MA) are used in biomedical devices since MAs have high absorption at wide angles of incidence for both transverse electric (TE) and transverse magnetic (TM) waves and a new MA with polarization independency and with different configuration was presented to be used in metamaterial (MTM) applications was presented [105]. Then, an MA with electromagnetic properties was designed which can be used in medical technologies as well as in sensors [106].

Phonocardiogram (PCG) is a biomedical device which determines heart defects through auditory perception of heart sounds. Wavelet types of PCG were examined and for the accuracy of this method, different wavelets on PCG signals were tested and Morlet wavelet was determined to be the most suitable wavelet for the time– frequency analysis of PCG signals [107]. A dynamic receive beamformer integrated circuit (IC) for High-Frequency Medical Ultrasound Imaging was developed in a study on biomedical devices [108]. High-Frequency Ultrasound has more resolution of some organs and arteries and in this study beamformer IC is developed for efficient intravascular ultrasound (IVUS) imaging [108].

Apart from technology used in biomedical devices, there are various studies related to biomedical engineering using advanced technologies. Ablation cooling is a method used in aerospace engineering, however, it is recently applied in biomedical engineering to increase ablation rate of tissues without side effects [109]. In that particular study, specifically as a research area of biophotonics, which is concerned with interaction of light and tissues, ultrafast laser pulses were used and ablation of brain tissue was achieved without a thermal damage [109]. Scaffold-free biomimetic aortic vascular structures were developed for 3D bioprinting and for this purpose, new algorithms and methods were designed [110]. A real human heart aorta was used to generate computer model of macro-vascular tissue so that the computer aided algorithms would be used to bioprint 3D scaffold free tissues [110].

IV. CONCLUSION

Turkey has a potential in biomedical engineering as there is a steady increase in published research in this area in the past 15 years (Figure 1). Turkey has been participating to EU funded framework programs and projects in recent years; therefore, its contribution to biomedical engineering is expanding [21–23]. Most of the studies in biomedical engineering area are conducted on biosensors, tissue engineering & biomaterials and biomedical devices with prominent results that would contribute to or has a potential to contribute to research and development sector in Turkey. More diverse study areas of biomedical engineering can be explored with the improvement of infrastructure in biomedical engineering and with the aid of fast developing technologies; therefore, Turkey can reach advanced countries in biomedical engineering research field.

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