

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Interdisciplinary crossover for rapid advancements – collaboration between medical and engineering scientists with the focus on Serbia

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SUMMARY

Over the past decades, development of engineering sciences has vastly contributed to advancements in medicine by production of numerous devices for diagnostics and treatment. In the middle of the 20th century, a new scientific field, biomedical engineering (BE), was established, which has developed into an extremely complex scientific discipline requiring a distinctive educational profile. Various study programs in BE have been established at universities around the world but also at several universities in Serbia. Also, intensive research in this field is performed at several scientific institutions in Serbia. In the present paper, short summaries of the research results of several groups of engineers and medical doctors are presented as an illustration of the wide field of BE research and possibilities of its application in diagnosis and therapy of various diseases.

Keywords: biomedical engineering; research; education; Serbia

INTRODUCTION

The Academy of Medical Sciences of the Serbian Medical Society (AMS-SMS) and the Academy of Engineering Sciences of Serbia (AESS) signed the Protocol on Cooperation on February 26, 2020 with the aim to enable the exchange of experiences and knowledge in the fields of medicine and engineering sciences, encourage new multidisciplinary scientific research, and contribute to education of doctors and engineers.

Over the past decades, the development of engineering sciences has incredibly contributed to advancements in medicine by production of numerous devices for diagnostics and treatment of various diseases. However, it should be noted that certain technical devices were already in use in medicine back in ancient times. Nevertheless, the number of technical discoveries that contributed to the development of medicine increased significantly in the 19th century and almost unthinkably so in recent decades.

BIOMEDICAL ENGINEERING

In the middle of the 20th century, a new scientific field, biomedical engineering (BE) (Figure

1), was established, which has developed into a largely expanded discipline divided into the following sub-disciplines [1, 2]:

Biomechanics – examines the kinetics and dynamics of healthy and diseased individuals in order to better understand and solve problems in various fields of medicine (orthopedics, traumatology, surgery, dentistry, etc.);

Biomechatronics – deals with intelligent electromechanical systems that help correct disturbed or lost body functions;

Bioinformatics – an interdisciplinary field, combining computer science, statistics, mathematics, and engineering for the analysis and interpretation of biological data;

Biomaterials science – directed towards surfaces or materials that come into permanent or temporary contact with human tissues, cells, or body fluids;

Tissue engineering – defined as “an interdisciplinary field that applies the principles of engineering and the life sciences towards the development of biological substitutes that restore, maintain, or improve tissue function” [3];

Genetic engineering – includes methods of direct manipulation of genetic material;

Neuroengineering – uses engineering techniques to investigate, explain, repair, replace, and improve the functions of nervous systems;

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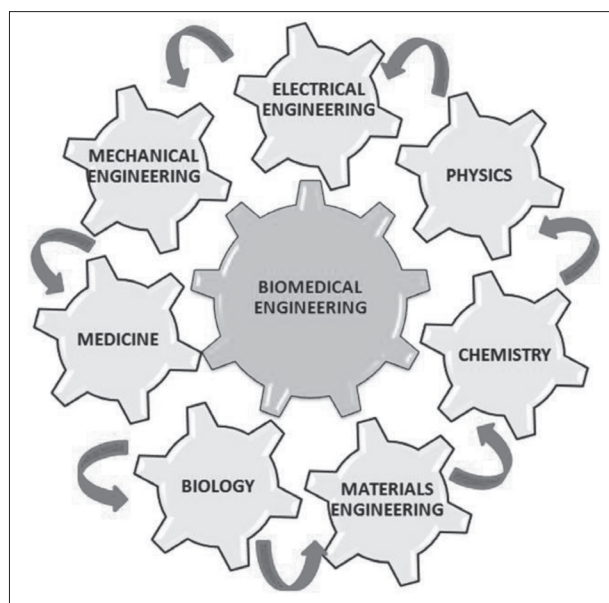


Figure 1. General scheme of integration of technical, medical and natural sciences in biomedical engineering

Bio-instrumentation – focuses on the development of instruments used in the diagnosis and treatment of diseases.

EDUCATION IN BIOMEDICAL ENGINEERING

BE is an extremely complex and extensive scientific discipline, so it requires a special educational profile. Over the past decades, BE education has grown rapidly all over the world, as well as in Serbia. At technical faculties in Belgrade, Novi Sad, Niš, and Kragujevac there are several study programs in BE.

The University of Belgrade has united experts in medical, technical, and natural sciences working in the fields of reconstructive, preventive, and regenerative medicine and has formed an integrated doctoral study program titled *Biomedical Engineering and Technology*. Also, some faculties independently offer courses within master and doctoral study programs that belong to the BE field (e.g., tissue engineering, controlled release, biomaterials, biomedical informatics, etc.). At the University of Niš, within the framework of a Tempus project in 2014, the elective BE course was established within the doctoral studies.

Also, in the field of dentistry at the faculties in Serbia, new subjects have come to life: computerized dentistry, visualization techniques, etc. Most clinical subjects (oral implantology, maxillofacial surgery, prosthodontics, orthodontics) use 3D images, video clips, and simulation programs as teaching aids.

BIOMEDICAL ENGINEERING RESEARCH IN SERBIA AND APPLICATION OF THE RESULTS IN PRACTICE

In Serbia, several scientific institutions and many scientists are engaged in research in various fields of BE. Also, much

research in the field of engineering that is not primarily focused on medicine often contributes significantly to its progress [4, 5]. The main goal of the AMS-SMS and AESS cooperation is to encourage collaborations of all of these institutions and scientists and thus improve the research in BE and contribute to the promotion of the achieved results. This paper, prepared by several physicians and engineers, marks the beginning of our cooperation. The following summaries of some of their studies present only an illustration of the wide field of BE research and possibilities of its application in diagnosis and therapy of various diseases.

Biomechanical study of fractured bone fixation

Great progress in orthopedic surgery has been achieved through multidisciplinary research in the field of biomechanical characterization of bone and skeletal system. In the early 1980s, a team was formed at the University of Niš, which compared the intensities of forces necessary for the fracture of human long bone in the laboratories at the Faculty of Mechanical Engineering. The results of this investigation led to the assumption that, if such a device for fixing a fractured bone was constructed, which would provide stability very similar to the natural stability of the human bone, fractures would heal much better, with fewer possible complications [6]. At that time, the conventional concept of external fixation implied fixing the fracture with a device with all components in one plane, which resulted in excessive stability in one and insufficient stability in the perpendicular plane. Application of the new concept resulted in the construction of new original implants and devices that proved to be significantly more effective in clinical practice compared to conventional implants. The first invention based on the new concept was an external skeletal fixator (Figure 2) [7, 8]. At the same time, it was the simplest device at the international level, so it was quickly introduced into routine use and to date it has been applied to over 28,000 patients with severe fractures in domestic and foreign clinics. Thereafter, the patent was recognized not only in our country but also as a European (European Patent Office) and a world patent (World Intellectual Property Organization). This patent was nominated for the best world patent by the Patent Office in 2012. The application of the patent, commercially termed “External Fixator According to Mitković” played a key role in rescuing about 5,000 wounded during the war on the territory of the former Yugoslavia and the subsequent bombing of Serbia. Another patent resulting from these and additional studies is “Self-Dynamizing Internal Fixator According to Mitković” (Figure 3), which is also routinely used and has already been applied to about 10,000 patients [9]. This implant is based on the original concept of spontaneous dynamization, i.e. it can spontaneously change its biomechanical characteristics depending on the stage of fracture healing, so its other name is “Intelligent Implant.”

Ten years later, this knowledge began to influence the scientific thought in this narrow field of science at the international level, so that it has been accepted by most of the scientific institutes today.



Figure 2. External fixator according to Mitković

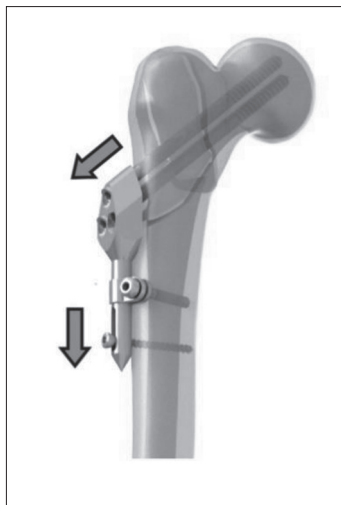


Figure 3. Self-dynamizing internal fixator according to Mitković

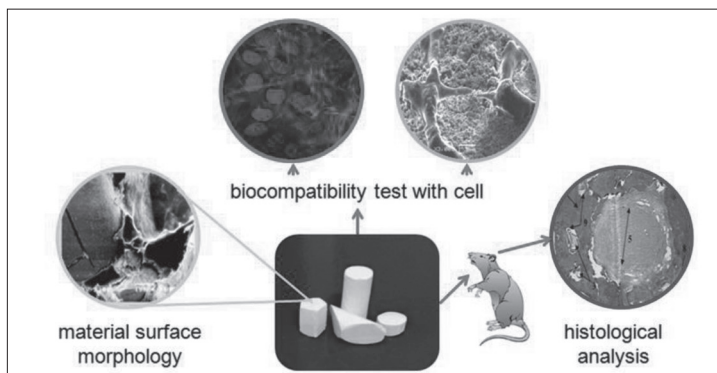


Figure 4. 3D scaffolds based on nano-hydroxyapatite (N-HAp) and a bioresorbable polymer in bone tissue engineering

In the 1990s, the same team at the University of Niš biomechanically tested a new original concept of artificial hip. It was thereafter produced by the Electronics Industry Niš and successfully applied to hundreds of patients. Many of them still walk today thanks to this endoprosthesis, the replacement of which was not deemed necessary even after 20 years of use. Progressive decay of the domestic producer and availability of prostheses of foreign companies in Serbia's market led to stopping the production of this hip endoprosthesis.

Research in the field of biomaterials science

Within the BE field, and the discipline of biomaterials, significant results have been achieved in the team work of researchers of various educational profiles. All researchers (engineers and medical doctors) jointly participated in solving current problems in bone tissue engineering. Bone tissue is an especially interesting subject of scientific research, due to frequent osteoporosis, as well as potential frequent fractures. The mineral phase in natural bone is mostly composed of nano-crystals and nanoparticles of calcium phosphates. The research brought together several institutions across the country (Institute

of Technical Sciences of the Serbian Academy of Sciences and Arts, Belgrade; University of Belgrade, University of Niš, and University of Novi Sad). Focusing on bone tissue engineering, the research included a complete research cycle, from synthesis and characterization of calcium phosphate-based materials (synthesized in the laboratory, but similar to human bone tissue), design at the molecular level, characterization, *in vitro* cell-based assays, *in vivo* studies on small and large animals, and pre-clinical tests, to patients, with the prior approval of the ethical committee. The concept underlying this bio-material and resulting implants is innovative and different from all known concepts. To put it simply, after the implantation, this "smart material" becomes "alive," it attunes itself to the needs of the organism and its metabolism, and finally disappears (dies), replaced by a newly formed tissue. It is composed of a non-bioresorbable component (calcium phosphate-hydroxyapatite – HAp), needed by the organism, and of a bioresorbable polymer component. In the course of time, the polymer gets resorbed and disappears, whereas the final products of its degradation, water and carbon dioxide, are entirely harmless to the organism. The polymer disappears simultaneously with the formation of new organic tissue; at the end of the reparation process, the place of the polymer is taken by a new tissue generated by the organism. Thus, the implant allows tissue regeneration and growth [10, 11]. The first stage of the study included pre-clinical research carried out on cell cultures (Figure 4). The experimental study carried out

on human cell cultures confirmed high potential for the application of these biomaterials as the cytotoxicity level was significantly below that observed for other biomaterials [12, 13].

Upon successful confirmation of the advantages of the application of these biomaterials in pre-clinical studies, the researchers proceeded to further studies in clinical conditions. The synthesized biomaterial was applied in the treatment of bone tissue deficiency caused by advanced resorption of alveolar bone in systemic osteoporosis. The results of the study have shown that the application of this composite biomaterial led to an increase in the density of the alveolar bone; the quality of prosthetic supporting tissue was satisfactory so that it could bear the load of inserted dentures. In short, the application of the biomaterial resulted in enhancement of the healing process in post-extraction wounds and a decreased need for additional interventions. It enables the creation of new bones, which are very similar to natural bone tissue, induces osteogenesis, and prevents resorption. Such reconstruction fully meets both aesthetic and phonetic requirements [14, 15].

The use of soft lasers (the so-called low-intensity or low-energy lasers) has made a significant contribution to modern medicine. The increasing evidence of the beneficial

effects in various therapeutic procedures is obvious. Low-energy lasers have powerful biostimulative effects reflected in more vigorous cell metabolism and microcirculation, resulting in increased mitosis of epithelial, connective tissue and bone cells. The results achieved so far confirm the use of lasers as stimulants in regenerative therapeutic methods and implantation of biomaterials based on HAp in bone defects. The use of lasers contributes to an increased bone tissue density, thus diminishing the possibility of undesirable processes [16].

Nanotechnology and nano-materials have enabled significant improvements in the application of the reconstructive materials based on HAp in bone tissue engineering. Composite biomaterials based on nanoparticulate bioresorbable polymer/HAp (particle size 1–100 nm) significantly accelerated the reconstruction of bone defects compared to the same material, but in micro-sizes (> 1 µm). Nano-particulate biomaterials in the form of fillers are highly convenient for practical applications; easily handled, they make a surgical intervention easier and simpler, whereas the final goal is achieved in a considerably shorter time [17].

Another example of the use of nanomaterials in biomedicine is in multifunctional wound dressings, which can contain, e.g., silver nanoparticles (AgNPs), inducing antibacterial activity by the controlled release of silver nanoparticles and/or ions [18, 19, 20]. Wound dressings based on AgNPs and alginate solutions and hydrogels enhanced healing of second-degree burns in rats [21].

Along with the development of novel products for medical and pharmaceutical applications, BE provides conception and introduction of new methodologies and protocols in preclinical and clinical studies as well as in the clinical practice. For instance, biomimetic bioreactors, which imitate physiological conditions in a certain tissue or organ, are primarily being developed for tissue engineering purposes. Still, these bioreactors also provide physiologically relevant studies of novel biomaterials and interactions of biomaterials with cells and tissues [22, 23, 24]. Thus, by this approach, it is possible to address the *in vitro* – *in vivo* gap, that is, discrepancies between results obtained in traditional monolayer cell cultures (in 2D environment) and those found in animal studies [25, 26, 27]. It was shown, for example, that nanocomposite alginate hydrogels with AgNPs had moderate to strong cytotoxic effects on chondrocytes in monolayers, while such effects were entirely absent in 3D bioreactor cultures of immobilized chondrocytes in alginate microbeads, as well as in cartilage tissue cultures in direct contact with the nanocomposite hydrogel [23, 28]. The results obtained from the bioreactor cultures were in agreement with the enhancement of wound healing without any adverse effects found in the treatment of second-degree burns in rats by the same nanocomposite hydrogels [21]. Mimicking the physiological conditions is necessary for a reliable prediction of biomaterial behavior upon implantation at a certain tissue site. Studies of novel macroporous, composite scaffolds based on gellan gum and bioactive glass particles have shown that the fluid flow in perfusion bioreactors significantly promoted the

formation of a mineral phase as compared to static conditions, which could be related to scaffold implantation in vascularized tissues [24]. Finally, an integrative approach to optimization of biomaterial properties and operating conditions in biomimetic bioreactors may provide tools for evaluation of new drugs and treatment procedures on 3D models of human tissues, as well as for development of personalized medical therapies, and thus contribute to decrease the level of needed animal experimentation [29].

Dentistry and engineering

Dentistry is a very dynamic scientific field, and its progress is a reflection of the development of basic, and, above all, technical sciences. Today, it is almost impossible to find an area in dentistry which has not been influenced by technical and technological achievements.

The third industrial revolution – the change from analog and electronic technology to the digital technology (1980s) made a breakthrough in clinical dentistry. The term ‘digital dentistry’ was coined, which was defined as “any dental technology or device that incorporates digital or computer-controlled components in contrast to that of mechanical or electrical alone” [30]. Digital dentistry opens up completely new areas, such as digital impressions, computer-assisted designed and computer-assisted manufactured (CAD/CAM) dentures technology, digital radiography and cone-beam computer topography (CBCT), digital face-bows and virtual articulators, tooth shade matching, computer-guided implant surgery, etc.

Building on the third revolution, in less than four decades, there is a new, remarkable turnaround – the fourth industrial revolution, which leads to automation and robotics in industry, but also in other areas. The dental profession and science, as well as the accompanying industry, have embraced at incredible speed the new concept of digital transformation called Dentistry 4.0. [31]. This new concept, as a synergy of doctors and engineers, has enabled almost all clinical and laboratory dentistry procedures to be supported by digital technologies. The progress in various fields of dentistry will only be enumerated here.

Medical imaging is the visualization of anatomical structures by computerized imaging techniques that provide a digital image as the first step in digital dentistry. Many diagnostic and therapeutic procedures were developed based on generation of digital images: digital tooth impression, cone-beam computed tomography, etc.

Data processing is now enabled by a large number of commercial software packages to support diagnostic and therapeutic procedures in dentistry. These include CAD-CAM software, digital face-bow and virtual articulators, tooth shade matching, digital smile design, computer-guided implant surgery, and computer-guided diagnostics and treatment in orthodontics [32, 33].

Computer-aided production is the application of software to control machine tools in the production of various 3D items. The most commonly used devices in dentistry are those for milling, sintering, rapid prototyping, and 3D printing different dental restorations [34].

Biomaterials used in dentistry are classified in the group of advanced materials and materials of the future (nanomaterials and smart materials) [35, 36].

Education and science – the introduction of digital technologies in the curricula of dentistry faculties has started globally and has reached different levels of application depending on local resources [37].

A commonly used method of numerical analysis in the dentistry research is the finite element method (FEM). Simplified, FEM considers the physical domain (tooth, dental implant, denture or bridge, temporomandibular joint, etc.) as a real continuum with infinitely many degrees of freedom of point movement and replaces it with a discrete (virtual) geometric model [35].

Patient record management – the first step in digitalization in the dental profession was the introduction of computers in clinics, health centers, and private practices. Today, the complete management of health care institutions has been digitized, which simplifies and speeds up all management activities.

Cochlear implants – the most successful neural prosthesis

A cochlear implant provides an opportunity for patients with severe-to-profound hearing impairments to hear again, for children to learn to speak, to be involved in everyday life and regular schooling, and gain confidence to live a full life [38, 39, 40]. Cochlear implantation would not have been possible without the close collaboration of engineers, neurotologists, otorhinolaryngologists, and speech and hearing health professionals.

A cochlear implant is an electronic device, which bypasses damaged or destroyed receptor cells and transmits electrical stimulation directly to the fibers of the auditory nerve. A modern multi-channel cochlear implant, Nucleus® 24 Contour (Cochlear Americas, Lone Tree, CO, USA) was installed for the first time in Serbia, in Novi Sad, at the Clinical Center of Vojvodina, the Clinic for Ear, Throat and Nose Diseases on November 26, 2002, in a patient 40 years old with postlingual bilateral severe hearing impairment [40]. In May 2005, the Republic Health Insurance Institute made a decision on financing the purchase of cochlear implants in the Republic of Serbia, thus reviving the national program of cochlear implantation in our country. Four clinical centers in Serbia have been trained for cochlear

implantation: the Clinical Center of Vojvodina, the Clinical Center of Serbia, the Zvezdara Clinical Hospital Center, Belgrade, and the Niš Clinical Center.

By the end of 2019, over 500 patients with the most severe forms of hearing impairment underwent surgical procedures in our country, primarily children, while the total number of cochlear implant recipients worldwide reached over 470,000. In the period from 2002 to 2020, a total of 147 patients underwent surgical procedures at the Clinic for Otorhinolaryngology and Head and Neck Surgery at the Clinical Center of Vojvodina.

Today, cochlear implantation is the standard treatment of severe-to-profound sensory-neural hearing loss in adults and children that enables patients to achieve good rehabilitation and a higher quality of life.

IS BETTER COOPERATION BETWEEN MEDICAL DOCTORS AND ENGINEERS NEEDED?

Research in the field of engineering sciences has significantly contributed to the development of medicine by production of numerous devices for diagnostics and treatment of various diseases. Nevertheless, although every medical doctor uses modern technologies in practice, few of them have any training in technological development. There are few medical schools in the world with programs that link medicine and engineering. However, even such education is not sufficient, because it is necessary to achieve understanding between doctors, who use different technical tools, and engineers, who design them. Engineers do not have complete information on what clinicians need, while clinicians cannot express their suggestions accurately, since they do not know the technological possibilities [41, 42]. It is necessary to educate teams of doctors and engineers in order to achieve better results in the application of existing technical achievements. This requires continuous education of both doctors and engineers through joint seminars, workshops, conferences, etc. The leading role in healthcare innovation will be bestowed on those institutions that will find methods to train engineers, doctors, nurses and others to work effectively in teams and solve challenges together. AMS-SMS and AESS will strive to contribute to achieving this goal.

Conflict of interest: None declared.

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Интердисциплинарни приступ за брзи напредак – сарадња научника из области медицине и инжењерства с посебним освртом на Србију

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САЖЕТАК

Наплетку медицине су последњих деценија веома много допринели проналасци из различитих области инжењерства. Половином двадесетог века успоставља се нова научна област, биомедицинско инжењерство (БИ), које се до сада развило у веома сложена научна дисциплину која је захтевала и посебан образовни профил. На универзитетима широм света, као и на неколико универзитета у Србији установљени су различити програми из области биомедицинског ин-

жењерства. Такође, у неколико научних институција у Србији спроводе се интензивна истраживања у овој области. У овом раду приказани су резултати истраживања неколико група научника из области инжењерства и медицине са циљем да се илуструје колико је широко поље истраживања у области биомедицинског инжењерства и какве су могућности њихове примене у дијагностици и лечењу различитих болести. **Кључне речи:** биомедицинско инжењерство; истраживања; едукација; Србија