INTERNATIONAL ROADMAP FOR DEVICES AND SYSTEMS™

2018 UPDATE

MEDICAL DEVICES MARKET DRIVER

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MEDICAL DEVICES MARKET DRIVER

1. INTRODUCTION

In this report, Medical Devices (MDev) are intended as devices designed to interface the human body. This category focuses on implantable or long-term-use external devices, rather than diagnosis devices used in a clinical setting, that are analysed in the specific Market Driver on Medical Diagnosis. MDevs are an important driver for future electronic market, as highlighted at the recent Sensors Summit held in December 2017 [1] where it was reported that "Wearable Medical Device Market is expected to exceed $7.9 Billion by 2021", and this is just a subset of the global market that medical devices can bring.

Medical devices can be classified in two general categories, related to the application scenario in which they are used. These two different scenarios require very diverse technological approaches, with a direct impact in terms of request of performances, costs, reliability and accuracy:

1. *Clinical Applications*, related to medical application for health and disease treatment, enhancing of organ functions (eye implants, brain chips to control Parkinson's or seizure, etc…) or monitoring, requiring:
    a. More reliable and precise performances;
    b. Lower volumes, but higher costs.
2. *Consumer Applications*, like sports or self-monitoring, requiring:
    a. Low cost, but lower performances;
    b. High volumes;
    c. High user friendliness of the device interface.

Biomedical technology has already achieved numerous successes, improving the lives of a huge number of people. Nevertheless, a lot of challenges are still open. The role of engineering in the medical and biological research is becoming evident year by year. Several improvements can be ascribed to the constant technology improvement.

In the future perspective, the innovations will grow not only in terms of technology, but in policies too. The relation between the people health and the society wellness cannot be broken-up; the desire to open the innovation to more people and distribute the healthcare worldwide is one of the major goals for future applications.

1.1. CURRENT STATE OF TECHNOLOGY AND RESEARCH

The present research trends can be clarified considering the topics that are nowadays of higher interest in the scientific community.

Table 1 outlines the more important scientific journals in biomedical technology field during the last five years, as presented by Google Scholar thanks its metric tool. It is worth to note the great importance of materials and tissue engineering. Furthermore, the presence of the IEEE Transaction on Biomedical Engineering on the top positions of this list points out the need of electronic engineering in biomedical innovation.

As reported in Table 2, in IEEE biomedical societies the discussed topics range on a wide variety of applications and methodologies, from hardware to software, in a multidisciplinary framework. The table shows the most common keywords in the IEEE biomedical papers (considering IEEE Transactions on Biomedical Engineering and IEEE Transactions on Biomedical Circuits and Systems). This metric shows which are the topics on which researchers are more focused on, and it can be helpful to understand the future perspectives and the present achievements.

From Table 2 it is evident that research activities target the design of wirelessly connected small size and low power integrated electronic architectures, adapted to implantable/wearable applications and the innovation leverages on new and efficient computation models, machine learning technique, for classification and imaging. Brain Computer Interface (BCI) devices emerge too in the interest of biomedical research.

Table 1: Top ten list of publications in the biomedical technology field in 2012-2016 (according the H-index) [2]

1.	Biomaterials
2.	Acta Biomaterialia
3.	IEEE Transactions on Biomedical Engineering
4.	Annals of Biomedical Engineering
5.	Journal of Biomedical Materials Research Part A
6.	Journal of the Mechanical Behavior of Biomedical Materials
7.	Journal of Neural Engineering
8.	Tissue Engineering Part A
9.	Tissue Engineering Part B: Reviews
10.	Journal of Tissue Engineering and Regenerative Medicine

Table 1: Top ten list of most common keywords in IEEE Biomedical Journals

1.	Machine learning
2.	Wireless
3.	Integrated
4.	Implantable
5.	Imaging
6.	Classification
7.	Wearable
8.	Energy-efficient
9.	Neuromorphic
10.	Brain computer interface (BCI)

1.2. DRIVERS AND TECHNOLOGY TARGETS

During last years some goals were achieved thanks to the innovation growth. However, several challenges are left unsolved. The main topics that will lead the research and the market in the next future are strictly related to their impact on the society in terms of better quality of life.

Personalized Health Care. The first goal to be achieved in the next future is the improvement of the so-called *personalized health care*: the advancing of person-centred and self-management health, thanks to *precision medicine*. Improving medical care by exploiting expanded capabilities deriving from technology improvements, in particular, telemedicine, early diagnosis and non-invasive medical devices are key features to be considered [3].

The important improvements in biomedical technologies open new scenarios for the implementation of medical devices, fitting the personal parameters and behaviours. Fundamental contributions are given by data availability thanks to electronic health records, recent advances in the study and manipulation of DNA, proteins and metabolites, and the possibility of continuous monitoring with low invasive devices. Scientific knowledge, crossed with detailed data about the specific person, will give the possibility to:

- exploit large-scale databases, computational tools, and omics methodologies to characterize individuals and extract the needed information for tailoring the medical intervention [4];
- develop optimised prevention and screening strategies;
- apply treatments at the most opportune times and adapting their dose to the specificities of the patient.

Mobile-Health (m-Health) is becoming a reality, trying to implement apps for clinical research. App-accompanied clinical trials (smartRCTs) can improve health care following all-day-long the patients [5].

Neurodegenerative Disorders. Neurodegenerative disorders are a major challenge to be addressed and, thanks to the innovation in technology and engineering, they can be faced with efficient solutions. Alzheimer, Parkinson, Epilepsy, Multiple Sclerosis and other degenerative conditions are increasing due to population ageing. In 2050 the percentage of population over 65 is expected to double [6]. The improvement and personalization of treatment of these diseases can drastically increase the quality of life of people, as example strengthening clinical trials with neuroimaging.

Neurostimulation used for treating Parkinson and epilepsy gave remarkably positive effects in some patient cases. The problem is that current solutions are not suitable for everyone, and some diseases, as for example Alzheimer, are still nowadays essentially untreatable. The application of neural engineering and targeted gene delivery to neurological disorders is a very promising approach for covering actual gaps between research results and their clinical application [7].

Combating Cancer. The fight against the cancer is a quite old challenge that appears in any medical strategic plan since a lot of year. The new technology innovation could produce further step forward, as already done in the recent past. The engineering must continue to strike on this goal, as one of the most common problems which afflicts people all around the world.

Nanomedicine is another fundamental player in this challenge, exploiting the properties of matter at the nanoscale for developing innovative and more efficient drugs, with in parallel the important reduction of side effects than standard therapies [8]-[9].

Reducing Disparities. The access to treatments is not yet possible to everyone. In the next years a positive challenge to face is to bring efficient medical solutions to the largest possible population. For reaching this target engineering is a key issue, in fact can produce low cost devices and instruments, enlarging the possibility of the access to efficient medical solution to a larger number of patients, also from less industrialized and poor areas of the planet [10].

1.3. VISION OF FUTURE TECHNOLOGY

Thanks to the innovation brought by biomedical engineering the health care can be improved. This progress is carried forward by the birth of new techniques and methodologies. In this section some examples of emerging technologies which will be important in the next future to address the nowadays challenges are pointed out.

Machine learning. Machine learning and neural network techniques are becoming perfect solutions to a huge variety of application fields, comprising the biomedical one. The emerging biomedical solutions, typically based on imaging and multiparametric sensors, are producing a huge amount of data. The application of machine learning is the most efficient approach for analysing this large, complex and heterogeneous, mostly unstructured and poorly annotated set of information. Traditional data mining and statistical learning approaches typically need to first perform feature engineering to obtain effective and more robust features from those data, and then build prediction or clustering models on top of them. The application of machine learning algorithms, mapped into customized hardware, is a promising approach for bringing biomedical data into improved clinical devices [11].
As mentioned, precision and personalized medicine are taking every day more importance in medical practices. Big data and machine learning approaches are able today to identify targeted active biomolecules from millions of candidate compounds quickly and cheaply [12]-[14]. The first exploitation of this outstanding result is the customization of healthcare, tailoring the treatments to individual patients as consequence of machine learning based personalized monitoring and related medical decisions. Same considerations are valid for wearable and portable devices, where the quantity of data and the level of decisions to be taken are requesting sophisticated methodologies, only possible if effective algorithms of machine learning and artificial intelligence in general are applied, mostly in optimized and low consumption custom electronics.

Brain-computer interface (BCI). BCI are used for interfacing human brain with electronic devices, reading and interpreting encephalographic biosignals, with either invasive or non-invasive methods. There are different levels of invasiveness of BCI solutions, from non-invasive use of planar electrodes (Electroencephalography - EEG), to the implant of the device on the cortex (ElectroCorticoGraphy - ECoG), up to the direct implant of electrodes on brain surface [15],[16]. The impact of BCI on healthcare is a fact, opening new scenarios in disease diagnosis, therapeutic applications, as example in neurorehabilitation (restoration of upper limb function by implanted BCI [17] or in the spinal cord injury disease [16],[18]). The new open challenges have an impact on all technology levels: on the processes for production of biocompatible bio-interfaces; on the devices, requiring miniaturisation, low power and autonomy; on system level, for the integration of multi-sensing capabilities with an efficient treatment and transmission of the information.

Nanomedicine. Biomedical devices and bio-nanotechnology, thanks to the application of innovative micro&nano techniques, are effective for developing bio-devices and bio-systems for interfacing living cells and biomolecules in general. The most important purposes for building devices for nanomedicine are the development of nano-bio-sensors, of devices for living cell imaging and analysis, for implantable devices for disease treatment and smart diagnosis, of integrated devices for point-of-care in vitro and in-vivo diagnosis (see following section on Implantable, Ingestible and Injectable Devices).

In general, a nanomedicine device can be defined as a miniaturized system for delivering nanocarriers, nanotherapeutics or nanodrugs. Best application target is the improvement of the therapeutic efficacy of currently available therapeutic agents, combining nanoscale delivery components, control electronics and, in case, nanoparticles [19].
New scenarios will appear in this framework in the following years; the nanoelectronics will provide architecture so small that can be drunk or can fly in the human bodies as small drones, both to deliver drugs and to monitor the patient metabolism [20]. These types of applications are defined as IIIDs, Implantable, Ingestible and Injectable Devices.

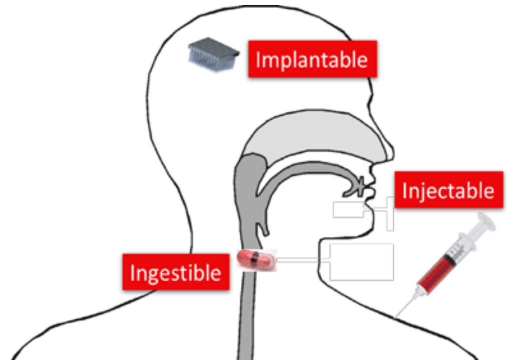

Figure 1 *Implantable, Ingestible and Injectable Devices*

Implantable, Ingestible and Injectable Devices (IIIDs)

A specific analysis should be dedicated to the *in-body* solutions (Figure 1) that are appearing on the market and are present nowadays more in research area, but they are of very high interest for the future of medical devices [21]:

1. *Implantables*: devices implanted inside the human body;
2. *Ingestibles*: devices ingested like regular pills;
3. *Injectables*: devices injected into the human body via needles.

A key technology need common to all *in-body* devices is the wireless communication for interconnecting the IIID with external components for monitoring and control, avoiding the use of intrusive wires or penetrating structures. Main target is to implement devices always less unobtrusive for medical diagnosis, prevention, prognosis, and disease treatment.

Implantable devices are typically installed in the human body (generally immediately under the skin) with a surgical operation. Their purpose is in general for both sensing and stimulating/delivery functionalities. One of the most important future market requests will be to build closed-loop systems for measuring physical parameters and taking decision for actuation in terms of stimuli or drug delivery, for example. Some of the most interesting implantable applications are:

- *Neurosensors*: devices applied to study diseases such as Epilepsy, Parkinson and Alzheimer or for cardiac arrhythmias and irregular heartbeats;
- *Neurostimulators*: devices for stimulating the nervous system and recover functionality, used for example in spinal cord stimulation for back pain treatment [22]. Significant research is being already done to interface nerves in severed limbs to prosthetics. Also, to provide the sensation of touch to the nervous system from the prosthetic limb;
- *Pacemakers*: miniaturized devices, installed inside the chest or abdomen, devoted to help the control of cardiac arrhythmias, detecting the heart status and stimulating heart beat in case of anomalies. Pacemakers are the most mature devices of this category;
- *Cardio Vascular Pressure Monitors*: devices placed as catheters or wires inside cardiovascular system for long-term monitoring of blood pressure. They are applied in case of chronic blood pressure monitoring as well as for tracking real-time the progress of surgical interventions;
- *Intra-cranial Pressure Monitors*: devices placed in the skull for measuring intra-cranial pressure preventing the risk of severe brain damage in case of localized intracranial mass lesion or cerebral edema, but also in case of cerebrospinal fluid disorder head injury.

Ingestible devices are in general miniaturized devices in capsule-shape, normally taken as the regular pills for drug ingestion. They travel inside the gastrointestinal system for collecting information about their status. The most common solutions are based on real-time videos, images, measurement of physiological parameters for monitoring or diagnostic purposes, release of drugs. One of the most important targets is the collection of data that should be wirelessly transmitted for displaying or processing. The most representative applications in this field are:

- *Imaging capsules*: used for imaging the gastrointestinal tract and digestive system. They are smart endoscopy capsules (as some already present in the market as the PillCam by Given Imaging and Medtronic) [23],[24]. This is the most advanced area in this field in actual market, but several issues are still open as image quality, real-time monitoring and capsule control;
- *Drug delivery capsules*: electronic pills used to deliver a precise quantity of a drug along the gastrointestinal tract.

Injectable devices are minimally invasive with respect to the others and are considered the most promising solution for next generation of this type of medical devices. The injectable can be associated to:

- highly miniaturized micro-sensors or micro-stimulators, exploiting the reduced dimensions for flowing in cardiovascular system, injected by means of a needle. They are the less invasive and unobtrusive alternative to the implantable devices previously described;
- three-dimensional medical electronics that are directly build inside the human body through sequential injections, as the device for ElectroCardioGram (ECG) and stimulator electrodes developed by [25].

<u>Future directions of IIIDs</u>

Recent advances in electronics, materials, power harvesting and smart systems can be a boost for the clinical application of *implantable devices*. First application domain examples are well listed in [21]:

- heart stents for wirelessly transmitting the health of an artery;
- implants for detecting performance-enhancing drugs;
- closed-loop glucose meters and insulin pumps for monitoring and controlling blood sugar levels;
- implants capable of detecting the presence of oral cancers.

Ingestible devices can be very effective for personalized drug delivery, using capsules for treating digestive disorders and diseases. The possibility of having higher-bandwidth data transmission can improve the quantity of information exchanged with the capsule and so enable better diagnosis. By ingesting capsules equipped with sensors, in combination with regular pills, gives the possibility of monitor the intake. Electronic capsules can better monitor the physiological reactions due to the released dose of drug. It is possible to imagine devices that track the electrical activity at the gastrointestinal system, measuring transit times. The merge of sensing and actuation capabilities can drive the implementation of smart capsules that release specialized drug profiles when they reach a specific location or when they detect specific species in the environment.

Finally, *injectable devices* are a promising solution too. Future challenges for this type of devices are mostly powering issues, due to the high level of miniaturization, requiring fabrication of injectable antennas/electronics with micrometric footprints.

2. CHALLENGES AND TECHNOLOGY REQUIREMENTS

All the mentioned targets, in particular mHealth, personalization of the diagnosis and cure, portability of the solutions, are high demanding in terms of technology challenges.

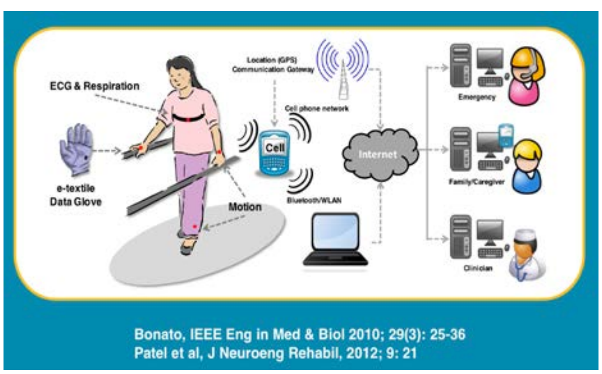

Figure 2 *mHealth impact on different implementation levels*

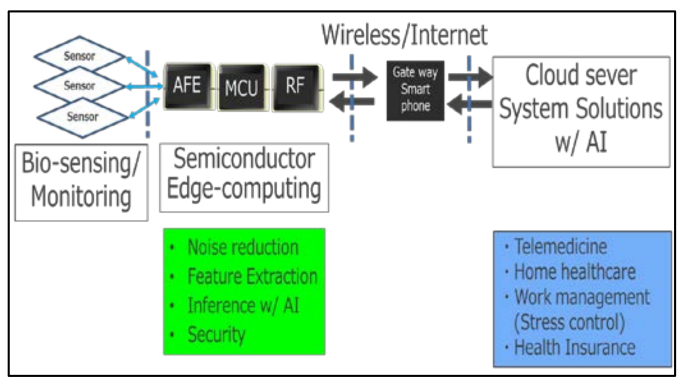

Figure 3 *mHealth for monitoring human health condition to detect potential diseases and/or stress conditions in daily life*

Considering *Wearable Devices*, as depicted in Figure 2, Bonato et al. [26] highlighted the impact of mHealth on all the implementation levels both in terms of devices and communication systems.

The low power edge-computing for noise reduction from the raw sensing data, security control, feature extraction and inference by the sensing data with techniques of machine learnings and/or artificial intelligence (AI) as shown in Figure 3.

6 Challenges and technology requirements

The most important challenges to face are:

- biocompatibility in devices in contact with human skin or tissues;
- for mHealth solutions
    - Ultra-Low power;
    - always connected devices (real monitoring);
    - cloud management;
- Closed Loop Systems for measuring the patient data, elaborating them efficiently, transmitting them in case and, for example, making decisions for actuating countermeasures or raising alarms;
- bio-signal detection and interpretation (BCIs, EMGs, ECG, …);
- efficient and fast decision making;
- realisation of customised patches, implants, … exploiting *additive manufacturing* potentialities.

Medical Devices must be able to become much more personalized for:

- building personal emergency response systems;
- implementing Wearable devices for monitoring for example:
    - heart, respiration;
    - skin for hydration;
    - movements;
    - brain activity;
- implementing methods for taking best decisions based on smart and efficient technologies, where machine learning and neuromorphic/bio-inspired approaches will take a key role.

About *in-body* devices, their design is performed starting from human body analytical models and advanced Multiphysics simulation software, as by Finite Element Methods. Then it is performed the experimental validation using in-vitro phantoms emulating biological tissues electrical properties, and/or by in-vivo using animals (rats, pigs, etc.) and, where possible, human subjects. In this case the most important challenges to consider are:

a) *Operation Frequency*. The selection of the optimised operation frequency is a trade-off of different areas. Working at low frequencies (the most used band is the Medical Device Radio Communication Service, 403.5MHz) guarantees lower losses passing through the biological tissues, but limits the communications speed and requests large antennas and components, increasing the size of the device [21]. The high frequencies (the most used band is the Industrial, Scientific and Medical, 2.4GHz) achieve a better miniaturization, reaching higher data rates and obtaining an improved image resolution and it is typically used for ingestible devices. In general, the range of frequencies vary between hundreds of kHz [27] and GHz.

b) *Integration of Wireless interface*s (inductive links to antennas) into the in-body device. This aspect is highly critical and is the best enabler of unobtrusive and efficient communication with the external monitoring and control equipment, such as smart-phones, smart-watches or in general more customized smart-wearable garment. Antenna solutions useful for *in-body* devices are [21]:
    a. planar Inverted-F antennas (implantables);
    b. helical antennas (ingestibles). They provide a circular polarization and an omnidirectional radiation pattern, having too a consistent bandwidth for good range of different tissues;
    c. loop or dipole antennas (injectables) that should be designed considering the strict specification in terms of size and shape of the device.

c) *Powering*. Nowadays almost all *in-body* devices on the market use batteries for powering. But batteries are usually large, and so they dramatically increase the size of the device moreover, the batteries are made out of not biocompatible materials. They add too an important issue in terms of maintenance and long-term operating time, requiring frequent replacement and/or recharging. Batteries are still the largest component present inside *in-body* devices. For the IIIDs success it is fundamental to find efficient power harvesting techniques, avoiding the presence of the battery and allowing a self-sustainability in terms of power supply. Possible choices are related to harvesting energy from environmental or bodily sources. Electromagnetic energy (RF, ultrasound) is a valid option. Mechanical vibrations are an interesting power source, exploiting heartbeat or tissue and human motion. In the body are present thermal gradients that can be used for thermoelectric energy generation. Electrochemical reactions can be a further possibility, like extracting power from glucose oxidization [28],[29]. Simpler, but less efficient and integrated solutions, are related to Radio-frequency IDentification (RFID), with the drawback of requiring an external interrogator in the close proximity of the device and inducing an undesired heating inside the tissues.

d) *Biocompatibility* is a further critical issue to be considered. Several techniques have been explored to achieve biocompatibility for *in-body* devices, including the use of biocompatible materials, the coating with thin biocompatible polymers or the addition of superstrates to cover the exposed metal parts, the most critical to be protected. Actually, titanium jackets are the most common solution, as is in pacemakers, but more flexible and integrated approaches have to be studied, as *Biodegradable Electronics*, that are bringing very important results having today the possibility of realising active devices and so to integrate in future implementations signal detection and wireless transmission [30],[31].

2.1. Challenges and Possible Solutions

Challenges	Metrics	Roadblocks	Potential solutions
Form Factor	#Sensors, #ICs, #Antennas, #Components PCB routing complexity Flexibility Miniaturisation	Increasing PCB footprint occupied by connectors and components Need of Flexible PCB Substrates	1. Package-level integration 2. 3D integration
		Integration of heterogeneous components	3. 3D integration 4. Unified technology (CMOS RF/CMOS MEMS)
		Die area explosion due to more functionalities	5. Technology scaling
Power Consumption	Max frequency, Operating Speed, Low standby current, Sensor Power Consumption, Low Noise Analog Front-End (AFE) Battery Power Density (Watt-Hr/Litre) Peak Tx/Rx current (mA for wearables, <µA for IIIDs), Tx/Rx power per bit (µW/bit for Wearables, nW/bit for IIIDs)	System Power Consumption increasing	1. Neuromorphic/Bio-Inspired Architectures 2. Asynchronous and Event Driven computing 3. Approximate computing 4. Quality/Energy Trade-off 5. Low leakage/low voltage SOI devices
		Increase of data to be transmitted	6. Optimisation of amount of Tx/Rx data by on-site elaboration 7. Machine Learning / Neuromorphic for data filtering
Heating Reduction	#ICs, Max Frequency	Die&PCB areas increase due to more functionalities	1. Best trade-off choice of Operational Frequency 2. Heating reduction at device level by technological improvements
	Heating for Tx/Rx & Remote Powering	Tissue Filtering requests more power for remote powering	3. Quality/Energy Tradeoff 4. Increase of efficiency in power transmission
Biocompatibility	Toxicity level, Inflammation	Need of different materials because of the increase in functionalities request	1. Study of new materials (material science and engineering)
Communication Bandwidth Scaling	RF Data rate	Increasing communication modes/bandwidth requirement for RF communication	1. Technology scaling for high performance RF devices 2. High-performance RF/baseband 3. Integrated multi-standard communication circuits
IP/Sensor integration and scaling (More than Moore)	#Sensors, Max Sensor Power (µW for wearable, < µW for IIDs), DC-DC efficiency (%), DC-DC power density (W/mm^2)	Exclusive technology (analog, MEMS, logic… etc.)	1. Heterogeneous 3D integration 2. Sensor Fusion
Supply voltage scaling challenge	V_{DD}	Threshold voltage scaling and performance requirement	1. Quality (Performances)/Energy (Power Consumption) Tradeoff 2. Technology scaling

2.2. Impact on IRDS IFTs

IFT	*Personalized Healthcare*	*Neurodegenerative disorders*	*Combating cancer*	*Reducing Disparities*
Beyond CMOS (BC)	-	-	-	-
Emerging Research Materials (ERM)	***	***	***	*
Packaging Integration (PI)	***	***	***	*
Outside System Connectivity (OSC)	***	***	*	***
Metrology (MET)	*	*	*	*
System Architecture (SA)	***	***	**	**
Factory Integration (FI)	-	-	-	-
Environment, Safety, and Health (ESH)	***	***	***	***

- No impact
* Low Impact
** Medium Impact
*** High Impact

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