Swift introduction into

Bio-MicroElectroMechanicalSystems

(Bio-MEMS)

Abstract

Bio-technological research is about to revolutionize the way common tasks in health care industry are being usually performed. This review is therefore aimed to provide brief summary and basic knowledge for people, who have not came across this area yet, as well as enhance its understanding to those with some level of knowledge in this scientific field. Various types of devices performing different tasks are classified, briefly described and linked to each other in the latter section. Examples and possible applications are provided when appropriate, as well as peculiarities associated with subject discussed. What can be currently achieved with such devices and by which means they can perform their main tasks is discussed in context with subject being described. Finally, probable future development in next few decades and its presumable implications is outlined, along with challenges inherent to this technology, as well as its possible pay-offs.

***Keywords*:**

Bio-MEMS, biotechnology, microfluidics, implantable medical devices, biosensors, actuators, nanobiogenerator, neuroprosthesis, total-analysis-system, lab-on-chip, human-on-chip, bioethics

Contents

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Introduction

During second half of 20th century, electronic devices experienced tremendous transformation through miniaturization. Integration of multiple formerly distinct components into one complex unit reduced costs and dimensions, turning implementation of formerly infeasible technical solutions into common practice. Painstaking development of modern computing systems from utilizing vacuum tubes (1940s), through transistors (1950s), up to integrated circuits (1970s) and consequently whole systems on chip (1974), incorporating all components of a computer into a single platform, paved the way for today's ubiquitous computational technologies, including smart and mobile devices commonly used by many people on everyday basis.

Similar process happens currently in field of biotechnology and particularly with biological micro-electro-mechanical-systems (bio-MEMS). When laboratory equipment components, required for biochemical analysis, started to be seriously emerging within μ-scale dimensions in early 1990's ("vacuum tube" to "transistor" analogy), first concepts of lab-on-chip systems have emerged as well. Their design and construction was just a matter of time and during mid 1990's these systems feasibly integrated various laboratory analysis processes into one single chip ("transistors" to "integrated circuits").

1. What are Bio-MEMS?

These systems are usually defined as *"devices or systems, constructed using techniques inspired from micro/nano-scale fabrication, that are used for processing, delivery, manipulation, analysis, or construction of biological and chemical entities"*. [3] They open whole new range of possibilities in diagnosing various health conditions, monitoring and evaluating actual health status of patient and, in some cases, subsequently taking proper actions in treating these conditions (pacemakers, drug delivery systems, neuro-stimulators). Large potential emerges in proteomics (reconnecting mechanically dissected nerve fibers) and HMI (human-machine-interface) areas.

Bio-MicroElectroMechanicSystems usually consist of silicon-based structures containing electronical integrated circuits, micro-reservoirs, micro-pumps, cantilevers, rotors, channels, valves, sensors, and other components, although some devices, which do not have any electro-mechanical components (such as DNA and protein arrays) are also sometimes categorized under BioMEMS. [2]

In a nutshell, Bio-MEMS are basically **pieces of technology injected into biological system, which they may evaluate and stimulate by various physical, chemical, or electrical means.**

2. Basic components

Basic functional devices can by divided into three main groups by their general purpose:

2.1. Bio-sensors

Biosensors are analytical devices that combine a biologically sensitive element with a physical or chemical transducer for selective and quantitative detection of specific compounds presence in a given external environment. If properly manufactured, they are able to detect cells, proteins, DNA (presence of the molecule itself, or, more specifically, some particular sequence by binding of single strand molecule to its complementary one in biological system), as well as small molecules.

Although vast majority of typical Bio-MEM sensors is based on artificially created substrates (silicon compounds, surface immobilized polymers (i.e. PEG), self-assembled monolayers (SAMs)), cell-based sensors are very attractive at the present time, due to their highly selective and sensitive receptors, channels, and enzymes. This built-in natural selectivity, of intact living cells, to biologically active chemicals, allows them to react with analytes in a physiologically relevant way.

Significant challenges exist for long-term operation since the cells need to be kept alive and healthy under various harsh operating conditions. Whole cell-based sensors will potentially offer tremendous benefits for the evaluation of drug candidates and effects of bio-chemicals on multi-cellular organisms, since the response of these sensors is directly predictive of the physiological response of an organism. [3, 6]

Biosensors utilize whole variety of detection mechanisms, depending on measured quantity (physical, or chemical) and target destination (certain tissue/bulk body water), as well as our demands on them. Most commonly employed methods are:

2.1.1. Mechanical

Cantilever sensors works usually by *bending of cantilever* (mechanical deformation may be converted into electrical signal through piezo-resistor), or *mechanically created vibrations* (mass sensing mode). Selection of appropriate material depends on the substances, or quantities, we want to evaluate:

Silicone cantilever sensors are widely used for detecting DNA and proteins, as well as cancer markers (prostate specific antigen).

Environmentally sensitive **hydrogel coating** (i.e. PMAA in pH sensing) is favorable for measuring various biological conditions in chip’s surroundings (temperature, pH, electric field, ionic strength). Currently, UV free-radical photolithography process allows fabrication of highly sensitive pH detectors (sensitivity of 1 nm/5x10^{-5} ΔpH). [6]

2.1.2. Electrical

Electrochemical methods utilize well-known electrical quantities (conductance, electric current, voltage) for convenient detection in various situations:

Amperometric biosensors for redox processes (glucose detection for monitoring hydrogen peroxide formation, or oxygen consumption), gas and lactate detection, as well as evaluation of metabolic blood parameters.

Potentiometric biosensors measuring changes in potential (voltage) between electrodes. Base component is appropriate type of field-effect transistor (i.e. ion-sensitive ISFET), fabricated with utilization of silicon nanowires and carbon nanotubes, allowing production of multiple sensors in nanoscale dimensions (high surface area to volume ratio).

Conductometric biosensors measuring conductance changes associated with changes in the overall ionic medium between the two electrodes, indicating biomolecular reaction between DNA, proteins, and antigen/antibody reaction, or excretion of cellular metabolic products (extracellular neuronal activity). Their simplicity makes them convenient for detecting various bio-threating agents, toxins, and similar chemical compounds.

2.1.3. Optical

Detection techniques utilizing fluorescence (single molecule detection, as well as discriminating single-nucleotide mismatches at femtomolar DNA concentration), or chemi-luminiscence (generation of light through releasing its excessive energy induced by a chemical reaction) are also of great interest for their prevalence in life sciences.

2.2. Actuators

Although "*actuators*" usually refers to device components, which are responsible for executing some particular action, in this context however, we use it also for identifying whole **devices** (or their modules), which are **purposefully and deliberately affecting biological system,** or its physiology (e.g. drug delivery systems).

Actuation systems basically stimulate biological organism, either chemically, or electrically (action potentials).

2.2.1. Artificial Cardiac pacemaker

First of such actuation systems was an artificial cardiac pacemaker substituting impaired function of sinoatrial node – primary biological pacemaker of human heart. Some models incorporate defibrillator function (CRT-D devices), allowing them to reset electrical activity of heart in arrhythmia occurrence. Due to variety of functions in contemporary pacemakers, we may consider them as integrated cardiac rhythm management systems.

2.2.2. Precise drug delivery systems

These devices usually utilize "*micro-pumps*" as driving components for dispensing drugs, or other therapeutic agents into the target destination inside a human body. They may be categorized as ***mechanical*** *(electrostatic, thermo-pneumatic, SMA)* and ***non-mechanical*** *(magneto-hydro-dynamic, electro-osmotic, chemically-based),* depending on mechanism performing pumping function.[1] Indispensable advantage of bio-MEMS in drug delivery, over other currently employed methods (orally administered drug capsules, liquid substance injection into patient's blood stream), is their precise temporal, spatial and parametrical control. Chemical agent may be therefore released at very specific time, when the device itself is already in proper area (cancerous tissue), after all required conditions are met (environmental temperature, prevalence of particular protein/DNA sequence, or presence of another therapeutic agent). This quality opens a whole new world in treating various diseases and paves the way for highly individualized drug therapy at very reasonable costs.

[1] Brief review and comparison of commonly used mechanisms can be found in [16]

2.2.3. Neural stimulation

Stimulation of nervous system represents challenging area with great potential, especially for patients with sensory organs impairments. **Cochlear implants**, as well as **retinal implants**, allows restoration of sensory information to some extent (e.g. speech recognition), in certain health conditions (damaged sensoric receptors, while sensory information processing abilities remained intact). [11]

Neuroprostheses allow people, who cannot control movement of their limbs (limb amputation, CNS damage), to recover their former abilities. In case of CNS injuries, when peripheral nerves remained intact, **functional electrical stimulation** (FES) systems may artificially replace central motor control to generate movements or functions that mimic normal actions. When whole parts of body are substituted, **artificial prosthesis** has to be appropriately coupled with nervous system (electrodes implanted within peripheral nerve trunk for selective stimulation of multiple nerve fibers). Additionally, non-invasive EMG electrodes on the body surface may be utilized in some instances, but recorded signals are less accurate and stimulation capabilities are heavily limited (stimulating signal overspreads to multiple nerve fibers). Implementation of interface between the peripheral nervous system and the artificial device could allow stimulation of peripheral nerves in a selective manner (e.g. transmitter-receiver system allowing control unit to unambiguously identify individual nerve fibers). [7, 13]

Remote control of behavior may be achieved either by genetic modification (flies' movement induced by photo-stimulation of optically gated ion channels in specific groups of neurons), or by implanting stimulating electrodes into specific brain cortex areas (rat's somatosensory cortical area for whisker "touch" sensations, along with medial forebrain bundle as rewarding system providing pleasurable sensations, allows operator remotely control rat's behavior via operant learning process). [1, 8, 12, 15, 17]

2.3. Energy harvesters

In order to perform certain action (generate stimulating electric impulse), abovementioned devices require power supply. In some cases, battery may be sufficient (artificial cardiac pacemakers), provided that for long-term functionality it needs to be occasionally replaced (4.7 years for lithium-based batteries), or regularly charged when using rechargeable batteries. [18]

If battery power source would be inappropriate, **embedded power generators** may provide necessary energy by harvesting energy from body's vital functions (temperature gradients within the body for thermoelectric generators). Biomechanical energy of muscular contraction can be converted into electricity by **piezoelectric nanowire based generator**, allowing low-frequency energy scavenging from regular and irregular biomotions generated by living biological systems. Main challenge here is material biocompatibility, although *in vivo* usable materials already emerged (ZnO). [19]

Regenerative **micro fuel cells** (glucose-based systems) seems to be the single most versatile of all technologies, since the fuel and oxidation reagent is replenished constantly through the electrochemical reactions that continuously generate power. Their major advantage is location independence (glucose abundancy in various biological structures), predetermining them for long-term use as part of "migrating" devices, or within stationary ones in areas, where other energy harvesting technologies could not be deployed. [9]

3. Lab on chip (/μTAS)

Lab on chip, as well as “micro-total-analysis-system” – μTAS, commonly refers to rather complex device, integrating all the basic components (ports, sensors/detectors, integrated circuits) into fully functional units, offering at least some level of biological system’s parameters evaluation. From certain biological condition, through data acquisition, up to overall evaluation (and potentially taking relevant action), usually leads quite a long journey: obtaining appropriate sample properly, preparing it for further processing (i.e. via electrophoresis), detecting particular substances (cells, proteins, DNA), evaluating overall biological condition and desirably utilizing acquired information (storing it into embedded memory module, transmitting to physician’s computer, or taking desirable action subsequently – i.e. releasing optimal amount of drug for treating life-threatening situation (insulin release in case of diabetes mellitus)).

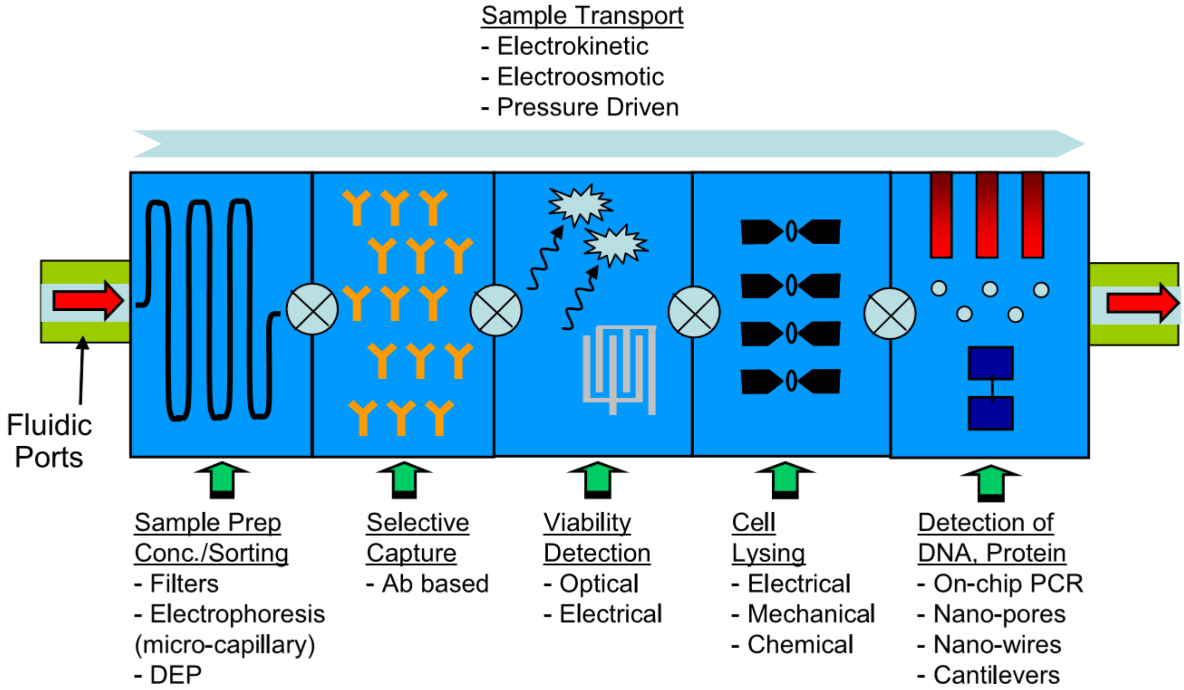

Figure 1: Possible integrated platform for a lab-on-a-chip for detection of cells and microorganisms [3]

Whereas typical μTAS systems usually provides valuable **diagnostic information**, adding selected “actuator” modules, which are affecting the biological system based on information obtained from μTAS module, allows creation of complex device suitable for **quickly diagnosing certain health conditions and consequently treating those conditions efficiently on long-termly sustainable basis.**

4. Human on chip

Utilizing cell cultures as fundamental elements of Bio-MEMS devices allows us to create 3D structures, which simulates the activities, mechanics and physiological response of entire organs and organ systems. In comparison to *in vitro* models, that are useful for studying the molecular basis of physiological and pathological responses, **organ-on-chip** structures provides complex cell–cell and cell–matrix interactions crucial for regulating cell behavior *in vivo*. [5] By integrating multiple organs on one single platform and appropriately interconnecting them (channels interconnecting organs (in separate chambers) based on their sequence *in vivo*), drug effect and metabolism may be assessed on a systemic level. Although these **human-on-chip** systems are currently in their infancy (challenges include mainly developing suitable platforms, incorporating barrier-tissue analogs and resolving long-term sustainability), they could ultimately replace animal models in clinical trials, overcoming thus ethical problems with animal testing, as well as their shortcomings (validity due to deficiencies in cross-species extrapolation, limited control of individual variables, cumbersome harvesting of specific information). Additionally, commercially available devices manufactured in large amounts would allow conducting studies in more cost-effective manner. [10]

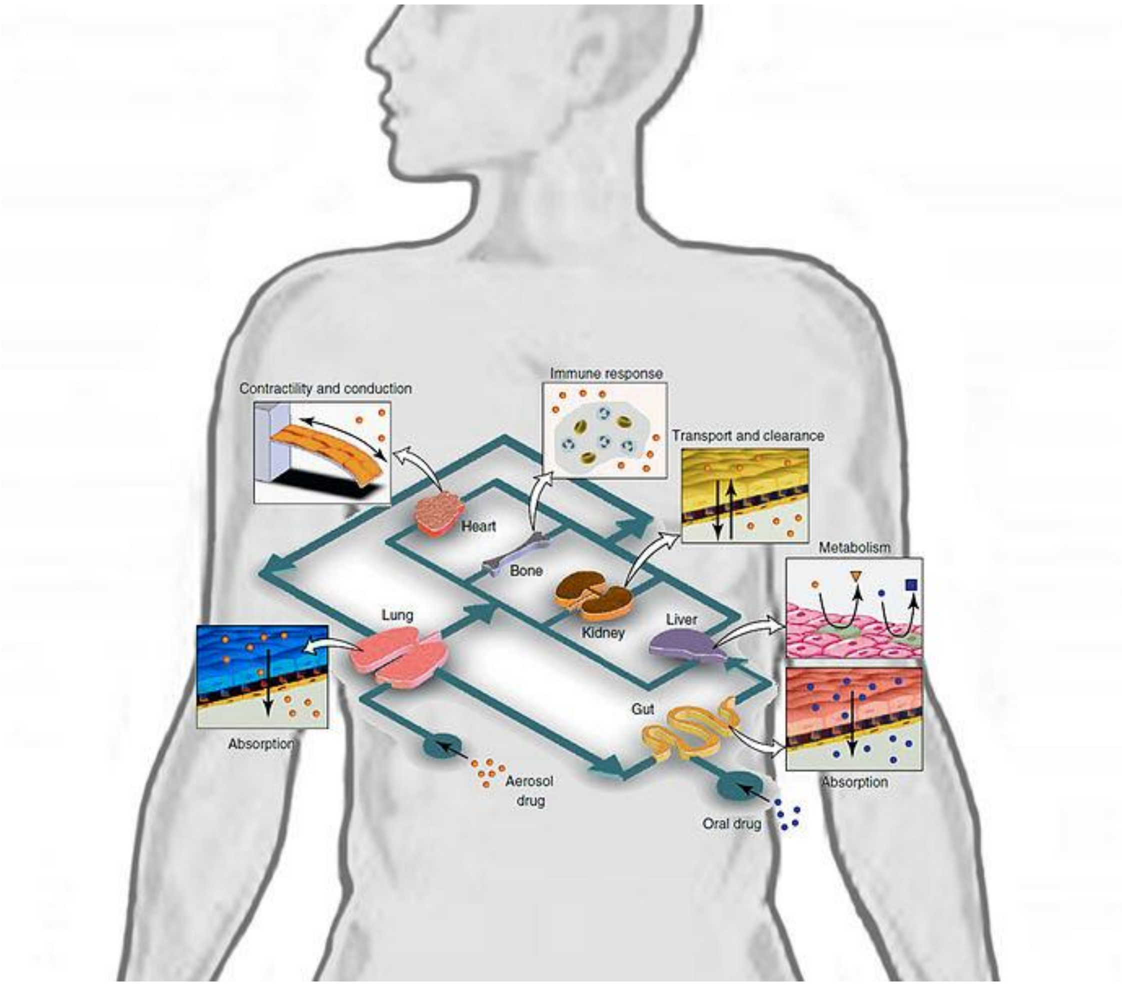

Figure 2: Conceptual Schematic of a Human-on-a-Chip [14]

Conclusion

Since fundamental components of bio-MEMS begins to reach their maturity, complex systems, providing considerable opportunities in health care applications and scientific research, slowly emerges. As such, this technology struggles with pioneering challenges, inherent to any new technology development (technological issues, biocompatibility, expensive research). Since their resolution is basically matter of time in painstaking trial and error process, considerable attention should be currently paid also to the ethical and security aspects of their future utilization (especially in neural stimulation and life vital devices), because develop-then-patch failures may prove quite disastrous in this case, which would consequently lead to widespread rejection of the technology itself.

On the other hand, certain systems utilizing this technology (human-on-chip) may solve some objectionable ethical issues associated with current practice of scientific and medical research (animal models replacement), while providing higher payoffs in their overall assessment (lowering costs, shortening project execution time, providing more accurate and informative data).

Deployment of diagnostic devices (μTAS), combined with corresponding actuator modules (e.g. precise drug delivery system), would allow invaluably quick diagnosis of certain health conditions and their consequent effective treatment on long-termly sustainable basis, or even saving the life in life threatening situations, where necessary medical care could not be deployed rapidly enough (implantable cardioverter defibrillator, therapeutic agent release in ship-wreck situation, remotely controlled rodent delivering life-saving medicine to casualty trapped inside collapsed building).

Even though we do not know precisely, when these technologies will become common practice, question remains to what extent they will be utilized and how this bio-technological revolution changes our everyday life, as well as humanity as a whole. While we can predict some possible implications, based on current technology development and the way it is being utilized, these still remain our assumptions, but whether they will actually take place, or completely different ones will do so, we cannot tell precisely today, just assume which possibilities are likely to happen – and realize, that only time let us know for sure…

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