BioMEMS in Medicine: Diagnostic and Therapeutic Systems

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Abstract:
The applications of bio-microelectromechanical systems (bioMEMS) in medicine can be classified as diagnostic or therapeutic systems. In the laboratory, microfluidic systems for cell analysis and characterization will contribute to the development of new diagnostic systems. Implantable biomedical microdevices can benefit many patients with neurological conditions or spinal cord injury, and flexible polymer-based microelectrode arrays will be a key technology in future neuroprosthetic devices. Advances in both lab-on-a-chip diagnostic systems and implantable biomedical microdevices have the potential to advance new therapies and solutions to improve our well-being.

1. Introduction
The realms of bioMEMS and bioelectronics include devices which use biological elements as integral elements: DNA computing or DNA microarrays [1], glucose sensors, and neuronal networks [2]. In contrast, biomedical microdevices can also be used to study biological systems: dielectrophoretic cell separation [3], high-throughput planar patch clamp [4], chip-based capillary electrophoresis [5], and other lab-on-a-chip drug development systems [6]. This paper surveys a few of the emerging technologies at EPFL for improved, inexpensive health care.

2. Diagnostic BioMEMS
In the laboratory, microfluidic systems for cell analysis and characterization will contribute to the development of new diagnostics and therapies. Automatic sample preparation, automatic cell analysis, shortened analysis time and reduced reagent volumes are only some of the advantages offered by lab-on-a-chip systems.

2.1 Planar Microelectrode Arrays
In order to examine the neural circuits in the brain, planar multi-electrode arrays (MEA) are used to study the network activity of excitable cells and record the responses of these cells to external stimuli [7]. MEAs permit simultaneous probing of many neurons in a controlled environment, either from cultured networks of dissociated neurons or acute tissue slices.

Evidently, networks of dissociated cultured neurons respond differently from cell networks in the intact brain. A tip-shaped array of protruding electrodes permits recording from living cells within a tissue slice which are often shielded by a layer of dead cells at the slice surface [8]. Results were obtained with chicken dissociated neuron cultures, rat spinal cord slice cultures, and neonatal rat cardiomyocyte cultures.

2.2 Electric Impedance Tomography
Because the electric impedance of a tissue depends on its cellular morphology, permeability, and organization, impedance tomography can be used to non-invasively characterize a tissue sample. Since healthy tissues and damaged or cancerous tissues can have different resistivities, microscale electric impedance tomography (EIT) can be used as a diagnostic tool to probe epithelial tissue for skin cancer screening.

![Electric Impedance Tomography](image_url)

Figure 1. Electric impedance tomography used to characterize a tissue sample with layers of different thicknesses and resistivities.

A microfabricated planar EIT system featuring electrodes at increasing spacing was used to investigate sub-millimeter-scale cellular structures. Bipolar measurements measure the resistivities of a stratified sample. This system allowed the characterization of an engineered hydrogel structure, representing epithelial and adipose tissue, discriminating between 3 layers of different conductivities on artificial tissue, and is currently used to monitor cell growth [9].
Dielectrophoretic cell manipulation has already been integrated into a device for lab-on-chip electroporation [12]. Cells are trapped in electric cages while bipolar pulses of various field strengths are applied to open pores in the plasma membrane for cell transfection. DEP forces have also been used for cell dipping [13], in which cells are deviated from a buffer stream into an adjacent, perfused in a parallel reactant stream, then finally back into the original buffer stream for washing.

These DEP-based building blocks will be the basic tools for focusing, concentrating, sorting, analyzing and cell handling in lab-on-a-chip devices.
2.4 Impedance Spectroscopy Flow Cytometer

The microfabricated impedance spectroscopy flow cytometer developed at EPFL permits rapid dielectric characterization of a cell population with a simple microfluidic channel [14-16]. As a non-invasive technique, dielectric spectroscopy is suitable for the characterization of living biological cells. Impedance measurements over a wide frequency range give information on cell size, membrane capacitance, and cytoplasm conductivity as a function of frequency [17, 18]. The amplitude, opacity, and phase information can be used to discriminate between different cell populations without the use of fluorescent, magnetic, or other cell markers.

Figure 5. Measurement data showing the sub-micron size discrimination between 4, 5, 6 µm beads. Red blood cells have a conductive interior and so are differentiated from polystyrene beads at high frequency (10 MHz).

Figure 6. Opacity measurement of red blood cells, ghosts, and fixed red blood cells. Fixed cells are clearly differentiated from normal red blood cells in the high frequency range of opacity.

Sub-micron size differentiation using calibrated polystyrene beads is easily achieved. Recent work shows differentiation among modified red blood cells and red blood cell ghosts [19]. Among other applications, detecting changes in cell conductivity and membrane capacitance may in the future allow the identification of cancerous cells. At the cellular level, dielectric properties have already been used to separate several different cancerous cell types from normal blood cells [20]. In the nearer term, this tool can be used to study the differentiation of stem cells or the transformation of somatic cells. Data from dielectric spectroscopy, in addition to immunological data, can help to more fully characterize these cells.

3. Therapeutic BioMEMS

Biomedical microdevices can benefit many patients with neural disorders. Among the most successful examples are cochlear implants [21] for the hearing impaired, cardiac defibrillators, and deep-brain stimulators for the treatment of Parkinsons disease and other movement disorders. Current efforts include drug delivery systems, visual prostheses [22, 23], sieve electrodes [24] and cuff electrodes [25] for nerve regeneration, and other neural interfaces [26].

Implantable neural probes for recording or stimulation have traditionally consisted of microwire arrays. More recently, the advent of microfabrication technology has led to the development of silicon-based arrays [27, 28], permitting the mass production of probes with precise electrode spacing. However, these stiff, brittle arrays may not have the long-term stability required for reliable implants.

3.1 Flexible Microelectrode Arrays

Flexible microelectrode arrays will be a key technology in future devices. Polymide thin films are deposited onto a carrier substrate, platinum electrodes are patterned using a deep reactive ion etch process, and the finished polymide structures are released from the carrier substrate in an anodic release process [29-32] in saline solution. This is a simple technology with many applications for retinal, intra-cortical, and intra-modiolar implants.

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Figure 7. Implantable, microfabricated flexible polymer-based microelectrode array.
3.2 Intraocular Pressure Sensor for Glaucoma Management

Today, applanation tonometry, the standard procedure for measuring intraocular pressure (IOP), is performed in the ophthalmologist’s office. It does not monitor variations over time. However, increased IOP and wide daily IOP variations indicate risk of glaucoma, and detailed information would be invaluable toward the clinical management of glaucoma.

Since changes in IOP are correlated to changes in cornea curvature, a MEMS strain gauge for the measurement of spherical deformation of the cornea due to intraocular pressure changes could provide continuous, minimally invasive monitoring over prolonged periods [33]. This strain gauge is based on the same flexible polyimide technology with embedded Pt-Ti structures. This polyimide device is then embedded in a soft contact lens.

Figure 9. The strain gauge measures the change in pressure on the eye with blinking (eyes are closed but the eyelids are pressed more firmly). Also evident is ocular pulsation due to the heart rate. This pulsation is the smallest signal ever measured in the eye and corresponds to 1.5 – 2 mmHg.

3.3 Neural Implant

One of the most pressing issues facing implantable electrode arrays today is the mechanical mismatch between the tissue and the probe, which is often made of silicon or another stiff and brittle material. With time, implanted electrodes may lose their functionality due to the glial scar that blocks signals from the cells. Since scarring is exacerbated by micromotion between the rigid electrode and the soft neural tissue, the development of more flexible probes is essential for improving their biocompatibility. Current intracortical recordings are also limited by the number of electrodes (wire bundles) that can be implanted into the cortex. The development of a reliable, microfabricated, multielectrode array for long-term use will provide neuroscientists with a tool of greater functionality. Current work is using a flexible multielectrode array to monitor changes in hippocampal theta rhythm by auditory stimulation.

Figure 10. Acute recordings from the mouse cortex and hippocampus during auditory stimulation using a 16-channel flexible microelectrode array.
4. Future Directions

Future bioMEMS diagnostic instruments will increase the efficiency and speed in detection and diagnosis of many diseases. Some key issues remaining are sample loading and fluidic interconnect to make truly point-of-care systems for underserved communities.

Further development of therapeutic bioMEMS will require improved material biocompatibility, including surface chemistry and mechanical properties. For reduced risk of infection and increased convenience, future implanted devices will have wireless links for data communication. In some applications, wireless power transfer may also obviate the need for battery replacement.

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References:


