Lecture Notes in Bioengineering

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BioMEMS

Biosensing Applications

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ISSN 2195-271X ISSN 2195-2728 (electronic)
Lecture Notes in Bioengineering
ISBN 978-981-15-6381-2 ISBN 978-981-15-6382-9 (eBook)
https://doi.org/10.1007/978-981-15-6382-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Over the past few decades, biological microelectro-mechanical systems (BioMEMS) have been commonly designed, fabricated, and used for a wide range of applications including cell studies, therapeutics, tissue engineering, drug delivery, implantable devices, and biosensors, among others. BioMEMS are portable, low-cost, rapid, and robust platforms designed to automate one or more analysis steps such as mixing, separation, sedimentation, etc. into one monolithic device. BioMEMS have proven to be excellent candidates for biosensing applications. Such devices act as miniaturized laboratory systems that can be used in remote and/or rural areas for detection of multiple analytes with minimal human involvement, which, in turn, makes the detection procedure of fatal diseases safer for laboratory technicians. This book is dedicated to the latest advancements of BioMEMS in biosensing applications. Different detection strategies including colorimetric, fluorescence, luminescence, bioluminescence, chemiluminescence, biochemiluminescence, and electrochemiluminescence are thoroughly reviewed in this book, and different types of BioMEMS designed and fabricated for the mentioned detection strategies are presented with recent examples. These BioMEMS devices include paper-based, microfluidics such as lab-on-chip (LOC), lab-on-compact-disk (LOCD) systems and interesting alternative techniques that offer new solutions. This book also provides an overview on the history of BioMEMS and the pioneered devices in the history of science which were designed and fabricated for different purposes.

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Acknowledgements The authors would like to acknowledge the financial and technical support of Writing Lab, TecLabs, Tecnologico de Monterrey, in the production of this work. The authors would also like to acknowledge the kind support of Dr. Aida Rodriquez-Garcia and Mrs. Niousha Mousavi in editing this work.

Contents

Abbreviations

2D	Two dimensional
3D	Three dimensional
ABTS	2,2′-Azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid)
ACh	Acetylcholine
AChE	Acetylcholinesterase
acpcPNA	Pyrrolidinyl peptide nucleic acid
ADCs	Analog-to-digital converters
AgNPs	Silver nanoparticles
Al	Aluminum
ALP	Alkaline phosphatase
AMPPD	3-(2′-Spiroadamantyl)-4-methoxy-4-(3″-phosphoryloxy) phenyl-1,2-dioxetane
Ann-V	Annexin V
anti-hCGα	Anti-human chorionic gonadotropin Gα
AP	Alkaline phosphatase
APTES	(3-Aminopropyl) tri-ethoxysilane
a-Si:H	Hydrogenated amorphous silicon
a-SiN_x	Amorphous silicon nitride
AST	Antimicrobial susceptibility testing
ATChI	Acetylthiocholine iodide
ATP	Adenosine 5′-triphosphate
ATP-BLA	ATP bioluminescence assay
AuNC	Gold nanoclusters
AuNPs	Gold nanoparticles
BioMEMS	Biological microelectro-mechanical systems
BL	Bioluminescence
BL-CL	Biochemiluminescence
BSA	Bovine serum albumin
BuChE	Butyrylcholinesterase
BuTChI	Butyrylthiocholine iodide

CAMPT	Camptothecin
CBM	Carbohydrate binding module
CCD	Charge-coupled device
CCGTSs	Chemiluminescence cloth-based glucose test sensors
CD	Compact disk
C-dots	Carbon dots
C-dots@NPG	Carbon dots dotted nanoporous gold
CL	Chemiluminescence
CMG	Water-soluble carboxymethylated β-1,3-glucan
CMOS	Complementary metal oxide semiconductor
CMVs	"Culture medium veins"
CNC	Computer numerical control
CRP	C-reactive protein
Cu	Copper
CVD	Chemical vapor deposition
C-μPAD	Chemically patterned μPAD
DC	Direct current
DDS	Drug delivery system
DED	Dry eye disease
DHBS	2-Hydroxy-3,5-dichlorobenzenesulfonic acid
DNA	Deoxyribonucleic acid
DNase	Deoxyribonuclease
DO	Dissolved oxygen
DRIE	Deep reaction ion etching
DSC	N,N'-disuccinimidyl carbonate
E. Coli	Escherichia coli
ECL	Electrochemiluminescence
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
e-ELISA	Electronics-based enzyme-linked immunosorbent assay
ELISA	Enzyme-linked immunosorbent assay
EMVs	Electromagnetic valves
EPOC	Extreme point of care
Exo	Exonuclease
FEP	Fluorinated ethylene propylene
FITC	Fluorescein isothiocyanate
FMN	Flavin mononucleotide
FRET	Förster resonance energy transfer
FTA	Fast technology analysis
GDNA	Guanine-rich DNA
GLU	Glucose
GOx	Glucose oxidase
GQD	Graphene quantum dots
GS	Gas chromatography
H_2O_2	Hydrogen peroxide
HbA1c	Blood glycated hemoglobin

HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRP	Horseradish peroxidase
HSL	Hue–saturation–lightness
IATP-BLA	Immunosorbent ATP-bioluminescence assay
icELISA	Indirect competitive enzyme-linked immunosorbent assay
IFNγ	Interferon gamma
IgG	Immunoglobulin G
IgY	Immunoglobulin Y
ISS	International Space Station
ITO	Indium tin oxide
KPC	*Klebsiella pneumoniae carbapenemase*
LAMP	Loop-mediated isothermal amplification
LED	Light-emitting diode
LFIA	Lateral flow immunoassay
LOC	Lab-on-chip
LOD	Limit of detection
LoPCB	Lab-on-a-printed circuit board
LPCVD	Low-pressure chemical vapor deposition
LSA	Long spacer arm
LSA-MPs	Long spacer arm-functionalized magnetic particles
MB	Molecular beacon
MDMHA	3,4-Ethylenedioxy-N-methylamphetamine
MEMS/MOEMS	Micro-(opto)-electromechanical systems
MERS	Middle East respiratory syndrome
MERS-CoV	Middle East respiratory syndrome coronavirus
miRNA	MicroRNA
MNC-EC	MNC-E. Coli
MNCs	Magnetic nanoparticle clusters
MNPs	Magnetic nanoparticles
MORP	Morpholinopyridine
MOTiF	Multi-organ-tissue-flow
MPA	3-Mercaptopropionic acid
MPs	Magnetic particles
mRNA	Messenger ribonucleic acid
NC	Nanocluster
NHS	N-hydroxysuccinimide
NP	Nanoparticle(s)
NPG	Nanoporous gold
O_2	Oxygen
OFSE	Oral fluid sampling equipment
OLED	Organic electroluminescent diode

OPD	Organic photodiode
OPs	Organophosphate pesticides
OTA	Ochratoxin A
PAD	Paper-based analytical devices
PBS	Phosphate buffer saline
PCB	Printed circuit boards
PCR	Polymerase chain reaction
PDMS	Polydimethylsiloxane
PECVD	Plasma-enhanced chemical vapor deposition
PEDOT	Poly(3,4-ethylenedioxythiopene)
PEG	Poly(ethylene glycol)
PEGDA	Polyethylene-glycol diacrylate
P-ELISAs	Paper-based enzyme-linked immunosorbent assays
PGMEA	Propylene glycol methyl ether acetate
PIF	Parity inner fails
PIP	P-iodophenol
PLSR	Partial least square regression
PMMA	Poly(methyl methacrylate)
POC	Point of care
POCT	Point-of-care testing
Poly(HEMA-co-AEMA)	Poly(2-hydroxyethyl methacrylate-co-2-aminoethyl methacrylate)
PP	Polypropylene
Ps	Phosphatidylserine
PS	Polystyrene
PSA	Pressure-sensitive adhesive
Pt	Platinum
PtOEP	2,3,7,8,12,13,17,18-Octaethyl-21H,23H-porphyrin, platinum (II)
PVC	Hydrophobic polyvinyl chloride
RCA	Rolling circle amplification
RhB	Rhodamine B
RhB-ITC	Rhodamine B isothiocyanate
RIE	Reactive ion etching
RNA	Ribonucleic acid
RPM	Revulsion per minute
RT-PCR	Reverse transcription PCR
SA-AP	Streptavidin–alkaline phosphatase
SDA	Strand displacement amplification
SiPMs	Silicon photomultipliers
SLA	Stereolithography
SmartBA	Total bile acid smartphone-based assay
SmartChol	Total cholesterol smartphone-based assay
SPTZ	3-(10'-Phenothiazinyl)propane-1-sulfonate
SSC	Saline sodium citrate

ssDNA	Single-stranded DNA
T1D	Type 1 diabetes
Tb	Tuberculosis
TC	Tetracycline
TC	Total cholesterol
$tcpO_2$	Transcutaneous O_2 pressure
TCS	Trichlorosilane
TEOS	Tetraethyl orthosilicate
TG	Triglyceride
TiO_2 NPs	Titanium dioxide nanoparticles
TIRCA	Toehold-initiated RCA
TiW	Titanium tungsten
TLC	Thin-layer chromatography
TMB	3,3',5,5'-Tetramethylbenzidine
TNFα	Tumor necrosis factor alpha
ULOC	Unibody-LOC
UTI	Urinary tract infection
UV	Ultraviolet
UV–vis	Ultraviolet–visible
WFP	Whatman filter paper
ZnO-NRs	Zinc oxide nanorods
μCAD	Cloth-based analytical devices
μPADs	Microfluidic paper analytical devices
μ-TAS	Micro-total analysis systems

Chapter 1
History of Bio-microelectromechanical Systems (BioMEMS)

Ricardo Garcia-Ramirez and Samira Hosseini

1.1 Introduction

MEMS are miniaturized devices that transduce signals in different domains using semiconductor manufacturing techniques to produce non-electrical elements (Council 1998). The acronym MEMS was coined in the United States before the start of the 1990s by Professor Roger Thomas Howe, along with other scientists, after microscale fabrication was established as a growing engineering field (Maluf and Williams 2004). The first conference regarding MEMS was held in Berlin in 1988 as part of the International Conference on Micro, Electro and Optomechanical Systems and Components (Madou 2011).

MEMS' potentials arose with microelectronics, as these complex devices became more sophisticated. Their materials and designs were enhanced in order to perform better on fixed tasks needed in the microelectronics industry (Madou 2011; Folch 2016; Saliterman 2006). As time and research advanced, biological applications were added to the domain of their use. Currently, the MEMS industry has several established milestones in the microfabrication technologies, such as micromolding, photolithography, 3D structure assembly, among others (Borenstein 2008). Since MEMS could also contain mechanical components including cantilevers or membranes, they are ideal for fulfilling sensing (pressure and flow sensors) and/or actuation (optical-beam handling) tasks (Council 1998).

Biomedical or Biological Micro-Electro-Mechanical Systems, more commonly referred to as BioMEMS, are defined as micro or nano-scaled devices or systems that are used for processing, delivering, manipulating, or analyzing biological and chemical entities for biological or biomedical applications (Bashir 2004). Even though its name suggests the incorporation of both electronic and mechanical elements, it should be acknowledged that these devices do not necessarily integrate all functions in

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S. Hosseini et al., *BioMEMS*, Lecture Notes in Bioengineering,
https://doi.org/10.1007/978-981-15-6382-9_1

every single device. Despite the fact that BioMEMS are a trend nowadays, the origin of micro systems used in life sciences, such as biology and/or neurology, are surprisingly old. Figure 1.1 shows a timeline with some of the most important BioMEMS milestones. Although many authors (Madou 2011; Folch 2016; Saliterman 2006) have reported the origins of BioMEMS in the late 1980s and early 1990s, preceding studies had already created BioMEMS technology without the use of such term. Table 1.1 demonstrates the first BioMEMS platforms in chronological order in great detail.

1.2 BioMEMS

1.2.1 Advantages of BioMEMS

BioMEMS offer various advantages over traditional methods that are worthwhile exploring, including a small device dimension and sample volume, portability, reliability in replication, high throughput performance, multifunctionality, possible automation, among others. The small device dimension provides obvious advantages as these devices possess a potential for miniaturization, whether *in-vivo* or *in-vitro*, including reduced manufacturing costs for devices as μTAS (micro-total-analysis systems) and LOC (lab-on-a-chip) devices. The smaller devices also benefit from the small sample size and reagents, in order to perform the same reaction that bulkier devices would need. The physical space they require and ease of portability is another advantage that BioMEMS have in contrast to their counterpart large pieces of lab equipment. Furthermore, BioMEMS devices provide multifunctionality that allows individual instruments to be integrated within one single device. This, in turn, facilitates automation, a feature that plays vital role in such devices. Fully integrated and automated devices can run the analysis with least human intervention. This is of great importance particularly when facing unknown or newly known dangerous illnesses. Considering the portability and the lightweight of such devices, they make great candidates for extreme point of care (EPOC) in remote and/or rural settings where there are no centralized laboratories. Equipment-free readouts, mass transfer of data, and/or readouts via smart phones and devices are the alternative analytical strategies linked to BioMEMS.

Nowadays, BioMEMS are one of the fastest growing fields in the world, because of the implications that it could create in multiple industries including the health sector, in particular in hospitals and healthcare facilities (Experts 2019). The current research regarding BioMEMS has increased at an accelerating rate. Since the first use of the term BioMEMS in the 1990s, there has been a constant increase in publications regarding this field. According to Clarivate Analytics the number of cites per year containing BioMEMS as a keyword has increased from less than 100 in the year 2000 to over 1600 in 2018. The global BioMEMS Market stood at 2.45 billion dollars in 2014 and predictions suggest it will grow above 25% by 2024, mostly due to the

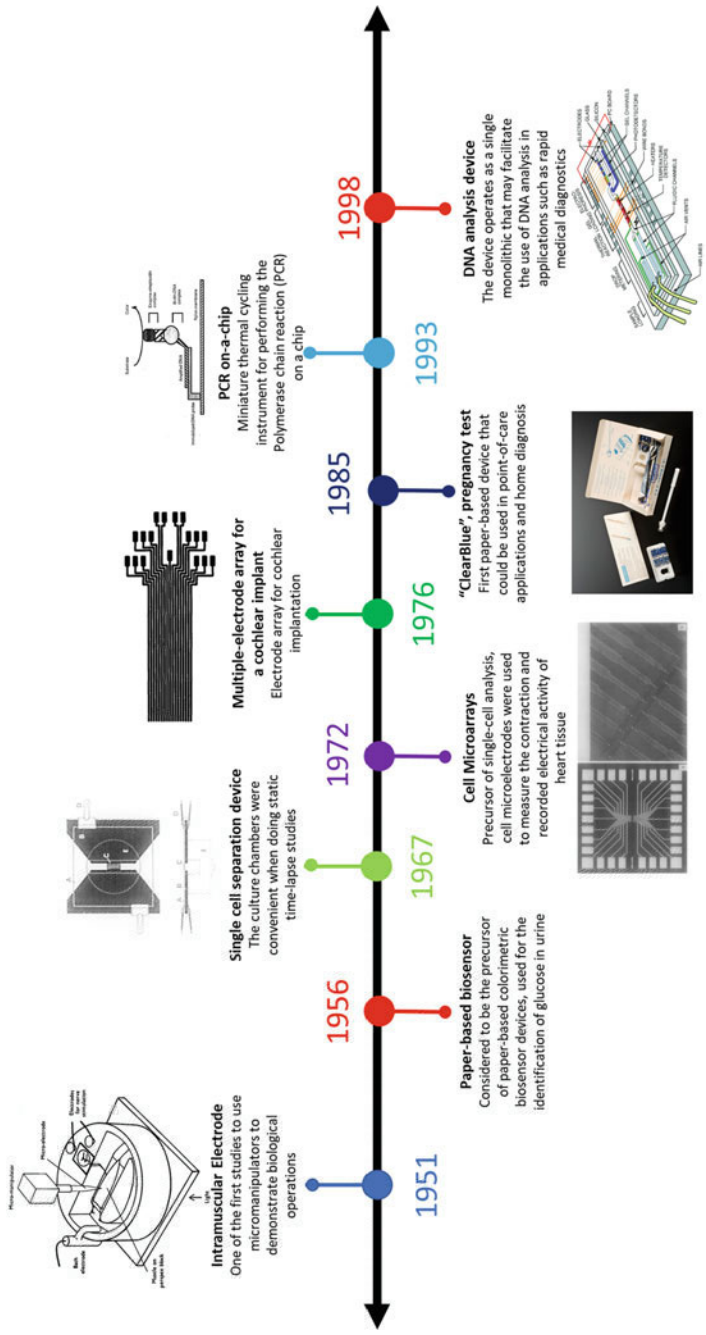

Fig. 1.1 Timeline of the History of BioMEMS including milestones in different areas of applications

Table 1.1 The first platforms in the history of BioMEMS

BioMEMS platform	Year	Scientist/authors/group	Company/institution	Country	Fabrication strategy	Application	Specific or remarks	References
Intramuscular microelectrode	1951	Paul Fatt and Bernhard Katz	University College London	England	Glass capillary tubing with external tip diameter of less than 0.5 μm were dipped into a beaker bridged to a calomel half-cell. Subsequently, the tips with electrodes were placed in a metal shield with a switch to connect the stimulator	Electrodes were used to measure the end-plate potential or local depolarization of muscle fibers	One of the first studies to use micromanipulators and microelectrodes to demonstrate biological operations	Fatt and Katz (1951)
Paper-based biosensor	1956	Alfred Free et al	Miles-Ames Research Laboratory Elkhart, Indiana	United States	A strip was impregnated with glucose oxidase, orthotolidine, and peroxidase	Simple test used for the identification of glucose in the urine based on a change in color	Considered to be the precursor of paper-based colorimetric biosensor devices	Free et al. (1956)
Single cell separation device	1967	Stephen Carter	Imperial Chemical Industries, Ltd.	England	A mask made by nickel electrodeposition was created, and palladium was deposited by evaporation onto a glass cover through the mask, building the desired culture chambers	The culture chambers allowed cells to attach to the surface of the device, and was proved useful for cell bonding, and single-cell studies	The culture chambers were convenient when doing static time-lapse studies, this is usually recorded as the first BioMEMS publication	Carter (1963)

(continued)

Table 1.1 (continued)

BioMEMS platform	Year	Scientist/authors/group	Company/institution	Country	Fabrication strategy	Application	Specific or remarks	References
Cell Microarrays	1972	C. A. Thomas Jr. et al	Harvard Medical School	United States	An acid-resistant, photosensitive polymer was used for coating glass. The platform was exposed to light via a photographic negative of each pattern. The platform was further developed and subsequently, a glass ring created within the insulated array using bees' wax in order to fix the position of the microelectrode tips	Cell microelectrode arrays were used to measure the contraction and recorded electrical activity of embryonic chick heart tissue	This device allowed multiple simultaneous recordings of electrical measurements in an array, the manufacturing process needs a special clean room facility and is costly	Thomas et al. (1972)
ISFET sensor for electrophysiology	1972	Piet Bergveld	Technische Hogeschool Twente	The Netherlands	Ion-sensitive field-effect transistor technology (ISFET) was manufactured with the help of the complementary metal–oxide–semiconductor (CMOS) technology and without any post processing steps	The sensor was intended to measure the ion activities in electrochemical and biological environments	The device measures ion activities without using a reference electrode, this limits the background noise and allows distinguishing series and parallel contribution of different ions	Bergveld (1972)

(continued)