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# CMOS Readout Chips for Implantable Multimodal Smart Biosensors

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Moustafa Nawito

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Dedicated to

My parents for their never-ending love, sacrifice and encouragement,

My wife for her tireless support and patience,

And to my dear daughters, you make every day a blessing.

## Abstract

Smart biomedical implantable devices, or simply smart implants, are playing a pivotal role in the development of new directions in medicine and health care. These modules are typically placed in a solid metal housing and consist of biocompatible electrodes which are in direct contact with biological tissue, in addition to a central electronic part which controls the electrodes, stores the data and communicates with units outside the body. With the use of such devices, novel diagnostic and therapeutic paradigms in personalized medicine can be developed, so as to find solutions to challenging illnesses, such as chronic and age related diseases.

One of the most important medical procedures which rely heavily on the use of smart implants is long-term monitoring of metabolic and neuronal activities, based on continuous detection of clinical biomarkers via direct tissue measurement. However, due to the fact that subcutaneous implanting is required, this application demands a very high degree of integration of the module, since large and bulky wires and batteries cannot be used. To fulfill these requirements, the entire implant must be miniaturized and, new techniques are needed to implement all functions on a much smaller scale.

Since the electronic part of the implant, and, specifically speaking, the Readout Integrated Circuit (ROIC), controls the diagnostic operations, any progress towards further miniaturization of the implant is based on this component. In order to achieve the sought after level of integration and simultaneously maintain the accuracy and quality of the measurements, readout chips that are energy efficient, programmable and most importantly multifunctional must be developed.

This work presents a family of ROICs used in an implantable electrochemical biosensors system. The chips are developed as Application Specific Integrated Circuits (ASICs) and are used as the central module for a multiparameter biomedical implant intended for long-term use. The analog frontend is designed to conduct fully integrated pH-value, Oxygen concentration and temperature measurements.

Furthermore, a novel technique for wide-range and digitally-driven impedance spectroscopy is presented in addition to a novel technique for fully integrated sinusoidal signal generation.

Throughout the development process of the chips, great emphasis is placed on optimizing the energy efficiency, programmability and flexibility of operation and accuracy, as well as on reducing the utilized area. The chips are designed with a digital core which is responsible for communication with external modules, control of the measurement sequence and data acquisition and management. The work also

presents circuit implementations optimized towards fabrication using ultra-thin chip technology.

All presented circuits, modules and ROIC versions are fabricated in a 0.5  $\mu\text{m}$  semi-custom CMOS technology. The different functions and features of the presented family of chips are successfully demonstrated via an array of experiments, ranging from basic electrical validation tests in the lab to actual electrochemical measurements using activated electrodes and chemical analytes.

## Zusammenfassung

Intelligente implantierbare biomedizinische Komponenten, auch bezeichnet als intelligente Implantate, spielen eine entscheidende Rolle bei der Entwicklung neuer Problemlösungen in Medizin und Gesundheitswesen. Diese Module sind typischerweise in einem starren Metallgehäuse untergebracht und bestehen aus biokompatiblen Elektroden, die in direktem Kontakt mit biologischem Gewebe sind, zusätzlich zu einem zentralen elektronischen Schaltungsteil, der die Elektroden steuert, die Daten speichert und mit Einheiten außerhalb des Körpers kommuniziert. Mit der Verwendung solcher Geräte können neue diagnostische und therapeutische Paradigmen in der personalisierten Medizin entwickelt werden, um Lösungen für chronische und altersbedingte Krankheiten zu finden.

Eines der wichtigsten medizinischen Verfahren, die sich stark auf den Einsatz intelligenter Implantate stützen, ist die Langzeitüberwachung von metabolischen und neuronalen Aktivitäten auf der Basis einer kontinuierlichen Detektion klinischer Biomarker. Aufgrund der Tatsache, dass eine subkutane Implantation benötigt wird, erfordert diese Anwendung jedoch einen sehr hohen Integrationsgrad des Implantats, da großvolumige und sperrige Verdrahtung und Batterien nicht verwendet werden können. Um diese Anforderungen zu erfüllen, muss das gesamte Implantat miniaturisiert werden. Es sind deshalb neue Techniken erforderlich, um alle Funktionen in einem wesentlich kleineren Maßstab umzusetzen.

Da der elektronische Teil des Implantats und besonders der Auslesechip die Messungen steuern, ist eine fortschreitende Miniaturisierung des Implantats vom Auslesechip abhängig. Um das angestrebte Integrationsniveau zu erreichen und gleichzeitig die Genauigkeit und Qualität der Messungen zu gewährleisten, müssen Chips, die energieeffizient, programmierbar und vor allem multifunktional sind, entwickelt werden.

Diese Arbeit präsentiert eine Familie von Auslesechips, die in einem implantierbaren elektrochemischen Biosensorsystem verwendet werden. Die Chips sind als anwendungsspezifische integrierte Schaltungen entwickelt und dienen als zentrales Modul für ein biomedizinisches Multiparameter-Implantat, das für den Langzeiteinsatz bestimmt ist. Das analoge Frontend ist ausgelegt, um vollständig integrierte pH-Wert-, Sauerstoffkonzentration- und Temperaturmessungen durchzuführen.

Weiterhin ist ein neuartiges Verfahren für breitbandige und digital angetriebene Impedanzspektroskopie neben einer neuartigen Technik zur vollintegrierten sinusförmigen Signalerzeugung vorgestellt.

Der gesamte Entwicklungsprozess der Chips verlief mit besonderer Achtsamkeit auf die Optimierung der Energieeffizienz, Programmierbarkeit und Flexibilität des Betriebs und der Genauigkeit sowie auf die Reduzierung der Chipgröße. Die Chips

sind mit einem digitalen Kern konzipiert, der für die Kommunikation mit externen Modulen, die Steuerung des Messablaufs und die Datenerfassung und -verwaltung zuständig ist. Die Arbeit zeigt auch Schaltungsimplementierungen, die auf die Fertigung mit ultradünner Chip-Technologie optimiert sind.

Alle dargestellten Schaltungen, Module und Chip-Versionen sind in einer „semi-custom“ CMOS-Technologie von 0,5  $\mu\text{m}$  hergestellt. Die verschiedenen Funktionen und Eigenschaften der vorgestellten Chips sind durch eine Reihe von Experimenten demonstriert, angefangen von grundlegenden elektrischen Validierungstests im Labor bis hin zu echten elektrochemischen Messungen mit aktivierten Elektroden und chemischen Analyten.



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## List of Abbreviations

ADC	Analog to Digital Converter
AMID	Active Medical Implant Devices
ASIC	Application Specific Integrated Circuit
BCB	Benzocyclobutene
CE	Counter Electrode
CRSAR	Charge Redistribution
CTAT	Complementary to Absolute Temperature
DAC	Digital to Analog Converter
DDFS	Direct Digital Frequency Synthesizer
DNL	Differential Nonlinearity
EIS	Electrochemical Impedance Spectroscopy
EIS	Electrochemical Impedance Spectroscopy
ESD	Electrostatic Discharge
FFT	Fast Fourier Transform
FOH	First Order Hold
FRA	Frequency Response Analysis
HSG	Hahn-Schickard-Gesellschaft
ICs	Integrated Circuits
IMS CHIPS	Institut für Mikroelektronik Stuttgart
INL	Integral Nonlinearity
IUPAC	International Union of Pure and Applied Chemistry
LSB	Least Significant Bit
LUT	Look Up Table
MCS	Multi Channel Systems GmbH
MDAC	Multiplying Digital to Analog Converter
MID	Molded Interconnect Device
MSB	Most Significant Bit
NLDAC	Nonlinear DAC

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NMI	Naturwissenschaftliches und Medizinisches Institut
NTC	Negative Temperature Coefficient
OSR	Over Sampling Ratio
PEEK	Polyether Ether Ketone
PNOISE	Periodic Noise
PSS	Periodic Steady State
QWS	Quarter Wave Symmetry
RCDAC	Resistive Chain DACs
RE	reference electrode
RFID	Radio-Frequency Identification
RMS	Root Mean Square
ROIC	Read-Out Integrated Circuit
S/H	Sample and Hold
SAR	Successive Approximation Register
SD	Synchronous Detection
SFDR	Spurious Free Dynamic Range
SNR	Signal to Noise Ratio
SPI	Serial Peripheral Interface
SS	Synchronous Sampling
SUT	System Under Test
THD	Total Harmonic Distortion
TIA	Transimpedance Instrumentation Amplifier
UGB	Unity Gain Bandwidth
WE-pH	Working Electrode
ZIF	Zero Insertion Force
ZOH	Zero Order Hold

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