

Handheld Total Chemical and Biological Analysis Systems

Ka-Meng Lei • Pui-In Mak
Man-Kay Law • Rui Paulo Martins

Handheld Total Chemical and Biological Analysis Systems

Bridging NMR, Digital Microfluidics,
and Semiconductors

 Springer

Ka-Meng Lei
State-Key Laboratory of Analog
and Mixed-Signal VLSI
University of Macau
Macau, China

Pui-In Mak
State-Key Laboratory of Analog
and Mixed-Signal VLSI and FST-ECE
University of Macau
Macau, China

Man-Kay Law
State-Key Laboratory of Analog
and Mixed-Signal VLSI
University of Macau
Macau, China

Rui Paulo Martins
State-Key Laboratory of Analog and
Mixed-Signal VLSI and FST-ECE
University of Macau
Macau, China

Instituto Superior Técnico Universidade de
Lisboa
Lisbon, Portugal

ISBN 978-3-319-67824-5 ISBN 978-3-319-67825-2 (eBook)
DOI 10.1007/978-3-319-67825-2

Library of Congress Control Number: 2017952196

© Springer International Publishing AG 2018

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

This book investigates the handheld total chemical and biological analysis system implemented with complementary metal–oxide–semiconductor (CMOS) based on nuclear magnetic resonance (NMR) technique. The global market for in vitro diagnosis is expanding in both developed and developing countries ascribed to the growing population and longer life expectancy. Conventional benchtop tools for disease diagnosis such as PCR (DNA amplification) are costly, bulky, and time-consuming and require trained technicians for operation, which confound their usages in the centralized laboratory.

CMOS is a promising alternative solution for rapid and quantitative diagnosis at a low cost. It overcomes the miniaturization of healthcare diagnostic tools, allowing low-cost and rapid detection of specific targets in tiny fluid samples. Among numerous possible solutions to POC sensing mechanism, NMR stands out as a trailblazing option since it is versatile and low-cost as it requires little processing on both the samples and interfacing hardware, i.e., the transducers. However, the reported NMR systems in literature encounter some issues such as bulky hardware, sample managements, and magnetic field shifting. So herein the materials presented in this book are focused on optimizing CMOS NMR platform for enhancing their applicability by bridging NMR, semiconductor chips, and microfluidic technique and promoting the application of NMR outside standard centralized laboratory with the aid of CMOS chips. The proposed miniaturized NMR systems in this project achieve (1) accurate and sensitive chemical/biological detection from microliter samples by the CMOS integrated circuits; (2) electronic-automated sample management scheme inside the space-limiting portable magnet, which significantly reduces the labors and turnaround time of the assay; and (3) robust operation against environmental

variation such as temperature or displacement of the sample. The platforms show promise as robust and portable diagnostic devices for a wide variety of biological analyses and screening applications.

We hope the readers will enjoy the contents of this book.

Macao, China
July 2017

Ka-Meng Lei
Pui-In Mak
Man-Kay Law
Rui Paulo Martins

Contents

1	Introduction	1
1.1	Overview.....	1
1.2	Global Necessities for In Vitro Diagnostic Tools.....	2
1.3	Nuclear Magnetic Resonance for In Vitro Diagnosis.....	4
1.4	Organization.....	6
	References.....	7
2	State-of-the-Art CMOS In Vitro Diagnostic Devices	11
2.1	Introduction.....	11
2.2	Transducing Mechanisms of CMOS IVD Tools.....	11
2.2.1	Electrical-Based.....	12
2.2.2	Optical-Based.....	18
2.2.3	Magnetic-Based.....	20
2.2.4	Mechanical-Based.....	21
2.2.5	NMR-Based.....	25
2.3	In Vitro Diagnostic Applications.....	26
2.3.1	Immunoassay.....	26
2.3.2	DNA Hybridization Assay.....	28
2.3.3	Cell/Bacteria Diagnosis.....	29
2.4	Discussions and Selection Guide.....	32
2.4.1	Integration Level.....	32
2.4.2	Labeling.....	32
2.4.3	Hardware Preparation.....	33
2.4.4	Operation.....	33
2.4.5	Specificity.....	34
2.4.6	Summary.....	34
	References.....	36

3	Electronic-Automated Micro-NMR Assay with DMF Device	41
3.1	Introduction	41
3.2	First Prototype: Primary Investigation on NMR–DMF	42
3.2.1	Discrete Electronics and Back-End Signal Processing	43
3.2.2	Magnet	44
3.2.3	RF Coils	44
3.2.4	DMF Device Fabrication and Actuation	46
3.2.5	Experimental Results	47
3.3	Second Prototype: CMOS Micro-NMR Platform with DMF	51
3.3.1	Design and Implementation of CMOS TRX	53
3.3.2	Portable Magnet and RF Coil Codesign	58
3.3.3	DMF Device and Its Control Circuit	60
3.3.4	Experimental Results	60
3.3.5	Discussion and Outlook	67
3.4	Summary	68
	References	69
4	One-Chip Micro-NMR Platform with B_0-Field Stabilization	73
4.1	Introduction	73
4.2	Platform Design	74
4.2.1	Micro-NMR Transceiver	75
4.2.2	Multifunctional Planar Coil	76
4.2.3	Hall Sensor, Readout Circuit, and Current Driver	76
4.3	Prototype and Experimental Results	82
4.3.1	Experimental Setup and Electrical Measurements	82
4.3.2	Biological/Chemical Measurements	84
4.3.3	Comparison and Discussion	86
4.4	Summary	88
	References	89
5	Conclusion and Outlook	91
5.1	Summary of Researches	91
5.2	Future Prospects	92
	References	92
	Appendix A: Modular NMR Electronic Components and Measurement	95
	Appendix B: DMF Device and Electronics	97
	Appendix C: Software and Hardware Interface of Micro-NMR Platform	99
	Index	101

List of Abbreviations

<i>1/f</i> noise	Flicker noise
AC	Alternating current
ADC	Analog-to-digital converter
AIDS	Acquired immune deficiency syndrome
B ₀ -field	Static magnetic field
B ₁ -field	Radio-frequency magnetic field
BJT	Bipolar junction transistor
BW	Bandwidth
CMOS	Complementary metal–oxide–semiconductor
CPMG	Carr–Purcell–Meiboom–Gill
DAC	Digital-to-analog converter
DC	Direct current
DMF	Digital microfluidic
DNA	Deoxyribonucleic acid
EC	Eddy current
EIS	Electrochemical impedance spectroscopy
ELISA	Enzyme-linked immunosorbent assay
EWOD	Electrowetting-on-dielectric
FoM	Figure of merit
FPGA	Field-programmable gate array
GBW	Gain–bandwidth product
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
hMAM	Human mammaglobin
IC	Integrated circuit
IDT	Interdigital transducer
IF	Intermediate frequency
IgG	Immunoglobulin G
IgY	Immunoglobulin Y
IIP3	Third-order intercept point
IRN	Input-referred noise

ISFET	Ion-sensitive field-effect transistor
ITO	Indium tin oxide
IVD	In vitro diagnostic
LNA	Low-noise amplifier
LO	Local oscillator
LOC	Lab-on-a-chip
LoD	Limit of detection
LPF	Low-pass filter
LSB	Least significant bit
MNP	Magnetic nanoparticle
MOSFET	Metal–oxide–semiconductor field-effect transistor
MP	Magnetic particle
MUX	Multiplexer
NMOS	N-channel MOSFET
NMR	Nuclear magnetic resonance
NW	Nanowire
PA	Power amplifier
PBS	Phosphate-buffered saline
PC	Personal computer
PCB	Printed circuit board
PLL	Phase-locked loop
PM	Phase margin
PMOS	P-channel MOSFET
PNIPAM	Poly(N-isopropylacrylamide)
PoC	Point of care
PoU	Point of use
PSS	Pulse sequence synthesizer
qPCR	Quantitative polymerase chain reaction
RBC	Red blood cell
RF	Radio-frequency
RX	Receiver
SAL	Supercritical angle luminescence
SAW	Surface acoustic wave
SNR	Signal-to-noise ratio
SPAD	Single-photon avalanche diode
TAT	Turnaround time
THD	Total harmonic distortion
TIA	Transimpedance amplifier
TRX	Transceiver
TX	Transmitter
UART	Universal asynchronous receiver/transmitter
VHS	Vertical Hall sensor
WHO	World Health Organization
XO	Crystal oscillator
β -LG	β -Lactoglobulin

List of Figures

Fig. 1.1	World population from 1950 to 2050, with a medium variant estimation from 2015. Data collected from the United Nations <i>World Population Prospects: The 2015 Revision</i> [14]. More developed countries: countries in Europe and Northern America, plus Australia/New Zealand and Japan. Less developed countries: countries in Africa, Asia (except Japan), Latin America, and the Caribbean plus Melanesia, Micronesia, and Polynesia	2
Fig. 1.2	The old age dependency ratio (<i>solid line</i>), which is defined as the ratio of population of 65+ years old to the population of 15–64 years old with medium variant estimation from 2015. The children dependency ratio (<i>dotted line</i>), which is defined as the ratio of population of 0–14 years old to the population of 15–64 years old, is also shown on the graph as reference. Data collected from the United Nations <i>World Population Prospects: The 2015 Revision</i> [14]. More developed countries: countries in Europe and Northern America plus Australia/New Zealand and Japan. Less developed countries: countries in Africa, Asia (except Japan), Latin America, and the Caribbean plus Melanesia, Micronesia, and Polynesia	3
Fig. 1.3	(a) Macroscopic view of the non-zero spin nuclei. With an external magnetic field B_0 applied to the nuclei, part of them will align with this magnetic field. (b) The effect of RF excitation on the nucleus under external magnetization. When excited by the RF magnetic field at f_L , the nuclei precess around the magnetization. After this excitation, the nuclei still resonate and return to the equilibrium, with this relaxation recorded and analyzed	4
Fig. 1.4	The state of the probe-functionalized MNPs. (a) Without the target, the MNPs stay monodisperse in the solution without any aggregation. (b) When the targets exist in the sample, the targets bind with the probe, and the MNPs aggregate to form micro-clusters.....	6

Fig. 2.1 Architecture and operation of *electrical-based* detection CMOS biosensor. An extra layer of noble and biocompatible metal such as gold is deposited on the original built-in metal layer. The capturing probe is then immobilized on the gold electrode to capture the target. Upon hybridization the electrical properties such as impedance or charge are sensed directly by the readout circuit 16

Fig. 2.2 Cell culturing and monitoring with CMOS capacitive sensing chip. (a) The photograph showing the overall chip with dual in-line package. A well encloses the cell culturing site, and the CMOS chip is at the center of the well. The polymer protects the bond wires of the chip. (b) Photomicrograph of the electrodes. Since the system measures only the capacitance of the single electrode, the built-in passivation layer such as silicon nitride and silicon dioxide can be preserved without further post-processing. This simplifies the hardware preparation steps for biosensing. (c) The experimental results for cancer cell MDA-MB-231 culturing. The capacitance at specific site increases due to the proliferation of the cancer cells ascribed to the increased number of cells, allowing real-time monitoring for the growth of the cancer cells (Reproduced with permission from [38]. Copyright 2008 Elsevier)..... 17

Fig. 2.3 Architecture and operation of *optical-based* detection CMOS biosensor. The capturing probe is immobilized on a solid substrate such as glass or the built-in passivation layer atop the CMOS chip. Then fluorescence-labeled or chemiluminescence-labeled target will bind with the probe, and other unbound biomolecules will be washed away. The CMOS photodetector, which is formed by the embedded PN-junction, transduces the optical signal to current for subsequent signal processing 18

Fig. 2.4 Lens-free cell/microparticle counting system with CMOS image sensor. (a) The overall platform of the digital cell counting device. (b) The micrograph of the microcavity array for cell trapping. The sample under analysis is put atop the microcavity array. Then the suspended cells/microparticles will be pulled toward and trapped in the cavities attributed to the negative pressure. This negative pressure is produced by peristaltic pump, which extracts the air inside the chamber. (c) Detection principle of the system. The light from the external UV light source will arrive at the CMOS image sensor through the unoccupied cavity, while the trapped cell on the cavity blocks the light from arriving at the CMOS image sensor. (d) The schematics of the expected CMOS image acquired from (c). Since the cell blocks the UV light from passing through the cavity, the pixels under those occupied cavity will report a darker region, while the pixels under the vacant

cavity will report a brighter result. Thus the number of cells on the microcavity array can be identified from the result of the CMOS image sensor (Reproduced with permission from [43]. Copyright 2014 Saeki et al.) 20

Fig. 2.5 Architecture and operation of *magnetic-based* detection CMOS biosensor. The capturing probe is immobilized on a solid substrate such as glass or the built-in passivation layer atop the CMOS chip. Then the sample labeled with MP will mix with the capturing probe. Matched target will be captured, and unbound objects will then be rinsed off. A magnetic transducer such as LC oscillator or Hall sensor will transduce the magnetism of the sample to electrical signals, which will be processed by the readout circuit subsequently 21

Fig. 2.6 The magnetic-based handheld diagnostic device for antigen and nucleic acid detection. **(a)** The overall diagnostic device. The CMOS chip can be easily connected with the PCB by a cartridge. **(b)** The disposable cartridge with the CMOS chip. The CMOS chip is attached to the cartridge with silver epoxy and connected with bond wires to the carrier leads. This arrangement enables a disposable, low-cost, and multiplexed assay and simplifies the sample handling module such as microfluidic to manage the sample to the sensing sites. **(c)** The CMOS chip. It has 48 on-chip sensing sites together with 16 reference sensors. Each coil together with its own capacitor forms an LC oscillator, which has an oscillating frequency inversely proportional to the square root of the inductance of the coil. The surface of the chip is bio-functionalized for probe immobilization. The sample with the MP is then applied to the surface of the chip, followed by a washing step to rinse the unbound molecules and MPs. The bound MPs increase the inductance of the coils. Thus by detecting the oscillation frequency, the concentration of the target at the specific site can be selectively evaluated. **(d)** The experimental results for DNA detection. The frequency shift of the oscillation frequency is commensurate with the concentration of the target. With the novel magnetic freezing scheme, a limit of detection of 100 pM DNA can be achieved (Reproduced with permission from [22]. Published by the RSC 2014)..... 22

Fig. 2.7 Architecture and operation of *mechanical-based* detection CMOS biosensor. **(a)** *Mechanical-based* detection with cantilever. A cantilever can be exploited to transduce the mass attached on it to electrical signals such as resistance. A gold layer is deposited on the cantilever for growing the capturing probe on it. In order to allow the cantilever to bend upon the biomolecule attached, the neighbor insulating dielectrics and the base of the cantilever are etched away. A piezoresistor can be adopted to transduce the bending force on the cantilever to resistance change, and the readout

circuit will detect this variation. **(b)** *Mechanical-based* detection with SAW transducer. A complete SAW transducer consists of three modules, input metal interdigital transducer (IDT), the piezoelectric delay line where the acoustic wave travels through, and the output metal IDT. The input IDT generates the SAW. Then the wave travels through the delay line to the output IDT, where the SAW is transduced back to the electrical signal. The bio-functionalized gold layer atop the delay line captures the entity under analysis. The increased mass here will affect the characteristics of the delay line, resulting in change of resonant frequency, amplitude, or phase shift on the SAW, which then can be detected on the output IDT 23

Fig. 2.8

A CMOS cantilever-based biosensor for DNA detection. **(a)** The operation procedures of the biosensor. After post-processing to implement the cantilever on the CMOS chip, the capturing DNA is then immobilized on the Au surface of the cantilever. Then the cantilever is immersed in the PBS buffer, and the sample of interest is injected around the cantilever to allow hybridization of DNA. After washing unbound biomolecule, the cantilever is left to dry. After all of the water molecules are evaporated, the matched target DNA will stay on the Au surface. Their masses incur bending of the cantilever, and an embedded piezoresistor implemented by N+ polysilicon is entailed to sense this bending and transduce it to variation of its own resistance, causing a frequency shift on the ring-type oscillator. **(b)** The SEM image of the cantilevers. In order to allow the cantilever bending freely in air, the surrounding materials such as the insulating dielectrics and underneath the p-substrate have to be etched away, creating a suspending cantilever. **(c)** Experimental results for the biosensor. The resistance variation of the polysilicon piezoresistor attributed to the bending of the cantilever incurs in a deviation of the oscillating frequency. After DNA sample injection, washing, and drying steps, the final steady-state frequency can be measured to selectively quantify the concentration of the target DNA inside the sample with limit of detection of 1 pM from hepatitis B virus (Reproduced with permission from [19]. Copyright 2013 IEEE) 24

Fig. 2.9

Architecture and operation of *NMR-based* detection CMOS biosensor. NMR focuses on the measurement of the NMR signals from the samples. First, the MNP functionalized with the capture probes reacts with the sample under analysis. Then the mixture will be put atop the spiral sensing coil to perform NMR experiment. The existence of target inside the sample incurs in MNPs aggregation; thus a larger micro-cluster will be formed, changing the spin-spin relaxation time of the NMR signal from the sample 25

Fig. 2.10 The one-chip CMOS NMR-based biosensor. (a) The prototype of the platform. The system consists of a portable permanent magnet for magnetizing the ¹H nuclei and the CMOS chip to excite the nuclei and receive the NMR signal from them. The samples are put directly on top of the CMOS chip without further post-processing. (b) The experimental results from the biological samples. Without the target the functionalized MNPs stay monodispersed, and the sample has a higher *T*₂. With the target hCG cancer marker inside the samples, the hCG antibody binds with the hCG cancer marker, and they together form the micro-cluster. Thus the *T*₂ of the sample decreased, and the concentration of the target can be identified from the NMR signal (Reproduced with permission from [28].

Copyright 2011 IEEE) 27

Fig. 2.11 Smart CMOS system-on-chip platform for rapid blood screening test of risk prediction. (a) The experimental procedure of the platform. Firstly, the blood under analysis is put atop the anodic aluminum oxide membrane. The biomarkers will be diffused to the mixing reservoir and separated from other blood cells (>1 μm). After the filtration, the filtered sample in the mixing reservoir together with the bio-functionalized magnetic bead will be pumped to the sensing site by the force from the electrolytic pumping. Upon capturing by the coated antibody at the surface of the CMOS chips, the target and the magnetic bead will be seized, while the unbound magnetic bead will be flushed away by the magnetic force from the on-chip coil. Thus the Hall sensor can sense the magnetic bead and identify the concentration of the targeted biomarker. (b) The photograph showing the electrolytic pumping and magnetic flushing. At first, the sample is on the right of the sensing reservoir. Then, voltage is applied to the electrolytic electrodes, and bubbles are formed consequently. The bubbles here induce gas force and pump the sample to the sensing reservoir. After the sample arrived at the sensing site, the immobilized antibodies capture the targets and the magnetic beads. Then the unbound magnetic beads will be flushed away by the on-chip coil. (c) The experimental result (TNF-alpha) of the immunoassay. The Hall sensor detects the target analyte from the magnetic beads on the sensing site. The system can detect 0.8 pg/mL–80 ng/mL of TNF-alpha and NT-proBNP from whole bloods (Reproduced with permission from [34]. Copyright 2015 IEEE) 28

Fig. 2.12 Integrated qPCR system on CMOS chip. (a) The CMOS chip and illustration of its functions. The chip has three main modules to enable on-chip qPCR. An electrowetting-on-dielectric device serves as an electronic-automated droplet management module to extract the target, PCR reagents, buffer, and intercalator dye

- from the reservoirs, respectively, and guides them to different electrodes for mixing and subsequent operations by applying voltage on corresponding electrodes. A thermal module, which includes a resistive heater and temperature sensor, regulates the temperature of the droplets to perform thermal cycling for PCR. SPAD is embodied on the CMOS chip to detect the fluorescent emission from the target DNA in real time for qPCR. **(b)** Experimental results of the qPCR. The fluorescent signal from the sample increases with the PCR cycle. The qPCR system achieves a linear relationship between the cycle threshold and logarithm of initial DNA concentration from 1 to 10,000 copies per 1.2 nL of droplet, resulting in a 40,000-fold of reduction on reagent consumption (Reproduced with permission from [24]. Copyright 2014 RSC publishing)..... 30
- Fig. 2.13** CMOS multimodal sensor array for cell-based assay. **(a)** Schematic of the multimodal cell-based assay platform. The entire platform consists of 3×3 sensor array, and each pixel consisted of a photodiode, a temperature sensor (shared within a pixel group), a voltage amplifier, and an impedance detector for multimodal study and monitoring of the cultured cell exposed to drug or pathogen stimulation. **(b)** The micrograph of the CMOS cellular sensor chip. The chip contains 9 pixel groups for individual cell-based assay, and each pixel group further contains 16 individual pixels. Each pixel is formed by a gold-plated electrode for action potential and impedance reading with a photodiode. **(c)** Real-time experimental results from the bioluminescence experiment at 2 pixels. The human ovarian cancer cell emits luminescence upon the addition of luciferin, enabling verification of cell viability. The photodiode captures this bioluminescence, and the readout circuit processes the signal for subsequent analysis (Reproduced with permission from [48]. Copyright 2015 IEEE) 31
- Fig. 2.14** A radar chart showing the conceptual requisites to perform the in vitro diagnosis on biomolecule targeting with different transducing mechanism..... 35
- Fig. 3.1** The overall schematic and operations of the NMR–DMF system. **(a)** The placement of the DMF device, magnet, RF coil, and PCB in 3D view; **(b)** schematic of the NMR electronics; **(c)** the filtered results from the PCB are captured by the oscilloscope for easier demonstration purpose and then analyzed in MATLAB; **(d)** the photograph of the DMF device and its structure; **(e)** the detection mechanism of the NMR–DMF system. The target-specific MNPs, which act as probes, are placed on the sensing site initially (in *purple*). The sample at other electrodes (in *cyan*) will be transported to the sensing site and mixed with the probe to perform NMR assay..... 42

Fig. 3.2	Timing diagram of the pulses, including the excitation CPMG pulse sequence delivered to the TX to excite the nuclei and the response from the nuclei, which is picked up by the coil.....	43
Fig. 3.3	(a) Geometry and limitation from the opening gap of the portable magnet. (b, c) The EM simulation of the magnetic field direction and strength from a spiral coil (with 14 turns) and a Butterfly-coil (with 7 turns on each spiral), respectively, with a flowing current of 1 A.....	45
Fig. 3.4	Ratio of EC loss generated by the seven-turn (each loop) Butterfly-coil to coil magnetic energy against the thickness of the ITO. The figure was plotted based on (3.2) with $f = 20$ MHz, $\rho = 1 \times 10^{-6} \Omega\text{m}$, and $A = 40 \text{ mm} \times 24 \text{ mm}$. The <i>dotted line</i> shows 0.5% level and corresponds to the ITO thickness of 80 nm.....	47
Fig. 3.5	Nutation curve of the seven-turn (each loop) Butterfly-coil. The normalized amplitude from different durations of RF excitation signals was recorded and fitted to the sinusoidal wave. The estimated $\pi/2$ -pulse width for the coil is 144 μs	49
Fig. 3.6	(a) Received NMR signal from water. Inset shows the received NMR signal. The echoes were bounded by the <i>gray-dotted</i> trend line. (b) T_2 of the samples <i>versus</i> concentration of CuSO_4 solution, and results were shown on the graph (■). The <i>trend lines</i> were drawn together with their equation and $1/T_2$ value, together with error percentages (defined as half of 95% confidence level/true value) marked on the graph with dot lines where the values were displayed on the right axis.....	50
Fig. 3.7	(a) Fabricated DMF device. For illustration, the electrodes are numbered 1–8; (b, c) operation of the DMF platform. The droplet was originally placed at electrode no. 1 (highlighted by the <i>circle</i>). By applying a signal on electrode no. 2 and then turning off electrode no. 1, the droplet moved to electrode no. 2. As such, the droplet can be transported to electrode no. 8, which is the NMR sensing site.....	51
Fig. 3.8	(a) Illustration of droplets mixing. The droplets at electrode no. 1 (samples) and no. 8 (probe) were driven to electrode no. 7 and mixed together. (b) The NMR assay results from the mixed droplets.....	52
Fig. 3.9	Portable electronic-automated micro-NMR system. It features a CMOS TRX and a PCB-based Butterfly-coil inside the magnet to transduce between magnetic and voltage signals. The analyte is placed inside a glass substrate DMF device atop the Butterfly-coil for sample management (only one electrode is shown for simplicity).....	52
Fig. 3.10	Three-phase operation of the micro-NMR system: setup, sample preparation, and analysis.....	53

Fig. 3.11	Block diagram of the micro-NMR TRX cooperated with the DMF device. It includes a CMOS micro-NMR TRX with a Butterfly-coil input, a DMF device, and DMF electronic. An electrode has the Butterfly-coil placed underneath for performing micro-NMR assays. An FPGA connected to a computer coordinates the hardware	54
Fig. 3.12	Pulse-sequence synthesizer. FPGA commands control the logic gates to master the start and duration of the excitation signals with different phases as well as the switching between TX and RX modes.....	55
Fig. 3.13	(a) Butterfly-coil-input LNA and its noise model. (b) Double-balance quadrature mixer with RF-sharing stage. (c) Source-follower-based tunable bandwidth LPF	56
Fig. 3.14	Simulation results of the mixer with LO = 20 MHz and input frequency = 20.002 MHz (i.e., IF = 2 kHz): (a) output against input for fundamental and third harmonic. (b) THD of the mixer at different input amplitudes	57
Fig. 3.15	(a) Simulated pole plot of the LPF. The sixth-order LPF implements a Butterworth filter (poles form a <i>semicircle</i>) with various cutoff frequencies obtained by changing only their bias currents. (b) Simulated THD of the LPF with an input frequency of 2 kHz and a cutoff frequency of 5 kHz for different input levels.....	58
Fig. 3.16	The micro-NMR pulse sequence. It includes the CPMG pulse, filter current control, and micro-NMR output signal where the dead time of the RX is shown	59
Fig. 3.17	Simulated SNR of the Butterfly-coil-input CMOS RX with different number of turns in the coils	60
Fig. 3.18	(a) Chip photo. (b) Measured performance summary of the micro-NMR TRX. The RX's IRN, gain, and BW can only be assessed by simulations as the RX input has been tied to the Butterfly-coil.....	61
Fig. 3.19	(a) Block diagram of the image-reject RX. (b) Measured RX output spectrum with an externally coupled magnetic field at 19.999 MHz and a LO of 20 MHz after image noise removal. (c) Cutoff frequency and settling time of the LPF versus the bias current. Working regions of the LPF at different modes are labeled	62
Fig. 3.20	Measured B_0 with and without calibration.....	63
Fig. 3.21	The system hardware of the micro-NMR system. It is linked with an FPGA (DE0-Nano) and a program implemented in C# which facilitates the system control, result collection, and displays.....	63
Fig. 3.22	The pulses counted on the electrodes covered by air and water, respectively. As the permittivity of water is substantially larger than air (80:1), the capacitance of the electrode covered by water is higher, causing lower pulses to be counted, and thus the system can detect if the electrode is vacant	64

Fig. 3.23 Operation of the micro-NMR system. **(a)** Initial position of the sample and its projected path. **(b)** Droplet moves to the adjacent electrode. **(c)** Final position (micro-NMR sensing site) of the droplet. **(d)** Measured micro-NMR signal from water droplet excited by CPMG pulse sequence with 256 echoes and 4 ms interval. The envelope is extracted and fitted to a mono-exponential function, as shown in the inset 65

Fig. 3.24 **(a)** The correlation of ΔT_2^{-1} (with reference to 0 mM of CuSO_4) with the concentration of CuSO_4 . The echoes amplitude for the case of CuSO_4 at 1 mM concentration is plotted above. One hundred twenty-eight echoes were collected for each single experiment. **(b)** The correlation of ΔT_2 (with reference to 0 μM of avidin) with the concentration of avidin. The echoes amplitude for the case of avidin at 0.2 μM concentration is plotted above. Sixty-four echoes are collected for each single experiment..... 66

Fig. 3.25 **(a)** Illustration of the motions of the droplets for multistep multi-sample handling. T_2 for the water sample: 256 ms; for avidin: 211 ms. **(b)** A Gantt chart of the operation of an individual droplet. The total time for the experiment is 2.2 min..... 67

Fig. 4.1 Conceptual diagram of the proposed micro-NMR platform for PoU applications. Different samples such as protein and DNA can be put directly atop the CMOS chip for assays. A portable magnet is entailed to magnetize the nuclei inside the samples 74

Fig. 4.2 System block diagram. The TX and RX transduce between magnetic and electrical signals with a thermal-controlled spiral coil. The B_0 -field sensor and calibrator automatically stabilize the bulk magnetization on the μL sample. No frequency synthesizer is required 75

Fig. 4.3 **(a)** Simulated 3D temperature distribution of the droplet at applied power of 8 mW in COMSOL Multiphysics®; **(b)** Simulated droplet average temperature at applied power from 0 to 20 mW..... 76

Fig. 4.4 The cross section of a single VHS element and its current path. **(a)** Without lateral magnetic field; **(b)** with lateral magnetic field B_0 77

Fig. 4.5 Proposed current-mode fourfolded VHS arranged in Wheatstone bridge to sense the lateral B_0 -field and its readout circuit (spinning circuitry is omitted for simplicity). The latter features a nominal B_0 -field compensator to offset the strong nominal B_0 -field (0.46 T) for better sensitivity (3.75 mT). The *green arrows* highlight the current paths of I_{Hall} . Inset shows the timing diagram for the switches and overall operations..... 78

Fig. 4.6 Illustration for the two-phase spinning technique on the VHS. The bias direction (U_1 and U_3) together with the output terminals (U_2 and U_4) of the VHS is swapped periodically to eliminate the $1/f$ noise and offset of the elements..... 78

Fig. 4.7 Simulated frequency response of the TIA with various T_{INT} 79

Fig. 4.8	Simulated channel resistance (R_{DS}) and parasitic capacitance (C_S+C_D) of the MOS versus channel width	80
Fig. 4.9	Simulated output waveforms of the integrator. Without the nominal B_0 -field compensator, the integrator is saturated due to the large current induced by the nominal B_0 -field before it accumulates an adequate voltage difference. Whereas with the compensator, the nominal B_0 -field can be compensated; thus, the integration time can be prolonged to produce sufficient voltage differences at the output	81
Fig. 4.10	(a) Chip photo of the fabricated chip in 0.18- μ m CMOS. (b) Prototype of the micro-NMR platform with B_0 -field stabilization and lab-on-a-chip feasibility for multi-type biological/chemical assays, including (1) permanent magnet, (2) CMOS micro-NMR chip (inside magnet), (3) PCB, (4) FPGA, and (5) current driver. (c) Experimental setup. A program developed in C# is entailed for hardware control and visualizing the experimental results. The platform is powered by two batteries for portability	82
Fig. 4.11	Timing diagram of the B_0 -field calibration and its frequency-domain illustration	83
Fig. 4.12	(a) Measured hall sensor response; (b) B_0 -field with and without calibration. Actual B_0 -field is the sum of the B_0 -fields from the permanent magnet and the auxiliary coil driven by the current driver	84
Fig. 4.13	(a) Measured power consumption and FoM of the XO at different supply voltages. (b) Measured phase noise of the XO ($V_{DD} = 0.9$ V, $f = 78.5$ MHz). Compared with the LO generated from signal generator (Agilent 3350A), the XO shows a much better phase noise at low power	84
Fig. 4.14	Experimental results from biological samples. (a) Target quantification from human IgG as target and chicken IgY as control. (b) Target quantification from <i>Enterococcus faecalis</i> -derived DNA together with single-base mismatch DNA	85
Fig. 4.15	Experimental results from biological/chemical samples. (a) Protein (β -LG) state detection with different heating temperature. (b) Polymer (PNIPAM) dynamics with the solvent during heating from the on-chip heater	86
Fig. A.1	Measured gain of the NMR RX	96
Fig. A.2	Measured output spectrum of the RX with a 100-nV, 20-MHz sinusoidal input	96
Fig. B.1	Visualized waveform applied to the electrode before and after the droplet arrives at the electrode	98
Fig. C.1	The communication between the PC and the FPGA board to drive the micro-NMR relaxometer. It is done by adopting the TTL-232R_ PCB module to interfacing between the PC and FPGA board, which mastered the hardware of the micro-NMR relaxometer	100

List of Tables

Table 2.1	Recent CMOS-based DNA-related biosensors.....	13
Table 2.2	Recent CMOS-based protein-related biosensors.....	14
Table 2.3	Recent CMOS-based cell-related biosensors	15
Table 3.1	Summary of the measured and simulated coil parameters at 20 MHz.....	48
Table 3.2	Simulated noise summary of the LNA	56
Table 3.3	Comparison with the existing CMOS-based NMR system.....	68
Table 4.1	Summary and benchmark with other CMOS-based PoU systems	87
Table 4.2	Benchmark with previous CMOS NMR systems.....	88