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An Intelligent Digital Microfluidic System with Fuzzy-Enhanced Feedback for Multi-Droplet Manipulation

Jie Gao, Xianming Liu, Tianlan Chen, Pui-In Mak, Yuguang Du, Mang-I Vai, Bingcheng Lin, and Rui P. Martins

FEATURES

Control-engaged droplet manageability
Profiling ability of different droplet's hydrodynamics
Fuzzy-enhanced control saving 21% charging time
Expert manipulability of multi-droplet routings

DESCRIPTION

The electrowetting-on-dielectric (EWOD) behavior of microdroplets, under variable-charged surface electrodes, has inspired the development of digital microfluidic (DMF) systems for large-scale micro-reactors, which have underpinned a wide variety of chemical or biological applications in tiny droplet volumes e.g., molecular probe synthesis, proteomics, immunoassays, enzyme assays, clinical diagnostics, DNA sample processing and cell-based assays.

This work is an intelligent DMF technology to address the complexity of droplet hydrodynamics on a digital microfluidic (DMF) system. A wide variety of control-engaged droplet manageability is proposed and demonstrated through the operation of our modular DMF prototype, which comprises: (i) rigid profiling ability of different droplet's hydrodynamics under a real-time trajectory track of droplet-derived capacitance, permitting accurate and autonomous multi-droplet positioning without visual setup and heavy image signal processing; (ii) fuzzy-enhanced controllability saving up to 21% charging time when compared with the classical approach, enhancing the throughput, fidelity and lifetime of the DMF chip, while identifying and renouncing those weakened electrodes deteriorated over time, and (iii) expert manipulability of multi-droplet routings under counter-measure decisions in real time, preventing droplet-to-droplet or task-to-task interference. Altogether, this work exhibits the first modular DMF system with built-in electronic-control software-defined intelligence to enhance the fidelity and reliability of each droplet operation, allowing future manufacturability of a wide range of life science analyses and combinatorial chemical screening applications.

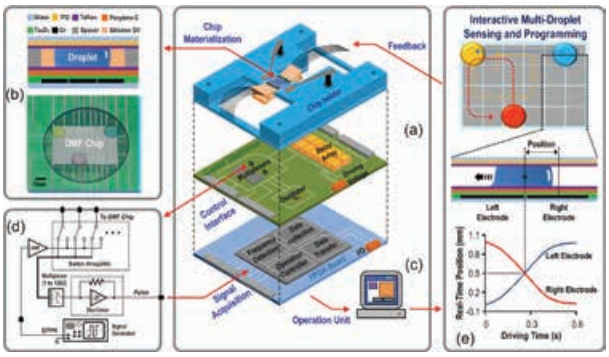

Fig. 1. Scheme of Kth stage of the proposed binary-search ADC.

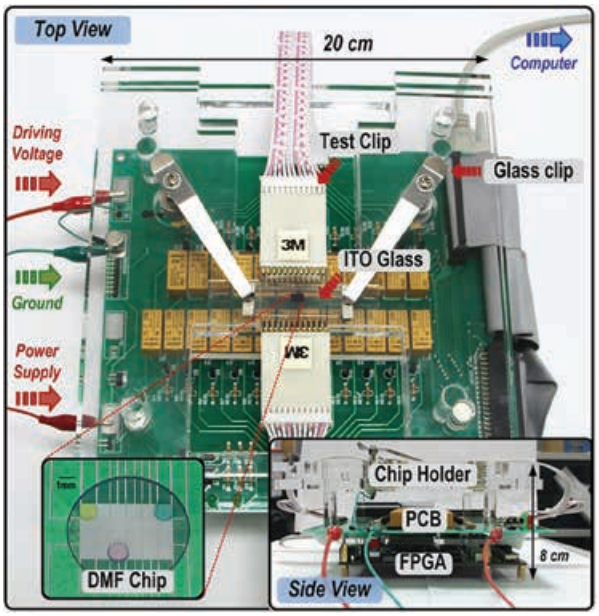

Fig. 2. Chip Photograph.

Publication(s):

[1] J. Gao*, X. Liu, T. Chen*, P.-I. Mak*, Y. Du, M.-I Vai*, B. Lin and R. P. Martins*, "An Intelligent Digital Microfluidic System with Fuzzy-Enhanced Feedback for Multi-Droplet Manipulation," Lab on a Chip, 2013, 13, 443-451.

* Contributors with University of Macau

Sponsorship:

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Construction of a Microfluidic Chip, Using Dried-Down Reagents, for LATE-PCR Amplification and Detection of Single-Stranded DNA

Yanwei Jia, Pui-In Mak, Conner Massey, Rui P. Martins, and Lawrence J. Wangh

FEATURES

Microfluidic system
On-chip LATE-PCR
Single copy DNA detection
Multiplex PCR on-chip
Dried-down PCR reagents on-chip
Easy storage and transportation

DESCRIPTION

LATE-PCR is an advanced form of non-symmetric PCR that efficiently generates single-stranded DNA which can readily be characterized at the end of amplification by hybridization to low-temperature fluorescent probes. We demonstrate here for the first time that monoplex and duplex LATE-PCR amplification and probe target hybridization can be carried out in double layered PDMS microfluidics chips containing dried reagents.

Addition of a set of reagents during dry down overcomes the common problem of single-stranded oligonucleotide binding to PDMS. These proof-of-principle results open the way to construction of inexpensive point-of-care devices that take full advantage of the analytical power of assays built using LATE-PCR and low-temperature probes.

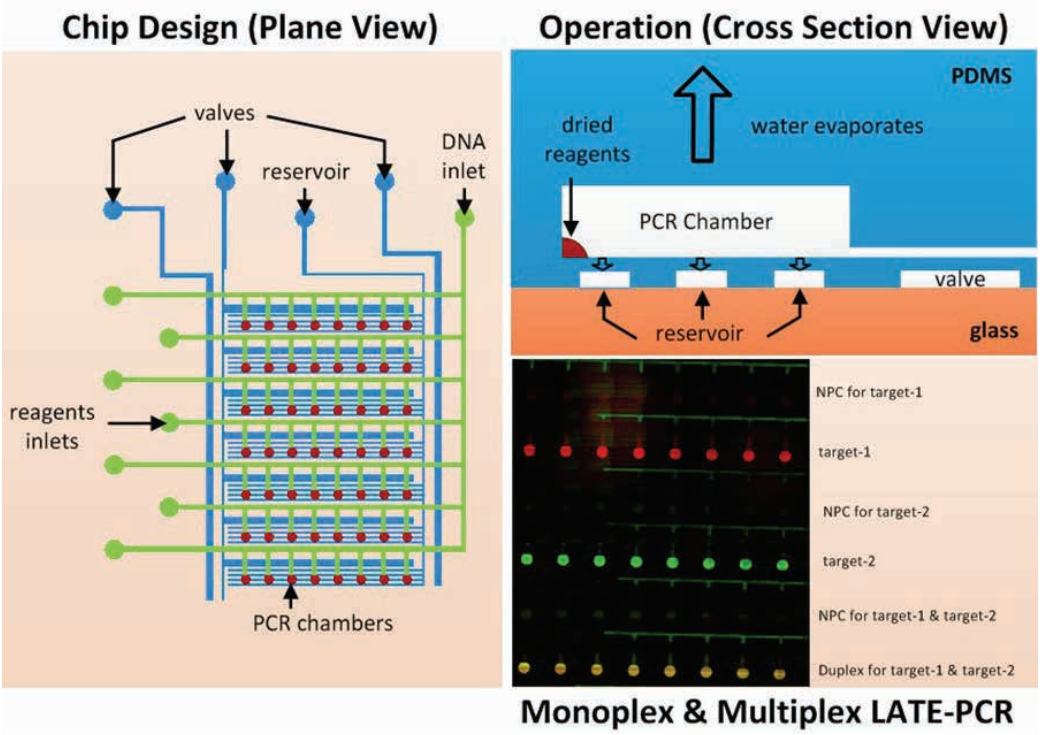

Fig. 1. preloading all of the reagents required for on-chip LATE-PCR amplification and detection of monoplex and multiplex single-stranded DNA products.

Publication(s):

[1] Y. W. Jia*, P. I. Mak*, C. Massey, R. P. Martins* and L. J. Wangh, "Construction of a Microfluidic Chip for LATE-PCR Amplification and Detection of Single-Stranded DNA using Dried-Down Reagents," Lab on a Chip, 13, 4635-4641, 2013.

* Affiliated with University of Macau

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

Natural Discharge After Pulse and Cooperative Electrodes to Enhance Droplet Velocity in Digital Microfluidics

Tianlan Chen, Cheng Dong, Jie Gao, Yanwei Jia, Pui-In Mak, Mang-I Vai, and Rui P. Martins

FEATURES

Digital microfluidic system
Natural discharge after pulse
Cooperative electrodes charging
Droplet movement dynamics
Droplet actuation signal investigation

DESCRIPTION

Digital Microfluidics (DMF) is a promising technology for biological/chemical micro-reactions due to its distinct droplet manageability via electronic automation, but the limited velocity of droplet transportation has hindered DMF from utilization in high throughput applications.

In this paper, by adaptively fitting the actuation voltages to the dynamic motions of droplet movement under real-time feedback monitoring, two control-engaged electrode-driving techniques: Natural Discharge after Pulse (NDAP) and Cooperative Electrodes (CE) are proposed. They together lead to, for the first time, enhanced droplet velocity with lower root mean square voltage value.

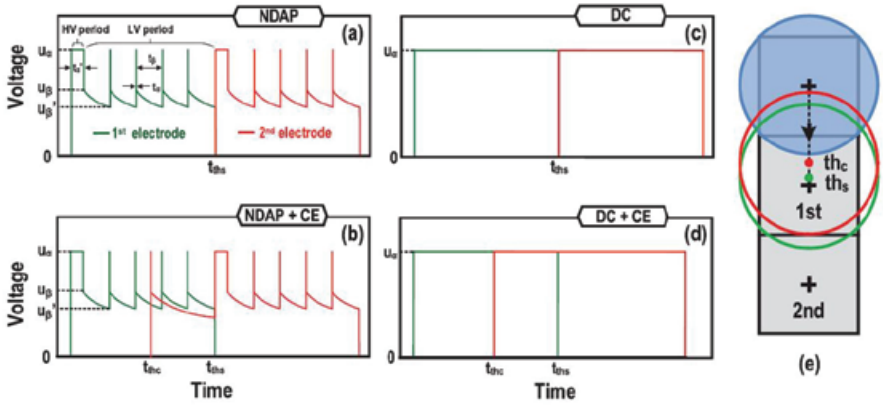

Fig. 1. Sketches of four possible electrode-driving schemes for droplet movements over two electrodes: (a)Natural Discharge after Pulse (NDAP): The high-voltage (HV) period lasts shorter, while the low-voltage (LV) under natural discharge lasts longer with short pulse recharging periodically. (b) DC signal. (c) NDAP with cooperative electrodes (CE) overlaps the charging time of neighboring electrodes. (d) DC plus CE driving. (e) Droplet moving toward two target electrodes and location of the two thresholds on the first target electrode.

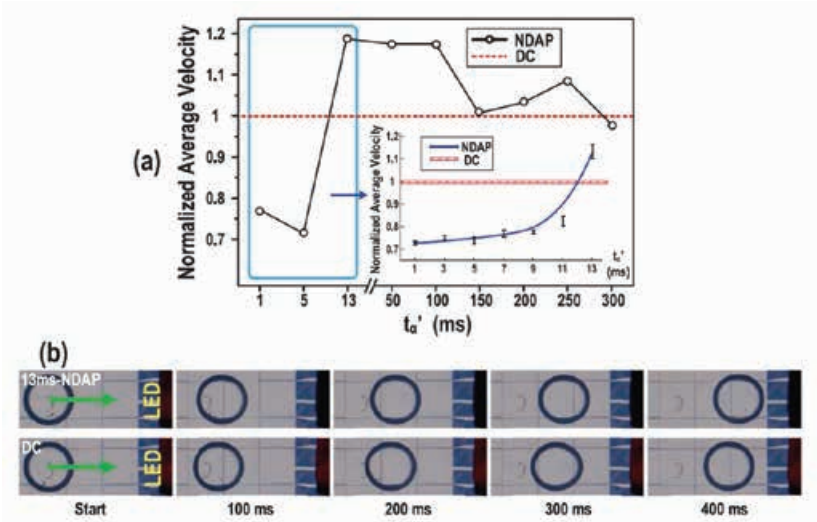

Fig. 2. (a) Normalized average velocity of a droplet under NDAP signals with different t_a and DC. Inserted curve shows the droplet velocities with t_a < 13 ms. The data were normalized at the average velocity under DC. (b) Video frames of a droplet actuated by NDAP and DC crossing 2 electrodes.

Publication(s):

[1] T. L. Chen, C. Dong, J. Gao, Y. W. Jia, P. I. Mak, M. I., Vai and R. P. Martins, "Natural discharge after pulse and cooperative electrodes to enhance droplet velocity in digital microfluidic," AIP Advances, 4, 047129, 2014.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

Adhesion Promoter for a Multi-Dielectric-Layer on a Digital Microfluidic Chip

Jie Gao, Tianlan Chen, Cheng Dong, Yanwei Jia, Pui-In Mak, Mang-I. Vai, and Rui P. Martins

FEATURES

Digital microfluidic system
Multi-dielectric layer
Adhesion promoter
Low droplet actuation voltage, 5 V

DESCRIPTION

A silane-based adhesion promoter suitable for a multi-di-electric-layer coating on a digital microfluidic chip is reported. It measures >100 improvement in chip lifetime via transforming the bonding of the dielectric layers (Ta2O5 and Parylene C) from nonspecific to chemical.

The refined chip-fabrication protocol also allows low EWOD actuation voltages down to 5 V. Put some general descriptions here. Please keep in mind that the main targets of this AMSV research report is the researchers and engineers in our field.

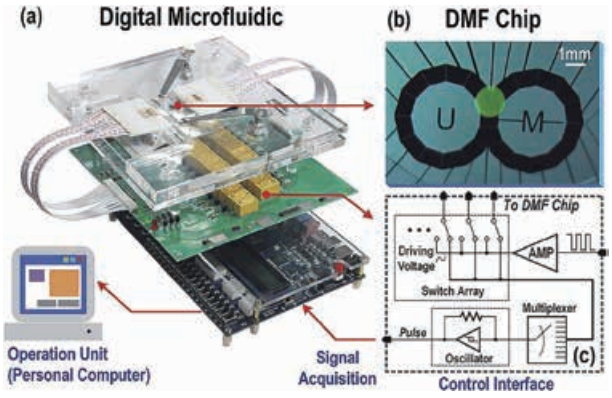

Fig. 1. Setup of the control-engaged DMF system.

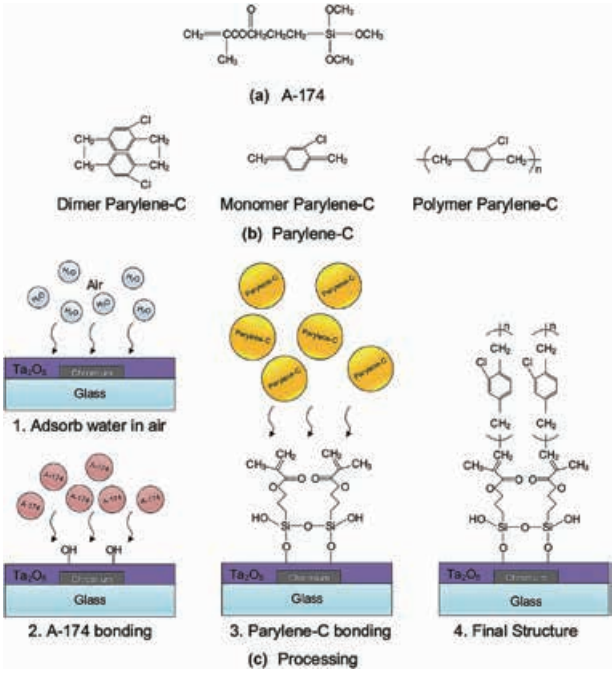

Fig. 2. Schematics of A-174 promoting adhesion between Ta2O5 and Parylene C.

Publication(s):

[1] J. Gao, T. L. Chen, C. Dong, Y. W. Jia, P. I. Mak, M. I. Vai, and R. P. Martins, "Adhesion Promoter for Multi-dielectric-layer on digital microfluidic chip," RSC Advances, 5, 48626-48630, 2015.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

On the Droplet Vvelocity and Electrode Lifetime of Digital Microfluidics: Voltage Actuation Techniques and Comparison

Cheng Dong, Tianlan Chen, Jie Gao, Yanwei Jia, Pui-In Mak, Mang-I Vai, and Rui P. Martins

FEATURES

Digital microfluidic system
Improved droplet transportation velocity
Elongated electrode lifetime
Natural discharge after pulse
Actuation signal comparison

DESCRIPTION

The distinct manageability of digital microfluidics (DMF) has rendered it a promising platform for building large-scale micro-reactors on a single chip for closed-loop automation. However, the limited velocity of the droplet transportation has hindered DMF from being utilized in high-throughput applications. This work investigates a control-engaged droplet actuation technique involving regular electronic hardware and computer-based software to simultaneously raise the velocity of the droplet transportation and elongate the electrode lifetime by lowering the root-mean-square value of the actuation voltage. The technique is based on a series of direct current (DC) pulses and multi-cycles of natural discharge coordinated with the droplet dynamic motions, facilitating realtime droplet position sensing.

We found that the proposed technique was superior to both DC and AC in terms of the velocity. As to the electrode lifetime, all showed excellent performance under normal dielectric coating conditions, while AC (alternating current) performed the best under critical conditions. Altogether, this work exhibits a control-engaged electrode-driving scheme with a higher velocity and a longer lifetime compared with traditional DC actuation and for the first time provides a fundamental comparison among the techniques engaging different actuation signals.

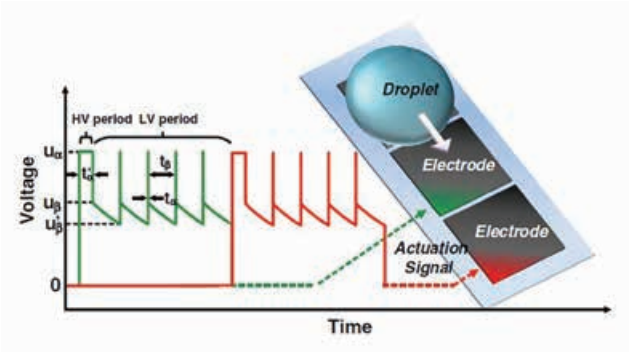

Fig. 1. Profiles of the electrode-driving signal, Natural Discharge after Pulse (NDAP), for a droplet moving across two electrodes. The high-voltage uα (HV) period lasts a period of t′. The low-voltage (LV) period includes multi-cycles of natural discharges (tβ) and DCpulse (tα). uβ is the instantly decreased voltage when disconnecting an electrode. u′ is the lowest voltage to maintain the movement of a droplet.

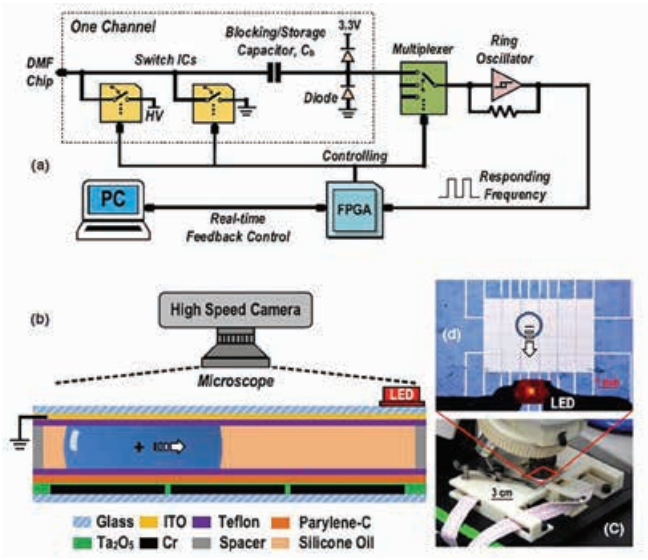

Fig. 2. Experimental setup for measuring the droplet dynamics under different electrode-driving signals.

Publication(s):

[1] C. Dong, T. L. Chen, J. Gao. Y. W. Jia. P. I. Mak, M. I. Vai and R. P. Martins, "On the droplet velocity and electrode lifetime of digital microfluidics: voltage actuation techniques and comparison," Microfluidics and Nanofluidics, 18, 673-683, 2015.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

Sub-7-Second Genotyping of Single-Nucleotide Polymorphism by High-Resolution Melting Curve Analysis on a Thermal Digital Microfluidic Device

Tianlan Chen, Yanwei Jia, Cheng Dong, Jie Gao, Pui-In Mak, Rui P. Martins

FEATURES

Digital microfluidic system
Ultrafast DNA melting curve analysis, 7 second
High resolution, single nucleotide discrimination

DESCRIPTION

We developed a thermal digital microfluidic (T-DMF) device enabling ultrafast DNA melting curve analysis (MCA). Within 7 seconds, the T-DMF device succeeds in differentiating a melting point difference down to 1.6 °C with a variation of 0.3 °C in a tiny droplet sample (1.2 μL), which represents 300 times faster, and 20 times less sample spending, than the standard MCA (35 minutes, 25 μL) run in a commercial qPCR machine. Such a performance makes it possible for a rapid discrimination of single nucleotide mutation, relevant to prompt clinical decision-making. Also, aided by electronic intelligent control, the TDMF device facilitates sample handling and pipelining in an automatic serial manner.

An optimized oval-shaped thermal electrode is introduced to achieve high thermal uniformity. A device-sealing technique averts sample contamination and permits uninterrupted chemical/biological reactions. Simple fabrication using a single chromium layer fulfills both the thermal and typical transport electrodes. Capable of thermally-modulating DNA samples with ultrafast MCA, this T-DMF device has the potential for a wide variety of life science analyses, especially for disease diagnosis and prognosis.

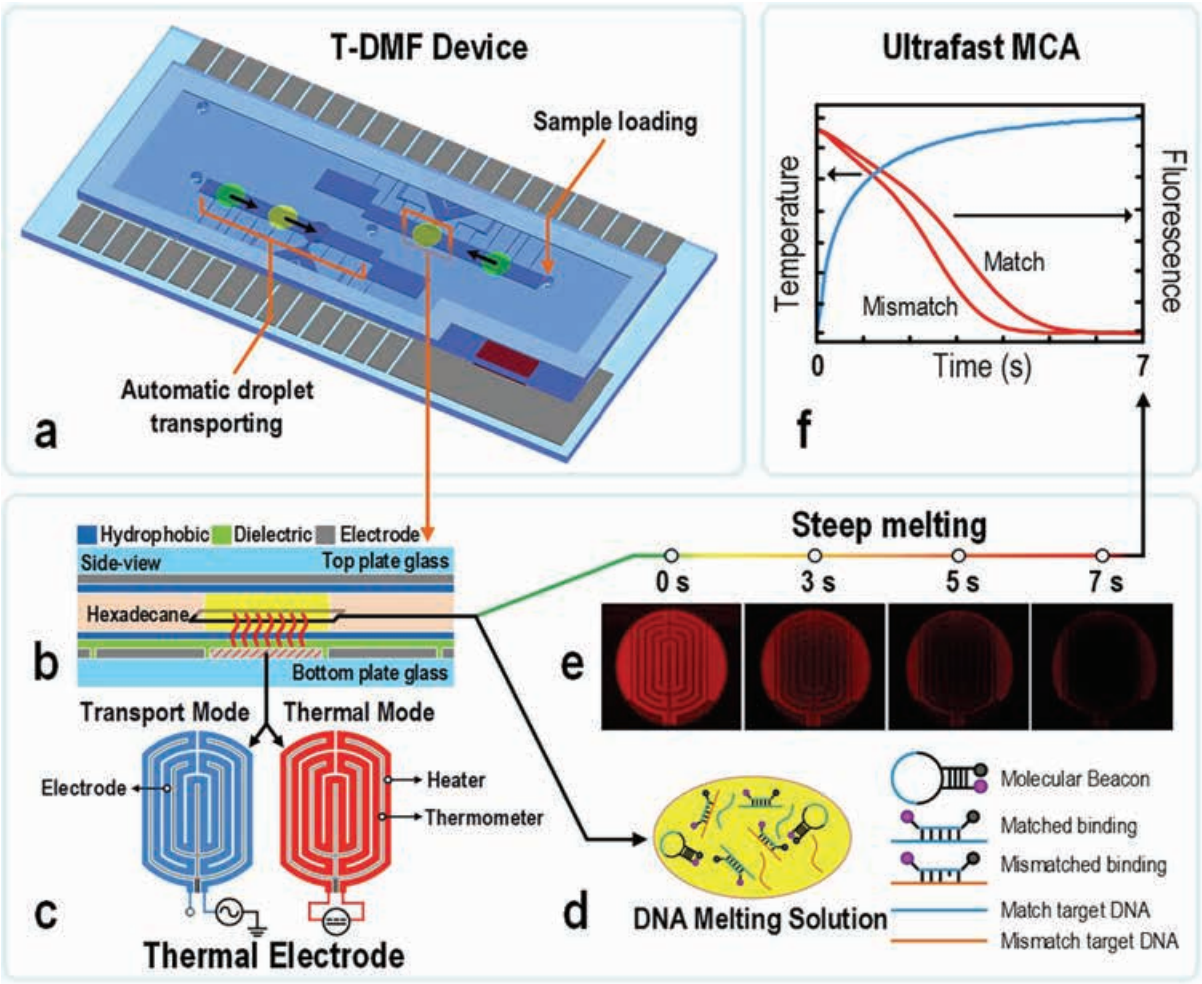

Fig. 1. Thermal digital microfluidic (T-DMF) device for ultrafast DNA melting curve analysis (MCA).

Publication(s):

[1] T. L. Chen, Y. W. Jia, C. Dong, J. Gao, P. I. Mak, and R. P. Martins, "Sub-7-second genotyping of single-nucleotide polymorphism by high-resolution melting curve analysis on a thermal digital microfluidic device," Lab on a Chip, 16, 743-752, 2016.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

A μNMR CMOS Transceiver Using a Butterfly-Coil Input for Integration with a Digital Microfluidic Device inside a Portable Magnet

Ka-Meng Lei, Pui-In Mak, Man-Kay Law, and Rui P. Martins

FEATURES

Co-integration of microelectronics (0.18-μm process) and digital microfluidics technologies.
Multi-sample manipulation
(and chemical/biological sensing)
inside portable magnet (1.2 kg, 0.46 Tesla).
Cross-domain optimized Butterfly-coil to expand the effective electrodes.
Flexible route projection and optimization.

DESCRIPTION

There is demand to develop a "Lab-on-a-Chip" device for in vitro diagnostic μNMR, which includes automated sample management capability. Lab-on-a-chip devices overcome miniaturization of healthcare diagnostic tools, allowing low-cost and rapid detection of specific targets in tiny fluid samples. This work reports the world-first electronic-automated μNMR relaxometer for multi-step multi-sample chemical/biological assays. Co-integration of microfluidic and microelectronic technologies allows association between droplet managements and μNMR assays inside a portable sub-Tesla magnet (1.2 kg, 0.5 Tesla). Targets in unprocessed biological samples, captured by specific probe-decorated magnetic nanoparticles, can be sequentially quantified by their spin-spin relaxation time (T_2) via multiplexed μNMR screening. A digital microfluidic device with capacitive sensing actuates and locates distinct droplet samples over the electrode arrays (15 electrodes, each 3.5 x 3.5 mm^2) in real time, and a Butterfly-coil-input 0.18-μm CMOS transceiver transduces between magnetic and electrical signals to/from a sub-10μ L droplet sample for μNMR screening. Auto-handling and identification of two biological samples with a pre-designed probe complete in 2.2 mins.

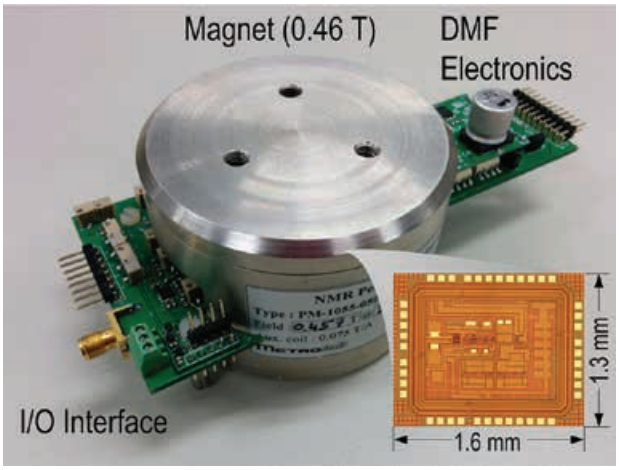

Fig. 1. The prototype of the platform and the fabricated CMOS NMR transceiver in 180nm process (inserted inside the magnet).

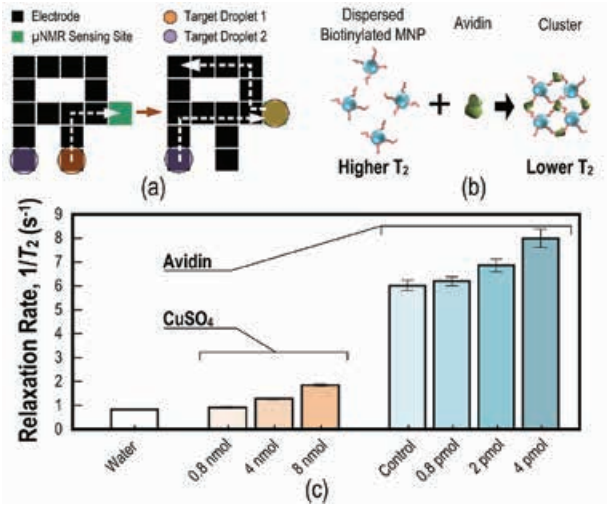

Fig. 2. (a) Multi-sample management scheme for the system. (b) Illustration of the sensing mechanism for avidin. (c) Relaxation rate ($1/T_2$) from various targets.

Publication(s):

[1] K.-M. Lei, P.-I. Mak, M.-K. Law, and R. P. Martins, "A μNMR CMOS Transceiver Using a Butterfly-Coil Input for Integration with a Digital Microfluidic Device inside a Portable Magnet," IEEE J. Solid-State Circuits, vol. 51, no. 10, pp. 2274-2286, Oct. 2016.

[2] K.-M. Lei, P.-I. Mak, M.-K. Law, and R. P. Martins, "A palm-size μNMR relaxometer using a digital microfluidic device and a semiconductor transceiver for chemical/biological diagnosis," Analyst, vol. 140, no.15, pp. 5129-5137, Aug. 2015.

[3] K.-M. Lei, P.-I. Mak, M.-K. Law, and R. P. Martins, "A μNMR CMOS transceiver using a Butterfly-coil input for integration with a digital microfluidic device inside a portable magnet," in Proc. IEEE Asian Solid-State Circuits Conf. (A-SSCC), pp. 1-4, Nov. 2015.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

A 3D Microblade Structure for Precise and Parallel Droplet Splitting on Digital Microfluidic Chips

Cheng Dong, Yanwei Jia, Jie Gao, Tianlan Chen, Pui-In Mak, Mang-I Vai, and Rui P. Martins

FEATURES

Digital microfluidic system
3D microblade structure
Precise droplet splitting
Multiple droplet generation with one-step splitting
Parallel DNA analysis
Sepsis pathogen detection

DESCRIPTION

Existing digital microfluidic (DMF) chips exploit the electrowetting on dielectric (EWOD) force to perform droplet splitting. However, the current splitting methods are not flexible and the volume of the droplets suffers from a large variation. Herein, we propose a DMF chip featuring a 3D microblade structure to enhance the droplet-splitting performance. By exploiting the EWOD force for shaping and manipulating the mother droplet, we obtain an average dividing error of <2% in the volume of the daughter droplets for a number of fluids such as deionized water, DNA solutions and DNA–protein mixtures.

Customized droplet splitting ratios of up to 20: 80 are achieved by positioning the blade at the appropriate position. Additionally, by fabricating multiple 3D micro-blades on one electrode, two to five uniform daughter droplets can be generated simultaneously. Finally, by taking synthetic DNA targets and their corresponding molecular beacon probes as a model system, multiple potential pathogens that cause sepsis are detected rapidly on the 3D-blade-equipped DMF chip, rendering it as a promising tool for parallel diagnosis of diseases.

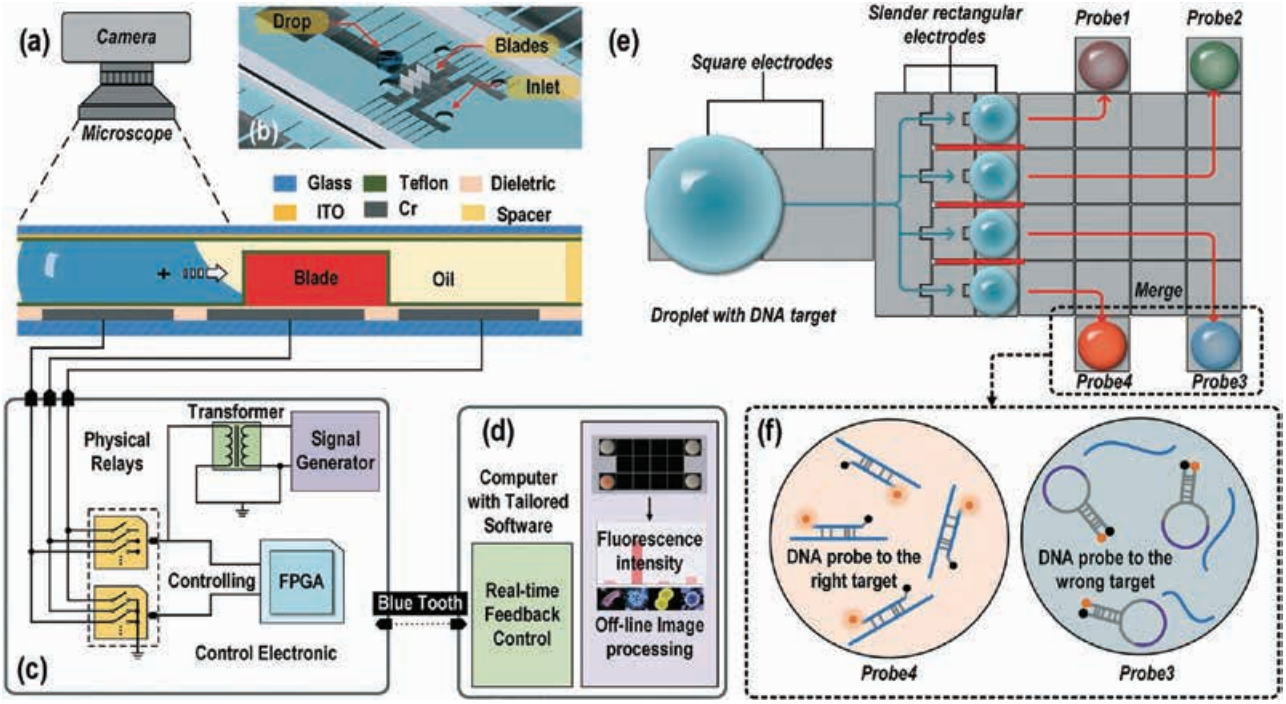

Fig. 1. Thermal digital microfluidic (T-DMF) device for ultrafast DNA melting curve analysis (MCA).

Publication(s):

[1] C. Dong, Y. W. Jia, J. Gao, T. L. Chen, P. I. Mak, M. I. Vai and R. P. Martins, A 3D microblade structure for precise and parallel droplet splitting on digital microfluidic chips, Lab on a Chip, 17, 896-904, 2017.

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau

A Handheld High-Sensitivity Micro-NMR CMOS Platform with B-Field Stabilization for Multi-Type Biological/Chemical Assays

Ka-Meng Lei, Hadi Heidari, Pui-In Mak, Man-Kay Law, Franco Maloberti, Rui P. Martins

FEATURES

First Micro-NMR CMOS Platform with close-loop magnetic field stabilization.
Handheld size platform powered by AA batteries for enhancing the portability.
Sensitive and selective biomolecule (protein and DNA) detection, down to 100pM of DNA from 2.5μL sample.

DESCRIPTION

Nuclear Magnetic Resonance (NMR) is promising for chemical and biological assays as it can reveal atomic level information and is quasi-label-free and washing-free for the samples. By integrating the transceiver and NMR sensing coil on CMOS chip, this micro-NMR platform can decrease the cost, volume, weight and sample consumption of the tool.

The CMOS transceiver can unify necessary electronic with minimal footprint. The transmitter programs pulses to perform NMR experiments while the receiver featured low-noise and low-distortion amplifies the NMR signal from the coil and downconvert it to baseband. The on-chip coil transduces between the magnetic signal of the nuclei and electrical signal of the transceiver. It reduces the sample consumption for the assays down to 2.5μL. This CMOS chip can significantly save the power and costs of NMR electronic.

A permanent NdFeB magnet is equipped to enhance the portability of the platform. To assure the robustness against temperature variation, a magnetic field stabilization module consisted of an on-chip vertical Hall sensor and current driver is entailed to soothe the temperature effect on the magnet. The hall sensor tracks the magnetic field variation and transduces the result, and the current driver feeds the corresponding current to the auxiliary coil of the magnet to stabilize the magnetic field at a certain level. This inspires the use of a simple crystal oscillator as LO and facilitates the electronics.

The micro-NMR platform is capable of detecting distinct bio-molecule selectively such as proteins and DNA with probe-decorated magnetic nanoparticles by analyzing the spin-spin relaxation time of the samples. For instance, with this micro-NMR platform, down to 100pM of E. faecalis derived DNA were detected from 2.5-μL sample.

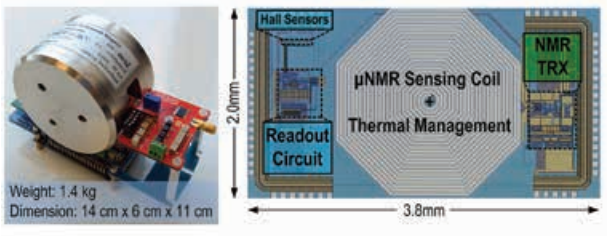

Fig. 1. The proposed NMR platform with magnetic field calibration and the chip micrograph.

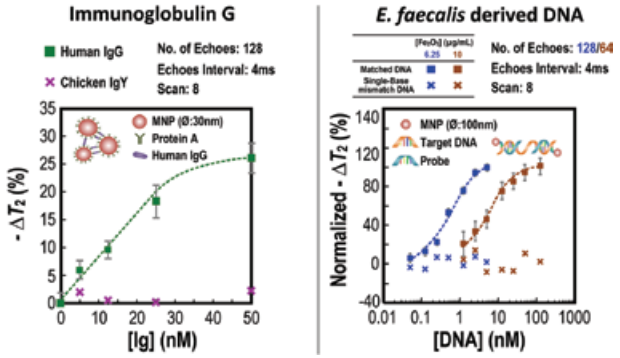

Fig. 2. Experimental results from the detection of Human IgG and synthesized DNA from E. faecalis.

Publication(s):

[1] K.-M. Lei*, H. Heidari, P.-I. Mak*, M.-K. Law*, F. Maloberti, and R. P. Martins*, "A handheld high-sensitivity micro-NMR CMOS platform with B-field stabilization for multi-type biological/chemical assays," IEEE J. Solid-State Circuits, vol. 52, no. 1, pp. 284-297, Jan. 2017.

[2] K.-M. Lei*, H. Heidari, P.-I. Mak*, M.-K. Law*, F. Maloberti, and R. P. Martins*, "A handheld 50pM-sensitivity micro-NMR CMOS platform with B-field stabilization for multi-type biological/chemical assays," in IEEE Int. Solid-State Circuits Conf. (ISSCC), 2016, pp. 474–475.

* Contributors with University of Macau

Sponsorship:

Macau Science and Technology Development Fund (FDCT), Research Committee of University of Macau