COMMENTS AND OPINIONS

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Lab-on-CMOS — an in-vitro diagnostic (IVD) tool for a healthier society

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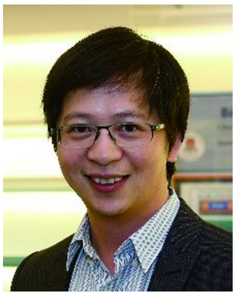

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Towards a sustainable healthcare system, the clinical-grade diagnostic platform should be decentralized into low-cost consumer-grade handheld devices, for broadly and early disease screening and diagnosis. The joint advancement of CMOS biosensors and signal-processing capability has recently transformed bulky laboratory instruments into handheld devices, leading to cost, size and weight reduction by orders of magnitude. This article gives a glimpse of the lab-on-CMOS in-vitro diagnostic (IVD) tools for point-of-care applications.

What is in-vitro diagnostic (IVD) tool?

The failure of healthcare services is largely associated with the lack of proper equipment for diagnosis. The pandemic of COVID-19 signifies once again the leak of low-cost easy-to-use point-of-care diagnostic tools suitable for self-assessment when the people have unobvious symptoms. Delays in screening and treatment not only worsen the situation of individuals, but also the communities for heavily contagious diseases. An easy-to-use and comfortable diagnostic tool is also the key to encourage the participation of kids and elderly people. Especially for deadly contagious diseases like COVID-19, the turnaround time strongly affects their level of transmission to the community. An ideal in-vitro diagnostic (IVD) tool should be very low cost, easy to use, tiny sample consumption from the human body (e.g. blood, urine, sputum and tissue), and provide accurate result in a short time.

What is lab-on-CMOS IVD tool?

CMOS biosensors can underpin a number of transducing mechanisms (e.g. impedance, fluorescence, and nuclear spin) suitable for a wide variety of biological/chemical detection such as DNA, protein and bacteria/cells. A high-sensitivity biosensor allows a tiny specimen consumption, which can sit directly on the chip surface for direct reading and actuation by the readout circuitry underneath. A typical readout circuitry consists of an analog front-end (e.g. low-noise amplifier and filter) for signal conditioning, an analog-to-digital converter for digitization, and a digital back-end for signal processing. The final diagnostic result can be collected offline by reading the on-chip memory, or online via an on-chip wireless radio (Bluetooth). The overall technology goal is to achieve sample-in result-out diagnosis with minimum cost and human intervention.

IVD tool markets

According to a report by the World Health Organization (WHO), the leading infectious diseases (lower respiratory infections, HIV/AIDS, diarrhoeal diseases, malaria, and tuberculosis) account for roughly one-third of all deaths in low-income countries. Also the strong growth in population in these areas gives rise to the demand for affordable IVD tools. A forecast of the global IVD market will grow from USD 68.12 billion in 2018 to USD 87.93 billion by 2023.

Case study — nuclear magnetic resonance (NMR) for biological/chemical assays in CMOS

An example of our previous works is a handheld nuclear magnetic resonance (NMR) CMOS platform for multi-type biological/chemical assays, as depicted in Fig. 1. It mainly consists of a palm-size magnet (0.46 T, 1.25 kg) for nucleus magnetization and a transceiver chip fabricated in 0.18 μm CMOS. With an on-chip spiral coil, a micro-liter droplet sample can sit on the chip surface for direct measurement. Other key components are a system PCB for I/O interface, an FPGA for system control, a current driver for trimming the magnetic field of the magnet. The transceiver chip also integrated a current-mode vertical Hall sensor and a low-noise readout circuit to facilitate closed-loop B-field stabilization, as shown in Fig. 2, which otherwise fluctuates with temperature or sample displacement. The entire system achieves: 1) selective biological target pinpointing; 2) protein state analysis; and 3) solvent-polymer dynamics, suitable for healthcare, food and colloidal applications, respectively. Compared to a commercial NMR-assay product (Bruker mq-20), this platform greatly reduces the

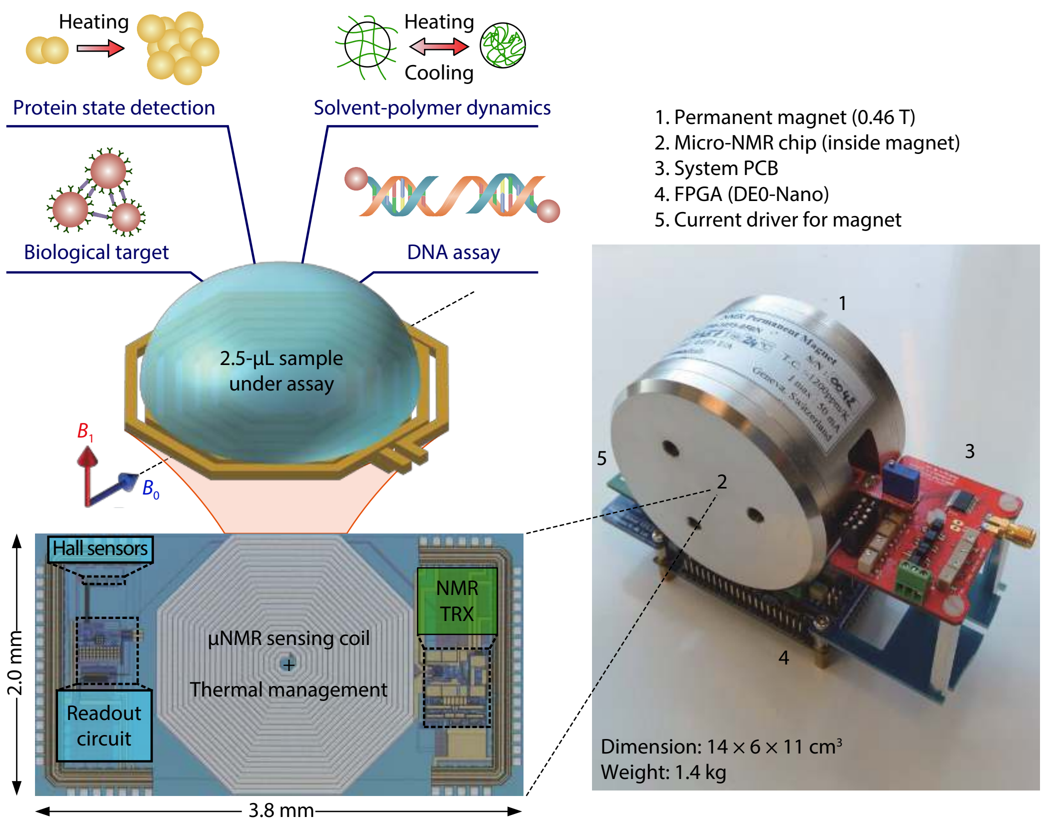

Fig. 1. (Color online) A handheld NMR CMOS platform: (left) chip photo and its applications for multi-type assays, and (right) platform assembly. Courtesy K.M. Lei ISSCC 2016.

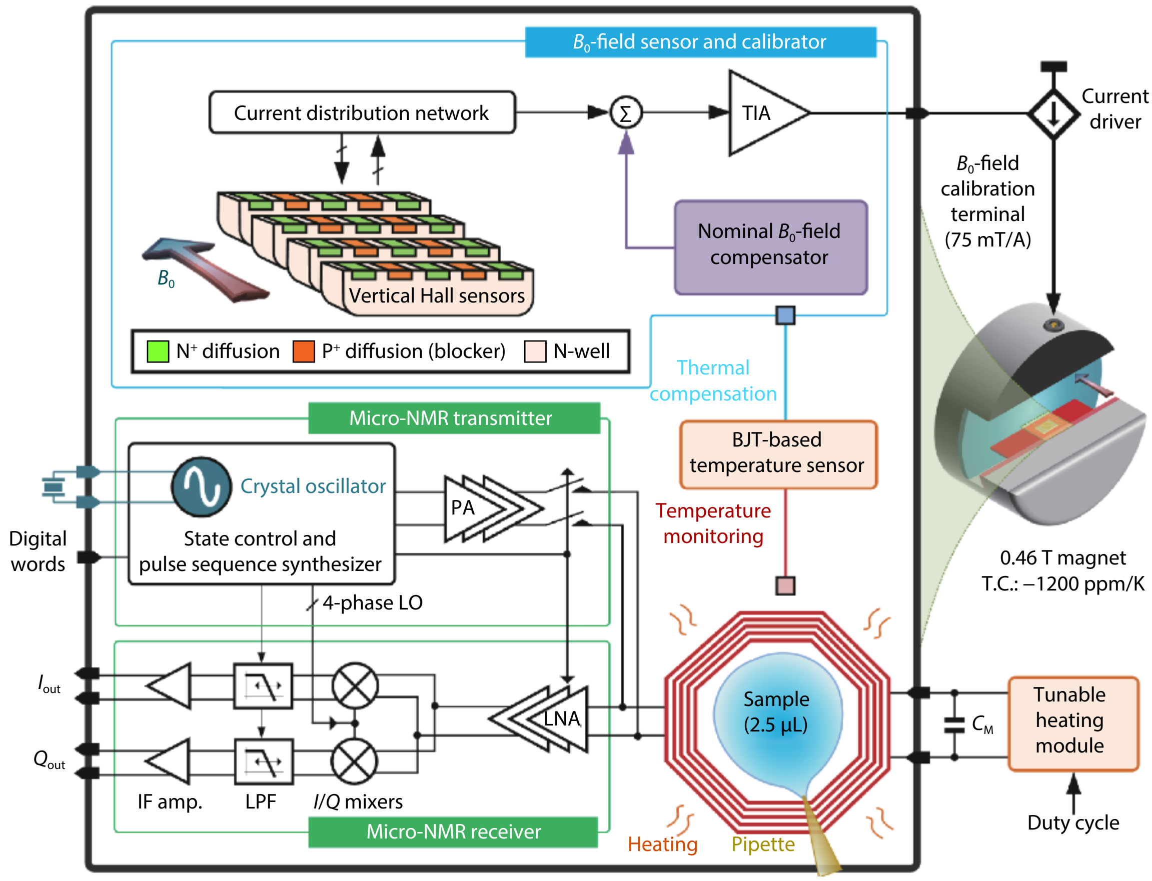

Fig. 2. (Color online) System block diagram of the NMR transceiver. The transmitter and receiver transduce between magnetic and electrical signals with a thermal-controlled spiral coil. The B_0-field sensor and calibrator automatically stabilize the bulk magnetization on the μL-sample. Courtesy K.M. Lei ISSCC 2016.

sample consumption (120×), hardware volume (175×), and weight (96×). With this experience, the author is currently investigating a low-cost portable magnetic resonance imaging (MRI) technology for diagnostic and therapeutic purpose such as diagnosis of anterior cruciate ligament tears, inflammation and tumors.

Opportunities and challenges

To leap up the possibility of lab-on-CMOS diagnosis (e.g. one-sample-in multiple-result-out), the fusion of multi-type CMOS biosensors-on-a-chip is prospective. We also can take advantages of post-processing after chip manufacturing such as chemical deposition and micromachining to raise the versatility and sensitivity of the CMOS biosensors. However, researchers/engineers having a multidisciplinary research background are hard to train/find, but their presence in a team will certainly boost up the creativity level for solving the unconventional problems in a smart way. This argument inspires that our education model for microelectronics should be broadened to include cross-disciplinary subjects in the syllabus. On the other hand, multiphysics software tools have enabled co-design between the biosensors and analog interfaces for years, but it is rare to see a simulation software for chemistry research with multiphysics and electronics. A successful one will play a key role in performance prediction and implementation of advanced lab-on-CMOS systems. In overall, the opportunities and challenges fairly come together in this synergy of electronic engineering, material sciences, biology and chemistry. Are we ready for a new era of the talent education system?