Solid-State and Biological Systems Interface

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***Abstract*—Solid-state electronic devices can be engineered to detect and manipulate biological molecules and cells by using electric or magnetic interactions. The integrated circuits, which can contain a large number of such devices, may then potentially be developed into low-cost chip-scale platforms to perform bioanalytical tasks in a multiplexed manner for applications in biology, biotechnology, and personalized medicine. This paper reviews some recent developments in this solid-state electronic and biological systems interface.**

I. Introduction

It is well known that field-effect transistors can be arranged to operate as biomolecular sensors [1-6]. Imagine an integrated circuit, where a top metal connected to a transistor's gate is surface treated with a thin dielectric layer and then with single-stranded DNA molecules of a known sequence, which one may call probe DNA (Fig. 1). The thin dielectric layer is exposed to an electrolyte containing single-stranded DNA molecules of varying sequences. If these include DNA molecules whose sequence is complementary to the probe DNA sequence, binding will occur at the dielectric-electrolyte interface. As DNA molecules are negatively charged in typical buffer condition, the binding event will alter the transistor's conductance, offering the basis for electrical DNA detection. This ion-sensitive field effect transistor configuration [1-4] can be also used to detect other types of biological molecules such as proteins, by surface treating the device with the antibodies that can specifically bind to target proteins. With bottom-up nanoscale transistors, femto-molar sensitivity and single virus particle detection have been demonstrated [5,6].

As illustrated with the ion-sensitive field effect transistor example, solid-state electronic devices can be engineered to execute biomolecular sensing. Not only the charge-based electric sensing, but also spin-based, magnetic sensing is possible [7,8]. Furthermore, the electronic devices can be used to manipulate the motion of individual biological cells using electric or magnetic fields [9,10]. As a large number of electronic devices can be integrated inexpensively, integrated circuits have been envisioned as low-cost chip-scale multiplexed bioanalytical platforms for applications in biology, biotechnology, and personalized medicine. For example, instead of the optical DNA microarray requiring a bulky and expensive optical scanner [11], one can imagine developing a low-cost all-electronic DNA microarray that can be used like a memory stick with a personal computer. While optics-based bio-analytical systems will continue to be used broadly into the foreseeable future and although electronic bioanalytical chips still require much improvement in fidelity and yield, the latter devices have attractive features such as low-cost chip-scale operation and easy accessibility, and developing them represents a growing branch of engineering. The recent exciting development of the CMOS integrated circuit for DNA sequencing [12] (not to be confused with DNA array) shines positive light on this direction; this work employs a large array of ion-sensitive field effect transistors, with each transistor designed to detect the local pH change that arises from the nucleotide incorporation.

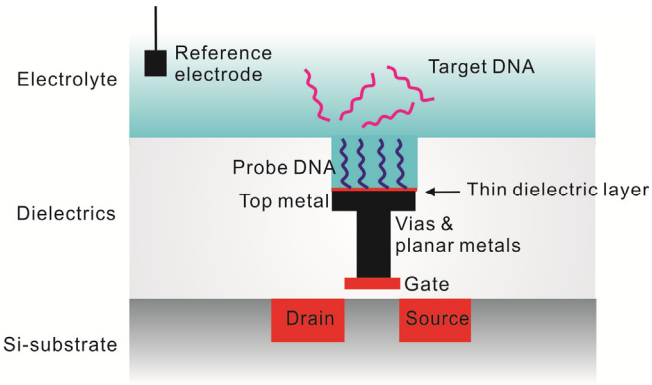

Fig. 1: Ion-sensitive field-effect transistor.

This invited paper is *not* a new technical contribution, but *reviews* some recent developments in this interdisciplinary field of solid-state electronic and biological systems interface, in the hope for providing a perspective on the on-going scene in this field. This review will include some of our own works that have been published elsewhere. Images that appear from here on are adopted from these prior publications of ours.

II. Biological Cell Manipulation

The ability to control the motion of individual biological cells can be useful in single cell interrogation, cell mechanics

study, cell sorting, and designer tissue assembly. Biological cells can be manipulated on the integrated circuit, by using the electric or magnetic fields it generates.

Non-uniform electric fields exert a force on electric dipoles, thus, charge-neutral dielectric objects like biological cells, and move them towards where the field is stronger (if the background electrolyte's dielectric constant is larger than that of the objects, the movement will be towards where the field is weaker). This dielectrophoresis can be performed on top of an integrated circuit containing an array of micro-electrodes made out of top metals; by controlling the voltage of each electrode independently, the array can produce a variable electric field pattern, with which one can manipulate cells suspended above the chip in a microfluidic environment [10]. In order to prevent charged particles such as ions from accumulating to electrodes and screening their effect, AC voltages are applied to the electrodes. With the resulting time-varying electric fields, the charged particles will oscillate back and forth, not accumulating onto electrodes; by contrast, despite the field's periodic polarity change, charge-neutral biological cells will move in one local direction determined by the field magnitude gradient, as opposed to oscillating back and forth. The integrated circuit executing dielectrophoresis may be thought of as electric tweezers.

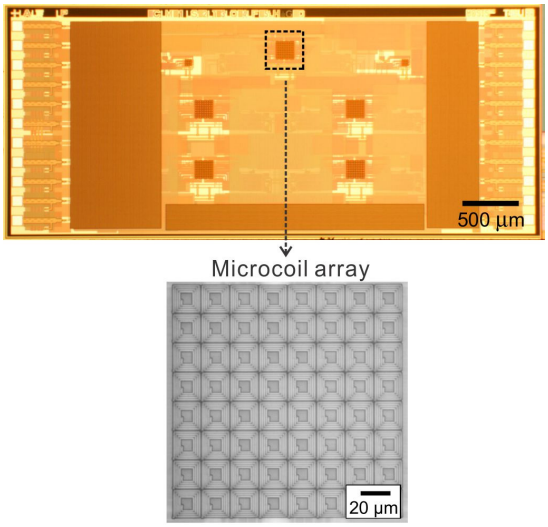

Fig. 2: CMOS magnetic manipulator. Modified reprint from our paper, *IEEE J. Solid-State Circ.*, **41**, 1471 (2006) [9]. © IEEE.

Integrated circuits can be used as magnetic tweezers, too. Non-uniform magnetic fields exert force on magnetic dipoles, thus can move cells attached to magnetic particles (most cells are non-magnetic; more accurately, they are not strongly magnetic enough to receive appreciable magnetic force). An array of planar microcoils made from top metals in an integrated circuit produces a variable magnetic field pattern, by controlling each coil's current individually. This variable field pattern can actuate magnetic-particle-bound cells.

Fig. 2 is a microcoil array CMOS chip we developed a number of years ago [9]. Each coil produces a magnetic field of about 30 G at the coil center on the chip surface with a *dc* current of 20 mA, and can pull a magnetic particle or a magnetic-particle-bound cell into its center. Fig. 3 shows a manipulation of an 8.5-µm-diameter magnetic particle, from our prior work [9]; as the magnetic field peak position is moved by successively turning on and off the microcoils along a particular path, the particle is transported along that path on the chip surface, suspended inside a microfluidic chamber fabricated on top of the CMOS chip. Fig. 4, again from [9], shows an example manipulation of two bovine capillary endothelial cells, which have engulfed antibody-treated 250-nm diameter magnetic nanoparticles; these two cells are joined together by appropriately operating the microcoil array in the CMOS chip.

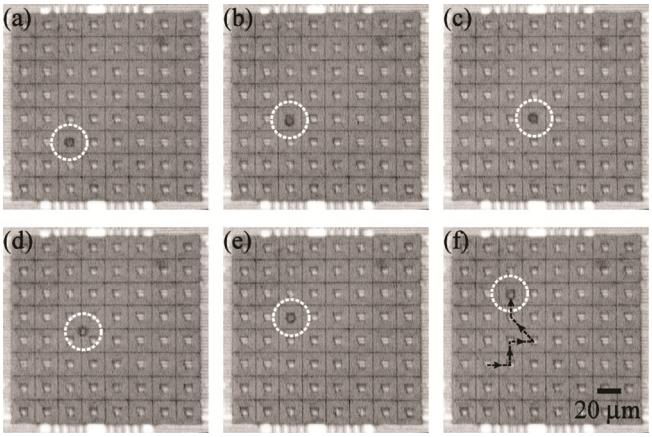

Fig. 3: Magnetic particle manipulation. Reprint from our earlier paper, *IEEE J. Solid-State Circ.*, **41**, 1471 (2006) [9]. © IEEE.

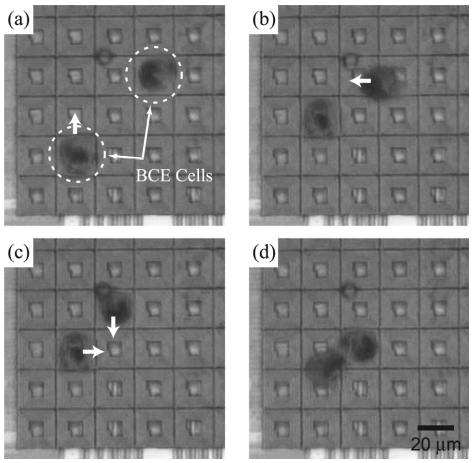

Fig. 4: Magnetic manipulation of bovine capillary endothelial cells. Reprint from our earlier publication, *IEEE J. Solid-State Circ.*, **41**, 1471 (2006) [9]. © IEEE.

The electric and magnetic manipulation of biological cells on the CMOS chips is limited to two dimensions, lacking vertical control, due to the planar nature of integrated circuits. Despite this limitation, the individual cell manipulation with integrated circuits may still offer opportunities in facilitating cytometry, cell mechanics study, high-precision cell sorting, and layer-by-layer designer tissue assembly.

We now turn to biomolecular sensing, where the planar nature of integrated circuits imposes less limitations. In fact, biomolecular sensing with integrated circuits may have far broader applications and impacts.

III. Biomolecular Detection

The ion-sensitive field effect transistor discussed at the start of this review detects biomolecules by way of charge sensing. Biomolecular detection with integrated circuits can be also done by resorting to spin-based magnetic sensing; e.g., we recently developed CMOS biomolecular sensors using nuclear magnetic resonance (NMR) [7,8]. The charge-based electric sensing and spin-based magnetic sensing contrast each other in an interesting way; the former has a larger signal, but also has a larger noise due to irrelevant ions in the electrolyte; the latter has a smaller signal, but also has a smaller noise, for the ions in the electrolyte have no first-order effect on magnetic interactions.

We illustrate how spin-based biomolecular sensing works, using our CMOS NMR system as an example. While rigorous description of NMR can entail quantum mechanics, classical picture suffices here. The nuclei of hydrogen atoms, which are single protons, are tiny magnets due to their spin, and interact with magnetic fields. Apply a static magnetic field B_0 produced from a permanent magnet or an electromagnet to a sample of water, which contains a large number of hydrogen atoms. After a while, the hydrogen proton magnetic moments line up preferentially along the static magnetic field B_0 to minimize the overall potential energy; not all proton magnetic moments line up along the static magnetic B_0 due to thermal agitation, but their vector sum per unit volume (*i.e.*, magnetization) does. Now we add an RF magnetic field $B_1(t)$ perpendicularly to the static magnetic field B_0 by wrapping a coil around the water sample and injecting an RF current into the coil. If the RF field's frequency is tuned into a value given by $f_0 = B_0 \times \gamma/(2\pi)$ [γ: proton gyromagnetic ratio; its numerical value is such that B_0 of 1 T gives f_0 of 42.6 MHz], the magnetization resonantly absorbs energy from the RF field, which is NMR. The absorbed energy increases the overall potential energy of protons; equivalently, the magnetization originally aligned with the static magnetic field B_0 is then rotated away from B_0, enlarging the angle θ it makes with B_0.

If the RF field is turned off when θ becomes, say, 90°, the magnetization will stay in the θ=90° plane orthogonal to B_0 for a while, before it eventually sheds its potential energy and lines back up with B_0. With the non-zero θ, the magnetization undergoes a precession motion about B_0, for B_0 exerts a torque on it and alters its angular momentum associated with the proton spin. The precession frequency is also f_0. This precession will produce a periodically varying magnetic flux across the aforementioned coil, inducing a voltage across the coil. This reception-phase voltage may be referred to as NMR signal, although NMR actually occurred during the excitation phase.

The NMR signal of the pure water after the 90° excitation is an exponentially damped sinusoid, and the characteristic relaxation time is called T_2 (Fig. 5, top). This damping occurs, as each individual proton precession is randomly disturbed by nearby protons (spin-spin interaction), developing what is like the oscillator phase noise. Hence, precessions of a large number of protons grow increasingly phase incoherent with one another, leading to the exponential decay of the overall magnetization. The damping also occurs due to the gradual potential energy loss of the magnetization, which reduces θ. Since the phase decoherence due to spin-spin interaction occurs faster than the energy relaxation, T_2 is largely governed by the former effect.

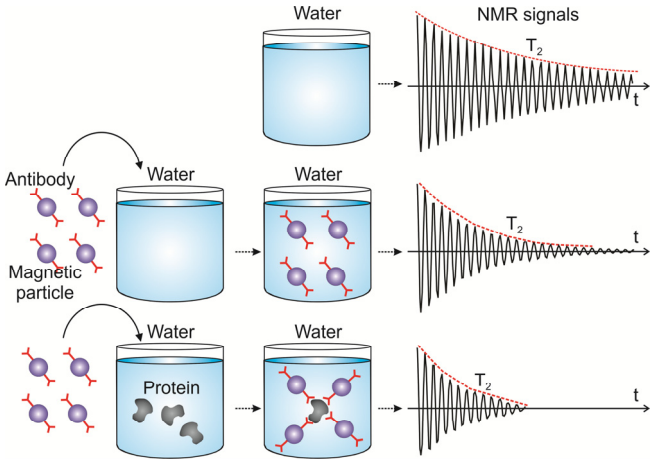

Fig. 5: NMR-based biomolecular sensing [13]. The illustration is a modified reprint from our earlier publication, *IEEE J. Solid-State Circ.*, **44**, 1629 (2009) [7]. © IEEE.

Consider detecting a certain type of proteins in a biological sample, which contains a large number of water molecules. Nanoscale magnetic particles coated with antibodies that can specifically bind to the target proteins are introduced into the sample. If target proteins are absent (Fig. 5, middle), the magnetic particles stay mono-dispersed. These magnetic particles constantly move around, creating fluctuating magnetic fields. These perturb precessions of individual protons, increasing the phase noise beyond that due to the basic spin-spin interactions. Consequently, the phase coherence is lost more rapidly, reducing T_2. In the presence of the target proteins (Fig. 5, bottom), the magnetic particles self-assemble into larger local clusters, which are even more effective in accelerating phase decoherence [13], leading to an even smaller T_2. In sum, by monitoring the NMR relaxation time, target proteins can be detected [13].

Conventional NMR relaxometry systems are heavy, bulky, and expensive. E.g., a state-of-the-art commercial benchtop NMR relaxometer weighs over 100 kg. This is because they use large-sized magnets to produce a highly homogenous static magnetic field. Even for the same static field strength, a more uniform field yields a larger NMR signal, hence the use of the large-sized magnets. Through a series of developments, we miniaturized NMR relaxometry systems significantly, e.g., Figs. 6, 7 [7,8]. The key to this miniaturization was opting for much smaller magnets (the magnet in Fig. 6 is comparable to a hamburger in size; the magnet in Fig. 7 is as small as a ping-pong ball), and then designing highly sensitive CMOS RF transceivers to deal with the NMR signal substantially weakened by the small-sized magnets. The 0.1-kg NMR system of Fig. 7 is three orders of magnitude lighter and smaller than the commercial benchtop system, yet two orders of magnitude more spin-mass sensitive. Since the ping-pong ball size magnet severely degrades the NMR signal, this system of Fig. 7 uses an off-chip high-quality solenoidal coil (hidden inside the magnet in Fig. 7), not to further degrade the

signal. The NMR system of Fig. 6 integrates the coil in the CMOS chip together with the RF transceiver; here, biological samples are placed directly on the coil portion of the CMOS chip for on-chip detection of target biomolecules. As the on-chip coil degrades the NMR signal, not to further degrade it, this system of Fig. 6 uses the larger, hamburger sized magnet. Yet, this system still weighs only 1.5 kg, and is 60 times more spin mass-sensitive than the commercial system.

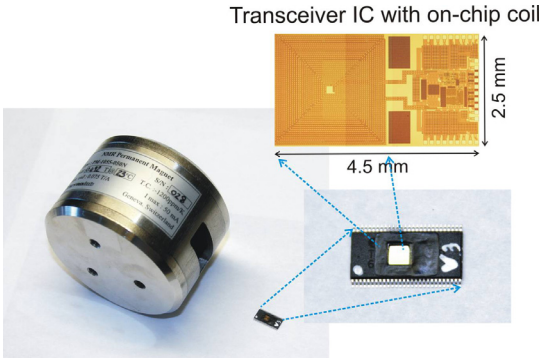

Fig. 6: A CMOS NMR biomolecular sensor. Reprint from our earlier paper, *IEEE J. Solid-State Circ.*, **46**, 342 (2011) [8]. © IEEE.

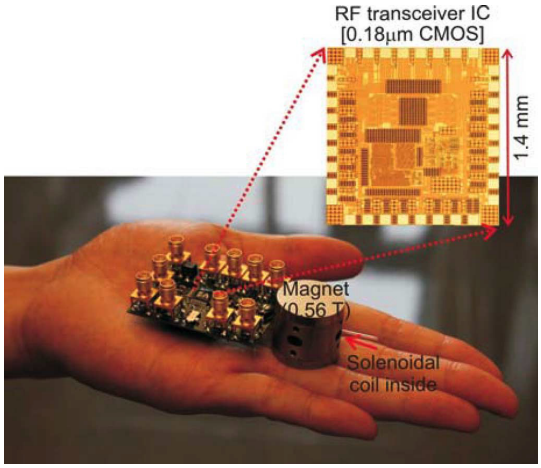

Fig. 7: Another CMOS NMR biosensor. Reprint from our prior paper, *IEEE J. Solid-State Circ.*, **46**, 342 (2011) [8]. © IEEE.

With these CMOS NMR systems, we demonstrated the detection of avidin, hCG, and human bladder cancer cell [7,8] (multiplexed measurements were demonstrated in [14]). These CMOS NMR systems, implemented in the low-cost, hand-held platform, are examples of the solid-state and bio systems interface using magnetic interactions. We find them also interesting in that they showcase how CMOS RF integrated circuits can be used for biomolecular sensing, beyond their traditional wireless applications.

IV. Another Avenue: CMOS-Neuron Interface

Another interesting avenue to explore is the CMOS-neuron interface [15-17]. Understanding how the neuronal network in the brain codes information is one of the most celebrated problems in all of science. The challenge is colossal. To help make a step forward in tackling this problem, a variety of approaches have been proposed. One approach is to interface a CMOS integrated circuit with interconnected neurons to interrogate them simultaneously [15-17] *in vivo, ex vivo,* or *in vitro*. In principle, the density of CMOS circuits promises sufficient spatio-temporal resolution in massively parallel recording at least with two-dimensional neuronal networks. Nonetheless, massively parallel recording of a large number of neurons with single-cell resolution has yet to be achieved, let alone its biologically relevant interpretation in connection with functions and behaviors. Developing the CMOS-neuron interface offers exciting opportunities at the intersection of devices, circuits, electrochemistry, and neurobiology.

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