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Contents

1. Introduction

Building on the invention of the transistor by Brattain and Bardeen,[1] an enormous amount of research in semiconductors and integrated circuits (ICs) has established the modern complementary metal−oxide−semiconductor (CMOS) technology. The combination of accumulated techniques in semiconductor processing technology and the good mechanical properties of silicon led to the development of microelectromechanical systems (MEMS) in the early 1970s.[2] MEMS technology produced a variety of micrometer-sized mechanical structures, such as overhanging, suspended, and freestanding elements fabricated with silicon processing techniques[2−4] that have been utilized in sensors and actuators such as accelerometers, pressure sensors, and micromirrors for video projection systems. Silicon-based liquid chemical sensors, the first of which were reported in 1970,[5] are considered a branch of the MEMS family tree, though they often do not include any micromechanical components. Solid-state liquid chemical sensors can also be fabricated on glass, ceramic, or plastic substrates. Use of a semiconducting substrate, such as silicon, opens the possibility of integrating electronics with the chemical sensors (or other MEMS devices) on a single silicon chip to reduce noise, improve manufacturing control, reduce size, and enable batch fabrication of the whole system.

Chemical sensors present a particularly challenging application for integrated electronics. Integrated circuits are generally packaged in such a way as to protect the circuit from any liquid, and even from humidity, but liquid chemical sensor chips must be in contact with the solution under test. Certain restrictions are placed on the materials and processing steps for chemical sensors if they are to incorporate CMOS, the dominant electronics technology. If contaminated with alkali or other ions, CMOS suffers from drifting transistor threshold voltages, so the manufacturing process must be cleaner than it would need to be to fabricate just the sensor. High temperatures or high electric fields during the manufacturing process can also destroy the circuits.[6,7] There are materials issues to consider; in addition, the metals used in some chemical sensors are not compatible with the interconnect metals used in CMOS. However, with the use of barrier layers it is possible to fabricate a sensor on top of a fully passivated CMOS circuit or to connect a separately fabricated CMOS circuit to a sensor chip. Combining CMOS and MEMS technologies, one can fabricate a sensor system that incorporates the sensor, amplifier, signal processing, analog-to-digital converter, and microcontroller on a chip. Such a system-on-a-chip (SoC) provides computerized control of the sensor, less noise from the interconnection wires between sensor and data acquisition system, low power operation, less reagent use, and high reproducibility. On the other hand, if a sensor's lifetime is relatively short, as is the case with many chemical sensors, the additional cost for including electronics may overwhelm these advantages.

In this review, enough background information is provided to put each sensor type into perspective, but because an excellent survey of the literature on sensors with integrated CMOS electronics was done in 2002,[8,9] our focus is on papers published since then. The current review does not cover sensors having a single metal−oxide−semiconductor (MOS) transistor or hybrid systems in which separately fabricated chips—generally one sensor chip and one CMOS circuit chip—are connected by wire-bonding or other means.

The review is organized by the operating principle of the sensor system. Section 2 describes integrated electrochemical sensors, including potentiometric, conductometric, and voltammetric sensors. Sections 3 and 4 cover optical- and mass-sensitive sensors, respectively. Section 5 surveys systems that integrate several sensors having different operating principles on a single chip. Section 6 offers concluding comments and a brief outlook for CMOS-integrated sensors.

2. Electrochemical Sensors

Electrochemical sensors are the oldest and most widely available group in the solid-state chemical sensor field. Many solid-state electrochemical sensors have been commercialized, such as glucose monitors for diabetes and ion sensors for blood electrolytes. Electrochemical sensors detect charge

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Segyeong Joo was born in 1976 in Busan, Korea. He received his B.S. degree in 1999 with a major in Electrical Engineering and a minor in Chemistry and his M.S. degree in 2001 in Electrical Engineering from the Korea Advanced Institute of Science and Technology (KAIST). In 2006, he received his Ph.D. degree in Biomedical Engineering from Seoul National University (SNU) on developing a rapid field-free electroosmotic micropump incorporating charged microchannel surfaces. He worked on the instrumentation of a medical analysis system and developing a microfluidic component for BioMEMS in the Medical Research Center at SNU Hospital as a research engineer from 2004 to 2006. He is currently a postdoctoral fellow in the College of Engineering at the University of Utah. His fields of interest are a chemical/biosensor system with integrated electronics and its medical instrumentation.

Richard B. Brown received his B.S. (with highest honors) and M.S. degrees in Electrical Engineering from Brigham Young University in 1976. Following graduation, he designed computers, analog-to-digital converters, and computer peripheral devices for companies in California and Missouri. In 1985 he received his Ph.D. degree in Electrical Engineering from the University of Utah and joined the faculty of the University of Michigan's Department of Electrical Engineering and Computer Science. He has conducted major research projects in the development of sensors, circuits, and microprocessors. At Michigan he developed the highly respected integrated circuit design (VLSI) program and served as Associate Chair and Interim Chair of EECS. He holds 15 patents and has consulted in the areas of solid-state sensor and microprocessor design. He is a founder of Sensicore, i-SENS, and Mobius Microsystems. He was honored to receive the second ECE Distinguished Young Alumnus Award from the University of Utah in 2003 and was appointed the eleventh Dean of the College of Engineering at the University of Utah in July 2004.

transport between chemical phases or changes of electrical properties that arise due to chemical reactions on the sensor.[10−12] These electrochemical sensors require specialized electrodes, depending upon the sensing mechanism, that come in contact with the solution under test and generate the signal that is correlated with the concentration of the target analyte. In every case, the detected signal also requires amplification or signal processing. The circuitry required to perform these functions can be advantageously integrated with the sensor electrodes.

Electrochemical sensors are classified as potentiometric, conductometric, or voltammetric sensors based upon their analytical principles of operation.[10,13] Potentiometric sensors measure an equilibrium potential difference between a sensing electrode and a reference electrode. Ideally, there is no current flow through the electrodes at equilibrium. In general, the potential difference shows a linear relationship with the logarithm of the activity of the analyte, as in the Nernst equation.

Conductometric sensors quantitate the changes of electrical properties between two electrodes. Resistive sensors measure the resistivity change due to chemical reactions, while capacitive sensors detect the capacitance change due to a dielectric-constant modification.

Voltammetric sensors measure the current from the charge transport of an electrochemical reaction on a sensing (working) electrode when a varying potential or a constant potential (amperometric detection) is applied between the working electrode and the solution. Voltammetric sensors use an auxiliary (counter) electrode to control the solution potential and as an electron source or sink for the counter reaction to the one at the working electrode. For more stable analysis, most voltammetric sensors also use a nonpolarizable reference electrode to monitor the solution potential.[12]

2.1. Potentiometric Sensors

Many papers describing the integration of CMOS circuits with potentiometric sensors are based on chemically sensitive field-effect transistors (ChemFETs). The structure of a ChemFET is the same as that of the normal metal−oxide−semiconductor field-effect transistor (MOSFET) except for the transistor gate, which incorporates the means of transduction from a chemical concentration to a voltage. Another popular type of integrated potentiometric sensor is based upon the ion-selective electrode (ISE), a relatively simple sensor that is widely used in the detection of ions in aqueous solutions. The miniaturized, solid-state versions of these sensors mimic the internal filling solutions of ISEs with hydrogel layers between the selective membrane and the electrode. An even simpler version that is called a solid-contact ISE eliminates the hydrogel layer, resulting in a structure that is more like a coated wire. Light-addressable potentiometric sensors (LAPS)[14] also employ CMOS-like fabrication techniques, but integration of CMOS electronic circuits with LAPS has not yet been reported. In this section, potentiometric sensor systems that include integrated electronic circuits are surveyed.

2.1.1. ChemFETs

FET-based potentiometric sensors were introduced in 1970.[5] Figure 1 shows the general structure of an n-channel MOSFET and an ion-sensitive field-effect transistor (ISFET), the most common type of ChemFET. In place of the gate and gate oxide of a general MOSFET, the ISFET has ionic solution with a reference electrode immersed in the solution and an insulating layer appropriate for detecting a specific analyte. More than 650 papers describing the development of ChemFET sensors have been published.[15] Many of these papers address structural issues, selection of the insulation/detection layer, and improvement of sensing accuracy. ChemFETs fabricated on a semiconducting substrate have the possibility of being integrated with electronic circuits

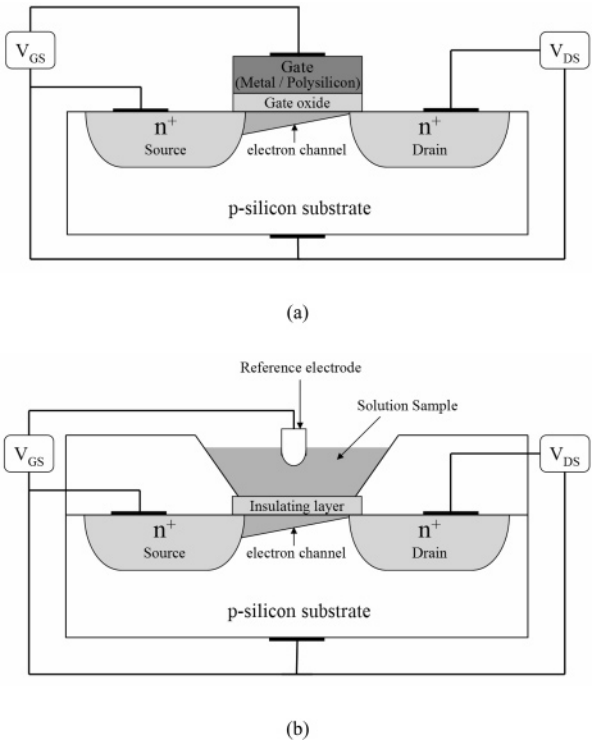


Figure 1. Schematic diagrams of general (a) n-channel MOSFET and (b) ISFET. V_{GS} is the gate-source voltage, and V_{DS} is the drain-source voltage.

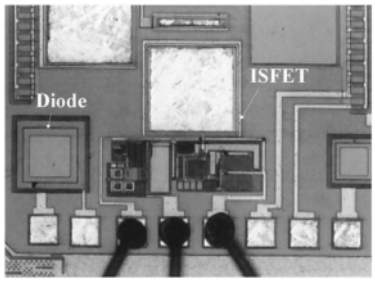


Figure 2. Photograph of diode-temperature-compensated pH ISFET sensor. Reprinted with permission from ref 21. Copyright 2001 Elsevier.

on the same chip, and thus in the 1980s, several papers reported the fabrication of ChemFETs with integrated circuits.[16−18] Furthermore, Bausells et al.[19] demonstrated ISFETs fabricated in a commercial CMOS foundry process, which is seen as a practical path toward commercialization. The encapsulation challenges of integrating active electronic circuits with chemical sensors still requires special attention, and standard CMOS processes allow little opportunity for engineering of the gate material or sensor structure.

In an effort to compensate for the intrinsic thermal instability of ISFETs,[20] Chin et al.[21] integrated a temperature sensor and readout circuit (see Figure 2) with a pH-sensitive ISFET. A simple *p-n* diode was used for temperature detection. Integrating this temperature sensor reduced the temperature coefficient of the output voltage, which is normally between 1 and 12 mV/°C depending on the measuring conditions, to 0.16 mV/°C. Morgenshtein et al.[22] showed an interface circuit for body effect elimination and temperature compensation using a complementary ISFET/MOSFET pair technique. They also introduced the Wheatstone-bridge readout interface for ISFETs[23] to improve noise performance and temperature compensation. Yang et al.[24] presented a pH-ISFET integrated with an on-chip differential measurement circuit; the sensitivity was 53.67 mV/pH.

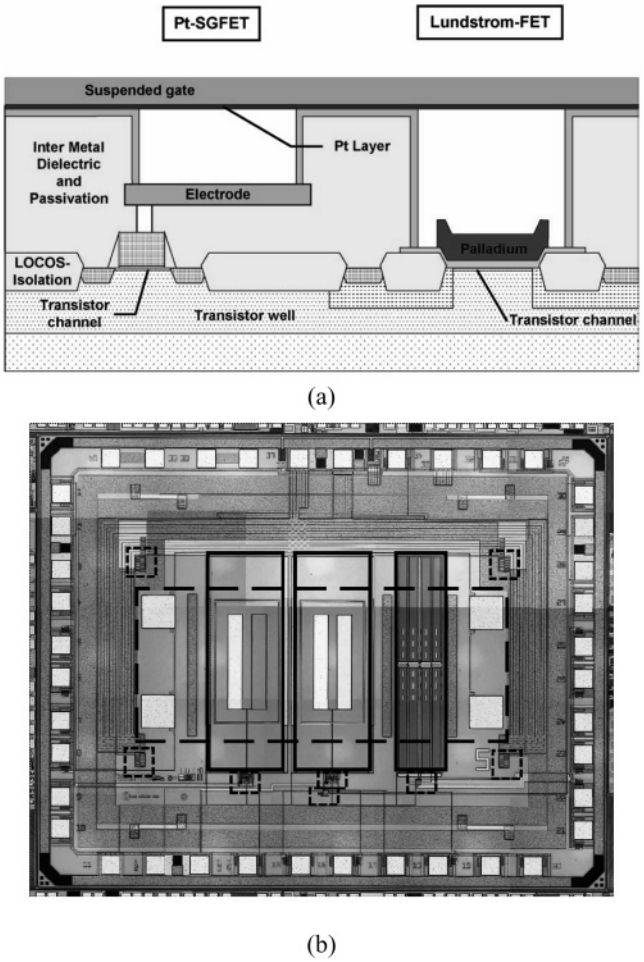


Figure 3. (a) Schematic view of Lundstrom-FET/suspended gate FET double sensor, and (b) photograph of the fabricated chip, where the solid-lined rectangles on the center and right surround the suspended gate FET region, the solid-lined rectangle on the left side surrounds the Lundstrum-FET region, the dashed rectangle in the center indicates the suspended gate area, and the small dotted-line rectangles indicate integrated circuits. Reprinted with permission from ref 27. Copyright 2005 Elsevier.

It is common to modify the gate structure of ChemFETs to improve the performance or measure specific chemicals. Integration of readout circuitry for a specifically modified ChemFET is reported in several papers.[25−27] An ISFET pH sensor with a discrete tin dioxide/aluminum (SnO_2/Al) gate structure and an integrated readout circuit showed a linear sensitivity of 58 mV/pH within the pH range of 2−10.[25] A differential read-out architecture was used for the extended gate approach to reduce leakage and drift.[26] A hydrogen sensor was implemented with a suspended gate FET[28] and a Lundstrom-FET[29] integrated on a same chip with appropriate circuits.[27] Figure 3 is the schematic diagram of this sensor and a photograph of the fabricated chip.[27] The suspended gate FET has a gas-sensitive membrane separated a specific distance from the active FET layer, while in the Lundstrom-FET, the gas-sensitive layer is deposited directly on the transistor gate insulator.[30]

Another application for integrated electronics on ChemFET chips is for read-out of an array of sensors. Milgrow et al.[31] presented a scalable 2 × 2 array of pH-sensitive ISFETs with a memory-like (row and column) decoder for the sensor

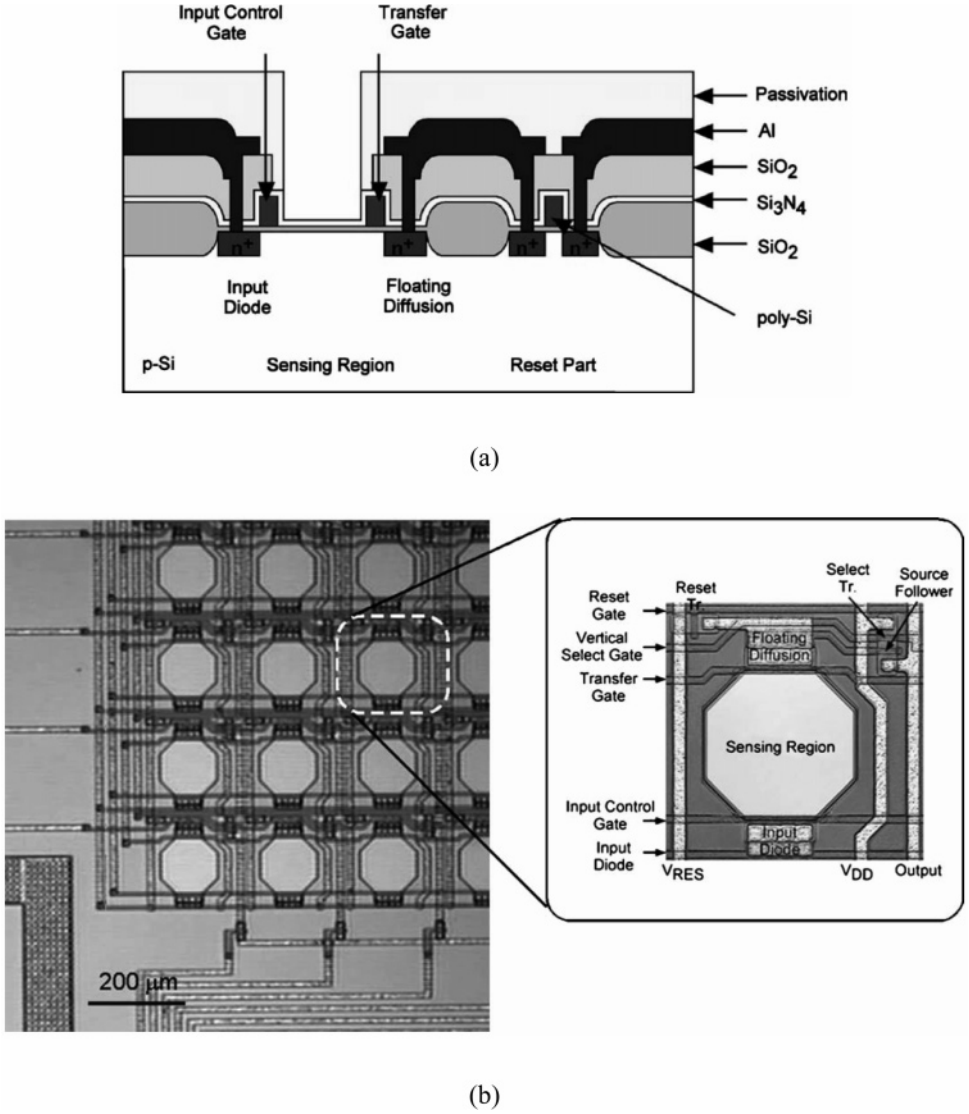


Figure 4. (a) Schematic diagram of a single pixel of the pH image sensor for charge storing, transfer, and readout, and (b) photograph of a fabricated pH image sensor array and enlarged view of a single pixel. Reprinted with permission from ref 33. Copyright 2006 Elsevier.

array and an on-chip analog-to-digital converter (ADC). This group extended their work to a 16 × 16 array of ISFETs the following year for direct extracellular imaging.[32] Hizawa et al.[33] also developed a two-dimensional pH image sensor chip with a 10 × 10 pH-ISFET array. They measured the amount of charge which is stored in the potential well under the sensing region since the depth of this potential well is determined by the pH of the sample. Figure 4 shows the schematic diagram of the pH image sensor and a photograph of the fabricated sensor array.[33] By incorporating charge-transfer readout circuits, the chip was able to produce pH images at up to 30 frames per second,[34] a rate that can be used for two-dimensional monitoring of chemical reactions.

An example of the system-on-a-chip (SoC) concept with chemical sensors is the digital pH meter introduced by Professor Cummings' group.[35,36] These systems use an ISFET with a floating gate as the transducer and include a microcontroller unit (MCU), static random access memory (SRAM) for program and data, ADC, and programmable voltage reference on a single chip. Figure 5 shows the structure of the floating electrode CMOS ISFET and the fabricated system.[35,36] The chips had sensitivities of 43 mV/pH in ref 35 and 48 mV/pH in ref 36.

As mentioned above, one of the challenges of integrating electronics with ChemFETs is that the circuitry must be protected from the ion-containing solution because the ions can migrate in silicon dioxide and cause shifts in transistor characteristics. Most sensors fabricated in CMOS processes employ the standard silicon nitride passivation layer as a barrier to ion migration and also as an ion-sensitive layer.[19] A comparison of characteristics of several ChemFET-based sensors with integrated circuitry is presented in Table 1.

2.1.2. ISEs

The history of ISEs is much longer than that of ISFETs. The first ISE, the glass electrode,[37,38] was invented more than 100 years ago. Since then, many other types of ion-selective membranes have been developed and characterized, including polymeric membranes having various ionophores, which extend the sensing capabilities of ISEs to a wide range of ions.[39,40] Electrochemical analysis systems based on ISEs are widely used to measure ionic concentrations in biomedical, food processing, water quality, and pollution monitoring applications.[41] The ISE structure was miniaturized using thin-film (photolithographic), thick-film (screen printing), and/or automatic dispensing methods to pattern metals,

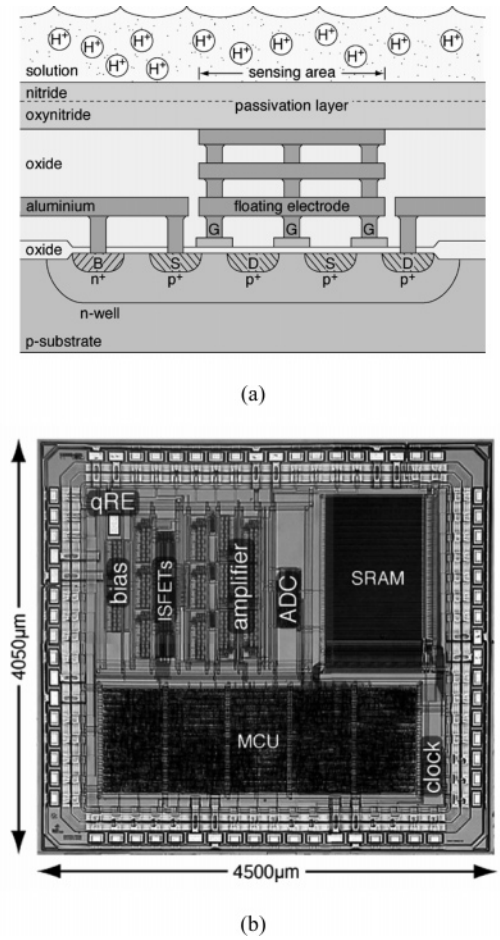


Figure 5. (a) Schematic diagram of the cross-section through a p-type floating-electrode CMOS ISFET. (b) Photograph of the integrated SoC pH sensor. Reprinted with permission from (a) ref 36 and (b) ref 35. Copyright (a) 2005 and (b) 2004 IEEE. (b)

insulators, and chemical-selective membranes on semiconductor, ceramic, or plastic substrates.

Some of the earliest chemical sensors that were integrated with more extensive electronic circuits were miniaturized ISEs fabricated on silicon.[42,43] The line dividing ChemFETs from ISEs having integrated electronics is thin; the ISEs put a conductor between their chemically selective membrane and the transistor gate (like an extended gate ISFET) and replace the single transistor of the ChemFET with an operational amplifier configured as a voltage follower. The active ISE configuration significantly improves thermal stability and photoinduced junction currents. Miniaturized ISEs typically use polymeric membranes as the sensing element, but these have been used in many ChemFETs as well. The membranes are composed of a polymer, ionophore, and usually a plasticizer and lipophilic additives. These components are typically dissolved in a solvent and dispensed onto the sensor surface, where a membrane forms as the solvent evaporates.[44] Membrane deposition must be done after the CMOS processing is completed. While passive ISEs tend to be slower responding to chemical changes than ChemFETs, active miniaturized ISEs recover the speed. Multiple-ion sensing chips can be made by depositing several different ion-selective membranes on a single chip.

Membrane lifetime is an issue for integrated ISE sensors. The primary causes of membrane failure are detachment of the membrane from the surface, causing an electrolyte shunt around the membrane,[45] or loss of plasticizer, carrier, or ionophore from the polymeric film due to leaching into the sample solution.[40] The integration of circuitry with a sensor that has a short lifetime is not cost effective, so lengthening the lifetime of ISEs is a priority. This might be accomplished by modifying the composition of the ISE membrane to slow the leaching process, developing a practical method for replacing ISE membranes after they lose sensitivity, or forming an array of ISE membranes on the sensor chip with a method for sequentially exposing a fresh membrane to the solution when the old membrane begins to lose sensitivity.

There are fewer papers about the integration of CMOS circuits with ISE sensors than with ChemFETs, but the published papers in this field show very notable results. Integration of an on-chip CMOS buffer with a silicone rubber-based ISE showed a 7.5 times faster response time than that of a conventional ISE that was 225 times larger.[46] In addition, these ISEs survived more than 120 days with a response within 5% of ideal and a detection limit of 10 μM. Figure 6 shows the schematic view of the cross-section of an ISE sensor and scanning electron micrographs of an integrated ISE sensor.[46] The ISEs were postprocessed on the foundry-fabricated CMOS circuit. In 2005, this group improved the detection limit by 25 times and shortened the response time by 200 times.[47]

Depositing the ISE membranes onto active ISE chips is challenging because the membrane sites are usually made quite small in order to keep the chip size small since the CMOS wafers cost the same whether they contain few or many sensor chips. Use of a microdispenser and thin wells to define the membrane boundaries facilitates the deposition of very small volumes of membrane cocktail and enables the repeatable formation of small, uniformly thick membranes.[46,47]

2.2. Conductometric Sensors

Conductometric sensors measure the impedance change between two electrodes before and after analyte exposure. In general, conductometric sensors consist of two electrodes with a sensitive layer between them.[10,13] If the resistance of the sensitive layer changes when it reacts with the analyte, the structure is a chemoresistor. If the capacitance changes upon exposure to the analyte, the device is a chemocapacitor. In this section, various conductometric sensor systems which are integrated with CMOS circuits will be surveyed.

2.2.1. Resistive Sensors

Most of CMOS-integrated resistive sensors are gas sensors based on a metal oxide sensing layer. Various metal oxides have been used for these applications,[48,49] and the deposition methods of many different metal oxides for CMOS integration are well known.[50] The conductivity change due to reaction of the metal oxide layer with the gas is a measure of the concentration of the gas. In general, when the gas takes electrons from the surface of a metal oxide (oxidizing gas), the conductance of the metal oxide layer decreases, and when the gas gives electrons to the metal oxide (reducing gas), the conductance of the metal oxide layer increases. To activate these reactions, high temperature (>200 °C) is required, and thus, CMOS metal oxide gas sensors must have microhotplates to increase the temperature of the sensitive metal oxide layer. The paper by Barsan et al.[51] presents a complex conduction model of metal oxide gas sensors.

Table 1. Characteristics of Several ChemFET Sensors with Integrated Circuits

authors	target	detection range	sensitivity	functions of integrated circuits	CMOS process detail (Foundry Company)	area of chip	power consumption[a]
Yang et al.[24]	H^+	pH 4−12.5	53.7 mV/pH	amplifier	0.35 mm, 4-metal, 2-poly (Charterd)	5 mm^2	N/A (Vdd = 3.3 V)
Chin et al.[25]	H^+	pH 2−10	58 mV/pH	amplifier	0.5 mm, 2-metal, 2-poly (UMC)	3.24 mm^2	N/A
Milgrew et al.[32]	H^+	pH 3−7.4	46 mV/pH	amplifier, decoder, ADC	0.35 mm, 3-metal, 2-poly (Austria Micro Systems)	12.3 mm^2 (16 × 16 array)	∼60 mW (Vdd = 3.3 V)
Hizawa et al.[33]	H^+	pH 4−9.1	229 mV/pH	charge-transfer, source follower	5 mm, 1-metal, 1-poly	26 mm^2 (10 × 10 array)	N/A
Hammond et al.[36]	H^+	7 pH unit	48 mV/pH	MCU, SRAM, ADC	0.6 mm, 3-metal (Austria Micro Systems)	15 mm^2	∼30 mW (Vdd = 3.3 V)

[a] N/A indicates the information was not available in the reference.

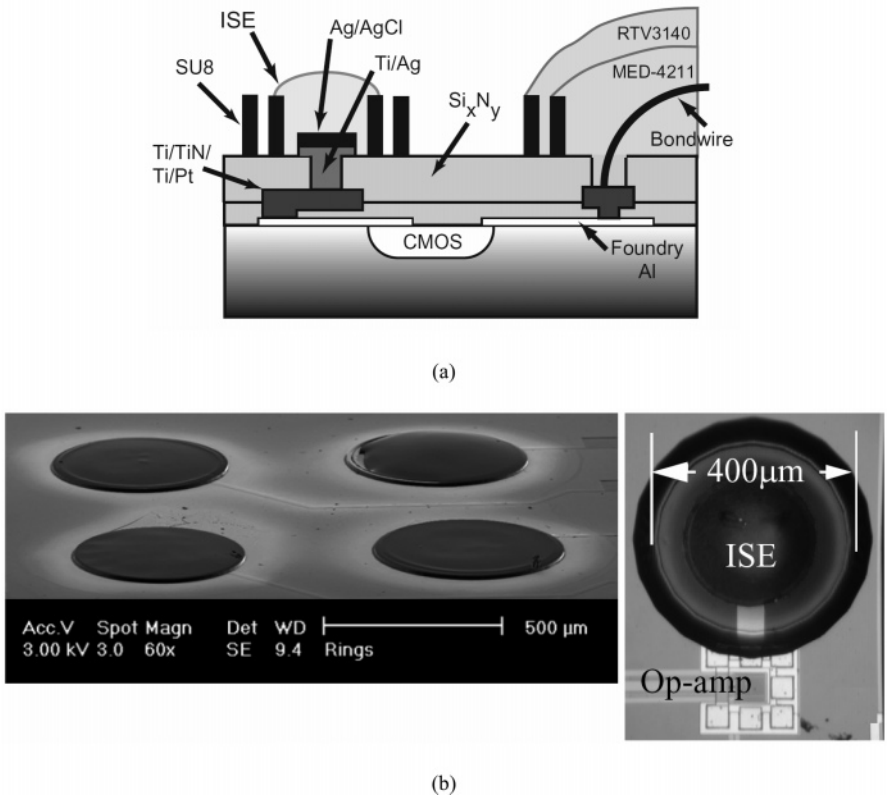


Figure 6. (a) Cross-section of an ISE sensor, and (b) SEM images of four ISEs and an active ISE. Reprinted with permission from ref 46. Copyright 2004 Transducers Research Foundation.

Useful electronics to integrate with a metal oxide gas sensor include a readout circuit for the sensor, a temperature monitoring and control circuit, a heater driving circuit, and an interface circuit for the output connection. A system developed by Graf et al.[52] is an example of such a monolithic metal oxide gas sensor for carbon monoxide (CO). This sensor used tin oxide (SnO_2) as the gas-sensitive material and integrated a polysilicon heater, polysilicon temperature sensor, and platinum electrodes on the sensing region. Figure 7 is a picture of the microhotplate and the complete system.[52] This research group has demonstrated several similar sensors for CO detection.[53−56]

Another application of electronics for resistive sensors is in controlling arrays of metal oxide sensors. Afridi et al.[57] fabricated four microhotplate gas sensors on a chip with a polysilicon heater and two gas-sensitive materials: SnO_2 and titanium oxide (TiO_2). They also integrated op-amps, MOSFET switches, a decoder for selecting the gas sensors, and bipolar junction transistors (BJTs) for switching the heaters. The sensor was tested using hydrogen, carbon monoxide, and methanol. The same group extended their work to the integration of feedback control for the heater circuits, including an analog-to-digital converter (ADC), digital gain control amplifier, and digital-to-analog converter (DAC).[58] Bota et al.[59] also introduced a chip with four SnO_2 gas sensors with a heater controller circuit that used pulse-width modulation (PWM). Barrettino et al.[60] extended their sensor system of ref 52 to an array of three sensors having logarithmic conversion and offset correction in their readout electronics and a proportional integral derivative (PID) controller for each of the sensors in the array. This group also introduced an array of three SnO_2-based gas sensors for not only CO but also methane gas.[61] Guo et al.[62] introduced a 4 × 4 array of SnO_2 gas sensors with on-chip multiplexing and readout circuits for measuring methane (CH_4), hydrogen (H_2), ethanol, and CO. The base of the microhotplate (MHP) was

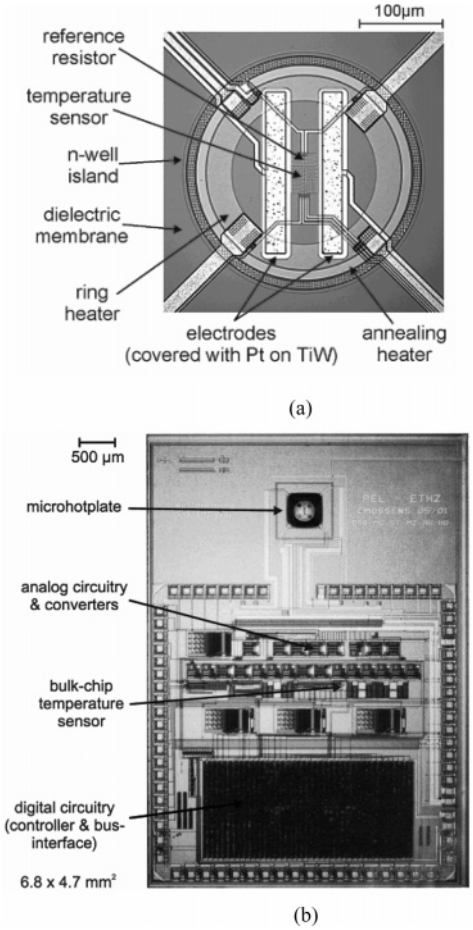


Figure 7. Photograph of (a) the microhotplate with heater, temperature sensor, and sensing electrodes and (b) the integrated sensor chip with microhotplate sensor and CMOS circuitry for signal acquisition and processing. Reprinted with permission from ref 52. Copyright 2004 American Chemical Society.

made with a multilayer stack consisting of 800 nm densified low-temperature oxide (LTO), 1 μm low-stress silicon nitride, and 2 μm LTO. Figure 8 shows the structure and SEM image of this sensor and fabricated sensor array chip.[62]

Fabrication of metal oxide resistive sensors requires bulk micromachining (etching of the silicon substrate) after fabrication of the CMOS circuits. Since the thermal conductance of silicon is high, the sensor structure must be thermally isolated from the other components on the chip so that the circuits can be cool while the sensing site is hot. This is accomplished by etching the substrate to suspend the sensor structure, which is attached to the rest of the chip by thin tethers of material. Resistive sensors based on cantilever deflection also require silicon substrate etching to form the cantilever structure.

When a microcantilever is coated with a polymer layer that expands when it absorbs a specific analyte, the analyte-induced stress of the polymer causes deformation (bending) of the cantilever.[63] Zimmermann et al.[64] applied this phenomenon to detect ethanol and humidity. Their system has a polymer-coated microcantilever with integrated piezoresistors, an ADC, and a serial digital interface. With the analyte-induced resistance change being detected with an on-chip Wheatstone bridge, the system showed sensitivities of 6 nV/ppm/V for ethanol and 5 μV/%RH/V for humidity.

Another type of resistive sensor, made of carbon black polymer, has been shown previously to be able to detect

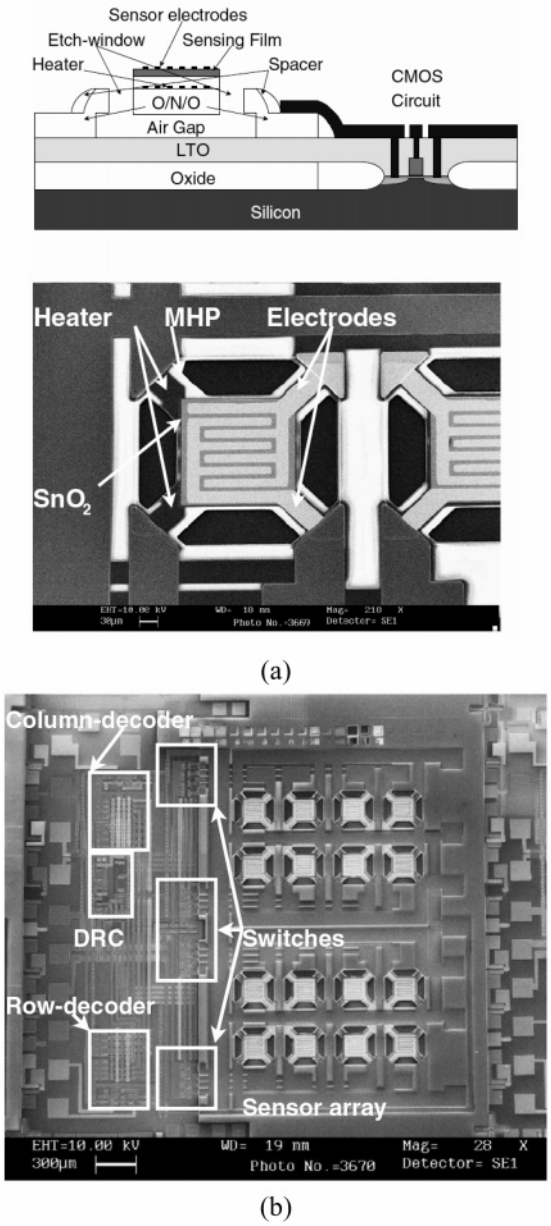


Figure 8. (a) Structure and SEM picture of the sensor element, and (b) photograph of a fabricated chip with a 4 × 4 gas sensor array and on-chip decoders, switches, and differential readout circuit (DRC). Reprinted with permission from ref 62. Copyright 2007 Elsevier.

various organic solvent vapors.[65] Unlike the metal oxide gas sensors, these devices operate at room temperature. Recent papers have described carbon black polymer as a sensing material for the development of an olfaction chip or electronic nose.[66−68] These papers integrate multiple polymer sensors with CMOS circuits for signal processing and classification of analytes. After training with known analytes, the sensor developed by Tang et al.[66,67] was able to distinguish eight odors with three polymer sensors using integrated learning and classifying circuits. Koickal et al.[68] showed an olfaction chip with five different polymer sensors and an on-chip spike-time-dependent learning circuit.

Dai et al.[69] described a resistive humidity sensor with integrated microheater and amplifier circuits. They used nanowire tungsten trioxide (WO_3) as a humidity-sensitive material. The integrated microheater controlled the operating temperature up to 75 °C, and the operational amplifiers were

Table 2. Characteristics of Several Resistive Sensors with Integrated Circuits[a]

authors	detection method	target	sensitivity	functions of integrated circuits	CMOS process detail (Foundry Company)	area of chip	power consumption
Graf et al.[52]	SnO_2	CO	N/A (detection limit = ±0.1 ppm)	temperature control, ADC, DAC, digital interface	0.8 μm, 2-metal, 2-poly (Austria Micro Systems)	17 mm^2	~100 mW (Vdd = 5.5 V)
Guo et al.[62]	SnO_2	ethanol CH_4 H_2 CO	high high medium low	readout circuit, decoder	5 μm, 1-metal, 1-poly	3.24 mm^2 (4 × 4 array)	~15.5 mW
Zimmermann et al.[64]	polymer-coated cantilever with piezoresistor	ethanol humidity	6 nV/ppm/V 5 μV/%RH/V	amplifier, ADC, DAC, digital interface	0.8 μm, 2-metal, 2-poly	14 mm^2 (2 sensors)	~50 mW (Vdd = 5 V)
Koickal et al.[68]	carbon black polymer	ethanol toluene	0.00012%/pm 0.00644%/pm	signal processing, on-chip learning	0.6 μm (Austria Micro Systems)	50 mm^2 (70 sensors)	N/A (Vdd = 5 V)
Dai et al.[69]	nanowire WO_3	humidity	4.5 mV/%RH	amplifier	0.35 μm (TSMC)	15 mm^2	~30 mW (Vdd = 3.3 V)

[a] N/A indicates the information was not available in the reference.

used for signal processing. Chow et al.[70] integrated multiwalled carbon nanotubes (MWCNT) with CMOS circuits for flow and chemical vapor sensing. They formed MWCNT on a foundry fabricated CMOS chip. A circuit for current control and an ADC were designed to measure the resistance change of the MWCNT due to flow variation or a chemical vapor initiated reaction on the surface of the MWCNT.

The characteristics of various resistive sensors with integrated circuits are summarized in Table 2.

2.2.2. Capacitive Sensors

Humidity sensors are the prototypical application for CMOS integrated capacitive sensors since the high dielectric constant of water (78.4 at 25 °C, liquid phase)[71] causes a large capacitance change when water is absorbed into a membrane placed between electrodes. The most common type of capacitive humidity sensor uses a polyimide membrane as the sensing material and interdigitated electrodes for measuring the capacitance.[72,73] Qui et al.[72] integrated signal processing and a calibration circuit to form a capacitive humidity sensor on a chip. Dai[73] used an integrated ring oscillator to convert the capacitance change to an oscillator frequency change.

Kummer et al.[74] demonstrated configurable electrodes on a capacitive gas sensor. Two polymers, poly(etherurethane) and poly(dimethylsiloxane), used as gas-sensitive layers, were coated on interdigitated electrodes. On-chip integrated circuits were used for control of the configurable electrodes and signal acquisition. This sensor system was able to detect low concentrations of volatile organic compounds (n-octane and toluene) in humid air.

Stagni et al.[75] developed a label-free deoxyribonucleic acid (DNA) sensor array utilizing the capacitance change of probe DNA-coated interdigitated gold electrodes when hybridization of the prove DNA and target DNA occurs. They integrated circuits for signal processing of each of 128 sensors in the array and an ADC for data conversion on the same chip, showing the possibility of label-free DNA detection.

2.3. Voltammetric Sensors

In voltammetry, the electrodes, which are typically made of gold, silver, platinum, palladium, carbon, or graphite, are critical to the operation of the sensor. Deposition of these metals is not CMOS compatible, and thus, the electrodes must be formed after fabrication of any CMOS circuits. The reference electrode also presents challenges for miniaturized electrochemical sensors. A small, stable, long-lived reference electrode is needed. Silver/silver chloride (Ag/AgCl) has been used as a reference electrode in many electrochemical applications, but it maintains a fixed potential only when the chloride concentration is fixed, and its lifetime is limited because silver chloride can be dissolved in aqueous solutions.

A key component to be integrated with voltammetric sensors is the potentiostat, which applies the potential between electrodes and measures the current from the resulting reaction. Many papers report the development of CMOS potentiostats for general electrochemical sensors or a specific application.[76−85]

Zhang et al.[86] developed an electrochemical sensor array with an integrated potentiostat for monitoring electrochemical reactions using cyclic voltammetry. The system has a 3 × 3 array of gold working electrodes, a gold counter electrode, and a Ag/AgCl reference electrode on top of CMOS range-programmable amperometric readout amplifier circuits for cyclic voltammetry, which can measure currents in the range from 10 pA to 10 μA.

Martin et al.[87] introduced a microinstrument for trace detection of heavy metals that was designed as an in situ rainwater analyzer. For heavy metal detection, they used subtractive anodic stripping voltammetrs since this method reduces the signal from interfering analytes such as dissolved oxygen. Amplifiers, a pseudo-differential potentiostat, and data conversion circuits were integrated for signal acquisition and processing. The sensor, having a gold working electrode, platinum counter electrode, and Ag/AgCl reference electrode, was fabricated on top of the CMOS circuits. The system detected 0.3 ppb of lead. The passivation layer for protecting the circuit from solution uptake can endure more than 100 days in saturated salt solution. However, the integrated Ag/AgCl reference electrode failed after 10 h in solution due to poor adhesion.

Several recent publications describe on-chip electrical DNA detection utilizing a chronocoulometric detection method by Dr. Thewes' group.[88−91] These detection systems measure the redox-cycling current at the electrodes in the

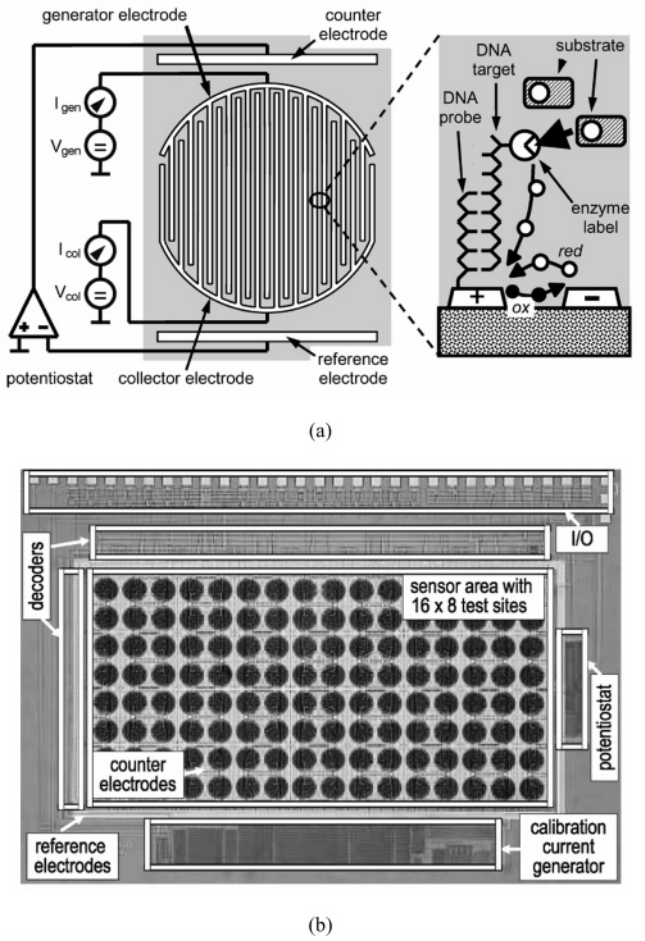


Figure 9. (a) Schematic plot of the electrode configuration, schematic illustration of the redox-cycling process, and (b) chip microphotograph. Reprinted with permission from ref 90. Copyright 2004 IEEE.

time domain by applying an appropriate potential when the labeled target DNA is hybridized with the probe DNA. If the probe DNA is not hybridized with the target DNA, there is no electron exchange on the electrodes. The CMOS potentiostat[89] and in-pixel ADC were monolithically integrated.[90] Figure 9 shows the electrode configuration, an illustration of the redox-cycling detection, and a photograph of the fabricated chip, which has a 16 × 8 sensor array, along with circuits for calibration current generation, a potentiostat, and decoders.[90]

3. Optical Sensors

Optical-based chemical sensors detect the intensity of photon radiation that arrives at a sensor. The intensity can be modulated by absorption, or the direction of wave propagation or wavelength can be modulated by scattering, refraction, or reflection. The detected photons could be emitted by fluorescence, phosphorescence, or chemi-/bioluminescence. Each of these photon sources has a known relationship to a given chemical reaction, facilitating chemical sensing with high selectivity.

Fiber-optic sensors[92] are the most common type of optical sensors, but they are not suitable for CMOS integration (even with on-chip waveguides) because the indirect band gap of silicon[6] makes it difficult to generate the light source. Direct band gap semiconductors such as gallium arsenide (GaAs) and indium phosphate (InP) (III−V semiconductors) are

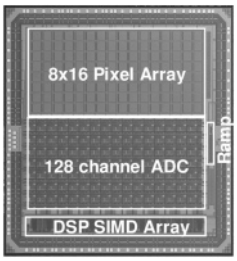


Figure 10. Photograph of luminescence detection SoC with pixel array, ADC, and DSP SIMD array. Reprinted with permission from ref 97. Copyright 2006 IEEE.

suitable for photon generation and detection, but these technologies are more expensive than silicon and have not been used for integrating more complex electronics with optical sensors. Light detection, on the other hand, can be done with silicon-based devices using a photodiode or phototransistor. Image sensors fabricated in CMOS technology are expanding their share of the image sensor market because, unlike charge-coupled devices (CCDs), they can incorporate pixel-level analog and digital processing circuits.[93] This capability is also advantageous for optical chemical sensors utilizing CMOS photodetectors.

Fluorescence- and phosphorescence-based sensors require bulky excitation sources, so they are not as compatible with miniaturized solid-state photosensors and electronics, but many papers report bioluminescence detectors having integrated CMOS circuitry.[94−98] Simpson et al.[94] showed a bioluminescent bioreporter integrated circuit (BBIC) having integrated signal processing circuits; the sensor was able to detect 4×10^5 cells/mL using the *Pseudomonas fluorescens* 5RL bacterial cell as a bioreporter. The following year, this group modified their signal processing circuit to reduce leakage current in the photodiode and lower the detection limit.[95] Vijarayaghavan et al.[98] also showed a BBIC for liquid- and air-based detection of salicylate and naphthalene using the *P. fluorescens* 5RL bacterial cell as the bioreporter.

Iordanov et al.[96] developed a 4 × 5 photodiode array with front-end electronic circuits for bioluminescence detection and a 5 × 5 photodiode array for fluorescence detection. Luciferin and luciferase were mixed with different concentrations of adenosine triphosphate (ATP), and the decay of luminescence intensity was monitored over time. For fluorescence detection, an enzyme of Protein Tyrosine Phosphate was mixed with 6,8-difluoro-4-methylumbelliferyl phosphate (DiFMUP) since the reaction product 6,8-difluoro-4-methylumbelliferone (DiFMU) exhibits an excitation/emission maxima of ~358/455 nm. The fluorescence intensity increased with time when the mixture was exposed to an ultraviolet (UV) light source since the concentration of product (DiFMU) increased as the reaction progressed.

A system-on-a-chip (SoC) approach for optical sensors was demonstrated by Eltoukhy et al.[97] The chip included a CMOS bioluminescence detection sensor with an 8 × 16 photodiode array, a 128-channel 13-bit ADC, and a column-level single-instruction multiple-data (SIMD) digital signal processing (DSP) circuit. Figure 10 shows the fabricated bioluminescence chip.[97] A mixture of luciferin and luciferase with ATP was used as a bioluminescence source. The system was able to detect emission rates below 10^{-6} lux over 30 s of integration time at room temperature.

Photodetectors for optical sensors can be fabricated concurrently with electronic circuits as part of the CMOS process flow, avoiding the need for complex postprocessing

steps. Selection of a photodetector for a given optical sensor can be a challenge because of the variety of semiconductor photodetectors: *p-n* photodiode, *p-i-n* photodiode, avalanche photodiode, and phototransistor. The characteristics of these photodetectors are summarized in a review article by Yotter et al.[99] that provides the information needed to select the most appropriate detector for a given application.

4. Mass-Sensitive Sensors

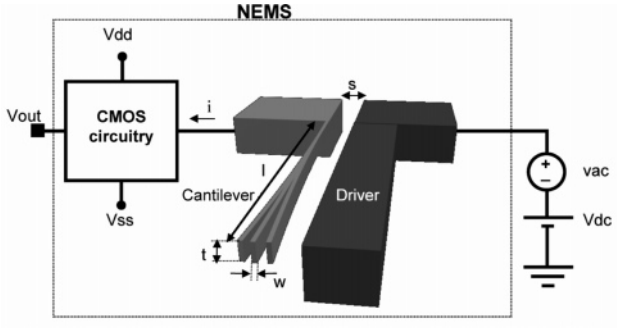
Mass-sensitive sensors detect the change of mass on a sensing layer. In the case of chemical sensors, the mass changes arise from absorption, evaporation, deposition, or erosion due to chemical reactions. Several sensing structures have been employed to detect these mass changes, such as the thickness shear mode (TSM) resonator, quartz crystal microbalance (QCM), and surface acoustic wave (SAW) device.[100] Most of these devices are not suitable for integration with CMOS circuits.

The mass-based sensors that do incorporate CMOS circuits use the resonant frequency shift of a cantilever beam to detect the change in mass.[101−105] The resonant frequency is very sensitive to the beam's mass. The cantilever is electrostatically actuated, and the resulting vibration of the cantilever changes the capacitance between the cantilever and a sensing electrode. The integrated electronics are used to monitor the frequency through this capacitance change.[101−105] Verd et al.[102] developed an integrated submicroelectromechanical resonator with readout circuits. Figure 11 shows the schematic of the cantilever-based mass-sensitive sensor and a photograph of the fabricated chip.[102] The cantilever, driver electrode, and polarization capacitor (nanocapacitor) were fabricated in the "nanoarea" after the CMOS circuitry was fabricated and passivated. The cantilever dimensions were 40 μm (length) $\times$ 840 nm (width) $\times$ 600 nm (thickness).

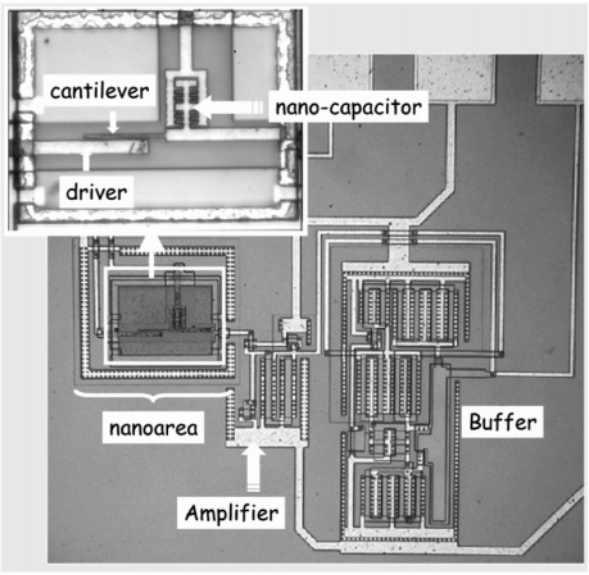
Cantilever structures, which are essential to this type of sensors, are not CMOS compatible. The above papers used two different ways of fabricating cantilevers on CMOS circuits. For polysilicon cantilevers,[101−104] a region of polysilicon was patterned in the CMOS circuit layout. After completion of CMOS processing, the passivation layer in the region of the polysilicon cantilever was removed and the polysilicon was patterned and etched to form a cantilever structure. Finally, the oxide under the polysilicon layer was removed to release the cantilever. Li et al.[105] fabricated a vertical cantilever composed of a stack of metal and dielectric materials. They covered the circuit and cantilever areas with a metal layer that was used as a mask. Dielectric material between the cantilevers was anisotropically etched down to the silicon surface. Finally, the exposed silicon was etched to release the cantilever.

5. Integration of Different Transducers on a Single Chip

Integration of two or more types of sensors on a single chip offers a number of potential advantages. Signals from one transducer could help compensate or calibrate other sensors, and simultaneous detection could increase the selectivity or sensitivity of the system. With different transducer technologies available, a broader set of chemicals can be detected. If the analyte of interest is detectable by two different sensor types, the confidence in the measurement is significantly increased. From a circuit point of view, it might be possible to share circuit blocks such as an ADC, DAC, and digital modules between the sensor types, thereby minimizing the total chip size and number of output pads.



(a)

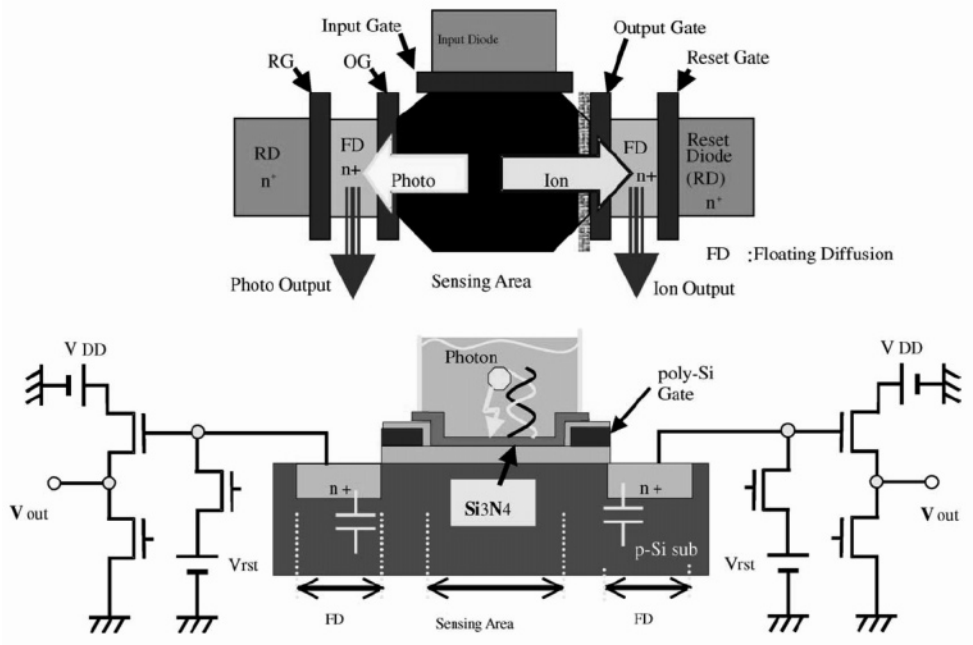


(b)

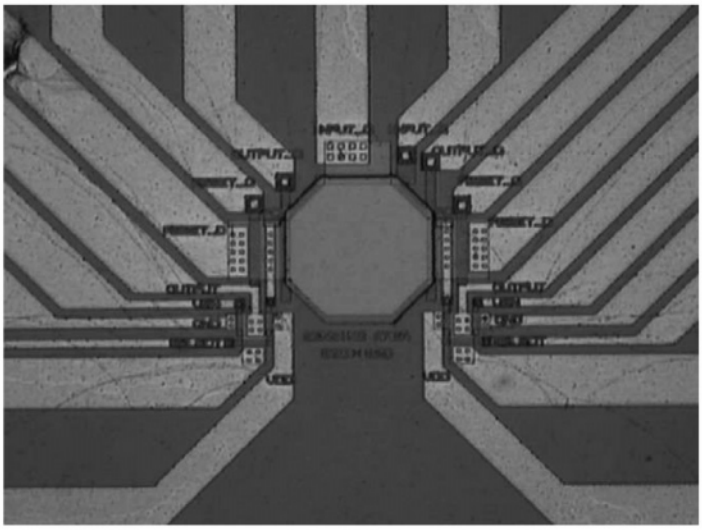
Figure 11. (a) Schematic drawing of a cantilever-based CMOS integrated mass-sensitive sensor, and (b) a photograph of a fabricated chip with resonator and readout circuit. Reprinted with permission from ref 102. Copyright 2005 IEEE.

As a simple example of integrating two different types of transducers on a chip, Covington et al.[106] made a CMOS integrated sensor with both a ChemFET and a chemoresistor on the same site. They used a carbon black polymer composite membrane for both a resistive gas-sensing membrane and the gas-sensitive membrane of a ChemFET. This integration improved the discrimination when detecting ethanol and toluene vapor in air.

Sawada et al.[107] presented an interesting device that can sense both photons and ions on the same pixel for the near-simultaneous detection of a photosignal and ion concentration. They used different mechanisms for photosensing and ion sensing and detected each parameter in a separate time period. For ion sensing, the depth of a surface potential well under the sensing region is converted to charge, and this charge is moved to a floating diffusion by a charge-transfer technique.[34] The amount of charge, which is proportional to the pH of the solution over the sensing area, is measured using an integrated source-follower circuit. For photon sensing, the electrons generated by incident photons are transferred to the floating diffusion and the accumulated



(a)



(b)

Figure 12. (a) Concept, schematic diagram, and (b) photograph of the device in ref 107. Reprinted with permission from ref 107. Copyright 2005 Elsevier.

charge is measured. Figure 12 shows the concept, schematic diagram, and photograph of the device.[107] The performance of each sensing mechanism was tested using solutions of various pH and under several light intensities. The output of each sensor was unaffected by the other parameter, i.e., there was no cross-talk between the two sensors.

A programmable CMOS electrochemical sensor array for biomolecular detection was developed by Hassibi et al.[108] The digitally programmed system has a 5×10 sensor array that can perform impedance spectroscopy, voltammetry, potentiometry, and field-effect sensing. The chip was fabricated in a standard CMOS processes with no postprocessing, and the circuits for electrode configuration, array control, and signal readout for each analysis method are fully integrated on a single chip. Figure 13 shows the pixel configuration of the sensor and a photograph of the fabricated chip.[108] However, application of the system is limited to biosensor or nonfaradaic electroanalytical techniques because the system was fabricated by a standard CMOS process. The working electrode of the system was made of aluminum/1% silicon (Al/1%Si), which is commonly used for interconnect in CMOS circuits, rather than platinum, gold, or silver, which would have been much better electrochemically. Therefore, applications are limited to the conditions in which aluminum is not disruptive or corroded (within $\pm$200 mV of the applied bias). Nevertheless, the authors believe that this device could be applied to many biochemical detection platforms, including DNA and protein assays.

For biomolecular sensing, a CMOS integrated system with on-chip optical and electrochemical dual-image CMOS

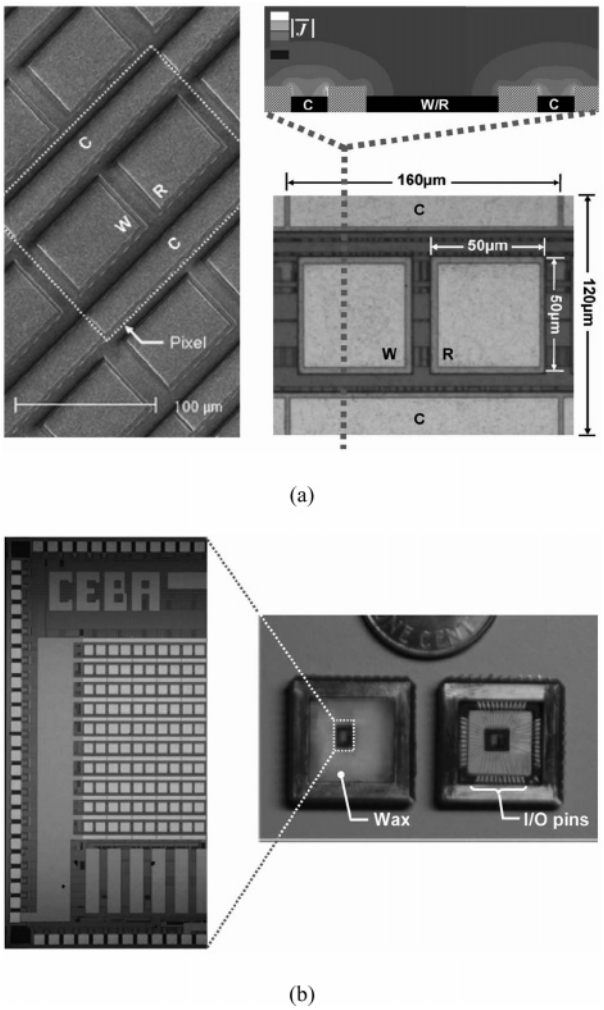


Figure 13. (a) SEM picture and top view of the micrograph picture of the differential transducer structure, and (b) microphotograph of fabricated chip and package. Reprinted with permission from ref 108. Copyright 2006 IEEE.

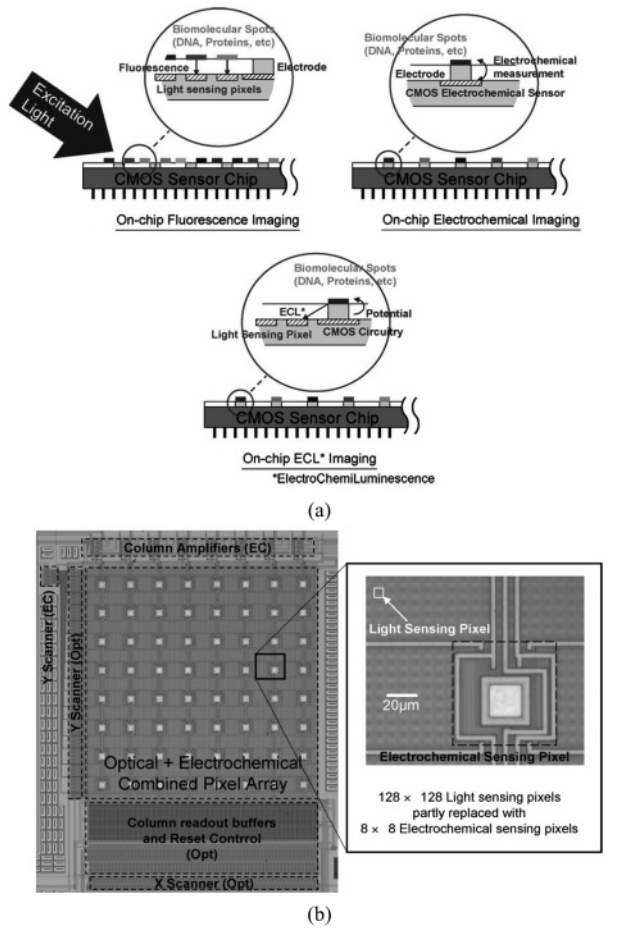


Figure 14. (a) Concept of on-chip biomolecular detection using optical and electrochemical dual-image CMOS sensors, and (b) photograph of fabricated optical and electrochemical dual-image CMOS sensor chip. Reprinted with permission from ref 109. Copyright 2007 Elsevier.

sensors was presented by Tokuda et al.[109] The system can measure two-dimensional voltammetry with an 8 × 8 electrochemical sensor array and perform simultaneous image analysis using a 128 × 128 CMOS image sensor array with on-chip readout circuits. Figure 14 shows the concept of the dual-image sensor and a photograph of the fabricated chip.[109] In addition to the separate optical and electrochemical detection, the integrating image sensor and electrochemical sensor make possible on-chip electrochemiluminescence imaging. The chip uses a modified three-transistor CMOS active pixel sensor[110] for light sensing and has deposited gold on the working electrode site. For voltammetric tests, a two-electrode configuration is used with an external Ag/AgCl reference electrode. The performance of simultaneous detection of optical and electrochemical sensing was tested using an agarose gel island in a saline droplet.

6. Conclusions and Outlook

From the papers reviewed here, it is clear that integration of electronics with chemical sensors provides a number of performance advantages. The system signal-to-noise ratio can be improved by buffering and converting signals close to the transducers. System size and power dissipation can be reduced by integrating the instrumentation with the sensors. Sensing systems, rather than just sensors, can be batch fabricated. Multiple and complex analyses can be performed by precise on-chip control circuits. The chemical sensors that called for non-CMOS-compatible metals, insulators, or membranes realized these through appropriate postprocessing.

Ongoing research in integrating circuits with chemical sensors will bring remarkable advances in the field of sensing and lead to true systems-on-chips. Realization of complete SoC chemical sensors calls for more circuits to be integrated, including not only signal processing circuits for data readout and conversion but also circuits such as microcontrollers, digital signal processing circuits, memory, and circuits for wired or wireless communications. Recently developed low-power wireless communication standards such as Bluetooth[111] and ZigBee[112] could be good options for sensor systems requiring remote monitoring or in vivo biochemical analysis.

Applying microfluidics techniques or lab-on-a-chip (LOC) technology with CMOS integrated chemical sensors, whether monolithic or hybrid, is another promising research direction. LOC devices are widely used in chemical and biological analysis.[113] Linder et al.[114] and Ghafar-Zadeh et al.[115] have shown examples of such devices. An on-chip processor could control the microfluidic flow of sample, reagents, and calibration solutions, reducing the volumes of these needed, and performing on-chip calibration and reconditioning of the sensor. Merging the techniques for sample transport, filtering, and mixing from microfluidics with CMOS integrated chemical sensors may lead to a great synergy.

There are challenges in fabricating CMOS integrated chemical sensors. Development of such sensors requires expertise in chemical/biological analysis, circuit design, semiconductor chip fabrication, and packaging. The cost of these sensors makes them ill suited for disposable or short-term use. Still, integration of CMOS circuits with chemical sensors is a solution for applications requiring fast, accurate, complex analyses, and the functionality per unit cost of semiconductor processing continues to improve.

7. Acknowledgments

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