

An integrated CMOS high voltage supply for lab-on-a-chip systems

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Electrophoresis is a mainstay of lab-on-a-chip (LOC) implementations of molecular biology procedures and is the basis of many medical diagnostics. High voltage (HV) power supplies are necessary in electrophoresis instruments and are a significant part of the overall system cost. This cost of instrumentation is a significant impediment to making LOC technologies more widely available. We believe one approach to overcoming this problem is to use microelectronic technology (complementary metal-oxide semiconductor, CMOS) to generate and control the HV. We present a CMOS-based chip (3 mm × 2.9 mm) that generates high voltages (hundreds of volts), switches HV outputs, and is powered by a 5 V input supply (total power of 28 mW) while being controlled using a standard computer serial interface. Microchip electrophoresis with laser induced fluorescence (LIF) detection is implemented using this HV CMOS chip. With the other advancements made in the LOC community (e.g. micro-fluidic and optical devices), these CMOS chips may ultimately enable 'true' LOC solutions where essentially all the microfluidics, photonics and electronics are on a single chip.

Introduction

Despite progress in lab on a chip (LOC) systems, the cost effectiveness, ease of manufacturability and portability of the external instrumentation remains largely unaddressed.¹ Microfluidic chips have been demonstrated in a wide range of medical diagnostic applications, from genetic profiling and diagnosis² to disease monitoring,³ but this has been done in conjunction with expensive and large instruments. To realize a truly portable LOC system it is necessary to replace this external infrastructure while simultaneously reducing cost, size and power consumption. Capillary electrophoresis (CE), a key LOC technology, has important medical applications but typically requires high voltage (HV) power supplies, optics, and interface circuits that limit portability and hinder the development of a LOC-based point-of-care tool. Several advancements in the integration and cost-effectiveness of optical detection on microfluidic chips^{4,5} have been made and many photonic components have been ported to microelectronic chips,⁶ yet so far, little has been achieved in miniaturizing HV components. Much of the infrastructure needed for CE is for the high voltage sub-system, consisting of high voltage generation and control, switching and interfacing. We recently demonstrated⁴ a \$1000 genetic analysis tool that implements CE and is an advancement in portability and cost-effectiveness. In that system, the HV subsystem accounts for almost 50% of the system cost and most of its size. In a more general context, HV components are central to the operation of many micro-electro-mechanical system (MEMS) devices in addition to CE systems, yet there are no demonstrations of truly miniaturized HV sub-systems.

In terms of electrophoresis, there are presently several bench-top electrophoresis platforms such as the ABI PRISM 3100 (Applied Biosystems, Foster City, CA, USA), Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA), and the Microfluidic Tool Kit (μ TK, Micalyne Inc., Edmonton, AB, Canada). These systems are based on relatively large external high-voltage power supplies (and relays) requiring complex control/interface hardware and software, thus are not suitable as portable systems. In recent reports relating to HV sub-systems for CE,⁷⁻¹⁰ the required HV is generated using either one or multiple off-the-shelf DC–DC converters (e.g. a widely used commercial component made by EMCO, Sutter Creek, CA), and switching is performed either by manual switches or electro-mechanical relays assembled on printed circuit boards (PCBs). Often, to also ensure electrical isolation, multiple circuit boards are used, one for the HV components, and the other for the control circuitry—this further increases size. Additionally, the interface and communication with these components adds to complexity and cost. Recent developments involving HV sub-systems include: Jackson *et al.*⁷ incorporated a DC–DC converter into a CE system with electrochemical detection. In another demonstration, Kappes *et al.*,¹⁰ presented a battery-powered CE system that could generate up to 30 kV with amperometric, potentiometric and conductometric detection. Similarly, Garcia *et al.*⁹ built a battery operated 3-channel HV supply (with 3 DC–DC converters). Erickson *et al.*¹¹ introduced a single HV module that generates up to 700 V, but provides only a single channel (i.e. a single DC–DC converter) with manual switching. In a related demonstration, to achieve HV precisely, Collins *et al.*¹² presented a resistor divider network to vary the generated voltages, based on the use of a DC–DC converter. One of the first demonstrations of a portable CE system was by Sandia laboratories,⁸ in work that miniaturized the entire CE system (with DC–DC supplies and relays) and is

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directed towards protein separations. A particularly impressive and optimized HV module reported recently by Jiang *et al.*¹³ demonstrated a HV sub-system that is powered from a universal serial bus (USB) port. In that work multiple DC–DC converters with multiple control circuit boards were used.

Although the development of the LOC technologies, including the above work in HV sub-systems, has been impressive, there have been no reports to date of a HV sub-system that is compatible with a very inexpensive, portable and highly integrated diagnostic. Our goal is ultimately to build ‘true’ LOC diagnostic instruments consisting, almost entirely, of a single (or several) chips. In order to do this, there is a need to realize an integrated HV sub-system (*i.e.* a single module that could generate and control high voltages) that is inexpensive and highly compact—to our knowledge there have been no prior demonstrations of such sub-systems.

In the present work, we demonstrate a single-chip HV sub-system that generates, controls, and distributes HV potentials, and interfaces with an external controlling device (a laptop computer). This chip is designed and fabricated with a mixed high/low voltage microfabrication process. Because of the mixed high/low voltage devices, both low voltage and high voltage components are integrated in a single chip. The low voltage (high density) electronics provides an interface capability over a serial link to a personal computer, while the high voltage (lower density) electronics interfaces directly to the microfluidic chip. As a result, one serial link (with power delivery capability, such as USB) can be used to power and control this chip. Eight independent HV outputs are provided in the design, which facilitates the implementation of wide range of CE protocols. Rapid switching capability (in the range of several kHz), coupled with longevity, is achieved by replacing the commonly used mechanical relays with solid-state HV switched-output circuits, integrated on the complementary metal-oxide semiconductor (CMOS) chip. In addition to the CMOS chip, only a few external discrete components such as capacitors and a single inductor and diode are required to perform a complete CE functionality (Fig. 2b). Thus, the small footprint (3 mm × 2.9 mm) of the chip itself and its low power consumption (28 mW) make this module highly suitable for portable and manufacturable LOC solutions. To the best of our knowledge, this is the first demonstration of a microelectronic chip-based LOC HV sub-system.

System description

To demonstrate the functionality of the HV CMOS chip for CE we replace the HV module in our earlier demonstration,⁴ with the present microelectronic chip. As shown below, the system uses a CCD camera, a filter (not shown), a lens and a solid state laser for fluorescence detection. Although the HV CMOS chip could be interfaced through any serial interface, it was convenient to use a microcontroller (PIC 16F877, Microchip Technology Inc., Chandler, AZ, USA) to perform the USB to serial peripheral interface, SPI (a standardized communication protocol) conversion. Although both SPI and USB interfaces are serial in nature, the latter is far more complex and would require a very considerable amount of additional CMOS design. Such USB interfaces are commonly implemented in silicon and are not the focus of this work.

CMOS chip

This HV chip (Fig. 2a) was designed with the Cadence integrated circuit design tools (Cadence Design Systems Inc., CA, USA) and fabrication was performed using DALSA Semiconductor's (Bromont, QC, Canada) three metal layer, triple well, dual gate oxide 0.8 μm 5 V HV CMOS/DMOS (double diffused MOS) process. This process supports both the HV circuitry, along with the low-voltage circuitry (5 V) for digital logic control and communication. From a functionality standpoint, this chip consists of three main units (Fig. 2c): (a) DC–DC boost converter that generates the required voltage, (b) eight independently controlled HV switched-outputs that are coupled to the microfluidic chip and, (c) communication and control interface (CCI) that controls and monitors the operation of the chip.

DC–DC boost converter

A common non-isolated inductive DC–DC boost converter is implemented in CMOS to generate up to 150 V using a 5 V input supply. The operating principle of this is detailed in ref. 14,15. Briefly, the implementation involves storing energy on an inductor from the 5 V supply and periodically breaking the current flow. By doing so, the inductor opposes any changes (a decrease in this case) in current by reversing its potential and inducing high electric potential across its terminals, briefly supplying current at high voltage through a diode to the HV supply capacitor. This HV supply is programmable *via* the serial interface, with an internal voltage comparator shutting down the boost converter when the supply reaches the set point specified by a digital to analog converter (DAC) (all of these function integrated on chip). This closed loop control mechanism has a resolution of less than 2 V at the output. Further details can be found in ref. 16,17.

HV switched-output circuit

The CCI circuitry controls the HV transistors, which drive the eight HV 300 V-tolerant outputs, with each output separately controlled. Five of these outputs can be driven to the positive supply voltage (*e.g.* 150 or 300 V), ground (0 V) or disconnected (alternatively described as open circuit, float, high impedance or tri-state). To reduce the number of HV-transistors, three of the outputs can only be driven to ground or disconnected. The HV outputs are coupled to the microfluidic chip wells by platinum electrodes (Fig. 1).

Communication and control

Communication between the HV CMOS chip and a microcontroller (or any other control system such as a computer) is *via* a standard serial interface protocol (SPI). The communication and control interface decodes the SPI commands sent by the microcontroller using standard logic. These commands set and control the on-chip high-voltage supply output, as well as the state of the HV outputs.

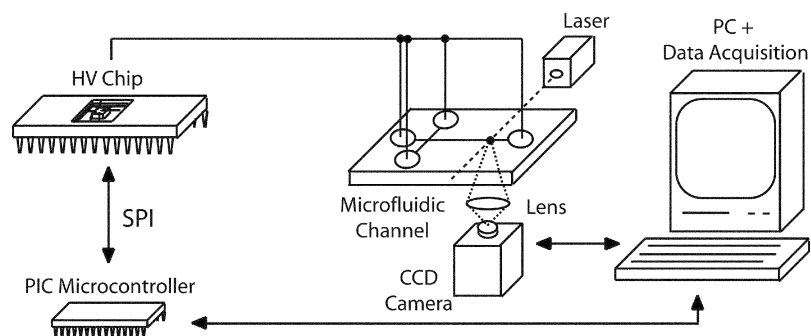


Fig. 1 System level block diagram of the set-up to perform microchip electrophoresis.

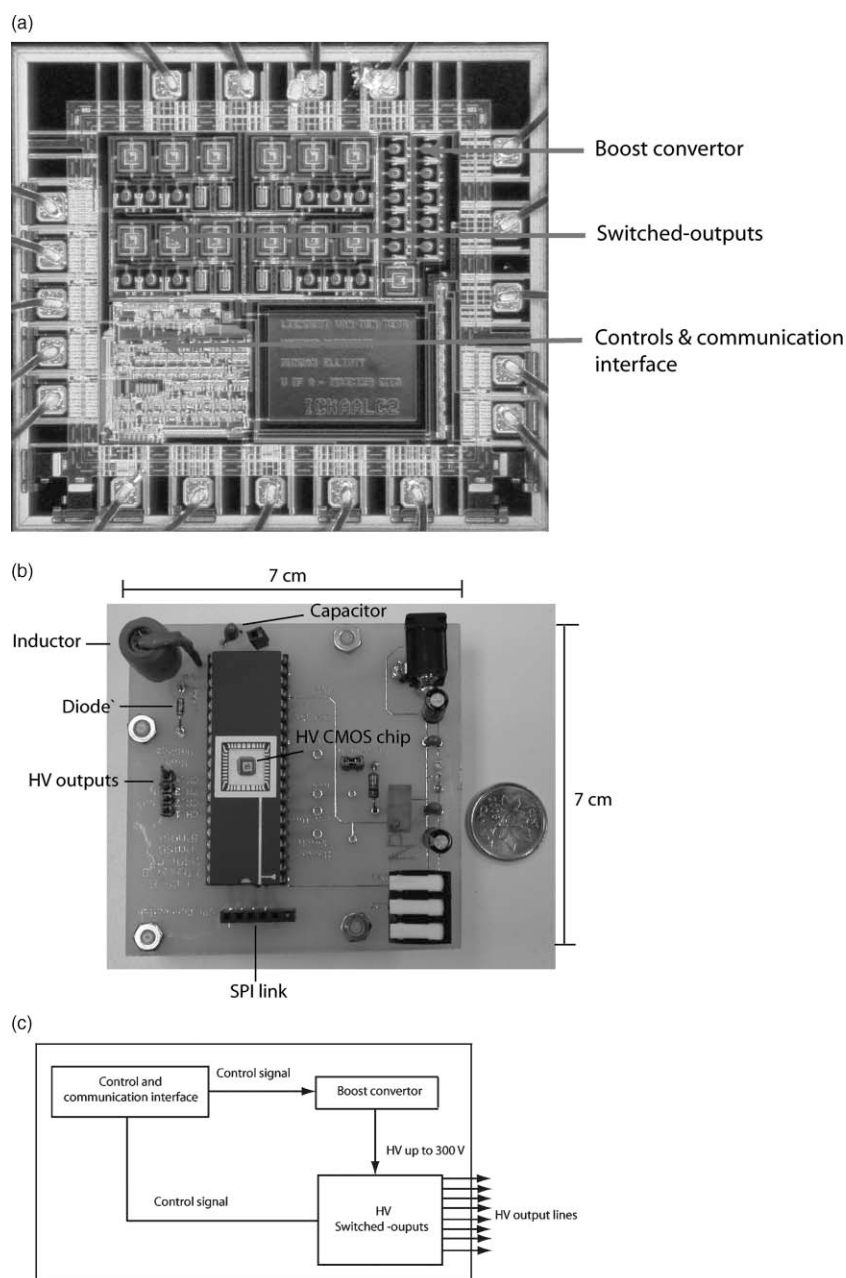


Fig. 2 (a) Photograph of one of our HV CMOS CE chips (3 mm × 2.9 mm)– we are developing several variations of this HV microelectronic chip. (b) The printed circuit board (7 cm × 7 cm) for hosting the HV CMOS chip. This board can readily be shrunk by compact placement of the few components and the use of smaller footprint components. To operate this HV CMOS chip, in addition to the CMOS chip, an inductor, a capacitor and a diode were used. (c) High voltage switched-output design, providing eight HV outputs.

Electrophoresis

Electrophoresis system

The optical set-up is based on a CCD camera detection much as described in ref. 4. A 5 mW commercial red laser (635 nm, M635-5, U.S. Lasers Inc., Baldwin Park, CA, USA) is used for excitation of the fluorophores. The emitted fluorescence is focused on a CCD detector (Meade Instrument Corporation, Irvine, CA, USA) by a 15 mm lens (MGF2TS, Edmund Optics Inc., Barrington, NJ, USA) through an interference filter (D715/100 m, Chroma Technology Corp., Rockingham, VT, USA) that prevents the excitation light (from the laser) from reaching the detector. Data acquisition software (running on a computer) captures and stores a sequential set of images taken during the electrophoresis run. This set of images is processed by custom-developed software to determine the intensity of the fluorescence. The analysed data is then plotted against time, producing an electropherogram (graph of fluorescence intensity vs. time) as shown in Fig. 4(a).

Electrophoresis protocol

Prior to the usage of the microfluidic chip (Fig. 3), pre-treatment of the channel surface is performed using a commercial dynamic coating (Gel Co., San Francisco, CA, USA) solution. The channel is then filled with 4% linear polyacrylamide (LPA) that is prepared by mixing 900 μL of water with 100 μL $10 \times \text{TTE}^{18}$ (Tris TAPS EDTA) and 400 mg of 10% LPA

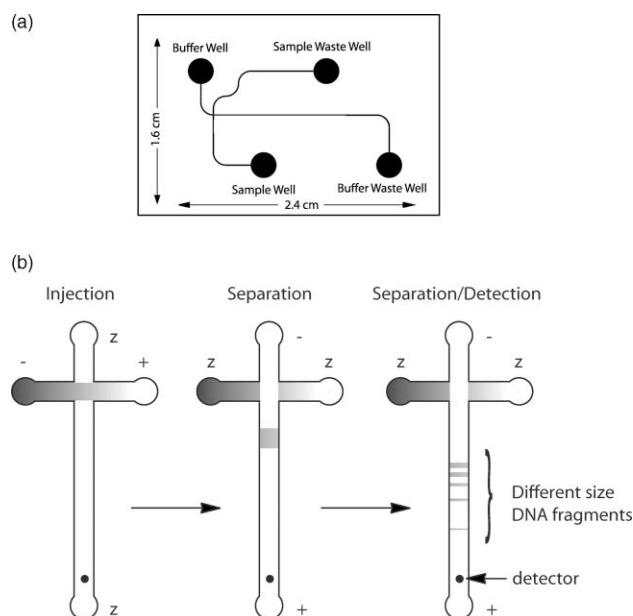


Fig. 3 (a) Glass-glass CE chip with separation channel length of 21 mm and optical detection performed at 13 mm from the intersection of the two channels (b) During the injection stage of CE, positive HV is applied to the sample waste well, with a ground state applied to the sample well and a floating state (high impedance) to both buffer well and buffer waste well. Injection is performed for 120 s. During separation, positive HV is applied to the buffer waste well for 180 s while the buffer well is set to ground and the sample well and sample waste well are set to a floating state—thus producing electrophoretic migration of DNA.

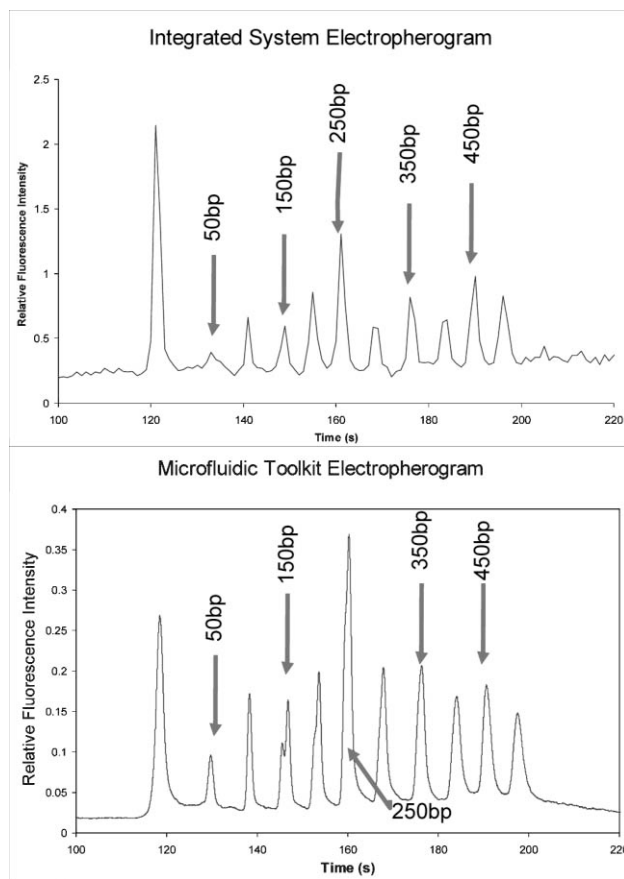


Fig. 4 Comparison of electropherogram results between the presented design and the commercial electrophoresis equipment (μTK).

(Polysciences, Inc, Warrington, PA (cat # 19901, MW 600 000–1 000 000). TTE buffer was prepared from 0.01 mM EDTA (ethylenediaminetetraacetic acid, Sigma, USA), 0.5 mM TAPS ((2-hydroxy-1,1-bis(hydroxymethyl)ethyl)amino)-1-propanesulfonic acid, *N*-[tris(hydroxymethyl)methyl]-3-aminopropanesulfonic acid, Sigma, USA) and 0.5 mM Tris (tris(hydroxymethyl)aminomethane, Fisher Scientific, Canada). The buffer well, sample waste well, and buffer waste well are then filled with 3.0 μL $1 \times \text{TTE}$ buffer solution while the sample inlet well (where the DNA to be separated is included) is filled with 0.3 μL of $1 \times \text{TTE}$, 1 μL sample (ALFExpress, 50–500 base pair sizer, Amersham Bioscience, Piscataway, NJ, USA and labelled with VIC dye that has an excitation wavelength of 532 nm and emission wavelength of 570 nm) and 1 μL distilled water. We adapted and optimized the CE protocols for adequate performance at short distance detection (e.g. 13 mm from the intersection). The protocol is detailed elsewhere.⁴

Results and discussion

Electrical characterisation

The integrated DC–DC boost converter supplies 150 V to the outputs at up to 15 μA . A leakage path in an internal rectifier diode limits the HV supply to 150 V. This limitation has been corrected in the next integrated circuit design, now being manufactured. The remaining functionality of the HV chip,

including the switched output, internal comparator, and control circuitries were all demonstrated successfully up to 300 V (using an external power supply). In the present work, we perform electrophoresis with 150 V applied, corresponding to electric fields of 71.4 V cm^{-1} . The output voltage ripple is measured to be $\approx 0.8 \text{ V}$ using a digital oscilloscope (MSO6034 A, Agilent Technologies, Santa Clara, CA, USA) for a $10 \text{ M}\Omega$ load (further details can be found in Table 1). The electrical resistance of the CE channel filled with 4% LPA is approximately $100 \text{ M}\Omega$, and hence, the output voltage ripple in practice will be lower than 0.1 V , since the output voltage ripple is inversely proportional to the load.

For certain applications, such as field inversion electrophoresis,¹⁹ switching of the HV outputs at up to 1 kHz is necessary. Commonly used mechanical relays have an operation life on the order of 10^6 switching cycles. Therefore, when they are rapidly switched the mean time to failure as per the lifetime specification is about 20 minutes. Hence, for such applications, solid-state switches are necessary—such as the ones integrated in our HV CMOS chip. The measured HV output combined rise time plus fall time is $16.45 \mu\text{s}$, far exceeding the requirements for 1 kHz switching, thus demonstrating the applicability of this HV CMOS chip for CE variants such as field inversion.

CE experiment

The HV CMOS chip is used to perform CE with the set-up in Fig. 1 with a standard injection–separation electrophoresis procedure to analyse fragments of end-labelled DNA. Using the same microfluidic chip, comparable performance (peak arrival times of the DNA fragments) was the present chip-based CE system (Fig. 1) as with a commercial confocal-based CE system, the μTK (manufactured by Micralyne, Edmonton, Canada). Additionally, we adapted our CE protocols to achieve short distance electrophoresis (21 mm long channel and 150 V) to realize comparable performance (resolution in separation of the DNA fragments) to our earlier demonstrations using a 95 mm long chip and 6 kV .²⁰ In our earlier CE-based diagnostics we typically detected the presence or absence of a fragment of DNA (signifying the presence or absence of the genetic sequence or pathogen) in the size range of 200 base pairs to 300 bps ,²⁰ hence, here we evaluate the fragment resolution of the electropherograms in this particular range. Using the approach in ref. 21, the resolution in DNA separation for this prototype system was evaluated and found to be 15 bps , which is comparable to the 12.6 bps on the commercial μTK system.⁴

The signal to noise ratio (SNR) of the present system is somewhat lower than that of the commercial system and this is due to the simplified optics and CCD camera in our set-up (Fig. 1) as compared to the expensive confocal optics in the commercial system (μTK). Although we are in the process of improving the performance of the optical detection, the present system is adequate for performing genetic analysis. Hence, the present chip enables the simple system shown in Fig. 1, along with a CCD, a solid state laser, a lens and filter, to provide comparable capabilities to more conventional electrophoresis instruments (Fig. 4).

Table 1 Switched-output circuit measurements for up to 300 V (driving a $52 \text{ pF} \parallel 10 \text{ M}\Omega$ load)

Parameter	Measured	Unit
Rise time (10%–90%)	9.99	μs
Fall time (10%–90%)	5.82	μs
Slew rate (rising)	24.00	$\text{V}/\mu\text{s}$
Slew rate (falling)	42.00	$\text{V}/\mu\text{s}$
Min operating voltage	5.00	V
Source current (@ $\text{VOH} = 299 \text{ V}$)	149.9	μA
Sink current (@ $\text{VOL} = 1 \text{ V}$)	−387.6	μA

Conclusion

Here, we demonstrate HV generation, switching and low voltage control and interfacing using a single microelectronic chip. With this demonstration of a CMOS-based HV sub-system, we replace the widely used DC–DC converters, relays, control and interface circuits on multiple boards with a $3 \text{ mm} \times 2.9 \text{ mm}$ HV microelectronic chip. We demonstrate separation of a DNA sizer by combining this HV microelectronic chip with a microfluidic chip, and have found comparable performance with a commercial bench-top system, yet the HV chip could cost as little as $\$10$ in mass production.

With this technology and with minimal additional cost, we expect to integrate other functionality on the CMOS chip to realize a complete CMOS-based LOC CE system. The present HV chip halves the cost of our earlier $\$1000$ (component cost) genetic analysis system demonstration⁴ by eliminating all other HV components. In the future, with the integration of other sensing technologies on CMOS silicon wafers, the cost of the entire system is expected to be below $\$100$. We expect such manufacturable CMOS technology will greatly simplify the CE infrastructure while having a major impact on the development of LOC technologies.

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