

CMOS Low Current Measurement System for Biomedical Applications

Brian Goldstein*, Dongsoo Kim*, Angelo Rottigni†, Jian Xu‡, T. Kyle Vanderlick‡ and Eugenio Culumciello*

*Department of Electrical Engineering, Yale University, New Haven, CT, USA

†Dipt. di Elettronica e Informazione, Politecnico di Milano Via Golgi, Milano, Italy

‡Department of Chemical Engineering, Yale University, New Haven, CT, USA

Email: eugenio.culumciello@yale.edu

Abstract—We present a micro-chip implementation of a low current measurement system for biomedical applications using capacitive feedback that exhibits 190 fA of RMS noise in a 1 kHz bandwidth. The sampling rate is selectable up to 100 kHz. When measuring the amplifier noise with a 10 G Ω resistor and a 47 pF capacitor at the input, typical of cell membrane capacitance in DNA and patch clamp experiments, the measured RMS noise was 2.44 pA on a 50 pA signal in a 10 kHz bandwidth. Two channels were implemented on 630 \times 440 μm^2 using a 0.5- μm CMOS process. Each channel consumes 1.5 mW of power from a 3.3 V supply. We used our device to measure the characteristics of an artificial lipid bilayer similar to the ones used in DNA sequencing experiments via nanopores.

I. INTRODUCTION

Integrated multi-channel low-noise current measurement systems are becoming extremely important components to interface and study physical phenomena at the sub-micro-scale for use in biological research and instrumentation. For example, patch-clamp is the electrophysiology gold standard technique to measure ion-channel currents when the cell membrane is “clamped” to commanded voltages. A low current measurement system (LCMS) is required to study the effect of drugs and medical treatments on ion channel dynamics [1] [2]. During single channel recording, the current level can be as low as tens of pico-amperes in 1-10 kHz bandwidth with a 50 pF electrode capacitance.

Another application that requires an integrated low current measurement system is a potential rapid DNA sequencing system where base pairs passing through a nanopore as shown in Fig. 1 can be detected using current measurements in the range of 10-100 pA with a 10 kHz bandwidth and an input capacitance of 60 pF [3]. This system will dramatically reduce the cost and increase the speed of DNA sequencing and genomic research. Genomic information has a wide range of applications including human medicine, agriculture, security and defense, and evolutionary biology [4]. All of these measurements require a compact instrumentation headstage that has a very low input current noise at high sampling frequencies due to the magnitude and the speed of the signals being measured. It is very difficult to design an LCMS that can do high speeds such as 10 kHz with low-noise such as <1 pA RMS input-referred noise measurements with a large load such as 60 pF because the bandwidth and input capacitance have a direct and large affect on the final measurement noise. It

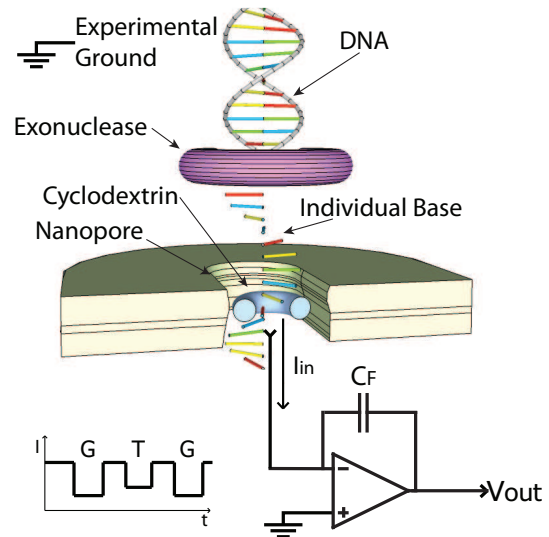


Fig. 1. Biomedical applications of this low current measurement system include DNA sequencing. An exonuclease cleaves individual bases from a strand of DNA. The bases enter the nanopore and temporarily bind to a cyclodextrin ring. An electrode in the pore applies a known voltage and the resulting current is measured to determine which base is in the nanopore.

is desirable to have an integrated system with a high dynamic range capable of being used in recording for both applications.

Commercial patch-clamp amplifier systems are available, such as Molecular Devices’ Axopatch 200B [5], but these systems are currently bulky, expensive, and not particularly suitable for simultaneous automatic measurements on a large number of cells in parallel, a very desirable feature [6]. A current amplifier front-end for nanobiosensors that uses a sophisticated integrator-differentiator circuit was presented in [7], but it requires a large silicon area which is less amenable to large array integration. Integrated multi-channel systems have the advantage of reducing the main noise source of the system, the electrode capacitance, and enable simultaneous and automatic measurement on a large number of cells in parallel. While an integrated patch-clamp system has been presented in [8], it is only for use in whole cell recording where the recorded currents are larger, in the range of 1-10 nA while typical recording bandwidths are 5-10 kHz. While there is much literature on potentiostats, these systems work in the μA or nA level, and only achieve low noise when measuring at low frequencies, below the requirements of these applications.

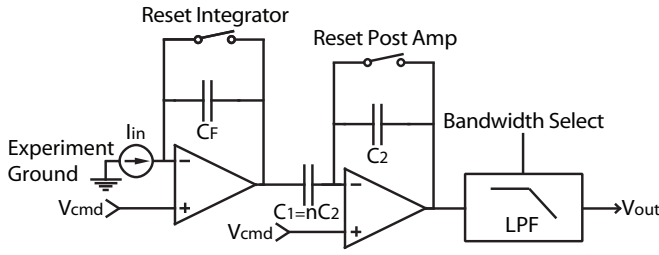


Fig. 2. System block diagram for the fabricated LCMS.

This work is the foundation for an integrated system capable of recording whole cell experiments and also single channel experiments. Currently, there are no commercial arrays of low-noise current amplifiers for biomedical interfaces that can scale up to multiple ($>1,000$) channels on a single microchip. This work presents a multi-channel low-noise integrated low current measurement system that features high bandwidth, sensitivity, and dynamic range to measure bidirectional currents in the range required for biomedical recording while allowing control of the voltage at the input node, known as voltage clamping.

II. SYSTEM OVERVIEW

The system, shown in Fig. 2, features a current integrator for the first stage with selectable gain, followed by an inverting post amplifier stage. The feedback capacitance of the integrator is selectable as either 100 fF or 1 pF and the post amplifier can supply a further gain of 10 or be bypassed if it is not needed. The low-pass filter is used to filter out high frequency noise that is higher than the selected sampling frequency.

In this system, an amplifier with capacitive feedback is used to fix the applied voltage to the cell under test. Either resistive or capacitive feedback could have been chosen, each with its own advantages and disadvantages. A resistive feedback system enables continuous time recording, while our capacitive feedback system is a discrete time system because it requires resetting the capacitor to avoid the amplifier reaching saturation. Capacitive feedback was chosen because a resistive feedback system would add thermal noise due to the resistor. In order to reduce the thermal noise of the resistor, a very large value resistor would be necessary which would have too much distributed capacitance to be implemented in this 0.5- μm bulk CMOS technology [9]. The capacitive feedback system adds noise only due to the switching effect on the capacitor. The overall noise of the measurement with this system will depend on the equivalent input circuit and the sampling frequency, and has previously been analyzed in [10].

The current integrator consists of an OTA with a cascoded output stage and is shown in Fig. 3. The cascoded output stage boosts the gain of the mirrored OTA. Wide input transistors are used to reduce thermal noise, along with large area to decrease flicker noise. The input capacitance due to the transistors is much smaller than the electrode capacitance. In this technology, the NMOS mirror transistors exhibit higher levels of flicker noise than the PMOS, so the lengths of these were also increased, while the W/L ratio of the PMOS to NMOS transistors was kept at 1. The OTA tail transistor was

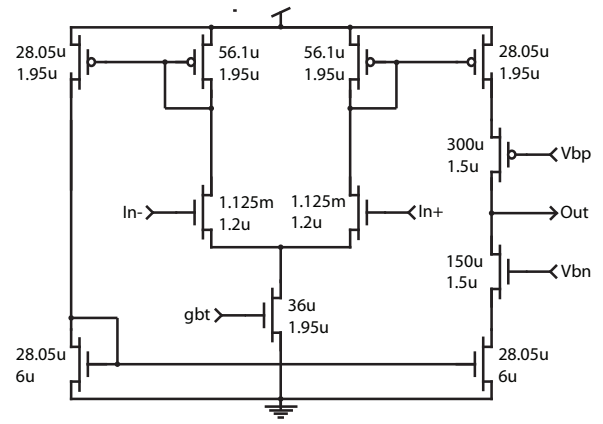


Fig. 3. OTA used in the integrator.

biased for a current of 233 μA , while the current in the left and right branches is reduced by the ratio of the current mirror. In open loop configuration, the DC gain is 90 dB which will ensure high linearity. The integrator is periodically reset, so the OTA was designed to have a phase margin of 60 degrees when in a follower configuration. The reset time of the integrator depends on the OTA bandwidth, which decreases with the load capacitance. With a high 60 pF load at the input during the reset, the GBP is 3MHz and the minimum reset time is 2 μs . In this system, the integrator is the dominant noise source and was designed to have 5.850 nV/ $\sqrt{\text{Hz}}$ of input-referred noise at 10 kHz and 4.715 nV/ $\sqrt{\text{Hz}}$ at 100 kHz to compromise between power, noise, and area. The OTA has an output swing greater than 1.5 Volts. The common mode input range is 1 V, allowing for a wide range of command voltages to be applied. Typically only 100-500 mV are applied in patch-clamping.

The integrator has two phases: *reset* and *integration*. During the *reset* phase, the switch between the negative input terminal of the OTA and its output is closed, shorting the feedback capacitor and setting the output voltage to V_{cmd} . In this phase, the only noise source is the op-amp. During the *integration* phase, the switch is opened, the feedback capacitor has an initial charge of zero and integrates the input current. The op-amp offset and switching effects due to clock feed through and charge injection are eliminated by correlated double sampling (CDS). The CDS function reduces the effect of the the low frequency noise by the subtraction operation. Since thermal noise is not correlated, the thermal noise is doubled, which is the reason for designing the OTA to exhibit low thermal noise.

Since the integration time is dictated by the sampling frequency, and C_F is limited by the manufacturing process limits, more gain may be required to sample the output voltage. The post amplifier can be enabled for this purpose. The inverting configuration is chosen to reduce the input common mode voltage range requirement. The gain is determined by the ratio $n = C_1/C_2$. The low-pass filter is used to reduce the noise component above half of the sampling frequency.

The input current can be determined from the sensor's output voltage by first dividing by the voltage gain of each voltage amplifying stage to determine the integrator's output

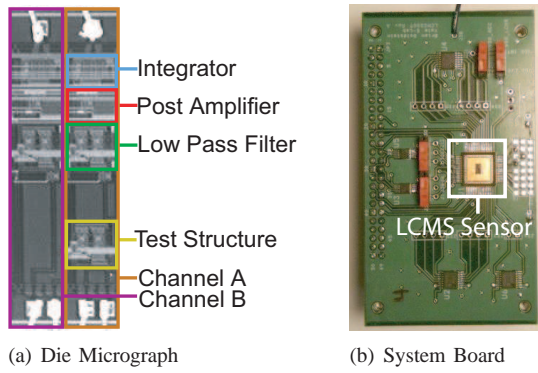


Fig. 4. The fabricated LCMS chip. Each channel is only $630 \times 220 \mu\text{m}^2$. It is soldered onto a custom 4 layer PCB board with supporting circuitry.

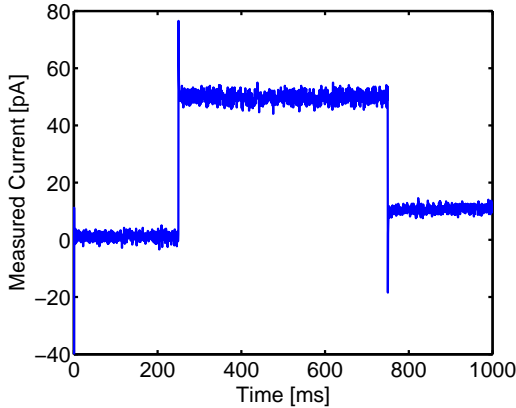


Fig. 5. Measured current output of a 50 pA step using a 10 GΩ resistor, showing 1.35 pA RMS noise at a sampling rate of 10 kHz when $C_F=100$ fF.

voltage, and then converting this voltage to current by using the relation $I = C_F \cdot \frac{dV}{dt}$.

III. MEASUREMENT RESULTS

The designed LCMS was fabricated in a $0.5\text{-}\mu\text{m}$ CMOS process and the die micrograph is shown in Fig. 4(a). We designed a custom 4-layer printed circuit board with separate analog and digital power planes shown in Fig. 4(b). The fabricated LCMS has two channels, each occupying $630 \times 220 \mu\text{m}^2$ die area. The external ADC is an Analog Devices AD7685 and the system uses an Opal Kelly XEM3001v2 board which features a Xilinx Spartan-3 FPGA and a USB Controller to communicate with a PC for user configuration and data logging. The LCMS was tested by applying voltages across a 10 GΩ resistor using a Keithley 236 Source Measure Unit to generate a known current. Load capacitors were inserted to simulate electrode load capacitance, which greatly affects the overall noise performance. A 500 mV step was applied resulting in a 50 pA current which was accurately measured by the LCMS with 1.35 pA RMS input referred noise at a 10 kHz sampling rate as shown in Fig. 5. After adding a 47 pF capacitor at the input, typical for the intended applications, the measured RMS noise was 2.44 pA at the same sampling rate. The linearity error with a 100 fF and 1 pF integrating capacitor was measured and is less than $\pm 0.5\%$ for the input

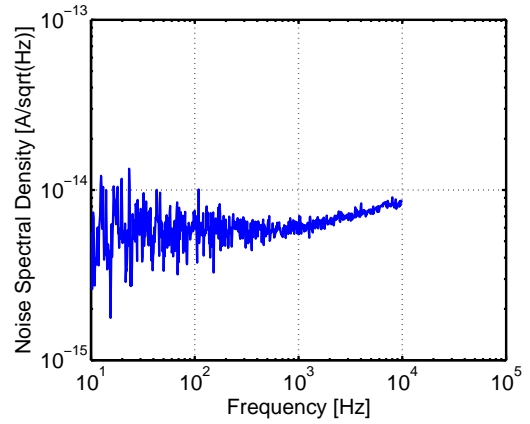


Fig. 6. Measured Noise Spectral Density when $C_F=100$ fF using a 10 GΩ resistor.

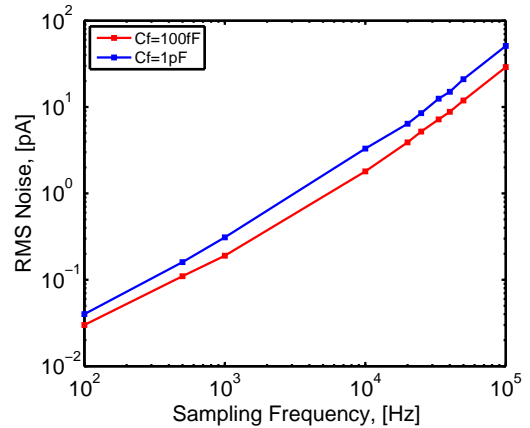


Fig. 7. Measured RMS Current Noise at different sampling frequencies using a 10 GΩ resistor.

current range of (-1300 1200 pA) @100 fF, (-12 nA 13 nA) @ 1pF and is presented in Fig. 8. By switching between the available on-chip integrating capacitors, the measured dynamic range is 83 dB with less than $\pm 0.5\%$ linearity error at 10 kHz sampling rate. If the integrating capacitor is not switched, a dynamic range of 63 dB was measured at the same sampling rate. The noise spectral density was recorded and is shown in Fig. 6. The measured RMS current noise at different sampling frequencies is presented in Fig. 7.

The LCMS was then used to characterize the electrophysiological properties of a planar lipid bilayer. A planar lipid bilayer was formed in a hole of Teflon membrane between two aqueous compartments by the Montal-Mueller method [12] and is shown in Figs 9(a) and (b). The square and triangular voltage signals shown in Fig. 9(c), from an external function generator, were applied across the lipid bilayer while the current through the lipid bilayer was recorded by the chip in order to characterize it. The bilayer can be modeled electrically as an RC circuit. From the recorded signals, the specific capacitance of the lipid bilayer was calculated as $1.0495 \mu\text{F}/\text{cm}^2$ and the specific resistance as $1.7365 \text{M}\Omega\text{cm}^2$, which is consistent with the reported properties of the black lipid membrane [13]. While the Keithley tests indicate our

TABLE I
PERFORMANCE COMPARISON

	This work	TBCAS'09 [8]	ISSCC'09 [11]
Structure	Capacitive Feedback	Resistive Feedback	Capacitive Feedback
Technology	0.5- μm CMOS	0.5- μm SOS	0.35- μm CMOS
Power Supply	3.3 V	3.3 V	3.3 V
Power consumption	1.5 mW	6 mW	23m W
Number of channels	2	2	1
Core area	0.27 mm ²	0.8 mm ²	0.5 mm ²
Input RMS current noise	1.35 pA @ 10 kHz	5 pA @ 10kHz	0.15 pA @ 1 kHz
Linearity Error	$\pm 0.5\%$	unknown	$\pm 0.02\%$
Input current range	± 1200 pA, ± 13 nA	± 20 nA	± 200 pA, ± 5 nA

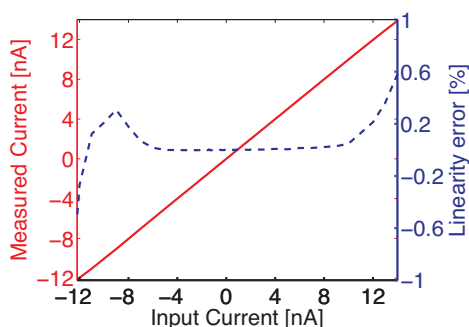
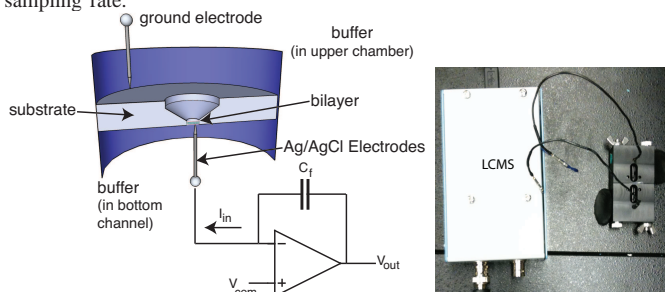
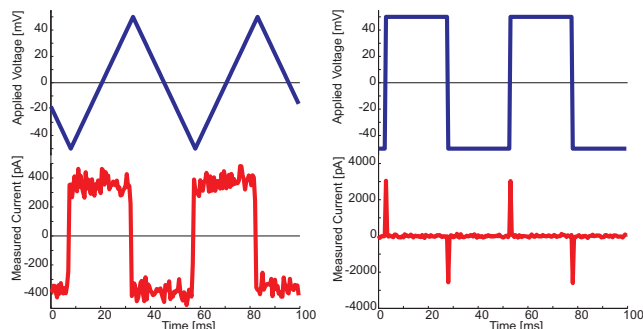


Fig. 8. Linearity Error Measurement Results for $C_F=1$ pF with a 10 kHz sampling rate.



(a) Measurement setup diagram.

(b) Experimental setup.



(c) Experimental results measuring the current across a black lipid membrane in a hole of Teflon film

Fig. 9. Lipid Bilayer Experimental setup and results.

sensor should have less noise than we recorded during this experiment, we also measured the noise when the electrodes were placed in a 1M KCL solution (the same solution the bilayer was created in) where we measured an RMS noise of 26pA. When performing the same test with a commercial amplifier at the same sampling rate, the Axopatch 200B with a 10kHz LPF, we observed an RMS noise of 33pA. A

comparison of this work to previous works is presented in Table I.

IV. ACKNOWLEDGEMENTS

The authors would like to thank Berin Martini for his programming assistance. This project was partly funded by NSF IDBR DBI-0649349, ONR N00014-08-1-0065 and N00014-08-1-1014, and NIH R01 NS06511.

REFERENCES

- [1] O. Hamill, A. Marty, E. Neher, B. Sakmann, and F. Sigworth, "Improved patch-clamp techniques for high-resolution current recording from cells and cell-free membrane patches," *Pflügers Archiv European Journal of Physiology*, vol. 391, no. 2, pp. 85–100, 1981.
- [2] F. Sigworth and K. Klemic, "Microchip technology in ion-channel research," *IEEE Transactions On Nanobioscience*, vol. 4, pp. 121 – 127, 2005.
- [3] J. Clarke, H. Wu, L. Jayasinghe, A. Patel, S. Reid, and H. Bayley, "Continuous base identification for single-molecule nanopore DNA sequencing," *Nature Nanotechnology*, vol. 4, pp. 265–270, 4 2009.
- [4] D. Branton, D. W. Deamer, and et al, "The potential and challenges of nanopore sequencing," *Nature Biotechnology*, vol. 26, pp. 1146 – 1153, 2008.
- [5] R. Sherman-Gold, "The Axon Guide for Electrophysiology & Biophysics Laboratory, Axon Instruments inc., URL www.moleculardevices.com."
- [6] C. Wood and C. Williams, "Patch-clamping by numbers," *Drug Discovery Today*, vol. 4, pp. 434–441, 2004.
- [7] G. Ferrari, F. Gozzini, and M. Sampietro, "A Current-Sensitive Front-End Amplifier for Nano-Biosensors with a 2MHz BW," in *Solid-State Circuits Conference, 2007. ISSCC 2007. Digest of Technical Papers. IEEE International*, 11-15 2007, pp. 164 –165.
- [8] P. Weerakoon, K. Klemic, F. Sigworth, and E. Culnerciello, "An Integrated Patch-Clamp Potentiostat with Electrode Compensation," *IEEE Transactions on Biomedical Circuits and Systems*, vol. 3, pp. 117–125, 2009.
- [9] P. Weerakoon, K. Klemic, F. Sigworth, and E. Culnerciello, "A Low-Noise Miniaturized Patch-Clamp amplifier," *IEEE LISA 2007 conference proceedings, NIH*, November 8th, 2007.
- [10] D. Kim, W. Tang, B. Goldstein, P. Weerakoon, and E. Culnerciello, "Performance Comparison of Low Current Measurement Systems for Biomedical Applications," *IEEE International Symposium on Circuits and Systems 2010, Paris, France*, May 2010.
- [11] M. Bennati, F. Thei, M. Rossi, M. Crescentini, G. D'Avino, A. Baschirotto, and M. Tartagni, "A Sub-pA Delta-Sigma Current Amplifier for Single-Molecule Nanosensors," in *Solid-State Circuits Conference - Digest of Technical Papers, 2009. ISSCC 2009. IEEE International*, 8-12 2009, pp. 348 –349,349a.
- [12] M. Montal and P. Mueller, "Formation of Bimolecular Membranes from Lipid Monolayers and a Study of Their Electrical Properties," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 69, no. 12, pp. 3561–3566, 1972.
- [13] F. Yi, J. Xu, A. M. Smith, A. N. Parikh, and D. A. LaVa, "Nanofiber-supported phospholipid bilayers," *Soft Matter*, vol. 5, no. 24, pp. 5037–5041, 2009.