FA Application Case Study

Redefining the Interface Between Biological and Electrical Engineering

About Jacob Rosenstein

Jacob Rosenstein is an Assistant Professor in the School of Engineering at Brown University. He holds Ph.D. and M.S. degrees in Electrical Engineering from Columbia University, where he worked on low-noise electronics for ion channel recordings and nanopore sensors. Prior to pursuing graduate degrees at Columbia, he spent several years as a hardware systems engineer with the semiconductor companies Analog Devices and MediaTek Wireless, contributing to the SoftFone line of baseband chipsets for wireless handsets. Learn more at Professor Rosenstein's website: http://rosenstein.engin.brown.edu

Dr. Jacob Rosenstein is applying his considerable expertise in IC technology to the development of new analog circuitry capable of measuring the subtle current fluctuations within so-called nanopores, which allow the rapid analysis of biological materials, such as DNA strands, at the molecular level. Dr. Rosenstein and his colleagues are actively addressing the challenge of reducing the noise generated by electrochemical processes in the nanopore current flow. In pursuit of this goal, their lab at Brown University employs a Cascade EPS150FA probe station to support diverse applications, from electrode probing to laser cutting.

Dr. Jacob Rosenstein and the lab he directs at Brown University's Engineering Department stand at the crossroads of two megatrends in science and technology. One is the application of microelectronics that leverages IC technology to create ever faster and more efficient devices in clinics and laboratories. The other involves the ongoing advances in biotechnology and nanotechnology that are pushing analytic methods from the microscopic down to the molecular level.

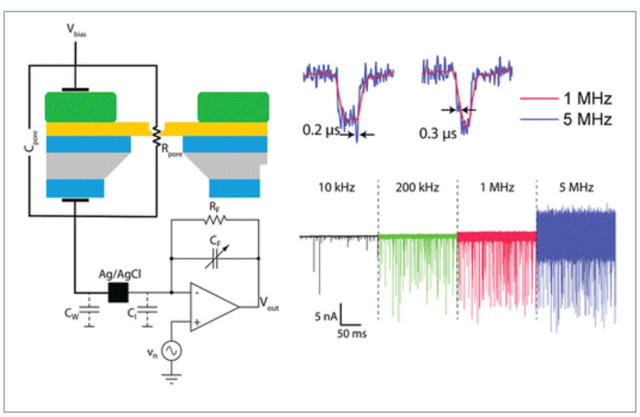

Figure 1: CMOS-based amplifier circuit measures the current generated by the flow of molecules through a nanopore in a silicon nitride membrane (yellow). At a bandwidth of 5 MHz, it reveals transient events as brief as 200 ns, thus yielding significantly more information about the molecular flow though the membrane [1].

Recent breakthroughs in DNA sequencing provide a good case in point. Conventional sequencing techniques use enzymes to create many copies of particular DNA molecules, and the sequences of these copies are measured using fluorescence microscopes. A newer process leverages

“The EPS150FA includes high-resolution probes that allow manual positioning onto exposed electrodes designed to interface with electrochemical solutions when the device is placed into operation.”

nanopore technology, which can literally read long stretches on a single strand of DNA. It starts with a voltage being applied across a microscopically thin film, which has been perforated with the pores only a few nanometers in diameter. Each pore creates a channel for the flow of ions, thus producing an electrical current. As a single strand of DNA passes through the pore, it disrupts this current in signature ways that identify the particular molecules involved, such as the base nucleotides that form the genetic code of all living things (Figure 1 and 2).

The challenge to Dr. Rosenstein and his colleagues is to develop microcircuits capable of measuring this nanolevel current in a manner that yields both speed and accuracy. The principal problem is one of noise reduction. The ion flow through the nanopores reflects the stochastic nature of electrochemical processes, which introduce random noise along with pertinent information. It thus becomes imperative to develop low-noise, current-mode analog circuitry at the front end of a microelectronic system that provides the best possible signal-to-noise ratio.

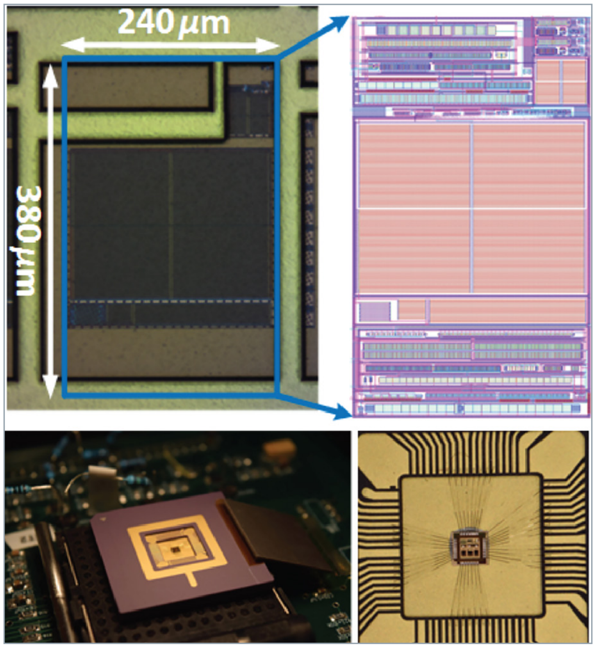

Figure 2: Custom CMOS-based amplifier with special multi-mode architecture that lets it achieve both low noise and a very wide dynamic range [2].

Dr. Rosenstein’s lab includes a Cascade EPS150FA probe system (Figure 3), which permits his research team to perform real-time measurements and modifications on CMOS circuits when they arrive from the fab. It includes high-resolution probes that allow manual positioning onto exposed electrodes designed to interface with electrochemical solutions when the device is placed into operation.

The EPS150FA system flexibility lets the team mount a laser cutter to perform micromachining operations such as patterning the fluid channels that route electrochemical solutions, or modifying the metal layers that define the wiring.

“The EPS150FA system flexibility lets the team mount a laser cutter from New Wave Research to perform micromachining operations.”

Figure 3: EPS150FA in the School of Engineering at Brown University laboratory.

With this diversity of applications, the EPS150FA rapid adaptation has been major asset in Dr. Rosenstein’s lab. High-quality microscope optics, precise probe positioners and easily configurable hardware have all made a contribution.

How far will the integration of microcircuits and nanopores take us? Dr. Rosenstein envisions a portable system that can be interfaced with a laptop to process fluid samples in the field and identify specific viruses and bacteria. FormFactor is proud to support Dr. Rosenstein and his fellow researchers. We view this kind of close collaboration with the academic community as a fundamental part of our commitment to progress in all of the physical sciences.

References

1. Shekar, S., Niedzwiecki, D.J., Chien, C.C., Ong, P., Fleischer, D.A., Lin, J., Rosenstein, J.K., Drndić, M., and Shepard, K.L., “Measurement of DNA Translocation Dynamics in a Solid-State Nanopore at 100 ns Temporal Resolution,” Nano Letters, 2016.

2. Dai, S., Perera, R. T., Yang, Z., Rosenstein, J. K., “A 155-dB Dynamic Range Current Measurement Front End for Electrochemical Biosensing,” IEEE Transactions on Biomedical Circuits and Systems, 2016.

The EPS150FA Probe System Meets Your Lab Requirements

"EPS150FA has high-quality microscope optics, precise probe positioners and easily configurable hardware."

Contact submicron features with less effort by using

/ Positioner with a resolution of 200 TPI
/ High magnification optics up to 4000x

Quick transition from wafer, to chip, to package DUT gives you faster data

/ 40 mm platen drive
/ 10 mm chuck Z adjustment
/ Positioner with vacuum bases
/ A chuck which is ready for single DUT

Highly confident measurement results through a contact stability, driven by

/ A rigid and reliable station base design
/ 16 mm stainless-steel stable probe platen
/ ± ≤3 µm chuck and stage planarity

The ability to reconfigure and upgrade your probe system enables you to stay flexible and protects your investment

/ The modular design
/ The unique upgrade paths including laser cutter

The probe system incorporates the best-known methods for electrical failure verification, localization and debug with the ability to probe features smaller than 1 µm.

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