Secure Bio-Engineered Sensors for Healthcare and Environmental Monitoring

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Biomanufacturing is a critical infrastructure for synthesizing pharmaceutical actives, food ingredients, and industrial materials, yet its optimization is often limited by a reliance on offline sampling that compromises temporal resolution and increases contamination risks. To address these limitations, we developed a floating, wireless sensor platform capable of *in situ*, spatially distributed monitoring within large-scale bioreactors[1]. A key challenge in deploying such Industrial Internet of Things (IoT) devices is securing data integrity against eavesdropping without exceeding strict power budgets. To solve this, our system [1] integrates a novel Physical-Layer Security (PLS) mechanism directly within the sensor readout interface, enabling robust protection for real-time multimodal sensing of glucose kinetics and cell biomass.

To accommodate the vast dynamic range required for diverse electrochemical assays, the sensor architecture centers on a highly reconfigurable potentiostat front-end. The drive circuitry utilizes a 12-bit R-2R DAC to establish precise DC bias potentials, coupled with a Class-AB amplifier to ensure high-current drive capability for both 2- and 3-electrode configurations.

The readout chain employs a low-noise Transimpedance Amplifier (TIA) designed as a two-stage Miller topology. This TIA features four digitally programmable gain settings, ranging from 3.30 kΩ to 3.05 MΩ, allowing the system to resolve currents from picoamperes up to a maximum of 101.6 µA. This design achieves a measured input-referred noise floor of 9.48 pA (integrated over a 100 kHz bandwidth) and a dynamic range of 140.55 dB, ensuring fidelity across varying reaction kinetics [1].

Biological utility was validated through two primary indicators of bioreactor health: metabolite concentration and biomass density. Amperometric experiments applying a -0.1 V bias successfully tracked glucose concentrations between 1.5 and 5.6 mM, demonstrating high linearity (R^2=0.9981). Furthermore, Electrochemical Impedance Spectroscopy (EIS) measurements (up to 100 kHz excitation) effectively quantified *E. coli* cell densities spanning two orders of magnitude (4.0×10^7 to 2.4×10^9 cells/mL), confirming the sensor's ability to monitor real-time bacterial cell growth phases [1].

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To further process the sensor information, the analog front end is followed by a continuous-time delta–sigma modulator (DSM). The DSM continuously samples the input analog signal and converts it into a binary bitstream, where the signal amplitude is represented by the density of bits. A digital low-pass filter then converts this bitstream into a digital value, forming a delta–sigma analog-to-digital converter (ADC). The resulting digital information can be used for further processing on the software side. Using a second-order, 1-bit DSM, a resolution of 13 effective number of bits (ENOB) was achieved, enabling precise conversion of the sensor data into the digital domain.

In addition, a novel physical-layer security technique is embedded within the DSM, forming a secure delta–sigma modulator (SDSM). Sensors are typically unsecured due to limitations in power, computational capability, and area, which creates a significant security risk for wireless applications. The SDSM utilizes the quantization noise that naturally arises in the DSM to secure the information in a stream-cipher manner. This quantization noise is enhanced using dithering, which is commonly employed in DSMs to suppress idle tones, but is used here for the first time for security purposes. Leveraging inherent analog noise makes cryptanalysis more difficult and enables the use of lower-resource pseudo-random number generators (PRNGs). By employing a 16-bit linear-feedback shift register (LFSR) as the PRNG, the SDSM achieves 9.16× lower power consumption than Trivium, one of the lowest-power lightweight stream ciphers, while maintaining a practical level of security [1].

We are also pleased to report the publication of our review article, 'Improving engineered biological systems with electronics and microfluidics,' in *Nature Biotechnology* (2025) [2]. This paper establishes a novel classification framework for hybrid bio-electronic systems, offering critical design strategies for the next generation of 'Cyber-Secure Biological Systems.' To ensure this resource remains current in such a rapidly evolving field, we have also launched a companion 'Living Roadmap' website (https://www.programmingbiology.org/csbs). This digital platform serves as a dynamic community hub, featuring a curated and growing collection of literature, design tools, and educational resources. Both the publication and the website acknowledge the generous support of the Catalyst Foundation, highlighting the foundation's pivotal role in advancing this interdisciplinary research frontier.

<u>New Publications and Presentations:</u>

2025

1. **Yasar, A., Caygara, D.**, Patel, Y. H., Pemaraj, A., Boisvert, L., Magyar, A., Yu, T., Dufort, B., Poo, T.-L., **Yazicigil, R. T.** (2025). A Secure Multimodal Electrochemical Sensor for Sustainable Biomanufacturing. In European Solid-State Circuits Conference (ESSERC)

2. **Yazicigil, R. T**., Bali, A., **Caygara, D.**, **Densmore, D**. (2025). Improving engineered biological systems with electronics and microfluidics. Nature Biotechnology, 43, 1067–1083. doi: 10.1038/s41587-025-02709-6
3. Yazicigil, R. T., "The Circuit Frontier: Innovating and Expanding ASIC Solutions for Enhanced Biosensing and Seamless Wireless Communication":
    - WPI, Virtual, December 2025

    IEEE Distinguished Lectures:
    - IEEE SSCS/CASS, IEEE-IISc VLSI Chapter, Virtual, December 2025
    - IEEE SSCS Oregon Chapter, Virtual, November 2025
    - IEEE SSCS NY Chapter, Cornell University, Ithica, September 2025
    - IEEE SSCS Toronto Chapter, University of Toronto, March 2025
4. Yazicigil, R.T., "Cyber-Secure Biological Systems":
    - GESDA (Geneva Science and Diplomacy Anticipator) Anticipatory Leadership Summit, Sabanci University, October 2025
    - IEEE Biomedical Circuits and Systems Conference, October 2025
    - Symposium on VLSI Technology and Circuits, Workshops, June 2025
    - Materials Research Society (MRS) Spring Meeting & Exhibit, April 2025
5. Yazicigil, R.T., "Living Networks: Bioelectronic IoT and the Future of Secure, Energy-Efficiency Wireless Systems":
    - IEEE Radio Frequency Integrated Circuits Symposium, June 2025

2024

6. **Liu, Q.**, Arguijo Mendoza, D., **Yasar, A., Caygara, D.,** Kassem, A., **Densmore, D.**, **Yazicigil, R. T**. (2024). Integrated Real-Time CMOS Luminescence Sensing and Impedance Spectroscopy in Droplet Microfluidics. IEEE Transactions on Biomedical Circuits and Systems, 18(6), 1233–1252. doi: 10.1109/TBCAS.2024.3491594

<u>**Awards / Achievements:**</u>

1) **Best Paper Award** for the paper [6] "Integrated Real-Time CMOS Luminescence Sensing and Impedance Spectroscopy in Droplet Microfluidics" published in IEEE Transactions on Biomedical Circuits and Systems. This work was supported by NSF SemiSynBio-II Program under Grant 2027045, the Catalyst Foundation, NIH T32 Training Program in Synthetic Biology and Biotechnology under Grant 1T32GM130546-01, the Semiconductor Research Corporation (SRC) ESH Program (Task No.: 3245.001), NSF CAREER Program under Grant 2338792.

2) **Best Poster/Demo Award** for "Hybrid Bio-Electronic Microfluidic Memory Arrays", 2023 International Solid-State Circuits Conference (ISSCC) Student Research Preview,

February 2023. This work is supported by NSF SemiSynBio-II program under Grant 2027045 and the Catalyst Foundation.

Achievements of Dilara Caygara

1) Selected to participate at the Next Generation Circuit Designer Workshop at International Solid State Circuits Conference (ISSCC) 2026.