High-Resolution Biochemical Activity Measurements with Commercial Transistors

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ABSTRACT

We demonstrate that single-gated, commercially-sourced, field-effect transistors (FETs) operated with a lock-in amplifier (LIA) under closed-loop control can achieve an average pH resolution of 9×10^{-4}. This performance represents an ≈8-fold improvement over previous FET measurements[1]. The pH sensitivity was found to be ≈56 mV, consistent with the Nernst potential at room temperature. The precision of our approach makes it ideally suited for sensitive bioanalytical measurements. We show that the technique can be applied to measure the therapeutic efficacy of small polypeptide molecules that regulate enzymes implicated in Alzheimer's disease.

KEYWORDS: Single-gate FET, pH measurement, PID controller, Lock-in amplifier, TiN, Sensitivity, Resolution

INTRODUCTION

The demand for high-performance biochemical measurements has dramatically increased to support applications such as biomanufacturing, marine ecology, and DNA sequencers[2]. Electronic measurements that leverage the field-effect are particularly attractive because they allow real-time signal detection without the need for specialized labeling of biomolecules. Their small size, low-cost, and scalability by leveraging foundry processes can allow a straightforward route to commercial deployment. FET-based biochemical measurements can allow the direct measurement of ions concentration (H^+ or OH^-) in a solution when paired with an appropriate sensor. As an example, measurements of pH can allow rapid quantification of enzymatic activity[3]. Improving the resolution of these measurements will allow the sensors to operate under physiological conditions. Therefore, many biochemical research groups are actively developing devices and methods to improve the sensing performance. Here, we demonstrate that commercial single-gate FETs combined with novel signal processing can allow nearly an order of magnitude improvement in pH resolution over conventional FET measurements.

EXPERIMENTAL

A single-gate commercially sourced n-channel FET was soldered onto a printed circuit board. The initial electrical characterization of the devices was performed with a semiconductor parameter analyzer. The pH measurements were performed in a remote configuration by connecting a TiN pH sensor connected to the top-gate metal contact using a shielded coaxial cable. The pH sensor was comprised of tungsten needle coated with 100 nm TiN thin film using sputter deposition[4]. The measurements were performed using two configurations. Figure 1a shows the schematic of single-gate FET measurement with a proportional-integral-derivative (PID) controller, operated in a constant current mode[1]. The PID controller was operated to maintain the drain current, I_D, at a constant value by continuously summing the controller voltage (V_{PID}) with the voltage from the pH sensor (V_{pH}). Figure 1e illustrates the schematic of single-gate FET measurement that combines a PID controller with phase sensitive detection using a lock-in amplifier (LIA). Similar to the measurement setup in Figure 1a, the FET operated in a constant current mode. The LIA allowed improved measurements of weak signals at a specific reference frequency and phase to improve the overall signal-to-noise ratio (SNR).

RESULTS AND DISCUSSION

Figure 1a describes single-gate FET measurement with PID control. The pH sensitivity (dV_{PID}/dpH) was determined to be ≈58.7 mV (R^2=0.99), consistent with the Nernst potential of 59 mV at room temperature from the time-series measurements shown in Figure 1b (*inset*). The time-series measurements also allowed the estimation of the pH resolution to be $\Delta pH = (7.2 \pm 0.3) \times 10^{-3}$ at a bandwidth of 10 Hz. This value was 3 times higher than when the single-gate FET operated in an open-loop without PID controller[1]. The improved pH resolution allowed high-

resolution measurements of the effect of a polypeptide therapeutic, p5, on the regulation of the pathological enzyme complex, Cdk5/p25, shown in Figure 1c. Importantly, the measurements were made under physiological conditions with appropriate buffering conditions. As seen from Figure 1d, upon addition of the 24 amino acid polypeptide p5 we observed a significant inhibition in Cdk5/p25 activity as is evident from the change in V_{PID}. The observed p5-based inhibition of Cdk5/p25 activity had a threshold of [p5]=0.7 μM, consistent with literature values[5]. The performance of the measurements were improved by using a LIA in conjunction with PID control. In this configuration, the sensitivity of the FET was ≈56 mV (R^2=0.99) as seen from Figure 1f. The average resolution of FET extracted from the time-series measurements in Figure 1g improved 8-fold to an average of 9 x10^{-4} (Figure 1h). This improved resolution will allow enzymatic measurements at sub-physiological concentrations, allowing new tools for drug discovery and diagnostics of neurological disease.

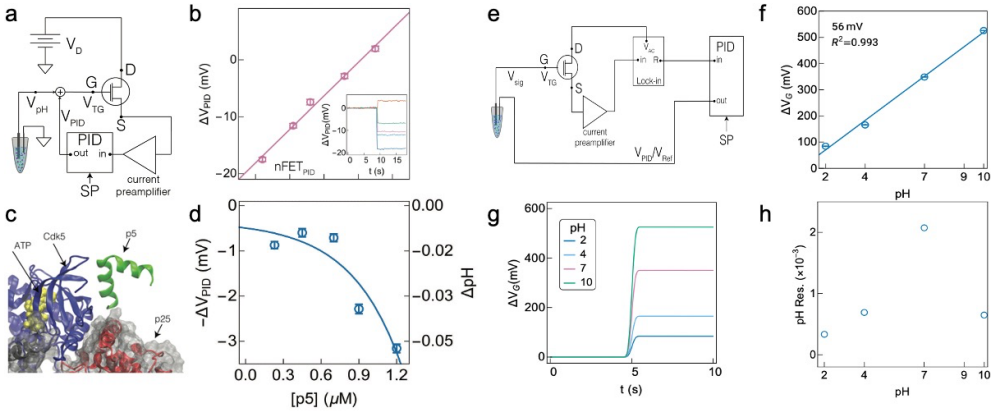

Figure 1: (a) Biochemical measurement using FET with PID control. (b) Response of ΔV_{PID} under different pH conditions. (inset) Time-series data as a function of pH. (c) p5 interactions with the Cdk5/p25 complex. (d) Response of ΔV_{PID} as a function of p5 concentration ([p5]). (e) Schematic of oprating a FET with a LIA and PID controller to improve measurement resolution. (f) Response of ΔV_{PID} uder different pH conditions. (g) Time-series under different pH condition relative to a reference potential. (h) pH resolution under a wide range of pH conditions.

CONCLUSION

We show that FET-based biochemical measurements can be substantially improved by combining commercially-sourced devices with PID and LIA techniques. The observed pH resolution was found to be ≈8-fold higher than conventional measurements where the FET was operated in an open-loop. The substantially improved resolution demonstrated by our results can lead to new tools for robust therapeutic development and diagnostic tools for use in neurological disease research.

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