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Review Article

Using an Active Complementary Metal-Oxide-Semiconductor Biosensor Array with Integrated Sensor Electronics, Multiplexed Electrochemical DNA Detection in Real Time

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Abstract

However, new electrochemical detection methods are emerging that may make it possible to design portable devices for point-of-care applications without the need for physically bulky optical instrumentation. Multiplexed electrochemical detection, in contrast to fluorescence detection, which can work well with a passive substrate, requires an electronically active substrate to analyze each array site. Multiplexed electrochemical detection makes use of integrated electronic instrumentation to further reduce platform size and get rid of electromagnetic interference that can come from bringing non-amplified signals off the chip. For the purpose of performing quantitative DNA hybridization detection on chip using targets conjugated with redox labels, we present an active electrochemical biosensor array constructed using standard complementary metal-oxide-semiconductor (CMOS) technology. On a custom-designed mm2 CMOS chip, a collection of gold working electrodes and integrated potentiostat electronics, including control amplifiers and current-input analogy-to-digital converters, use cyclic voltammetry to drive redox reactions, detect DNA binding, and transmit digital data off the chip for analysis. We show that conventional fluorescence-based microarrays are difficult, if not impossible, to perform real-time monitoring of hybridization and multiplexed, specific detection of DNA targets.

Keywords: DNA detection, CMOS, Electrochemical biosensor array

INTRODUCTION

After non-hybridized targets are removed from the array through a washing step, the locations of hybridized targets on the surface of the microarray are measured using a scanner that uses a photomultiplier tube or charge-coupled device camera to detect the emitted light and one or more sources for excitation (Steel AB, 1998). From the resulting image, relative expression levels of bound targets at various array sites can then be quantified. Even though fluorescence-based microarray platforms have very low detection limits, they cannot be carried to the point of care because the optical instruments they require are physically bulky. It is also impossible to distinguish between unbound targets in solution and those that have hybridized on the surface because both will fluoresce when imaged, so real-time monitoring of hybridization is impossible (Schienle M, 2004). Through temporal averaging, real-time sensing could increase assay throughput and enhance detection limits. By removing the need for light to act as an intermediary between sensing and integration, newly developed electrochemical methods are promising. The hybridization of ssDNA targets with probes immobilized on metallic or carbon "working" electrodes immersed in an electrolyte is measured by electrochemical DNA sensors (Peterson AW, 2001). The method of sensing used determines the nature of this electronic activity, which frequently involves the application of electrochemically active labels to the target DNA. A potentiostat measures the current flowing through the US after applying a desired input

voltage to the electrochemical cell. Multiplexed detection on electrochemical sensing-based high-density arrays necessitates the use of electronically active substrates due to the limited wiring resources available. A complementary metal-oxide-semiconductor microarray chip with individually addressable microelectrode sites and an external reader with actuation and measurement circuitry make up a CombiMatrix system that is available for purchase (Okahata Y, 1998). This system prevents real-time sensing because electro active labels are only conjugated with hybridized targets after hybridization has occurred. Sensing with redox-cycling and intercalation-based methods are two other pioneering developments in label-based CMOS DNA arrays with on-chip detection circuitry. However, neither of these approaches demonstrated real-time monitoring of hybridization or the capability to directly measure surface target coverage, and neither of these approaches supported generalized potentiostat functionality (Gong P, 2008). By constructing an integrated sensor array directly on an electronically-active CMOS substrate, we explore the limits of form-factor that can be achieved with electrochemical detection in this work. A variety of WEs and full potentiostat electronics, such as control-loop amplifiers, current-input analogy-to-digital converters, and data-processing circuitry, are included in the active CMOS biosensor described here (Levine PM, 2009). When unamplified signals are delivered to off-chip sensing electronics, unwanted electromagnetic interference effects are eliminated.

METHODS

DNA detection by electrochemistry

Maleimide redox labels, which are known to be electrochemically reversible and chemically stable, are used to covalently modify the targets (Song JM, 2003). For nucleic acid sequencing and sensing, electro active labelling has been recognized as an alternative to the use of radioactive isotopes. Ferrocene (Fc) redox labels, for instance, have previously been utilized, among other things, for label-based RNA hybridization detection and the thermodynamics of DNA probe binding. Over a clearly defined potential range, the redox reaction Fc Fc+ + e take place. By integrating the resulting current and connecting it to surface target coverage, Fc labels are used in this study to provide a quantitative measurement of the extent of surface hybridization (Yang X, 2019). A potentiostat—an electronic control system that applies a desired potential to an electrochemical cell and simultaneously measures the movement of charge through the cell as a result of electrochemical reactions and charging currents at the electrode-electrolyte interface—is typically used for electrochemical measurements (Panda SK, 2020). There are three electrodes in an electrolyte in a typical experimental electrochemical cell: a WE, to which DNA probes are attached, a "reference" electrode (RE), which maintains the buffer's stable potential, and a "counter" electrode (CE), which serves as the cell current's source or sink. The electronics of the potentiostat are depicted in, and the control amplifier's high gain on the left makes certain that the potential at the WE interface operates at the desired input level vin. The amplifier on the right uses an ADC to sample the current that is passing through the WE iWE before integrating it onto a capacitor.

Biosensor design with CMOS integration

In is a photograph of the chip as well as the system's overall architecture. A 4x4 array of simultaneously operating sensor sites makes up the 53 mm2 chip. A square WE, a 10-bit integrating ADC for sensing the WE's current and digital circuitry for setting ADC control signals and transmitting off-chip digital data make up each site (Akiyama T, 2000). For our label-based detection strategy, the ADCs can be programmed to sense currents of up to 250 Na at sampling rates of up to 10 kHz. The WEs in the top row have side lengths of 100 m, while the WEs in the rows that follow have side lengths of 90, 80, and 70 m. We can examine the effect of electrode area on signal level thanks to this variation. A 2500-15 m2 CE that is connected to the output of a low-noise control amplifier is shared by each row of four WEs. This amplifier's inputs connect to an external signal generator, an off-chip Ag/AgCl/3 M NaCl RE, and the WEs and supporting circuits of a standard potentiostat. A digital global-control unit, dc bias generators, and diagnostic circuits for ADC testing are also on the chip.

CONCLUSIONS

For point-of-care medical and biological applications, our active CMOS-integrated electrochemical biosensor array has the potential to make portable DNA diagnostic platforms. Additionally, traditional fluorescence-based assays are unable to detect DNA hybridization in real time due to the use of Ferrocene-conjugated DNA targets. We believe that our approach to the implementation of electrochemical biosensors will serve as a foundation for future technological advancements in portable DNA diagnostic platforms with high throughput.

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