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Metabolomics on integrated circuit

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Abstract

We have demonstrated a chip-based diagnostics tool for the quantification of metabolites, using specific enzymes, to study enzyme kinetics and calculate the Michaelis-Menten constant. An array of 256×256 ion-sensitive field effect transistors (ISFETs) fabricated in a complementary metal oxide semiconductor (CMOS) process is used for this prototype. We have used hexokinase enzyme reaction on the ISFET CMOS chip with glucose concentration in the physiological range of 0.05 mM – 231 mM and successfully studied the enzyme kinetics of hexokinase in detail. This will promote future research towards multiplexing enzyme-based metabolite quantification on a single chip, ultimately opening a pathway towards a personal metabolome machine.

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Keywords: Biosensor; CMOS; electrochemical sensor; enzyme kinetics; hexokinase; ion-sensitive field effect transistors (ISFETs); metabolomics; point-of-care (POC) diagnostics.

1. Introduction

Modern biomedical and life sciences are predicated on our understanding of the fundamental building blocks that underpin biological systems [1]. We can, for example, sequence a human genome for less than a thousand dollars and in just one day [2]. Quantitative measurement of proteins and the small molecule metabolites from which all biomolecules are made is advancing too. Metabolomics, the measurement of these small molecules, currently depends upon measurements using mass spectrometry or NMR based instrumentation [3]. However, diagnostic

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clinical chemistry often exploits specific enzymes to quantify metabolites. Multiplexing enzyme-based metabolite quantification could allow revolutionary chip-based metabolomics. Here we demonstrate substrate concentration-dependent electronic measurements using an enzyme-linked ion-sensitive field effect transistor chip, opening the way to multi-enzyme chips that can quantify many metabolites.

2. Experimental results and discussions

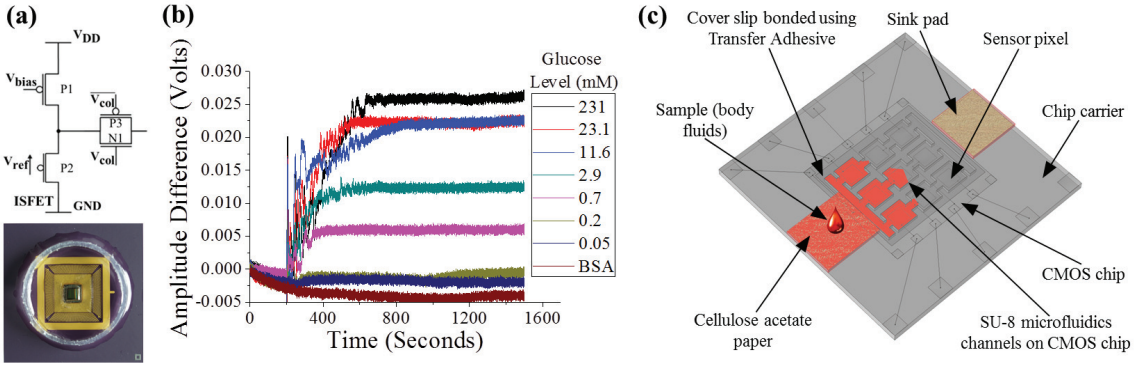

Fig. 1. (a) The sensor pixel circuit and a fully packaged CMOS chip; (b) The data obtained for different glucose concentration; (c) A multiplexing enzyme-based for multiple metabolites quantification.

Fig. 1(a) shows the circuit architecture of a single ISFET sensor pixel and a fully encapsulated CMOS chip, which is used to acquired data and received digital address signals using an acquisition system [4]. A layer of Ta_2O_5 is used to enhance the robustness and drift of the sensor, while also demonstrating a sensitivity of 45 mV/pH. Enzyme consumes or produces hydrogen ions in their reaction pathway that can be measured by ISFET. Therefore we have measured hexokinase enzyme reaction using a CMOS ISFET chip with glucose concentration in the physiological range of 0.05 mM – 231 mM, as shown in Fig. 1(b). From the data, we have successfully extracted the K_M value of 0.58 ± 0.36 mM. Using this method, we could integrate with microfluidics and immobilisation of different enzymes in different locations to measure several metabolites simultaneously, as shown in Fig. 4(c).

3. Conclusion

We have presented the activity of enzyme assays on a CMOS ISFET array chip. It is expected that these measurements will enable new and exciting handheld diagnostic devices to measure personal metabolome.

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