Front-End Electronics for Beta-Cell Function Monitoring with an Integrated FOPP Detector

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***Abstract*—This paper presents the front-end electronics for beta-cell function monitoring, which will be used for the study and treatment of the type 2 diabetes mellitus. A unique feature of the design is an integrated circuit solution for the Fraction of Plateau Phase (FOPP) detection. The FOPP is the percentage of time when beta-cells, in the islets of Langerhans in the pancreas, show burst activity, which is directly proportional to the extracellular glucose concentration. The proposed integrated FOPP detector circuit adopting a differential envelope detector structure keeps the design overhead to a minimum and only FOPP relevant information is well reserved and processed, resulting in a highly reduced data volume. This allows us to further apply this solution to more advanced in-vitro and in-vivo beta-cell activity monitoring. The concept is successfully validated by the measurement results of an application specific integrated circuit (ASIC) in XFAB XH018 CMOS process.**

Keywords—Type 2 Diabetes, Beta-cell monitoring, ASIC, burst, glucose concentration, FOPP detection

I. INTRODUCTION

According to the statistics from the World Health Organization (WHO), there are millions of people worldwide suffering from the type 2 diabetes mellitus, which is caused by the body's ineffective use of insulin [1]. Insulin is generated in the beta-cells that reside in the islets of Langerhans in the pancreas. The blood glucose concentration is directly sensed by the beta-cells and an instantaneous regulation of insulin will be perfectly matched to the changing glucose concentration. However, during type 2 diabetes mellitus, beta-cells produce more insulin (as a major reason due to excessive food uptake over prolonged time periods). This increased activity results in the production of reactive oxygen species within these cells which leads to a gradual decline in the number of available beta-cells. There is a direct relationship between the beta-cell's electrical activity in the form of membrane oscillatory bursts and extracellular glucose concentration [2]. The fraction of plateau phase (FOPP) which is the percentage of time with beta-cell burst activity, serves as an excellent bio-marker. A high FOPP percentage corresponds to a high glucose concentration and vice versa. If the electrical activity of the beta-cells in the form of FOPP can be accurately monitored, medical interventions can be applied accordingly. Conventional methods record all the oscillatory signals of beta-cells in vitro and calculate the FOPP in signal-post-processing [2][3]. Since alterations of the extracellular glucose level are slow processes, the recording usually takes hours and generates a very large data volume, which requires continuous high data transmission and processing power. In our research, we are aiming at developing power-efficient front-end electronics which can not only accurately amplify the small beta-cell signals, but also provides an integrated solution for the FOPP detection. The circuit presented in this paper can directly measure the FOPP on chip and highly reduce the output data volume. This will be useful for advanced in-vitro and in-vivo monitoring of beta-cell activities.

II. SIGNAL PROCESSING CONCEPT

A. Beta-cell Burst and FOPP

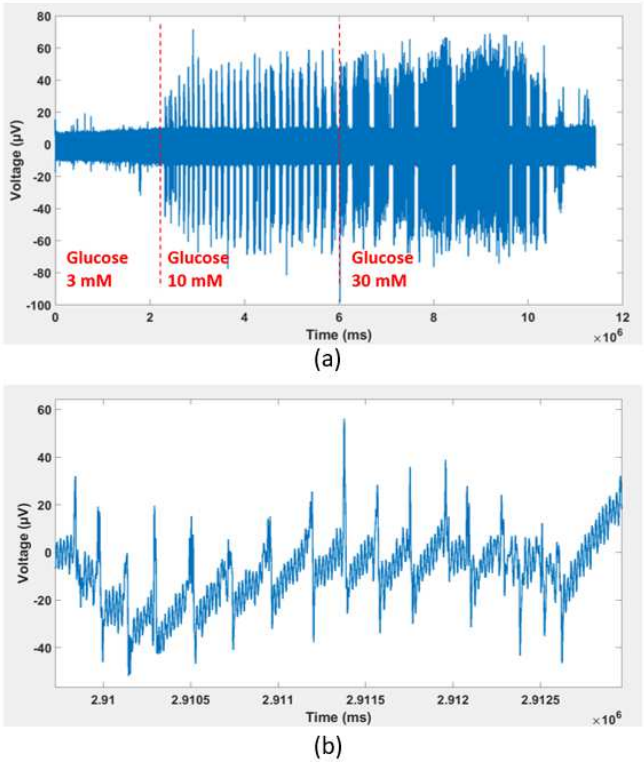

Fig. 1. Electrical activity of mouse's beta-cells changes with glucose level in long-term culture: (a) Recorded data sampled at 1kHz with 3 different extracellular glucose levels. (b) Zoom-in view of multiple spikes in a burst; the duration of a single spike is about 10 ms.

As mouse's beta-cells show a similar behavior as human beta-cells, they are often used in practical studies. Figure 1a shows the mouse's beta-cell bursts raw data picked up by extracellular electrodes using the conventional recording technique. The data is sampled at 1kHz, i.e., 1 ms per sample, for more than 3 hours. The extracellular glucose levels are at about 3 mM, 10 mM and 30 mM for timeslots

from about 0s to 2000s, 2000s to 6000s and 6000s to 10000s, respectively. The measured signal amplitude is about +/-50μV and the noise level is at +/-10μV. It can be clearly observed that the burst density changes along with the glucose level and each burst is a cluster of short spikes, e.g. about 10 ms spike duration (Fig. 1b), typical for mouse. A decisive observation is that for FOPP detection, single spikes are not of interest; instead bursts are important, as they hold the information of the percentage of time with beta-cell activity. Based on this observation, the signal processing chain can be tailored to only preserve the low-frequency bursts information and the corresponding circuit implementation can be highly simplified.

B. Monitoring Scheme and Signal Processing Chain

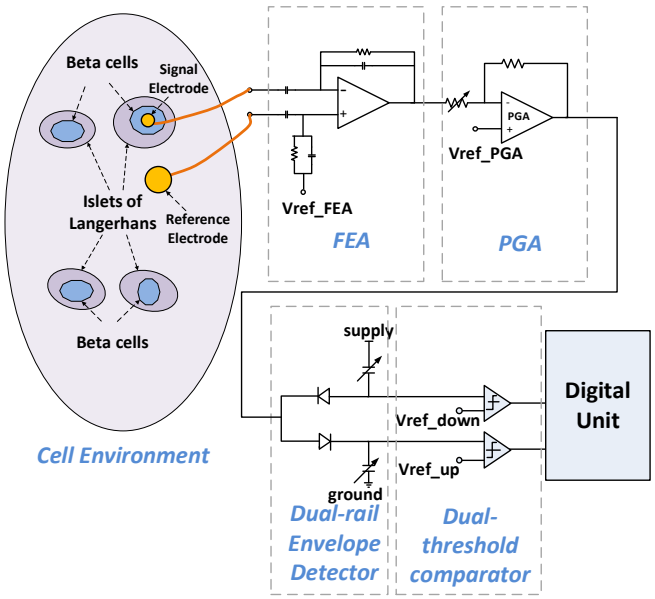

Fig. 2. Beta-cell monitoring scheme and the proposed signal processing chain

The beta-cell monitoring scheme and the proposed signal processing chain are illustrated in Fig. 2. The small burst signals generated in beta-cells are firstly picked by extracellular electrodes. In order to cancel out common mode interferences along the recording path, a differential measurement technique is used. For each beta-cell under monitoring, a signal electrode is placed directly on top of the cell to achieve an electrical contact. Meanwhile, a reference electrode is shared among all cells, i.e. to form a differential path with each signal electrode. The reference electrode is placed in the same environment without touching any active cells.

Both electrodes, i.e. a signal electrode and a reference electrode, are connected to a capacitively coupled front-end amplifier (FEA) [4], thus the DC offsets from the electrodes are rejected by the input capacitors. In the feedback path, a small capacitor and a pseudo resistor with resistance in the GΩ range provide a high-pass filter function with a very low corner frequency, which helps to eliminate low frequency noise. In order to keep the balance of the differential amplifier, an identical RC network is also designed for the positive input of the amplifier. The flatband gain of the FEA is defined by the ratio of the input capacitor and the feedback capacitor. The FEA output signal is further amplified by a programmable gain amplifier (PGA) to get a sufficiently large amplitude. The reference voltage of the PGA is tunable to compensate the possible DC offset due to the mismatch in the FEA. As long as the information of the burst activity is preserved, the gain accuracy of the amplifiers is not critical.

Next, a dual-rail envelope detector consisting of diodes and tunable capacitor banks is applied to capture the signal envelopes referred to both ground and supply rails. The dual-rail design allows us to tolerate the DC offset of the FEA and PGA, and provides effective activity detection results even when the circuit components do not match perfectly. Figure 3 shows the circuit simulation results when the raw data from Fig. 1 is applied as the input signal. It can be seen that the information of the burst density is very well reserved in the signal envelopes, while the high-frequency FOPP-irrelevant signals are filtered out. The signal envelope has a much lower frequency, which highly relaxes the design requirements for the following circuitry in terms of speed and power consumption. Afterwards, a dual-threshold comparator translates the dual-rail envelopes into digital signals and can be processed by the on-chip digital unit to calculate the FOPP.

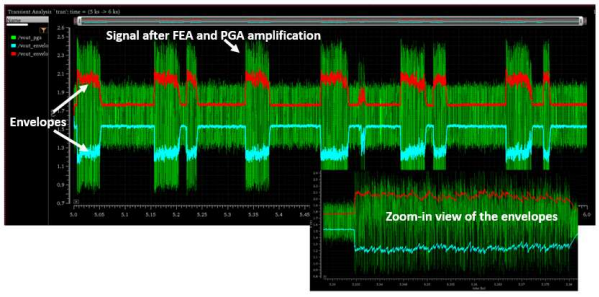

Fig. 3. Circuit simulation results: The green curve is the amplified bio-signal using the raw data in Fig. 1; The red and blue curves are the detected envelopes refer to both supply and ground rails.

III. ASIC Implementation and Validation

A. ASIC Implementation and Measurement Setup

A test ASIC which can interface up to 64 signal electrodes and 1 reference electrode is implemented in the XFAB XH018 CMOS technology. It occupies an area of 3.5 mm x 2 mm with a supply voltage of 3.3 V. The ASIC is packaged using the chip-on-board (COB) wire-bonding method (Fig. 4a). The layout of the ASIC is shown in Fig. 4b. The circuit blocks shown in Fig. 2 are implemented as one of the test configurations in the ASIC.

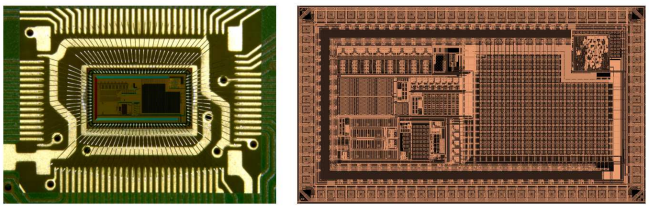

Fig. 4. ASIC Implementation: (a) The ASIC is wire-bonded onto a PCB; (b) Layout view of the ASIC

The complete measurement setup consists of a waveform generator (Keysight 33600A), a custom designed micro-volt signal generation PCB, a main test PCB, an ASIC board, a TI MSP430F5529 Launchpad, a PC based control software with

a graphical user interface (GUI) in PC and an oscilloscope (Fig. 5a). The micro-volt signal generation PCB takes the signal from the function generator and reduces its amplitudes to micro-volt level via on-board resistive dividers. The amplitudes of these test signals are in the same range as the amplitudes of the beta-cell bursts. Next, the test signals are connected via flat-flex cables to the ASIC board which is fixed on the main board. The main board is equipped with the additionally required peripheral components such as voltage regulators, test points, connectors to the TI Launchpad, etc. The TI Launchpad board is used to supply power to the measurement setup and controls the communication interface and transmits the measured ADC and FOPP values from the ASIC board using an SPI interface. The entire measurement setup is controlled via the USB interface from the PC using specially developed GUI software. The critical analog output signals of the ASIC are measured by the oscilloscope during characterization.

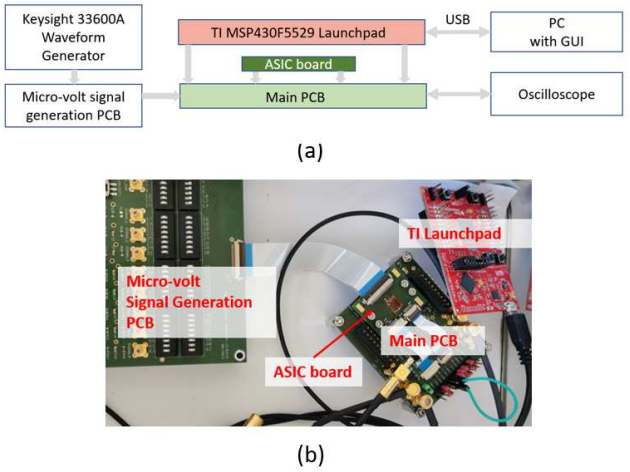

Fig. 5. The measurement setup: (a) Illustration of the setup; (b) Photo of the setup including the micro-volt signal generation PCB, the main PCB, the ASIC board and the TI Launchpad.

B. Experimental Results

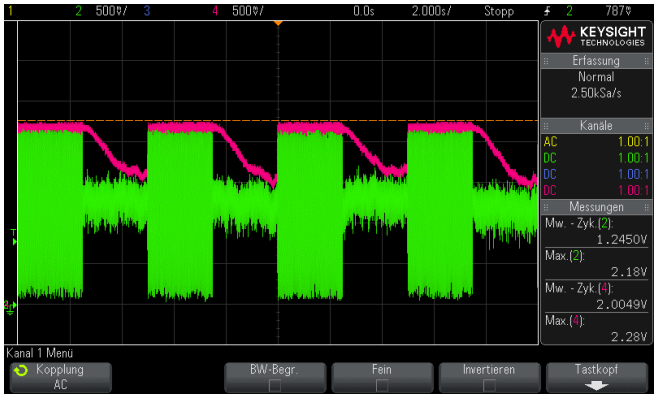

Fig. 6. Oscilloscope screen snapshot of the experimental results with the PGA output signal (green) and the envelope detector output signal (magenta).

In the experiment, a 500 mVpp, 1 kHz sinusoidal signal in the burst mode (2500 cycles, period of 5 s) from the Keysight 33600A waveform generator is applied to the signal generation PCB and the amplitude is reduced to about 50µVpp. This small signal is then fed into the input of the ASIC. The reference input is biased at a constant DC voltage. Figure 6 shows the oscilloscope screen snapshots of the PGA output signal and the envelope detector's output signal. Firstly, the burst signal at the output of the PGA has a sufficiently large amplitude of more than 2 Vpp with good signal-to-noise ratio, which proofs the effectiveness of the amplification function. Secondly, the envelope of the burst is detected correctly. As the capacitors in the envelope detection circuit have a wide tuning range, the decay time of the envelope can be tuned to fit various burst shapes during real beta-cell monitoring. The detected envelope is a low frequency signal and has sufficiently large amplitude, which can be easily processed by a low-speed low-power comparator. Finally, the output of the comparator is a digital signal which will be used for FOPP calculation.

IV. CONCLUSIONS

In this work, the design of front-end electronics for beta-cell function monitoring is presented, which will be used for the study and treatment for the type 2 diabetes mellitus. A unique feature of the design is an integrated solution for FOPP detection. The proposed integrated FOPP detector circuit adopting a differential envelope detector structure keeps the design overhead to a minimum and only FOPP relevant information is well reserved and processed, resulting in a highly reduced data volume. This allows us to further apply this solution to more advanced in-vitro and in-vivo beta-cell activity monitoring. The FOPP detection concept as well as the effectiveness of the amplification circuits are all successfully validated by the measurement results of an ASIC.

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