Fast Lock-in System for Biological Cell Impedance Analysis

N Li[1,2],T R Qureshi[1], A. Zarafshani[1], N Béqo[1], Z Zhou[2], H Xu[2], C Chatwin[1] and W Wang[1]
[1] *Biomedical Engineering Research Group, University of Sussex, Brighton BN1 9QT, U.K*
[2]*School of Electrical Science and Engineering, National University of Defense Technology, Changsha 410073, China*
E-mail: nl74@sussex.ac.uk

Abstract:
This paper presents a fast cell impedance measurement system for biological cell analysis. The system consists of a current source circuit, eight voltage detector circuits and a field programmable gate array (FPGA) device. A digital multi-tone generation algorithm, based on the CORDIC algorithm, was implemented in the FPGA. Test results show that the proposed system has good performance in which the time cost for each measurement is less than 1ms. This system has great potential for fundamental cell analysis.

Keywords: Cell impedance, biological impedance, lock-in, multi-tone

1. INTRODUCTION

Cell impedance analysis can provide the frequency dependent electrical properties of cells involved with cellular physiology or morphology. The spectrum of bioelectrical impedance of cells can reveal physiological conditions and biological events in cells such as proliferation(Rahman *et al.*, 2008), morphology(Malich *et al.*, 2002), and motility changes (Han *et al.*, 2007), toxic effect (Ko *et al.*, 1998),cell functions and intracellular processes (Malleo *et al.*, 2010; Cho and Thielecke, 2007).

The lock-in amplifier system is an instrument designed to measure the presence of small signals buried in large amounts of noise.(Michels and Redding, 1948) It applies a phase-sensitive detection (PSD) technique, where a reference signal is used to recover a narrow-band response from broadband noise.(Caplan and Stern, 1971) With the rapid development of the digital techniques, some modern digital lock-in amplifier (DLIA) systems were developed.(Barone *et al.*, 1995; Gaspar *et al.*, 2004) They can be used to remove large amounts of the analog circuitry by performing the signal processing digitally, however, because of the time constant limitations of a low-pass filter lock-in system, a major deficiency is the measurement speed. Furthermore, in designing such systems a compromise must be made between its noise rejection performance and measurement speed. By utilizing a multi-tone

lock-in technique and multi-channel hardware, we solved this problem and realized a high-speed lock-in system for cell impedance analysis.

2. HARDWARE SYSTEM DESIGN

The principle of the lock-in technique for impedance measurement is introduced in previous literature (Gaspar *et al.*, 2004). A brief hardware functional diagram of our lock-in system is shown in Fig. 1. The system mainly consists of a micro electrode array (MEA), a digital-to-analog converter (DAC), a voltage-to-current converter (V/I), 2 x 4-channel analog-to-digital converters (ADC) and a field programmable gate array (FPGA) device.

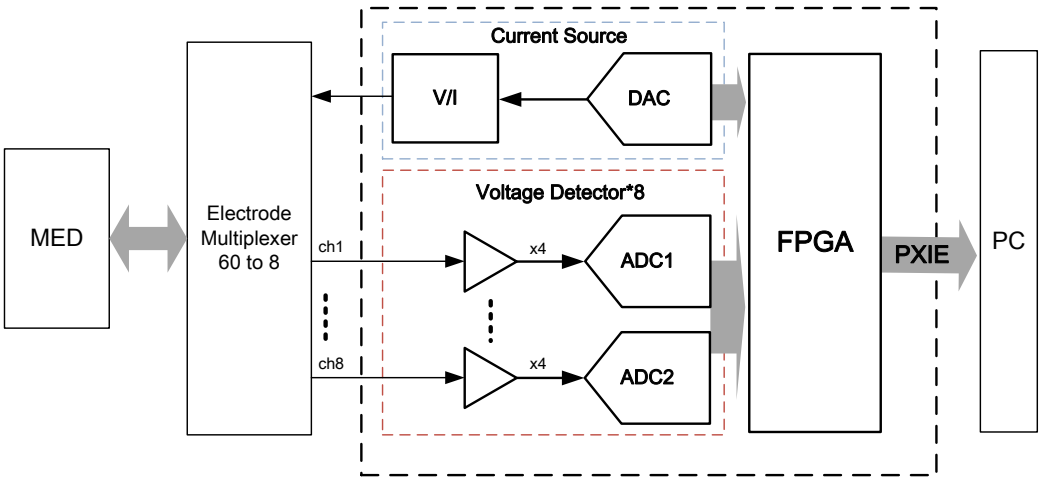

Fig1. The hardware architecture of the cell impedance analysis system.

3. SOFTWARE DESIGN

In our system, the software implemented in an FPGA performs the reference signal generation, digital phase-sensitive detection (DPSD), impedance calculation and the communication with the on-board peripheral chips and the PC. The architecture of our logic design in the FPGA is shown in Figure 2. The program mainly consists of a FIFO, a DDS module, 8 DPSD modules, and a PXIE controller. The FIFO is used for data synchronization between ADC inputs and internal logic. The DDS module is used to generate the multi-tone reference sine wave digital signals to the DAC. DPSD module extracts the amplitude and phase of the detected signal and then uses the FPGA to calculate the impedance. Finally, the impedance results are transferred to the PC via the PXIE controller.

The Multi-tone signal is generated by the CORDIC-based DDS module. CORDIC is a simple and efficient algorithm to calculate hyperbolic and trigonometric functions. The CORDIC algorithm is based on the concept of complex phasor rotation by multiplication of the phase angle by successively smaller constants.(Delosme, 1989) The algorithm can be implemented efficiently by a series of simple binary shifts and additions/subtractions.(Park *et al.*, 2000) Multi-tone signals are generated by time multiplexing the CORDIC module among the different phase increment values and processing each value with its associated increment angle and amplitude value.

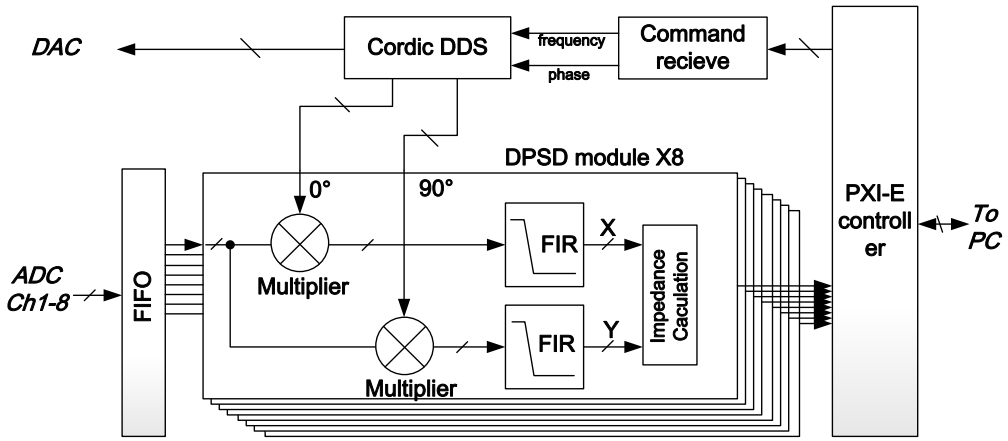

Fig2. Software architecture of the cell impedance analysis system.

4. SYSTEM PERFORMANCE TESTING

4.1. Multi-tone Testing

To verify the multi-tone function, we generated a multi-tone sine-wave signal including 10 different frequencies from 1 kHz to 1 MHz. The spectrum results are shown in Figure 3. From the graphics, we can see that the CORDIC based multi-tone generator functioned correctly.

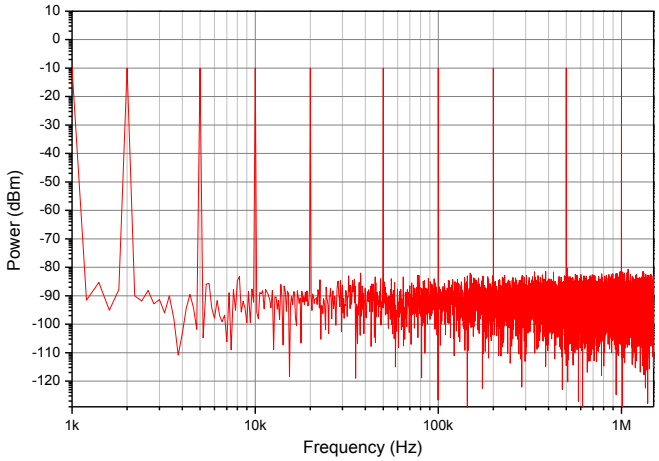

Fig.3. Spectrum analysis of multi-tone voltage output.

4.2. Speed Testing

In order to verify the speed of the impedance measurements, a commercial lock-in system (SR850) was used for comparison. We used two systems to measure several sets of impedance between different electrodes of MEA. The time requirements using the SR850 and our system are shown in Table I.

Table I. Time requirements of SR850 and our lock-in system

Measurement sets	SR850	Our lock-in system
1 sets	≈40 ms	≈1 ms
80 sets	≈3280 ms	≈160 ms
4000 sets	≈28 min	≈20s

5. CONCLUSION

In order to monitor the biological impedance characteristics of cell samples in real time, we designed a cell impedance measurement system based on the digital lock-in technique. We introduced the multi-tone signal into the lock-in method and realized a multi-frequency lock-in technique. Furthermore, we utilized multi-channel ADC and high speed FPGA devices to realize the DPSD algorithm. The evaluation results show that the time cost for each measurement is less than 1ms which can fulfill our requirements for real-time biological cell analysis.

.

REFERENCES

Barone F, Calloni E, Difiore L, Grado A, Milano L and Russo G 1995 High-Performance Modular Digital Lock-in Amplifier *Rev Sci Instrum* **66** 3697-702

Caplan L C and Stern R 1971 Inexpensive Lock-in Amplifier *Rev Sci Instrum* **42** 689-&

Cho S and Thielecke H 2007 Micro hole-based cell chip with impedance spectroscopy *Biosens Bioelectron* **22** 1764-8

Delosme J M 1989 Cordic Algorithms - Theory and Extensions *Advanced Algorithms and Architectures for Signal Processing Iv* **1152** 131-45

Gaspar J, Chen S F, Gordillo A, Hepp M, Ferreyra P and Marques C 2004 Digital lock in amplifier: study, design and development with a digital signal processor *Microprocess Microsy* **28** 157-62

Han A, Yang L and Frazier A B 2007 Quantification of the heterogeneity in breast cancer cell lines using whole-cell impedance spectroscopy *Clin Cancer Res* **13** 139-43

Ko K S C, Lo C M, Ferrier J, Hannam P, Tamura M, McBride B C and Ellen R P 1998 Cell-substrate impedance analysis of epithelial cell shape and micromotion upon challenge with bacterial proteins that perturb extracellular matrix and cytoskeleton *J Microbiol Meth* **34** 125-32

Malich A, Boehm T, Facius M, Mentzel H J, Fleck M, Boettcher J, Anderson R and Kaiser W A 2002 Use of electrical impedance scanning in the differentiation of sonographically suspicious and highly suspicious lymph nodes of the head-neck region *Eur Radiol* **12** 1114-20

Malleo D, Nevill J T, Lee L P and Morgan H 2010 Continuous differential impedance spectroscopy of single cells *Microfluid Nanofluidics* **9** 191-8

Michels W C and Redding E D 1948 An Improved Lock-in Amplifier *Phys Rev* **74** 1562-

Park M, Kim K and Lee J A 2000 CORDIC-based direct digital frequency synthesizer: Comparison with a ROM-based architecture in FPGA implementation *Ieice Transactions on Fundamentals of Electronics Communications and Computer Sciences* **E83a** 1282-5

Rahman A R A, Register J, Vuppala G and Bhansali S 2008 Cell culture monitoring by impedance mapping using a multielectrode scanning impedance spectroscopy system (CellMap) *Physiol Meas* **29** S227-S39