# iCAMS: An FPGA-Based System for the Real-Time Monitoring of the Activity of In-Vitro Cells

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***Abstract*—In order to employ biological neurons within technical applications, they (1) must expose themselves to a monitoring system and (2) must allow external (stimuli) signals to influence their spontaneous activity in order to guide their growth. A first step towards this goal has recently been made by the development of so-called neuro-chips, which provide an excellent bio-physical interface. This paper proposes the in-vitro cell-activity-monitoring system (iCAMS) that links the neuro-chip with a regular PC. iCAMS (pre-) processes all the data from all the electrodes in parallel, does further user-specified filtering, analyses, and temporary storage in local memory. iCAMS also provides a USB or Ethernet-based communication link to the PC. Even though, iCAMS is implemented on a low-cost, standard field-programmable gate array (FPGA), it processes the 52 electrodes at about 10 KHz with a resolution of 10 bits.**

## I. Introduction

In terms of neural networks, the world seems to consists of two parts. The first part looks at neural networks more from a biological/medical point of view. This type of research is concerned with, for example, a cell's metabolism, how the action potential evolves, how the action potential is transmitted by means of ions, how a cell's three-dimensional structure depends on exogenous disturbances, how different spike trains correlate to each other to mention but just a few issues. For biological-oriented research, the interested reader is referred to the pertinent literature [1]–[4].

As opposed to the "biological world", the engineering world is more concerned with the *usage* of neural networks in, for example, control [5], reinforcement learning [6], character recognition [7], speech recognition [8], data mining [9], etc. Thus, a nerve cell's three-dimensional structure or its actual metabolism is at most of secondary interest for an engineer. Rather, an engineer focuses on functionality, learning, network topology, average cell activity, and so forth. Of course, those properties are also of interest for a biologically oriented research. In other words, the engineer considers the very same aspects but on a much higher abstraction level.

From a computational point of view, a more detailed level has always the potential of providing more and/or better functionalities. However, these add-ons come to the expense of (significantly) increased computational demands. Thus, for a given technical application, an engineer aims to find an appropriate compromise.

Regardless of all the progress, research has made in the last decades, many engineers might still find it stimulating to bring together both worlds. In other words, they might ask the question whether or not biological nerve cells can be used in technical applications, and whether or not a computer might be able to control or at least influence the growth of phyisical in-vitro or in-situ nerve cells. Both options would probably have great advantages in both the technical as well as the biological/medical world.

A first step towards this goal has already been made by the development of glass-based multi-electrode arrays [10]. These chips have a surface made from glass, which is isolated with silicon nitride. Because of its construction, the in-vitro cells are able to attach to the sensor's surface, which allows the integrated electrodes to derive the electrical activity that is going on in the substrate. As an example, Section II briefly reviews such a chip.

With 52 integrated electrodes on an area of 1 mm $\times$ 1 mm in size, the following two physical aspects have to be taken into account: (1) the number of nerve cells is about 2 times larger than the number of electrodes and (2) due to the cells' sizes, the electrodes are often far off a cell. Thus, the electrodes measure all the current activity, which is often a mixture of very many sources. Therefore, the raw data is normally amplified and than analyzed by some sophisticated software products.

Unfortunately, the existing software products, including their high-impedance amplifiers, which perform the required signal amplification and noise filtering, are not open-source products. The non-disclosure of the products' internals limit the indepth research options. Therefore, Section III describes a new system which allows for the online monitoring of up to 52 electrodes with a sample rate of up to 10 KHz. The in-vitro cell-activity-monitoring system (iCAMS) is able to store up to 24 seconds of monitored data before sending it to a host. The system also performs the noise filtering for all the electrodes in parallel. And due to the architectural design, the user may exchange or self-program any of the filters at his or her own disposal.

The system is currently under development, with a Nios II

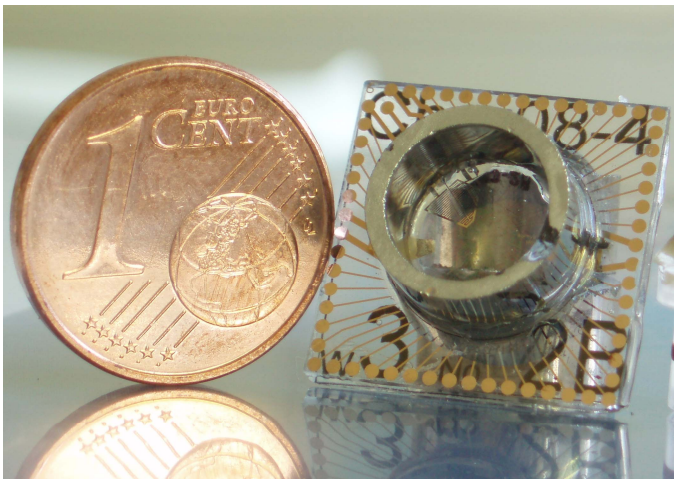


Fig. 1. World's smallest glass chip with a platinum coated glass ring, which was developed by the chair of biophysics at the University of Rostock
*Fig.: Philipp Köster*

Development Kit, Cyclone II Edition board [11] as its target platform. On this field-programable gate array (FPGA), the system is expected to consume about 65 % of the ressources, which leaves enough capabilities for further (parallel) processing stages on chip. These options are briefly discussed in Section IV, which also concludes this paper with a brief discussion.

## II. A Glass-Based Multi-Electrode Array

One may wonder, why multi-electrode arrays are important for research. In June 2007, the European Community has launched new regulations on chemicals. The focus of these regulations is the registration, evaluation, authorization, and restriction of chemical substances. These new test guidelines require the investigation on the effects of neurotoxic and developmental-neurotoxic substances. Unfortunately, most of these tests are still based on animal experiments. To reduce the number of such experiments the acquisition of electrophysiological signals, for example, can be done on in-vitro cells by means of such multi-electrode arrays.

As Fig. 1 shows, a glass-based multi-electrode array consists of a glass plate of approximately 16 mm × 16 mm in size with a small bin of 1.4 mm in diameter attached to it. Within the bin area, the glass plate employs 52 micro electrodes for the detection of electric cell activity. The impedance detection is realized with an integrated interdigitated electrode structure. Furthermore, a thermostatic system controls and regulates the chip's temperature using an integrated temperature sensor.

Due to the features described above, these glass-based multi-electrode arrays might be interesting tools for, for example, producers of pharmaceuticals. Basic research could include, for example, the correlation of the electric activity with the structure of a neuronal network to differentiate between neuron types. Furthermore, these multi-electrode arrays can be used as high-content screening applications as well as for the bio-analysis of substances [10].

## III. iCAMS: the in-vitro-Cell-Activity-Monitoring System

This section provides a more detailed description of iCAMS, a system that monitors the electrical activity of in-vitro (nerve) cells. Its main function is, as Fig. 3 sketches, to provide a data link between the neural glass chip and the PC. In so doing, iCAMS has to perform the analog-to-digital conversion, some noise and user-specific filtering, some local temporary storage, and finally the data transmission to the PC. Accordingly, iCAMS hosts a proper number of analog-to-digital converters, local processing and data storage facilities, as well as some USB and ethernet interfaces. The overall design is shown in Fig. 2.

A standard way of implementing such a system would consist in using a microcontroller or perhaps in using a digital signal processor. Either of these processors would connect all the analog-to-digital convertes to appropriate (interrupt) inputs, and would read the data in, for example, in a round robin way. With 52 input channels and a sample rate of about 10 KHz per channel, the processor would have to process 500.000 channels per second, which might provide a fairly high load even for state-of-the-art signal processors.

Furthermore, as the number of inputs (chip electrodes) and the required filtering operations may grow, such a centralized system might be quickly over loaded. Therefore, this section proposes a scalable, parallel architecture for which field-programmable gate arrays (FPGAs) seem to provide an ideal platform.

Basically, an FPGA consists of a huge number of logical elements that can be freely combined in order to obtain virtually any functionality, which include entire processors. Some well-known examples are the Nios and Nios II CPUs from ALTERA [12], the LEON CPUs from Gaisler Research [13], and the Microblaze CPU from XILINX [14]. Standard, state-of-the-art FPGAs such as Cyclone II [15] or Cyclone III [16] provide at most 68.000 or 120.000 logic elements, which allow, for example, for the implementation of three simple processors (e.g., Nios II) on the very same chip. Furthermore, most FPGAs feature some local memory chunks that are distributed over the entire FPGA and that can be freely used. In

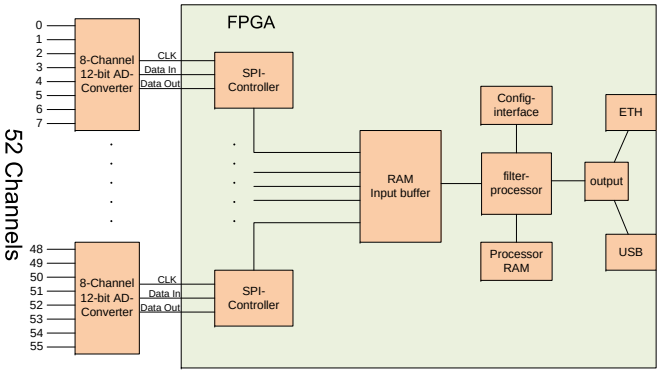


Fig. 2. Design of the new in-vitro-Cell-Activity-Monitoring System – iCAMS

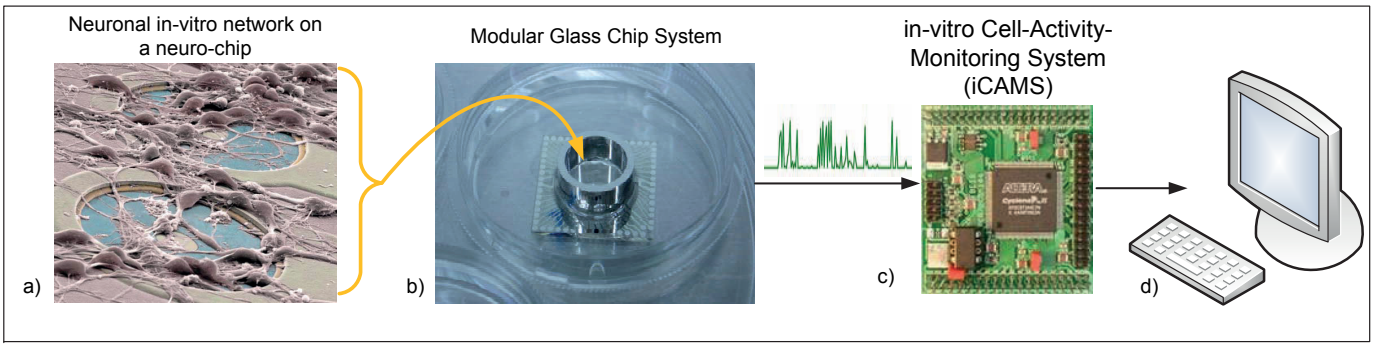


Fig. 3. Overview of the entire system: a) unknown structure of an neuronal in-vitro network based on a neuro-chip b) the nerve cells are located in the middle of a glass-based multi-electrode array c) electrical activity measured by the electrode array is send to the new in-vitro Cell-Activity-Monitoring System, called iCAMS d) the processed data can be analyzed on a normal computer

addition to the logic elements and their interconnections, most FPGAs also provide an infrastructure, which consists of one or more clock generators, several I/O ports, and a significant number of embedded memory cells. A particular configuration (process) consists of a high-level description language in, for example, VHDL [17] or Verilog [18], such that the hardware can be configured (programmed) almost like an ordinary C program. With all these user-configurable pieces, an FPGA can realize simple modules, such as state-machines, counters, adders, and ALUs, as well as entire systems.

Due to an FPGA's very flexible configuration features, iCAMS is going to employ an application-specific processing unit for every input channels. These processing units are of course not entire CPUs, but rather tuned to perform various signal preprocessing and noise filtering operations. Each single processing unit has a certain number of configuration registers. These registers define the cut-off frequency and select the filtering algorithm. Furthermore, every channel can utilize up to four different preprocessing/filtering algorithms in order to allow for rather complex data manipulations. After the preprocessing, the data can be locally stored in a per-channel RAM of 300 KB in size.

The system as described above can locally store up to 24 seconds of recorded data. This data can be further processed by an on-board Nios II CPU [12], which operates at a clock rate of 50 - 200 MHz. Basically, this central processor allows for the data integration of different channels for further analyses. Furthermore, the central processor is able to send the data to the host PC via either the USB or the Ethernet interface.

The system configuration as described above results in the following performance figures: it consumes about 65 % of the available logic elements of the used low-cost Cyclone II EP2C35F672 FPGA, and the Nios II processor is expected to run at a load of about 45 %. Both numbers offer significant resources for further modules.

## IV. Discussion

This paper has argued that some technical applications might benefit if their controller would be able to employ biological (in-vitro) nerve cells; those in-vitro cells would provide their functional abilities on a way smaller room any digital device would currently capable of. In order to do so, this paper has proposed iCAMS that processes all the incomming data and does the required preprocessing. Due to its modular architecture, iCAMS is also able to apply additional user-defined noise filtering.

This system is currently under development and intended to be implemented on a low-cost, standard field-programmable gate array (FPGA). All the parts have been specified, and some of them have already been verified in simulation. With an additional Nios II processor, the current system consumes about 65 % of an Altera Cyclone II board. With all the components, iCAMS will be processing 52 channels in real time at a rate of 10 KHz with a resolution of 10 bits per channel.

The next steps consists of building a complete system, which is expected to be done by spring 2010. The system will then be used for actually monitoring in-vitro cells, to detect synaptic transmissions and for pharma-screening. The analysis, for example, of the structure of neuronal networks or reconstructing the analyzed network will still be done in software on the host PC.

These laboratory experiments will also include artificial stimulations. The effects of these stimulations will then be analyzed with the very same system. The ultimate goals of these experiments are (1) a set of rules that allow for controlling the growth processes of the in-vitro cells and (2) to control and manipulate the communication between nerve cells of a neruonal network.

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