The Application of a Real-Time Rapid-Prototyping Environment for the Behavioral Rehabilitation of a Lost Brain Function in Rats

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***Abstract*—In this paper we propose a Rapid Prototyping Environment (RPE) for real-time biosignal analysis including ECG, EEG, ECoG and EMG of humans and animals requiring a very precise time resolution. Based on the previous RPE which was mainly designed for developing Brain Computer Interfaces (BCI), the present solution offers tools for data preprocessing, analysis and visualization even in the case of high sampling rates and furthermore tools for precise cognitive stimulation. One application of the system, the analysis of multi-unit activity measured from the brain of a rat is presented to prove the efficiency of the proposed environment. The experimental setup was used to design and implement a biomimetic, biohybrid model for demonstrating the recovery of a learning function lost with age. Throughout the paper we discuss the components of the setup, the software structure and the online visualization. At the end we present results of a real-time experiment in which the model of the brain learned to react to the acquired signals.**

Keywords-Rapid Prototyping; Biomedical Systems; Real-Time; Neurological analysis; Biomedical Engineering

I. INTRODUCTION

Nowadays, rapid prototyping systems are widely used in different types of applications. Prototyping itself involves the construction of a model or prototype for the purpose of testing, to have a quick estimation whether the development ideas (specific algorithms, model approaches) can achieve good performance and furthermore to tune the algorithms before final implementation. Rapid prototyping for biosignal analysis and related fields means a program environment that allows fast development of analysis algorithms and furthermore real time implementations. Once the algorithms are defined and optimized for the corresponding purposes they can be implemented in a system that totally fits to the requirements.

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The RPE for electrophysiological applications consists of a high resolution biosignal amplifier, a digital output device and the software environment embedded into MATLAB/Simulink. As already presented in a first version of the RPE [1] the timing of the whole system is defined by the internal and precise clock of the amplifier. This allows the control of real time applications. This first version of the RPE was mainly designed for developing EEG-based Brain Computer Interfaces and for fast implementation of feature extraction and classification methods. Electrophysiological research however covers a wide range of different signals. Neurophysiological laboratories require systems to analyze ECG (electrocardiogram), EOG (electrooculogram), EMG (electromyogram), respiration, temperature, GSR (galvanic skin response) and ECoG (electrocorticogram). Additionally to those signals researchers more and more focus on the analysis of neuronal events like single-unit activity [2] or multi-unit activity (MUA) [3] in specific brain regions. For this latter applications brain waves are recorded using electrodes which are placed close to the center of interest inside the brain. Therefore the requirements for the RPE increase as the time resolution for detecting single neuronal events like a firing neuron has to be much more precise. Therefore a revised platform was designed and developed which is capable of working with sufficiently high sampling frequencies (up to 38.4 kHz per channel) [2]. This system is specialized for single-unit activity. By thresholding it cuts out the time-periods of the incoming data which contain spikes. The proposed RPE approach goes a step further. It is designed to deal with single- as well as with multi-unit activity using all the data which come in from multiple input channels.

A real-time system for electrophysiological research acquires biosignals and analyses the data continuously in order to activate a response or to give feedback within a defined time

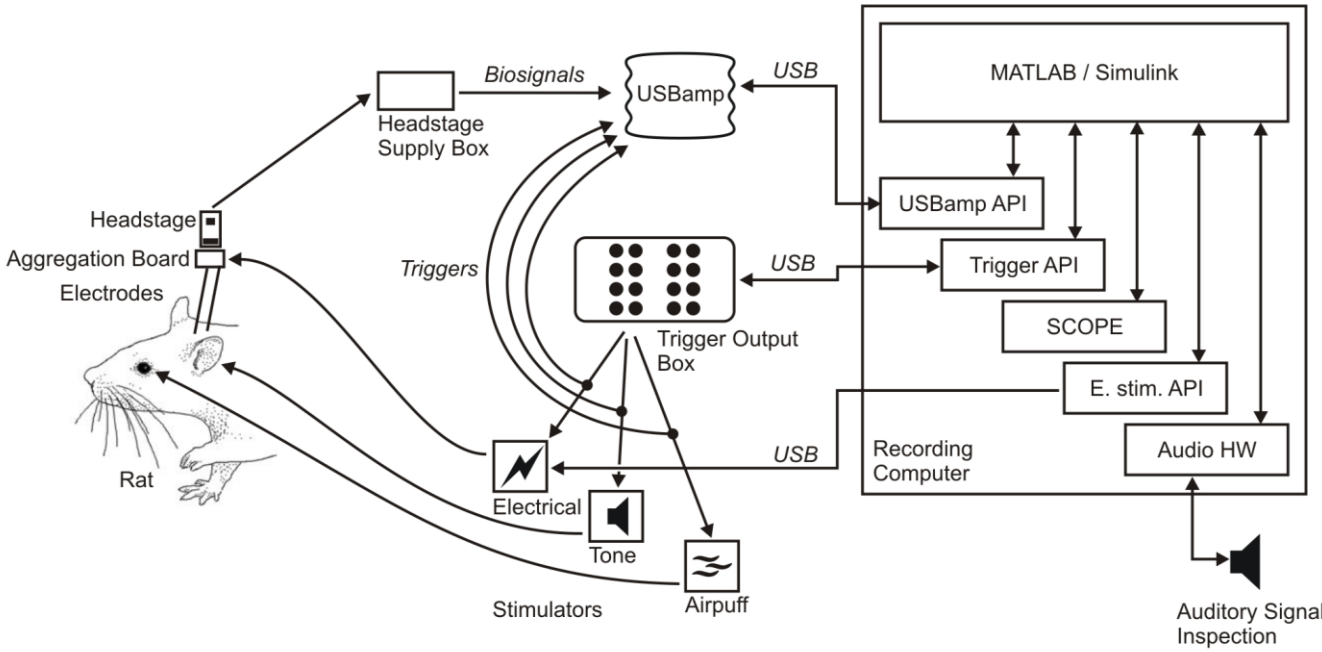

Figure 1. The hardware setup of the RPE which includes the recording computer with auditory output, the g.USBamp biosignal amplifier connected to the electrodes implanted in the brain of the rat with the headstage. Furthermore the trigger output box connected to the electrical-, tone-, and airpuff-stimulators.

interval. One example of real-time systems in this area of research is the control of a prosthetic limb based on signals taken from an electrode directly implanted in the patient's motor cortex [4]. The limb must be controlled well-timed, acts as feedback to the user and helps to improve performance over time. Instead of visual feedback also an electrical stimulator can be controlled as it is done with deep brain stimulation (DBS) in Parkinson patients [5]. Beside these two applications, real-time systems are also used to investigate if it is possible to replace functions of the brain. If the replacement can be proven to work successfully in real-time the hardware and software components can be transferred into a biomimetic chip executing the same function but with limited flexibility and size [6, 7].

The components of the proposed RPE will be explained and discussed on a particular experiment in which data recorded from the cerebellum of a rat are analyzed in order to explain and behaviorally restore a function of the brain.

II. Experiment and System Components

The paradigm of classical conditioning was introduced by Pavlov in the early 20th century [8, 9]. It utilizes procedures which provide good control of the events of an experiment [10]. The subject is exposed to repeated trials of paired conditioned and unconditioned stimuli (CS-US), commonly a tone or light-CS and a peri-orbital airpuff-US. Generally, a tone is presented and after a short interval an airpuff directed at the cornea of the rat is applied such that the CS and US co-terminate. In naïve animals, the tone-CS does not elicit any response, while the airpuff-US elicits an unconditioned eyeblink response (UR). After the association between the tone-CS and the aversive airpuff-US is established, the rat blinks after the CS onset and before the expected US, i.e., it performs a conditioned response (CR).

The acquisition of the conditioned response becomes dysfunctional due to the aging process. This was discovered by Woodruff-Pak and Thompson [11] who reported a significant decrease in the acquisition of eyeblink responses first observed in human subjects about 40 years old. Subjects of an age of 70 years show less than half the performance of 20 year old subjects. Rats at the age of 26 months (comparable ~60 yrs old human) show a significant decrease in the rate of acquisition of the eyeblink response compared to 12 month old rats [12, 13]. The cerebellar circuit involved in the eyeblink conditioning is relatively simple and consists of only two sensory inputs and a single motor output [14].

A. Experimental Paradigm

A paradigm is implemented that presents first the CS (white noise, 65dB) with a duration of 450 ms to the ear through a hollow ear bar of the stereotaxic apparatus. 300 ms after CS onset the airpuff-US is applied for 150 ms through a plastic tube directed to the rat's cornea (1.5 bars at the source, ~2.5 mc from the cornea). The inter-trial-interval (ITI) is 15 seconds.

B. Electrodes

For deriving the neuronal data electrodes are implanted into the brain of an anesthetized rat. The animal is implanted with a titanium-nitride multielectrode array (Faculty of Engineering, Tel Aviv University) with ten channels in the pontine nucleus (PN) to detect the CS, with a tungsten needle electrode (A-M Systems, USA) into the inferior olive (IO) to detect the US, and with a twisted-wire electrode in the facial nucleus (FN) to produce the eyeblink using an electrical stimulator. The electrodes are connected to aggregation boards, which provide appropriate connectors for the different electrode types and lead the signals to a compact miniature connector which fits to a headstage amplifier. The boards can be used in acute as well

as in chronic experiments. The headstage amplifies the signal at the electrode site and is connected with a 3 m long cable to the main amplification system. This is done to prevent the contamination of the signal with artifacts on its way to the main amplifier. The electrode channels are referenced against the potential of the connective tissue on the head of the rat which is routed to the reference input of the main amplifier through the headstage. In between the headstage and the g.USBamp an additional box is situated which provides the voltage supply for the headstage.

C. *Biosignal amplifier and data acquisition*

The biosignal amplifier g.USBamp (g.tec medical engineering GmbH, Graz, Austria) is connected via USB to the recording computer. The amplifier has 16 analog inputs to measure a variety of biosignals with a sensitivity of < 30nV and an input range of ±250 mV. Every channel is sampled with a frequency of up to 38.4 kHz per channel with 24 bits precision. Due to the 24 bits of resolution of the amplifier it is possible to record and store biosignals unfiltered without losing information. This is useful for adjusting filters off-line. In addition the device has eight digital TTL-level inputs which are sampled synchronously to the analog inputs to read in trigger signals. For experiments which require more than 16 analog input channels the amplifiers can be stacked and synchronized. In this way it is possible to acquire up to 64 analog channels. The data bandwidth then is limited only by the speed of the USB controllers and the processing capabilities of the computer running the real-time environment. With the g.USBamp Highspeed Online Processing Toolbox it is possible to integrate the device very fast and conveniently into the real-time system. The internal clock of the amplifier is used as clock source for the whole system. All the software implemented in Simulink is required to execute one simulation step in between two hardware interrupts of the clock of the amplifier to ensure the real-time behavior.

D. *Tone, Airpuff and electrical stimulation*

To control CS and US delivery as well as the blink-inducing stimulation, digital outputs are required. For this purpose a trigger output box is used. It provides 16 digital outputs (0/+5 V) which can be programmed with MATLAB/Simulink. Hereby two possibilities are offered to the user. For independent paradigms which do not depend on calculations based on the recorded signals the microcontroller of the box can be programmed to control the on/off times of the outputs based on different rules. This method gives a precise and computer-independent timing. For signals generated from within the software as a result of the recorded biosignals, output channels can also be controlled directly by the RPE. In this mode a data transfer delay of about 10 ms (±8 ms) takes place from the time of the creation of the signal in Simulink until it reaches the output pin of the trigger output box. For having these triggers precisely aligned with the biosignal data they are fed back into the system by using the digital inputs of the g.USBamp. This makes sure that transport delays are neglected and stimulation takes place exactly when the trigger can be seen in the recording channel. In Figure 1 the three stimulators required for the described experiment are depicted: an electrical constant-current stimulator (for deep-brain stimulation for eyeblink elicitation), an airpuff stimulator (somatosensory stimulation) and a tone stimulator (auditory stimulation). The parameters for the airpuff stimulator (intensity) and the tone-generator (tone/white noise, intensity) are settable on the devices manually. The length of the trigger inputs equals the length of the stimuli respectively. The electrical stimulator is able to deliver trains of variable length consisting of constant-current pulses of variable width, intensity, and frequency. Its parameters are set via software and a USB connection from within the real-time system.

E. *Signal Inspection*

For signal visualization a scope application was developed which provides real-time access to the recorded biosignal data. It is designed in a distributed manner. The first part resides within the Simulink model and the second part is an external C++ application. The Simulink part receives the data and downsamples them as far as it is necessary to display them in the external application. This downsampling mechanism in general reduces the amount of data which have to be transferred between the two parts of the application and is depending on the sampling frequency, the time resolution of the scope and the size of the scope window. This architecture allows sharing the workload of the computer between processor cores on multi core systems. For a convenient access to past sections of a recording the application also stores rendered versions of the whole recording on the hard disk. With this functionality the scope view can be frozen anytime during a recording session to inspect the acquired data in more detail. By having multiple resolutions of the recording the amount of data which has to be loaded from the hard disk is greatly reduced even if the view is set to a time resolution of several minutes. The freezing functionality is important especially during the insertion of the electrodes to investigate spike shapes in high temporal resolution, to check if the signal is contaminated by artifacts and whether reactivity to the CS-US stimulation can be seen.

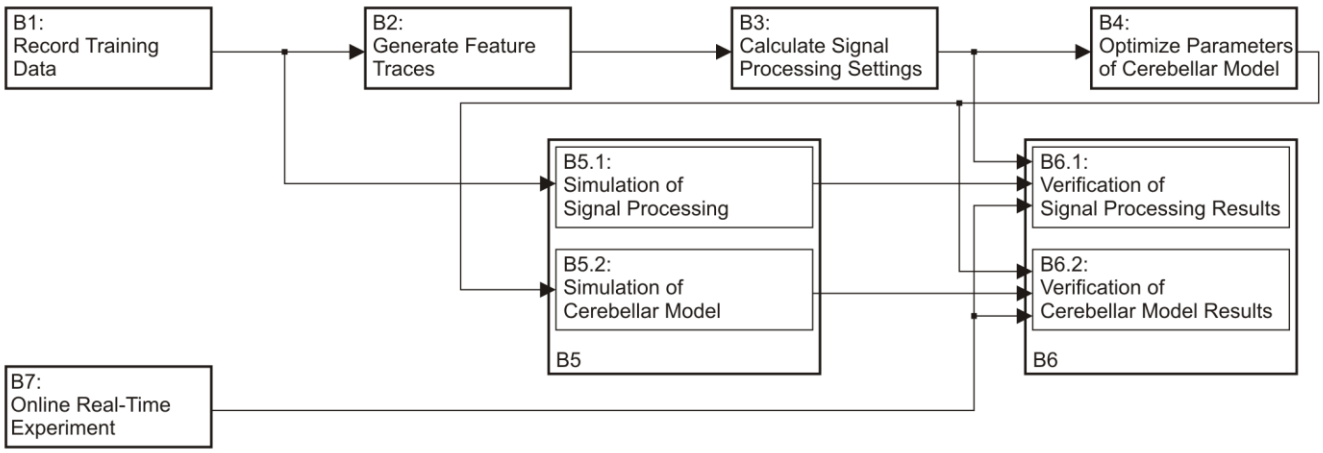

Figure 2. Processing steps of the experiment. In B1 training data is recorded which is used in B2 to extract relevant feature traces which can be used to detect the stimulation onsets. B3 calculates a threshold value to assure a certain detection performance. This performance is used for optimizing the parameters of the cerebellar model in block B4. Simulated test runs with the results of these calculations are done in Block B5 and are validated in block B6. Block B7 uses all the settings and parameters and symbolizes the real-time experiment with all the components integrated.

In addition to the inspection of the signal in the time domain also the frequency spectrum of the biosignal channels can be displayed. This is also important for identifying artifacts which can come for example from the power line. For the analysis of reactivity time averaging plots, scatterplots and the peri-stimulus time histogram (PSTH) plots are available for use. Also these functions follow the distributed architecture described above to distribute the workload between processor cores.

In parallel to visual inspection it is also useful during experiments to hear what is recorded. If the electrode is for example in an area surrounded by single units a very characteristic sound is produced. We use auditory inspection as a tool for orientation while maneuvering the electrodes through the layers of the brain during an operation. For this task the stream of biosignals is upsampled in real-time to a sampling frequency suitable for common computer-audio interfaces (i.e. 44.1 kHz) and is fed with special driver software to the audio device to minimize delays. The average delay of the audio output is around 50 ms (±10 ms). The operator can conveniently choose the electrode channel he/she wants to hear via software and can adjust the output gain to prevent clipping.

F. Replay

The RPE is equipped with a replay-option which enables simulating a connected amplifier. In this way biosignals and triggers that were recorded in a previous experiment can be used to simulate a recording session for improving algorithms. In this way it is possible to assess the behavior of modifications and compare results based on exactly the same input data.

III. Software Framework

This section describes the software implemented within the rapid-prototyping environment which was designed to fulfill the functionality of the experiment.

To allow a correct identification of stimulus onsets in the online system, training data recorded during conditioning are used offline to calculate parameters for the detection algorithms. Concurrently, parameters for the cerebellar model [15, 16] are calculated. After these steps the online system reacquires biosignals, detects the onsets of the stimulation and feeds these time-points into the cerebellar model which uses them to simulate cerebellar plasticity and learns the required behavior to avoid the airpuff. The CR-output of the model is used to control an electrical stimulator connected to the electrode implanted in the facial nucleus (FN) of the animal. In this way the eye-blink is elicited. Once the output of the model is well-timed after a sufficient number of acquisition trials, the eye of the rat closes shortly before the airpuff is applied.

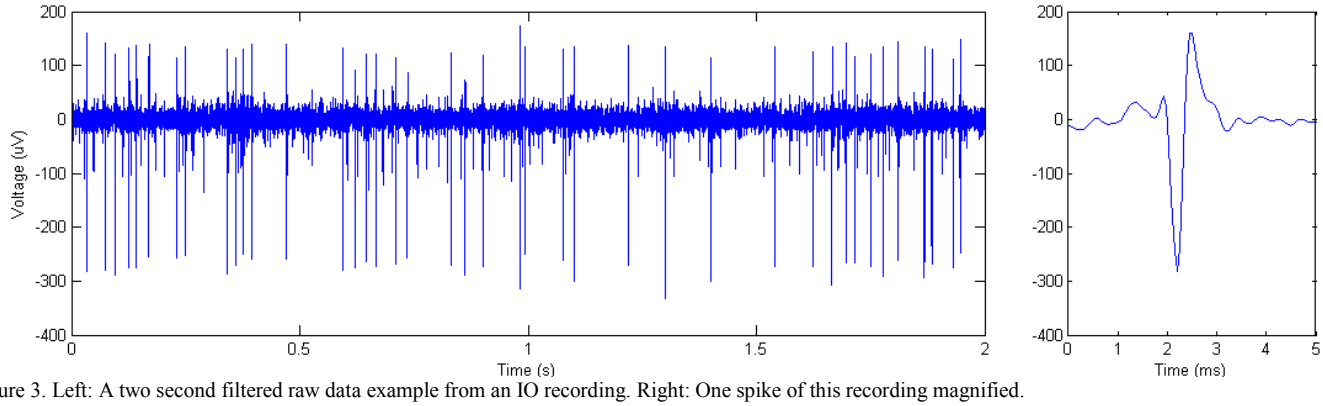

Figure 3. Left: A two second filtered raw data example from an IO recording. Right: One spike of this recording magnified.

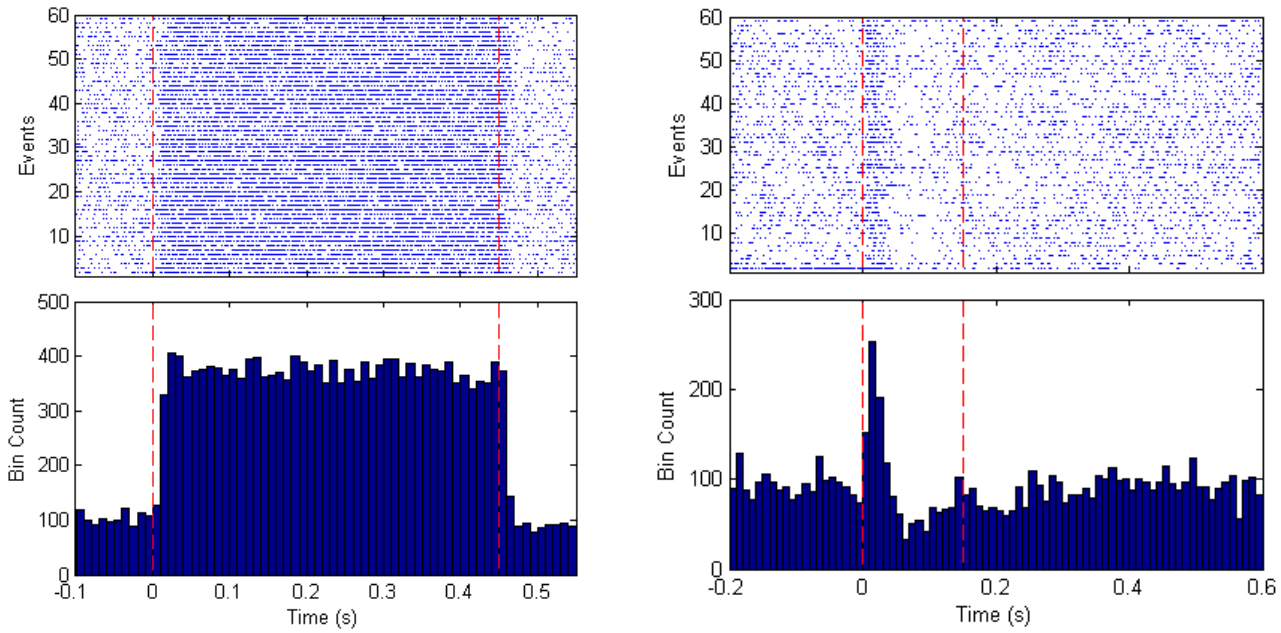

Figure 4. Left: PSTH of 60 trials of PN reactivity to white noise stimulation. Right: PSTH of 60 trials of IO reactivity to airpuff stimulation. The scatterplots at the top of the figures show for each trial the crossings of the signal with a threshold calculated from the mean baseline amplitude of the biosignal multiplied by three. The histograms at the bottom accumulate the crossing events shown in the scatterplots within 10 ms bins. The dashed red lines show the stimulation on- and offsets.

Figure 2 shows the different steps and components to run the experiment. These are explained a bit more detailed below.

A. B1 Record training data

The first step is the recording of unfiltered training data from PN and IO along with CS and US stimulation triggers. The procedure starts with the preparation of the animal and the insertion of the electrodes. During the insertion the system is already running and allows the examination of the incoming biosignals to prove good data quality and to identify different brain layers. Also the stimulation is applied during the insertion of the electrodes. Using the audiovisual signal inspection facilities of the real-time system the correct spot of interest in the brain is located based on the feedback the system gives to the operator in form of views of the recorded data reacting to the stimulation. The amount of reactivity is calculated online and peri-stimulus time histograms (PSTH, Figure 4) for the two spots are updated trial by trial. The PSTH is calculated in the following way: first the mean amplitude of the rectified baseline periods preceding the trigger onsets is calculated. This average multiplied by three is taken as threshold. The scatterplots in the upper parts of Figure 4 show the crossings of the signal with this threshold from a value below to a value above it. These crossings are called events. The histograms depict the number of events falling into a specified bin which has in case of Figure 4 a width of 10 ms.

The reactivity is verified by moving the electrodes to different locations, respectively by removing the speaker/air tube from the ear/eye of the animal to check if the reactivity becomes weaker or disappears completely. In this way it can be assured that no electrical artifacts are contaminating the recording. Once reactivity is detectable within the signal the actual training data are acquired with a sampling frequency of 19.2 kHz in MATLAB format for later processing. Figure 3 (left) shows an example of an IO recording. The signal was measured against a hardware-reference channel coming from the connective tissue on the head of the rat. It had a peak-to-peak range of approximately 140 mV before filtering. It was filtered offline with a bandpass from 300-3000 Hz, a commonly used setting for multi-unit recordings [3]. The SNR of this filtered signal is ~ 20.3 dB. Spikes of individual neurons which have in this case a peak-to-peak amplitude of about 400 µV can be easily seen (Figure 3, right).

B. B2 Generate feature traces / B3 Calculate signal processing threshold

After offline analysis of the recordings artifact channels resulting from damaged or broken electrode channels and artifact trials are excluded. A channel is excluded if its PSTH shows less than twice as much events during the stimulation period as during the baseline. Trials which include transient electrical artifacts hundred times higher than the baseline are excluded from the training data as well. The remaining channels are used as input for feature extraction procedures of the signal processing algorithms which include operations like filtering, combining channels, or smoothing and use several features like the mean or the standard deviation. The result is a down sampled signal which represents the reaction of the brain to the stimuli in a way that they can be detected. Block B3 takes the generated feature traces and calculates thresholds for the event detection. This is done according to a receiver operating characteristic curve (ROC) resulting in a certain amount of true detections and false alarms for each threshold. For the next step B4, the optimization of the cerebellar models parameters several points of the ROC curve are required. That means, a matrix of working points is provided for further analysis and serves as input to Block B4.

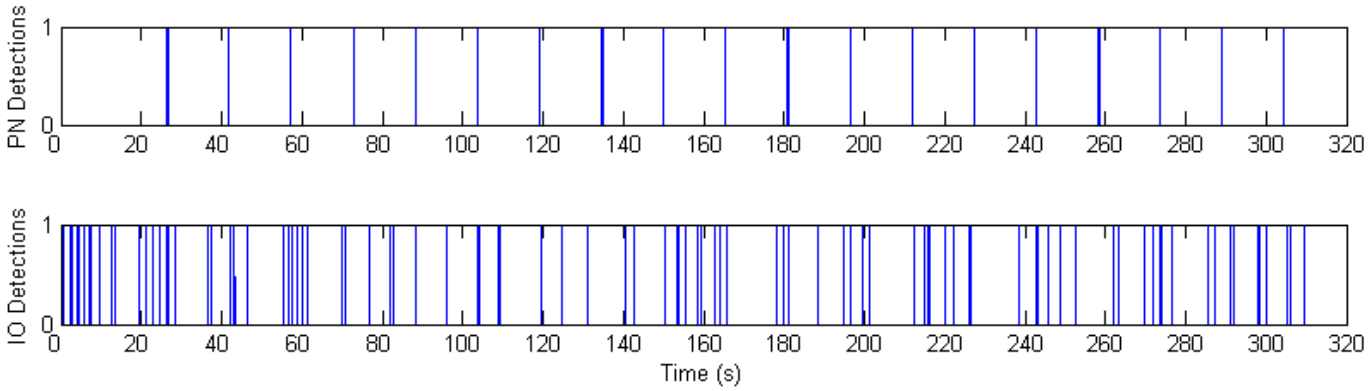

Figure 5. Detection triggers from the PN and IO signal processing algorithms.

C. *B4 Optimize parameters for cerebellar model*

Block B4 optimizes the parameters for the cerebellar model in a way that it provides a desired acquisition, extinction and stability behavior (comparable to the biological learning behavior of a senescent rat; i.e. within 300 trials) at a given performance of the signal processing methods. This means it chooses one pair of points on the ROC curves for PN and IO out of the vectors provided by the signal processing stages. The process determines values for tong-term depression (LTD) and long-term potentiation (LTP) which influence the weight of the synapse based on the detections [16].

D. *B5 Simulation / B6 Verification*

For the verification of the calculations of blocks B2 to B4 the functional software components are executed offline in simulation runs (B5) using the calculated parameters. This test runs provide data which are compared in Block B6 to results of the training phase (Blocks B2 to B4). As the input to Block B5.1 was the originally recorded data the resulting detection timestamps and therefore also the true positive percentage and the false positive rate must be identical to the results of B3 in order to pass the verification implemented in Block B6.1. This ensures coherent calculations in the online and offline parts of the signal processing algorithms which is vital to allow correct operation of the real-time implementation. The same applies for the evolution over time for the cerebellar model which is validated in Block B6.2. Also here the comparison of the online and offline results has to lead to identical results.

E. *B7 Real-time Experiment*

The final step of the procedure is the real-time experiment itself (B7). After successful simulation runs and verifications all the initially provided parameters and settings as well as the calculated parameters are used to initialize the algorithms of the real-time experiment. The g.USBamp again is connected to the rat and the paradigm is driven by the trigger output device. The signal processing methods are producing the feature traces now in real-time and provide event detection results based on the calculated thresholds. These detections are forwarded to the cerebellar model which uses them to model synaptic plasticity and to acquire the desired behavior of giving CRs after a number of well-timed, correctly detected trials as defined in the optimization. Once this is achieved the CR signal is sent via the trigger output box to the electrical stimulator which gives a constant current train to the FN of the animal and elicits the eye-lid closure. During this experiment the same data inspection facilities as in Block B1 are available. That means that the data-quality and reactivity to the stimuli can be checked again in real-time. Moreover the true/false positive rates of the signal processing methods and the state of the cerebellar model are assessable. For later offline analysis and re-verification in Block B6 all the parameters of the experiment are stored.

IV. RESULTS

In the experiment reactivity to white noise stimulation and airpuff stimulation was found in PN and IO respectively (see Figure 4).

Training data were recorded in Block B1. It was used as input for blocks B2 and B3. For the IO data the signal processing algorithm achieved 65% true positive detections at a false positive rate of 1 Hz. For the PN the signal processing reached 100 % true detections at a false alarm rate of 0.004 Hz. For the PN it is important to have a low rate of false alarms as the model would give conditioned responses whenever a CS is detected once it has learned to respond.

With this detection performances block B4 was fed. The cerebellar model was configured to learn within 60 trials. That means that after 50 trials more than 50 % of the CRs should be correctly timed.

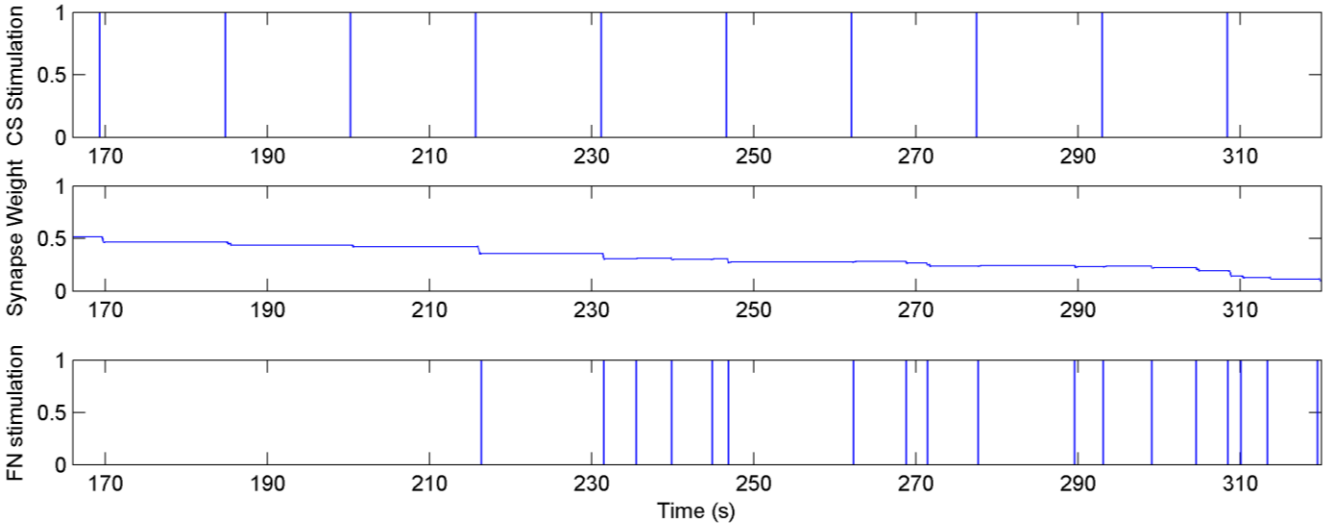

Figure 6. Triggers of the CS stimulation (top), the evolution of the synaptic weight (middle) and the CR output of the cerebellar model (bottom).

After the parameters were calculated and the correct operation of online and offline implementations were verified the real-time recording was started. Figure 5 shows the PN and IO detections for the first 19 trials of the experiment. In the PN the accuracy was 100 % with no false alarms. In the IO 63.2% of true positives were detected with a false positive rate of 0.3 Hz. These detections were forwarded continuously to the cerebellar model. Figure 6 shows the plot of the CS stimulation triggers, the synapse weight of the cerebellar model, and the CR output of the model which is fed as trigger to the electrical stimulator. The synapse weight is the variable which expresses the state of the model. With correct appearance of CS and US detections the weight of the modeled synapse goes down by the value of LTD calculated in Block B4. With every detection of a CS without a correct timed detection of a US the weight goes up by the value of LTP. Once the weight is below 0.4 the model outputs a CR after a detected CS. It can be seen, that false alarms in the PN like in second 240 in Figure 6 cause undesired CRs once the model has learned.

V. Discussion

In this paper we propose a real-time rapid-prototyping system for electrophysiological research and show its application in an experiment using multi-unit activity recorded from two different locations in the brain of a rat. For recording signals derived by electrodes placed within the brain headstages have been developed which ensure high signal-to-noise ratio and an artifact-free transmission of the signals to the main amplifier. With the aggregation boards it is possible to connect different kinds of electrodes to the headstages very flexibly. They can be used for both acute and chronic experiments.

The main amplifier is capable of measuring different kinds of biosignals like ECG, EMG or the output of devices like microphones or other sensors by providing a high sampling rate, high bit-depth and high signal-to-noise ratio. Different kinds of signals can therefore be easily integrated into an experiment.

With the real-time environment in MATLAB/Simulink extended with specialized functionality for electrophysiological research a rapid-prototyping approach of software development is used. It supplies various facilities which allow a smooth workflow during an experiment, from the insertion of an electrode until the real-time analysis stage. The system is able to drive precisely timed paradigms and to give feedback in form of stimuli.

It was successfully shown that with the RPE it is possible to assess the recorded biosignals in real-time to figure out desired properties in order to make conclusions about insertion depths and positions for the electrodes and the signal quality. In the described experiment the RPE is able to acquire multi-unit activity, is able to prove and detect reactivity in two different brain regions and to update a computational model in real-time.

It is noticeable that the detection performance of the signal processing algorithms on the training data of the shown experiment is different to the performance in the actual experiment whereas the cerebellar model assumes that the rate of false alarms and true positives stay constant. This fact can cause instability in the model. As the system provides access to all the acquired data and calculated intermediate results it is easy to find opportunities for enhancing the performance of the implemented algorithms. The proposed system enables the inclusion of such features with relatively low effort. As it is able to re-use real-time code, modifications can be done selectively even in complex systems. The behavior of modifications can also be assessed in the case that the amplifier is not connected to the animal by simulations with previously recorded data.

In the technological context the proof-of-concept achieved with the rapid-prototyping system can be used for producing a highly integrated miniature chip, which is small enough to be implanted directly to the subject. Although also with an integrated device several signal inspection points are necessary to ensure that the physiological inputs and outputs are working correctly.

VI. CONCLUSION

In this paper the key technologies and methods for the correct and convenient operation of a real-time rapid-prototyping system were discussed. It is vital to ensure an optimal cooperation between operators, system designers and the recording system itself in order to provide a correct implantation of recording electrodes, good data quality, good development progress and correct function. The proposed system enables conducting experiments in real-time providing access to all the relevant intermediate results and variables.

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