System on Chip for Closed Loop Neuromodulation Based on Dual Mode Biosignals

***Abstract*—Closed loop neuromodulation, where the stimulation is controlled autonomously based on physiological events, has been more effective than open loop techniques. In the few existing closed loop implementations which have a feedback, indirect non-neurophysiological biomarkers have been typically used (e.g. heart rate, stomach distension). Although these biomarkers enable automatic initiation of neural stimulation, they do not enable intelligent control of stimulation dosage. In this paper, we present a novel closed loop neuromodulation System-on-Chip (SoC) based on a dual signal mode that is detecting both electrical and chemical signatures of neural activity. We use vagus nerve stimulation (VNS) as a design case here. Vagal chemical (pH) signal is detected and used for initiating VNS and vagal compound action potential (CAP) signals are used to determine the stimulation dosage and pattern. Although we used the paradigm of appetite control and neurometabolic therapies for developing the algorithms for neurostimulation control, the SoC described here can be utilised for other types of closed loop neuromodulation implants.**

I. Introduction

Neuromodulation is a fast growing treatment paradigm for a number of diseases and conditions such as epilepsy, depression, obesity, inflammation, etc [1]. Apart from implementing it for drug resistant cases, the primary reason behind this is the ability for neuromodulatory therapies to enable a more precise intervention by targeting a certain nerve or brain area than drug therapies. Furthermore, the dosage can be tuned for each individual case [2].

Neuromodulation therapies can be divided into two therapeutic paradigms: *open loop* and *closed loop*. The stimulation dose control aspect of neuromodulation implants consist of answering two questions: *when* to stimulate and *how much*. Open loop neuromodulation therapies involve crude manual tuning of stimulation time and dosage by healthcare professionals based on factors such as patient vitals, discomfort or pain, etc [3]. *Closed loop* involves autonomous decisions based on physiological events, hence it tends to be more patient-specific. Closed loop neuromodulation therapies have been demonstrated to be more efficient than open loop [4], [5].

In this paper, we introduce a System on Chip to implement an adaptive stimulation based on dual mode signalling i.e chemical and electrical, see Fig. 1. Our immediate aim is to use it to develop a closed loop VNS implant for appetite control, but it can be used as generic platform for developing adaptable neurostimulation systems. This SoC is able to address the two primary concerns of a closed loop implant by initiating stimulation based on the presence of specific chemical signature in the neural response to a specific physiological condition and controlling the stimulation dose based on CAPs elicited say during an interrogative low frequency stimulation.

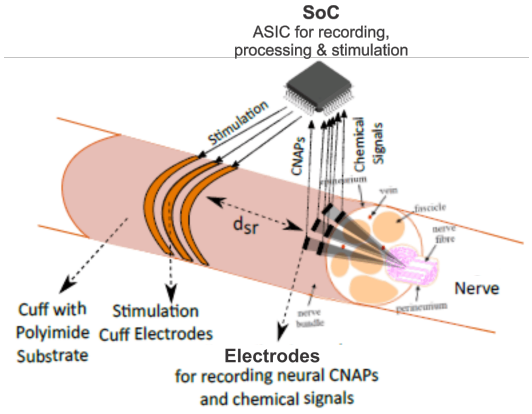


Fig. 1. Overview of closed loop neuromodulation system based on dual mode neural signal recording - example of interfacing with Peripheral Nervous System.

The SoC was initially created for the development of a closed-loop stimulation of the gastric branch of the vagus nerve in order to regulate appetite. A previous study has shown how to identify chemical pH signatures specific to the vagus response to cholecystokinin (CCK), a gut hormone released during meal intake, during *in vivo* experiments [6]. CCK is responsible for reducing appetite and it has been previously demonstrated that VNS introduced in correlation to meal intake leads to greater effective weight loss [3]. The use of chemical sensors, such as the pH sensor, provides signals of a higher amplitude, and hence easier and more robust to detect compared to neural mass activity. We use the CCK-induced chemical (extracellular pH) changes to initiate VNS in correlation to meal intake. However, apart from knowing when to stimulate we needed to adjust the stimulation to a certain level which always varies from case to case due to electrodes proximity to the nerve, contact impedance etc. We utilise CAPs elicited during an interrogative VNS protocol to characterise the vagus nerve for individual subjects and determine the precise stimulation parameters necessary.

II. System Architecture

The system architecture of the complete closed loop neuromodulatiom system is shown in Fig. 2. The dual signal neural amplifers are interfaced with sensors to capture pH and CAP activity on the vagus nerve. The signals are digitised by SAR ADCs at a sampling rate of 160 kHz. The SYS CLK is 20 kHz, which accounts for availability of an 8 bit long

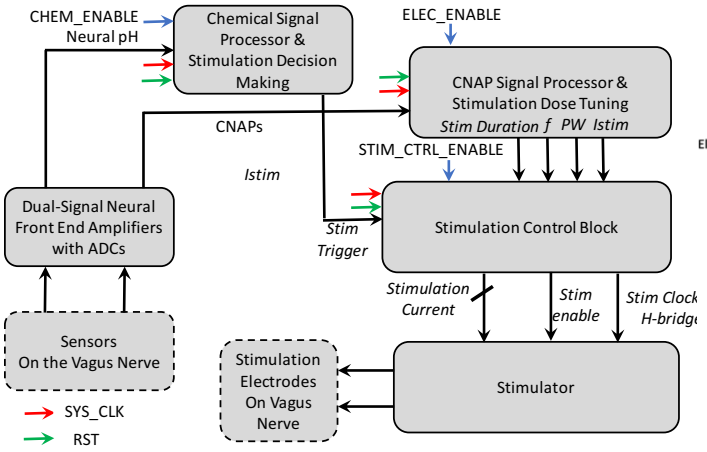


Fig. 2. System architecture of the complete closed loop neuromodulation system: analogue neural front-end amps, chemical signal processor, CAP signal processor and stimulation control.

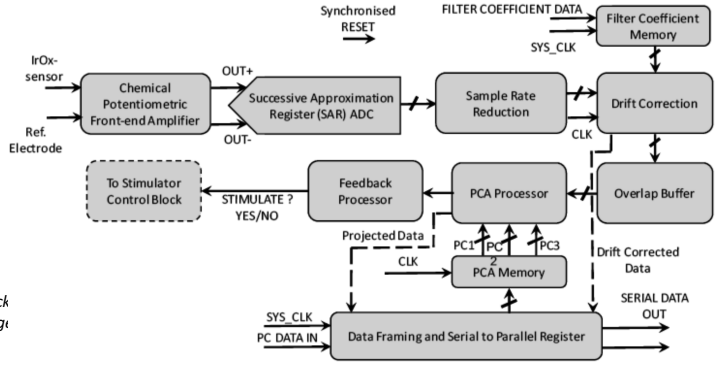


Fig. 3. The system architecture of the chemical signal processor.

sample from the ADC. The Chemical Signal Processor and Stimulation Decision Making Unit, processes the incoming chemical signal and decides *when* to stimulate. The CAP signal processor processes the CAP signal and determines *how much* to stimulate. The stimulation dose tuning unit also ensures that the stimulation parameters are within stimulation thresholds of the nerve and does not exceed stimulation limits. Each unit is described below in more detail.

A. Front-end Amplifier

We have developed a modified switched bias amplifier (MSB), which exibits a low input referred noise and can be configured to record both electrical and chemical signals (ref to be included after review). The electrical amplifier has the closed loop gain of 60 dB and it operates over a frequency range 200 Hz to 5 kHz. The MSB amplifier offers significant noise and area trade-off. The chemical amplifiers are based on the MSB amplifier with the closed loop gain clipped to a maximum of 20 dB and a maximum frequency range of 10 Hz. The electrical amplifier is used to pickup CAP signals.

B. Neural Stimulator

The heart of the bi-phasic stimulator is a 6 bit current DAC. The DAC has a Least Significant Bit (LSB) of 50 μA, and a maximum current output of 3.2 mA. To maintain charge balance a current leakage estimator is included as part of the circuitry. If there is a loss of charge when driving a current pulse from the anode through the nerve tissue to the cathode, an additional current pulse for the difference in charge, is sent to the driving terminals. The design of the bi-phasic stimulator was carried out using commercially available High Voltage TSMC 0.18 μm technology which included a low voltage 0.18 μm extension. A high voltage technology is needed to drive a 3.2 mA current into a tissue with a nominal impedance of 10 kΩ, resulting in a minimum voltage compliance of 32 V to drive the output stage of the bi-phasic stimulator.

The H-bridge was used to drive the anode and cathode terminals, and form the basis of the bi-phasic operation. High Voltage cascoded mirrors were designed to interface between the low voltage 6 bit current DAC and the H-bridge. Careful design consideration was given to the H-bridge high voltage transistors to ensure junction voltages do not exceed and cause fatigue of the oxide and eventual break down. To avoid such situations a high voltage regulator was designed to ensure junction voltages within the H-bridge doesn't exceed compliance voltage.

C. Processing Unit

The Processing Unit operates on the chemical and CAP signals input. The Chemical Signal Processor and Stimulation Decision Making Unit, processes the incoming chemical signal and decides when to stimulate. The CAP signal processor processes the CAP signal and determines how much to stimulate. The stimulation dose tuning unit also ensures that the stimulation parameters are within stimulation thresholds of the nerve and does not exceed stimulation limits. The chemical signal processor (Fig. 3) includes the downsampling and pre-processing unit to remove drift, a Principal Component Analysis (PCA) processor to perform dimensionality reduction and pattern recognition, see Fig. 4. It also has a feedback processor unit which determines when to trigger the stimulator. The CAPs are processed as shown in Fig.5.

Choice of electrodes is a crucial part of the platform development. The instrumentation specification and design very much depend on it. Initially we have targeted to measure the pH, but potassium electrodes can be a good candidate as well [7]. For pH we decided to use IrOx wires. The mechanism behind ability of the IrOx to sense pH changes lies in the existence of redox chemical reaction between two IrOx types, namely Ir(III)Ox and Ir(IV)Ox. The sensitivity of potentiometric IrOx sensors range from $60-90$ mV/pH. For the typical pH variation observed in biomedical applications of $0.02-1$ pH units and assuming minimum sensitivity, the signal levels will range from 1.2 mV to 60 mV. The response time for IrOx sensors i.e. time required to reach 90% of the equilibrium value, for the relevant ranges, is $6-12$ s for a change of 1 pH

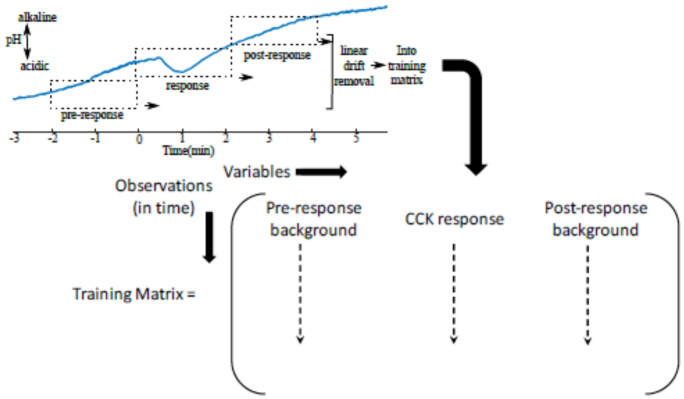


Fig. 4. A training matrix is constructed from a set of previous collected in vivo CCK experiments to generate relevant PCs. The different variables that are considered are pre-injection pH background, CCK-induced pH response and post-injection pH background. More details about the technique in [11].

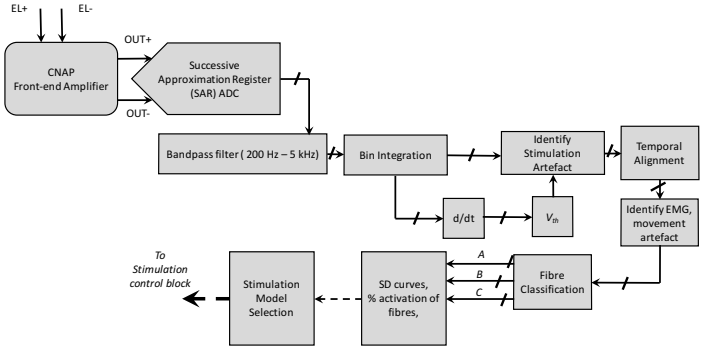


Fig. 5. The system architecture of the CAP signal processor.

unit [8]. Hence the pH signal is a low frequency signal with bandwidth less than 0.1 Hz.

An outstanding issue with IrOx sensors is presence of drift in the OCP. The origin of the drift could be due to hysteresis in the IrOx sensor or change in ambient conditions, such as temperature, which affect pH [8]. IrOx microneedles have small sensing area and in order to preserve this sensing layer, it is essential to ensure no leakage current flow through the electrode. Otherwise, this will lead to reduction of IrOx layer and hence loss of sensitivity. Therefore, it is crucial to use front-end amplifiers that have extremely low input bias current or gate leakage current in order to prevent sensor degradation and erroneous readings.

III. Closed Loop Implementation

A. Decision Making

The closed loop implementation consists of three different steps: *Nerve classification*, *Stimulation strength determination*, *Physiological Trigger Detection*, see Fig. 6.

1) Nerve classification:: This step is performed to determine the excitability of the nerve, including the types of fibres present and the stimulation thresholds for different fibre types. For this purpose we use the Strength–Duration protocol [9]. The CAP waveform analysis consists of partitioning the CAP waveform to separate the contribution of different fibre

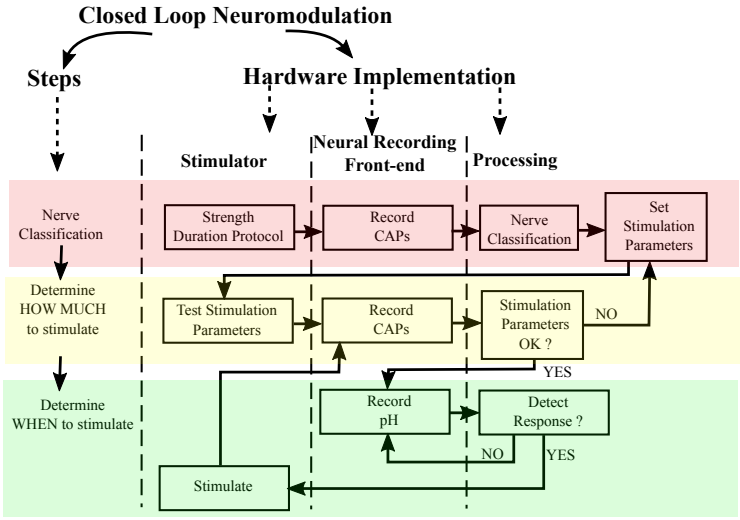


Fig. 6. Overview of closed loop neuromodulation system.

types based on fibre conduction velocity and distance between stimulation and recording electrode [2]. As an example we show some of our experimental results in Fig. 7.

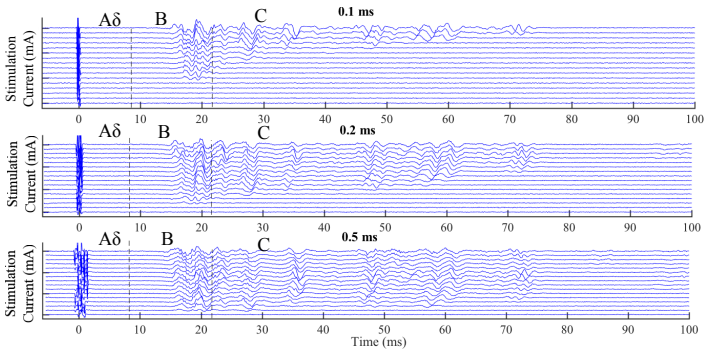


Fig. 7. CAPs elicited during *in vivo* stimulation of the cervical part of vagus nerve in a rat and recording in the gastric part. The pulse widths (PWs) shown here are: 0.1 ms (top), 0.2 ms (middle) and 0.5 ms (bottom). More PWs were used in the experiments. There are 16 different current amplitudes for each PW in the span between 0.2 mA-3 mA for PW=0.1 and 0.2 ms, and between 0.1 mA-2 mA for PW=0.5 ms.

2) Stimulation strength determination: is performed by setting the stimulation parameters i.e stimulation current, pulsewidth, and stimulation waveform based on the neuromodulatory application. A test stimulus is performed to verify the set stimulation parameters. Once the stimulation parameters are verified, the next step is to set up the platform to detect the physiological trigger for initiating stimulation.

The strength-duration curves were used to establish the nerve excitability. Parameters such as rheobase and chronaxie [9] can be calculated from the recordings, such as those shown in Fig. 7. Then we set the stimulation dose (and stimulus profile), depending on which fibre types are targeted.

3) pH signal processing unit - Stimulation decision making: In the application described here the physiological trigger is the pH change due to vagus nerve response induced by release

of CCK. The incoming data which is sampled at 20 kHz is downsampled using a decimation filter to 50 samples per second. The decimation filter is composed of a CIC filter and a compensation low pass filter.

pH Electrode Drift Removal - The chemical signal has an overall linear drift due to the drift in open circuit potential of the IrOx electrode as shown in Fig. 4. This drift is cancelled using linear interpolation over a fixed time window.

pH Detection Algorithm Training - In order to detect the CCK specific pH response, the temporal profile of the pH waveform is considered over a period of 2 minutes and compared with the known CCK induced temporal pH profile. In general, the CCK specific pH response exhibits a negative slope or a downward trend for 1-1.5 minutes followed by a reverse trend for the same length of time, see Fig. 5(top). However, under *in vivo* conditions, the pH waveform is affected by several interfering processes. Hence, in this algorithm, a multivariate approach is adopted by using PCA. This is similar to the application of PCA on cyclic voltammetry curves described in [10], [11].

PCA is performed by first mean centering the data and constructing a training matrix using *in vivo* experimental data, in which CCK was injected intravenously and the change due to CCK was recorded, consistently over a number of trials in different animals. The training matrix consists of *pre* (2 min), *response* (2 min) and *post* (2 min) CCK injection as shown in Fig. 4. The principal components (PC) for *pre*, *post* and *response* (P_{train}) are extracted. PCs which capture at least 95% of the variance in data are retained.

Real Time pH Response Detection Details about the IrOx pH sensor calibrations are given in our previous publication (ref removed). The incoming real time pH data is filtered and a projection matrix of the data in the principal component subspace is calculated: $D_{\text{proj}} = U_c' \times D_{\text{actual}}$, where D_{actual} is the real time experimental data and U_c is the PC matrix extracted from the training matrix. The specific response to a physiological stimulus is detected by calculating *residual values* E, defined as the difference between the actual incoming data and back-transformed projected data set: $E = D_{\text{actual}} - (U_c \times D_{\text{proj}})$. From residuals a factor Q is calculated [10]: $Q = diag(E' \times E)$. Now the value of the Q is used to determine the presence of a specific neural response by establishing a threshold value for Q. In our case, if the Q-value is less than 0.01, it is treated as a neural response. Validation of our algorithm is shown in Fig. 8.

B. Stimulation

The closed loop implementation was eventually verified by detecting the change in the rat's heart rate due to electrical stimulation of vagus from our stimulator, the details are shown in (ref removed).

C. Final IC design

Each individual block described above has been integrated into a mixed signal SoC with both anlogue front-end interface and digital back-end processing to implement a dual-mode closed loop neuromodulation system. The micrograph of the final chip is shown in Fig. 9.

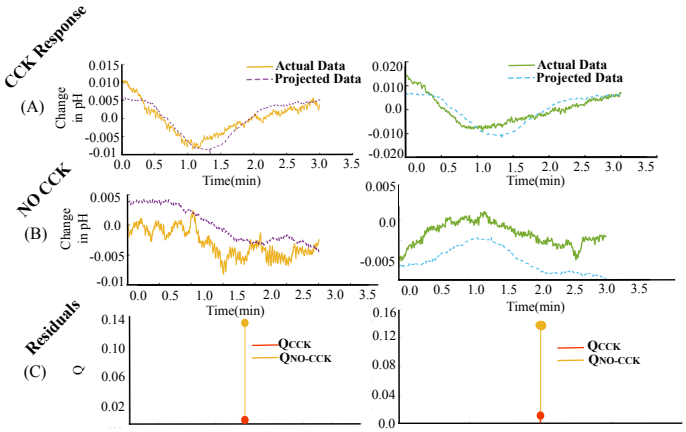


Fig. 8. Two examples of the implementaion of our algoritm, shown in left and right columns. (A,B) The projected data is calculated using the PCs and compared with the actual data. (C) The resiuduals are calculated and Q-value shown. $Q < 0.01$ is treated as a response.

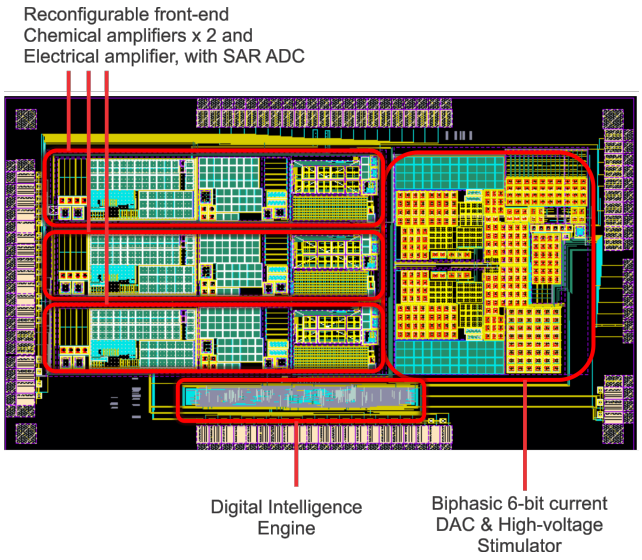


Fig. 9. SoC chip microphotograph. Designed and fabricated in the standard TSMC 0.18 μm CMOS High Voltage BCD Gen II technology.

IV. Conclusion

The creation and development of a comprehensive SoC for closed-loop neuro-stimulation implantable systems, based on dual chemical and electrical sensors recording, has been successfully demonstrated. For the development tests we used a neurometabolic therapy related to vagus nerve stimulation. This chip can be utilised to implement closed loop neuromodulation therapies and processing algorithms, which require multivariate classification capabilites. The use of dual mode signals also enables sepration and better addressing of two important aspects closed loop neuromodulation paradigm i.e when and how much to stimulate.

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