Nano-Power Implantable Autonomous Closed-Loop CMOS Nerve-Growth-Factor Delivery Microsystem for Neurological Disorders Personalized Therapy".

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ABSTRACT

These 480 million patients around the globe suffer from neurological disorders which are the fastest-growing disease worldwide. Many neurological and psychiatric conditions are the result of abnormal neurotransmitter concentrations in the brain. Our ultimate goal is to develop a nano-neural-prosthetic device that can maintain therapeutic levels of chemical concentrations in the brain in real time exploiting closed-loop delivery method. The nanosystem consists of neural probes fitted with novel sensors and embedded negative feedback circuits that will control the flow of neurotrophic-factor agents in microfluidic channels. The negative consequences of systemic drug-delivery and aberrant neurotransmitter concentrations will be eliminated by personalizing neurotherapy and delivering neurotrophic-factor at the exact required location. We developed a low power neurotransmitter bio-sensor which can be applied in an implantable closed-loop CMOS neurotrophic factor delivery nanosystem which by protecting the healthy neurons and restoring damaged ones can maintain therapeutic levels of chemical concentrations in the brain. it consist of novel biosensor that can sense micromolar concentration of neurotransmitters and embedded negative feedback circuits that control the flow of pharmacological agents in micro fluidic channels. Additionally MEMS (Micro Electro Mechanical System) pumps connected to the probes to inject micromolar concentration of neurotrophic factors into the brain.

Keywords: nano power, implantable, CMOS closed-loop delivery microsystem, micro neural prosthetic, nerve-growth-factor, neurological disorders, personalized therapy, biosensor

1 INTRODUCTION

Recent successful neural prosthetic experiments with paralyzed humans have supported the feasibility of translating the proof of concept studies performed in monkeys to the clinic [1]. Although these human studies focused on paralysis, neural prosthetic systems have the potential to improve the lives of those suffering from many other disabling diseases. Many neurological and psychiatric conditions are the result of abnormal neurotransmitter concentrations in the brain. Our ultimate goal is to develop a neural prosthetic device that can maintain therapeutic levels of chemical concentrations in the brain in real time. The prosthetic will be composed of neural probes fitted with novel sensors and embedded negative feedback circuits that will control the flow of neurotrophic factor agents in microfluidic channels as shown in Fig-01. The negative consequences of systemic drug delivery and aberrant neurotransmitter concentrations will be eliminated by personalizing neurotherapy and delivering drugs at the exact location they are needed.

The expression of "personalized medicine" is widely used in genetic science as a method to customize medications based on every individual's genome and it achieved promising results [2, 3]. We would also like to try to personalize the treatment for neurological disorders such a Parkinson's disease (PD) by using different concept; negative feedback. For example, death of Dopaminergic neurons in the substantia-nigra depletes dopamine concentration in the striatum leading to PD [4]. By personalizing neurotherapy, our device measures the depletion of dopamine in substantia-nigra and inject the proper dosage of the nerve growth factor (Glial cell line-Derived Neurotrophic Factor (GDNF) in the case of PD) [5] in to the brain to protect healthy neurons and regenerate damaged ones to maintains the concentration of dopamine in the striatum.

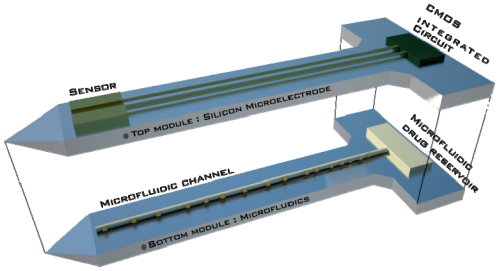

Figure 1: 3D view of the Implantable CMOS Based Neurotrophic factor Delivery Microsystem

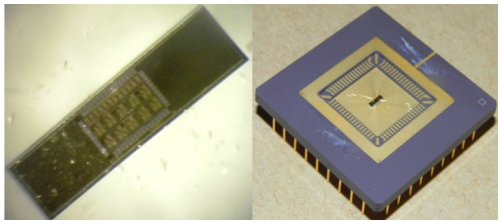

Figure 2: Fabricated microsystem in 0.18 um

We have developed a low power neurotransmitter biosensor which can be applied in an implantable closed-loop CMOS neurotrophic factor delivery microsystem which by protecting the healthy neurons and restoring damaged ones can maintain therapeutic levels of chemical concentrations in the brain. The hybrid microsystem is composed of novel biosensor that can sense micromolar concentration of neurotransmitters (dopamine) and embedded negative feedback circuits that control the flow of pharmacological agents in micro fluidic channels. Additionally MEMS (Micro Electro Mechanical System) pumps connected to the probes to inject micromolar concentration of neurotrophic factors such as GDNF into the brain in order to protect and restore Dopaminergic neurons in the nigrostraital pathway. Circuit is fabricated in CMOS 0.18 um with low power consumption of 921 nW, as shown in Fig-02.

2 SENSING AND CONTROLING CIRCUIT ARCHITECTURE

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The first step of a "target derived GDNF delivery microsystem" development is designing a chemical sensor, capable of measuring micromolar dopamine concentration. Previous studies suggest that electrochemical sensors are suitable for neurotransmitter sensing [6-8]. Electrochemical sensors are the largest and the most developed group of chemical sensors [9]. Every neurotransmitter is associated with a certain voltage [10]. To measure neurochemical concentration, this voltage is applied between the working and reference electrode. The potential difference generates a reduction-oxidation (red-ox) current which is proportional to the neurotransmitter concentration [9].

Our design goal is to have a device that possesses high sensitivity, high chemical selectivity, and fast temporal resolution. We are applying Fast-scan cyclic voltammetry technique which possesses good chemical selectivity while maintaining subsecond temporal resolution [10]. Fast-scan cyclic voltammograms are repeated every 100 ms, allowing changes in chemical concentration to be monitored on a sub-second time scale [10]. These characteristics make fast-scan cyclic voltammetry suitable for detecting phasic neurotransmitter changes in behaving animals. Currently in order to increase selectivity we use Nafion coated carbon fiber electrodes [11]. However, due to their short life time they may not be suitable for long term implantation. Thus, we are investigating a novel dopamine specific nano wire sensor to rectify the mentioned limitation.

To measure dopamine concentration and control GDNF administration, implementation of a low power, low noise CMOS circuit is necessary Fig. 3. The microsystem circuitry consists of two major components. The first component is a current conveyor that establishes the $V_{red\text{-}ox}$ voltage between the sensor electrodes. The integrating capacitor subsequently collects the corresponding current, which is proportional to dopamine concentration. The second component is a comparator which compares the recorded voltage with V_p. V_p presents minimum acceptable dopamine concentration in the nigrastriatal pathway. If the recorded voltage is less than V_p, the comparator sends an "ON" signal to a MEMS pump to inject required GDNF.

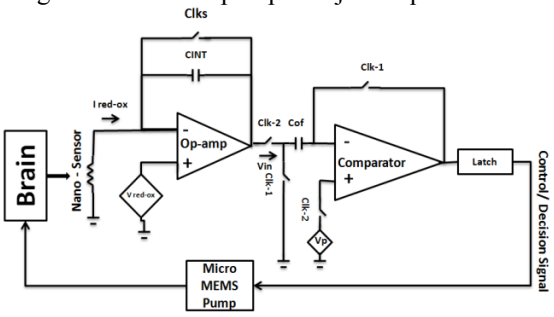

Figure 3: Sensing and Controlling Circuitry of the Implantable Intelligent CMOS Based Neurotrophic factor Delivery Microsystem

2.1 Low Power Current Conveyor

To measure the electrochemical current, the red-ox potential is applied between working and reference electrode. The current conveyor converts pico to nano-amp red-ox current to voltage. The core of the current conveyor is the operational amplifier. Instead of using power hungry front end amplifiers; a wide swing folded cascade amplifier Fig. 4 is used for its high gain and stability [12]. Power dissipation is minimized since the Op-Amp is designed to operate in the subthreshold region. We chose a folded cascade due to its high gain and low bandwidth. We have reported a low power low noise immune current conveyor in [8]. However In our new design we reduce the power consumption even more by decreasing the unity gain bandwidth.

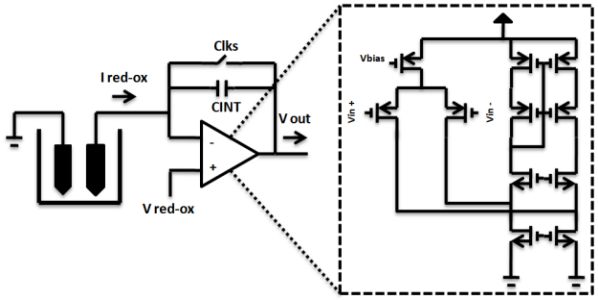

Figure 4: Wide Swing Folded Cascode Circuit

$V_{red\text{-}ox}$ is applied across R_{Sensor}. $I_{red\text{-}ox}$ which is proportional to neurochemical concentration accumulates charge on C_{INT} over the integration period T_{INT}. Output

voltage is calculated by Equation (1). In addition since integration is an averaging operation, this circuit provides high noise immunity.

$$V_{out} = \frac{1}{C_{INT} \times R_{Sensor}} \int_0^{T_{INT}} V_{red-ox}\, dt \quad (1)$$

The designed Op-Amp consumes 0.47 µW. This power dissipation is one of the lowest reported [12, 13]. Table I summarizes the amplifier's specifications in addition to comparing our work to other similar designs.

Specifications	[13]	[12]	This Work
Fabrication Year	2009	2013	2013
Technology (µ m)	0.18	0.18	0.18
DC Gain (dB)	62	48.36	65.1
Unity Gain Bandwidth (MHz)	0.54	2.408	4.75
Phase Margin (deg)	52	59	83.8
Supply Voltage (V)	0.9	0.9	1
Output Swing (V)	-0.2,0.2	-0.2,0.2	-0.4,+0.4
Power (µ W)	9.9	3.741	0.47

Table 1: Amplifire Specifications and Comparison

2.2 Comparator with Offsent Cancelation

To compare dopamine concentration with its nominal value in substantia nigra, we designed a low power comparator followed by a digital latch. We employed autozero offset cancellation technique to improve comparator's performance. In phase one, clk-1 is "ON" and capacitor C_{of} stores pre-amp's offset. In the second phase when clk-2 is "ON", offset voltage is eliminated by being subtracted from Vin. Equations (2) and (3) illustrate the cancelation technique. A is the open loop gain of the amplifier.

$$Phase\ 1: V_- = V_{offset} \quad (2)$$

$$Phase\ 2: \begin{cases} V_{out} = A \times (V_+ - V_-) \\ V_{out} = A \times (V_p + V_{offset} - V_{in} - V_{offset}) \\ V_{out} = A \times (V_p - V_{in}) \end{cases} \quad (3)$$

There are several circuit topologies for comparators. The one that is used here is latched comparator. A low gain pre-amplifier (25 dB) is followed by a D- Latch Fig. 6. The Op-Amp minimizes the kick-back noise. The latch acts as positive feedback and its output swings between 0 to 1.8 Volts. D-latch stores comparator's state until the next comparison Fig. 5. By applying low power design techniques, we designed a very low power comparator with 451 nW power dissipation.

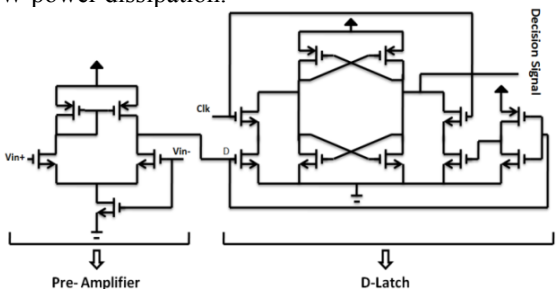

Figure 5: Latched comparator with offset cancelation circuit

3 RESULTS AND DISCUSSION

Fig. 6 shows the measured red-ox current in response to addition of five uM Dopamine. From Fig. 8 it is clear that by changing Dopamine concentration in Micro scale the red-ox current varies in order of 100 Pico Amperes.

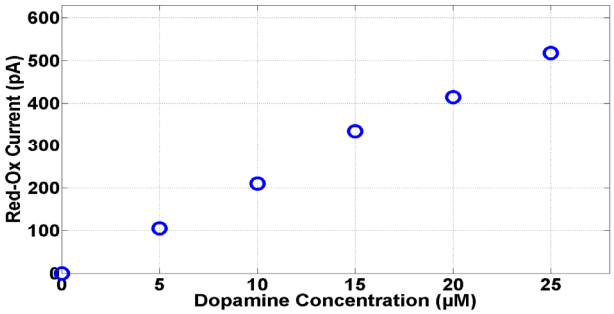

Figure 6: The Static red-ox Current in Response to Addition of 5 uM DA.

To validate the system's electrical functionality we conducted a transient analysis. We applied a sawtooth current with 24 nA peak and 1 ms period to the microsystem. This signal resembles dopamine concentration. [14] A study suggests normal dopamine concentration in a healthy rat generates 8 nA current. Since we chose the integration period to be 1 mS and integration capacitor 16 pF, therefore this current creates a 0.5 V voltage at the output of current conveyor. This implies that if the measured voltage is less than 0.5 volts, dopamine concentration is less than the normal value. Thus, the measured voltage is repeatedly compared with 0.5 Volts and if it is less, the comparator sends "ON" signal to MEMS pump to inject GDNF Fig. 7.

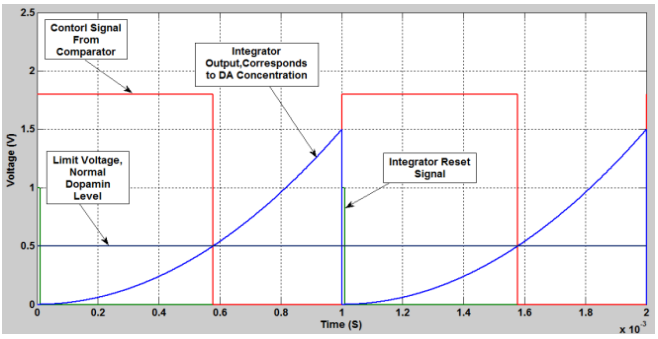

Figure 7: Microsystem Transient Analysis, Blue: Current Conveyor Output, Red: Control Signal, Black: Limit Voltage, Green: Integrator Reset Signal

Fig. 8 depicts when dopamine concentration reaches its normal value comparator stops GDNF injection.

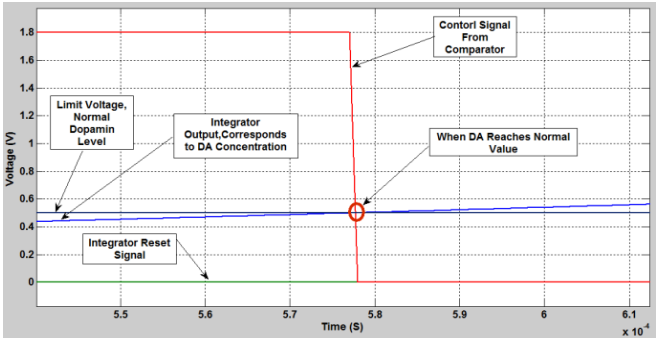

Figure 8: When Dopamine Concentration Reaches its Normal Value, Comparator Turns the MEMS Pump Off.

4 CONLUSION

A sensing, controlling and signal processing circuit for implantable CMOS (0.18 um) based neurotrophic factor delivery microsystem was presented. It provides a closed loop mechanism which may provide a solution for neurological disorders such as Parkinson's disease by protecting healthy neurons and restoring the damaged ones. Although this microsystem may promote personalized neurotherapy and rectify some of the drawbacks in the current GDNF administration strategies such as controlling dosage and infusion rate; however other obstacles such as diagnosing PD at its early stage needs further investigations.

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