Frequency and Phase Synchronization in Distributed (Implantable-Transcutaneous) Neural Interfaces

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***Abstract*— Synchronized oscillations are a ubiquitous feature of neuronal circuits and can modulate online information transfer and plasticity between brain areas. The disruption of these oscillatory processes is associated with the symptoms of several brain disorders. While conventional therapeutic high-frequency deep brain stimulation can perturb neuronal oscillations, manipulating the timing of oscillatory activity between areas more precisely could provide a more efficient and effective method of modulating these activities. Here we describe a prototype circuit for synchronizing the clocks between an active implantable and an external sensing and stimulation system that could be used to achieve this goal. Our specific focus is on synchronizing the systems for paired-associative stimulation. The ability to repetitively drive two brain regions with a fixed latency has specific implications for neural plasticity. Furthermore, the general concept can be applied for many potential applications involving distributed neural interfaces.**

I. INTRODUCTION

Precise timing of activity throughout the brain is necessary for carrying out complex behaviors and processes. Neural oscillations are prevalent across all spatiotemporal scales and provide a natural mechanism for temporally coordinating activity within and across distributed brain regions [1]–[5], thereby affecting the transfer of information [6]–[12]. The dynamics of this rhythmic activity can contribute to synaptic plasticity [13], which relies on the specific timing of activity between interconnected brain regions. Depending on the latency, connections are either strengthened or weakened.

When the timing of neuronal activity has been pathologically disrupted, stimulation can be used to help restore the dynamics. In Parkinson's disease, exaggerated oscillatory activity [14] is reduced following high frequency deep brain stimulation (DBS), thereby restoring function [15], [16]. In stroke patients transcranial stimulation can be used to enhance plasticity, thereby improving rehabilitation efforts [15], [17]. Most devices currently use a stimulation pattern preset by the clinician. However, future stimulation algorithms may use more complex patterns designed to interact with the timing of neural activity in order to more selectively target pathological activity or achieve longer lasting therapeutic effects [18]. This will be possible through a combination of sensing capabilities on new generation implantable devices [19], and combining stimulation modalities to drive multiple brain regions [20].

This paper develops a method for phase synchronization that coordinates implanted and external neural stimulators. Phase synchronization between stimulation pulses and sensed physiological oscillatory signals has been effective at specifically targeting rhythmic activity in PD and Essential tremor [15], [21] (Fig. 1), and we wish to explore further applications with distributed neural systems. The proposed system is intended to modulate plasticity by driving two regions, such as a cortical area and subcortical structures, at fixed relative latencies. The active implantable can provide access to subcortical structures not readily reached with existing minimally invasive techniques, while the external stimulator can provide broader cortical coverage that can be difficult to achieve with an active implantable system.

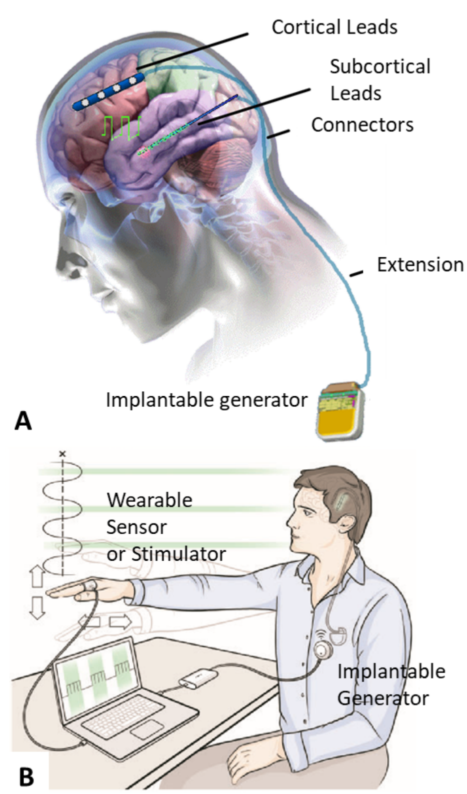

Fig. 1. Examples of synchronization. A) Within an implant, stimulation might be provided at specific phases of a discrete physiological oscillation. Examples include within both subcortical and cortical networks [15]. B) interactions between an implantable system and external wearable sensors and stimulators. Phase synchronization with sensors might help break pathological oscillations [21], while synchronized stimulators might help explore novel plasticity [20]. Subfigures reproduced from [22] and [21].

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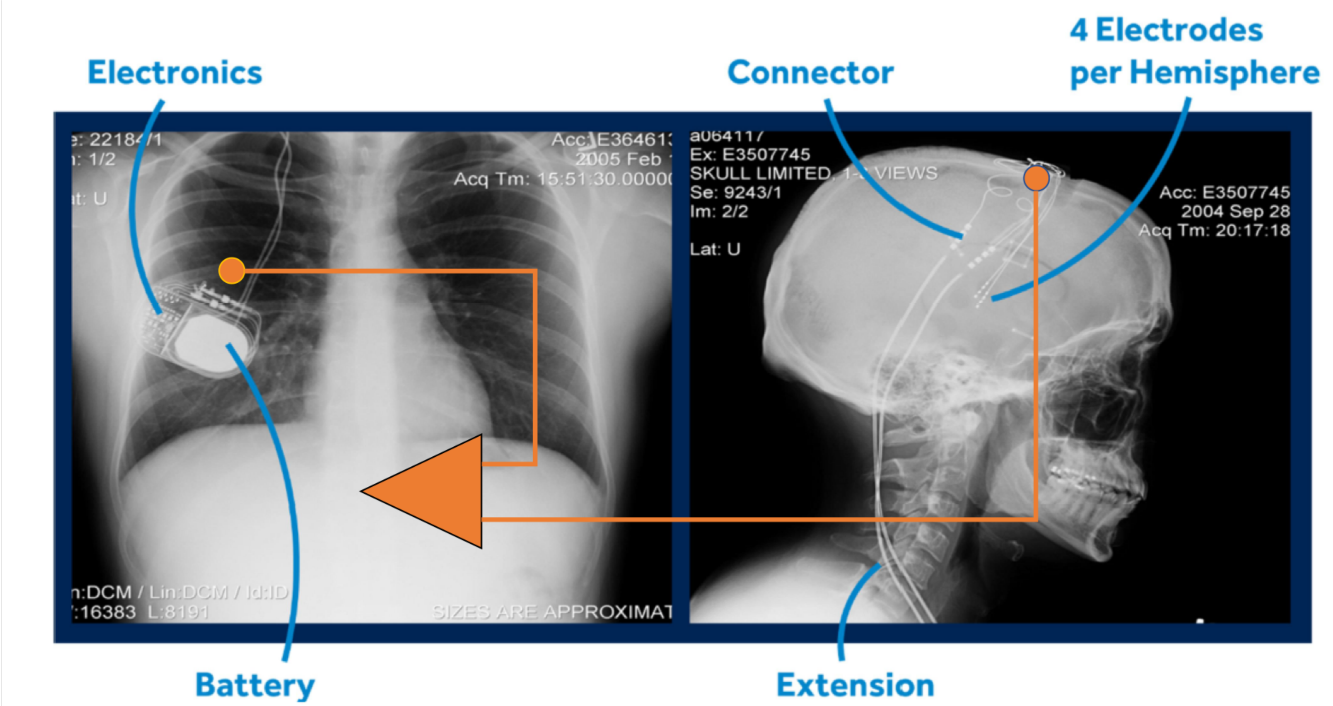

Fig. 2. Acquisition of the master clock – the implantable stimulator is used as the master clock to drive other systems. The electric field of monopolar current stimulators can be measured differentially through the skin by two electrode pads. One electrode is placed close to the stimulus generator on the chest, and the other above the burr hole on the head. This measurement dipole allows recovery of the stimulus pattern, with around 100 mV typical amplitude. This is sufficient to reliably trigger a comparator, producing a logic-level square pulse train into the phase detector. Adapted from [23].

II. PROTOTYPE DESIGN OVERVIEW

The aim of this design is to provide synchronized stimulation patterns between an implanted neural stimulator and external stimulators to explore plasticity effects. To achieve this we chose to implement a phase-locked loop. The phase-locked loop is a common technique for synchronizing a master and slave clock. The parameters for the circuit can be tuned for the specific requirements of the application.

As shown in Fig. 2 the implantable stimulator is used as the master clock from which other stimulation clocks, specifically the transcutaneous methods, can be derived. Essential requirements for the design include:

- Automated frequency capture and phase tracking across nominal therapy parameters for brain stimulation
- The ability to select a programmable phase lead or lag between the two stimulation sources that also tracks with variations in the implanted stimulator's clock
- Minimal output pulse-to-pulse jitter to ensure robust paired-associative stimulation
- Compliance with very low duty cycle input signals that are typical with brain stimulation therapy
- A lock-in detector that ensures the clocks are synchronized prior to activation of the external stimulator

The full design of the phase-lock loop is presented in Fig. 3. Given the low duty cycle of DBS pulses, the system uses a sequential, positive edge-triggered phase detector. The lead-lag compensation filter was implemented to help balance the low frequency disturbances while maintaining stability of the loop. To generate the phase of the input signal in real time, we used a frequency synthesizer topology. In this configuration, the voltage controlled oscillator's (VCO) center frequency is set as 2^N times the average input frequency. Feeding this high-speed clock into a binary counter, each period of the input signal can be subdivided into 2^N segments, thereby quantizing the phase. By choosing an edge-triggered counter (matching the phase detector), bits 0 through $N-1$ represent the phase code, where bit 0 is the high-speed clock itself. Bit N can be used to reset the counter. To enable successful locking, the high-speed VCO clock has to be divided by 2^N to be of similar magnitude to the input – this signal is available on bit $N-1$ of the counter. Using an 8-bit phase accumulator, we were able to keep track of the phase at a resolution of $1.4°$. The phase selector commands the external stimulation generator, which can be further gated from the lock-in detector (details not shown due to space limitations).

III. DESIGN CHARACTERIZATION

The design of Fig. 3 was evaluated using validation signals representing challenging end-cases of monopolar brain stimulation (Fig. 4), where the potential measurement is taken between the burr hole on the surface of the head and the implantable pulse generator. Key characteristics identified in the previous section are presented in Table I below.

The system shows quick settling dynamics due to the choice of an underdamped loop-filter response (Fig. 5). Overshoot in the VCO input signal (by extension in the output

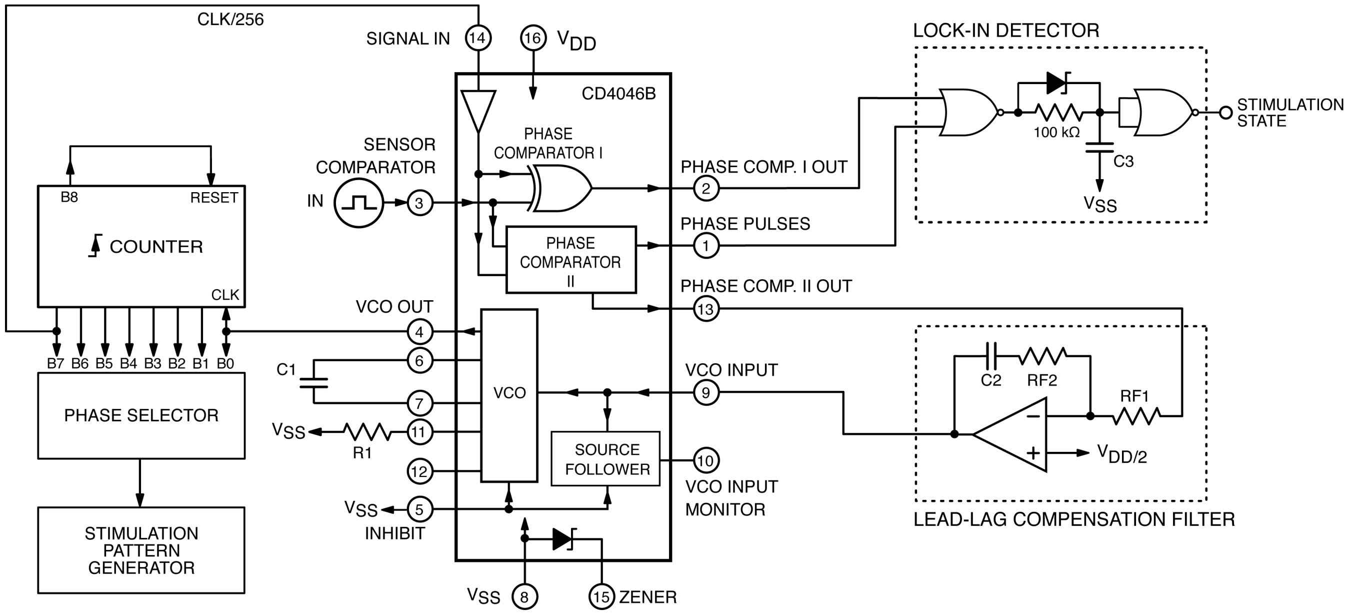

Fig. 3. Phase-locked loop implementation for DBS frequencies. Phase comparators and voltage controlled oscillators were provided by a CD4046B integrated PLL device [24]. The counter used was a CD4040B 12-bit counter converted to positive edge triggering with an inverter-configured CD4007UB. The 8-bit phase code is available as parallel output to interface with stimulation controllers. Lock-in status detection is implemented with a CD4001B NOR gate chip. Component values of $\mathrm{V_{DD}} = 5\,\mathrm{V}$, $\mathrm{R1} = 1\,\mathrm{k\Omega}$, $\mathrm{RF1} = 47\,\mathrm{k\Omega}$, $\mathrm{RF2} = 5.6\,\mathrm{k\Omega}$, $\mathrm{C1} = 7\,\mathrm{nF}$, $\mathrm{C2} = 10\,\mu\mathrm{F}$, $\mathrm{C3} = 10\,\mu\mathrm{F}$ were selected for DBS-like inputs signals.

TABLE I

KEY CHARACTERISTICS OF THE PROTOTYPED DESIGN

Specification	Value	Units
Capture range	$135 - 230$	Hz
Lock range	$135 - 230$	Hz
Lock-in time (140 Hz)	128	ms
Jitter (peak to peak)	± 18.5	μs
Minimum input pulse	14	μs

frequency) while often undesirable, is mitigated by the lock indicator signal that can be used to prevent applying stimulus during the settling phase. As the experienced jitter translates to a phase uncertainty of about $\pm 0.8°$ at DBS frequencies, 8-bit phase resolution using a 12-bit counter reaches the limitations of this circuit. The use of an edge-triggered phase comparator ensures that the capture range and lock range of the circuit fully overlap, meaning that the system is able to lock on any signal within it's range without a priori knowledge of the stimulator frequency, without significantly affecting the lock-in time.

IV. DISCUSSION

This paper describes a method for synchronizing implanted and external stimulators. We chose to implement a phase-lock-loop to allow for flexible programming of relative stimulation clocks immune to drifts and other variations. The time to lock can be traded off against the stability to clock perturbations, and our design using a lead-lag filter attempts to optimize this choice while maintaining loop stability. The design is implementable with a small circuit that can operate in portable, battery-operated systems with minimum computational overhead. The system is applicable in a wide range of distributed stimulation setups, as it is possible to compensate for any deterministic phase error by programming the phase selector appropriately, allowing to take into account factors such as propagation delays between peripheral and central nervous system stimulators.

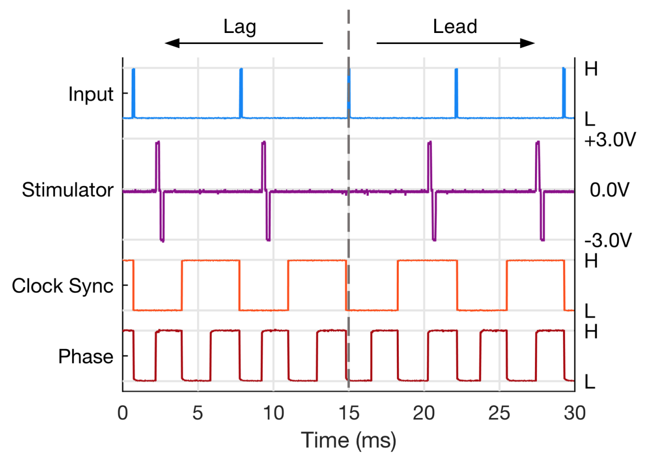

Fig. 4. Phase partitioning example. Four-quadrant phase partitioning is demonstrated by observing bit B6 of the counter along with the synchronized clock. Relative timing for the external stimulation pattern generator is selected through binary word recognition in the phase selector. The system was successfully interfaced with a biphasic DBS pulse generator, demonstrating the ability to apply both phase lead and lag ($\pm 90°$ in this example) compared to the master signal. The input signal consists of 100 μs pulses at 140 Hz, showing the potential of the design to synchronize to DBS.

Our specific design choice does create limitations for the general applicability of the method. First, the use of a sequential phase detector makes the design susceptible to a missing clock or excess noise. For the well-defined pulses from monopolar brain stimulation this is an acceptable trade-off. But for tracking physiological signals and perhaps bipolar stimulation we would use alternative

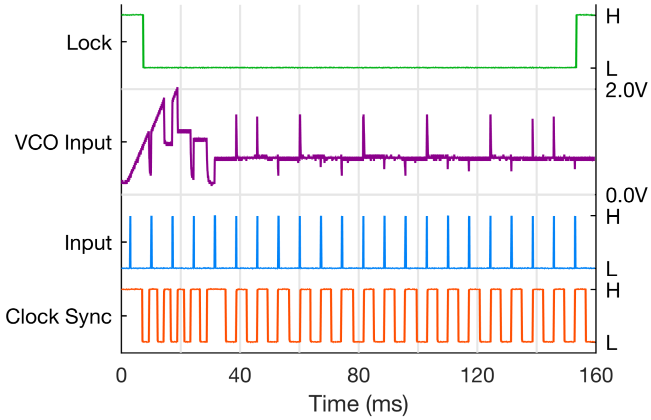

Fig. 5. Locking dynamics with 140 Hz pulse train. Once the device is powered on and an input signal (blue) is available, the lock-status indicator signal (green) goes low within one period of the input signal. The phase mismatch between the divided oscillator output (orange) and the input signal causes the VCO input (purple) to change, thus adjusting the VCO frequency. Successful lock is marked by the status indicator signal going high. The overshoot dynamic observed is dictated by the damping ratio of the filter.

phase comparators such as an analog mixer. Second, the locking of lower frequency signals pushes the boundary of acceptable analog components, and an alternative variant using digital signal processing might provide more degrees of freedom, at the expense of computational energy [18]. Finally, the application of stimulation from an external source can perturb our master clock measurement. Care must be taken to avoid a "re-entrant" loop that might self-clock based on artifacts. To prevent this mode of operation, appropriate isolation methods must be taken, such as those described in [19]. Finally, and most importantly, it is imperative that each use-case be evaluated for patient safety and any undesirable interaction between the stimulators identified and mitigated.

V. CONCLUSION

We present a prototype design for synchronizing neural stimulators. With this approach, subcortical neural circuits accessible chronically with deep brain stimulators can be synchronized with cortical networks activated through transcranial stimulation. The aim is to exploit these paired-associative stimulations to expand our capability to study brain physiology, and potentially open new avenues to disease treatments.

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