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博 士 論 文

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Doctoral Dissertation

應用於神經調節並實現於低壓製程之
雙組態雙模式刺激器設計

Design of Dual-Configuration Dual-Mode Stimulator in Low-Voltage CMOS Process for Neuro-Modulation

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摘 要

近年來，功能性電刺激 (functional electrical stimulation, FES) 早已發展成為能有效用於神經系統疾病的治療方式。舉例來說，深層腦部刺激 (deep brain stimulation, DBS) 最廣為人知的就是可以有效控制原發性顫抖症及帕金森氏症。而脊髓損傷、視網膜假肢、耳蝸植入、阿茲海默症和癲癇抑制的治療也都與電刺激有關。此外，為了方便臨床使用，使醫療設備更適合穿戴或植入，其體積也日趨微型化。結合微電子與生物醫學，植入式單晶片 (system-on-chip, SoC) 在生物醫學應用上具有極大優勢。因此，為了提供臨床治療上更多電刺激的選擇，本篇提出一具有多種刺激模式及功能的電刺激器系統。

本篇提出的雙組態雙模式刺激器可以產生所有常用於神經調節之電刺激形式。雙組態表示單端或雙端的架構；而雙模式意即電流或是電壓的刺激輸出。且不論選擇何種刺激情境，雙相位或是單相位的刺激波形都可以任意選擇。由於可支援多樣性的刺激形式，搭配可調整的控制參數，本篇所提出之刺激器將能更彈性地根據病患的症狀給予出對應的治療，於生物醫療的應用上可以體現極大優勢。此外，由於是透過 0.18-μm 1.8-V/3.3-V 互補式金屬氧化物半導體 (CMOS) 的低壓元件實現，且具備 p 型基板共同接地的設計，使其非常有利於與其他類比或數位電路做單晶片的整合，以完成植入式生醫裝置的應用。以可植入式閉迴路深腦刺激單晶片系統 (closed-loop DBS SoC system) 為例，神經訊號採集類比前端 (neural-signal acquisition analog-front end) 收集到

的生物訊號經過生理訊號處理器 (bio-signal processor) 的適當分析，將可透過適當的刺激參數調整 (刺激頻率、刺激強度、刺激通道等)，抑制不正常的腦部電訊號，達到有效的電刺激治療；而整個系統的供電會由電源管理單元 (power management unit) 提供穩定的工作電壓。此單晶片系統搭配市售擷取卡及醫療級電腦螢幕，即可完成體外機建置。因方便攜帶且包含完整的閉迴路功能，結合所開發之圖形化使用者介面 (graphical user interface, GUI) ，將更有利於神經訊號的觀察、分析與治療。

由於本刺激器系統使用低壓元件來實現，但必須有正負電壓的輸出，因此在設計上需注意元件於負電壓操作中可能會發生的可靠度問題；且因為正負供電壓差達 12 V，遠高於低壓元件的耐壓，在電路設計上也需要避免元件的過壓情況。本篇提出之刺激器晶片克服了低壓元件在上述情況可能發生的可靠度及過壓問題，並可達到最大輸出電流 ±3.6 mA 及最大輸出電壓 ±3.6 V。且因為所有通道共用電流/電壓源的設計，不僅能減少輸出不匹配的程度、降低功耗，也能將佈局面積優化，縮小每個刺激通道的面積 (單個通道只佔 0.052 mm^2 的面積)。此外，本篇提出之刺激器可藉由放電功能，將刺激後的殘留電荷消除，因此在電刺激中電荷不平衡的生物安全性考量可以被適當的解決。也透過全面的電性測試，驗證符合 ISO 14708-1 的國際安全規範。於仿真實驗中，電性量測的實驗結果可以被重現，足以證明本刺激器系統的穩定度。另外，所提出之刺激器系統也於動物實驗中驗證成功。藉由記錄局部場電位 (local field potential, LFP) 的變化，可以觀察到在給予電刺激之前，實驗豬的腦電波於 β 波段 (beta band) 會出現不正常的峰值；而給予電刺激之後，不正常的 β 波段峰值可以被有效地抑制。

關鍵字— 神經調節、雙相刺激、單端刺激、雙端刺激、電壓刺激、電流刺激、閉迴路單晶片系統、植入式生醫裝置、電荷平衡、生物安全性、動物實驗。

Design of Dual-Configuration Dual-Mode Stimulator in Low-Voltage CMOS Process for Neuro-Modulation

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Abstract

Functional electrical stimulation (FES) has been developed into a useful therapeutic tool for neurological disorders these days. For instance, deep brain stimulation (DBS) is well known for its effective control of essential tremors and Parkinson's disease. The treatments of spinal cord injury, retinal prosthetics, cochlear implants, Alzheimer's disease, and seizure suppression are related to electrical stimulation as well. Furthermore, for the convenience of clinical usage, the physical size of medical devices tends to be smaller, which is more suitable for wearing or implantation. By combining microelectronics and biomedicine, the implantable system-on-chip (SoC) has great advantages in biomedical applications. Therefore, a stimulator system with various stimulus patterns and functions is proposed in this design, which is able to provide more widely choices on clinical treatments.

All the electrical stimulation patterns that are frequently used for neuro-modulation can be generated by the proposed dual-configuration dual-mode stimulator. Dual-configuration represents the bipolar or monopolar structure, meanwhile dual-mode stands for the current or voltage output. No matter what stimulation circumstance is chosen, biphasic or monophasic waveforms can be fully supported by the proposed stimulator chip. With various stimulation patterns and adjustable control parameters, the proposed stimulator is able to provide

corresponding treatments more flexibly according to the patient's symptoms, which has significant advantage in biomedical applications. Furthermore, the stimulator chip is realized in 0.18-μm 1.8-V/3.3-V CMOS process and common grounded p-type substrate, which offers great benefit to SoC integration with other analog or digital circuits together for implantable biomedical devices. Take the implantable closed-loop DBS SoC system as an example, the bio-signal collected by neural-signal acquisition analog-front end will be analyzed by the bio-signal processor. Through the proper adjustment of stimulation parameters (such as stimulation frequency, intensity, and the output channel), the abnormal brain signals can be suppressed, which completes the efficient electrical stimulation therapy. The power of the closed-loop SoC system is provided by the power management unit that ensures the stable operational voltages. Associate with the compact DAQ cards and the medical all-in-one computer, an extracorporeal system can be established. Due to its portability and the comprehensive closed-loop functionality, as long as the SoC is combined with the developed graphical user interface (GUI), the whole system will be more conducive to the observation, analysis, and treatment of neural signals.

The proposed stimulator system is realized with low-voltage devices, however, with the necessity of providing both positive and negative voltage outputs, the reliability issue of the devices that are operated in the negative power domain should be taken into concern. Since the voltage difference between the positive and negative power supply reaches 12 V, which is much higher than the breakdown voltage of low-voltage components, the overstress problem should also be dealt with carefully. The proposed stimulator chip has conquered the overstress and reliability issues that mentioned above with the maximum ±3.6 mA stimulus current and the maximum stimulus voltage achieved to ±3.6 V. Due to the fact that all the stimulus channels share the same current/voltage source, the stimulator not only minimizes the output mismatch and reduces the power consumption, it also optimizes the layout area (each channel only occupies the silicon area of 0.052 mm^2). Moreover, with the built-in discharge function, the

redundant charge after stimulation can be eliminated, thus the bio-safety concern of unbalanced charge in neuro-stimulation can be dealt with properly. Additionally, through the comprehensive electrical verification, the proposed stimulator has been proven that meet the ISO 14708-1 standard. In the imitation experiments, the measurement results are reproducible compared to the electrical verification, which affirms the stability of the stimulator system. Furthermore, the proposed stimulator chip has been applied successfully on the in-vivo animal test. By recording the changes of local field potential (LFP), the abnormal peak in the beta band was observed before the electrical stimulation in the experimental mini-pig. After delivering the electrical stimulation from the stimulator system, the abnormal beta band peak was suppressed effectively.

Key words— neuro-modulation, biphasic stimulation, bipolar stimulator, monopolar stimulator, current stimulation, voltage stimulation, closed-loop SoC system, implantable biomedical device, charge balance, bio-safety, in-vivo animal test.