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Master thesis : Computational Analysis of Lidocaine-Induced Modulations on the Excitability of Two Heterogeneous DRG Neuron States Connected to a Projection Neuron (including introduction to research methodology)

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UNIVERSITE DE LIEGE
FACULTE DES SCIENCES APPLIQUEES

Computational Analysis of Lidocaine-Induced Modulations on the Excitability of Two Heterogeneous DRG Neuron States Connected to a Projection Neuron

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Thesis presented to obtain the degree of :
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Thesis supervisors:
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Abstract

Neuronal excitability is a neuron's ability to respond to a stimulus by generating an electrical signal known as an action potential. These electrical pulses form the foundation of neuronal communication, with the information encoded in pulse trains depending on both their frequency and duration. Hyperexcitability is a specific state in which a neuron responds abnormally to weak stimuli, exaggerates its responses, or exhibits spontaneous firing.

Pain serves as the body's warning system, triggering an unpleasant sensation that draws attention to harmful stimuli. These stimuli may involve acute threats, such as intense heat or high pressure capable of causing tissue damage, or minor contact with an existing injury to safeguard the healing process. This latter scenario occurs through sensitization, a phenomenon that affects both the peripheral nervous system (at the level of the dorsal root ganglion) and the central nervous system (at the level of the dorsal horn) by inducing neuronal hyperexcitability as an adaptive response to a vulnerable injury site.

Pathological states arise when sensitization occurs without a functional trigger, generating false alarms that offer no protective benefit. To manage these unwanted pain sensations, modulating the system to reverse, or at least attenuate, the underlying hyperexcitability represents a promising therapeutic approach. Crucially, because this state can severely impact patients in their daily lives, treatments must effectively alleviate chronic discomfort while preserving everyday sensory function, such as normal touch and the vital ability to feel acute, protective pain.

The primary focus of this work is the analysis of distinct pharmacological modulations aimed at treating both peripheral and central sensitization, with particular emphasis on how peripheral modulation influences central neuronal responses, a framework demonstrated through the application of lidocaine as a representative therapeutic agent.

To do so, this thesis investigates the effects of lidocaine in treating hyperexcitability by targeting two primary mediators of sensitization: voltage-gated sodium channels, which play a key role in peripheral neuronal excitability, and NMDA receptors, which serve as key mediators of central sensitization. To achieve this, a conductance-based model is implemented, featuring a dorsal root ganglion neuron connected to a dorsal horn neuron. The dorsal root ganglion neuron incorporates two parameter sets corresponding to healthy and hyperexcitable states, each characterized by distinct profiles of voltage-gated sodium channels. The various types of modulations induced by lidocaine are first simulated individually and then in combination on the peripheral neuron, allowing for an evaluation of their indirect consequences on the postsynaptic dorsal horn neuron. Finally, lidocaine's modulation of NMDA receptors in the central neuron is evaluated, culminating in an assessment of combined peripheral and central modulations. This work also introduces a visual methodology to illustrate drug mechanisms, representing a pharmacological agent as a trajectory across a modulation space.