Presenting a Neuroid model of wind-up based on dynamic synapse: a more realistic approach

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Abstract

The treatment of chronic pain depends mainly on our understanding of the mechanisms such as central sensitization which is involved in it. Wind-up of spinal cord is one of the most important phenomena in the study of central sensitization which has received considerable attention in recent years. Wind-up is a form of short-term synaptic plasticity (STP) that can lead to central sensitivity. Although several models have been proposed for wind-up, none of them are based on the experimental evidence. In this study, we have introduced a new model based on the gate control theory of pain. Neuroids are used as neuron models in our network. Its parameters are captured from available experimental data. Adjusting the weights of the network is based on the short-term synaptic plasticity. The results of the time and frequency domain show that the model can well simulate wind-up behavior. This model can be used for analyzing, predicting and controlling chronic pain in the future.

Introduction

Pain is considered one of the most important sensory factor in humans which affects people's quality of life. In many cases, pain alerts a person to a disturbance, an adverse reaction, or a harmful agent. However, there are some cases in which pain causes conditions that are intolerable including chronic pain. Development of appropriate and effective methods for the treatment of chronic pain depends on our understanding of the mechanisms which lead to it. Some evidence has confirmed that central sensitization can be a reason for chronic pain (Meeus and Nijs, 2006).

Central sensitization refers to an enhancement in the function of neurons in nociceptive pathways which is the result of increases in membrane excitability and synaptic efficacy (Meeus and Nijs, 2006; Ji et al., 2003; Latremoliere and Woolf, 2009). Studies show that there is a relationship between wind-up and central sensitization. It is determined that neuronal procedures which can produce wind-up, can also induce some characteristics of central sensitization. Hence, the study of wind-up may help us to understand the mechanisms of central sensitization (Li et al., 1999; Staud et al., 2001).

Wind-up was observed by Mendell in 1965 for the first time when he was working on his cases. He realized that when a fixed stimulation with low frequencies is applied to C fibers of cat repeatedly, the amplitude of dorsal horn neurons response increases progressively (Li et al., 1999; Woolf, 1996). It is shown that wind-up is the consequence of short-term synaptic plasticity that occurs due to the electric stimulation of C fibers in the range of 0.3 to 3 Hz (Russo and Hounsgaard, 1994). The best range of frequency that wind up can

be observed is around 1-2 Hz (Herrero, 2000). This phenomenon is distinct from central sensitivity but may facilitate the occurrence of long-term potentiation (LTP) in C fibers (Li et al., 1999; Staud et al., 2001; Woolf, 1996).

Throughout history, numerous efforts have been made to identify the pain pathways (Moayedi and Davis, 2013). In this regard, theories such as gate control theory (GCT) have been proposed which were presented by Melzack and Wall in 1965. They explained that the substantia gelatinosa in dorsal horn acts like a gate and the opening or closing of the gate is modulated by the signals that reach from the higher centers of the brain and the peripheral fibers such as Aβ, Aδ and C fibers. Aδ and C fibers cause the gate to be opened, but the activation of Aβ fibers may cause it to be closed (Melzack and Wall, 1996; Melzack, 1996; Mendell, 2014).

After presenting GCT, many researchers attempted to model pain and some phenomena such as wind-up to understand the pain mechanisms and find new ways for its treatment. Britton and Skevington presented a mathematical model based on GCT. They considered only one T-cell, one inhibitory, and one excitatory SG cell in their model. They examined the stimulation of small fiber with assuming the role of NMDA receptors in happening of wind-up (Britton, 1996; Britton and Skevington, 1989; BRITTON et al., 1995). Prince and his colleagues extended Britton's model and considered more T-cells and SG cells. Their results showed that as the number of units increases, T-cell potential decreases ("(PDF) A computational model of Acute Pain", n.d.). Haeri et al. suggested a multilayer perceptron (MLP) neural network for modeling of acute pain. They used the hypothetical patterns and could produce basic patterns of acute pain (HAERI et al., 2003). Farajidavar et al. implemented a computational model for Aβ fiber wind-up including molecular mechanisms such as the activation of NMDA receptors due to the entry of and the sprouting of Aβ fibers towards the small pain fibers which causes the activation of AMPA receptors and consequently the activation of more NMDA receptors. Their results showed that sprouting phenomenon and NMDA receptors have a major role in wind-up (Farajidavar et al., 2006). In other work, they presented a model of wind-up in terms of the short-term and long-term synaptic plasticity mechanisms and suggested that increasing the long-term synaptic efficacy would lead to wind-up (Saeb et al., 2007; Farajidavar et al., 2008). Ropero Peláez and Taniguchi modified Melzack and Wall's circuit. In their model, the synapses between nociceptive afferents and substantia gelatinosa were assumed to be excitatory. They also revisited the gate control theory according to the mechanisms of NMDA synaptic plasticity and intrinsic plasticity and modeled different pain conditions including wind-up (Peláez and Taniguchi, 2016). Although many efforts have been made for modeling of pain especially wind-up phenomenon, none of them are based on the biological data.

In this study, the wind-up of the spinal cord is modeled using a network of spiking neurons. The neuron model is derived from the "Neuroid", which uses empirical data from the neurons of the dorsal horn. Regarding the importance of short-term synaptic mechanisms (weakening and facilitation) in the occurrence of wind-up, these mechanisms are used to regulate network's weights.

Methods

Network Model Structure

The proposed model consists of Aβ (mechanoreceptive) fiber, Aδ, and C (nociceptive) fibers as the inputs of the Neural network, Inhibitory and excitatory interneurons as the inhibitory and excitatory SG-cells in the dorsal horn, and a projection neuron as the output (Fig. 1). Neuroid is used for simulating neurons. The mechanism of short-term synaptic plasticity is applied for modeling the synapses between neurons and fibers in the network model.

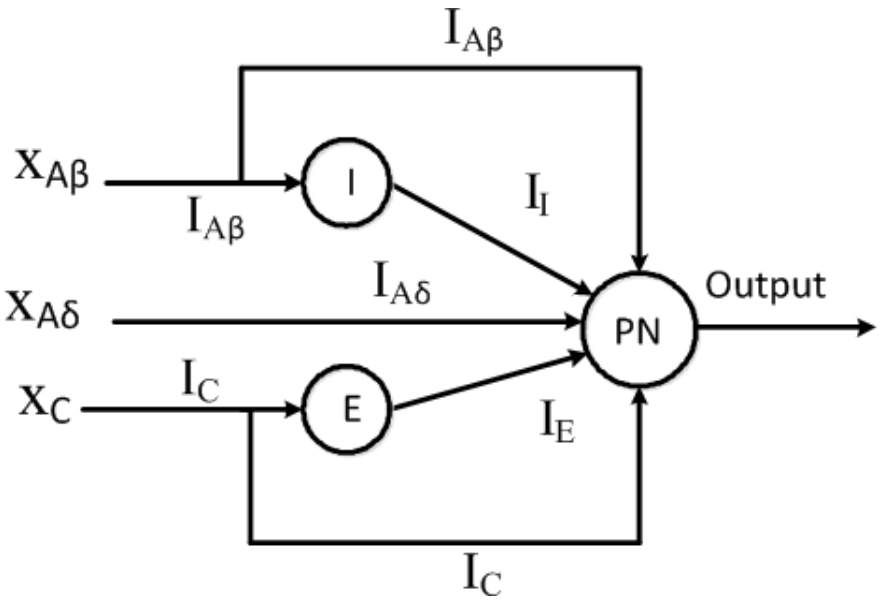

Figure 1: The structure of the proposed network model. I, E and PN are Inhibitory Interneuron, Excitatory Interneuron, and Projection neuron, respectively.

Neurons Model: Neuroid

Neuroid is a spiking neuron model implemented by Arguello and his colleagues. The output of Neuroid is obtained by three operations including comparison, frequency pulse modulation, and demodulation. Initially, the incoming signal will be compared with a threshold value, and if it exceeds the threshold, then the next operation will be done. Otherwise, the output value will be zero. Afterward, the signal will be converted to an impulse train which its frequency is proportional to the amplitude of the incoming signal. Finally, the impulse train will be demodulated, and a signal which is more likely to the input will be produced. The function of Neuroid is formulated as follows:

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