# Feed forward inhibitory control of nociceptive signal transfer through the dorsal horn network: theoretical and experimental approach using the hybrid network technique.

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Abstract:
Feed forward inhibition is a recurrent organization in sensory systems.
To explore the functional role of this synaptic architecture on the nociceptive integration in the dorsal horn network, we study the transfer of a nociceptive signal, using both NEURON modeling and hybrid method approach. Our result shows that the efficacy and the reliability of the sensory signal transfer are controlled by the inhibitory strength, the precise timing between excitatory and inhibitory input, as well as the post synaptic cellular intrinsic properties. These mechanisms might be involved in the physiopathology of chronic neuropathic pain.

Amongst synaptic inhibition principles, that plays a central role in spike transmission in many brain region, the feed forward structure is a recurrent organization in a lot of networks including relay sensory systems such as spinal cord.

Our goal is to study the influence of this feed forward inhibition, in the reliability of spike train transmission in the dorsal horn network, which is the first relay for sensory and pain information processing. Sensory information coming from peripheral nociceptors are impinging to the deep Dorsal Horn relay Neuron (DHN) both directly through AMPA excitatory synapses and indirectly through GABA and glycine feed forward inhibition.

To explore the functional role of this parallel architecture, we studied the transmission of a spike train in a simple three-cell network, using modeling as well as a hybrid network reconstruction. Hybrid networks allows real time interactions between a modeled neuron or network and a biological neuron recorded intracellularly through a dynamic clamp modeled synapse. Our system is based on a real time version of the NEURON software environment that uses a Digital Signal Processor associated with an I/O board.

We first constructed a simplified dorsal horn network by creating different conductance-based models: (1) A$\partial$ and C fiber models that reproduce the known discharge pattern of these afferent inputs, (2) an inhibitory model interneuron of a typical dorsal horn superficial laminae interneuron, and (3) a DHN model neuron expressing their known regenerative properties such as plateau potentials and after discharges. These models are then synaptically coupled to reproduce the connectivity of the direct excitatory AMPA drive from the afferent fibers together with the parallel GABA influences from the interneurons. We quantified the efficacy and the reliability of the spike train transfer through this network using various statistical tools: input/output cross correlation analysis (correlation and contribution index), Inter Spike Interval distribution, spike latency, mutual information. Analysis was done during a systematic screen of the AMPA versus GABA synaptic strength and delay, as well as for different state of intrinsic cellular properties of both the relay neuron and the interneuron (tonic, adaptation, plateau, oscillation).

This first theoretical approach was further validated using hybrid network experiments on mixed spinal cord and dorsal root ganglion organotypic co-culture. The modeled afference and interneuron were synaptically connected to a biological DHN neuron to reproduce the direct AMPA and the indirect GABA projections. The same parameter screening (synaptic

strength balance, delays) was studied. For changes in DHN intrinsic membrane properties, we removed or added voltage dependent channels using both pharmacological agents (specific agonists or antagonists) and dynamic clamp procedure based on conductance injection. The same statistical tools were used to compare theoretical and experimental data.

Our results shows that both spike transfer efficacy and reliability can be either improved or degraded by increased feed forward inhibition, depending on the post synaptic intrinsic cellular properties and the precise synaptic timing between excitation and inhibition. The temporal and statistical structure of the response signal is also specifically modified.
In the case of the DHN properties, the inhibitory interneuron can increase the correlation between the afferent and the efferent spike train and reduce or abolish the post discharge. As a result, sensory information from the periphery can either be faithfully transmitted, amplified or dramatically filtered depending on the relative importance of the direct and indirect pathway and on the neuro modulation of the DHN.

These effects in the sensory nociceptive signal transfer might be involved in the physiopatholgy of chronic neuropathic pain where a reduction or loss of GABAergic neuron as well as changes in the regenerative properties of the deep DHN have been described. These possible distortions of the sensory signal, could then participate to the painful sensation.