

Towards understanding mechanisms of pain transmission: a systems theoretic approach

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Summary. Chronic pain affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined. Despite their great need, neuropharmacology and neurostimulation therapies for chronic pain have been associated with suboptimal efficacy and limited long-term success as their mechanisms of action are unclear. Understanding the mechanisms of pain transmission to predict its modulation by therapies is therefore essential toward pain management, yet current models suffer from several limitations. In particular, they are not amenable to analysis and fail to provide a comprehensive mechanistic understanding of pain transmission. Using mathematical reduction techniques that exploit time-scale separation, we investigated the cellular dynamics in the dorsal horn of the spinal cord—the first central relay of sensory and pain inputs to the brain. This study proposes a low-dimensional reduced model of dorsal horn transmission neurons and discusses the impact of cellular changes on pain transmission to the brain. The reduced model is sufficient to capture the rich dynamics of transmission neurons in the dorsal horn—from tonic to plateau to endogenous bursting. This cellular switch of firing patterns contributes to a functional switch of information transfer—from faithful transmission to enhancement to blocking of nociceptive information, respectively. In addition, a dynamic balance of intrinsic membrane properties drives the cellular switch from one firing mode to another and therefore the functional switch from one information transfer mode to another. This low-dimensional reduced model is amenable to tractable analysis of the mechanisms of pain transmission and open the door to predict outcomes of refined and/or novel neuromodulation pain therapies.

Pain system and the role of the dorsal horn. The pain system builds on a tightly regulated dynamical crosstalk between the peripheral nervous system and the brain via the spinal cord. Physiological pain is initiated by specialized sensory nociceptor fibers in peripheral tissues. The sensory inputs activate neurons in the spinal cord, which project to the cortex via a relay in the thalamus, eliciting pain perception. Therefore, the dorsal horn of the spinal cord is the first central relay station for sensory inputs. It houses a combination of inhibitory (I) and excitatory (E) interneurons, which receive and integrate sensory inputs from peripheral nerves. The balance between their activities modulates the excitability of projection neurons and finely tunes spinal nociceptive transmission to the brain. Projection neurons include convergent neurons (C) in deeper lamina, which receive both noxious and innocuous inputs, and nociceptive-specific neurons (N), which are located mostly in superficial lamina. Studying pain modulation via these projection neurons via computational modeling is thus key to predicting outcomes of therapies for chronic pain.

High-dimensional conductance-based model. As a starting point, we considered a recent—and unique to our knowledge—conductance-based model of the dorsal horn circuit [1]. **(I)** The inhibitory interneuron model is composed of $(I_K, I_{K,Ca})$ in the soma, $(I_{K,Ca})$ in the dendrite, $(I_{Na,t}, I_K)$ in the axon hillock and the axon. **(E)** The excitatory interneuron model is composed of $(I_K, I_{K,Ca}, I_{KA})$ in the soma, $(I_K, I_{K,Ca}, I_{KA})$ in the dendrite, $(I_{Na,t}, I_K, I_{KA})$ in the axon hillock and the axon. **(C)** The convergent projection neuron model is composed of $(I_{KDR}, I_{Ca,L}, I_{CAN}, I_{K,Ca}, I_{Na,p})$ in the soma, $(I_K, I_{Ca,L}, I_{CAN}, I_{K,Ca})$ in the dendrite, and $(I_{Na,t}, I_K)$ in the axon hillock and the axon. **(N)** No nociceptive-specific projection neuron was included in this dorsal horn model. We modified the convergent neuron model and ensure that it reproduces behaviors observed in our experiments.

We then represented the dorsal horn circuit by interconnecting each individual neuron through synaptic connections as follows $I_{syn} = \sum_k g_{syn_k} (V - V_{syn_k})$, where the evolution of the synaptic conductance $g_{syn}(t)$ depends on the type of synapse (e.g., AMPA, NMDA, GABAa, or glycine). We started from the detailed circuits considered in [1], but we are also considering alternative topologies to reproduce behaviors observed experimentally.

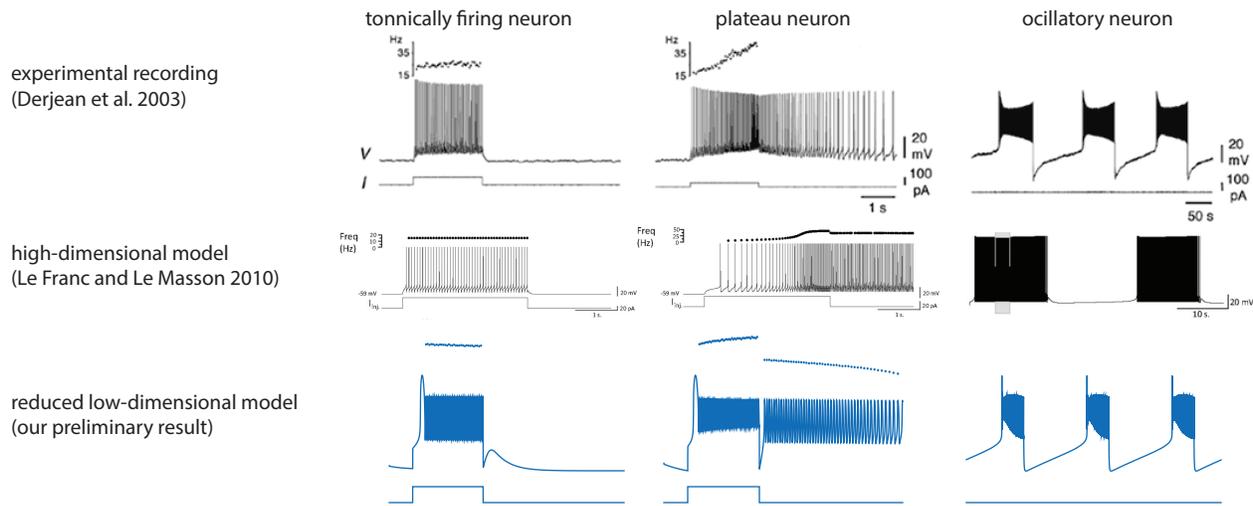


Figure 1: A low-dimensional reduced model is sufficient to capture the dynamics of convergent neurons.

Low-dimensional reduced model. The convergent neuron in the conductance-based model has 15 state variables, which makes analysis of its transmission properties difficult without extensive simulation. We therefore applied *mathematical reduction techniques* that exploit the time-scale separation between the gating of ion channels. In particular, the gating of ion channels—which occurs on many different time scales—can be grouped into three families, according to their influence on neuronal excitability [2]: (i) *fast* for spike upstroke, (ii) *slow* for spike initiation, spike downstroke, and afterspike period, and (iii) *ultraslow* for spike adaptation. From experimental firing patterns, we identified two ultraslow adaptation behaviors. The first ultraslow variable acts as a positive feedback and is responsible for the acceleration in the depolarized state and the deceleration in the hyperpolarized state. The second ultraslow variable acts as a negative feedback and is responsible for the interburst period. Each family can then be described by one state variable, producing a 4-dimensional model.

The model exhibits 3 functional states [3]: (i) a *tonically firing* neuron that is initially silent, but fires steadily during a depolarizing current; (ii) a *plateau* neuron that is also initially silent, fires during a depolarizing current, and then continues to fire after the depolarization stops; and (iii) an *endogenous bursting* neuron that fires bursts of action potentials. Fig. 1 compares experimental recordings [3], a high-dimensional model [4], and our low-dimensional reduced model. It shows that a low-dimensional reduced model is sufficient to capture the cellular switch of convergent neurons. We hypothesize that this cellular switch is driven by a dynamical balance of intrinsic membrane parameters and exogenous inputs.

References

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