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A Computational Model of Dorsal Horn Circuits' Contribution to Neuropathic Pain

2025 47th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) | 979-8-3315-8618-8/25/$31.00 ©2025 Authors | DOI: 10.1109/EMBC58623.2025.11253737

A mathematical model of dorsal horn circuits' contribution to neuropathic pain*

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***Abstract*— The spinal cord is the first site for a synaptic relay in the somatosensory nervous system, where peripheral afferents synapse onto second order neurons. Noxious somatosensory afferent input is primarily transmitted to interneurons and projection neurons in the dorsal horn of the spinal cord, and projection neurons then transmit the information to supraspinal neural circuits for further processing. Despite this crucial role in pain processing, little emphasis has been placed on the dorsal horn circuits' possible contribution to neuropathic pain conditions such as phantom limb pain. Here, a mathematical model of the integration of noxious and innocuous somatosensory afferent input in the dorsal horn is presented. Dynamics of the neuronal populations are modeled using a population rate-based approach. The model successfully recreates common observations related to pain, such as wind-up and inhibition by innocuous touch. Furthermore, changes in afferent input and modifications of the synaptic connections, which are hypothesized to occur following nerve injury, give rise to output consistent with allodynia and persistent spontaneous pain. These explorations provide insights into possible mechanisms contributing to neuropathic pain conditions such as phantom limb pain.**

***Clinical Relevance*— This model offers interesting predictions of how changes in the neural circuits at the spinal cord level may contribute to neuropathic pain conditions such as phantom limb pain and allodynia**

I. Introduction

Neuropathic pain is a complex condition that can arise from dysfunction at various levels of the nervous system. The perhaps most striking example of such a pain condition is phantom limb pain, in which pain is perceived as arising from a limb that is no longer there, for example following an amputation. The complexity and the limited understanding of the underlying mechanisms has impeded the development of effective therapies, making phantom limb pain particularly challenging to treat. Recent research efforts have largely focused on how changes in supraspinal regions and spontaneous activity in peripheral afferents neurons may contribute to phantom limb pain [1], [2], [3]. Little emphasis has been placed on spinal cord circuits' possible contribution to this pain condition. Meanwhile, recent studies have identified groups of excitatory interneurons in the dorsal horn or the spinal cord which primarily receive noxious input, but that develop responsiveness to low-threshold innocuous input under certain pathological conditions [4], [5], [6]. Due to their subsequent connection to projection neurons, these interneuron groups have been hypothesized to be involved in allodynia, a condition where low-threshold mechanical stimulation is perceived as painful [5], [6], [7], [8]. It is further hypothesized that these interneurons may act as amplifiers of pain signals and could play a role in prolonged pain even when there is no noxious stimulation of peripheral tissue.

This paper presents a mathematical model of the neural circuits in the dorsal horn of the spinal cord which are involved in pain processing. With a relatively simple connection scheme between the various neuron populations the model can account for several common pain phenomena. Additionally, changes in the input and structure of the model reveal how these neural circuits may contribute to neuropathic pain conditions such as allodynia and phantom limb pain. The model presented here has common aspects with previous models of spinal cord circuits involved in pain processing [9], [10], [11], but with some key differences described hereafter.

II. Methods

Noxious and innocuous sensations are conveyed from the periphery of the body to the central nervous system via different types of peripheral afferent neurons (Aβ, Aδ and C) [12]. In this model, the afferents are simplified into two distinct classes: innocuous and nociceptive. A similar simplification is made for the interneurons in the dorsal horn, which are reduced to two classes: excitatory and inhibitory. The interneurons further synapse onto projection neurons that transmit to higher order systems. This model does not consider descending modulatory effects from supraspinal regions, nor does it consider the exact morphology or neuron physiology. The outline of the proposed model and the various connections between neuron populations are illustrated in Figure 1. The connection scheme is largely the same as in a previous model by Crodelle & Maia [13], with two additional synaptic connections: from the innocuous afferents onto the excitatory interneurons, and a recurrent connection from the excitatory interneurons onto themselves, based on experimental evidence [4], [5], [6].

Simulations were used to study phenomena that are related to pain. The code used for simulations of the model was written in Python and was adapted from the Neuromatch Academy Computational Neuroscience e-book and tutorials on dynamic networks [14]. A population rate-based approach (sometimes also referred to as Wilson-Cowan model) was employed to model the firing rates of the coupled neuronal populations. The framework is simple but powerful, and in its essence consists of differential equations.

*Research supported by Promobilia Foundation.

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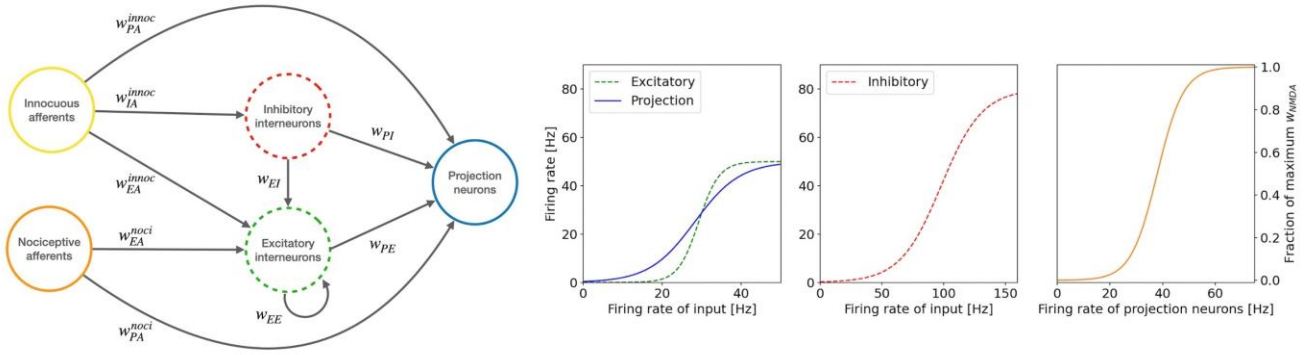

Figure 1 Left: Outline of the model. Circles represent neuron groups, where the leftmost groups are primary afferent neurons, the neuron groups in the middle represent interneurons in the spinal cord, and the rightmost neuron group are projection neurons which transmit the signals to the brain. Arrows represent connections between and within neuron groups, and w denotes the strength of these connections. Right: Sigmoidal activation function. All neuron populations have the same activation, but with different parameter values.

The input to the model is the firing rate of innocuous and nociceptive afferents, resulting from stimulation of the respective receptors. For innocuous afferents, the frequency is estimated to lay in the range 0-150 Hz [15], [16]. Nociceptive afferents have a lower range of firing frequencies, 0-40 Hz [17], [18]. The output of the model is taken to be the average firing frequency of the projection neurons, as a proxy for the intensity of the signal that is transmitted to higher order systems and ultimately interpreted as pain [7]. The firing rates of the afferent neuron populations are denoted as r_A^{innoc} and r_A^{noci} for innocuous and nociceptive afferents respectively, r_E and r_I for the inhibitory and excitatory interneurons, and r_P for the projection neurons. The differential equations for the system are:

Excitatory interneurons

$$\tau_E \frac{dr_E}{dt} = -r_E + F(w_{EA}^{noci} r_A^{noci} - w_{EI} r_I + w_{EE} r_E), \quad (1)$$

Inhibitory interneurons

$$\tau_I \frac{dr_I}{dt} = -r_I + F(w_{IA}^{innoc} r_A^{innoc}), \quad (2)$$

Projection neurons

$$\tau_P \frac{dr_P}{dt} = -r_P + F\left([w_{PA}^{noci} + w_{NMDA}] r_A^{noci} + w_{PA}^{innoc} r_A^{innoc} + w_{PE} r_E - w_{PI} r_I\right), \quad (3)$$

where $F(\cdot)$ is chosen as a sigmoidal activation function, the parameters τ_E, τ_I , and τ_P control the timescale of the dynamics in each population, and the connection strengths are given by w_{xy} ($y \to x$, see Figure 1). Here, $F(\cdot)$ is chosen to be the same as has been used in a few previous models [13], [19]

$$F(x; \alpha, \beta, f^{max}) = \frac{f^{max}}{2}\left[1 + \tanh\left(\frac{1}{\alpha}(x - \beta)\right)\right], \quad (4)$$

where $\frac{1}{\alpha}$ determines the slope of the activation function, β is a form of threshold, and f^{max} is the maximal firing frequency of the neuron population. All synaptic weights, w, are chosen as fixed parameters, except w_{NMDA}, which reflects the NMDA synapses contribution to the *wind-up* phenomenon, where repeated stimulation results in increased response in the projection neurons. This parameter is updated as

$$\tau_{NMDA} \frac{dw_{NMDA}}{dt} = -w_{NMDA} + w_{NMDA}^{max} F(r_P; \alpha_{NMDA}, \beta_{NMDA}, w_{NMDA}^{max}). \quad (5)$$

Values for the parameters of the activation functions were largely chosen as in the previous model by Crodelle & Maia [13], with a few exceptions. The maximum firing rate of the excitatory interneurons, f_{max}^E, was changed from 60 Hz to 50 Hz. This is the value used also in the earlier model by Crodelle *et al.*, [19]. Simulations showed that f_{max}^E=50 Hz gave wind-up characteristics more like those observed in experiments [20]. Additionally, parameters α and β for the inhibitory interneuron population were scaled so that the activation curve spans the whole range of input frequencies of the innocuous afferents. Parameters for the activation functions are listed in Table 1. The activation functions of the neuron populations and the NMDA-mediated synaptic input are shown in Figure 1.

The input to the dorsal horn circuit from each of the afferent neuron populations is drawn from a Gaussian distribution centered at the mean firing rate (s.d = 4 Hz). Finally, connection strengths between neuronal populations were tuned to give output in line with experimental results and previous models. Note that this approach to modelling neuronal population dynamics does not require the size of each population to be specified. The connection strengths between populations (denoted by *w*) are a compound value of the number of synaptic connections and the strength of each synapse.

Table 1 Parameters for the activation functions and differential equations describing the development of populations firing rates

	τ [s]	α	β	f^{max}[Hz] or w_{NMDA}^{max}
Excitatory	0.01	5.2	29.2	50
Inhibitory	0.02	33.25	98	80
Projection	0.001	11.5	28.2	50
NMDA	1.0	10	38	2

III. RESULTS

In Figure 2 a), the numeric values of the connection strengths for the model are presented. It is worth noting that this set of weights likely is not a unique solution, as there may exist many combinations of values that result in the same or similar behavior in the model. Simulations in the second part of this section reveal how a few variations of these connection strengths impact the output of the model.

A. Model validation

To validate the behavior of the model, some well-known pain characteristics are reproduced and compared to the output of previous models [13], [19]. First, the model response to a brief noxious stimulus in the periphery is examined, see Figure 2 b). A noxious stimulus is delivered to the periphery at t=0.5 s. Due to the differing conduction velocities related to thickness of axonal fibers and myelination, action potentials elicited in the periphery will arrive at the dorsal horn at slightly different times. The innocuous afferents primarily consist of faster conducting A-fibers, which trigger the first spike in activity. Nociceptive afferents primarily consist of slower conducting C-fibers, and elicit a more drawn-out response following a bit of a delay. Innocuous afferents are assumed to have a firing rate 100 Hz and nociceptive afferent at 20 Hz, based on experimental results [18]. The output of the proposed model (left) is qualitatively similar to that previously demonstrated by Crodelle & Maia (right) [13].

The second pain phenomenon considered as validation for this model is wind-up, shown in Figure 2 c). Wind-up is a phenomenon where repeated stimulation results in increased response in the projection neurons. The change in response depends on the frequency of stimulation, and has been well characterized experimentally [20] and in mathematical models of pain [19], [21]. The proposed model (left) shows a similar behavior as a previous model by Crodelle & Piltz, et al. [19].

The final pain phenomenon considered as validation is inhibition of pain by innocuous touch, also known as gate control theory. This phenomenon is often attributed to gating mechanisms in the dorsal horn. A theory for the neural structures involved in this process was proposed by Melzack and Wall already in 1965 [22]. The proposed model uses a slightly modified and more neurobiologically realistic neural structure, but still successfully reproduces the gating mechanism demonstrated in experiments [23]. Figure 2 d) reveals similar results of the proposed model (left) and a previously published model by Crodelle & Piltz, et al. [19].

B. Model predictions

The previous sections described that how the proposed model successfully reproduces various well-known pain phenomena. This section focuses on how perturbations to the model might relate to neuropathic pain. The first neuropathic pain condition to be considered is allodynia, a condition where low-threshold mechanical stimulation is perceived as painful. Sprouting of innocuous afferents has been hypothesized to happen after nerve injury [24], [25], [26], [27], possibly strengthening or creating new, aberrant connections from the afferent neurons to interneurons or unmasking previously existing but silent connections [5], [6]. Furthermore, recent experiments have identified excitatory interneurons in the dorsal horn that develop responsiveness to low-threshold innocuous input under certain pathological conditions [4], [5], [6]. It is hypothesized that these interneurons may act a amplifiers of pain signals. In the proposed model these changes are represented as increased connection strengths w_{EA}^{innoc} and w_{EE}, see Figure 3 a).

In the original set-up of the proposed model (Figure 2), the strong activation of inhibitory interneurons ensures that innocuous input does not result in activation of the projection neurons, and ultimately does not elicit pain. However, with the altered synaptic connections innocuous input alone does in fact elicit a response in the projection neurons. The level of activity in the projection neurons depends on the firing rate of the innocuous afferents, see the left panel in Figure 3 c). The graph was obtained by simulating 20 s of innocuous stimulation at different frequencies, to mimic a previous experiment examining the frequency dependence in allodynia [28]. In the experiment, allodynia was assessed by brushing capsaicin-sensitized skin at different velocities and asking participants to rate the unpleasantness of the sensation [28]. An earlier study reported on the firing rate of innocuous afferent in response to different brush velocities [16]. Hence, if the firing rate of innocuous afferents is taken as a proxy for brush velocity and the firing rate of the projection neurons as a proxy for the unpleasantness of the sensation, the model shows qualitatively similar results as the experiment.

The second neuropathic pain condition to be considered is spontaneous pain, i.e., pain that arises even when there is no noxious stimulation of peripheral tissue. Following nerve injury, spontaneous activity has been observed to arise in the dorsal root ganglion (DRG) of peripheral afferent neurons. Evidence from animal studies and humans indicate that this spontaneous activity contributes to spontaneous pain [29], [30], [31]. Up until recently the nature and mechanism of the spontaneous activity in DRG was poorly characterized, but recent *in-vivo* experiments in mice have identified two types of spontaneous activity: singly firing neurons and clustered firing [31]. Singly firing neurons are scattered throughout the DRG with no apparent synchrony in their activity. This type of spontaneous activity was found in multiple different pain models. In cluster firing, on the other hand, multiple adjacent DRG neurons fire together in synchrony. Such cluster events typically lasted for tens of seconds and were found to be unique to neuropathic pain. The study also identified the functional relevance of the neurons involved in the cluster events, revealing that the cluster events involve both nociceptors and low-threshold mechanoreceptors [31].

Here, such cluster firing is modelled as periods of elevated frequency firing of both the nociceptive and innocuous peripheral afferents populations. Since this activity arises in the DRG, the impact of differing conduction velocities is assumed to be negligible, and the input from the two afferent groups is modeled to arrive at the dorsal horn simultaneously. Additionally, the firing frequency in the noxious and innocuous afferents may differ since it is not associated with activation of mechanoreceptors in the periphery. Therefore, simulations were conducted for varies different combinations

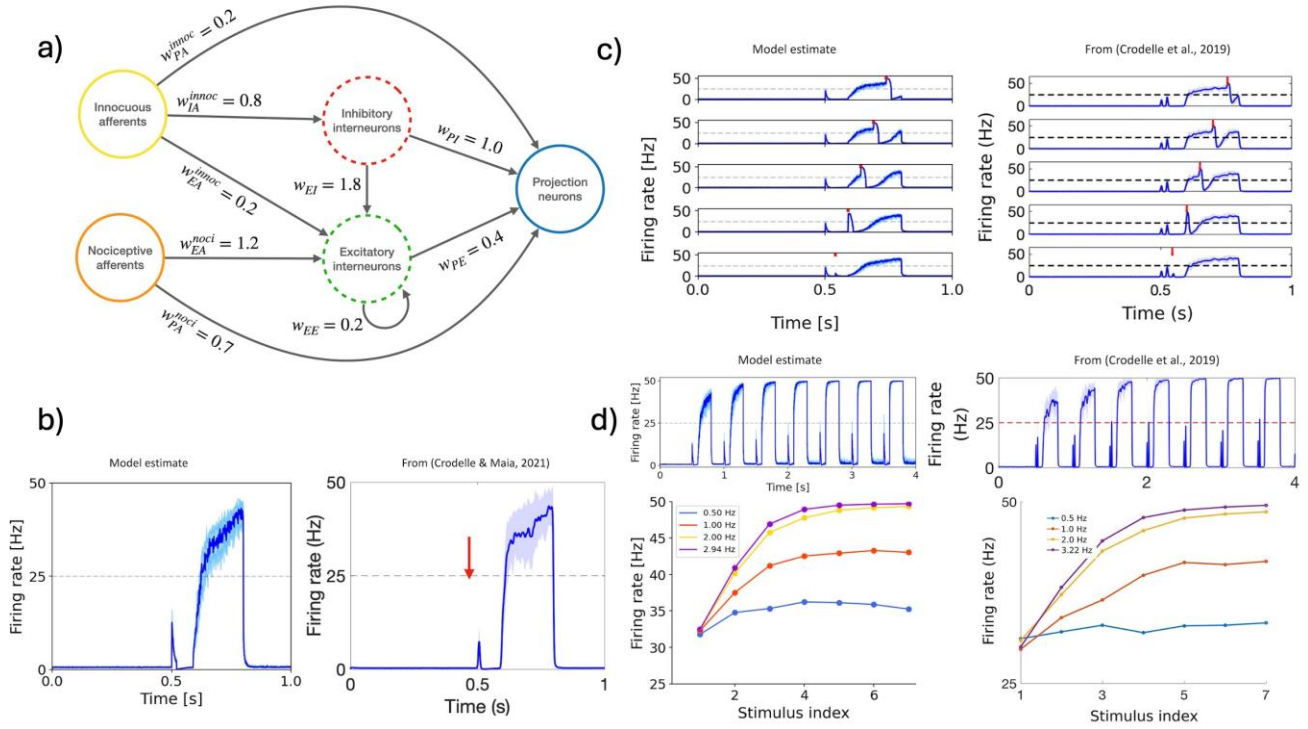

Figure 2 ***a)*** *Connection strengths for the proposed model. Each connection represents a compound value of the number of synaptic connections and the strength of each synapse.* ***b)*** *Model output (left) and output from a previous model by Crodelle & Maia (right) in response to brief noxious stimulus in the periphery, as previously described other in the Axonal damage-model [10] . The dark curve denotes the mean, and the shaded region the standard deviation, of 30 realizations of the simulation.* ***c)*** *Wind-up changes the response in projection neurons following repeated stimulation. The change in response is frequency dependent. The proposed model (left) and a previous model by Crodelle & Piltz, et al. (right) produce similar results [9].* ***d)*** *A brief nociceptive stimulus activates all fibers. When this is shortly followed by stimulation of only the A-fibers (e.g., by innocuous touch), the projection neurons are briefly inhibited. Our model (left) and previous model by Crodelle & Piltz, et al. (right), in agreement with each other and experimental results [9], [38].*

of afferent input during a 40 s long cluster event, see Figure 3 b). The left panel shows the original proposed model response to different combinations of afferent input, and the right panel shows the corresponding response of the neuropathic pain model. The singly firing neuron activity is modeled as an elevated baseline firing rate between clusters, 4 Hz instead of 1 Hz as in the uninjured case.

These results indicate that spontaneous activity arising in DRG could contribute to spontaneous pain. In particular, this could relate to so called "pain attacks" that are often observed in the context of neuropathic pain. Furthermore, structural changes in the dorsal horn circuits may exacerbate the pain and result in pain arising also from lower levels of activity in DRG (right panel in Figure 3 b)). However, this does not account for the persistent spontaneous pain that is also commonly experienced in neuropathic pain, such as phantom limb pain. Cluster firing is reported to last for several tens of seconds, but pain can often last much longer than that. One possible explanation for this could be persistent activity in dorsal horn pain circuits. In particular, if the recurrent connection of the excitatory interneurons is strong enough, this could result in a state of persistent self-excitation. Indeed, with the modified connection strengths the model does display this behavior. In Figure 3 d) the projection neuron activity is demonstrated before, during and after cluster firing events with different combinations of input from the nociceptive and innocuous afferents. For certain levels of input the projection neurons activity remains elevated also after the input from the DRG has ceased (i.e., after t=50 s in the figure).

IV. Discussion

Using a relatively simple, yet neurophysiologically grounded model of dorsal horn neural circuits, several characteristics typically observed in the context of nociceptive pain were demonstrated. In addition, perturbations of the model structure and input revealed how changes of the afferent input and connections between the neuron populations can contribute to allodynia and spontaneous pain, phenomena which are commonly reported in neuropathic pain.

Research related to phantom limb pain has largely focused on changes in cortex and other supraspinal regions and spontaneous activity in peripheral afferents neurons with little emphasis on spinal cord circuits' possible contribution [1], [2], [3]. The model proposed in this article makes predictions that changes in the neuronal circuits in the dorsal horn could contribute to the persistence of phantom limb pain also beyond spontaneous activity in peripheral afferent neurons. These same changes also render model output in line with experimental results relating to allodynia, another phenomenon often observed in the context of neuropathic pain. This indicates that there may be common mechanisms underlying these two neuropathic pain conditions.

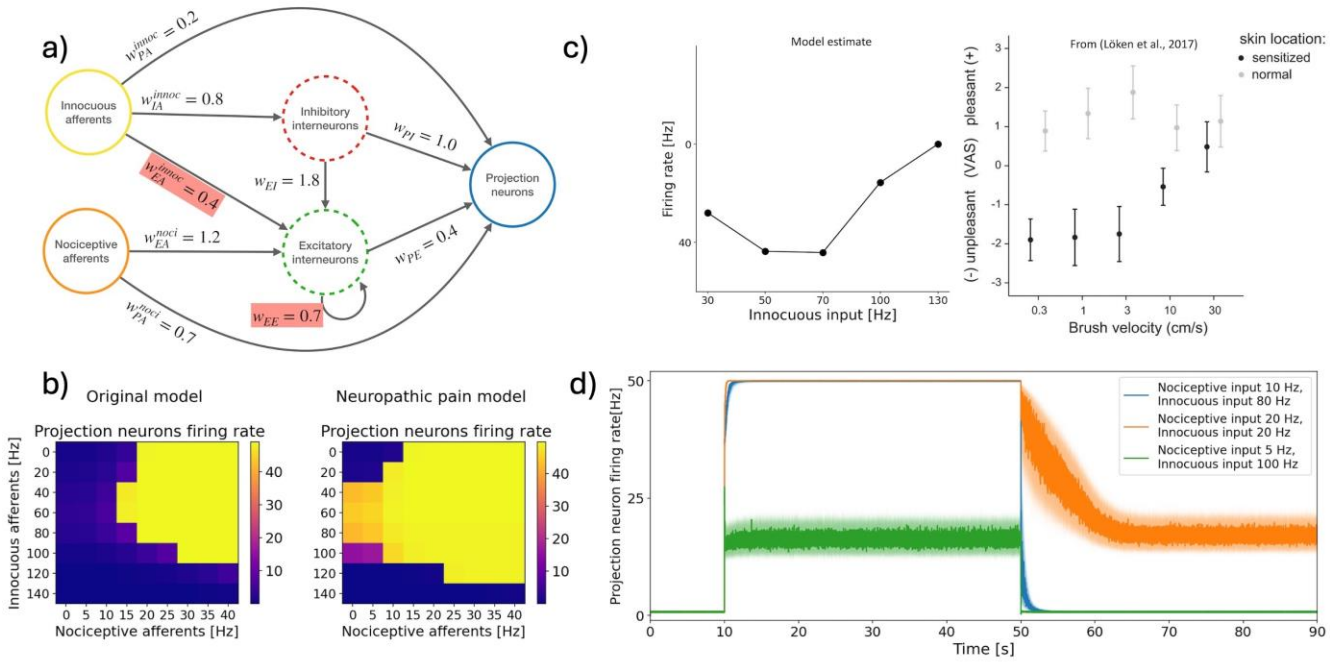

Figure 3 ***a)*** *Neuropathic pain model. Following sensitization or nerve injury, connection strengths within and between neuronal populations are hypothesized to be altered. Based on recent experimental evidence, the connection from innocuous afferents to excitatory interneurons and within the excitatory interneuron population seem to be of particular interest. Thus, these connections are increased compared to baseline.* ***b)*** *Following nerve injury spontaneous activity can arise in the dorsal root ganglion. These heatmaps indicate the projection neuron activity during 40 s long cluster events with different combinations of activity in nociceptive and innocuous afferents. The original proposed model (left) will show high model output if the activity in nociceptive afferents. In the neuropathic pain model (right) the output is high also for lower levels of noxious input.* ***c)*** *Allodynia. If the firing rate of the projection neurons is taken as a proxy for unpleasantness and the firing rate of the innocuous input as a proxy for brush velocity (as demonstrated experimentally [36]) the model estimate (left) shows qualitatively similar results as an experiment examining the frequency dependency of allodynia [37](right). Note that the firing rate on the x-axis is not entirely linear.* ***d)*** *Persistent pain. Average firing rate of the projection neurons during the 10 seconds before a cluster event, the 40 s during the cluster event and the 40 s immediately after a cluster event. For some combinations of nociceptive and innocuous input the projection neuron activity remains elevated also after the cluster event.*

The model presented here model has commonalities with previous population rate-based models [13], [19], [32], with some key differences. While all four models have similar general structure, with nociceptive and innocuous afferents synapsing onto interneurons and projection neurons, the specific connections differ. Here, a weak connection from the innocuous afferents to the excitatory interneurons was introduced. Typically, this connection is weak enough that the activity of the inhibitory interneurons prohibits pain from being elicited by innocuous touch. However, if this connection is strengthened, it can contribute to the development of allodynia, as demonstrated by the simulations above. Additionally, a recurrent connection within the excitatory interneuron population was added in this model, reflecting the role of excitatory interneurons in driving and enhancing excitation in dorsal horn circuits [4], [5], [6]. The model predictions indicate that this recurrent connection could play a role in persistent pain in absence of input, for example in phantom limb pain [1], [33]). The model by Ropero Peláez and Taniguchi suggests an alternative mechanism of phantom limb pain, which relies on a negative firing threshold in the projection neurons [32]. However, it is unclear what a negative firing threshold corresponds to in neurophysiology.

One limitation of the model proposed here is the omission descending inhibition and facilitation, which arguably play a key role in modulating pain. Another aspect that is known to play a role in dorsal horn pain circuits is presynaptic inhibition. This mechanism is included in model by Crodelle & Piltz *et al.* [19], and should be relatively straightforward to incorporate into a future version of the model presented in this article. The simulations described above explored how aberrant connections within the model can lead to various pain conditions, but not *how* these aberrant connections arise. It has been hypothesized that nerve injury can lead to sprouting of neurons in the spinal cord [24], [25], [26], [27] or unmasking of previously existing but silent connections [5], [6]. In the work by Ropero Peláez and Taniguchi, different forms of plasticity related to these processes were explored [32]. Incorporating such plasticity in the proposed model could provide further insight into how connections might be altered after disruptions to the system (*e.g.*, nerve injury) and how his can lead to the demonstrated pathological pain states. In another recent model Medlock and Sekuguchi *et al.*, noted that different synaptic weight combinations among the dorsal horn interneurons can produce equivalent circuit function under normal conditions, but result in vastly different responses to perturbations or pathologic insults [34]. This degeneracy in dorsal horn circuit structure, could indicate that some individuals may be predisposed to developing pathological pain states after injury, even without

the above-mentioned sprouting or plasticity.

The model presented here was not directly verified against data from neural recordings, but rather aims to recreate qualitative descriptions of common observations related to noxious and innocuous stimulation and the resulting perceived pain. Naturally, verification against neural recordings of spinal cord interneurons and projection neurons would be necessary to evaluate how realistic the model is. A rudimentary form of verification was achieved by choosing model parameters to yield results in line with previous experiments. Experiments that could further validate the accuracy of the model would involve recordings of primary afferent neurons (*e.g.*, with microneurography) as well as structural and functional studies of spinal cord interneurons and projections neurons. In-vivo recording of the neural activity in the spinal cord can be performed in experimental animals but are still rather challenging to perform in humans. Spinal cord fMRI studies have shown promising results in recent years [35], and could be a possible tool for further examination of the nociceptive responses in spinal cord neurons. However, the results relating to allodynia indicate that this approach to modelling neural circuits of pain can lead to insights in the possible underlying mechanisms of pathological pain conditions. Thus, clinical and experimental investigations of pain incidence and intensity in various conditions could serve as another avenue for verifying the predictions from this model.

Acknowledgment

I would like to thank Prof. Max Ortiz-Catalan for guidance and for securing funding to support this work, and Prof. Torbjörn Lundh for valuable discussions and final review of the manuscript. Figures 2 b), 2 c), 2 d) and 3 c) include images from previous publications and are reproduced under the terms of the Creative Commons Attribution License.

The author reports no conflict of interest.

Data availability

Code that reproduces the results presented in this article is available at: https://github.com/mramne/dorsal-horn-neuropathic-pain

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