A computational model of the integration of noxious and innocuous input in the dorsal horn

Malin Ramne
Chalmers University of Technology https://orcid.org/0000-0001-8021-5420
Max Ortiz-Catalan (maxortizc@outlook.com)
Chalmers University of Technology https://orcid.org/0000-0002-6084-3865

Research Article

Keywords: Computational Neuroscience, Pain, Dorsal Horn, Wilson-Cowan model, Neural rate model, Allodynia, Hyperalgesia, Phantom limb pain

Posted Date: October 24th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2197547/v1

A computational model of the integration of noxious and innocuous input in the dorsal horn

Malin Ramne[1,2] and Max Ortiz-Catalan[1,2,3,4]

1. Center for Bionics and Pain Research, Mölndal, Sweden
2. Department of Electrical Engineering, Chalmers University of Technology, Gothenburg, Sweden.
3. Operational Area 3, Sahlgrenska University Hospital, Mölndal, Sweden.
4. Department of Orthopaedics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Sweden.

Corresponding author:
Max Ortiz-Catalan
Center for Bionics and Pain Research
Sahlgrenska Universitetssjukhuset
R-huset, plan 7, Länsmansgatan 28,
431 80, Mölndal
Sweden
E-mail: maxo@chalmers.se

Abstract

The first site for a synaptic relay in the somatosensory nervous system is the spinal cord, where peripheral afferents synapse onto interneurons and projection neurons. Here, we present a model of the integration of noxious and innocuous somatosensory afferent input in the dorsal horn of the spinal cord. This model specifically examines the interaction of nociceptive responsive, innocuous responsive, and inhibitory interneurons, all of which receive afferent input from the periphery and in turn synapse onto projection neurons that transmit information to supraspinal neural circuits for further processing. We modeled the dynamics of these neuronal populations using a rate-based Wilson-Cowan approach. The model successfully recreates common observations related to noxious and innocuous stimulation, as well as the resulting intensity of pain. Furthermore, we explored how modifications of the synaptic connections between the different neuron populations can give rise to aberrant pain. These explorations provide insights into the possible mechanisms of neuropathic pain conditions such as phantom limb pain, hyperalgesia, and allodynia.

Keywords

Computational Neuroscience, Pain, Dorsal Horn, Wilson-Cowan model, Neural rate model, Allodynia, Hyperalgesia, Phantom limb pain.

Introduction

The way in which noxious and innocuous information is integrated in the dorsal horn of the spinal cord has been topic of research for many decades. Significant progress has been made in mapping the relevant neural circuits [1,14,19,41,44,46,49,50], and eventually a complete picture will emerge on the structural and functional mechanisms. Here, we modeled a minimalistic representation of these neural circuits and studied how a relatively simple connection scheme can give rise to common pain phenomena.

As a first step, we performed a systematic literature review on the neurophysiology of pain to inform our model [31]. We noted that noxious and innocuous sensations are primarily conveyed in peripheral nerves by different types of nerve fibers. Thin, lightly myelinated Aδ-, and even thinner, unmyelinated C-fibers transmit noxious stimuli [2,42,47,48], whereas innocuous sensations are primarily conveyed by larger, myelinated Aβ-fibers [18,42]. However, it has been established that innocuous sensations, such as pleasant touch, are also transmitted by C-fibers [21], and recent studies have revealed the existence of an ultrafast system (Aβ-fibers) for signaling pain in humans [25]. The first neurons to convey sensations (primary afferents) project from the peripheral parts of the body to the spinal cord, where they make synaptic connections with neurons of the central nervous system. This relay of sensorial information at the spinal cord is often described in terms of direct synaptic transmission, from primary afferents to projection neurons that transmit to the brain. However, polysynaptic networks involving excitatory and inhibitory interneurons in the spinal cord also exists [16,46,48], and this means that projection neurons receive input from primary afferents, as well as from various populations of excitatory and inhibitory interneurons. Recent studies have identified groups of excitatory interneurons in the dorsal horn which primarily receive noxious input, but that develop responsiveness to low-threshold innocuous input under certain pathological conditions [28,41,46]. Due to their subsequent connection to nociceptive projection neurons, these interneuron groups have been hypothesized to be involved in allodynia [28,38,40,46], a condition where low-threshold mechanical stimulation is perceived as painful.

We developed a model using the workflow suggested by Blohm *et al*., "*A How-to-model guide for neuroscience"* [6]*,* in which they highlight that *"as the most important rule, the model should always be kept as simple as possible!".* With this rule in mind, we simplified the various aforementioned afferent fibers (Aβ, Aδ and C) into two distinct classes: innocuous and nociceptive. Therefore, our model does not consider different conduction velocities. A similar simplification was made for the interneurons in the dorsal horn, which we reduced to three classes: innocuous responsive, inhibitory, and nociceptive responsive. We assumed that the innocuous and nociceptive responsive interneurons further synapse onto projection neurons that transmit to higher order systems. Our model does not consider descending modulatory effects from supraspinal regions, nor does it consider the exact morphology or neuron physiology. We outline the model in Figure 1.

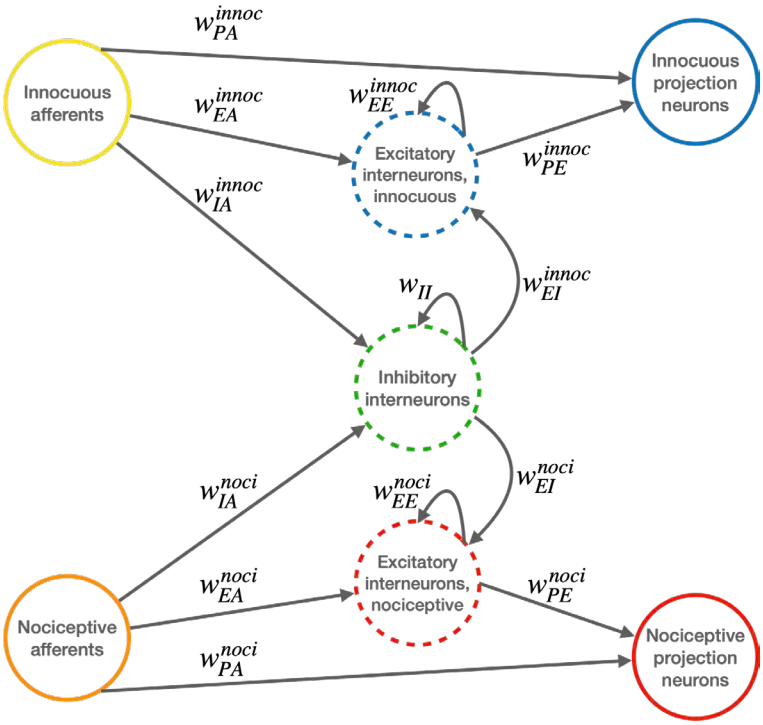

Figure 1. ***Outline of the model****. Circles represent neuron groups, where the leftmost groups are primary afferent neurons, the neuron groups in the middle represent interneurons in the spinal cord, and the rightmost neuron groups are projection neurons which transmit the signals to the brain. Arrows represent connections between and within neuron groups, and w denotes the strength of these connections. Interneurons are marked with dashed lines which is also consistent with the line styles used in the plots below.*

Methods

We used simulations to study certain phenomenon that involve the interaction between innocuous stimulation and pain, such as inhibition by innocuous touch and allodynia, where innocuous stimulation leads to pain perception. To do so, it was also necessary to consider the activity in the groups of innocuous responsive neurons.

We employed a population rate-based approach to modelling the firing rates of the different neuronal groups. 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 lie in the range 0-100 Hz [24] with approximately linearly increasing firing rates for increasing intensity of the stimuli [20]. Nociceptive afferents have a lower range of firing frequencies, 0-40 Hz [39] . The output of the model is taken to be the average firing frequency of the projection neurons, as a proxy for the intensity of different sensory modalities that are transmitted to higher order systems [38].

The code used for simulations of the rate-based model was written in Python and was adapted from the Neuromatch Academy Computational Neuroscience e-book and tutorials on dynamic networks [26]. The Wilson-Cowan model is traditionally used to model the dynamics of two coupled populations of excitatory and inhibitory neurons. The model is simple but powerful, and in its essence consists of two differential equations. Here, we have three populations of interneurons: two excitatory (innocuous and nociceptive responsive) and one inhibitory. The inhibitory population synapses onto the two excitatory populations,

but there is no reciprocal connection back to the inhibitory population. Each interneuron population also has a recurrent connection onto itself. We considered two external sources, the innocuous and nociceptive afferents, of which the firing rates are denoted r_A^{innoc} and r_A^{noci}, respectively. If we denote the firing rates of the interneuron populations as r_E^{noci} for the nociceptive responsive, r_E^{innoc} for the innocuous responsive, and r_I for the inhibitory, and then for the projection neurons we denote the firing rates as r_P^{noci} for the nociceptive, and r_P^{innoc} for the innocuous, we obtain the following differential equations for this system:

Excitatory interneurons

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

Innocuous responsive:
$$\tau_E \frac{dr_E^{innoc}}{dt} = -r_E^{innoc} + F(w_{EE}^{innoc} r_E^{innoc} - w_{EI}^{innoc} r_I + w_{EA}^{innoc} r_A^{innoc}) \quad (2)$$

Inhibitory interneurons

$$\tau_I \frac{dr_I}{dt} = -r_I + F(-w_{II} r_I + w_{IA}^{noci} r_A^{noci} + w_{IA}^{innoc} r_A^{innoc}), \quad (3)$$

Projection neurons

Nociceptive:
$$\tau_P \frac{dr_P^{noci}}{dt} = -r_P^{noci} + F(w_{PE}^{noci} r_E^{noci} + w_{PE}^{noci} r_A^{noci}) \quad (4)$$

Innocuous:
$$\tau_P \frac{dr_P^{innoc}}{dt} = -r_P^{innoc} + F(w_{PE}^{innoc} r_E^{innoc} + w_{PE}^{innoc} r_A^{innoc}) \quad (5)$$

where $F(\cdot)$ is often chosen as some 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 as

$$F(x; a, \theta, f^{max}) = f^{max}\left(\frac{1}{1+e^{-a(x-\theta)}} - \frac{1}{1+e^{a\theta)}}\right), \quad (6)$$

where a is the gain, θ is the threshold, and f^{max} is the maximal firing frequency of the interneurons. The parameters for the nociceptive and innocuous neuron populations (r_E^{noci}, r_P^{noci} and r_E^{innoc}, r_P^{innoc} respectively) were chosen to approximately match the range of firing rates of dorsal horn neurons observed by Ruscheweyh and Sandkühler [35]. The parameters for the inhibitory interneurons (r_I) were chosen to match the activity of inhibitory neurons in previous models [11,51], which in turn refer to experimental results [23,35]. The activation functions for the neuron populations are shown in Figure 2 and the corresponding parameters are found in Table 1.

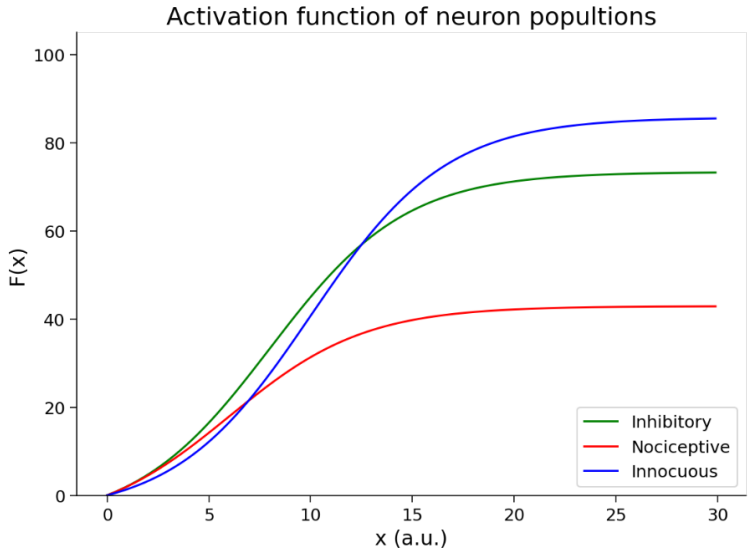

Figure 2. ***Sigmoidal activation function****. All interneuron populations have the same activation function (equation* (1)*), but with different values of the parameters* a*,* θ*, and* f^{max} *(Table 1).*

	τ [s]	a	θ	f^{max} [Hz]
Nociceptive	0.06	0.3	6	50
Innocuous	0.06	0.3	10	90
Inhibitory	0.06	0.3	8	80

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

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.

Hypotheses

The model should be able to recreate characteristics and phenomenon observed in the processing and experience of pain for it to be useful. In order to validate that this is the case, we formulated the following hypotheses based on the underlying knowledge of the neurophysiology of nociceptive transmission. These are characteristics that have also been recreated in various previous models of pain signal integration:

- Stimulation of innocuous fibers should elicit a response in innocuous interneurons proportional to the input frequency. Under normal circumstances, this should not result in pain regardless of stimulation intensity [18,42] (previously recreated in models [9,13])
- Stimulation of nociceptive fibers should elicit a response in nociceptive interneurons proportional to the input frequency. Meanwhile, innocuous afferent input should lead to increased activity in the inhibitory interneurons, which in turn will have an inhibitory effect on the nociceptive (and to a certain extent also the innocuous)

interneurons. Thus, stronger innocuous afferent activity should correspond to reduced nociceptive output [10,12,18] (previously recreated in models [9,13])

- There exist states of prolonged pain or pain arising seemingly by no stimulation (*e.g.*, phantom limb pain or complex regional pain syndrome) [27,29,36] (previously recreated in model [7]). Increased connection strength within the nociceptive interneurons can yield such a state of persistent pain and a disproportionately large pain response.
- Aberrant connections from innocuous afferents to the nociceptive interneurons can lead to allodynia (innocuous stimulation perceived as painful) [41,46]. The (un)pleasantness of allodynia should follow a U-shape, as described by Löken et al. [20].

Results

In Figure 3, we illustrate the connection strengths for the rate-based model. Recall that the rate-based model does not define the size of the different neuron populations, thus the connection strengths between populations are a compound value of the number of synaptic connections and the strength of each synapse. Values for the connection strengths were tuned to give input-output curves similar to those observed in experiments [35], while keeping in mind that the experiments used injected currents rather than peripheral stimulation as input. We acknowledge that this set of weights is not a unique solution. It is likely that are many different combinations of values that result in the same or similar behavior in the model. In the simulations below we explore how variations of some of these connection strengths impact the output of the model.

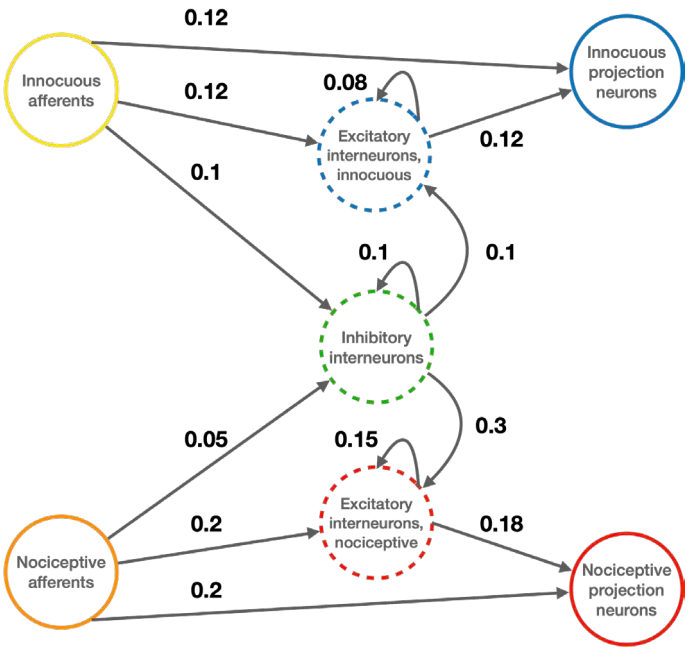

Figure 3. ***Connection strengths for the rate-based model.*** *Note that each connection represents a compound value of the number of synaptic connections and the strength of each synapse.*

Dynamical system analysis

A common approach to analyzing a dynamical system of coupled differential equations is to examine the phase plane. This tells us about how the dynamics of the neuron populations depend on each other. Here, we are particularly interested in the dynamics of the nociceptive projection neurons, as their activity are the output of the model. From inspection of Equation *(4)*, it can be noted that the activity in the nociceptive projection neurons is a monotonically increasing function of the activity in the nociceptive afferents and the nociceptive responsive interneurons. Furthermore, from Equation *(1)* we know that the nociceptive responsive interneurons also receive input from the afferent nociceptive neurons, as well as from the inhibitory interneurons. However, here the nociceptive afferents and the inhibitory interneurons have opposite influence, yielding more complex dynamics. To study these dynamics further, we examined the r_E^{noci}-r_I phase plane to determine how the nociceptive responsive and inhibitory interneurons interact for different combinations of input. As similar dynamics apply to the innocuous responsive interneurons as for the nociceptive responsive interneurons (with the only difference being the parameter values), hereafter we dropped the *noci* and *innoc* superscripts to simplify notation.

By studying nullclines, vector fields, and fixed points of the system, a few key observations can be made. Fixed points of the system correspond to firing frequencies of the interneurons (r_E^*, r_I^*) such that $\frac{dr_E}{dt} = \frac{dr_I}{dt} = 0$. The stability of a fixed point is given by the eigenvalues of the Jacobian matrix:

$$J = \begin{bmatrix} \frac{\partial}{\partial r_E}\frac{dr_E}{dt} & \frac{\partial}{\partial r_E}\frac{dr_I}{dt} \\ \frac{\partial}{\partial r_I}\frac{dr_E}{dt} & \frac{\partial}{\partial r_I}\frac{dr_I}{dt} \end{bmatrix} \text{ evaluated at the fixed point } (r_E^*, r_I^*).$$

Fixed points are stable if the real part of the eigenvalues are negative. In this system, a stable fixed point (r_E^*, r_I^*) corresponds to the firing rates r_E^* of the nociceptive responsive interneurons and r_I^* of the inhibitory interneurons that the populations converge over time (given that the afferent inputs r_A^{noci} and r_A^{innoc} are constant).

Nullclines are the lines in the r_E-r_I phase plane where $\frac{dr_E}{dt} = 0$ and $\frac{dr_I}{dt} = 0$. It follows that fixed points are found at the intersection of nullclines. In general, the r_E-r_I system has one stable fixed point. One can particularly note that if the inputs are r_A^{noci} = r_A^{innoc} = 0, then the fixed point is $r_E^* = r_I^* = 0$, which is to be expected in the context of somatosensation (no afferent input should correspond to no activity in dorsal horn interneurons).

Observation # 1 — In general, the system has one stable fixed point for each pair of inputs. In particular, for input r_A^{noci} = r_A^{innoc} = 0 the stable fixed point is $r_E^* = r_I^* = 0$.

By examining how the different synaptic connections impact the system, one can note that for certain values of the connection strength w_{EE}^{noci} additional fixed points for the nociceptive responsive interneurons. Figure 4 shows examples of nullclines and fixed points for different values of w_{EE}^{noci} and for inputs r_A^{noci} = r_A^{innoc} = 0Hz.

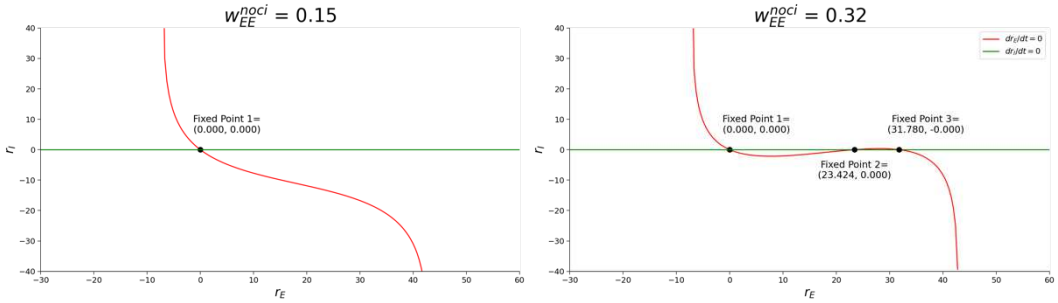

Figure 4. ***Nullclines.*** *Example nullclines for different values of w_{EE}^{noci} (left: w_{EE}^{noci} =0.1, right $w_{EE}^{noci} = 0.32$) and for inputs r_A^{noci} = r_A^{innoc} = 0Hz.*

As long as $w_{EE}^{noci} < 4/af^{max}$ there exist only one (stable) fixed point of the system for each combination of inputs $\left(r_A^{noci}, r_A^{innoc}\right)$. For $w_{EE} > 4/af^{max}$ additional fixed points may arise. In particular, for w_{EE}^{noci} large enough, there exist fixed points where $r_E^* > 0$ even though both inputs are 0, see the right panel in Figure 4.

Observation # 2 For certain values of w_{EE}^{noci} there exist stable fixed points such that $r_E^{noci} > 0$ even when the inputs are 0.

Simulations

We started by examining the first hypothesis by applying different frequencies of innocuous afferent input (10, 30, 50, 70, 90 Hz in Figure 5 left inset) and nociceptive (5, 15, 25, 35, 45 Hz in Figure 5 right inset). The difference in frequency range of the afferent input is motivated by reported differences in innocuous and nociceptive primary afferents [24,39]. As hypothesized, innocuous input yielded innocuous output and no nociceptive output, regardless of intensity. Similarly, nociceptive input yielded nociceptive output and no innocuous output. The nociceptive responsive neurons gave a stronger response to lower input frequencies than the corresponding innocuous responsive neurons, as one might expect in the biological system. This could reflect the contribution of NMDA receptors on the second order nociceptive responsive neurons, which are typically not present on the innocuous responsive neurons [5,45].

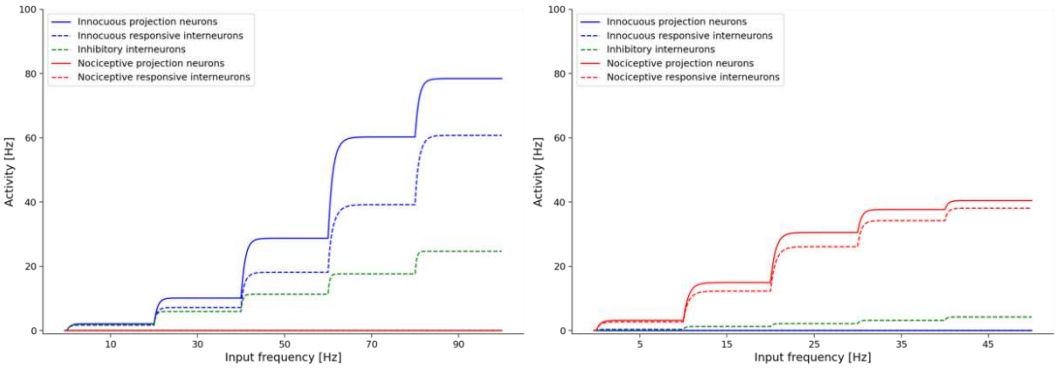

Figure 5. ***Model response to separate innocuous and noxious input****. Simulation results for application of different frequencies of afferent innocuous and noxious input.*

By applying simultaneous innocuous and noxious input one can note that increased noxious input leads to increased activity in the nociceptive responsive neurons, while increased innocuous activity reduces the activity in that same population. This is in accordance with the

second hypothesis and is demonstrated in Figure 6 and Figure 7.

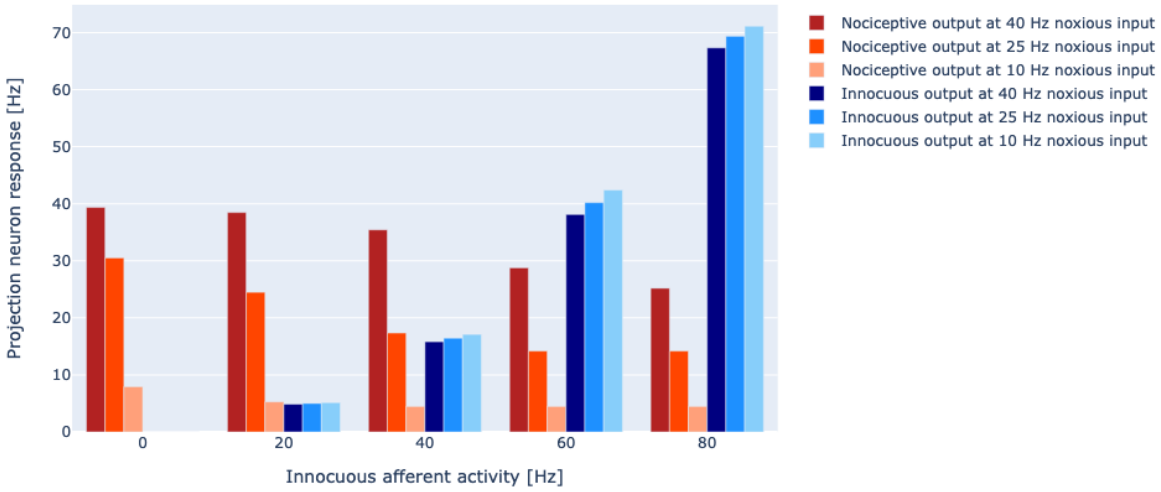

Figure 6. ***Model response to simultaneous innocuous and nociceptive input, bar graph.*** *Increased nociceptive input leads to an increased nociceptive output. Increased innocuous input correspondingly increases the innocuous output but reduces the nociceptive output.*

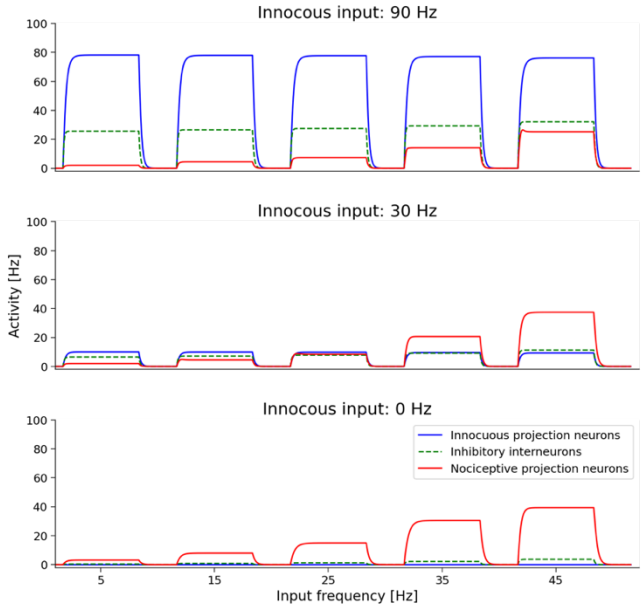

Figure 7. ***Model response to simultaneous innocuous and noxious input, simulation.*** *Increased noxious input leads to an increased response in nociceptive responsive interneurons, while increased innocuous input reduces the response of the nociceptive responsive interneurons*

Figure 7 also exemplifies Observation # 1, that the firing rates of the neurons converge to a fixed point of steady-state firing for constant input.

Next, we examined the third hypothesis, in which increased connection strength within the nociceptive interneurons can yield a state of persistent pain and a disproportionately large

pain response. Figure 8 demonstrates how the rate-based model responds to short pulses of noxious input (100, 250 and 500 ms at 25 Hz) with and without tonic innocuous input at 30 Hz, both in the original state where $w_{EE}^{noci} = 0.15$, and in a state where the recurrent connection of the nociceptive responsive interneurons has been increased to $w_{EE}^{noci} = 0.32$.

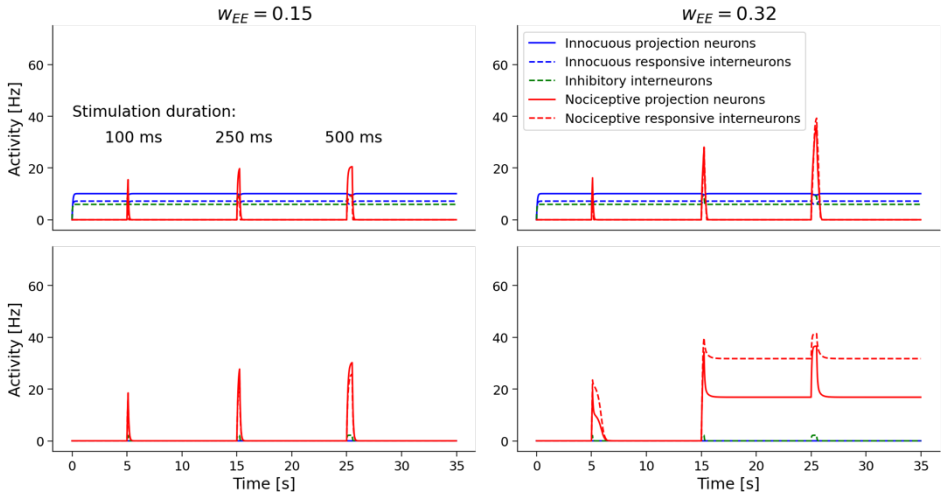

Figure 8 ***Model response upon strengthened recurrent connection****, w_{EE}^{noci}. Left: response to short pulses of noxious input (100 ms, 250 ms and 500 ms at 25 Hz) with and without tonic innocuous input at 30 Hz. Right: same as in the left figure, but with the recurrent connection in the nociceptive responsive interneurons increased to $w_{EE}^{noci} = 0.32$ (originally $w_{EE}^{noci} = 0.15$)*

For the original configuration ($w_{EE}^{noci} = 0.15$) the system responds to pulses of noxious input as one would expect: the activity in the interneurons increases during the application of the stimuli and immediately declines back to zero when the stimuli dissipate. The response is slightly larger in amplitude in absence of tonic innocuous input, due to the reduced input to the inhibitory interneurons. When the recurrent connections within the nociceptive responsive interneurons are strengthened ($w_{EE}^{noci} = 0.32$), the response to the noxious input pulses increases. This exaggerated response to noxious stimuli could play a role in hyperalgesia. When there is no tonic innocuous input that contributes to the inhibition of the nociceptive responsive interneurons, and when the pulses of input are long enough, the nociceptive interneurons converge to a state high frequency firing and stay in the steady state even when the input dissipates. This corresponds to Observation # 2, where the interneurons are in a state of persistent firing even in the absence of input and could correspond to certain forms of chronic and neuropathic pain conditions such as phantom limb pain or complex regional pain syndrome.

An additional observation that can be made is that the state of persistent firing in the nociceptive responsive interneurons can be "reset" by applying an innocuous stimuli. This is demonstrated in Figure 9.

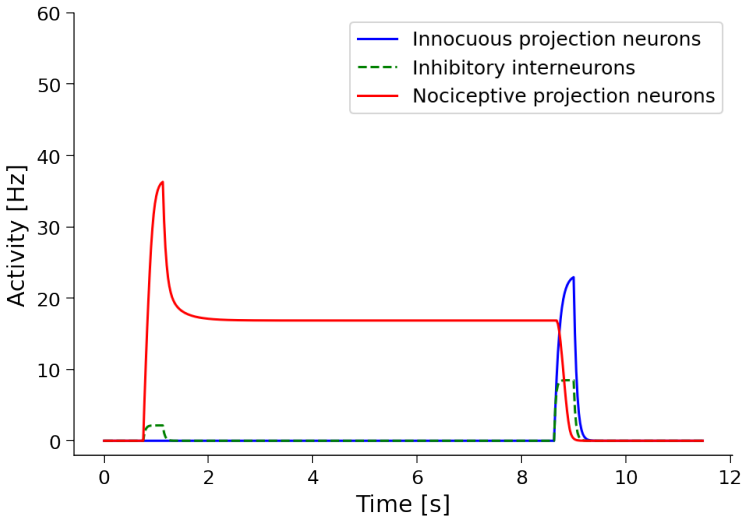

Figure 9. ***Persistent activity reset****. The state of persistent firing resulting from increased recurrent connection strength in the nociceptive responsive interneurons can be "reset" by applying a short pulse of innocuous input (250 ms at 40 Hz)*

Finally, we consider the fourth hypothesis, in which aberrant connections from innocuous afferents to the nociceptive interneurons can lead to allodynia. Sprouting of innocuous afferents has been hypothesized to happen after nerve injury [4,8,16,32], possibly strengthening the original connections from the innocuous afferents to the inhibitory interneurons, and creating new, aberrant connections with the nociceptive responsive interneurons or unmasking previously existing but silent connections [28,46]. Thus, we examine the model when the connections from the innocuous afferents to the inhibitory interneurons have been strengthened ($w_{IA}^{innoc} = 0.2$) and when a new connections have been made to the nociceptive responsive interneurons ($w_{EA}^{innoc\ to\ noci} = 0.18$). The new and altered connections are highlighted in Figure 10.

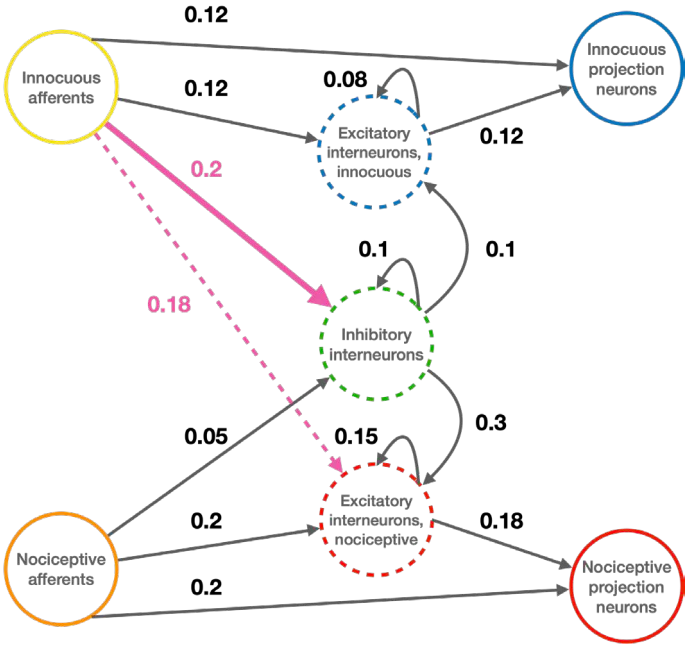

Figure 10. ***Modified model outline****. Modifications of the model such that it demonstrates properties characteristic of allodynia include aberrant connections from the innocuous*

afferents to the nociceptive responsive interneurons (pink, dashed) and strengthened connection from the innocuous afferents to the inhibitory interneurons (thicker, pink).

As might be expected, applying innocuous input to this model induces activity in all of the interneuron populations, including the nociceptive responsive neurons. This is exemplified in Figure 11.

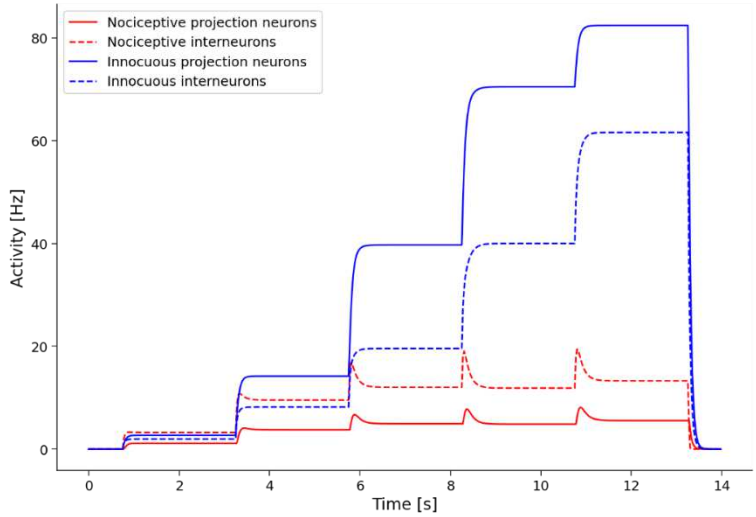

Figure 11. ***Allodynia, simulation results****. The aberrant connections from the innocuous afferents to the nociceptive interneurons lead to innocuous stimuli eliciting a nociceptive response.*

By arbitrarily defining pleasantness as being a weighted sum of the firing rates of the innocuous and nociceptive responsive interneurons and a threshold, $pleasantness = 0.05 \cdot r_P^{innoc} - 0.2 \cdot r_P^{noci} - 1.8$, a U-shape is obtained, which is similar (but not identical) to the reported pleasantness (or unpleasantness) in allodynia triggered by brush strokes in a study by [20]. In an earlier study, it was reported that the firing rate of innocuous afferents is linearly proportional to the brush velocity [21], thus a rough comparison between the two can be made in Figure 12.

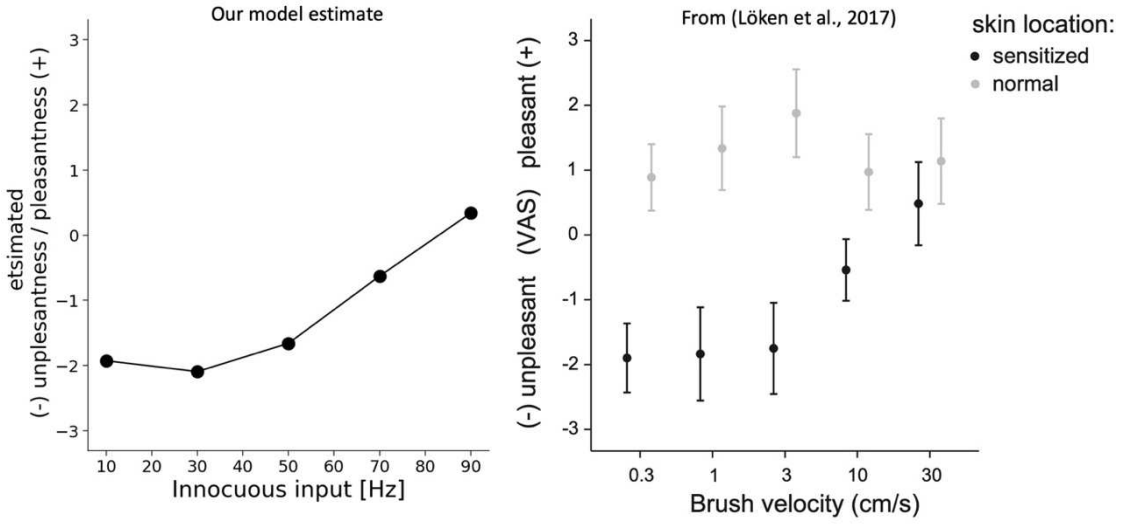

Figure 12. ***Allodynia, comparison with data****. By defining pleasantness as being proportional to a weighted sum of the firing rates of the innocuous and nociceptive responsive interneurons the pleasantness/unpleasantness as a function of input frequency takes on a U-shape, similar to the that reported by* [20] *(input frequency is linearly proportional to brush velocity* [21]*).*

Discussion

Using a relatively simple, yet neurophysiologically grounded model of dorsal horn neural circuits, we have shown several characteristics typically observed in the context of nociceptive pain. In addition, we have examined how modifications of the connections between the neuron populations can give rise to characteristics of certain neuropathic pain conditions such as chronic pain, phantom limb pain, hyperalgesia, and allodynia.

In a 2021 review by Lang *et al.*, the authors examined the field of mathematical and computational models of pain [17]. Thirteen mathematical models were identified. Several of these involve some version of *gate control theory* in the form of population rate-based models of the dorsal horn circuits [9,11,30]. Gate control theory, proposed by Melzack and Wall in 1965 [33], has been undeniably influential in pain research since its proposal in 1965 and has led to many significant discoveries in the field. However, the theory has also received some critique for being based on some neurophysiological implausible assumptions. One main point of concern is that afferent nociceptors are assumed to make inhibitory synapses onto inhibitory interneurons but excitatory synapses onto central transmission neurons. According to *Dale's principle* "the same chemical transmitter is released from all the synaptic terminals of a neuron" [43]. It follows that a neuron should perform the same action (excitation or inhibition) at all its synaptic connections to other cells, and thus, challenging the traditionally proposed structure of the gate control theory.

We found two biophysical models of dorsal horn pain circuits in the *ModelDB* database of neuroscience models [37]. These models assess the mechanisms underlying wind-up under detailed neurobiological constraints [3] and examine the effects of spinal cord stimulation on the dorsal horn network [51]. Another recent model examines changes in network processing in the dorsal horn associated with chronic pain [22]. While these models do capture several aspects of pain signal integration, they are relatively complex and require many assumptions and approximations to be made about the neurophysiology and morphology of the neurons and their connections. Others have attempted to model more physiologically plausible variations of the gating mechanism in the dorsal horn using population rate-based models. Ropero Peláez and Taniguchi developed such a model where the contradictory inhibitory synapses from nociceptive afferents in gate control theory have been exchanged for excitatory synapses [34]. The expected "gating" mechanism is achieved by the combined effect of intrinsic and synaptic plasticity. Crodelle *et al.*, also applied a modified model of the traditionally proposed gating mechanism in the dorsal horn by introducing additional populations of excitatory and inhibitory interneurons [11]. While their model focuses on the "daily rhythm" (variation of pain intensity during the day) of human pain processing, it also reproduces several other phenomena of pain processing (for example wind-up and inhibition of pain by innocuous touch). Their model also gives a possible explanation for shift in daily rhythm in neuropathic pain conditions, where the daily variation in the response of peripheral nociceptive neurons is altered.

As mentioned before, Blohm *et al.*, argued that "the most important rule [is that] the model should always be kept as simple as possible" [6]. We had this rule in mind in our effort to build a simple, yet neurophysiologically grounded model of the integration of noxious and innocuous signals in the dorsal horn of the spinal cord. Our model has commonalities with two previous population rate-based models [11,34], with some key differences. While all three models have similar general structure, with nociceptive and innocuous afferents synapsing onto interneurons and projection neurons, the specific connections differ. In our model, we introduced recurrent connections within the interneuron populations, reflecting the role of excitatory interneurons in driving and enhancing excitation in dorsal horn circuits [28,41,46]. This leads to model predictions in line with hypotheses of the underlying mechanism of allodynia [28,46] and with experimental data on the perceived unpleasantness of brush strokes in capsaicin induced allodynia [20].

The recurrent connections in the excitatory interneuron population play a role in the model prediction of disproportionately large pain response (hyperalgesia) and persistent pain in absence of input (phantom limb pain [27,29,36]). 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 [34]. However, it is unclear what a negative firing threshold corresponds to in neurophysiology.

We made certain simplifications regarding known neurophysiological properties of the neurons involved in this model. For one, we have disregarded the effect of different transmission velocities in primary afferent neurons. The reason for this was in part to keep the model as simple as possible (see [6]), but also due to the fact that the long held belief that nociceptive signals are transmitted by slowly conducting afferents and innocuous touch by fast conducting afferents is starting to unravel. It has been known for a while that pleasant touch is also transmitted by slowly conducting C-fibers [21], and recent studies have revealed the existence of an ultrafast system for signaling pain [25].

An additional simplification we made is the omission descending inhibition and facilitation, which arguably play a key role in modulating pain. Other aspect that are known to play a role in dorsal horn pain circuits are *wind-up* and presynaptic inhibition. These effects are included in the model by Crodelle *et al.*, as well as the daily rhythm of pain [11], and should be relatively straightforward to incorporate into future version of our model. We 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 [4,8,16,32]. In the work by Ropero Peláez and Taniguchi, different forms of plasticity were explored in a similar rate-based model [34]. Incorporating such plasticity in our 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 [22]. This degeneracy in dorsal horn circuit structure, along with our results of how different synaptic connections may relate to pain states such as allodynia and phantom pain, could indicate that some individuals may be predisposed to developing

pathological pain states after injury, even without the above-mentioned sprouting or plasticity.

Our model was not explicitly 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 [15], 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 computational model of the integration of noxious and innocuous input in the dorsal horn.

Acknowledgements

We would like to thank Prof. Johan Wessberg and Dr. Line Löken for the insightful discussions that helped guide us in the development of this model.

This work was supported by the Promobilia Foundation, the IngaBritt and Arne Lundbergs Foundation, and the Swedish Research Council (Vetenskapsrådet).

The authors report no conflict of interest.

References

[1] Abraira VE, Kuehn ED, Chirila AM, Springel MW, Toliver AA, Zimmerman AL, Orefice LL, Boyle KA, Bai L, Song BJ, Bashista KA, O'Neill TG, Zhuo J, Tsan C, Hoynoski J, Rutlin M, Kus L, Niederkofler V, Watanabe M, Dymecki SM, Nelson SB, Heintz N, Hughes DI, Ginty DD. The Cellular and Synaptic Architecture of the Mechanosensory Dorsal Horn. Cell 2017;168:295-310.e19. doi:10.1016/j.cell.2016.12.010.

[2] Adrian ED. Pain and its problems; the physiology of pain. Practitioner 1947;158:76–82.

[3] Aguiar P, Sousa M, Lima D. NMDA Channels Together With L-Type Calcium Currents and Calcium-Activated Nonspecific Cationic Currents Are Sufficient to Generate Windup in WDR Neurons. J Neurophysiol 2010;104:1155–1166. doi:10.1152/jn.00834.2009.

[4] Baker K. Recent advances in the neurophysiology of chronic pain. Emerg Med Australas 2005;17:65–72. doi:10.1111/j.1742-6723.2005.00689.x.

[5] Bennett GJ. Update on the Neurophysiology of Pain Transmission and Modulation: Focus on the NMDA-Receptor. J Pain Symptom Manage 2000;19:2–6. doi:10.1016/S0885-3924(99)00120-7.

[6] Blohm G, Kording KP, Schrater PR. A How-to-Model Guide for Neuroscience. eNeuro 2020;7:ENEURO.0352-19.2019.
[7] Boström KJ, De Lussanet MHE, Weiss T, Puta C, Wagner H. A computational model unifies apparently contradictory findings concerning phantom pain. Sci Rep 2014;4.
[8] Bourne S, Machado AG, Nagel SJ. Basic anatomy and physiology of pain pathways. Neurosurg Clin N Am 2014;25:629–638. doi:10.1016/j.nec.2014.06.001.
[9] Britton NF, Skevington SM. A Mathematical Model of the Gate Control Theory of Pain. 1989.
[10] Casey KL. Toward a Neurophysiology of Pain. Headache J Head Face Pain 1969;8:141–153. doi:10.1111/j.1526-4610.1969.hed0804141.x.
[11] Crodelle J, Piltz SH, Hagenauer MH, Booth V. Modeling the daily rhythm of human pain processing in the dorsal horn. PLOS Comput Biol 2019;15:e1007106. Available: https://doi.org/10.1371/journal.pcbi.1007106.
[12] Godfrey H. Understanding pain, part 1: physiology of pain. Br J Nurs 2005;14:846–852. doi:10.12968/bjon.2005.14.16.19725.
[13] Haeri M, Asemani D, Gharibzadeh S. Modeling of pain using artificial neural networks. J Theor Biol 2003;220:277–284.
[14] Harding EK, Fung SW, Bonin RP. Insights Into Spinal Dorsal Horn Circuit Function and Dysfunction Using Optical Approaches . Front Neural Circuits 2020;14. Available: https://www.frontiersin.org/article/10.3389/fncir.2020.00031.
[15] Kolesar TA, Fiest KM, Smith SD, Kornelsen J. Assessing Nociception by fMRI of the Human Spinal Cord: A Systematic Review. Magn Reson Insights 2015;8:31–39. doi:10.4137/MRI.S23556.
[16] Lamont LA, Tranquilli WJ, Grimm KA. Physiology of Pain. Vet Clin North Am Small Anim Pract 2000;30:703–728. doi:10.1016/S0195-5616(08)70003-2.
[17] Lang VA, Lundh T, Ortiz-Catalan M. Mathematical and Computational Models for Pain: A Systematic Review. Pain Med 2021.
[18] Lee GI, Neumeister MW. Pain: Pathways and Physiology. Clin Plast Surg 2020;47:173–180. doi:10.1016/j.cps.2019.11.001.
[19] Li L, Rutlin M, Abraira VE, Cassidy C, Kus L, Gong S, Jankowski MP, Luo W, Heintz N, Koerber HR, Woodbury CJ, Ginty DD. The functional organization of cutaneous low-threshold mechanosensory neurons. Cell 2011;147:1615–1627. doi:10.1016/j.cell.2011.11.027.
[20] Löken LS, Duff EP, Tracey I. Low-threshold mechanoreceptors play a frequency-dependent dual role in subjective ratings of mechanical allodynia. J Neurophysiol 2017;118:3360–3369. doi:10.1152/jn.00977.2016.
[21] Löken LS, Wessberg J, Morrison I, McGlone F, Olausson H. Coding of pleasant touch by unmyelinated afferents in humans. Nat Neurosci 2009;12:547–548. doi:10.1038/nn.2312.
[22] Medlock L, Sekiguchi K, Hong S, Dura-Bernal S, Lytton WW, Prescott SA. Multiscale Computer Model of the Spinal Dorsal Horn Reveals Changes in Network Processing Associated with Chronic Pain. J Neurosci 2022;42:3133 LP – 3149. doi:10.1523/JNEUROSCI.1199-21.2022.
[23] Melnick I V, Santos SFA, Safronov B V. Mechanism of spike frequency adaptation in substantia gelatinosa neurones of rat. J Physiol 2004;559:383–395. doi:https://doi.org/10.1113/jphysiol.2004.066415.
[24] Muniak MA, Ray S, Hsiao SS, Dammann JF, Bensmaia SJ. The Neural Coding of

Stimulus Intensity: Linking the Population Response of Mechanoreceptive Afferents with Psychophysical Behavior. J Neurosci 2007;27:11687 LP – 11699. doi:10.1523/JNEUROSCI.1486-07.2007.
[25] Nagi SS, Marshall AG, Makdani A, Jarocka E, Liljencrantz J, Ridderström M, Shaikh S, O'Neill F, Saade D, Donkervoort S, Reghan Foley A, Minde J, Trulsson M, Cole J, Bönnemann CG, Chesler AT, Catherine Bushnell M, McGlone F, Olausson H. An ultrafast system for signaling mechanical pain in human skin. Sci Adv 2019;5.
[26] Neuromatch Academy. Tutorial 2: Wilson-Cowan Model. 2021.
[27] Ortiz-Catalan M. The stochastic entanglement and phantom motor execution hypotheses: A theoretical framework for the origin and treatment of Phantom limb pain. Front Neurol 2018;9.
[28] Peirs C, Williams S-PG, Zhao X, Walsh CE, Gedeon JY, Cagle NE, Goldring AC, Hioki H, Liu Z, Marell PS, Seal RP. Dorsal Horn Circuits for Persistent Mechanical Pain. Neuron 2015;87:797–812. doi:10.1016/j.neuron.2015.07.029.
[29] Di Pino G, Piombino V, Carassiti M, Ortiz-Catalan M. Neurophysiological models of phantom limb pain: what can be learnt. Minerva Anestesiol 2021;87.
[30] Prince K, Campbell J, Picton P, Turner S. A computational model of Acute Pain. Artic Int J Simul Syst Sci Technol 2005. Available: https://www.researchgate.net/publication/226674243.
[31] Ramne M, Elam M, Löken LS, Ortiz-Catalan M. Neurophysiology of pain for non-neurophysiologists: a systematic review [In review]. 2022.
[32] Romanelli P, Esposito V. The functional anatomy of neuropathic pain. Neurosurg Clin N Am 2004;15:257–268. doi:10.1016/j.nec.2004.02.010.
[33] Ronald M, D. WP. Pain Mechanisms: A New Theory. Science (80-) 1965;150:971–979. doi:10.1126/science.150.3699.971.
[34] Ropero Peláez FJ, Taniguchi S. The Gate Theory of Pain Revisited: Modeling Different Pain Conditions with a Parsimonious Neurocomputational Model. Neural Plast 2016;2016:4131395. doi:10.1155/2016/4131395.
[35] Ruscheweyh R, Sandkühler J. Lamina-specific membrane and discharge properties of rat spinal dorsal horn neurones in vitro. J Physiol 2002;541:231–244. doi:https://doi.org/10.1113/jphysiol.2002.017756.
[36] Schone HR, Baker CI, Katz J, Nikolajsen L, Limakatso K, Flor H, Makin TR. Making sense of phantom limb pain. J Neurol Neurosurg & Psychiatry 2022;93:833 LP – 843. doi:10.1136/jnnp-2021-328428.
[37] Shepherd Lab YU. ModelDB. 2022.
[38] Simone DA, Sorkin LS, Oh U, Chung JM, Owens C, LaMotte RH, Willis WD. Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 1991;66:228–246. doi:10.1152/jn.1991.66.1.228.
[39] Slugg RM, Meyer RA, Campbell JN. Response of Cutaneous A- and C-Fiber Nociceptors in the Monkey to Controlled-Force Stimuli. J Neurophysiol 2000;83:2179–2191. doi:10.1152/jn.2000.83.4.2179.
[40] Sluka KA, Rees H, Chen PS, Tsuruoka M, Willis WD. Inhibitors of G-proteins and protein kinases reduce the sensitization to mechanical stimulation and the desensitization to heat of spinothalamic tract neurons induced by intradermal injection of capsaicin in the primate. Exp Brain Res 1997;115:15–24. doi:10.1007/PL00005675.
[41] Smith KM, Browne TJ, Davis OC, Coyle A, Boyle KA, Watanabe M, Dickinson SA,

Iredale JA, Gradwell MA, Jobling P, Callister RJ, Dayas C V, Hughes DI, Graham BA. Calretinin positive neurons form an excitatory amplifier network in the spinal cord dorsal horn. Elife 2019;8:e49190. doi:10.7554/eLife.49190.
[42] Sneddon LU. Comparative physiology of nociception and pain. Physiology 2018;33:63–73. doi:10.1152/physiol.00022.2017.
[43] Strata P, Harvey R. Dale's principle. Brain Res Bull 1999;50:349–350. doi:https://doi.org/10.1016/S0361-9230(99)00100-8.
[44] Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci 2010;11:823–836. doi:10.1038/nrn2947.
[45] Usunoff KG, Popratiloff A, Schmitt O, Wree A. Functional Neuroanatomy of Pain. 1st ed. Simon Rallison, editor Berlin: Springer, Heidelberg, 2006 doi:10.1007/3-540-28166-5.
[46] Warwick C, Salsovic J, Hachisuka J, Smith KM, Sheahan TD, Chen H, Ibinson J, Koerber HR, Ross SE. Cell type-specific calcium imaging of central sensitization in mouse dorsal horn. Nat Commun 2022;13:5199. doi:10.1038/s41467-022-32608-2.
[47] Weddell G, Sinclair DC. The anatomy of pain sensibility. Acta Neuroveg (Wien) 1953;7:135–146. doi:10.1007/BF01227053.
[48] Willis WD. Neurophysiology of nociception and pain in the spinal cord. Res Publ Assoc Res Nerv Ment Dis 1980;58:77–92.
[49] Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. J Clin Neurophysiol 1997;14:2–31. doi:10.1097/00004691-199701000-00002.
[50] Willis WDJ. Dorsal Horn Neurophysiology of Paina. Ann N Y Acad Sci 1988;531:76–89. doi:https://doi.org/10.1111/j.1749-6632.1988.tb31815.x.
[51] Zhang TC, Janik JJ, Grill WM. Modeling effects of spinal cord stimulation on wide-dynamic range dorsal horn neurons: influence of stimulation frequency and GABAergic inhibition. J Neurophysiol 2014;112:552–567. doi:10.1152/jn.00254.2014.