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ORIGINAL RESEARCH

A Pluripotent Progression of the Gate Control System Theory of Pain – Modeling Ascending & Descending Pain Pathways as a Lotka-Volterra Coupled Control & Feedback Loop

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Introduction: Pain is a subjective experience, the perception of stimulus input transmitted by neurons that respond to real or perceived tissue injury and propagate the information to the brain. Under normal conditions, the perception is a reliable indicator of the magnitude and duration of the sensory input (viz. threat), so that appropriate action can be taken (eg, fight-or-flight). Two pathways have been recognized: "ascending pathways" mediating sensory input→perception and "descending pathways" mediating perception→response. Interactions between the two are increasingly appreciated, ie, ascending signals often modulated by descending ones. Our thesis is that there is an interactive feedback loop that allows pain to be modeled as a control system (with a postulated thermostat-analogous "nocistat") and that such an undertaking could lead to better understanding of pain dynamics, and ultimately to recommendations for better pain treatment.

Methods: We here introduce a system-theoretical approach, based on the well-known Lotka-Volterra dynamics, to describe ascending and descending pain pathways as a coupled control and feedback loop. The resulting model is mathematically represented by a system of coupled differential equations with a non-linear interaction term, and poses a pluripotent progression of the Gate Control System Theory to a macroscopic, clinically applicable view of pain and its mitigation through modulation.

Results: We present preliminary, qualitative simulation results for a variety of sensory inputs (ie, pain stimuli) that are inspired by clinical pain conditions. These comprise, but are not limited to, sudden onset of (1) constant pain stimulus; (2) exponentially decaying pain stimulus; (3) linearly decaying pain stimulus; (4) exponentially increasing pain stimulus; and (5) linearly increasing pain stimulus.

Discussion: The introduced coupled control and feedback loop model is accessible and readily extensible, while mathematically rigorous, to approximate clinical findings more realistically, both qualitatively and quantitatively, the latter taking advantage of the fitting parameters in the model.

Keywords: ascending and descending pain pathways, feedback loop, control system, Lotka-Volterra coupling, system theory, differential equation, gate control system theory

Introduction

The "ascending" pain stimulus pathways have been described since ancient times.[1] Noxious stimuli activate, in a modality-, magnitude-, and rate-dependent manner, detectors ("nociceptors") of existing or pending tissue damage.[2,3] Nociceptors transduce (convert) the chemical signal (ions, prostaglandins, etc.) into an electrochemical signal transmitted via neurons.[4] Peripheral signals are transmitted to the dorsal horn of the spinal cord by primary afferents and then by ipsi- and contralateral tracts to higher processing centers where perception occurs.[5,6] More recent research has revealed the important contributions of "descending" modulating pathways and neurotransmitter systems to the overall phenomenon of pain.[7,8] The involvement of brainstem and midbrain structures was recognized when electrical stimulation of nuclei

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such as the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), which receives relay neuronal input from the PAG, produces analgesia.[9,10] Diffuse bilateral projections emanate from the RVM and terminate at multiple levels in the brainstem and dorsal horn of the spinal cord and there impinge on neurons of the ascending pathways.[11–13] Neurotransmitters in these projections (eg, norepinephrine and serotonin, etc.) affect nociceptive neurons in the dorsal horn, and thereby modulate nociception.

There are descending mechanisms that can amplify as well as attenuate incoming sensory input.[14] This capability derives from two types of RVM neurons: "OFF-cells" (cease firing during responses to noxious stimuli), which exert a net inhibitory effect on nociceptive transmission, and "ON-cells" (activated during responses to noxious stimuli), which have a net pro-nociceptive action.[15,16] The reciprocal action of ON and OFF cells at the level of the dorsal horn of the spinal cord modulates nociceptive transmission.

It seems intuitive that the ascending and descending pathways could not function properly if they acted as independent countercurrent pathways. Instead, to function in a controlled manner, we hypothesize that they must be connected (via links not yet fully elucidated) in a coordinated well-controlled feedback loop. This concept, which leads naturally to the extrapolation that pain can therefore be modeled as a control system, was introduced along with the introduction postulation of an overarching "nocistat" (analogous to a thermostat), for the first time to our knowledge, in a previous presentation.[17]

Brief Review of Current State-of-the-Art: Gate Control System Theory

In 1965, Melzack and Wall[18] introduced their now famous and influential *gate control system* theory in order to address the opposing strengths and weaknesses of the then extant major theories of pain known generally as *specificity theory* and *pattern theory* (reviewed by Moayedi and Davis[19]). A major contribution of the *gate control system* (GCS) theory is the inclusion of modulation of input at the spinal cord and the inclusion of "central control" mechanisms that project back to the GCS. The "central component" of the GCS closed a feedback loop through descending efferent fibers. Specifically, "… stimulation of the brain activates descending efferent fibers[20] which can influence [ascending] afferent conduction at the earliest synaptic levels of the somesthetic system". The balance between sensory facilitation and central inhibition was proposed to be the reason for the inter- and intra-variability of pain perception, and the influence on pain response and perception by "psychological factors" such as past experience, attention, and emotion.

Melzack and Wall present a schematic diagram of the GCS theory in their publication[18] (shown here as Figure 1A), in which the central control component is included, albeit the concept of a pain center in the brain is disparaged as "pure fiction", unless the whole brain is considered as the pain center – a distributive-system view that is now generally accepted.[21,22] Their schematic looks like the beginning of a modern control-systems representation (discussed later below).

In the intervening years since publication of the GCS, multiple more mathematical or computational models for pain have been proposed. The comprehensive review by Lang et al[25] identified more than thirty attempts for characterizing pain in this manner. They reported that most of the publications utilized "… machine learning algorithms to identify the presence or absence of pain, rather than to explore features of pain that may be used for diagnostics and treatment". The publications attempted to incorporate detailed physiological mechanisms such as ion channel operation, synapse physiology, axonal conduction velocity, etc. to pain – but it is probably fair to say that the detailed and advanced mathematics is somewhat obtuse for most readers, and that the clinical applicability is not made clear for most health-care providers.

Two of the 31 publications reviewed by Lang et al[25] were based on schematic diagrams that are adaptations of the original GCS, and addressed acute pain (with discussion of potential applicability to other pain types). The first, by Britton and Skevington,[23] casts the GCS in mathematical terms and was the first to use the GCS to explain a quality of pain. Of note, in their schematic (shown here as Figure 1B) the "Cognitive Control" is uncoupled from influence on the descending inhibitory control (except as it is summed at the substantia gelatinosa of the spinal cord). In the effort to make the model more amenable to a mathematical overlay, this important feature of the original GCS is unfortunately lost. The model is also stated in pure mathematical terminology, such as lemmas, bounded functions, and monotonicity properties.

The second of the two publications, by Prince et al,[24] states that it uses the model of Britton and Skevington, and that one of its goals is "… to produce a more biologically plausible model that can be used for further applications". Thus, it

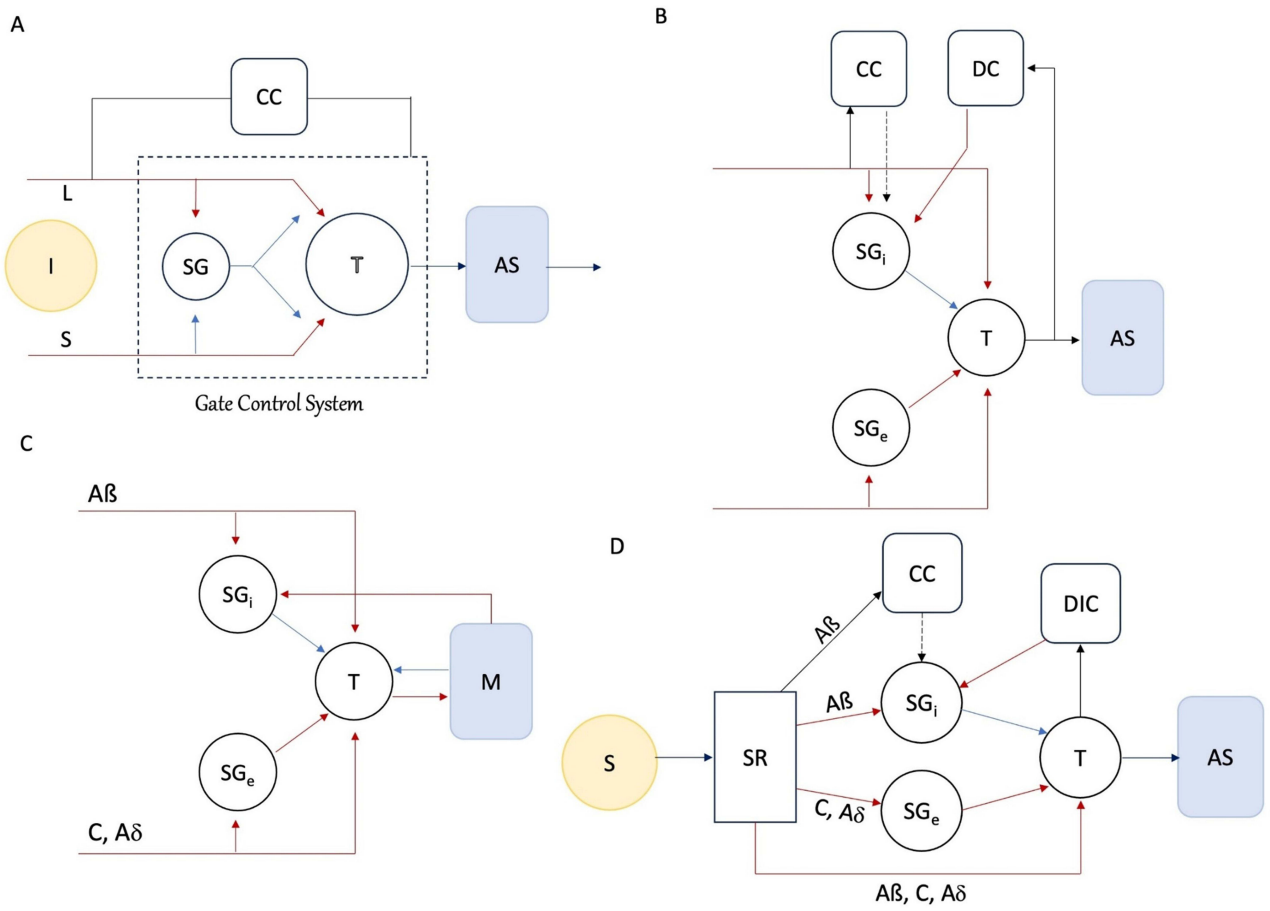

Figure 1 Schematic diagrams of the original gate control theory and adaptations.

Notes: (**A**) Schematic diagram of the gate control theory after.[18] Red lines represent excitatory influence, blue lines represent inhibitory influence. (**B**) Schematic diagram after.[23] Red lines represent excitatory influence, blue lines represent inhibitory influence, dotted line can be excitatory or inhibitory. (**C**) Schematic diagram after.[24] Red lines represent excitatory influence, blue lines represent inhibitory influence. (**D**) Schematic diagram after.[25] Red lines represent excitatory influence, blue lines represent inhibitory influence, dotted line can be excitatory or inhibitory.

Abbreviations: (**A**) I, input; L, large-diameter fibers; S, small-diameter fibers; SG, substantia gelatinosa; T, first central transmission cells; CC, central control; AS, action system. (**B**) SG_i, substantia gelatinosa-inhibitory; SG_e, substantia gelatinosa-excitatory; T, transmission cells; DC, descending inhibition; CC, cognitive control; AS, action system. (**C**) Aß, C, Aδ, afferents; SG_i, substantia gelatinosa-inhibitory; SG_e, substantia gelatinosa-excitatory; T, transmission cells; M, midbrain. (**D**) S, stimulus; SR, skin receptors; Aß, C, Aδ, afferents; SG_i, substantia gelatinosa-inhibitory; SG_e, substantia gelatinosa-excitatory; CC, cognitive control; DIC, descending inhibitory control; T, transmission unit; AS, action system.

minimizes the prior publication, and further, the schematic diagram explicitly eliminates Cognitive Control altogether (shown here as Figure 1C). So, unfortunately in an effort to be mathematically tractable, it is less comprehensive.

The stated goal of all of the 31 publications was *clinical applicability*. But based on the intervening years since, one might be forgiven for suggesting that this praiseworthy goal has not yet been realized. We posit that a possible explanation is that the models are hampered by being too detailed at the expense of being less practical for the clinician. An analogy might be the superior practical ability of the *ideal gas equation* to describe the relationship between the measurable macroscopic observables (ie, pressure, temperature, and volume) rather than microscopic, ab-initio quantum mechanical derivations to explain macroscopic gas behavior; or the practicality of control system engineering modeling of *temperature control of room temperature*, rather than a detailed, microscopic description of the gauge or impedance of the wiring of the heating or cooling equipment.[26] From a physics/modeling point-of-view, the general guiding principle of modeling should be that of *being as simple as possible and as complicated as necessary*, all the while being adequate enough to accomplish the end goal, ie, in our case practicality for the clinician.

We herein take the next logical step in the development of the GCS: the formal modeling of the GCS in control-systems terms. Counter to Britton and Skevington[23] and Prince et al,[24] we retain the Central Control

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concept of the GCS – with the best schematic being that from Lang et al,[25] shown here as Figure 1D – and we incorporate a logical equivalent of a thermostat (a "nocistat") into the model (specifically differentiated from the outdated concept of a brain pain center). It follows from such an analysis – and differentiates it from previous models – that there is a basal level of "pain-monitoring" by the nocistat for the purpose of fidelity of signal detection and transmission, just as there is the basal spontaneous release of a small amount of neurotransmitters from presynaptic sites for the purpose of fidelity of signal detection and transmission.[27]

Some Other Approaches to Modeling Pain

Other approaches to model pain comprise approaches with: (1) varying levels of detail, ie, ranging from modeling the cellular and molecular basis of noxious stimuli processing, individual neuronal behavior and neural circuits (eg, Britton and Skevington (1989)),[23] to macroscopic capabilities/descriptions of the nervous system; (2) realism/plausibility; as well as (3) clinical relevance/applicability.

For example, Britton and Skevington (1996)[28] shed light on the various levels of pain modeling, ranging from molecular, cellular, to large neural networks. Argüello et al (2015)[29] critically examine the limited impact of computational models in pain research. The authors argue that traditional models often lack biological plausibility, fail to produce clinically relevant outcomes, and cannot capture the stochastic nature of neural dynamics. They suggest that these limitations may stem from the inherent challenges in modeling the subjective experience of pain and advocate for the development of more biologically grounded and clinically applicable models, eg, by incorporating biophysical and physiological features, to enhance their utility in understanding and treating pain.

Possible explanations for the limited applicability of computational pain models, especially in the clinical context, include the lack of neuroanatomical evidence or the stochastic nature of neurons and neuronal firing in pain models, as pointed out, eg, in Argüello et al (2015)[29] and in Picton et al (2001).[30] Picton et al emphasize the importance of developing models that not only predict pain but also offer explanatory insights into its complex nature. An example of a physiologically more realistic, computational pain model, providing a unified explanation for phantom pain phenomena, is introduced by Böstrom et al (2014),[31] simulating spontaneous neural activity in sensory pathways using a Kohonen self-organizing map approach. Another example is provided by Argüello-Prada and Gómez (2024)[32] that describes a computational pain model – implemented on an Arduino microprocessor for pedagogical/educational purposes – that includes ascending/descending pathways.

Our Approach

Our approach does not aim at modeling pain by itself but tries to elucidate the interplay between pain and its time-delayed modulation from a phenomenological point-of-view, ie, resulting pain perception. The analogy to the ideal gas equation example above holds: applied to the modeling of ascending and descending pain pathways and associated modulation, it is the pain and its relief due to modulation that are relevant for and experienced by the patient, and not the individual neuronal action or cellular and molecular basis of noxious stimuli processing. A medical analogy for this is, for example, visual perception/performance: while Optical Coherence Tomography (OCT) tells a lot about the physiology and anatomy of the retina and its potential disease state (eg, macular degeneration), it tells little about the resulting visual performance, which is ultimately what is relevant to the patient.

We introduce in the following the basic concepts of control system analysis design and its potential application to pain signaling and analgesia. It is our thesis that the ascending and descending pathways do not function independently, but instead form a feedback loop that allows retention of protective detection of pain while avoiding excess, prolonged (chronification), or pathophysiologic pain.[33–35] We are developing the control system approach to model normal physiologic and abnormal pathophysiologic pain-processing conditions and to a variety of perplexing clinical phenomena. Ongoing extension of the model introduced here will allow us to evaluate the influence of various normal and abnormal endogenous and exogenous inputs. The ultimate goal of this work is to guide improved pain treatment by identifying optimal intervention points and/or strategies.

Methods

Figure 2 shows schematically the motivation (Figure 2, left) for a simple coupled control and feedback loop system to model the influence of a sensory input (ie, pain stimulus) on the pain perception and pain modulation (Figure 2, right). Figure 2, right in particular shows the ascending pathway from the sensory input to the pain perception, as well as the descending pathway from the pain perception to the pain modulation, which in turn influences the ascending pathway from the sensory input to the pain perception, eg, in a mitigating fashion.

To model mathematically this coupled control and feedback loop system, based on previous applications of control system design to other sensory input processes[36,37] and Lotka-Volterra predator-prey interaction models,[38–42] we introduced three time-dependent, interacting variables: sensory input (ie, pain stimulus) *S(t)*, pain perception *P(t)*, and modulation *M(t)*. These variables can be thought of as concentrations or intensities in arbitrary units for the following discussion. As such, it is assumed that *S(t), P(t)*, and *M(t)* are greater or equal to 0, ie, in particular non-negative. In the following, it is important to note that the time profile of the sensory input *S(t)* is directly modeled a priori, ie, no differential equations are necessary to describe the time change of *S(t)*. Example Sensory Input Modeling for Future Clinical Applications below provides a detailed discussion of example sensory input functions *S(t)* tested.

Originally, Lotka-Volterra models have been widely used in ecology to understand the underlying dynamics of predator-prey relationships and how species interact within an ecosystem. These models are mathematically represented by systems of differential equations that predict how the populations of typically two (sometimes more) interacting species change over time. Of particular importance – and rendering these models so powerful – are the non-linear coupling terms between these interacting species, which turn the differential equations into highly coupled differential equations. The main contribution and novelty of our approach is applying the Lotka-Volterra population dynamics to the modeling of the relationship and interaction between pain and modulation, since this relationship and interaction exhibit time-delayed interconnectedness and cyclical fluctuations. As such, using Lotka-Volterra dynamics as the basis for the ascending-descending pathway pain model proposed by us is a well-founded and well-understood approach both mathematically and modeling wise.

Pain Sensation to Perception

The time change of pain perception *P(t)*, ie, the pain perception rate $\frac{dP(t)}{dt}$, was at first modeled without any coupling to the modulation *M(t)* as the following 1st-order linear differential equation:

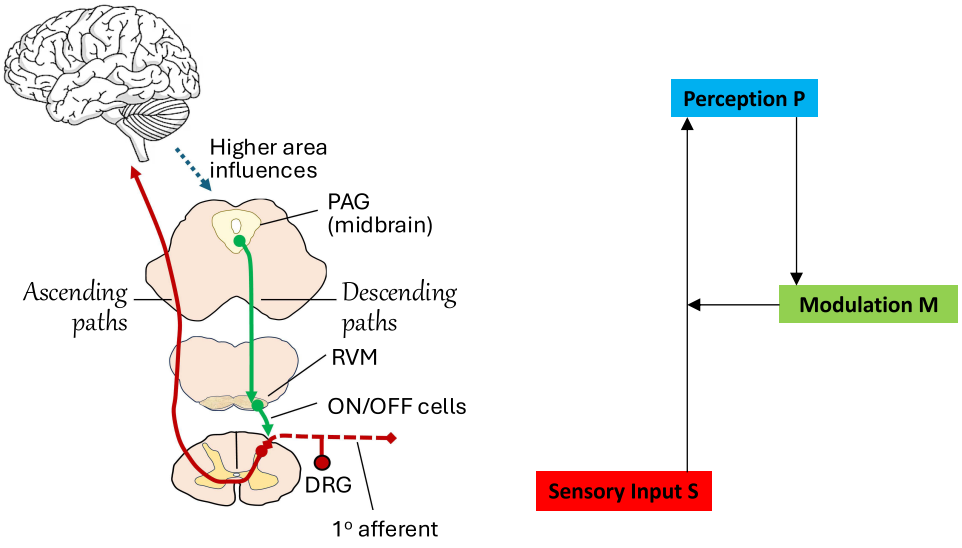

Figure 2 Representation of integrated pain pathways in an elementary control system diagram.
Notes: Left: Nociceptors are activated by painful stimuli and the resultant pain signal is transmitted via 1st-order afferent neurons to the dorsal horn of the spinal cord. 2nd-order neurons transmit the signals in "ascending" tracts from the spinal cord to the brain stem, thalamus and higher regions of the brain. "Descending pathways" (DNIC, diffuse noxious inhibitory controls) modulate (usually attenuate) signals in a modeled coupled control and feedback loop (right).

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$$\frac{dP(t)}{dt} = \varepsilon_p S(t) - \beta_p P(t) \tag{1}$$

with ε_p = upregulation fitting parameter, and β_p = natural decay fitting parameter. Here $\varepsilon_p S(t)$ contributes proportionally to the increase of the pain perception *P(t)* due to the sensory input *S(t)*. Conversely, $-\beta_p P(t)$ is an intrinsic self-decay term, which decreases pain perception *P(t)* proportionally over time.

In a similar fashion, the time change of the pain modulation *M(t)*, ie, the pain modulation rate $\frac{dM(t)}{dt}$, was modeled as the following 1st-order linear differential equation:

$$\frac{dM(t)}{dt} = \varepsilon_m P(t) - \beta_m M(t) \tag{2}$$

with ε_m = upregulation fitting parameter, and β_m = natural decay fitting parameter. Here $\varepsilon_m P(t)$ contributes proportionally to the increase of the pain modulation *M(t)* due to the presence of pain perception *P(t)*. Conversely, $-\beta_m M(t)$ is an intrinsic self-decay term, which decreases pain modulation *M(t)* proportionally over time.

Given *S(t)* and the rates, ie, time changes, for *P(t)* and *M(t)*, the 1st-order differential equations for *P(t)* and *M(t)* were subsequently solved using the standard Runge-Kutta-4 method with constant time steps.[43]

As a next step, we introduced a well-known *Lotka-Volterra coupling term*[38–42] $\alpha_p P(t)M(t)$ between the pain perception *P(t)* and the pain modulation *M(t)* in the rate equation for *P(t)*, thus implementing the full coupled control and feedback loop system as shown in Figure 2 (right), resulting in the following coupled 1st-order non-linear differential equation for *P(t)*:

$$\frac{dP(t)}{dt} = \varepsilon_p S(t) - \beta_p P(t) - \alpha_p P(t)M(t) \tag{3}$$

with α_p = coupling strength fitting parameter. The Lotka-Volterra coupling term $\alpha_p P(t)M(t)$ accounts for a proportional, non-linear interaction between the pain modulation *M(t)* and the pain perception *P(t)*.

The above *coupled* 1st-order non-linear differential equation for *P(t)* and the unchanged 1st-order linear differential equation for *M(t)* were again solved using the standard Runge-Kutta-4 method with constant time steps.[43]

Example Sensory Input Modeling for Future Clinical Applications

For the purposes of this initial study and to showcase the versatility and extensibility of our modeling effort introduced here, we provided below a set of example sensory input functions *S(t)* as potential examples of future clinical applications, cognizant that there are individual patient and clinician variations:

- Representing example conditions that could be modeled with a *sudden onset and relatively constant/persistent* sensory input:

$$S(t) = \alpha_s e^{\beta_s (t - t_{start})} u(t - t_{start}) u\left(t_{stop} - t\right) \tag{4}$$

with $\alpha_s > 0$ setting the strength and $\beta_s = 0$ (essentially eliminating the *e()*-term);

- Representing example conditions that could be modeled with a *sudden onset and exponentially decreasing* sensory input:

$$S(t) = \alpha_s e^{\beta_s (t - t_{start})} u(t - t_{start}) u\left(t_{stop} - t\right) \tag{5}$$

with $\alpha_s > 0$ setting the onset strength and $\beta_s < 0$ determining the decrease strength;

- Representing example conditions that could be modeled with an *exponentially increasing* sensory input:

$$S(t) = \alpha_s e^{\beta_s (t - t_{start})} u(t - t_{start}) u\left(t_{stop} - t\right) \tag{6}$$

with $\alpha_s > 0$ setting the maximum strength for the time interval under consideration and $\beta_s > 0$ determining the increase strength.

Note that the above sensory input modalities (Eqs. 4–6) were achieved with the same function for *S(t)* but with different parameter values. The goal here is to have a more generalized sensory input (ie, pain stimulus) *S(t)*.

- Representing example situations that could be modeled with a *sudden onset and linearly decreasing* sensory input:

$$S(t) = (\alpha_s + \beta_s(t - t_{start}))u(t - t_{start})u\left(t_{stop} - t\right) \tag{7}$$

with $\alpha_s > 0$ setting the onset strength and $\beta_s < 0$ determining the linear decrease slope;

- Representing example situations that could be modeled with a *linearly increasing* sensory input:

$$S(t) = (\alpha_s + \beta_s(t - t_{start}))u(t - t_{start})u\left(t_{stop} - t\right) \tag{8}$$

with $\alpha_s = 0$ and $\beta_s > 0$ determining the linear increase slope.

For all the above listed sensory input modalities, $u(t)$ is an index function with $u(t) = 1$ *if* $t \geq 0$ *else* 0, t_{start} is the onset of the sensory input, and t_{stop} is the stop/end of the sensory input.

Again, it is important to note that since the time profile of the respective sensory input *S(t)* is directly modeled as shown above, no differential equations are necessary for the time change of *S(t)*. Moreover, other, more realistic sensory input functions can readily be conceived, eg, informed by clinical findings or experience, and implemented in a similar fashion, including, but not limited to, oscillatory functions or discretely tabulated, potentially measured (if possible) or even arbitrary sensory input data as a function of time.

Results

Figures 3–7 show the simulation results of pain perception *P(t)* and modulation *M(t)* using the above model for the example sensory inputs, ie, pain stimuli *S(t)*.

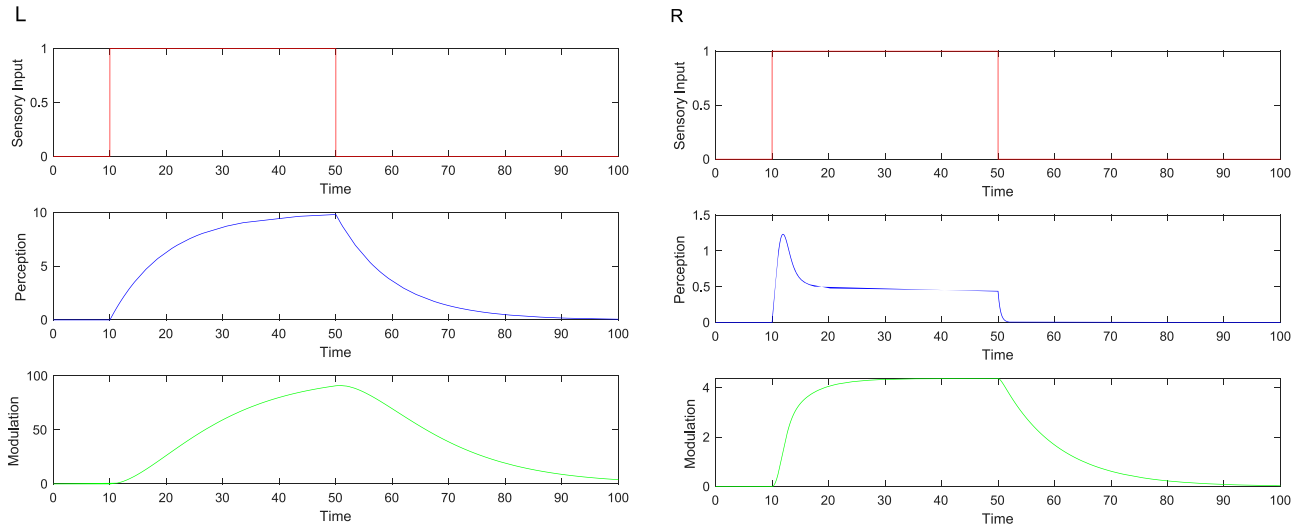

Figure 3 Control system model of perception and modulation of acute-onset, acute-offset pain.
Notes: Sudden onset of *constant*, ie, no decay, sensory input/pain stimulus (red, Eq. 4): Qualitative simulation of pain perception (blue) and modulation response (green) *without* (left, Eq. 1) and *with* Lotka-Volterra coupling/feedback (right, Eq. 3). The underlying parameter values are: $\alpha_s = 1$, $\beta_s = 0$, $\varepsilon_p = 1$,$\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$. The sensory input/pain stimulus onset time stamp is 10 and the turn-off time stamp 50, both in arbitrary time units (eg, seconds, minutes, hours, etc).

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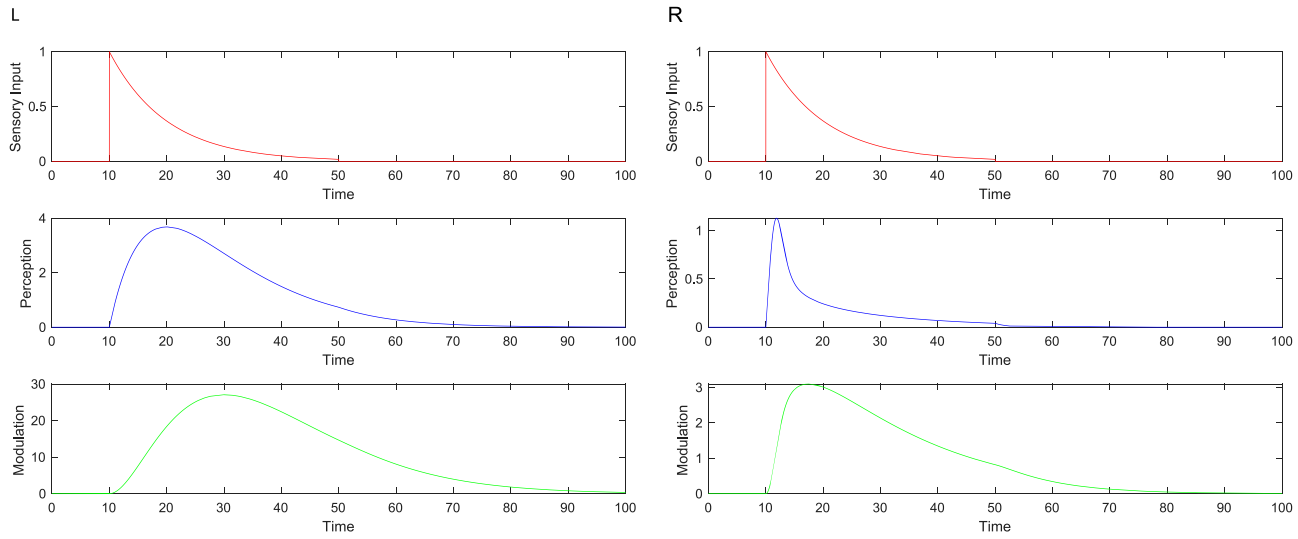

Figure 4 Control system model of perception and modulation of acute-onset, exponential-decay pain.
Notes: Sudden onset of *exponentially decaying* sensory input/pain stimulus (red, Eq. 5): Qualitative simulation of pain perception (blue) and modulation response (green) *without* (left, Eq. 1) and *with* Lotka-Volterra coupling/feedback (right, Eq. 3). The underlying parameter values are: α_s = 1, β_s = −0.1, ε_p = 1,β_p = 0.1, α_p = 0.5, ε_m = 1, and β_m = 0.1. The sensory input/pain stimulus onset time stamp is 10 and the turn-off time stamp 50, both in arbitrary time units (eg, seconds, minutes, hours, etc).

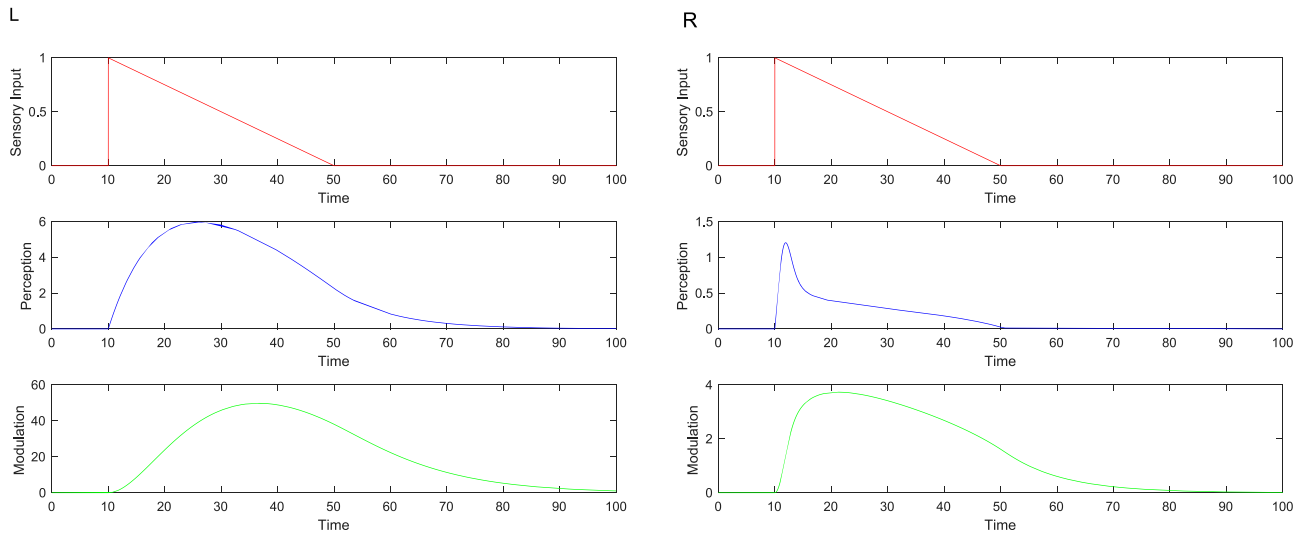

Figure 5 Control system model of perception and modulation of acute-onset, linear-decay pain.
Notes: Sudden onset of *linearly decaying* sensory input/pain stimulus (red, Eq. 7): Qualitative simulation of pain perception (blue) and modulation response (green) *without* (left, Eq. 1) and *with* Lotka-Volterra coupling/feedback (right, Eq. 3). The underlying parameter values are: α_s = 1, β_s = −0.025, ε_p = 1,β_p = 0.1, α_p = 0.5, ε_m = 1, and β_m = 0.1. The sensory input/pain stimulus onset time stamp is 10 and the turn-off time stamp 50, both in arbitrary time units (eg, seconds, minutes, hours, etc).

Sudden Onset of Constant, Ie, No Decay, Pain Stimulus

Figure 3, left, shows the pain perception *P(t)* (blue, Eq. 1) and the pain modulation *M(t)* (green, Eq. 2) *without coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 4). The pain perception *P(t)* saturates towards the end of the time window for the sensory input.

Figure 3, right, shows the pain perception *P(t)* (blue, Eq. 3) and the pain modulation *M(t)* (green, Eq. 2) *with Lotka-Volterra coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 4). Because of the modulation *M(t)* the pain perception *P(t)*, after a brief, but reduced spike, saturates much sooner and at a much lower level.

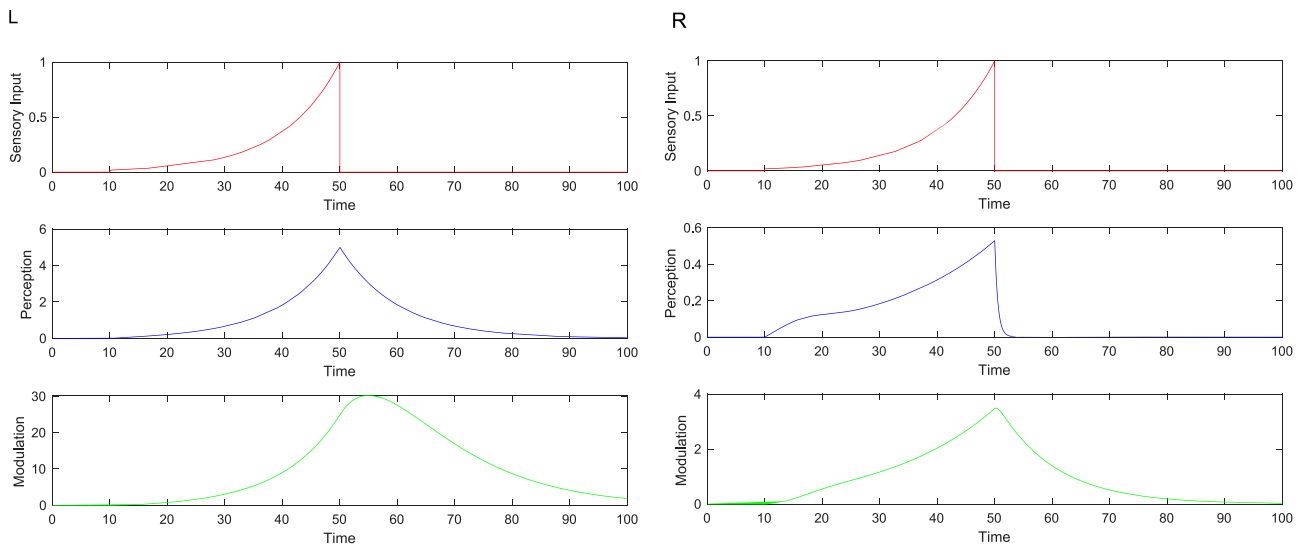

Figure 6 Control system model of perception and modulation of exponential-onset, acute-offset pain.
Notes: Sudden onset of *exponentially increasing* sensory input/pain stimulus (red, Eq. 6): Qualitative simulation of pain perception (blue) and modulation response (green) *without* (left, Eq. 1) and *with* Lotka-Volterra coupling/feedback (right, Eq. 3). The underlying parameter values are: α_s = 1.0/exp(4), β_s = 0.1, ε_p = 1,β_p = 0.1, α_p = 0.5, ε_m = 1, and β_m = 0.1. The sensory input/pain stimulus onset time stamp is 10 and the turn-off time stamp 50, both in arbitrary time units (eg, seconds, minutes, hours, etc).

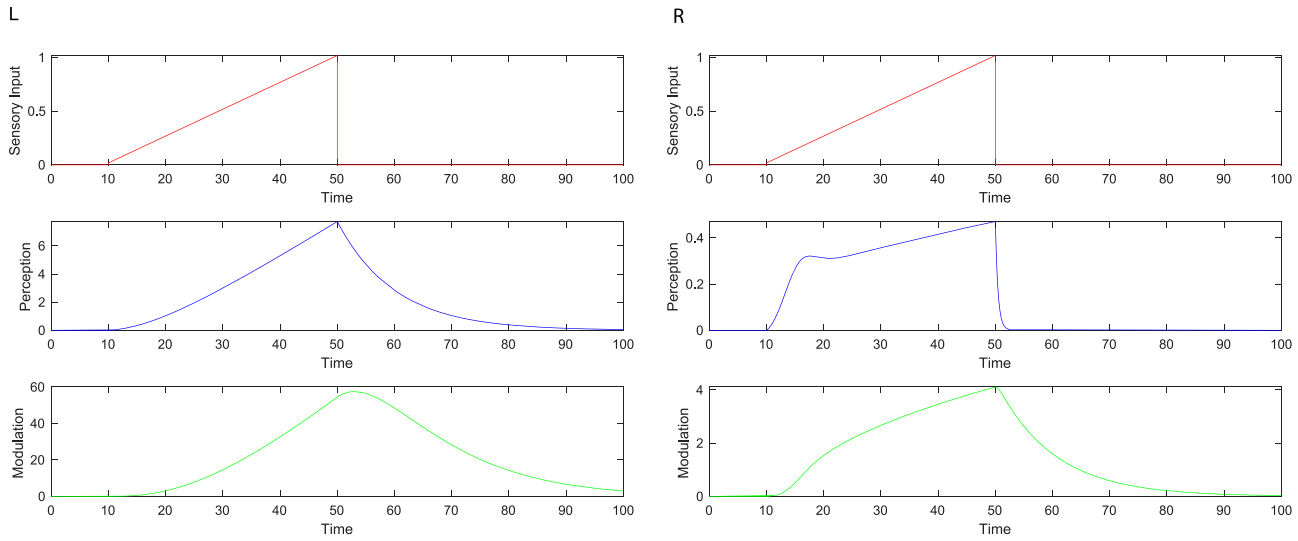

Figure 7 Control system model of perception and modulation of linear-onset, acute-offset pain.
Notes: Sudden onset of *linearly increasing* sensory input/pain stimulus (red, Eq. 8): Qualitative simulation of pain perception (blue) and modulation response (green) *without* (left, Eq. 1) and *with* Lotka-Volterra coupling/feedback (right, Eq. 3). The underlying parameter values are: α_s = 0, β_s = 0.025, ε_p = 1,β_p = 0.1, α_p = 0.5, ε_m = 1, and β_m = 0.1. The sensory input/pain stimulus onset time stamp is 10 and the turn-off time stamp 50, both in arbitrary time units (eg, seconds, minutes, hours, etc).

Sudden Onset of Exponentially Decaying Pain Stimulus

Figure 4, left, shows the pain perception *P(t)* (blue, Eq. 1) and the pain modulation *M(t)* (green, Eq. 2) *without coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 5). The pain perception *P(t)* bulges/ramps up before entering a milder exponential decay compared to the sensory input *S(t)*.

Figure 4, right, shows the pain perception *P(t)* (blue, Eq. 3) and the pain modulation *M(t)* (green, Eq. 2) *with Lotka-Volterra coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 5). Because of the modulation *M(t)* the pain perception *P(t)*, after a brief, but reduced spike, enters a much more pronounced and brief exponential decay compared to the sensory input *S(t)*.

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Sudden Onset of Linearly Decaying Pain Stimulus

Figure 5, left, shows the pain perception *P(t)* (blue, Eq. 1) and the pain modulation *M(t)* (green, Eq. 2) *without coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 7). The pain perception *P(t)* bulges over a prolonged period of time before entering a milder exponential decay towards the end of the sensory input time interval.

Figure 5, right, shows the pain perception *P(t)* (blue, Eq. 3) and the pain modulation *M(t)* (green, Eq. 2) *with Lotka-Volterra coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 7). Because of the modulation *M(t)* the pain perception *P(t)*, after a brief, but reduced spike, enters a much more pronounced and brief exponential decay, followed by a mildly declining linear downward slope compared to the sensory input *S(t)*.

Sudden Onset of Exponentially Increasing Pain Stimulus

Figure 6, left, shows the pain perception *P(t)* (blue, Eq. 1) and the pain modulation *M(t)* (green, Eq. 2) *without coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 6). The pain perception *P(t)* exhibits a stronger exponential increase compared to the sensory input *S(t)* profile, followed by an equally exponential decrease after the sensory input time interval.

Figure 6, right, shows the pain perception *P(t)* (blue, Eq. 3) and the pain modulation *M(t)* (green, Eq. 2) *with Lotka-Volterra coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 6). Because of the modulation *M(t)* the pain perception *P(t)* enters a much milder exponential increase after time stamp 20 following the sensory input profile, followed by an abrupt downregulation right after the sensory input time interval, matching the sudden turn-off of the sensory input signal at time 50.

Sudden Onset of Linearly Increasing Pain Stimulus

Figure 7, left, shows the pain perception *P(t)* (blue, Eq. 1) and the pain modulation *M(t)* (green, Eq. 2) *without coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 8). The pain perception *P(t)* exhibits a pseudo-linear increase, nearly matching the sensory input *S(t)* profile, followed by an exponential decrease after the sensory input time interval.

Figure 7, right, shows the pain perception *P(t)* (blue, Eq. 3) and the pain modulation *M(t)* (green, Eq. 2) *with Lotka-Volterra coupling* in response to the pain stimulus time profile *S(t)* (red, Eq. 8). Because of the modulation *M(t)* the pain perception *P(t)* ramps up pseudo-linearly, but at a lesser slope, but after time stamp 20 enters another linear regime with a much lesser slope, followed by an abrupt downregulation right after the sensory input time interval, matching the sudden turn-off of the sensory input signal at time 50.

Discussion

Pains are inherently complex physiological phenomena.[44–46] Because the absence of pain sensation deprives the body of alerts of acute or evolving tissue damage and results in significant morbidity, susceptibility to chronic pain, and early death, pain needs to be treated, but not eliminated, an almost unique challenge to medical practice and to the discovery and development of analgesic drugs.[47] Conceptually, and for convenience, the processing of pain-related information is often divided into four main components:[48] *signal transduction* (the conversion of tissue-damaging signals to activation of afferent neurons); *transmission* (the processes by which the information is carried from the site of injury to the brain regions underlying perception); *modulation* (neural processes that act at multiple levels to modulate, typically attenuate, activity in the transmission system), an example being diffuse noxious inhibitory control, DNIC);[7] and *perception* (the subjective awareness produced by sensory signals, which involves the integration of multiple sensory inputs into a coherent and meaningful whole). Each of these are subject to varying levels of influence to genetics, endogenous factors (eg, hormones, neurotransmitters, etc.) and exogenous (eg, analgesic and other drugs) factors, environment (eg, cultural, psychosocial, and religious influences), mental state (eg, prior pain experience, attention, expectation, interpretation, etc), and past history (eg, prior exposure to one's own or other's pain, training, etc).[49]

Interactions between these components lead to feedback loops in pain perception. For example, feedback loops in nociceptive input have been described previously [eg, Mendell (2011)[50]]. Mendell 2011 discusses the role of feedback loops in the modulation of pain, and highlights how both peripheral and central nervous system circuits exhibit feedback mechanisms that can enhance or diminish pain perception. These feedback loops are crucial in determining the intensity

and duration of pain responses, and their dysfunction can contribute to chronic pain states. Understanding these feedback systems is essential for developing effective treatments for pain management. Our model provides for both positive and negative feedback, analogous to a thermostat:[26] the nature of the feedback depends on the room temperature compared to the thermostat's set-point, ie, the feedback to the heater is *positive* if the room temperature is lower than the thermostat's set-point; the feedback is *negative* if the room temperature is higher than the set-point. The opposite is true for the cooling element.

In this work, we proposed that the ascending and descending pain pathways do not operate independently of each other, but instead form a coupled control and feedback loop system that maximizes information about tissue injury, with currency and high-fidelity, without detrimentally overwhelming the system with outdated or unhelpful input. Only in this way, for example, can coordinated fight-or-flight responses be successful.[51] Such a concept, using control systems theory analysis with practical clinical application in mind was previously proposed, to our knowledge, for the first time in 2016.[17] This concept is familiar in the non-medical context of temperature control of a room, where independent influence of a heater or cooler would not be efficient or effective. We propose extension of this analogy, including a thermostat-equivalent "nocistat" (yet to be identified),[26] and show that standard control and feedback system theory principles can be successfully applied to several examples of common clinical pain conditions.

Conclusion

To date, interactions between pain sensory input, perception, and modulation often lack a readily extensible, accessible, and clinically translational yet rigorous mathematical framework. Pharmaceutical intervention regimens are also based largely on clinical experience rather than informed and assisted by a formal framework. This work, for the first time, attempts to lay the foundation for a system-theoretical model of the ascending and descending pain pathways in form of a Lotka-Volterra-style control and feedback loop, which is readily extensible to a variety of clinical pain conditions – some not otherwise understandable from only empirical observation – and ultimately would help optimize analgesic *strategies and regimens.*

The general advantage of system-theoretical modeling, as shown here, is several fold (listed in no particular order): (1) ease of translation of interaction diagrams, eg, as shown in Figures 1 and 2, into coupled differential equations; (2) ease of model expansion; (3) full explainability, transparency, and freedom of interaction modeling, otherwise not expressible with interaction diagrams, eg, Lotka-Volterra-style coupling or higher order non-linear interactions, or catalytic interactions, etc.; (4) transparency of observables, eg, sensory input (ie, pain stimulus) $S(t)$, pain perception $P(t)$, and modulation $M(t)$ in our case; (6) quantification through the notion of a concentration or intensity for each observable; (7) quantitative fitting of experimental/clinical results or observations via the model-inherent parameters, thereby rendering the overall system-theoretical model quantitative in addition to being qualitative.

Ongoing work will (i) expand upon the utility of this model to inform about otherwise perplexing pains, and (ii) incorporate the influence of analgesic strategies and regimens on the model(s), leading to recommendations for improvement of pharmacotherapeutic outcomes. Future work will expand the sophistication and clinical applicability of the model introduced here.

Data Sharing Statement

The manuscript has no associated data.

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Disclosure

The authors have no conflicts of interest to declare.

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