Journal of Pain Research

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

A Pain Memory "Trace": Cumulative Pain Perception and Damping During Fight-or-Flight Response Modeled with a Lotka-Volterra-Style Coupled Feedback Control Loop System

Wolfgang Fink[1], Robert B Raffa[2,3]

[1]Visual and Autonomous Exploration Systems Research Laboratory, University of Arizona, Tucson, AZ, USA; [2]Temple University (Emeritus), Philadelphia, PA, USA; [3]University of Arizona (Adjunct), Tucson, AZ, USA

Correspondence: Wolfgang Fink, Visual and Autonomous Exploration Systems Research Laboratory, University of Arizona, 1230 E Speedway Blvd, P.O. Box 210104, Tucson, AZ, 85721, USA, Email wfink@arizona.edu

Introduction: Unlike a single acute pain (such as a single animal bite), cumulative pain arises from multiple sources or occurrences of pain stimuli (eg, multiple animal bites). We earlier introduced a mathematical framework of a coupled feedback control loop using Lotka-Volterra dynamics to model the choreographed interaction between "ascending" and "descending" pain-processing pathways. This model is based on the premise that these pathways, rather than acting independently, should act in a coordinated, coupled, well-controlled feedback loop.

Methods: In this work, we apply Lotka-Volterra dynamics – coupled first-order nonlinear differential equations used to describe the dynamics of biological systems in which two or more components interact – to examine the effect and magnitude of modulatory feedback (ie, "damping") on the response function (ie, pain perception) to the incidence of cumulative pain.

Results: Simulations demonstrate that our approach can model individual consecutive pain signals (i) if the inter-pain-signal time is larger than a certain threshold, (ii) if the magnitude of immediate consecutive pain signals differs, or (iii) if during superposition of (partially) concurrent pain signals the magnitude of the resulting superimposed pain signal changes during an ongoing pain signal event.

Discussion: Our results suggest that pain perception declines after an initial stimulus, but does not immediately return to zero (or baseline); instead, it settles at a lower plateau level that persists essentially for the duration of the stimulus input. With each subsequent pain stimulus, the effect on the plateau level is cumulative, amounting essentially to a pain memory "trace". Therefore, in addition to a measure of the damage of an individual event (eg, a claw swipe), a herein newly-described measure of the cumulative damage is also monitored (eg, multiple claw strikes). This would provide two critical types of information helpful to make a decision to either fight or flee.

Keywords: cumulative pain, damping, ascending and descending pain pathways, feedback loop, control system, Lotka-Volterra dynamics, dead time, modulation-mediated pain perception hyperpolarization

Introduction

In descriptions of the fight-or-flight response,[1–5] the actual decision-making process is rarely addressed, and to our knowledge never quantified. We have recently proposed that one of the major criteria in the decision-making process is the level of tissue damage, which is signaled by the level of pain perception.[6] The body's mechanism for detecting and transmitting the information about damage is pain.[7,8] Here, we propose that the decision whether to fight or flee should be informed by two important measures of damage: acute damage (acute pain), and cumulative damage (cumulative pain). Cumulative pain refers to the experience of pain that gradually accumulates over time due to the contribution of multiple sources or episodes of damage (eg, multiple animal bites). Unlike acute pain, which is typically a response to an immediate injury or threat, cumulative pain arises from the repetitive or multiplicative nature of pain stimuli.

https://doi.org/10.2147/JPR.S561278
Received: 18 August 2025
Accepted: 8 January 2026
Published: 21 January 2026

The body's pain signaling systems play a key role in how cumulative pain is perceived. Nociceptors, sensory receptors responsible for detecting harmful stimuli, transmit signals to the central nervous system when tissues are damaged or under stress.[7,9,10] In cases of cumulative pain, these signals may become more pronounced as the body experiences repeated or chronic stressors. Neuroplasticity – the brain's ability to adapt and reorganize its neural connections[11] – also contributes to the perception of cumulative pain. In some instances, the brain may "sensitize" to persistent pain signals, increasing sensitivity to pain, thereby making previously minor discomforts feel more intense.[12–14] Adaptation to pain can also occur. In the following, we illustrate positive cumulation.

Ultimately, the perception of cumulative pain reflects the interaction between the body's physiological responses, an individual's emotional and cognitive state, and the broader social environment in which the pain is experienced. This multi-input interaction informs whether the appropriate decision to a pain-generating situation is to fight or to flee.

In a recent publication we proposed the concepts of pain as a part of the fight-or-flight response,[6] postulated the existence of a "nocistat",[15] and introduced the mathematical framework of a coupled feedback control loop, using Lotka-Volterra dynamics – originally conceived for so-called predator–prey interaction models,[16–20] the dynamics of which are conceptually similar to the postulated relationship between ascending and descending pain pathways – to model the choreographed interaction between "ascending pathways" and "descending pathways" in pain processing.[21] This model is based on the realization that the ascending and descending pathways, rather than acting independently, should be connected in a coordinated, coupled, and well-controlled feedback loop. We have shown in another publication (submitted for publication) that our model exhibits an initial indication of the magnitude of the immediate injury by a spike in pain perception, followed by a saturation at a lower pain perception (ie, damping) for the remainder of the pain inflicting signal due to modulation. This current work explores and demonstrates the capabilities of our model when the individual is exposed to consecutive and/or multiple superimposed pain-inflicting events.

Methods

To simulate a cumulative pain experience, a sequence and/or superposition of rapid-onset and short-duration bite or swipe of a paw events inducing acute pain was modeled. Hereby, the sensory input (ie, pain stimulus) of each bite or swipe of a paw event was modeled as a rectangular function with a sudden onset of pain, where, in the absence of modulation $M(t)$, pain perception $P(t)$ rises rapidly in response to the constant pain stimulus $S(t)$ through the ascending pain-transmitting pathways, then returns back to baseline once the pain stimulus has stopped. We add $M(t)$ to include the influence of the descending pain-modulating (attenuating) pathways on the pain perception $P(t)$. The underlying model equations, derived in detail in Fink and Raffa,[21] were numerically solved/integrated using the standard Runge-Kutta-4 method with constant time steps,[22] and are as follows:

Modulation Change over time (rate): $\frac{dM(t)}{dt} = \varepsilon_m P(t) - \beta_m M(t)$, and

Pain Perception Change over time (rate) with Lotka-Volterra-style coupling (last term) to modulation:

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

Sensory Input: $S(t) = 0$ for $t < t_{\text{onset}}$; $S(t) = S_{\max}$ for $t_{\text{onset}} \leq t \leq t_{\text{off}}$; 0 for $t > t_{\text{off}}$.

Given the above model equations we were interested in simulating a variety of scenarios of cumulative pain experiences as follows:

1. Pain perception of a singular bite or swipe of a paw event as a baseline for comparison to the following scenarios;
2. Pain perception of two immediately consecutive bite or swipe of a paw events of the same magnitude;
3. Pain perception of two consecutive bite or swipe of a paw events of the same magnitude with increasing temporal spacing between the first and the second pain signal event;
4. Pain perception of three immediately consecutive bite or swipe of a paw events with differing respective magnitudes, which can be equivalently interpreted as a pain signal that momentarily intensifies/weakens to return back to its original initial level;
5. Pain perception of two immediately consecutive bite or swipe of a paw events with differing respective magnitudes, which can be equivalently interpreted as a pain signal that intensifies/weakens before it vanishes altogether;

6. Pain perception of three immediately consecutive bite or swipe of a paw events with monotonically increasing/decreasing respective magnitudes, which can be equivalently interpreted as a pain signal that intensifies/weakens in two subsequent stages (pain crescendo or decrescendo/diminuendo) before it vanishes altogether.

Results

Given the above equations from Fink and Raffa,[21] Figures 1–6 show the simulation results of the time development of pain perception $P(t)$ and modulation $M(t)$ given a sequence of consecutive pain stimuli $S(t)$ or partially overlapping pain stimuli, where each pain stimulus $S(t)$ is modeled using the above equations, but with varying pain input characteristics.

For each pain stimulus event, as a net result of an increasing pain perception magnitude and an increasing inhibitory pain modulation, pain perception rises rapidly as a function of stimulus intensity, then begins to decline. However it does not return to zero. Instead, it saturates/plateaus at some value that is intermediately between zero and maximum perception, ie, at a level that is related to the stimulus intensity. Depending on the inter-pain-signal period, a new pain signal is registered as another spike or goes unnoticed if it follows immediately. A new pain signal is also registered, regardless of inter-pain-signal period, if its magnitude differs from the preceding pain signal. This registration manifests either as a momentary spike or dent.

An example of a single acute pain input of rapid onset and rapid offset (a "step" function) is demonstrated in Figure 1. Because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level.

An example of two consecutive pain stimuli of the same amplitude without time spacing between them, thereby essentially doubling the duration of the pain signal, is demonstrated in Figure 2. Because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level across the remainder of the first pain signal and all of the second pain signal.

An example of two consecutive pain stimuli time profiles of the same amplitude with increasing time spacing is demonstrated in Figure 3. Because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then

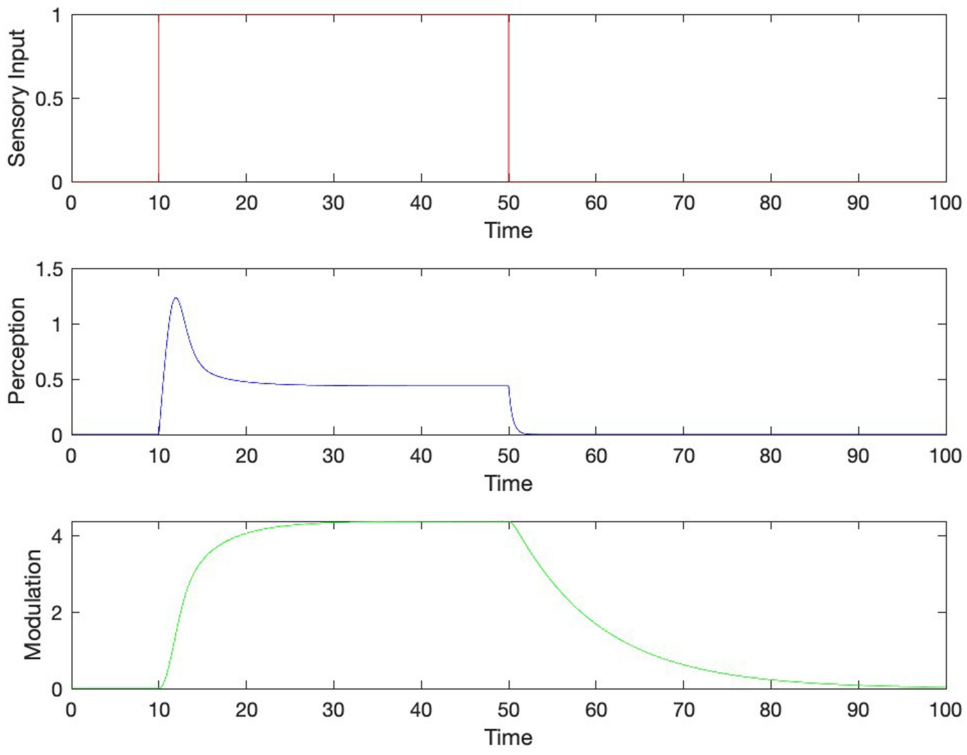

Figure 1 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to the pain stimulus time profile $S(t)$ (top tracing), where the sensory input = 1 AU.

Notes: The underlying parameter values for the simulation are: for stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 50, both in arbitrary time units (eg, seconds, minutes, hours, etc.), S_{max} = 1 AU. For all other simulation times *t*: $S(t)$ = 0 AU. For all other model parameters: $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

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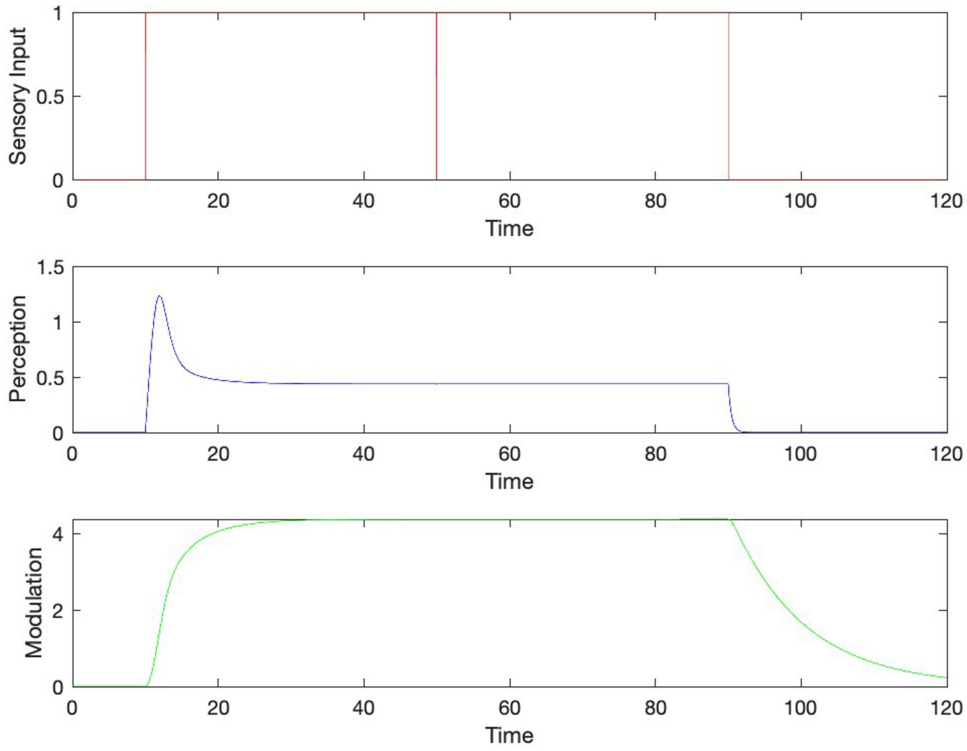

Figure 2 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to two consecutive pain stimuli time profiles $S_1(t)$ and $S_2(t)$ of same amplitude (top tracing) without time spacing, thereby essentially doubling the duration of the pain signal, where the sensory input = 1 AU for each pain stimulus.

Notes: The underlying parameter values for the simulation are: for stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 50, and for $S_2(t)$: t_{onset} = 50 and t_{off} = 90 – all in arbitrary time units (eg, seconds, minutes, hours, etc). For both $S_1(t)$ and $S_2(t)$: S_{max} = 1 AU. For all other simulation times t: $S(t)$ = 0 AU. For all other model parameters: $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

saturates/plateaus at a lower level during the first pain signal and the second pain signal, respectively. Of particular interest, the second spike in pain perception $P(t)$ is lower than the first one in the scenario on the *top* with shorter quiescence time between the two pain stimuli, because the modulation $M(t)$ has not fully returned to baseline yet when the second pain signal occurs. This could be interpreted as a temporary numbing or attenuating effect. This is in contrast to the second scenario (*bottom*), which results in two identical pain episodes because the inter-pain time period is sufficient for the modulation $M(t)$ to return to baseline before being triggered again by the second pain signal, resulting in the same original pain perception spike.

An example of three consecutive pain stimuli without time spacing and 1 AU (arbitrary units) sensory input for the first and last pain stimulus and double for the second pain stimulus is demonstrated in Figure 4 (*top*). In the scenario on the *top* of this Figure, because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike after the onset of the first pain stimulus, then saturates/plateaus at a lower level. It rises again momentarily upon the onset of the second pain stimulus, then saturates/plateaus at a lower but overall higher level than before. At the end of the second pain stimulus, the sensory input returns to the level of the first pain stimulus, which leads to a momentary modulation-mediated pain perception "hyperpolarization", ie, an inverse "peak" or dent, then saturates/plateaus at a higher level than the dent, which corresponds to the plateau reached during the first pain stimulus. In the scenario on the *bottom* of Figure 4, because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike after the onset of the first pain stimulus (2 AU), then saturates/plateaus at a lower level. A momentary modulation-mediated pain perception "hyperpolarization", ie, an inverse "peak" or dent, occurs upon the onset of the second pain stimulus (1 AU), then saturates/plateaus at a higher but overall lower level than before. At the end of the second pain stimulus, the sensory input returns to the level of the first pain stimulus (2 AU), which leads to a brief spike in pain perception, then saturates/plateaus at a lower level than the spike, which corresponds to the plateau reached during the first pain stimulus.

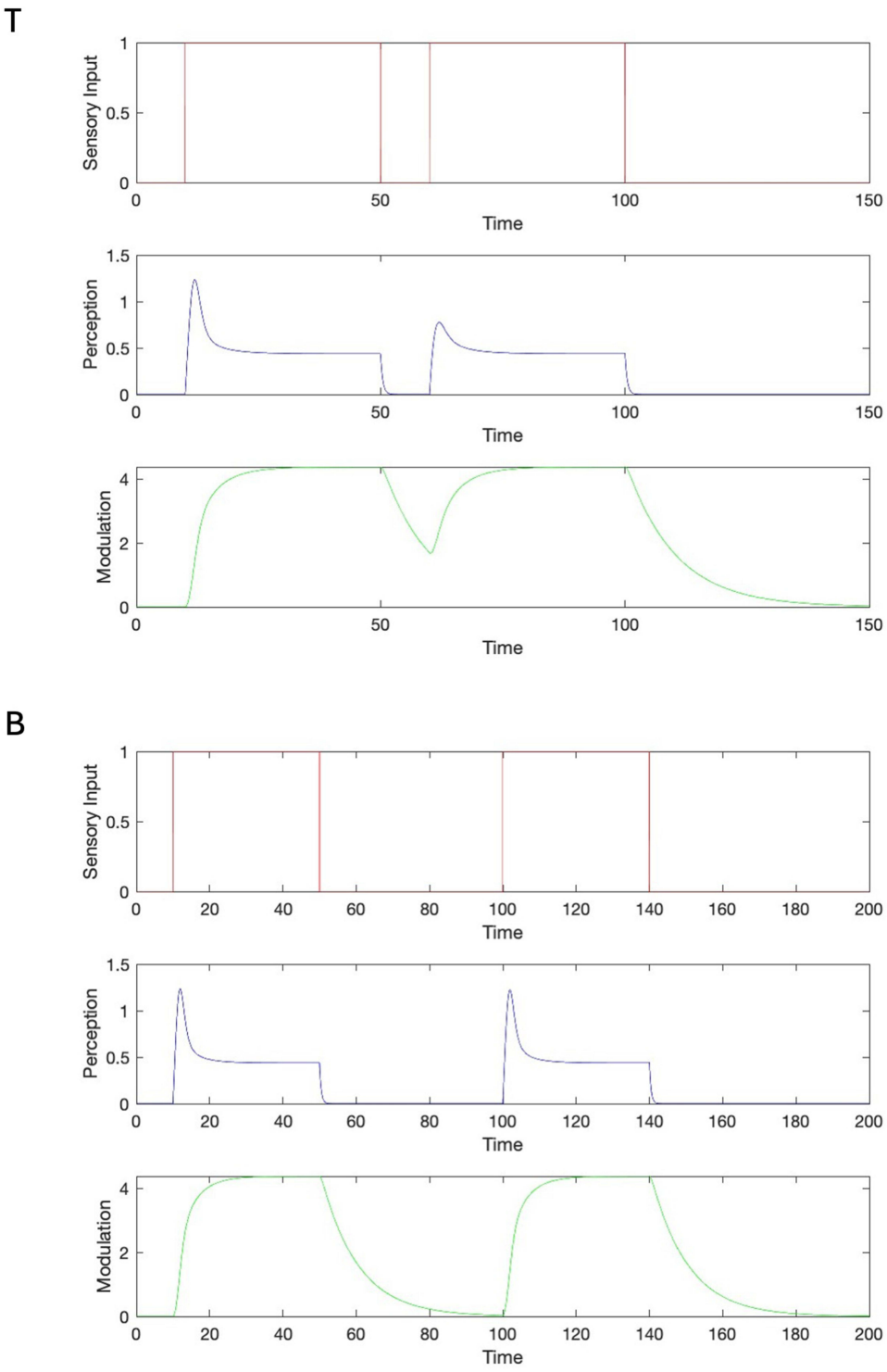

Figure 3 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to two consecutive pain stimuli time profiles $S_1(t)$ and $S_2(t)$ of same amplitude (top tracing) with increasing time spacing (T and B), where the sensory input = 1 AU for each pain stimulus.

Notes: The underlying parameter values for the simulation are: (T) For stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 50, and for $S_2(t)$: t_{onset} = 60 and t_{off} = 100 – all in arbitrary time units (eg, seconds, minutes, hours, etc.). For both $S_1(t)$ and $S_2(t)$: S_{max} = 1 AU. (B) For stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 50, and for $S_2(t)$: t_{onset} = 100 and t_{off} = 140 – all in arbitrary time units (eg, seconds, minutes, hours, etc.). For both $S_1(t)$ and $S_2(t)$: S_{max} = 1 AU. For all other simulation times t: $S(t)$ = 0 AU. For all other model parameters for (T) and (B): $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

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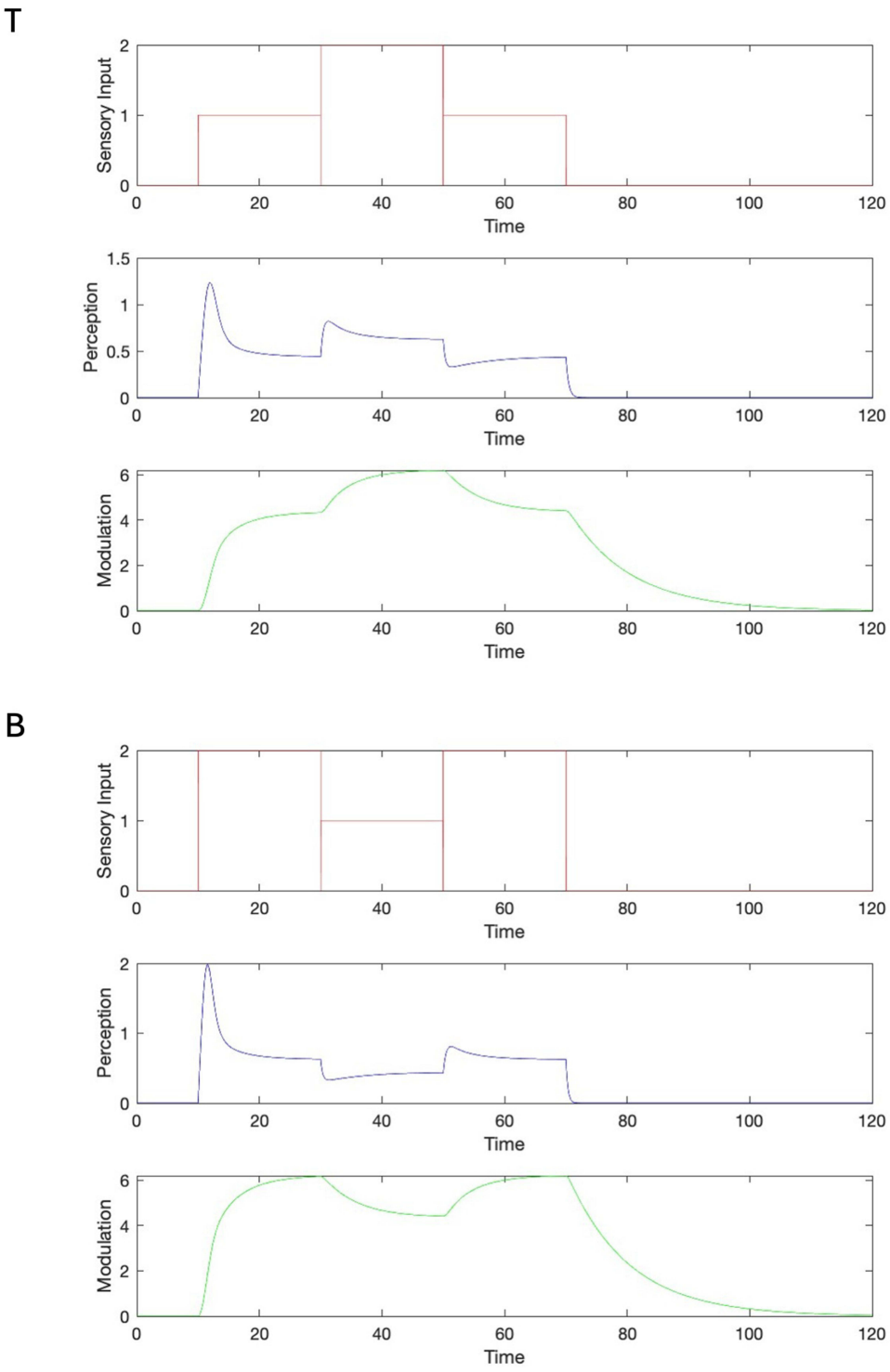

Figure 4 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to three consecutive (without time spacing) pain stimuli time profiles $S_1(t)$, $S_2(t)$, and $S_3(t)$ (top tracing), where the sensory input = 1 AU for the first and last pain stimulus and sensory input = 2 AU for the second pain stimulus (T); and the sensory input = 2 AU for the first and last pain stimulus and sensory input = 1 AU for the second pain stimulus (B).

Notes: The underlying parameter values for the simulation are: for stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 30, for $S_2(t)$: t_{onset} = 30 and t_{off} = 50, and for $S_3(t)$: t_{onset} = 50 and t_{off} = 70 – all in arbitrary time units (eg, seconds, minutes, hours, etc). (T): for $S_1(t)$ and $S_3(t)$: S_{max} = 1 AU, and for $S_2(t)$: S_{max} = 2 AU. (B): for $S_1(t)$ and $S_3(t)$: S_{max} = 2 AU, and for $S_2(t)$: S_{max} = 1 AU. For all other simulation times t: $S(t)$ = 0 AU. For all other model parameters for (T) and (B): $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

A more complex example of two consecutive pain stimuli of different amplitude without time spacing between them (essentially doubling the duration of the pain signal), with different combinations of input magnitudes, is demonstrated in Figure 5. Under one scenario (*top left and right portion of the Figure*), because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level of increasing magnitude for both pain stimuli. Depending on the magnitude of the second pain stimulus, the second spike in pain perception $P(t)$ is either lower or higher than the first spike, respectively. Under another scenario (*bottom left and right portion of the Figure*), because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level for the first pain stimulus, followed by a brief dent with subsequent saturation at a higher (compared to the dent) level. Note, the larger the drop in magnitude of the second pain stimulus, the larger the depth of the dent in pain perception $P(t)$.

A final example, of three consecutive pain stimuli time profiles of different amplitude without time spacing between them (thereby essentially tripling the duration of the pain signal) is demonstrated in Figure 6. Under one scenario (*top portion of the Figure*), because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level of increasing magnitude, respectively. Even though the increase in magnitude of the second and third pain stimulus is the

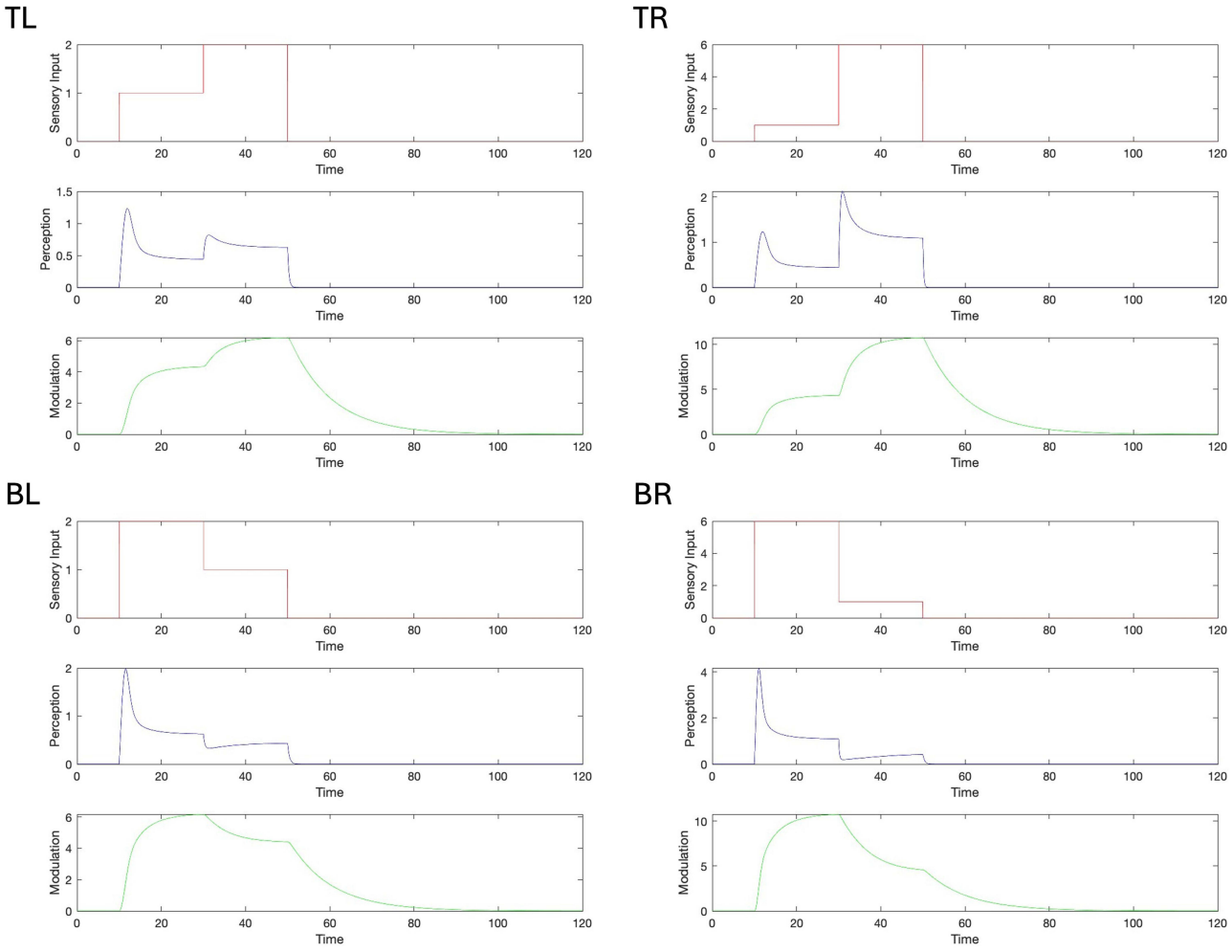

Figure 5 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to two consecutive pain stimuli time profiles $S_1(t)$ and $S_2(t)$ of different amplitude (top tracing) without time spacing, thereby essentially doubling the duration of the pain signal, where the sensory input = 1 AU for the first and sensory input = 2 AU for the second pain stimulus (TL); sensory input = 1 AU for the first and sensory input = 6 AU for the second pain stimulus (TR); sensory input = 2 AU for the first and sensory input = 1 AU for the second pain stimulus (BL); and sensory input = 6 AU for the first and sensory input = 1 AU for the second pain stimulus (BR).

Notes: The underlying parameter values for the simulation are: for stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 30, and for $S_2(t)$: t_{onset} = 30 and t_{off} = 50 – all in arbitrary time units (eg, seconds, minutes, hours, etc). (TL): for $S_1(t)$: S_{max} = 1 AU, and for $S_2(t)$: S_{max} = 2 AU. (TR): for $S_1(t)$: S_{max} = 1 AU, and for $S_2(t)$: S_{max} = 6 AU. (BL): for $S_1(t)$: S_{max} = 2 AU, and for $S_2(t)$: S_{max} = 1 AU. (BR): for $S_1(t)$: S_{max} = 6 AU, and for $S_2(t)$: S_{max} = 1 AU. For all other simulation times t: $S(t)$ = 0 AU. For all other model parameters for (TL), (TR), (BL), and (BR): $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

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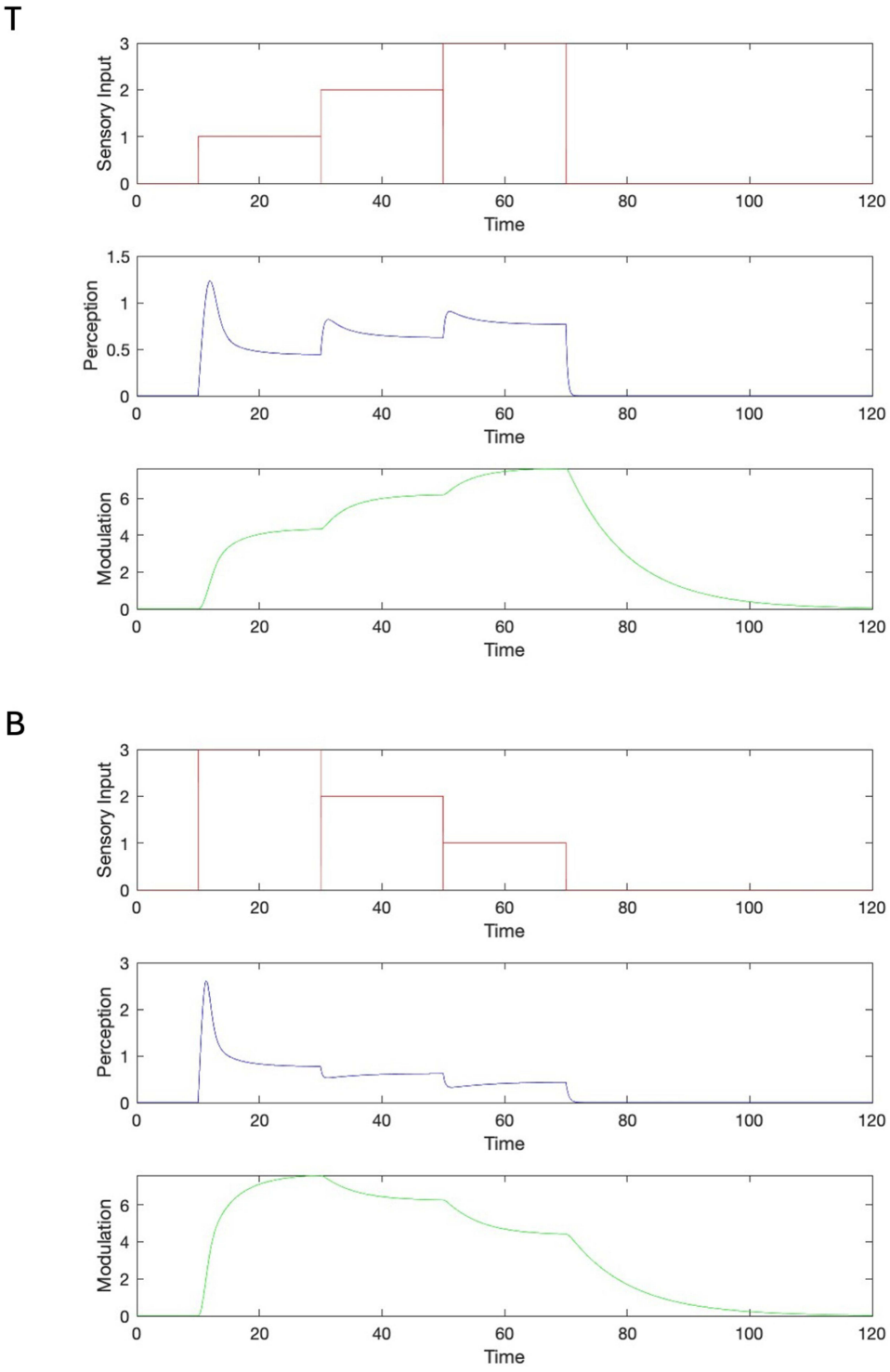

Figure 6 The pain perception $P(t)$ (middle tracing) and the pain modulation $M(t)$ (bottom tracing) with Lotka-Volterra coupling in response to three consecutive pain stimuli time profiles $S_1(t)$, $S_2(t)$, and $S_3(t)$ of different amplitude (top tracing) without time spacing, thereby essentially tripling the duration of the pain signal, where the sensory input = 1 AU for the first, sensory input = 2 AU for the second, and sensory input = 3 AU for the third pain stimulus (T); and sensory input = 3 AU for the first, sensory input = 2 AU for the second, and sensory input = 1 AU for the third pain stimulus (B).

Notes: The underlying parameter values for the simulation are: for stimulation event $S_1(t)$: t_{onset} = 10 and t_{off} = 30, for $S_2(t)$: t_{onset} = 30 and t_{off} = 50, and for $S_3(t)$: t_{onset} = 50 and t_{off} = 70 – all in arbitrary time units (eg, seconds, minutes, hours, etc). (T): for $S_1(t)$: S_{max} = 1 AU, $S_2(t)$: S_{max} = 2 AU, and for $S_3(t)$: S_{max} = 3 AU. (B): for $S_1(t)$: S_{max} = 3 AU, $S_2(t)$: S_{max} = 2 AU, and for $S_3(t)$: S_{max} = 1 AU. For all other simulation times t: $S(t)$ = 0 AU. For all other model parameters for (T) and (B): $\varepsilon_p = 1$, $\beta_p = 0.1$, $\alpha_p = 0.5$, $\varepsilon_m = 1$, and $\beta_m = 0.1$.

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same, the magnitude change of the second spike in pain perception $P(t)$ is slightly larger than the magnitude change of the third one (even though the absolute magnitude of the third spike is larger than the second one). This is due to the lower level of modulation during the second spike. This also explains why the second and third spike in pain perception are significantly smaller than the first spike even though the respective pain stimuli are increasingly larger than the first one. Under another scenario (*bottom portion of the Figure*), because of the modulation $M(t)$, the pain perception $P(t)$ registers as a brief spike, then saturates/plateaus at a lower level for the first pain stimulus, followed by two brief dents with subsequent saturation at a higher (compared to the dent) level, but overall decreasing magnitude.

Discussion

The simulation results (Figures 1–6) suggest that our model can be applied to cumulative pain. It can register, monitor, and discern individual consecutive pain signals:

1. If the inter-pain-signal time is larger than a certain threshold between two consecutive pain signal events during which the model is unable to register another pain event due to elevated modulation from the preceding pain event. This is akin to the notion of a "dead time" of a Geiger-Müller detector,[23] ie, the period of time following a radiation detection event where the detector is unable to register another event/count.
2. If the respective magnitude of immediate consecutive pain signals differs, ie, consecutive pain signals have different magnitudes.
3. If during superposition of (partially) concurrent pain signals the magnitude of the resulting superimposed pain signal changes during an ongoing pain signal event. For example, if the subject is bitten by a wild animal, and during that time suffers another bite by another animal.

Moreover, while a consecutive higher magnitude pain stimulus is registered as a momentary spike in pain perception, a consecutive lower magnitude pain stimulus is registered as a momentary "dent" in pain perception akin to hyperpolarization in cells. One might call it a *modulation-mediated pain perception hyperpolarization*.

It should be noted that the original "fight-or-flight" concept has been expanded to the "predatory imminence continuum theory".[24–26] This model categorizes three stages: pre-encounter, post-encounter, and circa-strike, each activated by different levels of fear. Our formulation models what occurs during the third stage.

We recognize that the decision to fight or flee in response to a given magnitude of pain (tissue damage) is based on more than the contemporary level of pain. Other influences and contributing factors include: past experiences, training, pre-encounter anxiety level, age, a disability that inhibits the ability to flee, genetic sensitivity to pain, environmental factors, physiologic drivers (eg, degree of hunger of the predator), pre-encounter assessment of the threat, whether or not others are present (ie, alone or in a pack), focus (distractions present), other damage-assessment modalities (eg, visual cues), and cognitive interpretation of events.

It recently has been proposed that the brain computes fear by integrating space and time to guide survival behavior.[27] Defensive responses are envisioned as organized along neural circuits that scale with threat imminence, shifting from higher cortical regions involved in planning and prediction to subcortical circuits that support rapid, reflexive action. Spatial distance, temporal proximity, and uncertainty shape fear-related decision-making and behavior. Fear is framed as an adaptive computational process that dynamically selects defensive strategies to maximize survival.

Conclusion

The modulation of pain, for example by the diffuse noxious inhibitory control (DNIC) pathways and mechanisms,[28] appears to provide an organism a quantifiable mechanism to monitor cumulative injury (ie, multiple pain signals), since as $P(t)$ declines after a single stimulus, it does not return to zero (or baseline). Instead it settles at a lower plateau level that is maintained essentially for the duration of the stimulus input. With each subsequent stimulus, the effect on the plateau can be cumulative, as a sort of pain memory "trace". Therefore, in addition to a measure of the damage of an individual event (eg, claw swipe), a measure of the cumulative damage would be monitored (eg, multiple claw strikes). This would allow for time and intensity discrimination helpful for deciding whether to fight or to flee.

 https://doi.org/10.2147/JPR.S561278

Funding

This research was supported in part by the Edward & Maria Keonjian Endowment in the College of Engineering at the University of Arizona.

Disclosure

The authors have no conflicts of interest to declare for this work.

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