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On the Generalization of Habituation: How Discrete Biological Systems Respond to Repetitive Stimuli

A Novel Model of Habituation That Is Independent of Any Biological System

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Habituation, a form of non-associative learning, is no longer studied exclusively within the fields of psychology and neuroscience. Indeed, the same stimulus–response pattern is observed at the molecular, cellular, and organismal scales and is not dependent upon the presence of neurons. Hence, a more inclusive theory is required to accommodate aneural forms of habituation. Here an abstraction of the habituation process that does not rely upon particular biological pathways or substrates is presented. Instead, five generalizable elements that define the habituation process are operationalized. The formulation can be applied to interrogate systems as they respond to several stimulation paradigms, providing new insights and supporting existing behavioral data. The model can be used to deduce the relative contribution of elements that contribute to the measurable output of the system. The results suggest that habituation serves as a general biological strategy that any system can implement to adaptively respond to harmless, repetitive stimuli.

1. Introduction

Biological systems sense their environments by converting stimuli into physiologically relevant packets of information that can be processed and interpreted downstream. Upon harmless repetitive stimulation, the stimulus–response pattern shifts such that the output is transiently reduced, usually with an exponential decay profile—a process referred to as habituation, which is a form of non-associative learning.[1] As would be expected, habituation has been thoroughly characterized in behaving organisms and is generally understood within the context of neural tissues (e.g., ganglia, brains, and spinal cords). Based upon decades of experimental work, a detailed list of common characteristics associated with habituation was published by Thompsons and Spencer,[1] and more recently revised by Rankin et al.[2] The combined features outlined by Rankin and colleagues, which have been experimentally corroborated over the last 50 years, continue to represent the most up-to-date checklist of the classic habituation profile.

Several theories have been forwarded to explain the intrinsic plasticity of neuronal circuits such as the "stimulus-model comparator theory,"[3,4] the "dual-process theory,"[5,6] and more recently, the "negative-image model,"[7] but little is still known about the specific mediators underlying such processes. Habituation is generally described to be an exponential decay process to an asymptotic level; indeed, habituation is usually modeled by a first-order differential equation in which arbitrary variables govern the rate of habituation and recovery.[8,9] A more sophisticated model by Wang[10] proposed an inverse S-shape profile of habituation and considers both short- and long-term components. However, all of the aforementioned theories approach habituation from a neuronal context. Interestingly, some of the major features of habituation are observed at the molecular[11] and cellular levels,[12,13] as well as in non-neuronal organisms[14–18] and even inorganic substrates,[19] suggesting that several unique mechanisms share a convergent function. So far, no single unified mechanism has been suggested to explain the habituation process independently of the cell source (i.e., neuronal vs aneural system) or the scale of the habituating system (i.e., cellular vs tissue levels vs organism vs population). Rather than treating each system as unique, here we explore the possibility that habituation is a generalized process that is independent of any one substrate, a common strategy that can and has been observed at scales ranging from molecules to organisms. This is important not only in order to understand the phylogenetic history of learning but also to establish a principled strategy for the implementation of functional cognitive capabilities in synthetic biology contexts.[20,21] The aim of this paper is to outline the abstract operations underlying the habituation response, their emergent properties, and the degree to which the proposed model predicts the characteristics of behavioral data.

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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/bies.201900028.

This article is commented on in the Idea to Watch article by Fred Keijzer, https://doi.org/10.1002/bies.201900079.

DOI: 10.1002/bies.201900028

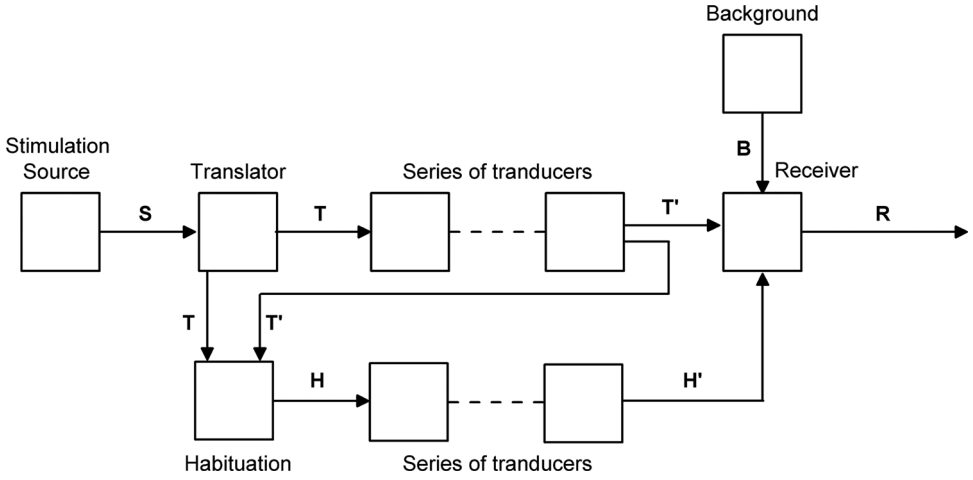

Figure 1. Schematic diagram of a habituation system.

2. Can We Discretize the Habituation Process?

To separate the underlying rules and concepts from their biological examples reported in the literature, we present an abstraction of habituation and define it as information flow between the stimulation source and the habituated system. By a habituated system, we mean a system as outlined in **Figure 1**, which consists of the following:

1) A translator element, which decodes the stimulation (S) and transmits it reliably to the receiver element in a time-independent fashion. If absent, the stimulation cannot be sensed by the system.
2) The habituation element, which, upon repetitive stimulation, changes its output in a time- and stimulus-dependent manner.
3) A series of transducers, which interpret, if necessary, the signals from the translator and the habituation elements (T and H, respectively) and generate an output (T' or H') in a time-independent manner that can be a readable input for the receiver element. These elements are mandatory if T and H are not suitable inputs for the receiver element.
4) The background element (B) is the ensemble of all the elements that can influence the receiver's output but are independent of the applied stimulation.
5) The receiver element, which receives the stimulation (through T' and H') and of which we monitor the output (R).

Despite the discretization of the process, time is considered continuous throughout the model.

Accordingly, the output of the system R is

$$R = T' + H' + B \tag{1}$$

We define the output of an i^{th} element (U_i) as a function of the number of modules that compose the element itself (S_i) and their intrinsic activity (α_i) as follows:

$$U_i = S_i \bullet \alpha_i \tag{2}$$

Combining Equations (1) and (2),

$$R = S_T \bullet \alpha_T + S_H \bullet \alpha_H + S_B \bullet \alpha_B \tag{3}$$

The activity α is either positive/negative if the recorded R is increased/decreased, respectively.

If present, the stimulation–receiver pair defines the profile of the habituation process. Indeed, the stimulation source limits the nature of the translator elements, whereas the series of transducer is restricted by the translator–receiver pair. Both the stimulation features and the receiver elements define the habituation elements.

The inputs of the habituation element are restricted to T or T'. If S is an input, we have a time-dependent translator; in this scenario, we define the fatigue or desensitization process.

3. What Happens During the Repetitive Stimulation?

Repetitive stimulation is defined as a protocol in which all the characteristics of the stimulation event (trial) are fixed and the time, between consecutive trials (nonstimulation time, $t_{(\text{ns})}$), is held constant. We therefore draw stimulation (s) and non-stimulation (ns) phases. Given a fixed stimulation protocol, T' will remain constant, whereas H' will change with successive trials.

Definition 1 During each trial, $H'_{(\text{ns})n-1}$ increases/decreases by a defined factor σ (stimulation factor).

$$H'_{(\text{s})n} = H'_{(\text{ns})n-1} \pm \sigma \tag{4}$$

where $H'_{(\text{s})n}$ is the output at the n^{th} trial and $H'_{(\text{ns})n-1}$ is the output before the n^{th} trial. σ is defined by the stimulation features (magnitude and time) and the nature of the habituation element(s). The magnitude of stimulation controls the rate of change of σ for any given $t_{(\text{s})}$: the explicit functions are explored in detail in the Supporting Information section. The stimulation can either increase or decrease S_H, α_H, or both,

hence affecting H'. At the n^{th} trial, we define the gain value (γ) as follows:

$$\gamma_{(s)_n} = |H'_{(s)n} - H'_{(ns)0}| \tag{5}$$

where $\gamma_{(s)_n}$ is the cumulative effect of the stimulation on the habituation element(s) at the n^{th} trial, $H'_{(s)n}$ is the output at the n^{th} trial, and $H'_{(ns)0}$ is the prestimulation output value. For a defined stimulation event, the sign of σ is invariant.

Definition 2 During each non-stimulation phase, a spontaneous decay of γ occurs:

$$\gamma_{(ns)_n} = \gamma_{(s)_n} \bullet \Delta \tag{6}$$

where $\gamma_{(ns)_n}$ is the cumulative effect of the stimulation at the end of the n^{th} non-stimulation phase, $\gamma_{(s)_n}$ is the gain at the end of the n^{th} stimulation phase, and Δ is the non-stimulation factor. It follows

$$H'_{(ns)n} = H'_{(s)n} \pm \gamma_n \bullet \Delta \tag{7}$$

Given a defined stimulation protocol and habituation element(s), Δ is influenced by $t_{(ns)}$ and defined by the nature of the habituation element(s), but not directly affected by the magnitude of the stimulation.

Both Δ and σ reflect the intrinsic characteristics of the habituation element(s) and are influenced by the stimulation protocol.

3.1. Description of Δ

When the stimulation is withheld, the spontaneous decay process occurs. However, the nature of the process cannot be assumed a priori. Here we describe three plausible profiles of Δ: exponential, linear, or sigmoidal (see Supporting Information):

$$\Delta = e^{-\lambda \bullet t_{(ns)}} \tag{8}$$

$$\begin{cases} \Delta = 1 - \dfrac{1}{t_h} \cdot t_{(ns)} & \forall \ \ t_{(ns)} < t_h \\ \Delta = 0 & \text{otherwise} \end{cases} \tag{9}$$

$$\Delta = \frac{1}{1 + h \bullet e^{t_{(ns)}}} \tag{10}$$

Independent of the nature of the profile, the decay process occurs since for any $t_{(ns)}>0$ follows $\Delta < 1$.

4. Progression of the Habituation Process

We now explore what happens to H' over the protocol. Before the stimulation,

$$H'_{(ns)n-1} = H'_{(ns)0} \tag{11}$$

where $H'_{(ns)0}$ is the output of the habituation element before the stimulation phase; its value is time- and stimulation-independent and defined by the state and nature of the habituation element(s).

During the first trial $(s)_1$ (**Figure 2**A,B; left, arrow), $H'_{(s)0}$ is increased/decreased by σ as follows:

$$\begin{cases} H'_{(s)1} = H'_{(ns)0} \pm \sigma \\ \gamma_{(s)_1} = \sigma \end{cases} \tag{12}$$

For the first trial, γ and σ coincide. When the stimulus is first withheld $(ns)_1$, $\gamma_{(s)_1}$ decays as follows:

$$\begin{cases} H'_{(ns)1} = H'_{(ns)0} \pm \gamma_{(s)_1} \cdot \Delta \\ \gamma_{(s)_1} = \sigma \end{cases} \tag{13}$$

$$\begin{cases} H'_{(ns)1} = H'_{(ns)0} \pm \sigma \cdot \Delta \\ \gamma_{(s)_1} = \sigma \end{cases} \tag{14}$$

During the second trial $(s)_2$, $H'_{(ns)1}$ is increased/decreased by σ as follows:

$$\begin{cases} H'_{(s)2} = H'_{(ns)1} \pm \sigma \\ H'_{(ns)1} = H'_{(ns)0} \pm \sigma \cdot \Delta \end{cases} \tag{15}$$

$$\begin{cases} H'_{(s)2} = H'_{(ns)0} \pm (\sigma \cdot \Delta + \sigma) \\ \gamma_{(s)_2} = \sigma \cdot \Delta + \sigma \end{cases} \tag{16}$$

When the stimulus is withheld a second time (ns_2), $\gamma_{(s)_2}$ decays as follows:

$$\begin{cases} H'_{(ns)2} = H'_{(ns)0} \pm \gamma_{(s)_2} \cdot \Delta \\ \gamma_{(s)_2} = \sigma \cdot \Delta + \sigma \end{cases} \tag{17}$$

$$\begin{cases} H'_{(ns)2} = H'_{(ns)0} \pm (\sigma \cdot \Delta^2 + \sigma \cdot \Delta) \\ \gamma_{(s)_2} = \sigma \cdot \Delta + \sigma \end{cases} \tag{18}$$

Generalizing for an n^{th} trial (s_n),

$$\begin{aligned} H'_{(s)n} &= H'_{(s)n-1} \pm \sigma \\ &= H'_{(ns)0} \pm \sigma \ (\Delta^0 + \Delta^1 + \Delta^2 + \cdots + \Delta^{n-1}) \\ &= H'_{(ns)0} \pm \sigma \sum_{i=0}^{n-1} \Delta^i \\ &= H'_{(ns)0} \pm \sigma \frac{1 - \Delta^n}{1 - \Delta} \end{aligned} \tag{19}$$

Generalizing for the n^{th} non-stimulation (ns_n),

$$\begin{aligned} H'_{(ns)n} &= H'_{(s)n} \pm \gamma_n \cdot \Delta \\ &= H'_{(ns)0} \pm \sigma \ (\Delta^1 + \Delta^2 + \cdots + \Delta^n) \\ &= H'_{(ns)0} \pm \sigma \sum_{i=1}^{n} \Delta^i \end{aligned} \tag{20}$$

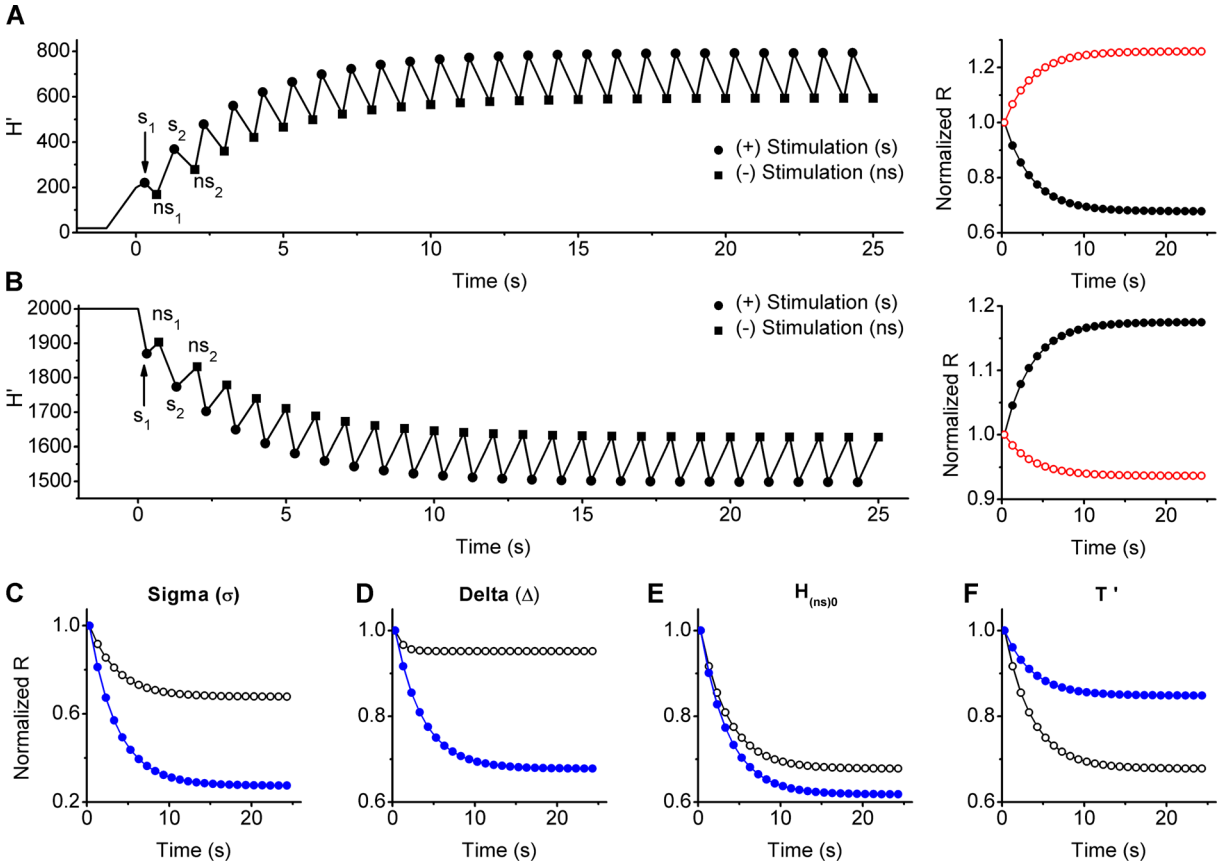

Figure 2. Profile of a generalized habituation process. The profile of H' is shown if $H'_{(ns)0}$ is A) increased or B) decreased (left). The normalized R profile is shown adding (empty circle) or subtracting (full circle) H'. (A and B, right, respectively) from R. Other parameters being equal, the normalized output of the system is shown increasing (full circle) the value of C) sigma, D) delta, E) $H'_{(ns)0}$, and F) T'. The values of the parameters are summarized in Table S1 (Supporting Information).

The profile of H' during the repetitive stimulation is outlined in Figure 2A,B (left) and in Figure S1 (Supporting Information), where $H'_{(s)n-1}$ increases (A) or decreases (B) (the arbitrary parameters values are summarized in Table S1 (Supporting Information). The convergence of the profile is predicted by $\Delta < 1$.

Combining Equations (1) and (19), we obtain R at the nth event as follows:

$$R_n = T'_n + H'_{(ns)0} \pm \sigma \sum_{i=0}^{n-1} \Delta^i + B \tag{21}$$

in which case T'_n, σ, and Δ are dependent on the stimulation. The normalized output R is shown in Figure 2A,B (right). As previously discussed, R can increase (empty red circle) or decrease (full black circle) according to the sign of α. It follows that the habituation and sensitization processes could equally arise. From this point, only the habituation profile will be discussed.

It is evident from Equation (21) that the habituation process is state-dependent. Given a defined protocol, the initial state of the system ($H'_{(ns)0}$ and B) and stimulation define its response.

5. What is the Role of the Variables?

Comparing two habituated systems and all things being equal, the higher is (Figure 2C–F; full blue circles):

- σ: more pronounced the habituation;
- Δ: more pronounced and less rapid the habituation;
- $H'_{(ns)0}$: more pronounced the habituation;
- T'_n: less pronounced the habituation.

Overall, the degree of the habituation is influenced by all four variables, whereas Δ is the only parameter that affects the kinetics of the curve and thus influences the rate of habituation.

6. Upper and Lower Limits of the Habituation Process

Considering a biological maximum number of modules, S_{MAX}, and of the activity, α_{MAX}, and taking into consideration Equation (2), we develop an H_{MAX} limit, which leads to

$$H_{(s)_n} = \begin{cases} H_{(s)_{n-1}} + \sigma & \text{if } H_{(s)_{n-1}} + \sigma < H_{max} \\ H_{max} & \text{otherwise} \end{cases} \tag{22}$$

Similarly, Equation (23) represents the lower limit H_{MIN}:

$$H_{(s)_n} = \begin{cases} H_{(s)_{n-1}} - \sigma & \text{if } H_{(s)_{n-1}} - \sigma > H_{\min} \\ H_{\min} & \text{otherwise} \end{cases} \quad (23)$$

If the stimulation is high enough to have

$$H_{(s)_1} = H_{\max} \quad (24)$$

H is saturated at the first event; thus, it will be time-invariant and no habituation profile emerges. However, if we assume that

$$\begin{cases} H_{(s)_1} < U_{H_{\max}} \\ H_{(s)_2} = U_{H_{\max}} \end{cases} \quad (25)$$

the saturation will occur during the second trial. This profile is compatible with one-trial habituation. Similar conclusions are drawn considering $H_{\min}$.

7. Emerging Properties of the Habituated System

Here we explore whether the process outlined above generates the major characteristics of habituation as defined in the literature.[1]

7.1. Decremental Response

"Given that a particular stimulus elicits a response, repeated applications of the stimulus result in decreased response (habituation). The decrease is usually a negative exponential function of the number of stimulus presentations."

As is clear from Equation (19) and Figure 2A,B, the response of the system decreases asymptotically with an exponential-like profile without exponential premises. Interestingly, the model does not exclude increases of the response over the stimulation; a sensitization profile can emerge without assuming any biological premises. In other words, the model can equally generate either a sensitization or a habituation profile.

7.2. Reversibility

"If the stimulus is withheld, the response tends to recover over time (spontaneous recovery)."

At the end of the stimulation, independently of the nature of Δ, $\lim_{t_{int}\to+\infty} \Delta = 0$ leading to $H'_{(ns)n} = H'_{(ns)0}$, fulfills the reversibility requirement of the habituation process (see Supporting Information).

7.3. Repeated Series of Habituation and Recovery

"If repeated series of habituation training and spontaneous recovery are given, habituation becomes successively more rapid/pronounced."

Even though with the present model we cannot strictly predict inter-trial outcomes, after the first train of stimulation, we speculate on three scenarios (**Figure 3**A; first stimulation: empty black circle; second stimulation: blue full circle):

- The recovery process is incomplete; thus during the second stimulation $H'_{(ns)0(2)} > H'_{(ns)0(1)}$ or $H'_{(ns)0(2)} < H'_{(ns)0(1)}$. This implies an incomplete recovery to $H'_{(ns)0(1)}$, leading to a more pronounced profile (Figure 3A, left).
- The first stimulation transiently changes the intrinsic characteristics of the habituation element; σ and Δ will thus change. Assuming an arbitrary lower value of Δ in the second stimulation, the profile is faster and less pronounced (Figure 3A, middle). The information is therefore stored in the habituation element itself. Considering biological modules, a recycling of the elements should be taken into account. In this context, memoryless elements will substitute the "trained" one, restoring with time the original value of Δ.
- The first stimulation leads to the addition/removal of habituation element(s) in the system. In this case, $H'_{(ns)0}$, σ, and Δ of the system will change (Figure 3A, right), indicating a potential long-term encoding of information. The information is therefore stored in the new composition of the habituation element. In other words, the first stimulation changed the composition of the habituated system. Long-term memory is linked to the stability of the new habituation element and is insensitive to the recycling.

Without ignoring the complexity and diversity of the memory encoding process, the examples listed above represent the minimal set of scenarios to potentially explain memory encoding when considering the habituation element alone.

7.4. Impact of the Frequency of the Stimulation

"Other things being equal, the more rapid the frequency of stimulation, the more rapid and/or more pronounced is habituation."

Here, rapid (or faster) means a profile that reaches the asymptote after a lower number of events or over less elapsed time. The increased frequency of the stimulation protocol is reflected in a decreased $t_{(ns)}$ and a corresponding increase of the Δ value. No other variables are affected. As is clear from Figure 3B (left), when the frequency of stimulation is increased (blue full circle), the habituation profile is more pronounced and less rapid when we consider the number of events required to achieve the asymptote; this seems to conflict with behavioral habituation data. However, we need to consider that when the habituation process is more pronounced, the higher is the probability of reaching either H_{MAX} or H_{MIN} according to Equation (24) (Figure 3B, middle). This profile, in which an abrupt asymptote is reached, is frequently reported in the literature.[22,23] Moreover, it is important to notice that the rapid-like profile is evident when the time rather than the number of events is displayed on the x-axis of a habituation curve[2] (Figure 3B, right). With a higher frequency of stimulation and no modifications of the number of habituation

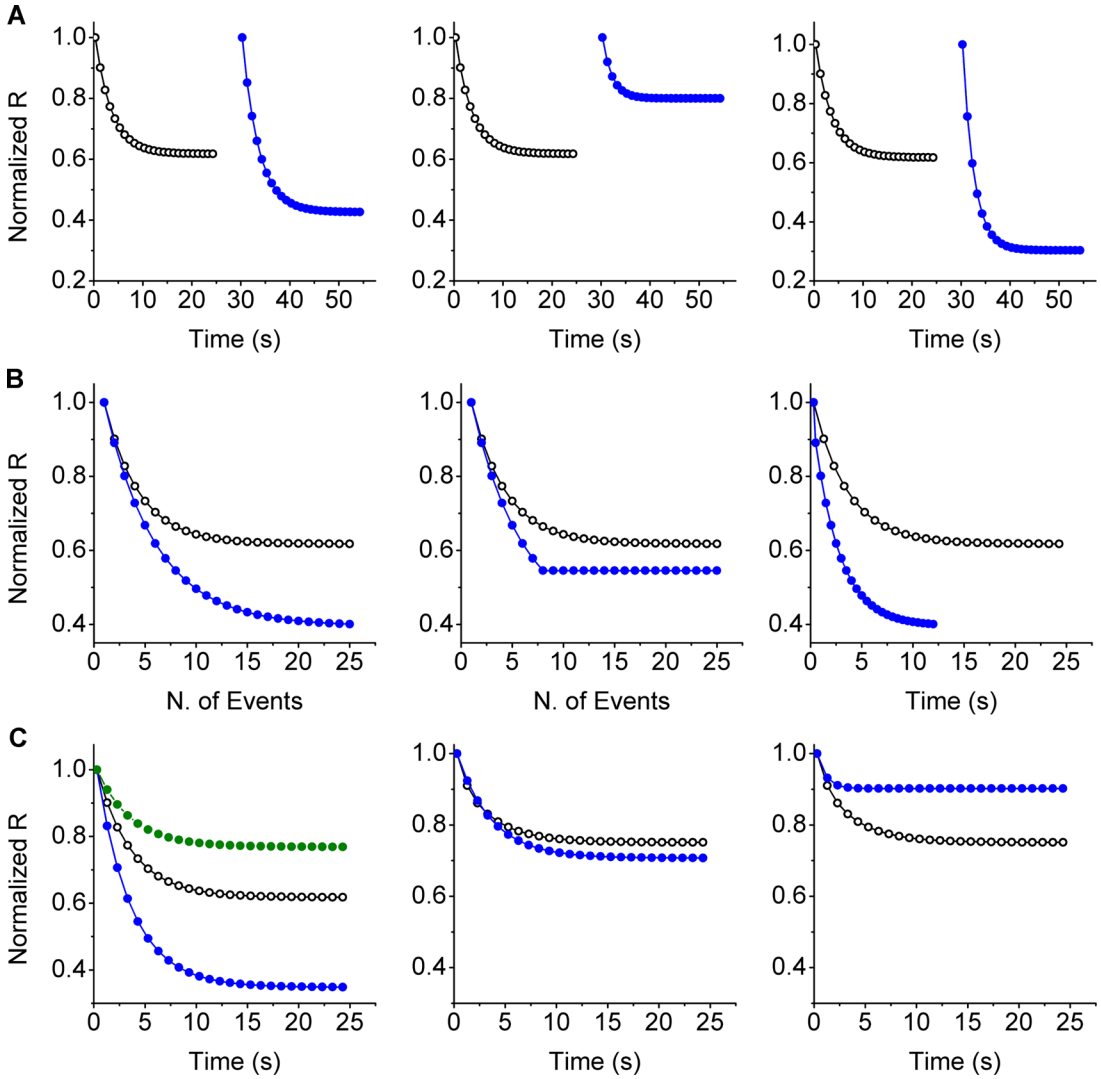

Figure 3. Impact of the stimulation on the habituation process. A) Habituation profile after repeated series of stimulations (first stimulation: black empty circle; second stimulation: blue full circle). B) A faster stimulation protocol (blue full circle) is considered plotting either events or time (left and right, respectively) or in the presence of a saturation event (middle). C) Considering one habituation element, if the magnitude increases, the profile could be either more/less pronounced (left; blue and green full circles, respectively). With more elements, the profile changes in both kinetic and magnitude (blue full circle, middle and right). The values of the parameters are summarized in Table S1 (Supporting Information).

elements involved, a slower profile is the only possible outcome. As the stimulation frequency increases, so too does the chance that a new habituation element will be activated/inhibited; in this case, R cannot be predicted a priori.

7.5. Impact of the Magnitude of the Stimulation

"The weaker the stimulus, the more rapid and/or more pronounced is habituation. Strong stimuli may yield no significant habituation."

The increased magnitude has an impact on σ and the translator element. This leads to a more/less pronounced habituation profile due to an increase of both σ and T' values; since Δ is not changed, the rate of change is not affected. The relative impact of σ and T' determines if the profile will be either more/less pronounced (Figure 3C, left, blue, and green full circle, respectively). The independence of Δ from the magnitude implies that when we consider a fixed number of modules, a modulation of the rate of change cannot occur. Considering a habituating system with at least two habituation elements (Figure 3C, middle and right, black lines), an increased stimulation could potentially bring one of the elements closer to either H_{MAX} or H_{MIN} (Equation 24), making the element itself time-independent. In the case where saturation is achieved with the higher value of Δ, the profile is less rapid (Figure 3C, middle, blue full circle). In case the element with the smaller Δ reaches saturation, the profile is more rapid (Figure 3C, middle, blue full circle). We cannot predict a priori which profile will emerge considering just the variables. The modification of the rate of change, thus, can only occur in the presence of more than one habituation element. In

cases where both systems reach the saturation point, no habituation occurs; this scenario is more likely to happen as the magnitude of the stimulation increases.

8. Identification of Δ from Raw Data

Given Equation (19), and considering that $T'_{(n)} = T'_{(n-1)}\ \forall\ n > 1$, we can use raw data from an experiment to calculate the Δ value as follows:

$$\Delta = \frac{R_{(n)} - R_{(n-1)}}{R_{(n-1)} - R_{(n-2)}} \tag{26}$$

or

$$\Delta^2 + \Delta + 1 = \frac{R_{(n)} - R_{(n-3)}}{R_{(n-2)} - R_{(n-3)}} \tag{27}$$

where n is the n^{th} trial of the stimulation protocol (see Supporting Information).

9. Limitations and Advantages

For each trial, we assume that the stimulation induces the same increase/decrease of $U_{H'}$. This is a simplification and does not account for remodeling of the habituation element as well as feedback from the receiver element. Moreover, the model predicts intra-trial features; any inter-trial considerations can be explored but are not robustly supported by the model.

Despite these limitations, the model is flexible and can be applied to show the behavior of a given system independent of any biological detail. The convergence of the output naturally emerges from the premises without assuming exponential-like profiles of decay a priori. Further, the model is coherent with gold-standard features of habituation outlined in the literature, explaining and expanding our knowledge of a wide range of conditions such as the effect of the frequency and magnitude of stimulation, the recovery of the process, and one-trial habituation.

10. Conclusions

Contemporary theories have attempted to explain the biological mechanisms by which habituation occurs.[2] In all cases, this explanation centers on the function of neurons and circuits—admitting a brain-based bias. However, habituation seems to be a much broader biological phenomenon that is not exclusive to neural tissues.[14–17] Consequently, models that aim to reflect the rules and concepts underlying habituation should not be restricted to neuronal systems. Habituation should be treated as a process that can be adopted by any system with the necessary elements. Here we have described a model that is independent of any biological system—an abstraction of the habituation process that emerges from a small set of operating elements (Figure 1). As discussed, the habituation profile is a function of the stimulation–receiver pair and of the presence of the habituation element, the only time-dependent block. During stimulation, the receiver element output changes in response to the modifications that occur in the habituation element. Interestingly, both habituation and sensitization processes emerge (Figure 2A,B), suggesting that they are different facets of the same phenomenon. The model also adapts in response to stimulus modification, as previously found, considering the possibility of recruitment/recycling of the habituation elements (Figure 3). However, when we consider a fixed number of habituation elements, the results have some discrepancies with the published data. This is indicative of the fact that different outcomes can be expected and predicted when the flexibility of the system is assumed or not, thus showing the relevance of the presented model. In conclusion, we have provided a generalized model that considers the mechanisms of habituation irrespective of the biological details underlying the process itself, provides insights into the nature of the habituation elements, and predicts the output of the system in response to perturbations. The model will be helpful as a guideline to recognize the habituation process in virtually any system.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

M.B. and N.R. contributed equally to this work. This research was supported by the Allen Discovery Center program through The Paul G. Allen Frontiers Group (12171). The authors thank Dr. Erndt-Marino for the helpful comments on the project.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

habituation, non-neuronal, repetitive stimulations, stimulus–response

Received: February 9, 2019
Revised: April 7, 2019
Published online: June 21, 2019

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