An adaptive network model for pain and pleasure through spicy food and its desensitization

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Abstract

This paper aims to map out the adaptive causal pathways of processes underlying capsaicin consumption and the desensitization process of the TRPV1 receptor as a feedback loop together with pain and pleasure perception. In order to map out these causal capsaicin pathways, adaptive causal network modeling was applied, which is a way of modeling biological, neural, mental and social processes from an adaptive causal modeling perspective.

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Keywords: Adaptive causal network model; Capsaicin consumption; Pain and pleasure; Desensitization

1. Introduction

For many, spicy food can bring joy but at the same time it can bring pain as well. Moreover, over longer time periods some forms of adaptation in the sense of desensitization take place. In this paper, it is analysed computationally from a network modeling perspective how such processes and their adaptation over time take place. From a domain analysis, the causal pathways behind these processes have been found and it also has been found out how they adapt over time. Within these pathways there are main roles of capsaicin, the receptor TRPV1, the secretion of endorphins, and triggering of both pain and pleasure perceptions.

As far as the authors know, there do not exist any computational models for these processes. As these processes are inherently dynamic and adaptive, a modeling approach is required that is able to address this extent of flexibility. To this end, the approach to adaptive causal network modeling described by (Treur, 2020) was applied. This modeling approach can be considered as a branch in the causal modeling area which has a long tradition in AI; e.g., see (Kuipers & Kassirer, 1983; Kuipers, 1984; Pearl, 2000). However, it distinguishes itself by a dynamic perspective on causal relations, according to which causal relations (1) exert causal effects over time, and (2) these causal relations themselves can change over time as well. The type of network model used is called an adaptive temporal-causal network model. It is shown that using such an upgraded form of causal modeling, by adding dynamics and adaptation to it, application domains become possible that otherwise would be out of reach of causal modeling.

In this paper, first in Section 2 the domain is described in some detail. Then in Section 3 the designed adaptive causal network model is described. Section 4 discusses a number of the simulation experiments that have been conducted. In Section 5 it is shown how mathematical analysis of
stationary points of the model was performed as a form of verification. Finally, Section 6 is a discussion.

2. Domain description: The role of capsaicin for spicy food

Spicy dishes are present in almost every kitchen around the world, with spiciness ranging from a little spicy to a feeling of a mouth that is set on fire. Examples are Indian hot curries, Thai soup or Chinese hot pot. The spiciness is often caused by the addition of chili peppers or an extract of these peppers and the spiciness can be expressed in the Scale of Scoville. Consumption of chili peppers is correlated with positive health outcomes, since they are filled with vitamins and antioxidants (Lee, Howard, & Villalon, 1995; Sun et al., 2007). The study (Lv et al., 2015) found some evidence that consumption of fresh chili peppers was related to reduced mortality and less chance to develop cancer and diabetes (Clark & Lee, 2016; Lee, Richardson, Dashwood, & Back, 2012; Zhang, Ma, Zhang, Sun, & Liu, 2017). In addition, chili pepper is used in a wide variety for therapeutic purposes, namely for treatment of osteoarthritis pain, migraine and peripheral neuropathic pain (Buntinx, Vermeersch, & de Hoon, 2015; Giménez-Milà et al., 2014; Laslett & Jones, 2014).

The main active compound in chili peppers that give them that unique spicy taste is called capsaicin (Fattori et al., 2016; O’Neill et al., 2012), which is known for its ability to bind to the transient receptor potential cation channel vanilloid subfamily V member 1 (TRPV1; Frias & Merighi, 2016). This particular TRPV1 receptor can be labelled as ion channels that are located in the terminal endings of primary nociceptive neurons that sense heat (Smutzer & Devassy, 2016). Notable, this indicates that individuals that consume capsaicin do not actually taste the spiciness, but feel it instead. Considering the consumption of capsaicin, a significant amount of TRPV1 receptors can be found in neurons in the nasal and oral cavities. Activation of the nociceptive neurons therefore leads to the secretion of endorphins by the pituitary gland (Sprouse-Blum, Smith, Sugai, & Parsa, 2010). The reason behind the secretion of these endorphins is their ability to reduce or eliminate pain signals. This effect is established by blocking the mu receptors on the axial terminal of the nociceptive neurons, which results in the inhibition of substance P release and thereby reducing or eliminating the pain signal (Dishman & O’Connor, 2009). Furthermore, endorphins are opioid neuropeptides that also play a role in increasing the level of dopamine, which leads to a higher pleasant or euphoric sensation (Sprouse-Blum et al., 2010). This might indicate the reason why a substantial amount of individuals enjoy the consumption of spicy food.

Evidently, many people enjoy the consumption of spicy food (Spence, 2018), while others do everything to avoid the stingy foods. Various factors are related to liking and intake of spicy foods and one of the most prominent one is the altering sensitivity of the TRPV1 receptor. After regular and continuous consumption of spicy food, an individual’s TRPV1 receptor usually adapts over time. This particular adaptation is referred to as the desensitization of the TRPV1 receptor (Touska, Marsakova, Teisinger, & Vlachova, 2011). Normally, when capsaicin binds to TRPV1, the channel opens allowing an influx of Ca2+. Besides the release of substance P, the influx of Ca2+ also leads to a depletion of 4,5 bisphosphate (PIP2), which is a phospholipid that is a component of intracellular plasma membranes. Consequently, depending on the duration of capsaicin consumption, this depletion of PIP2 leads to the desensitization of TRPV1 (Yao & Qin, 2009). This desensitization results in a less sensitive TRPV1 receptor, meaning that someone is able to enjoy more spicier food. On the other hand, a certain level of desensitization of the receptor can lead to decreased amount of endorphins release and subsequently results in an unsatisfying feeling of pleasure. This means that a higher capsaicin intake is needed in order to attain equal levels of joy induced by consumption of spicy food.

3. The design of the adaptive network model

In the literature, physical, biological and mental processes often are described by pathways through causal networks, also called causal pathways. Causal modeling has a long standing tradition in AI; e.g., see (Kuipers & Kassirer, 1983; Kuipers, 1984; Pearl, 2000). For the application domain addressed here, a particular causal modeling approach is required that is able to model dynamics and adaptivity of such causal pathways. The modeling approach based on reified adaptive temporal-causal networks, as presented in (Treur, 2020), fulfills such requirements and is used here. First, a brief introduction to this adaptive causal modeling approach. A temporal-causal network is defined by the following types of network characteristics:

- **connectivity characteristics**: the connections from nodes (also called states) to and from their weights \( \omega_{X,Y} \); here states \( X \) have varying values \( X(t) \) over time \( t \).
- **aggregation characteristics**: for each state \( Y \), by a combination function \( c_Y(\cdot) \) some form of aggregation is applied to the causal impacts \( \omega_{X,Y}(t) \) from its incoming connections from states \( X_1, \ldots, X_k \).
• **timing characteristics:** each state \( Y \) has a speed factor \( \eta_Y \) indicating how fast it changes upon causal impact.

The standard difference equations used for simulation and mathematical analysis incorporate these three types of network characteristics \( \omega_{X,Y}, c_Y(\cdot), \eta_Y \): for any state \( Y \) it holds
\[
Y(t + \Delta t) = \begin{cases} 
Y(t) + \eta_Y [c_Y(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t))] & \text{if } Y(t + \Delta t) \leq \mu_Y \\
Y(t) \Delta t & \text{otherwise}
\end{cases}
\]

where \( X_1, \ldots, X_k \) are the states from which \( Y \) gets incoming connections; this can also be expressed by an equivalent differential equation. These concepts enable to design and analyse causal networks with their dynamics by declarative mathematically defined relations. For example, for analysis of stationary points or equilibria (i.e., when no change occurs: \( dY/dt = 0 \)), based on (1), the criterion is
\[
c_Y(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t)) = Y(t)
\]

This far adaptive causal networks, in which the network characteristics \( \omega_{X,Y}, c_Y(\cdot), \eta_Y \) may change over time, are not covered yet. However, it was found out that extending the approach by the notion of network reification makes that this network modeling perspective becomes suitable to design adaptive networks as well, still by declarative mathematically defined relations. Reification (Galton, 2006) generally means making abstract things concrete; well-known examples are representing relations between objects by objects themselves, and representing logical statements by numbers. Network reification works by adding the (this time adaptive) network characteristics \( \omega_{X,Y}, c_Y(\cdot), \eta_Y \) in a reified form to the network as states \( W_{X,Y}, C_Y, H_Y \) at a second level, called adaptation level or reification level, while the original network forms the base level. For example, to model synaptic adaptation (e.g., Hebbian learning), reification states \( W_{X,Y} \) can be used to represent an adaptive connection weight \( \omega_{X,Y} \) for the connection from state \( X \) to state \( Y \); see also the quote from (Chandra & Barkai, 2018) below. Moreover, for any adaptive parameter \( \pi_Y \) of a combination function \( c_Y(\cdot) \) of state \( Y \), a reification state \( P_Y \) can be added. Below, this will be applied in particular to represent by reification states \( T_Y \), adaptive excitability threshold parameters \( t_Y \) of logistic combination functions used. Such reification states can be used to model adaptive intrinsic neuronal excitability as described, for example, in (Chandra & Barkai, 2018; Chen et al., 2020); e.g.

"Learning-related cellular changes can be divided into two general groups: modifications that occur at synapses and modifications in the intrinsic properties of the neurons. While it is commonly agreed that changes in strength of connections between neurons in the relevant networks underlie memory storage, ample evidence suggests that modifications in intrinsic neuronal properties may also account for learning related behavioral changes. Long-lasting modifications in intrinsic excitability are manifested in changes in the neuron’s response to a given extrinsic current (generated by synaptic activity or applied via the recording electrode)." (Chandra & Barkai, 2018, p. 30)

More specifically, reification states \( T_Y \) will be applied below to model adaptive excitability thresholds for pain and pleasure, and for the TRPV1 receptor.

Network reification introduces in the network modeling area ideas similar to those in another long standing tradition in AI, namely that of metalevel architectures and metaprogramming, which can be found in different forms in, e.g., (Bowen & Kowalski, 1982; Davis, 1980; Demers & Malenfant, 1995; Sterling & Beer, 1989; Weyhrauch, 1980). The obtained adaptive modeling approach comes with a dedicated modeling environment incorporating the above summarised reified causal network architecture and a generic computational reified causal network engine to run it, implemented in Matlab; see (Treur, 2020), Ch 9.

Fig. 1 depicts an overview of the connectivity of the base level of the designed network model. The causal pathways start with the intake of capsaicin (\( X_1 \)), after which the TRPV1 receptor becomes activated (\( X_2 \)). This activation leads to an influx of Ca\(^{2+} \) (\( X_3 \)) and subsequently to depletion of PIP\(_2 \) (\( X_4 \)). Additionally, the calcium increase leads subsequently to the release of Substance P (\( X_5 \)). The activation of the nociceptor (\( X_6 \)) follows, which causes the perception of pain (\( X_7 \)). Nociceptor activation also causes the release of endorphins (\( X_8 \)), which initiates the pleasure perception (\( X_9 \)). Secretion of endorphins has a negative feedback on the release of Substance P.

The adaptation of the base network is modeled at the adaptive level, also called the (first) reification level. At this level, three reification states \( T_{SC}, T_{pain}, \) and \( T_{pleasure} \) (also named as \( X_{10}, X_{11}, \) and \( X_{12} \)) model the adaptive excitability thresholds for the TRPV1 receptor, for pain perception, and for pleasure perception, respectively. An overview of the connectivity of the obtained overall adaptive causal network model is shown in Fig. 2. The states of the model are explained in Table 1.

Box 1 shows a complete overview in the form of role matrices of all network characteristics used in the model. These role matrices serve as a declarative design specification of the adaptive network model and are used as input for the modeling environment. The role matrices include matrices for the base connectivity (\( mb \)), connection weights (\( mcfw \)), function parameter (\( mcfp \)) and the speed factors (\( ms \)). For example, in role matrix \( mcfw \) for the combination function weights role, it is shown how multiple combination functions are used in the model; they are selected from the available combination function library. In a role matrix, each state (indicated in the leftmost column by \( X \), and in the second column by its more informative name) has its own row. In the other columns it is indicated which characteristics
affect that state $X_i$ from the given role. First, as can be seen in role matrix mcfw in Box 1, the function $\text{stepmodopp}_{p,d}(\cdot)$ is used for repetitive spicy food (capsaicin) intake ($X_1$) as an external input, where $p$ is the repetition time period and $d$ the duration. Second, the logistic function $\text{alognistic}_{r,s}(\cdot)$ is used for four of the base states ($X_2, X_7, X_8, X_9$) and for the three reification states ($X_{10}, X_{11}, X_{12}$) in order to model adaptive excitability thresholds; here $r$ is the steepness parameter and $s$ the excitability threshold parameter. Lastly, the identity function $\text{id}(\cdot)$ is used for four base states that only receive one incoming connection ($X_3, X_4, X_5, X_6$). The function $\text{alognistic}_{r,s}(V_1, \cdots, V_k) = \frac{1}{1 + e^{-r(V_{1}+\cdots+V_k)-s}} + \frac{1}{1 + e^{r}}(1 + e^{-s})$

For more details of the role matrices, see Box 1.

In particular, note the dark yellow cells in role matrix mcfp for combination function parameters in the column for the excitability threshold parameters $\tau$ that are not filled with values but with entries $X_{10} (= T_{SC}), X_{11} (= T_{pain}), X_{12} (= T_{pleasure})$. This specifies that the value of such a threshold parameter is not a static value, but can be found as the dynamic value of the indicated state.
4. Simulation results

When running the simulations according to the proposed role matrices shown in Box 1, the simulation outcome was as depicted in Fig. 3; the initial values of all states were 0, except the one for X12 which was 0.9. This figure shows the normal course of events. The reaction starts with the intake of capsaicin and the subsequent reactions follow. The reaction ends when the intake of capsaicin is ceased. Shown are multiple events of capsaicin intake, mimicking numerous capsaicin intake episodes. Besides the fluctuating base states, the graph also shows the three slowly increasing or decreasing adaptation states X10 (=TSC), X11 (=Tpain), X12 (=Tpleasure) from the reification level.

Fig. 4 focuses on the perception of both pain and pleasure. The upper graph in Fig. 4 shows that first the perception of pain (the red line) is stronger than the perception of pleasure (the green line). However, over time the perception of pleasure becomes dominant over the pain perception. The intake of capsaicin leads to the (indirect) increase of pain perception. The perception of pain is initiated by the activation of the nociceptor. Pain perception is in turn countered by the release of endorphins, which initiates feelings of pleasure. The intake of capsaicin leading to a feeling of pain is being battled by pleasure and as a result, the perception of pain is decreasing. The simulation shows that the perception of pain decreases over time as a result of an increasing threshold for pain and hence less activity of the TRPV1 receptor. The lower graph in Fig. 4 is in concordance with the latter described event.

As another form of adaptation the threshold for pain is increasing (the yellow upward curve for T-state X11 in the right graph in Fig. 4, which is the purple upward line in Fig. 3. Subsequently, the perception of pain decreases.

To demonstrate the impact of the adaptive factors incorporated in the model, in contrast the simulation displayed in Fig. 5 shows the situation in which the thresholds are not adaptive. The figure shows exactly equal episodes without changes over time, indicating the effect of the static thresholds on the TRPV1 state and on the pain and pleasure perception states.

The above simulation addresses a kind of ‘average’ person. In the real world, some persons are able to enjoy more spicy food than others. To mimic this, the model has been used to model specific types of persons. This can easily be done by adjusting some of the network characteristics as shown in Box 1. As a first example, depicted in Fig. 6, some adjustments are introduced to achieve a simulation in which the person at stake is not able to eat spicy, meaning that the pleasure perception is fairly low compared to the pain perception even though endorphins are released to counter the pain signals. In order to cover this type of person, the role matrices were adjusted as follows:

- The connection weight of X8 was increased from 1.0 to 1.1.
- The connection weight of X9 was decreased from 1 to 0.9.
- The connection weight of second incoming connection of X11 was decreased from 1.0 to 0.7.
- The connection weight of second incoming connection of X12 was increased from 1.0 to 1.3.
- The threshold of X11 was increased from 0.6 to 0.8.
- The threshold of X12 was decreased from 0.8 to 0.78.

These alterations resulted in the simulation outcome shown in Fig. 6. It shows that the perception of pain remains dominant, although the adaptive components are still present resulting in increasing pleasure and decreasing pain perception over time. However, the feeling of pain stays too high compared to the feeling of pleasure to enjoy the spicy food.
Fig. 3. Overall simulation outcome for all states of the adaptive network model for capsaicin intake.
In the next scenario, the person at stake is able to eat spicy food from the start. The perceived feeling of pain is thus low and feeling of pleasure is high. In this event, the TRPV1 receptor is already in a more desensitized state. The following alterations were used in order to cover this type of person:

- The connection weight of X₈ was decreased from 1 to 0.9.
- The connection weight of X₉ was decreased from 1 to 0.8.
- The speed factor of X₈ was decreased from 0.7 to 0.4.
- The speed factor of X₉ was increased from 0.7 to 0.9.
- The connection weight of second incoming connection of X₁₁ was increased from 1 to 1.2.
- The connection weight of the second incoming connection of X₁₂ was decreased from 1 to 0.8.
- The threshold of X₁₂ was decreased from 0.8 to 0.9.

The result is shown in Fig. 7. It depicts the situation in which the TRPV1 receptors desensitize quite fast, meaning that the pain perception decreases faster than in the original scenario. Despite the dominant pleasure perception, it must be noted that the perception of pleasure does not reach equal values as in the original scenario. The values in Fig. 7 are lower, implying that the person at stake has to increase his or her capsaicin intake in order to attain equal pleasure perception.

5. Mathematical analysis and verification

Analysis of the model to obtain a form of verification was performed in order to check the accuracy of the model. In such an analysis, the values shown by a simulation output of the model for stationary points of state $Y$ are com-
pared with the values obtained by using the combination function $c_Y(\cdot)$ to obtain the aggregated impact on $Y$. A state $Y$ has a stationary point at time $t$ if $\frac{dY(t)}{dt} = 0$ and this happens if and only if

$$c_Y(\omega_{X_1,Y}X_1(t), \ldots, \omega_{X_k,Y}X_k(t)) = Y(t)$$

where $X_1, \ldots, X_k$ are the states from which $Y$ gets incoming connections. The smaller the difference between the calculated value (left hand) and the generated value by Matlab (right hand), the higher the accuracy of the model.

Appropriate stationary points for well-chosen time points were used. Not all states were suitable for analysis and verification. However, analysis has been performed with the states with a logistic combination function, with exception of the ones with an adaptive threshold. The results are shown in Table 2.

Although the aggregated impact of only a small number of states has been calculated, it can be concluded that the values generated by the model are fairly accurate, with an deviation ranging from 0.007 to 0.03.
6. Discussion

This paper addresses computational modeling of the adaptive processes that occur when frequently eating spicy food (Flonta & Ristoiu, 2017). As far as the authors know, there does not yet exist any computational model for these adaptive processes. In the presented adaptive network model the incorporation of an adaptive TRPV1 receptor and hence a decreasing sensation of pain was obtained as aimed for. Altogether, based on literature it is an adequate adaptive network of the neural, biological and mental processes underlying the working mechanism of capsaicin. This adaptive network model could therefore be used to support future studies and, for example, for a basis of a virtual agent with more or less realistic ways to appreciate (or depreciate) the intake of spicy food.

Nevertheless, as extensions additional causal pathways and states could be taken into account besides the ones that were used in the presented model. For instance, taste phenotype, oral anatomy, exposure and familiarity with spicy foods, personality, and thrill and adventure seeking behavior also may play a role in the level of spiciness an individual experiences as pleasurable or painful (Byrnes & Hayes, 2015). The incorporation of these additional states would lead to a larger and more complex network. Moreover, in future extensions of the model, also adaptive connection weights, cross connections and even higher reification levels could be introduced. For example, the addition of an adaptive component linked to endorphins release and adventure seeking could be considered.

The presented causal network model fits in the long standing tradition of causal modeling in AI; e.g., see (Kuipers & Kassirer, 1983; Kuipers, 1984; Pearl, 2000). However, for the application domain addressed here, a particular causal modeling approach was required that is able to model dynamics and adaptivity of the relevant causal pathways. For dynamics, temporal-causal networks (Treur, 2016) are adequate modeling concepts. For adaptivity, another extension is required, which was obtained in (Treur, 2020) by introducing in the causal modeling area ideas similar to metalevel architectures and metaprogramming as found in different forms in another long standing tradition in AI: e.g., (Bowen & Kowalski, 1982; Davis, 1980; Demers & Malenfant, 1995; Sterling & Beer, 1989; Weyhrauch, 1980). Given these extensions to the more traditional ways of causal modeling, the causal modeling approach based on reified adaptive temporal-causal networks, as presented in Treur (2020), was used here and was shown to fulfill the indicated requirements concerning dynamics and adaptation for the addressed application domain. Therefore it is shown that an upgraded form of causal modeling in this way can address application domains in which dynamics and adaptation play an important role.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 2

| State X_i | Time point t | X_i(t) | aggimpact_X_i(t) | deviation |
|-----------|--------------|--------|------------------|-----------|
| 7         | 24           | 0.76717| 0.774717         | 0.007547  |
| 10        | 700          | 0.934918| 0.901397         | 0.033521  |
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