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*“A Bayesian Model for Chronic Pain”*

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Submitted by

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**Abstract**

Pain is ubiquitous in most living creatures and ensures survival through its protective function. Chronic pain, however, has lost its function as a warning sign and must be considered maladaptive. Recent ideas regarding the etiology of chronic pain originate in statistical and computational frameworks. According to this view, pain perception can be regarded as emerging from a Bayes-optimal combination of prior knowledge and sensory information. Chronic pain conditions then develop from suboptimal settings or events within this computational process.

To test this idea, we here describe a machine-learning model for chronic pain which is based on a hierarchical Hidden Markov Model (HMM). In this Bayesian network model, messages are passed via the Sum-Product algorithm to illustrate maladaptive changes in expectations or attention over time. A free energy learning is implemented […]

Results of the simulation with this HMM-based model suggest that […]   
We further applied the described model to questionnaire data of children with chronic abdominal pain and performed a model selection procedure. This procedure yielded that [xxx].   
  
In conclusion, we here demonstrate how computational models can help furthering current etiologic knowledge and approaches to understanding chronic pain. We propose a Bayesian model for chronic pain that extends current fear-avoidance models by specifying model parameters and their settings that lead to dysfunctional behavior on a computational level. The idea of a therapeutic ‘null space’ is discussed. Ideas on extensions of this model towards other mental conditions, such as conversion disorders or hypochondriasis, are outlined and discussed.

# 1. Theoretical background

## 1.1. Introduction to pain

*To be in physical pain is to find yourself in a different realm – a state of being unlike any other, a magic mountain as far removed from the familiar world as a dreamscape. Usually, pain subsides, one wakes from it as from a nightmare, trying to forget it as quickly as possible. But what of pain that persists? The longer it endures, the more excruciating the exile becomes.* Will you ever go home? y*ou begin to wonder, home to your normal body, thoughts, life?*

Melanie Thernstrom, *The Pain Chronicles: Cures, Myths, Mysteries,  
Prayers, Diaries, Brain Scans, Healing and the Science of Suffering*   
(New York: Farrar, Straus and Giroux; 2010, p.3)

Pain is a ubiquitous phenomenon in many creatures. The above quote from Melanie Thernstrom draws a rather pessimistic image of pain as a distressing experience, leaving the individual detached from its surroundings and consumed by its aversive experience. Despite its distressing emotional consequences, pain has a clear benevolent and adaptive function. Painful experiences demand immediate attention and a behavior that results in, or could result in, injury, such as touching a hot plate or a sharp object, is withdrawn from reflexively. This type of pain is also referred to as *nociceptive pain* (Basbaum, Bautista, Scherrer, & Julius, 2009; Woolf, 2010). A lack of nociceptive pain, as present in individuals with ‘congenital insensitivity to pain’, illustrates its adaptive, threat-signaling function. Individuals with this very rare abnormality are not able to perceive pain from birth (Schon, Parker, & Woods, 1993). As a consequence of this, they frequently present to physicians with self-mutilation injuries of the fingers, cuts, burns and bruises (Nagasako, Oaklander, & Dworkin, 2003; Schon et al., 1993). Hence, a lack of nociceptive pain poses serious threats to an individuals’ physical integrity.

Further, pain can promote recovery after an injury by discouraging moving or touching the injured body part. This second type of pain is also referred to as *inflammatory pain* (Flor & Turk, 2015; Woolf, 2010). Healing processes are supported by means of a heightened sensitivity to pain after tissue damage, which makes otherwise innocuous stimuli subjectively aversive (Kidd & Urban, 2001). This is referred to as ‘hyperalgesia’ (i.e., increased pain responses to noxious or harmless stimuli) and discourages, for example, touching an open wound or sunburn which in turn can reduce the risk of bacteria transmission and infection.

However, pain experiences also occur without a clear underlying physical pathology. In this context, the pain experience is dysfunctional as it is devoid of the signaling function that characterizes nociceptive and inflammatory pain. Experts refer to this as *persistent* or *chronic pain*. Before turning to the nature and prevalence of chronic pain, basic concepts and terms related to pain are introduced in the next paragraph.

## 1.2. Pain: terminology and theoretical concepts

One widely used definition of pain is given by the International Association for the study of Pain (IASP) that describes pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (see Wall, 1979). This definition encompasses several interesting concepts. First, it defines pain as an ‘experience’ which highlights its subjective nature and makes it conceptually different from nociception. Nociception is the term used to describe the ‘transduction and transmission of a noxious stimulus to the brain via the pain pathway’ (Steeds, 2016). Secondly, the above definition does not incorporate a pain-initiating stimulus. Indeed, a large body of research suggests a non-linear, ambiguous relationship between pain perception and actual bodily damage, or nociception (Moseley & Vlaeyen, 2015; Tabor, Thacker, Moseley, & Körding, 2017). Simple stimulus-response models are deemed inappropriate. Instead, pain perception is assumed to be subject to the modulatory influence of a multitude of interacting, individual and subjective (e.g., cognitive, attentional, motivational, individual) factors (Loeser & Melzack, 1999; Steeds, 2016).

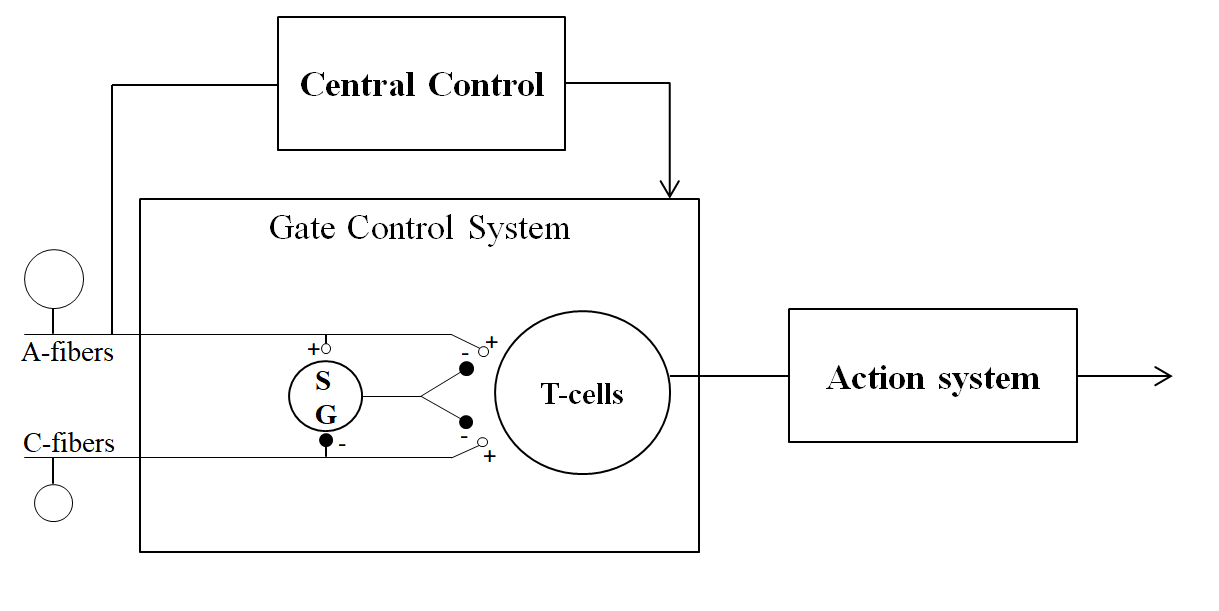
The idea of a non-linear relationship between nociceptive stimulation and pain perception evolved over several millennia. Initial ideas date back to the Cartesian mind-body dualism. In his treatise about the human (‘l’homme’), Descartes (ca. 1644) was one of the first to propose a detailed somatosensory pain system (Moayedi & Davis, 2013). Herein, he described pain as a perception within the brain that is distinctive from the neural transduction of the pain signal (today, a.k.a. nociception) via hollow nerve fibers. Very figuratively, Descartes proposed that pain had a function equivalent to a bell ringing in the brain in response to a pull on a thread (i.e. the nerve fiber) at the location where harmful stimulation occurred (Hadjistavropoulos & Craig, 2004; R Melzack & Wall, 1965). Consequently, this signal motivates actions that serve to avoid damage (e.g., allocating overt attention to the harmful event, avoiding further damage).   
Early Cartesian concepts were incorporated and refined within ‘specifity theory’. This theory refers to pain as emerging from stimulation of a distinct sensory modality (comparable to vision or hearing) with its own physiological components such as specific receptors and associated nerve fibers (Hadjistavropoulos & Craig, 2004; Moayedi & Davis, 2013). This pain modality and its receptors are assumed to be sensitive to one specific stimulus. Within the theory, it is proposed that innocuous stimuli are encoded via low-threshold mechanoreceptors, whereas noxious stimuli would activate nociceptors that transduce the pain signal to designated pain areas via pain fibers.   
In contrast to specifity theory, proponents of ‘pattern theory’ claimed that any somatosensory experience arises from a specific pattern of neural firing (Flor & Turk, 2015; Moayedi & Davis, 2013). The spatial and temporal profile of this pattern is then decoded by the brain which allows conclusions about stimulus type and intensity. According to this theory, the stimulation of any cutaneous nerve fibers (except those innervating hair cells, (Lele, Sinclair, & Weddell, 1954)) could in principle lead to the perception of pain. This theory ignored claims of specifity theory and any evidence of specialized receptors or a biomedical ‘pain system’(Nafe, 1929).

Psychological factors (such as attention, cognition, emotion) were not given significant roles within specifity or pattern theory. Indeed, the contributions of psychological and physiological mechanisms for pain were subject of intense debate. For example, some clinicians arrived at the conclusion that psychological and physical pain mechanisms were mutually exclusive (with pain being either psychological or physical). Stigmatization of patients whose pain was categorized as ‘psychogenic’ occurred commonly and the aftereffects of this ideation are prevalent to this date (Katz, Rosenbloom, & Fashler, 2015; Liebeskind & Paul, 1977).

In 1965, Melzack and Wall proposed the seminal Gate-Control Theory which revolutionized pain research (see *figure 1*; Melzack & Wall, 1965; Moayedi & Davis, 2013; Sternbach, 1986). Their theory is largely influenced by the enhanced understanding of the neural mechanisms underlying pain. The theory claims that the transmission of a noxious stimulus to the central nervous system (CNS) is subject to a gating mechanism. Specifically, the substantia gelatinosa in the dorsal horn of the spinal cord can either increase or decrease the transmission gain of incoming peripheral stimulation before pain perception emerges (Sternbach, 1986). This gate tends to be closed by large-fiber inputs and opened by small-fiber inputs. Further, Melzack and Wall assumed a central control component. The ‘central control trigger’ is thought to activate selective processes within the brain that exert control over incoming sensory data (Melzack & Wall, 1965). However, only little was known about descending pain modulation at the time (Nathan, 1976; Sufka & Price, 2002). The authors claim that the theory is able to incorporate a wide range of phenomena. For example, they offer an explanation for Beecher’s observations of majorly wounded soldiers who are not reporting pain, but relief about returning from the battlefield alive (Beecher, 1946; R Melzack & Wall, 1965). Despite some conflicting findings and a major revision of some of the basic concepts of the gate control theory (Moayedi & Davis, 2013; Nathan, 1976; Sufka & Price, 2002), the concept of input modulation is prevalent and influential in pain research and clinical pain management to this day (AH Dickenson, 2002; Steeds, 2016; Tabor et al., 2017).

One of the most important extensions of the gate control theory incorporates the so-called ‘neuromatrix’ (Hadjistavropoulos & Craig, 2004; R Melzack, 2001). This theoretical framework focuses on the anatomical substrate of the ‘body-self’. Specifically, the neuromatrix tries to solve the conundrum of how individual bits of information from the skin, muscles or joints are integrated in order to produce the coherent experience of a body that is distinctive from its surroundings (Melzack, 2001). Melzack and colleagues assume the neuromatrix to be hereditary, but modified by experience (Melzack, 1999). This hypothetical network, consisting of thalamocortical and corticolimbic loops, outputs the neurosignature, which is described as cyclical nerve impulses that travel through the neuromatrix (Hadjistavropoulos & Craig, 2004). These considerations have important psychological implications. Melzack claims that the neuromatrix imprints its signature on all inputs that flow through it (Hadjistavropoulos & Craig, 2004; Ronald Melzack, 1999). Experiential qualities, such as pain, are hence outputs of specific modules within the neuromatrix. This neurosignature is modulated by sensory inputs in order to produce qualitative experience. This means that a specific neurosignature can be triggered by a stimulus; however, an input cannot produce a neurosignature itself as all inputs from the body undergo transformations within the body-self neuromatrix. According to this, the brain is not just a passive, stimulation-receiving organ, but rather has an active role during the generation of experiential qualities. Hence, this theory offers an explanation for the generation of perceptual experiences in the absence of inputs as observed in phantom limb pain or feelings of effort, fatigue and pain in paraplegics with sections of the spinal cord (Melzack, Israel, Lacroix, & Schultz, 1997; Melzack & Katz, 2007; Melzack & Loeser, 1978).

***Figure 1.***Schematic illustration of the Gate-Control theory, proposed by Melzack & Wall (1965); figure adapted from Moayedi & Davis, 2013



***Annotations.*** As proposed by the Gate Control Theory, both large (A-) and small (C-) fibers synapse with neurons in the substantia gelatinosa (SG) and with first central transmission cells (T-cells). The SG has inhibitory effects (represented by ‘-‘; excitation: ‘+’) on the terminals of the primary afferent fibers at the T-cells. This inhibition is increased by A-fiber activity and decreased by C-fiber activity. The T-cells project to cells of the action system. Once a critical level of firing in the T-cells is exceeded (e.g., after unexpected skin damage), a set of adaptive behavioral responses is triggered (startle response, flexion reflex, postural readjustment, vocalization, orientation towards damage, etc.). The central control trigger mechanisms (potentially the dorsal column-medial lemniscus system and its projections to the thalamus) are associated with A-fiber activity and the effect of this central control mechanism project back to the Gate Control system. Figure adapted from Moayedi & Davis, 2013 and Melzack & Wall, 1965

Methodological advances have shed light on cellular and molecular mechanisms underlying nociceptive and inflammatory processes (as described in Basbaum et al., 2009; Davis, 2011; Kidd & Urban, 2001; Steeds, 2016). These insights have further determined the way researchers view pain. Firstly, there are two types of nociceptors (i.e., receptor cells that respond specifically to noxious information): high-threshold mechanoreceptors (HTM), which respond to mechanical stimulation and -deformation; and polymodal nociceptors (PMN), which respond to a variety of potentially damaging substances and factors (such as hydrogen ions, 5-hydroxypryptamine, cytokines, prostaglandins, histamines or leucotrienes; see Steeds, 2016). These nociceptors are free nerve endings of two different types of fibers. Aδ fibers are myelinated, of a relatively large diameter (2-5 μm) and allow rapid signal transduction (5-15 m/second). The associated pain experience is often described as prickling and well-localized. In contrast, C fibers are smaller in diameter (>2 μm) and unmyelinated. Transduction velocity is a lot slower (0.5-2 m/second) and the associated pain is usually experienced as diffuse, dull and aching (Basbaum et al., 2009; Steeds, 2016). Most of these fibers terminate in the dorsal horn of the spinal cord. In the spinal cord, these afferent fibers form synapses with second-order neurons which bifurcate in up- and downstream neural pathways. Further, complex interactions with excitatory and inhibitory interneurons take place here (Basbaum et al., 2009).

The outlined theoretical and biological considerations have advanced our understanding of pain, especially acute nociceptive and inflammatory pain. However, understanding the basis of chronic pain might require additional theoretical attention.

## 1.3 Chronic Pain

### 1.3.1. Definition

The distinction between acute (i.e., nociceptive or inflammatory pain) and chronic (or persistent) pain is often given by means of an arbitrary period of time during which pain experiences have to persist after an inciting event. Most commonly, periods of between 3 to 6 months are used to define chronicity (Johannes, Le, Zhou, Johnston, & Dworkin, 2010; Katz et al., 2015). However, pain that persists for more than 6 months can be considered acute when a physical pathology can be identified (Flor & Turk, 2015). However, pain that persists for more than 6 months can be considered acute when a physical pathology can be identified (Turk & Okifuji, 2002) as chronic. This definition allows diagnosing chronic pain even if it has been persisting for less than 3 months but no underlying medical explanation can be identified (Flor & Turk, 2015; Turk & Okifuji, 2002).

For clinical purposes, the DSM-5 offers criteria to diagnose debilitating forms of chronic pain under the category ‘Somatic Symptom and Related Disorders’ (American Psychiatric Association, 2013). This category allows diagnosing somatic symptoms that are related to significant distress and impairment in the individual, such as being in a state of chronic physical pain. Instead of focusing on the absence of an underlying pathology, the re-conception of the DSM-5 focuses on the individual’s response to the symptoms (i.e., cognitive, emotional and behavioral responses to pain perception). The diagnostic criteria for somatic symptom disorder can be found in *table 1.* These criteria are helpful in defining clinical chronic pain as there is no consensual definition of chronic pain per se. However, the DSM-5 diagnosis of somatic symptom disorder is criticized by numerous researchers who claim that chronic pain is ‘overpsychologized’ (Katz et al., 2015)

***Table 1.*** Diagnostic criteria for ‘somatic symptom disorder’ as listed in the DSM-5.

|  |  |
| --- | --- |
|  | One or more somatic symptoms that are distressing or result in significant disruption of daily life |
|  | Excessive thoughts, feelings or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following:   1. Disproportionate and persistent thoughts about the seriousness of one’s symptoms 2. Persistently high levels of anxiety about health or symptoms 3. Excessive time and energy devoted to these symptoms or health concerns |
|  | Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (Typically more than 6 months) |
| Specify if… | **With predominant pain** (previously pain disorder): This specifier is for individuals whose somatic symptoms predominantly involve pain |
| Specify if… | **Persistent:** a persistent course is characterized by severe symptoms, marked impairment and long duration (more than 6 months) |
| Specify if… | **Mild.** Only one of the symptoms specified in B is fulfilled.  **Moderate.** Two or more of the symptoms specified in Criterion B are fulfilled.  **Severe.** Two or more of the symptoms specified in Criterion B are fulfilled, plus there are multiple somatic complaints (or one very severe somatic symptom). |

### 1.3.2. Epidemiology and impact

Chronic pain is one of the most challenging health problems in the world today. Studies in western countries identified high, but varying prevalence rates of chronic pain. Between 19 to 34% in the general population seem to be affected by it, with increasing incidences in women and at an older age (Andersson, Ejlertsson, Leden, & Rosenberg, 1993; Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Johannes et al., 2010; Moulin, Clark, Speechley, & Morley-Forster, 2002). However, also a significant proportion of children and adolescents are affected by chronic pain. Here, similar prevalence rates are reported (between 20 and 35%, Friedrichsdorf et al., 2016; King et al., 2011). Persistence of chronic pain into adulthood is observed in about one third of all pediatric chronic pain patients (Walker, Deugler-Crish, & Rippel, 2010). The economic impact of chronic pain in the U.S.A. is severe with estimated costs of $560 to $635 billion annually for patients’ healthcare utilization and productivity losses (Gaskin & Richard, 2011; Phillips, 2006). Pediatric chronic pain is estimated to cause an economic burden of approximately $19.5 billion per year in the U.S.A. (Groenewald, Essner, Wright, Fesinmeyer, & Palermo, 2014). High rates of comorbid disorders further decrease quality of life and overall psychosocial functioning in these patients (Bair, Robinson, Katon, & Kroenke, 2003; Tunks, Crook, & Weir, 2008). For example, 18% of individuals suffering from chronic pain also meet diagnostic criteria for a major depression in a population-based setting (Bair et al., 2003)

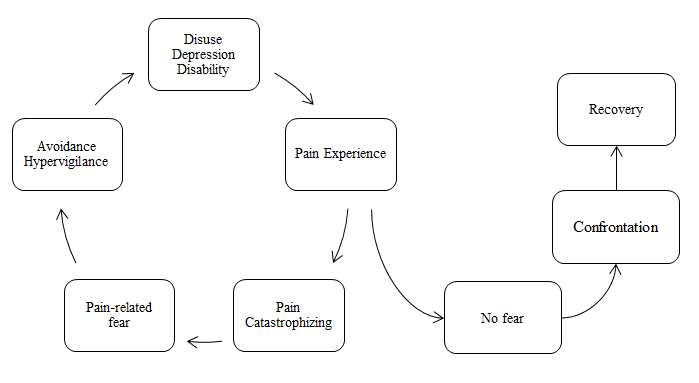
### 1.3.3. Etiology: The psychology of chronic pain

In a purely medical framework, chronic pain is difficult - if not impossible - to explain as a distinct physical pathology is usually hard to identify (Flor & Turk, 2015). Alternatively, in case there is a somatic pathology, some individuals respond to the symptom with disproportionate amounts of distress and disability. These observations suggest shortcomings of an exclusively medical view of pain. Indeed, pharmacological approaches to treat individuals with chronic pain have shown only limited success in the longer term and might cause serious adverse side effects (Ballantyne & Mao, 2003). All these observations prompt the consideration of psychological factors when thinking about the etiology of chronic pain.

#### Behavioral psychology

Behavioral formulations largely advanced the understanding of psychological mechanisms that underlie chronic pain (Fordyce, Fowler, Lehmann, & DeLateur, 1968; Fordyce, Fowler, & DeLateur, 1968; Fordyce, Roberts, & Sternbach, 1985). Here, non-associative and associative learning processes are assumed to be central etiologic factors that have to be taken into consideration. Habituation and sensitization are important non-associative learning mechanisms that behavioral psychologists assume to be central for the development of chronic pain syndromes (Flor & Turk, 2015). While *habituation* is defined as the reduction of response intensity when a stimulus is presented repeatedly, *sensitization* is the process that leads to increased response intensity towards a stimulus that is presented multiple times. Noxious stimuli usually do not lead to habituation, but rather, sensitization and hence an increased response (physiological, behavioral and subjective) to the stimulation. Important determinants of sensitization vs. habituation towards noxious stimuli seem to be psychological factors such as the organisms’ background arousal and the individual’s ability to accurately predict the noxious stimulation: the better an individual is able to anticipate a stimulus and the concurrent sensations, the more likely habituation towards the painful stimulus will take place (Arntz & Lousberg, 1990). Interestingly, researchers identified differences in non-associative learning processes within healthy individuals and chronic pain patients. When confronted with a painful stimulus in a laboratory setting (such as electrical stimulation or cold pressor pain), healthy controls seem to habituate whereas chronic pain patients tend to show signs of sensitization (Arntz & Lousberg, 1990; Arntz, Merckelbach, Peters, & Schmidt, 1991; Colloca, Benedetti, & Pollo, 2006; Kleinböhl et al., 1999). Specifically, chronic pain patients seem to perceive stimuli as painful that healthy subject did not perceive as painful (allodynia) and rated physical stimuli of lower intensity as more painful (hyperalgesia).   
Further, associative mechanisms such as classical and operant conditioning received much attention in behavioral pain research (Fordyce et al., 1968; Gentry & Bernal, 1977; Vlaeyen & Linton, 2012). Gentry and Bernal proposed that acute pain, especially pain that is associated with muscle tension (the unconditioned stimulus or US), can develop into a chronic pain problem by means of classical conditioning (Gentry & Bernal, 1977). By experiencing a frequent coupling between innocuous stimuli (e.g., a certain environment or body position, here: the conditioned stimulus or CS) and pain states (US), individuals respond with increased muscle tensioning (conditioned response or CR) to these previously neutral stimuli. According to the authors, this process is able to explain the persistence of pain independent from the original tissue damage. Linton and colleagues further developed this conditioning perspective on pain by examining the role of anxiety for sensitization processes. They argue that not neurological pain, but rather anxiety and related physiological activation are subject to conditioning processes. For example, a patient might have learned to associate a specific body position or movement with increases in muscle tension and pain. These movements (or even thoughts about these movements) then elicit anticipatory fear and increases in muscle tension. The fear of movement is also termed kinesiophobia and discussed as a core factor for the exacerbation of chronic pain (Flor & Turk, 2015).   
The above behavioral perspectives have led Vlaeyen and Linton (2000) to introduce their fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000). In their model (see *Figure 2*), they propose that an aversive event such as an injury is associated with fear (e.g., kinesiophobia) through classical conditioning. This fear leads to the avoidance of all movements or environmental cues that are related to the original injury and further generalizes towards similar movements or situations. Consequently, the patient’s disability and depression increases. This model is the most important theoretical basis for the cognitive-behavioral treatment rationale and is widely used in clinical practice to this day (Vlaeyen & Linton, 2012).

***Figure 2.*** The fear-avoidance model, from Vlaeyen & Linton, 2000



#### Attention

Besides learning processes, other cognitive factors seem to play an important role for the development of chronic pain. Attentional focus is a prominent mechanism in the fear-avoidance model described above, where chronic pain patients are assumed to put an excessive attentional focus on their pain symptoms. This dysfunctional attentional style is referred to as hypervigilance, which is assumed to maintain and amplify bodily sensations and pain (Van Damme, Legrain, Vogt, & Crombez, 2010). This has been observed in patients with chronic low back pain and fibromyalgia, a medically unexplained syndrome that is characterized by whole body pain (Peters, Vlaeyen, & van Drunen, 2000). Rumination and maladaptive attentional focus could also be determined by an individual’s affective state.

#### Affective State

In about 30-40% of patients who present for treatment of chronic pain, a comorbid depression is diagnosed (Bair et al., 2003; Rayner et al., 2016). The comorbidity with depression further decreases functioning and treatment response in chronic pain patients (Holmes, Christelis, & Arnold, 2013). It is not always trivial to distinguish symptoms of chronic pain and depression – features such as rumination, magnification of distress or catastrophisation and helplessness are characteristic symptoms of both disorders (Holmes et al., 2013). This common overlap is also summarized under the term “depression-pain-syndrome” (Bair et al., 2003). Research on the depression-pain syndrome implies that pain and depression frequently exacerbate one another, share a similar biological mechanism (i.e., the involvement of serotonergic and noradrenergic neurotransmitter systems) and respond to similar treatments (Blier & Abbott, 2001; Gallagher & Verma, 1999). The two disorders might hence emerge from a common underlying process (Holmes et al., 2013) – some researchers have even suggested formalizing chronic pain as a subtype of depression (Blumer & Heilbronn, 1982).

## 1.4. Current developments

Computational and cognitive neuroscientists argue that the brain must be viewed as an elaborate information-processing system (Lachman, Lachman, & Butterfield, 2015). Some researchers in clinical psychology adapted this notion in order to further the understanding of mental disorders (Beck & Clark, 1997; Ingram, 1986; Ingram, Kendall, & In, 1986) or pain perception (Büchel, Geuter, Sprenger, & Eippert, 2014; Tabor et al., 2017).

When analyzing information processing systems, David Marr has suggested doing so under consideration of three distinct, complementary levels of analysis (Marr, 1982). Marr’s so-called *Tri-Level Hypothesis* was initially based on his ideas on information processing in visual perception (McClamrock, 1991). However, this conceptualization can easily be expanded to perception and action in general (Peebles & Cooper, 2015). The three levels suggested by Marr are

1. the *computational level*. This level encompasses the non-trivial analysis of what problem the system solves (the goal of the computation) and the reasons the system has to cope with that specific problem. It also encompasses the logic of the strategy with that the computation is carried out.
2. the *algorithmic level.* On this level, it is specified the processes and representations that the system uses in order to implement the computational theory. For example, this level would be concerned with the representation of the input a system gets and the output it is trying to achieve as well as the algorithm necessary for this transformation.
3. the *implementational level.* Research on this level of analysis is concerned with the physical instantiation of the system’s representations and processes (e.g., neural basis).

Information processing approaches might also expand the current knowledge on the etiology and maintenance of chronic pain states. An abundance of research on the neural basis of chronic pain is available (i.e., the implementational level, see (Brown, El-Deredy, & Jones, 2014; Diatchenko et al., 2005; Anthony Dickenson, 2016)). Yet, these studies are very heterogeneous regarding their focus (for example: genetics, neurotransmitter systems, hormonal responses). They further do not aim at contributing to a mechanistic explanation of chronic pain from an information processing perspective. Modern psychiatry and clinical psychology, however, face the tremendous challenge of integrating physiological, neuroscientific, psychological and behavioral evidence into unifying nosological theories and models. Unifying models would permit mechanistic conclusions which are typically avoided in psychiatry and clinical psychology due to the sheer complexity and the quantity of the available data. Computational methods are emerging as promising approaches to this challenging endeavor, summarized under the term “Computational Psychiatry” (Adams, Huys, & Roiser, 2016; Huys, Maia, & Frank, 2016; Wang & Krystal, 2014; Wiecki, Poland, & Frank, 2015).

Recent theoretical advances might have the potential to facilitate research on mechanistic models underlying mental processes in health and disorder. These advances frame phenomena of the human mind as resulting from Bayesian inference. The next paragraph introduces the most prevalent concepts, theories and frameworks related to the idea of the brain performing Bayes-optimal inference.

## 1.4.1. The Bayesian Brain hypothesis and Predictive Coding

In recent years, the notion of the brain as a ‘Bayesian inference machine’ has become the predominant theoretical framework in neuroscience (Dayan, Hinton, Neal, & Zemel, 1995; Doya, Ishii, Pouget, & Rao, 2007; Karl Friston, 2012). The basic idea underlying the concept of the Bayesian Brain is that the brain is trying to infer the causes for a given state (or sensation) by means of an internal generative model of the world (Karl Friston, 2012). A generative model is a model that describes how data is given rise to, or generated, in a probabilistic fashion. To put it in other words, the brain needs a representation of the world (a model) in order to identify the environmental cause of the sensory information it receives and interact with it in a meaningful way (Hohwy, 2012). It hence has to infer the *causes* for sensory information that are located in the external world from the *effects* that this sensory input has on the brain or body (e.g., firing of a neural population in visual cortices, firing of auditory neurons). The internal model of the world is not innate or fix – it is shaped and constrained by the information it gets from the environment. The function of perception in the Bayesian Brain framework is similar to a hypothesis-testing mechanism .

The idea of perception as an active, top-down, hypothesis-testing process however is not novel. Philosophers like Immanuel Kant (1724-1804) argued that only the combination of ‘understanding’ and ‘sensing’ can give rise to knowledge. Helmholtz (1860) was probably the first to express this idea explicitly:

*“How do we escape from the world of sensations of our own nervous system into the world of real things? We are guided by the answers nature delivers when we query it, using unconscious perceptual inference based on prior learning.”*

Helmholtz, 1860, in *Treatise on Physiological Optics*

Helmholtz suggested that the way humans query the natural world is guided strongly by prior learning and knowledge. This idea evolved over decades, leading to Gregory’s (1980) notion of ‘Perceptions as Hypotheses’ and the emphasis on Bayesian principles for perception (Lee & Mumford, 2003). Helmholtzian ideas are still at the core of more modern approaches to perceptual inference (Dayan et al., 1995; Hohwy, 2013).

Above all, the Bayesian Brain hypothesis suggests that the combination of prior knowledge and current sensory information, or data, follows Bayesian principles. This combination then allows inferences about the real-world causes of a sensation. The theorem introduced by Bayes forms the mathematical basis of this hypothesis. It states that a model (a model can be an internal representation or a belief about the state of the world) and the sensory information (or data) a system received (e.g., visual, auditory or tactile information) are combined:

The theorem states that the probability of a certain model given the data the system has received (*posterior probability*) is equal to the the probability of the data given the model (*likelihood)* times the marginal probability of the model , divided by the marginal probability of the data . This implies that new sensory information is integrated in the light of existing internal models of the world (Fortier, Friedman, & Friston, 2018).   
An example: hearing a ticking sound in the library, one might have different beliefs (or models) about what causes that noise. The hypothesis that a clock on the library wall is causing this noise has a very high likelihood as it is highly likely to hear a ticking sound in case there actually is a clock on the wall. The probability of a clock hanging on the wall is a lot higher than, for example, the probability of a squirrel rhythmically beating a hazelnut against the library’s window. The hazelnut-beating squirrel might produce a similar sound as the clock; resulting in a comparable in both models. However, the marginal probability of a clock hanging at the library wall (model A, ) is a lot higher than the probability of a hazelnut-beating squirrel (model B, ). Hence, the posterior probability of model A, , is higher than the posterior probability of model B, and the clock-hypothesis determines the individual’s inference about what generates the ticking sound. This example illustrates how the credibility of a model is weighted by how well it fits with the sensory data as well as how likely the model is a priori.

This view of perception as a hypothesis-testing process implies that the brain predicts the information that the senses convey to it (Hohwy, 2013; Rao & Ballard, 1999). Predictions are thought to cascade down the cortical hierarchy where they are met by sensory input. A comparison between the prediction and the subsequent input then emerges as the central task for the brain in causal inference (K. Friston & Kiebel, 2009). The divergence between the prediction and the sensory input can be quantified and is proposed as the central quantity that is passed up the cortical hierarchy. This quantity, in the following referred to as ‘prediction error’, is a measure for the fit of the model for the incoming sensory data: a small error indicates a good capture of the circumstances in the external world by the model, whereas a large error indicates that substantial aspects of the sensory information were not well predicted by the brain. A large prediction error motivates a revision of the internal model or hypothesis so that subsequent hypotheses match the sensory data better (Hohwy, 2012). Other ways of minimizing the prediction error include moving the body in order to get the expected sensory input or sampling (e.g., attending to) sensory information differently (Clark, 2013; Hohwy, 2013). Following this idea, both action and perception emerge for the goal of minimizing prediction errors, an idea that tightly intertwines action and perception (K. Friston & Kiebel, 2009).   
An important feature of the predictive coding framework is the idea of hierarchies within the cortex (Ballard, 2015; Hohwy, 2012, 2013; Mumford, 1992). The prediction error that cannot be predicted at a lower level in the cortical hierarchy is passed up to a level higher up in the hierarchy. It is assumed that basic sensory attributes are predicted at a low level with a fast timescale, whereas more abstract and complex regularities are processed on higher cortical levels and on a slower time scale (K. Friston & Kiebel, 2009; Kiebel, Daunizeau, & Friston, 2008). Prediction error minimization occurs on all levels of the cortical hierarchy (Hohwy, 2012).

This predictive view is often contrasted with a more conventional view of the brain as a passive organ that soaks up sensory information in a bottom-up manner with neurons lying dormant until stimulated (Hohwy, 2013). Indeed, numerous researchers have suggested that predictions and internal models of the world determine perception (Dayan et al., 1995; Doya et al., 2007; Rao & Ballard, 1999).

## 1.4.2. Free Energy

The predictive coding framework described above can be considered a special instantiation of the free energy principle as introduced by Friston and colleagues (Karl Friston, 2009, 2010; Karl Friston, Kilner, & Harrison, 2006). The concept of free energy is borrowed from statistical physics and thermodynamics, where it refers to the work that can be extracted from a system (Karl Friston et al., 2006). The free energy principle is intended to describe adaptive exchanges between biological agents (i.e., humans, animals) and their environments (Karl Friston, 2010; Karl Friston et al., 2006). For the present purpose of understanding brain computations, free energy is of particular importance for the concrete implementation of Bayesian models.

The motivation of the free energy framework starts with the problems that

An dieser telle: variational updating variational Bayes erklären: insbesondere in Netzwerken mit schleifen klappt message passing. Und eine gangbare Näherung ist das free energy.

## 1.5. Interoception, Pain and Predictive Coding

Recent evidence suggests that not only perception (i.e., processing and perceiving of exteroceptive visual or auditory information) emerges from the minimization of prediction error or free energy. Also interoceptive processes seem to follow this principle (Barrett & Simmons, 2015; Seth, 2013; Seth & Friston, 2016). That is, the perception of signals from the internal milieu of the body seems to be emerging from an elaborate comparison of these signals with top-down predictions (Barrett & Simmons, 2015). The sensation and integration of signals that originate from inside the body is referred to as interoception (Khalsa & Lapidus, 2016). Bodily signals that are sensed through interoception include heart rate, glucose levels, build-up of carbon dioxide in the blood, temperature and inflammation (Barrett & Simmons, 2015). Interoception does not only include the processing and representation of afferent body signals, but also the attention, appraisal and response to bodily signals (Farb et al., 2015). The concept of interoception hence encompasses many aspects of psychological research on chronic pain mentioned above (i.e., learning, attention and affective state). Interoception hence could be an attractive means of furthering etiological knowledge in this field.

[ELABORATE]

# 1.6. Summary: Approaches to chronic pain and outlook

# 2. Methods

## 2.1. A Bayesian model for chronic pain: basic model requirements

To sum up preceding paragraphs, theoretical and computational perspectives suggest pain as emerging from the complex interaction between nociceptive signals and modulatory processes. More recent advances have further aimed at specifying the statistical process underlying pain perception. In particular, viewing pain perception as resulting from a Bayesian combination of prior knowledge and current sensory information could be helpful for the specification of the concrete statistical process. Regarding chronic pain, an interoceptive predictive coding approach could further etiological and mechanistic knowledge. Therefore, we develop a Bayesian model for chronic pain. Central model requirements are drafted in the following few paragraphs.

### Terminology

Observations

System

hidden

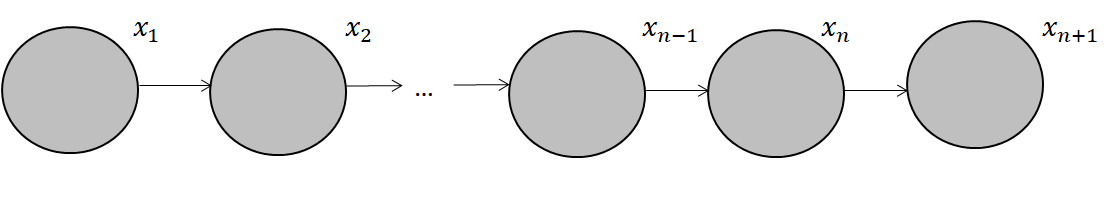
### Sequential data and change over time

When modeling pain perception and the development of chronic pain, it is crucial to incorporate a time-component into this model. The processing and evaluation of external signals from the environment (e.g., harmful or innocuous stimulation) or internal signals from within the body (e.g., inflammatory processes, blood sugar levels etc.) is based on a change in these signals over time. Hence, the data that the system is processing is not independent or identically distributed (i.i.d.), but sequential. Following a predictive coding perspective, the brain is constantly trying to predict the sensory information it will receive during the next time-step. Hence, an important model requirement is that it can account for time-series and allow predicting the future. However, it is unlikely to believe that the brain considers every previous time-points in order to make a prediction concerning the near future – data from the recent past, for example, might determine current predictions to a greater extent than observations from many time-steps ago. Further, models in which the entire history of data-points is considered are computationally expensive as the complexity of such models would grow infinitely with increasing numbers of observations (Bishop, 2006).

**Markov models** are well-established models that are applied across numerous disciplines when modeling time-sequence data (Bishop, 2006; Hastings, 1970; Norris, 1998). When considering a time-series of observations, Markov models exploit the product rule which expresses the joint distribution for :

The joint distribution is given by the product of all conditional probabilities within the model. A graphical model with time-steps is illustrated in *Figure 3.*

***Figure 3.*** A graphical model of a first-order Markov chain of observations

  
**Annotations.** Illustrated in this figure is a Bayesian graphical model of a first-order Markov chain. Filled circles in graphical models illustrate an observable random variable. The edges in this graph are unidirected.

An important characteristic of Markov chains is the **Markov property** which states that an observation is independent from all but the previous observation:

Applying the d-separation property to Markov chains (Bishop, 2006), it can be shown that the conditional distribution for given all previous is given by

That is, only the observation at is determining the present observation . In other words, a prediction of depends only on . In machine learning, the Markov property is also referred to as “memorylessness” (Feller, 2008). An important advantage of this property is an improved tractability of Markov models. Further, message passing between the variables is facilitated which will be discussed later in this section (see Sum-Product algorhithm).

### Hierarchies and latent vs. observable variables

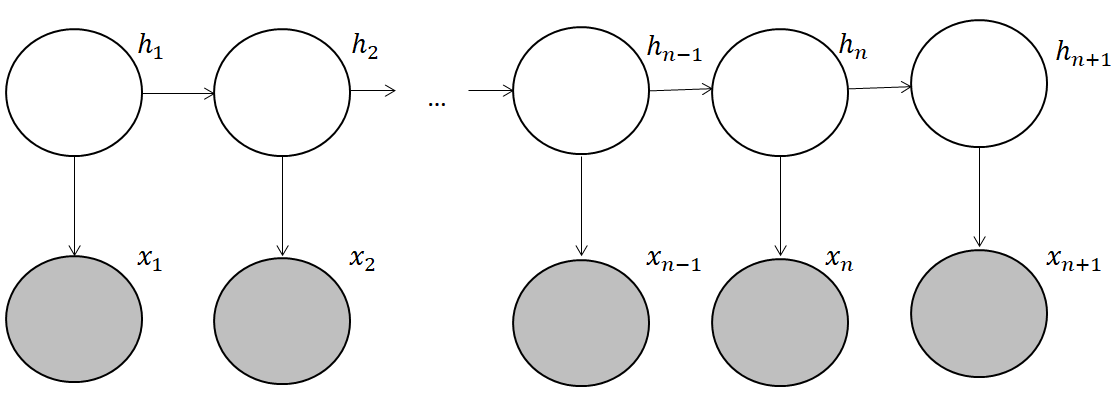
All definitions of pain discussed above make a distinction between the nociceptive stimulus and the perception of pain, indicating that the relationship between the intensity of the noxious stimulus and pain perception depends highly on (unknown) individual characteristics. This differentiation is an important requirement for any model of chronic pain. Here, we achieve this distinction by introducing different types of random variables in the model. The noxious stimulus, or, more general, the sensation can be quantified and observed; however, pain is a non-observable, hidden state. Therefore, **observable and latent random variables** are introduced into the model. A random variable is a function that maps from a set of possible worlds to a range so that. Every random variable has a probability distribution which is a function. The probability distribution over a random variable is denoted by.

Given the two different types of random variables (observable and latent) as well as the opportunity to model sequential data, a hierarchical structure of the proposed Markov model seems favorable. One hierarchy level should represent the sensory input (in the following referred to as S) whereas another level should contain the latent variables and represent unobservable states. From a predictive coding perspective, this unobservable state refers to the so-called **generative model** responsible for the sensory information the system receives. In the present implementation, pain is considered one of many generative models that the brain is identifying for the sensory input into the system. To further explain this logic: an individual might have to infer the cause of a given (interoceptive) sensory information via an internal model which is then compared to the actual sensory information. Pain is the most obvious generative model following nociceptive stimulation. In individuals with chronic pain, this logic might however be disrupted in a way in that also innocuous stimulation is “explained away” by the internal model of “pain”. By implementing hierarchies, this becomes a testable hypothesis.

So-called **Hidden Markov Models** (HMMs)incorporate observable as well as latent variables and are widely used for the modeling or simulation of time-dependent data (e.g., speech recognition or natural language analysis; Renals, Morgan, Bourlard, Cohen, & Franco, 1994; Young, 1992). The basic structures underlying HMMs are a Markov chain of latent variables and corresponding observable variables that are conditioned on the state of the associated latent variable (see *figure 4).* This model structure is also known as a state space model (Bishop, 2006), whereas the HMM is a special case of as its latent variables are discrete. In the case of a simple model for pain perception, the latent state of a system can be either “pain” or “no pain”. The sensory input a system receives will be modeled via the observable variables. The latent variables further fulfill the Markov property described above:

Hence, the probability distribution depends on the previous state through the conditional distribution . In the case of discrete variables, this conditional distribution refers to a matrix of probabilities also referred to as *transition probabilities.* The transition probabilities indicate the probability of transitioning from one state to another or the probability of a specific state being maintained in the next time-step. The assumed transition probabilities in an HMM are usually illustrated in a transition diagram.

**Figure 4.** A hidden Markov model (HMM) with a Markov chain of latent variables and corresponding observable variables.



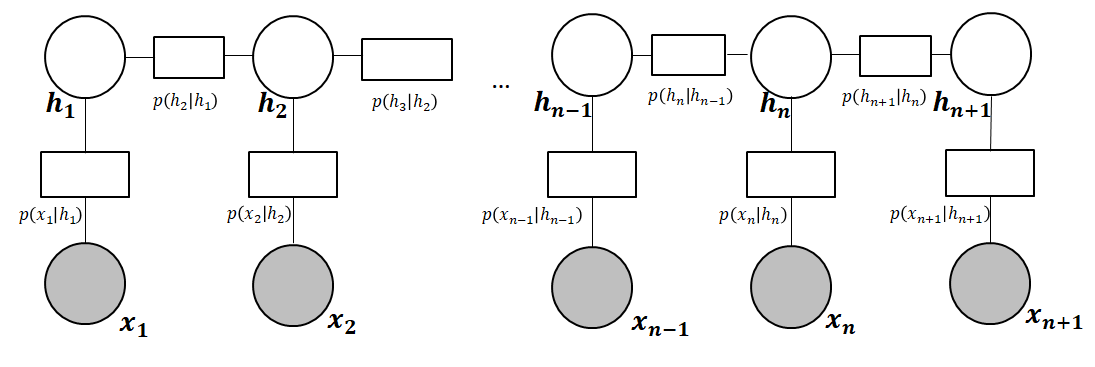
**Annotations.** In this HMM, a Markov chain of latent variables is associated with corresponding observable variables .

### Inference and message passing

Probabilistic graphical models, or Bayesian networks, as shown above are useful for the expression of the conditional dependence- and independence relationships between random variables. After instantiating a network with fixed relationships between the variables, it is possible to perform inference in this model (Bishop, 2006; D’Ambrosio, 1999). [In technical terms, inference allows determining the extent to which a variable changes once the knowledge about the value of another variable changes.] In the present case, it is of interest to what extent the probabilities of the latent variables change once an observation has been made. For this purpose, it is necessary to infer the marginal probabilities of the latent variables from the value of the observed variables. A marginal probability distribution results from summing out all variables except the one of interest. In the case of two random variables X and Y, the marginal probability of X is given by

An efficient means of performing inference in singly connected graphical models is given by the Sum-Product algorithm (Bishop, 2006). Before applying the sum-product algorithm, it is necessary to transform the Bayesian network into a factor graph. A factor graph is bipartite as it contains variable nodes and factor nodes with edges connecting any variable node with a corresponding factor node. Conditional probability distributions are represented through factor nodes (see *Figure 5).*

***Figure 5.*** Factor graph corresponding to the Bayesian graphical model in *Figure 4.*



***Annotations****.* In a factor graph, factors are represented via boxes. Factors contain conditional probability distributions and are the basis for message passing algorithms, for example the sum-product algorithm. See also (Bishop, 2006)

Message passing via the Sum-Product algorithm is also known as Belief-propagation as it enables calculating the marginal probability of any hidden nodes (here: ) in a model, given observed nodes (here ), (Pearl, 1982). The calculation of marginal probability distributions following the equation in [XXX] becomes computationally prohibitive even with a low number of binary variables as one would have to sum over many possible values in order to get marginal distributions. The Sum-Product algorithm allows efficient marginalization because it exploits the tree-structure of the graphical model (Bishop, 2006; Pearl, 1982). The basic idea of the algorithm is that of passing messages along the edges between the hidden nodes. The exact computation of the messages depends on whether the message is passed from a variable node to a factor node, where the product of all incoming messages is calculated and sent to all neighboring nodes except the node the message came from:

Or from a factor node to a variable node, where all incoming messages from neighboring factor nodes are collected and multiplied *with a local factor* before passing the message to neighboring factor nodes (except the factor node the variable node has received messages from):

The marginal distribution of the variable Y is then given by

A model as depicted in *Figure 5* represents some of the original assumptions underlying the Bayesian Brain hypothesis (Clark, 2013; Doya et al., 2007; Karl Friston, 2012) as it reflects how prior knowledge and sensory information can be combined to give rise to perception.

* Sum Product algorithm: marginale Knotenwahrscheinlichkeiten UND p(d gegebn Modell auch dazu).

### Learning from data 🡪 continuous messages: exp fam diss & conjugate priors

* Now that we want to learn from data we somehow have continuous messages. In den nodes: distributions die die perceptual expectations beschreiben. Wenn wir diese Zahlen lernen wollen mpssen wir distributions über kontinuierliche Variablen lernen. Plötzlich unendlich lange Summen.
* We can’t do that with old approach: updates too complicated (unendlich lange Summen)
* Exponential family distributions with conjugate priors allow for v simply parameter update.
* Show that.
* Oh and the exp fam dis that is used here is multinomial Dirichlet.

### Variational inference and free energy in loopy graphs

* We need an approximation as the old approach does not work with continuous messages and in loopy graphs.
* Wir brauchen Approximation. Variational free energy: lernen ist optimierung und ausserdem nice daran ist dass sie die loops kanckt und durch free energy verbindungen erstetzt. Das ist einfach eine besonders gängige Approxiamtion. Sie hat suer eigenschaften und wird genau dann exakt…. Und auch lernen im Hirn
* Bayesian updating: posterior ausrechen. In free energy: Berechnen wert: abweichen von dem
* Es kann bewiesen werden: dass die approximation die richtige Antwort ist wen man richtige Bayesian inference durchführt im limes ist es exakt.
* Why is graph loopy: bc we don’t instantiate our brain after every sensory info
* Free energy is a nice approximation based on Variational inference
* It makes it possible to derive a lower bound on P(D)
* Ingredients: KL divergence (and Jensen’s inequality)
* …. Anything else?

## 2.2. Model overview: intermediate conclusion

### 2.3. Model selection…

## 2.3. Hypotheses

**-** In welchen Parameterräumen gelangen die Simulationen immer in einem CP state?

* Expectations (hidden)
* Learning from data (free energy)
* Likelihood settings
* Role of a bad sample
* Role of active inference
* Effects of a heightened pain prior
* THERAPY: sensory information

THEN: Model selection procedure – with questionnaire data from pain patients  
What is model selection and how will we use it here, what is Information Criterion  
Describe questionnaire data and why we can use it for modelling  
Minimal surprise: concept erklären: wo sind die Daten für das model am wenigsten überraschend?

# 3. Results

SIMULATION: visualization of surprise and marginal likelihoods, trajectories  
MODEL COMPARISON: minimal surprise and parameter settings

# 4. Discussion

Results and stuff – repeat most important findings and discuss implications for diagnosis, definitions, etiology of chronic pain – to what extent does this speak for rethinking chronic pain?   
Make predictions as to how treatment can be optimized according to this data

Maybe: how can we integrate biological evidence on pain perception (see Comp. Psychiatry Book)

Make predictions on how this model can be extended to other conditions except the present one (chronic pediatric abdominal pain), from proximal generalizations (such as chronic lower back pain) to some more dramatic ones: how about hypochondria? How about congenital abnormalities in pain perception – what can we learn from them for the understanding of CP?

Extension of this model to depression?!

Discuss: nullspace of therapy

## 4.1. Limitations

## 4.2. Outlook

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