

1 Modeling the Action–Perception Loop and its role in 2 Phantom Limb Pain using Active Inference

3 Malin Ramne^{1*}, Torbjörn Lundh² & Jon Sensinger³

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- 5 1. Department of Electrical Engineering, Chalmers University of Technology, Gothenburg,
6 Sweden
 - 7 2. Department of Mathematical Sciences, Chalmers University of Technology and
8 University of Gothenburg, Sweden
 - 9 3. Institute of Biomedical Engineering, University of New Brunswick, Fredericton, Canada

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11 *Corresponding author: malin@ramne.com

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13 Abstract

14 Phantom limb pain is among the most prevalent and distressing consequences of limb
15 amputation. Theories regarding its underlying mechanisms remain disputed,
16 contributing to challenges in effectively treating the pain. In recent years, mathematical
17 models grounded in the Bayesian inference framework have been used to describe
18 various aspects of pain perception. However, pain is not only passively inferred but
19 actively shaped through interactions with the environment—a dimension that classical
20 Bayesian approaches typically do not capture. Because amputation disrupts both
21 sensory input related to the limb and the ability to perform actions, a model
22 incorporating both sensory and active components of pain may provide new insight into
23 the mechanisms underlying phantom limb pain. To this end, we developed a model
24 within the active inference framework, which extends Bayesian inference to include
25 action selection. The model provides a conceptual account of how loss of limb control,
26 ambiguity in sensory input pertaining to limb position, residual noxious input, and pre-
27 amputation pain may contribute to the emergence and persistence of phantom limb
28 pain. Furthermore, it offers insight into the possible mechanisms underlying common
29 interventions and may help account for their variable efficacy across individuals.

30 Author summary

31 Phantom limb pain is a condition where pain is perceived as arising from a limb that is
32 no longer present. Despite being one of the most prevalent and distressing
33 consequences of limb amputation, theories regarding the underlying mechanism of
34 phantom limb pain remain disputed. Here, we present a mathematical model that
35 investigates possible mechanisms underlying this complex pain condition. Using the
36 active inference framework, which combines sensory perception and action selection
37 processes, the model provides a conceptual account of how four distinct factors – loss
38 of control of the limb, ambiguity in sensory input pertaining to limb position, residual
39 activity in afferent nociceptive neurons, and pre-amputation pain – may contribute to
40 the emergence and persistence of phantom limb pain following amputation.
41 Furthermore, our model offers insight into the possible mechanisms underlying
42 common interventions and may help explain why their efficacy varies across
43 individuals.

44 Introduction

45 Pain is not merely a sensory experience, but a complex, inferential process shaped by
46 cognitive factors, such as expectations informed by previous experiences and
47 contextual cues [1,2]. Bayesian inference has successfully been applied to describe a
48 range of pain phenomena such as placebo hypoalgesia and nocebo hyperalgesia,
49 statistical pain learning under experimental pain paradigms, and how overly precise
50 priors and ambiguous observation likelihoods may contribute to chronic and
51 neuropathic pain conditions [3–11]. While considerable work has investigated how
52 expectations influence pain perception, another dimension of the expectation-pain
53 interaction remains less well understood: actions. Our expectations of pain influence
54 what actions we take, and the actions we take influence the pain that we perceive.

55 Thus, pain is not only passively inferred but actively shaped through interactions with
56 the environment [2,12–15]. Following amputation, the ability to perform actions and the
57 sensory input related to the state of the limb are severely affected. A model that can
58 account for both the sensory and active component of pain may provide insight to the
59 possible mechanisms contributing to pathological pain conditions such as phantom
60 limb pain.

61
62 One of the key challenges in modelling the action-perception loop is simultaneously
63 optimizing exploration, exploitation, perception and learning. One framework that has
64 garnered attention in recent years, that proposes a simple yet elegant solution to this
65 challenge, is active inference. The solution proposed by active inference is that all living
66 organisms follow a single objective: *minimizing the surprise of their sensory*
67 *observations* [16]. Importantly, in the active inference framework *surprise* has a
68 technical meaning - it measures how much an agent's current sensory observations
69 differ from its preferred sensory observations. With this governing philosophy, actions
70 are performed to achieve the following two objectives:

- 71 - to obtain *sensory observations that correspond* to desired outcomes or goals
72 (pragmatic value), or
- 73 - to *obtain sensory observations that reduce uncertainty* about the world
74 (epistemic value).

75
76 This formulation allows outcomes of actions to be quantified in the same units as
77 perception, enabling the optimization of exploration, exploitation, perception and
78 learning to all be cast as the minimization of surprise.

79
80 Here, we present an active inference model of pain perception and action, with a
81 particular aim of exploring how phantom limb pain may arise following limb loss. Our
82 results indicate the loss of ability to control the limb, ambiguity in noxious and
83 proprioceptive input, and pre-amputation pain are factors that may contribute to
84 phantom limb pain. Our results also provide insights to the possible working
85 mechanism of some interventions that are commonly used to relieve phantom limb
86 pain, and why the interventions may have different efficacy in different patients.

87 Results

88 Model description and validation

89 Before diving into the model predictions on pain after limb loss, we first give a brief
90 description of the model, and then validate that the model shows expected behavior on
91 a more well-known scenario: learning and context switching. A more thorough
92 description of the model is provided in the Methods section.

93

94 To model pain we must first have a clear definition of what pain is. The International
95 Association for the Study of Pain (IASP) provides the following definition [17] that we will
96 adopt in this paper:

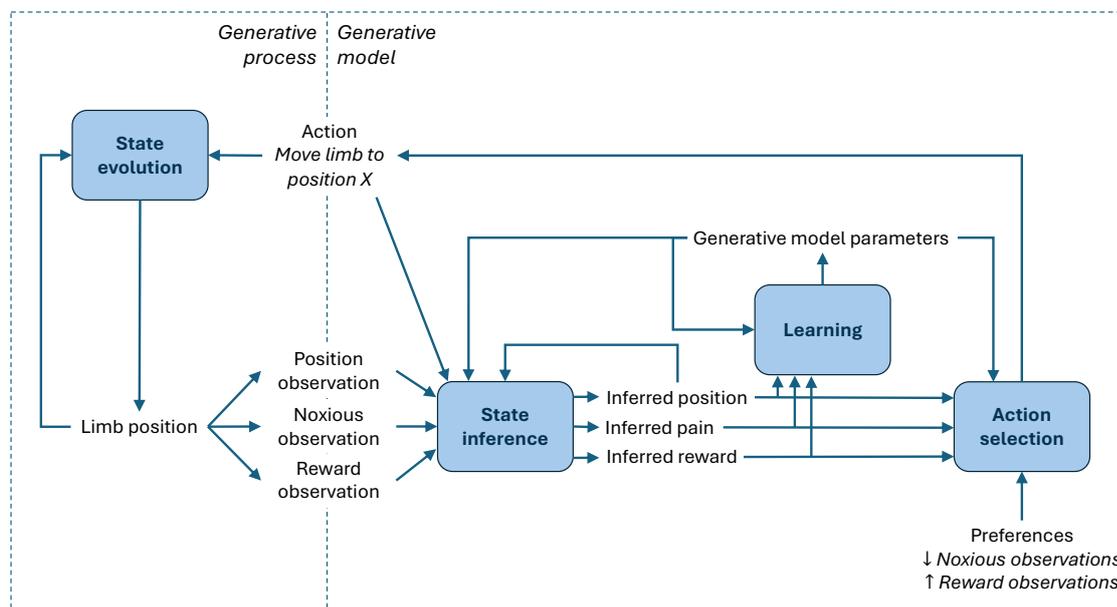
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98 *"An unpleasant sensory and emotional experience associated with, or*
99 *resembling that associated with, actual or potential tissue damage."*

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In any active inference model, there are two main interacting components: the environment, and the agent. Based on the definition by IASP, and since we are interested in studying the specific scenario of phantom limb pain, we let the environment be the tissue of the limb the agent is making inferences about, and we let the agent be the central nervous system (CNS) of the organism at hand. The interface between the environment and the agent consists of observations in the form of peripheral afferent sensory input to arriving to CNS, and actions in the form of motor control.

The *generative process* describes how observations are generated by the environment and how the environment changes in response to actions from the agent. The *generative model*¹ describes how the agent makes inferences about the environment based on observations and expectations, and how the agent chooses actions to obtain desirable outcomes. The agent's state inference is informed by three different *observation modalities*: position, noxious and reward observations. The agent has a prior preference for reward observations and against noxious observations. Position observations can be thought of as a combination of proprioceptive and visual input about the limb's position and is not associated with any preference. The agent's actions correspond to moving the limb to different positions. Figure 1 outlines how the generative process and generative model interface with each other, and how information flows between key processes in this active inference model.

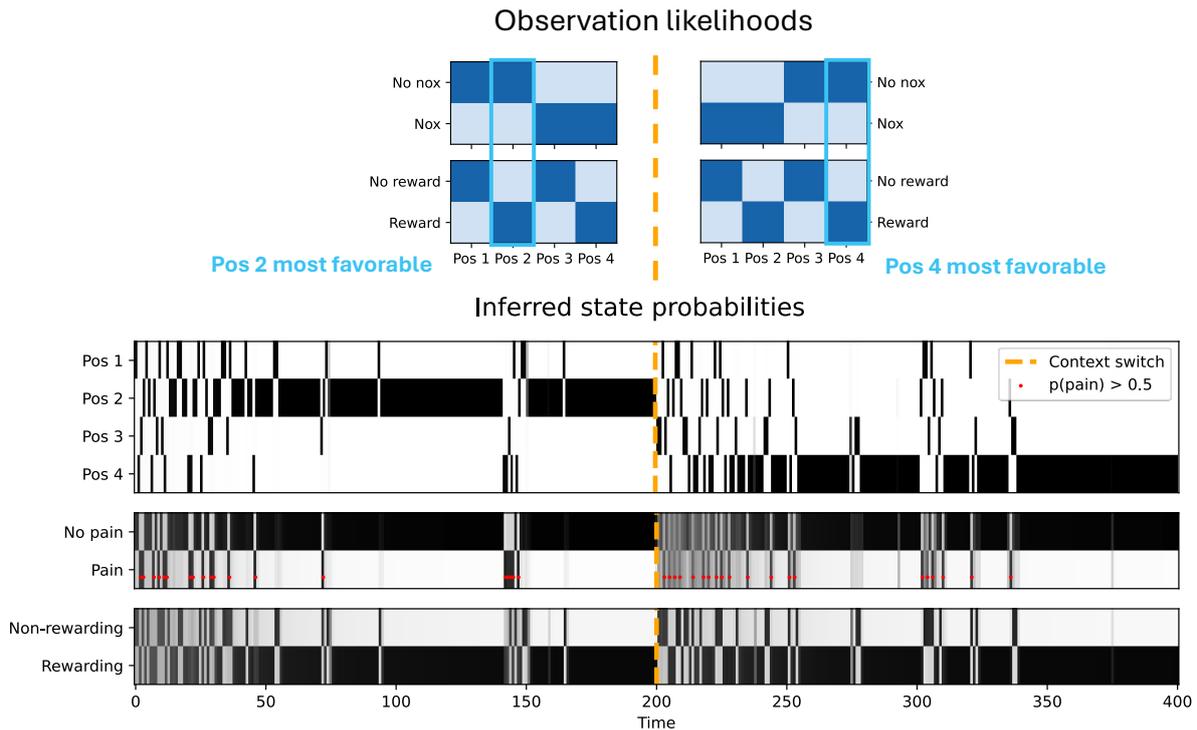


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Figure 1 Outline of the model, where the generative process describes how observations are generated by the environment and how the environment changes in response to actions from the agent, and the generative model describes how the agent makes inferences about the environment based on observations and chooses actions to obtain desirable outcomes. State inference, action selection, learning and state evolution are key processes in the active inference framework and are described in more detail in the Methods section and Supplementary Material.

¹ Here, *generative model* follows its usage in computational and cognitive neuroscience, denoting an internal model that generates predictions of sensory input from latent causes in the environment. This should not be confused with generative AI models that produce novel data samples (e.g., images or text) from learned distributions.

129 As model validation, we demonstrate that an agent with an initially flat expectation of
 130 the environment can 1) learn to navigate the environment to optimally fulfill its
 131 preferences, and 2) re-learn the environment when the locations of high- and low
 132 probability of noxious observations switch. Here, the environment consists of four
 133 different limb positions, each with either high or low probability of noxious and reward
 134 observations respectively. As demonstrated by the example in Figure 2, an agent with
 135 no prior knowledge of the environment learns through exploration that Position 2 is the
 136 most favorable (high probability of reward observations, low probability of noxious
 137 observations), and then re-learns and adapts its behavior when the environment
 138 changes such that Position 4 instead is the best.



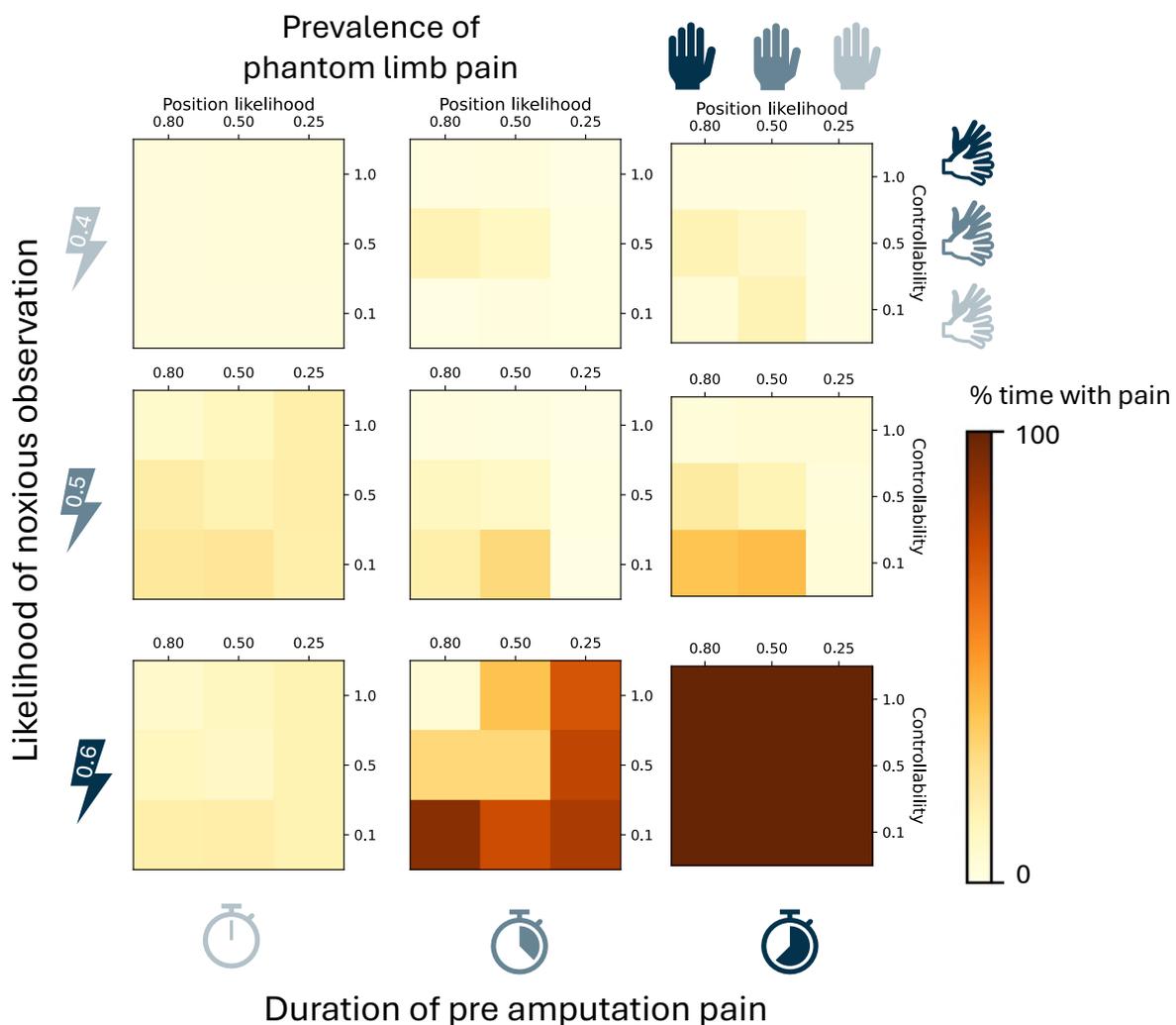
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 140 *Figure 2 Simulation of learning and context switching. In the initial environment Position 2 is the most favorable (low*
 141 *probability of noxious observations, high probability of reward observations). At onset, the agent has no prior*
 142 *knowledge of how locations relate to pain and reward-state. After some exploration, the agent becomes confident*
 143 *enough that Position 2 is the most favorable and switches to mostly exploitative behavior. When the environment*
 144 *switches at $t=200$, Position 2 is no longer favorable as it then has a high probability of noxious observations. Instead,*
 145 *Position 4 is the most favorable, which the agent learns after some initial trial-and-error following the switch. A more*
 146 *detailed visualization of the simulation parameters and results can be found in the Supplementary Material.*

147 **Model predictions**

148 Since we have defined the environment to be the tissue of the limb the agent is making
 149 inferences about, limb loss causes dramatic changes to the environment and its
 150 generative process. Peripheral afferent nerves that used to innervate the limb become
 151 severed and are no longer able to reliably signal information about the state of the limb.
 152 In the generative process, we represent this change as 1) increased ambiguity in the
 153 noxious observations, and 2) equal likelihood for noxious observations at all limb
 154 positions. To reflect differing levels of spontaneous activity in peripheral afferents we
 155 will study different levels of ambiguity in the noxious observations. Similarly, the level of
 156 ambiguity of the position observations (combined visual and proprioceptive input) and
 157 the ability to control the limbs position may vary depending on the level of amputation
 158 and reinnervation of the residual limb. Finally, we assume that agent's ability obtain

159 reward observations with the affected limb is impaired. To reflect this change, we set a
160 low probability for reward observations at all positions.

161
162 Taken together, we have identified three parameters that may be affected to a varying
163 degree following limb loss: the likelihood of noxious observations, the ambiguity of
164 position observation likelihoods, and the controllability of the limb. Here, we
165 investigate how these parameters might contribute to phantom limb pain following limb
166 loss. In our simulations we have included an additional parameter: duration of pre
167 amputation pain. Persistent pre amputation pain is a well-established risk factor for
168 phantom limb pain [18]. The facet plot in Figure 3 shows the prevalence of phantom
169 limb pain for different combinations of values of these four factors. For simplicity, we
170 have only included inferred pain state in the following section, additional figures
171 depicting the position and reward state can be found in Supplementary Material.



172
173 *Figure 3 Prevalence of phantom limb pain for different combinations of values for position likelihood, controllability,*
174 *likelihood of noxious observations, and duration of pre amputation pain. These four factors are denoted by the blue*
175 *icons with varying saturation along the axes of the facet plot. Higher likelihood of noxious observations, for example*
176 *due to residual peripheral noxious input, and duration of pre amputation pain, are associated with higher prevalence*
177 *of phantom limb pain. The influence of position likelihood and controllability is more complex and dependent on the*
178 *other parameters.*

179 These results provide insight to the possible complex interaction of factors contributing
180 to phantom limb pain. Such insights could help inform preventative measures. For

181 example, our results corroborate that pre amputation pain is a key risk factor for
182 phantom limb pain, and thus shall be avoided. But could these results also give us
183 insight to how to relieve the pain?

184

185 *If* some of the effects are reversible, one could imagine that interventions that move an
186 individual from a high-prevalence region of the facet plot to a low-prevalence region
187 might lead to some reduction in pain prevalence. Inspection of the patterns in the facet
188 plot reveal two types of inter-plot movement that potentially could be associated with
189 pain relief:

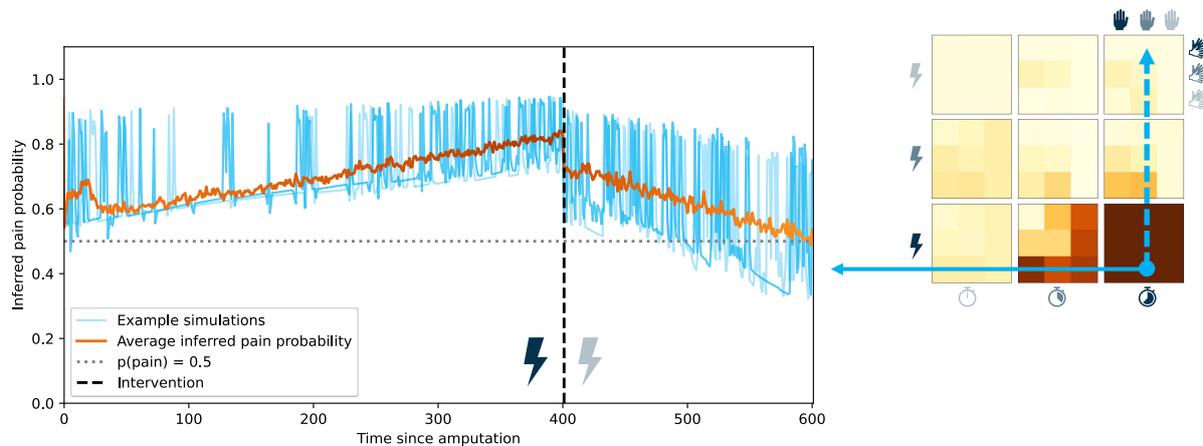
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- 191 1) vertical upward movement between heat maps
- 192 2) diagonal left/up movement within heatmaps.

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194 The first of these interventions would correspond to addressing peripheral sources of
195 residual noxious input. In practice, such interventions might correspond to applying a
196 nerve block to spontaneously active neuromas or the dorsal root ganglion [19–21], or
197 through surgical interventions promoting reinnervation of severed nerves into
198 denervated tissue [22–24]. Another possible approach could be to increase the ratio of
199 innocuous to noxious afferent input through stimulation of peripheral nerves [25–27].
200 Figure 4 shows an example of how this type of intervention might reduce the prevalence
201 of phantom limb pain.

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204 *Figure 4 Example of how reducing the likelihood of noxious observations can be used as a phantom limb pain*
205 *relieving intervention. The orange line indicates the average inferred pain probability across 100 simulations and the*
206 *blues lines represent three example simulations. In the facet plot, this intervention corresponds to vertical upward*
207 *movement between heatmaps. In practice, such interventions might correspond to applying a nerve block to*
208 *spontaneously active neuromas or the dorsal root ganglion, surgical interventions, or peripheral nerve stimulation.*

209 For the second intervention two things must happen simultaneously: i) the ability to
210 control the limb must be restored (upward movement), and ii) the information about the
211 position of the limb must become more precise (leftward movement). Apart from un-
212 amputating the missing limb, these changes might seem impossible. However, there
213 are other ways of achieving similar effects, for example by means of an active
214 prosthesis or an AR/VR limb that is controlled by electromyographic signals recorded
215 on the residual limb [28,29]. When the agent attempts to initiate a movement of the
216 missing limb, electromyographic activity is recorded from the muscles of the residual
217 limb, allowing the motor intent to be decoded and actuated in movement of the

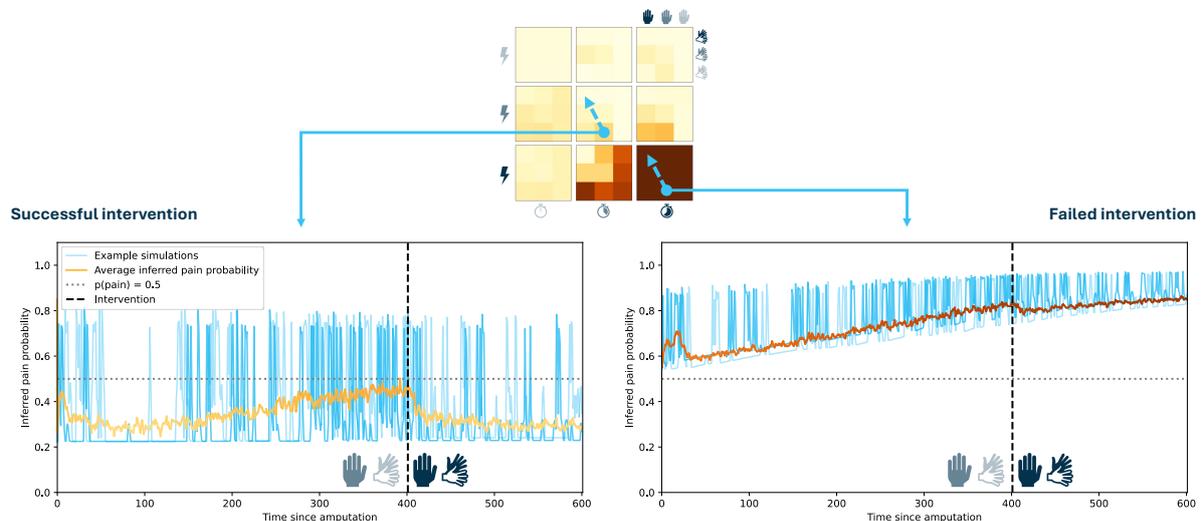
218 prosthesis or virtual limb, resulting in sensory input matching the intended movement
219 of the missing limb. Similarly, a mirror reflection of the contralateral, intact limb could
220 be used [30,31]. If the agent matches the movements of the intact limb with intended
221 movements of the missing limb, the visual input emanating from the mirror will match
222 the intended movement of the missing limb. Surgical interventions that promote
223 proprioceptive feedback from the severed nerves could also fall into this category of
224 intervention [32,33]. Importantly, in these interventions, the agent is given a means of
225 controlling some *source* other than the missing limb that generates sensory input that
226 matches the intended movements.

227

228 The left panel in Figure 5 exemplifies how such an intervention can result in reduction in
229 prevalence of phantom limb pain. However, as the right panel reveals, such
230 interventions are not guaranteed to succeed. For individuals who find themselves in the
231 bottom right heatmap, interventions corresponding to movement within the heatmap
232 will have no effect. Thus, in addition to predicting possible interventions for reducing
233 phantom limb pain, our model results also give an indication of how to prioritize among
234 these interventions based on patient characteristics. Note, however, that the colors of
235 the heatmap do not perfectly predict intervention success. Experiencing phantom limb
236 pain for an extended period of time may partially have the same effects as pre
237 amputation pain, possibly reducing the effectiveness of interventions as indicated by
238 these heatmaps. See the Supplementary Material for one such example, along with
239 more detailed visualizations of interventions.

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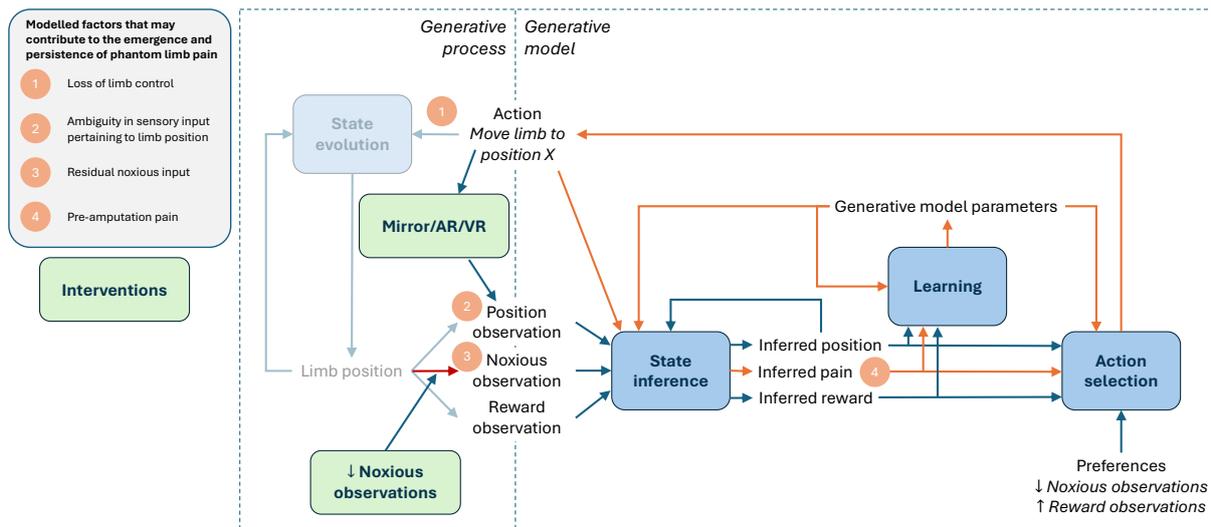
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243 *Figure 5 Examples of varying success of the second intervention (corresponding to diagonal up/left movement within*
244 *heatmaps) for different patient characteristics. For patients who are in the bottom right heatmap of the facet plot,*
245 *interventions corresponding to movement within the heatmap will have no effect. These patients are likely better*
246 *helped by the intervention exemplified in Figure 4.*

247 Figure 6 summarizes the four modelled factors that may contribute to phantom limb
248 pain, and how the two proposed interventions addresses some of these factors.



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Figure 6 The proposed model provides a conceptual account of how four distinct factors may contribute to the emergence and persistence of phantom limb pain following amputation: 1) loss of control of the limb, 2) ambiguity in sensory input pertaining to limb position, 3) residual activity in afferent nociceptive neurons, and 4) pre-amputation pain (through feedback loops indicated in orange). The first two factors can be addressed with interventions using mirrors, AR or VR, to give the agent a means of controlling some source of sensory input that matches the intended movements. Residual noxious input may be addressed through surgical interventions, nerve block to spontaneously active peripheral nerves or through peripheral nerve stimulation.

257 Discussion

258 Phantom limb pain is one of the most prevalent and distressing consequences of limb
259 amputation [18,34]. Theories about the underlying mechanism remain diverse and
260 poorly supported by empirical evidence, which contributes to challenges in effectively
261 treating the pain [34,35]. What is beyond dispute is that, following amputation, both
262 sensory input related to the state of the limb and the ability to perform actions are
263 profoundly altered. This led us to hypothesize that a model that can account for both
264 the sensory and active component of pain may provide insight to the possible
265 mechanisms contributing to phantom limb pain. To this end, we developed a model
266 within the active inference framework that provides a conceptual account of how four
267 different factors interact to influence the prevalence of phantom limb pain. Specifically,
268 the results suggest that loss of control over the limb, ambiguity in proprioceptive input,
269 residual noxious input, and pre-amputation pain may all contribute to the emergence
270 and persistence of phantom limb pain. Furthermore, the model offers insight into the
271 possible mechanisms underlying common interventions and may help explain why their
272 efficacy varies across individuals.

273
274 Based on the model predictions, we can coarsely identify two subtypes of phantom
275 limb pain: primarily peripherally driven – maintained by residual peripheral noxious
276 activity, and primarily centrally driven – maintained by the agent falsely inferring that the
277 limb is in a position that previously has been associated with pain. The second of these
278 is most likely to occur when the controllability and position likelihood precision both
279 are low, making it difficult for the agent to move the phantom limb from the painful
280 position. Furthermore, if there has been an extended period of pre amputation pain,
281 multiple positions are more likely to be associated with pain, making it even more
282 difficult to move the phantom limb into a “pain free” position. Phantom pain being

283 associated with a specific limb position is reported by some patients [36,37]; however,
284 not all phantom pain has this quality. Other common descriptors of phantom pain are
285 sensations like stabbing, burning or shocking, which are typical of neuropathic pain of
286 peripheral origin [36,38,39]. Thus, the quality and characteristics of phantom pain
287 could be a possible clinical predictor of the underlying cause of the pain and which
288 intervention is most likely to be successful.

289
290 These findings may also explain the varying efficacy of some interventions. As we have
291 already seen in Figure 5, the intervention targeting central mechanisms won't work if
292 the pain is driven by peripheral noxious input. This mismatch between pain subtype and
293 intervention mechanism could be one explanation for the differing efficacy of
294 interventions like mirror therapy [30,31]. Another factor could be the variability of
295 protocols used for such interventions [40]. Our model predictions emphasize the need
296 of restoring controllability along with position likelihood, meaning that actively moving
297 the phantom limb to match the movements of the mirror image is a crucial part of the
298 intervention. Due to the lack of a standardized protocol for mirror therapy, the
299 emphasis on the importance of phantom movements might vary between practitioners.

300
301 When searching for possible interventions informed by the facet plot in Figure 3 we
302 identified two beneficial movement directions in the plot and mapped them onto real-
303 life interventions. Some readers may have noticed that in several of the heat maps
304 within the facet plot, fully ambiguous position likelihood (rightmost column) looks to be
305 favorable. Following the same logic as earlier, this would indicate that rightward
306 movement within heatmaps might be another possible intervention. However, this type
307 of intervention may be challenging to actualize. Recall that we let position observations
308 be a compound of visual and proprioceptive input about the limbs position. Following
309 limb loss, and in absence of a prosthesis, the visual input about the limb indeed does
310 become fully ambiguous. As for the proprioceptive input, it is practically much harder
311 to ensure that it is fully ambiguous. The severed nerves that used signal proprioceptive
312 information about the limb will likely innervate new tissue or form a neuroma, resulting
313 in some form of proprioceptive input from stimulation of the tissue or spontaneous
314 activity. It is difficult to ensure that these severed nerves stay silent following
315 amputation. Meanwhile, surgical techniques are being developed to promote
316 meaningful proprioceptive feedback [24,32,33], implicating diagonal up-and-leftward
317 movement as a more feasible option for interventions.

318
319 For simplicity, we have assumed that the likelihood matrices for position observations
320 and control matrices for movement are symmetric. In reality, severed nerves might
321 reinnervate in such a way that they are more likely to signal one position than another
322 and that some movements might be more difficult than others. Thus, more complex
323 likelihood matrices could either exacerbate or reduce the prevalence of phantom limb
324 pain. We provide some such examples in the Supplementary Material.

325
326 Due to the omission of higher-level cognition, our model likely best describes
327 subconscious interactions of pain and action rather than more complex, goal-directed
328 behavior. For instance, it may capture automatic movement adjustments or avoidance
329 responses in the presence of pain. In contrast, a more advanced (and arguably more

330 realistic) agent might choose to act despite anticipating pain, if doing so serves a valued
331 long-term goal. A classic example is persisting in a marathon despite muscle cramps
332 due to the appeal of a medal and bragging rights. Sometimes, the long-term reward
333 could even be the promise of pain relief. Challenging the subconsciously avoided
334 movements in physical therapy might give pain in the moment, but pain relief in the long
335 term. Such scenarios highlight that the pain–action loop can involve complex trade-offs
336 between immediate discomfort and delayed reward—dynamics that extend beyond the
337 scope of our current model.

338

339 The omission of higher-level cognition also prevents our model from capturing the
340 emotional dimension of pain. Pain reprocessing therapy (PRT), for instance, suggests
341 that certain forms of chronic pain may be sustained by fear and other aversive
342 emotional states [41]. This mechanism is likely relevant in phantom limb pain as well,
343 particularly given the often traumatic circumstances surrounding limb loss. Recent
344 work further indicates that emotional valence may be encoded in the perceived
345 success or failure of actions [42]. Extending the model to incorporate valence could
346 therefore provide insight into cases of phantom limb pain that are resistant to
347 interventions, as well as into other chronic pain conditions not primarily driven by
348 sensory disruption.

349

350 There is additional complexity in the interaction between control and pain not captured
351 by our model. While it is difficult to disentangle the effects of controllability and
352 predictability, there is growing evidence of a stronger effect of expectancy modulation
353 when pain is controllable [15]. It is hypothesized that the sense of agency may play a
354 key role in these dynamics [15,43]. Our model captures certain aspects of agency—
355 specifically, the recognition of oneself as the causal agent of voluntary actions and their
356 sensory outcomes—but it omits other relevant components such as self-efficacy and
357 attentional processes [15]. The temporal relationship of action and outcome is crucial
358 for the perception of agency [15,44]. Thus, in addition to the aforementioned inclusion
359 of valence, incorporating temporal dynamics into the model may be essential for
360 capturing the emotional and motivational mechanisms by which control and agency
361 influence pain.

362

363 Because we employed a discrete state space, the model currently only captures the
364 presence or absence of phantom limb pain. Extending the model to a continuous state
365 space could allow for modeling of pain intensity. Another promising future direction
366 would be to separate visual and proprioceptive input modalities. Sensory weighting
367 may vary across individuals, which could in turn influence the effectiveness of different
368 interventions. For example, some patients may benefit more from surgically restoring
369 proprioceptive feedback, whereas others might respond better to visually based
370 approaches such as mirror therapy. Furthermore, the current model only considers
371 interventions where position observations are generated from the external
372 environment. Yet, interventions based on internal processes—such as mental
373 imagery—have also shown some efficacy in reducing phantom limb pain. If these
374 effects operate via mechanisms similar to mirror or virtual reality interventions, they
375 raise important questions about how to delineate the boundary between the agent and
376 the environment should be represented in the model.

377

378 Finally, since our model has not been fit to empirical data, but manually tuned to
379 qualitatively reproduce phenomenological characteristics and behavior, we can only
380 offer conceptual predictions. Moving to a quantitative model that can produce real
381 estimates would require two major steps. First, it must be determined how the model
382 parameters can be quantified using real-world measures. For example, how are
383 noxious observations quantified in the nervous system; is it by the firing rate of
384 nociceptive neurons, or the ratio of activity in nociceptive and innocuous neurons?
385 Answers pertaining to some of the model parameters might already be available in
386 literature, while others likely would require a battery of physiological and
387 psychophysical experiments to be determined. Second, once parameters have been
388 tied to some real-world metrics, empirical data would need to be collected to fit these
389 parameters in the model. This step requires data to be collected both from individuals
390 with intact limbs and from amputees. For example, such measurements might involve
391 microneurography in intact and residual limbs to measure activity in peripheral afferent
392 neurons, or quantification of the susceptibility to sensory illusions to identify the
393 individual likelihood mappings of different sensory modalities relating to limb position
394 [45–47]. In addition to these two steps, some of the extensions proposed in the
395 previous paragraphs may also be necessary to enable mapping of model parameters
396 onto real-life quantities.

397 Methods

398 To describe how the model is set up we follow the steps outlined in Chapter 6 of the
399 book *Active Inference: The Free Energy Principle in Mind, Brain, and Behavior* [16]:

400

401 **Step 1. Which system are we modeling?**

402 In this first step, we need to identify the four core components of any active inference
403 model: *the agent* (the generative model), *the environment* (the generative process), and
404 the *sensory data* and *actions* that form the interface between the agent and the
405 environment.

406

407 *The generative process* describes the true causal structure by which sensory data are
408 generated from some hidden states. The hidden states may be influenced by actions
409 performed by the agent. *The generative model* is a construct used by the agent to infer
410 estimates of the hidden states based on observations of sensory data. To match these
411 components onto pain, we recall the definition of pain: *An unpleasant sensory and*
412 *emotional experience associated with, or resembling that associated with, actual or*
413 *potential tissue damage* [17]. We suggest that, in the context of pain, the hidden state
414 corresponds to tissue damage, and that pain corresponds to an agent's inferred
415 estimate of tissue damage. It is worth noting that this mapping implies that the tissue
416 for which the level of damage is being estimated belongs to the environment.
417 Specifically, we define the agent as the CNS of the organism at hand, and the
418 environment as the tissue of the body part the agent is making inferences about. The
419 sensory interface between the agent and the environment thus becomes the relay point
420 between the peripheral afferent sensory neurons of the body and the CNS.

421

422 So far, we have identified three out of four core concepts of our active inference model
423 of pain: the agent, the environment and the sensory interface between the two. The
424 fourth and final puzzle piece is the second part of the interface between the agent and
425 the environment: actions. Since we have defined the agent to be the CNS, and the
426 environment as the tissue of the body part of interest, the relevant actions are *actions*
427 *initiated by the CNS that influence the state of the tissue*. While the CNS can affect the
428 body through various pathways, we will focus on what is arguably the most direct
429 causal link: motor control and movement.

430

431 **Step 2. What is the most appropriate form for the generative model?**

432 Once we have detailed exactly what system we are interested in modelling, we next
433 need to consider what modelling format is most appropriate for describing the
434 generative model. To this end, we must specify three attributes of the model: the type of
435 state space, the hierarchical depth, and the temporal depth.

436

437 For the first attribute, we can choose between categorical (discrete) or continuous
438 state space (or hybrid combining both). For this model, we have chosen to use a
439 discrete state space due to its relative simplicity in computation. With this type of state
440 space, state factors and observations can be described by categorical distributions.
441 For example, the pain state can take one of two values, e.g., {Pain, No pain}, with
442 probabilities $\{p, 1 - p\}$. This type of state space would allow us to describe the
443 probability of pain being present or absent. One of the main limitations with the
444 discrete state space is that it does not allow us to describe e.g., pain intensity.

445

446 For the hierarchical depth, we need to consider whether all model variables evolve on
447 the same or different time scales. Since we are interested in the development of
448 chronic pain states, we would like to be able to describe both inference of states and of
449 model parameters (i.e., learning). Thus, we need to include at least two levels of
450 inference in our model.

451

452 As for the final attribute, the temporal depth, we are interested in modelling an agent
453 that can anticipate consequences of actions or action sequences (policies or plans). To
454 this end, we need to be able to describe planning capabilities in order to predict action-
455 outcome contingencies – our model needs temporal depth. However, we will limit the
456 model to only planning one time step ahead.

457

458 **Step 3. How to set up the generative model?**

459 Now that we have defined the system we are interested in and specified the key
460 attributes of the generative model, it's time to dig into the specifics. In this step, we
461 want to lay out the exact set-up of the generative model: What are the generative
462 model's most appropriate variables and priors? Which parts are fixed and what must be
463 learned?

464

465 In describing the generative model (and later the generative process) we will use the
466 following terminology:

467

- *State factors* refer to independent sets of states (e.g., {Pain, No pain})

- 468 • *Observation modalities* refer to independent sets of observable outcomes (e.g.,
469 activity in peripheral afferent neurons)

470

471 In step 1 we identified pain as the inferred estimate of tissue damage and that
472 peripheral afferent neurons make up the sensory interface with the tissue. At any given
473 time, the tissue in question will give rise to sensory input that is informative of the
474 current level of tissue damage. The sensory input modality that is most closely linked to
475 tissue damage is the activation of nociceptors, although input through other sensory
476 channels (e.g., visual input) can also carry some information about the status of the
477 tissue. Activity in peripheral afferent nociceptors is received by the generative model as
478 *noxious observations* and is used to infer the pain state.

479

480 In step 1, we further defined actions to be movements of the body part in interest. One
481 way of representing these movements in a discrete state space is by letting a state
482 factor represent the *position* of the body part. Actions can then be thought of as
483 movement between the different positions. For the agent to be able to efficiently plan
484 and execute these movements, the agent will infer the current position based on
485 *position observations*. Position observations can be thought of as a combination of
486 proprioceptive and visual input about the limb's position.

487

488 So far, we have two state factors (position and pain) and two observation modalities
489 (position and noxious). In the active inference framework, preferences are specified
490 through the priors over observations. By doing so, undesirable observations become
491 surprising and, through the surprise minimization paradigm that governs active
492 inference, will be avoided. Since tissue damage could threaten an organism's survival
493 noxious observations indicative of such tissue damage should be undesirable. As for
494 the position observation modality, it is not immediately apparent that any observation
495 should be more or less desirable than any other. Thus, we let the agent have a neutral
496 preference for all position observations.

497

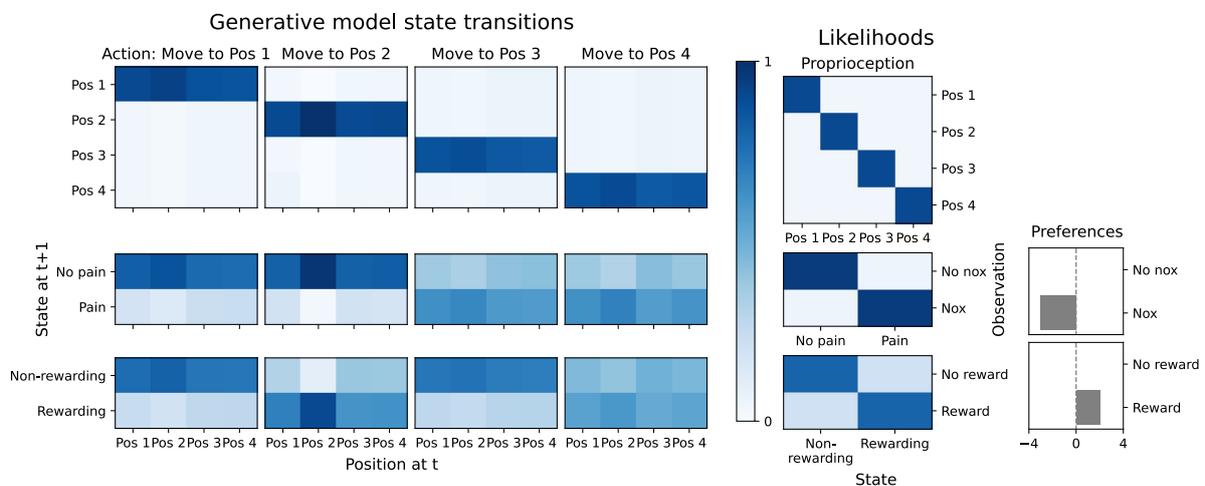
498 With the generative model described so far, the behavior of the agent will be rather
499 predictable: move to the position that minimizes noxious observations. The only reason
500 the agent would ever deliberately act to increase noxious observations would be to
501 reduce uncertainty about the world. Such an action might correspond to flexing a
502 sprained ankle to figure out how bad the injury is. The action is likely to increase
503 noxious observations, but also reduces uncertainty about the state of the ankle.
504 However, as anyone who has experienced pain during an extended period of time can
505 likely attest to, this type of action only makes up a small portion of the actions we take
506 in the face of pain. Typically, the availability of actions that reduce noxious observations
507 is limited and staying entirely passive while waiting for the tissue damage to heal is
508 rarely an option since most organisms have other competing interests to attend. While
509 minimizing noxious observations is desirable, there are other goals that also must be
510 optimized for to ensure survival, such as scavenging for food, fleeing from a predator or
511 going to the office to avoid loss of monetary income. These competing interests can,
512 and often do, motivate the organism to take actions that increase undesirable noxious
513 observations if they simultaneously generate alternate desirable *reward observations*.

514

515 To include these competing interests and alternate rewarding observations we extend
 516 the generative model in two ways. First, we add an additional observation modality to
 517 represent the *rewarding observations*. Second, we add an additional state factor
 518 (*reward state*) by which the agent infers if they are in a rewarding or non-rewarding
 519 state. For example, the rewarding observation could be finding a nutritious berry while
 520 foraging for food, by which the agent infers the probability that they are in a location
 521 with high or low berry-density (i.e., rewarding or non-rewarding state).

522
 523 Now, we have three state factors and three observation modalities. For each state
 524 factor-observation modality pair (position-proprioceptive observations, pain-noxious
 525 observations, rewarding-reward observations), we have a *likelihood matrix* describing
 526 the agent's belief about the probability that an observation was generated by a specific
 527 state.

528
 529 As described earlier, the actions available to the agent are movements between
 530 different positions. While the position is the only controllable state factor, movement
 531 between positions might still influence the other two state factors. As an example, you
 532 can control the flexion of your ankle, and while you cannot independently control the
 533 pain, some positions of the ankle may be more painful than others. Thus, we must
 534 specify *state transition matrices* describing how the agent believes each action will
 535 influence each of the state factors. The state transition and likelihood matrices, along
 536 with the prior preferences over observations, are key ingredients in the agent's decision
 537 of which policy (sequence of actions) to follow. Figure 7 shows an example of the
 538 generative model and its components.



539
 540 *Figure 7 The generative model consists of the expected state transitions (or control matrices) for each action, and*
 541 *likelihoods linking states to observations. In our model the agent makes inferences about three states: position,*
 542 *pain and reward state. The interface between the agent and the environment is made up of actions (movement of the limb)*
 543 *and sensory observations (noxious, position and reward observations). The agent has a preference for reward and*
 544 *against noxious observations.*

545 **Step 4. How to set up the generative process?**

546 Just as for the generative model, we need to describe the generative process, i.e., what
 547 the hidden states are, how observations are generated and how the agent's actions
 548 influence the environment.

549

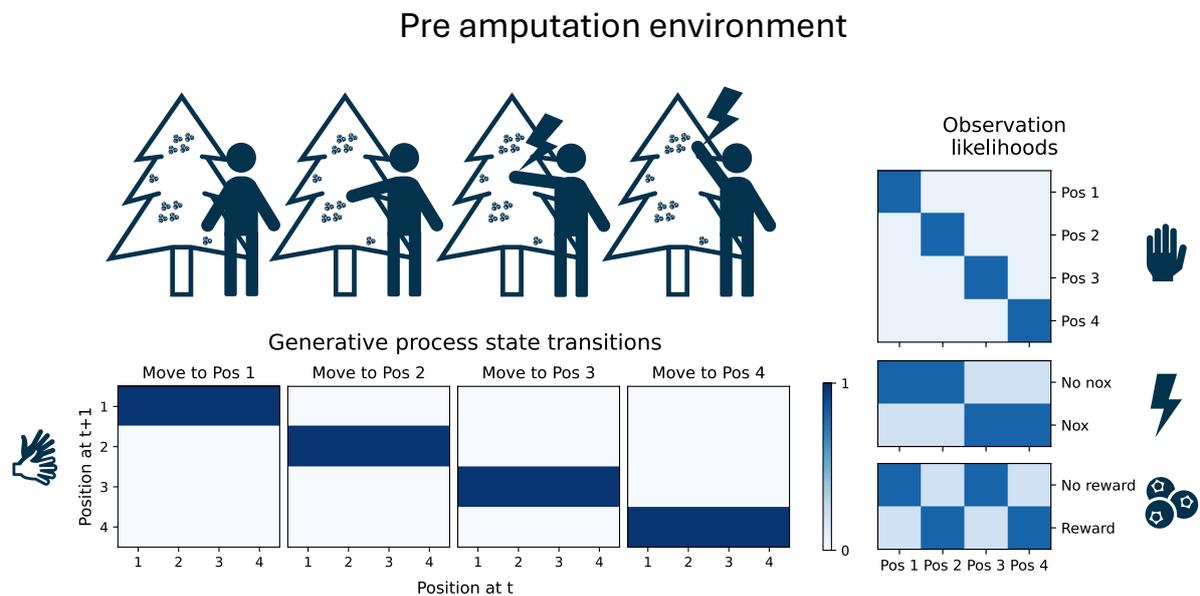
550 Following the same reasoning as in step 3 one could conclude that tissue damage,
 551 position and reward state all should be state factors of the generative process. While
 552 that certainly would be a viable approach, we have chosen to use an even simpler
 553 generative process to describe the environment. In our model position is the only state
 554 factor of the generative process, and we have let each position be associated with
 555 some probability for each of the three observation modalities. This means that we only
 556 need one state transition matrix to describe how the environment changes in response
 557 to the agent's actions.

558

559 Our reasoning for this simplification is that we primarily are interested in studying pain
 560 perception and action. In particular, we are interested in exploring how and when the
 561 perceived pain may dissociate from the noxious input. We have no interest in trying to
 562 describe tissue damage in detail. Thus, an environment that allows us to specify states
 563 with varying likelihood of noxious observations is sufficient for our purpose.

564

565 For our simulations we have chosen to let the position state factor have four different
 566 states, {Pos 1, Pos 2, Pos 3, Pos 4}, as this is the minimal environment that can account
 567 for all combinations of the noxious and reward observations: {No nox, No reward},
 568 {No nox, Reward}, {Nox, No reward} and {Nox, Reward}. We allow the agent to move
 569 to any position from any other position (i.e., the agent does not have to go via Pos 2 from
 570 Pos 1 to reach Pos 3). The generative process of the default environment is visualized in
 571 Figure 8.

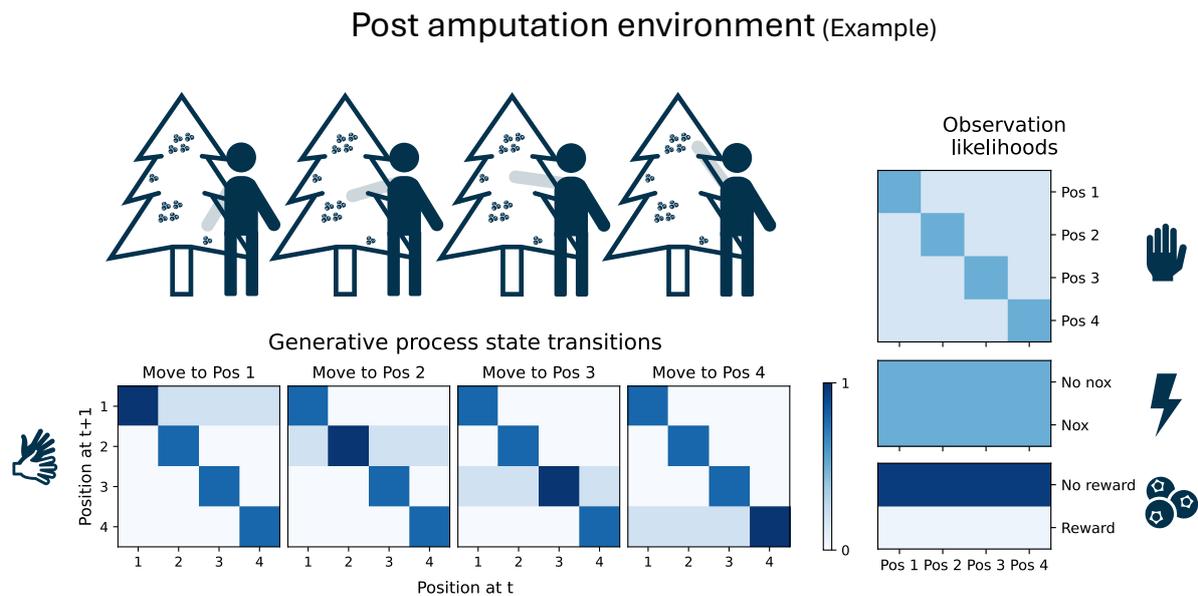


572

573 *Figure 8 For our model we have chosen to let the position state factor have four different states,*
 574 *{Pos 1, Pos 2, Pos 3, Pos 4}, as this is the minimal environment that can account for all combinations of the noxious*
 575 *and reward observations: {No nox, No reward}, {No nox, Reward}, {Nox, No reward} and {Nox, Reward}. We allow*
 576 *the agent to move to any position from any other position (i.e., the agent does not have to go via Pos 2 from Pos 1 to*
 577 *reach Pos 3). In the default (pre amputation) environment the state transition and likelihood matrices have high*
 578 *precision, allowing the agent to accurately perform movements and infer states from observations.*

579 We are particularly interested in studying how phantom limb pain may arise following
 580 limb loss. In our model, an injury directly affects the environment through changes to
 581 the generative process. An example of the generative process of the environment
 582 following limb loss is visualized in Figure 9.

583



584
585
586
587
588
589

Figure 9 Amputation causes dramatic changes to the environment, affecting the agent’s ability to control the limb position and altering the likelihoods of sensory observations. In the generative process these changes are reflected in the state transitions becoming a mixture of the original matrices (see Figure 8) and the identity matrix, increased ambiguity in position and noxious observation likelihoods, and a low probability for reward observations at all positions.

590 Below we provide some more context on the changes to the generative process:

591

592 *Ambiguous noxious observations.* Following limb loss, peripheral afferent nerves that
593 used to innervate the limb become severed and are no longer able to reliably signal
594 information about the state of the limb. Some neurons may find new tissue to innervate
595 in the residual limb, regaining some stability in their signaling. However, a significant
596 portion of neurons will likely either fall silent or become spontaneously active, causing
597 some level of ambiguity in the signal arriving to the CNS. In the generative process, we
598 represent this change as 1) increased ambiguity in the observations, and 2) equal
599 likelihood for noxious observations at all four limb positions. We will consider three
600 distinct cases corresponding to low, intermediate and high level of spontaneous
601 activity in nociceptive peripheral afferent neurons.

602

603 *Low reward observations.* Following limb loss, we assume that agent’s ability obtain
604 reward observations with the affected limb is impaired (e.g., picking berries). To reflect
605 this change, we set a low probability for reward observations at all positions.

606

607 *Altered ability to perform movements.* Since the limb is no longer present, the agent
608 cannot efficiently move it to different positions. In fact, following limb loss the “position
609 state” of the limb becomes ill defined in the generative process. To figure out how the
610 state transition and position likelihood matrices might look, we can turn to an
611 analogous scenario: regional anesthesia. When regional anesthesia is applied to a
612 limb, the limb’s position is still well defined, but the controllability and sensory input
613 from the limb become altered. When the agent attempts to initiate a movement the
614 limb partially or fully (depending on the intended movement and the level of anesthesia)
615 stays unchanged. Mathematically, a completely stuck limb would correspond to the

616 state transition matrices being identity matrices. However, turning back to limb loss,
617 depending on the level of amputation and the reinnervation of the residual limb, there
618 may exist some ability to control the limb position. As for position observations, visual
619 input about the limb's position becomes fully ambiguous. Just as with the noxious
620 observations, proprioceptive sensory input from the severed nerves also becomes
621 ambiguous when they no longer have a limb to innervate. However, the level of
622 ambiguity in proprioceptive feedback may vary depending on the level of amputation
623 and reinnervation of the residual limb. In what follows, we will consider three levels of
624 ambiguity: low ambiguity (as in the default environment) partial ambiguity, in which
625 position input still carries some information, and full ambiguity, in which all limb
626 positions generate the same observation.

627

628 **Bonus step 5: how to implement the model?**

629 Now that we have defined the generative model and process of the system we are
630 interested in studying, we are almost ready to start simulating, visualizing and analyzing
631 model outputs. However, before we dive into the results, we suggest one more step in
632 addition to those suggested by Parr et al. [16]: describing what modelling choices are
633 made in the specific model implementation. What method is used for variational
634 inferences? How is policy selection performed? How is learning implemented?

635

636 Our model implementation leverages the *pymdp* Python library for active inference in
637 discrete state spaces [48]. *pymdp* is a Python package that is inspired by and tested
638 against the active inference routines contained in the widely used DEM toolbox of SPM
639 [49]. While *pymdp* allows for a high degree of customizability, we have mostly used the
640 standard routines provided by the library. In what follows, we provide brief descriptions
641 of these routines and specify where and how our implementation deviates.

642

643 *Variational inference.* For state inference we use the default inference algorithm
644 (denoted 'VANILLA') provided by *pymdp* which leverages Fixed Point Iteration to find
645 the marginal posterior over hidden states.

646

647 *Policy distribution.* The policy distribution is computed as $\text{softmax}(G \cdot \gamma)$, where G is
648 the expected free energy for each policy and γ is the policy precision. We have chosen
649 to include information gain over states and parameters in the expected free energy
650 estimate, in addition to utility. The relative contribution of these quantities determines
651 whether the level of exploration vs. exploitation in the agent's actions. The expected
652 free energy is computed by 1) computing expected states under each policy, 2)
653 computing expected observations based on the expected states, 3) calculating the
654 expected utility based on the expected observations and the agent's prior preferences,
655 4) calculating the expected information gain about states (Bayesian surprise), 5)
656 calculate the expected Dirichlet information gain over the learnable parameters, and
657 finally 6) summing the utility, information gain over states and information gain over
658 parameters.

659

660 *Policy selection.* Once the policy distribution has been computed, the agent must
661 choose which policy to follow. This selection can be done either deterministically, by
662 selecting the policy corresponding to the highest value in the distribution, or by

663 stochastically sampling from the distribution. We have used deterministic policy
664 selection in our simulations to limit behavioral variability not attributable to exploration
665 or exploitation.

666

667 *Learning.* In our model implementation, the agent can update (learn) the entries of the
668 state transition matrices based on experiences. This learning procedure is
669 implemented through “learning by counting” by using Dirichlet priors as described in
670 [50]. As Dirichlet concentration parameters grow over time, the agent becomes more
671 and more confident in its beliefs. While this learning paradigm accurately reflects that
672 an agent should grow more and more confident upon repeated confirmatory
673 experiences, it can also lead to the agent becoming overconfident and slow to update
674 their beliefs in a changing environment. One way to remedy this is by introducing a
675 “forgetting factor”, in which the concentration parameters are scaled by a factor $w_B \in$
676 $(0,1]$ [50]. Note, however, that this forgetting factor doesn’t imply that the agent
677 “forgets” or changes its beliefs, but rather that it, in absence of additional confirmatory
678 experiences, becomes less confident in its beliefs, allowing for more readily adaptive
679 updates in light of new evidence. Applying a flat forgetting rate at all iterations may lead
680 to some undesired behavior, such as intermittent bursts of exploratory behavior even
681 when the environment is unchanged. Thus, we only apply the forgetting factor when
682 $F - F_{avg} > \theta$, where F is the current variational free energy, F_{avg} is a moving average of
683 the variational free energy within a predefined window, and θ is some threshold. In the
684 active inference framework, variational free energy is a proxy for surprise in cases
685 where the exact surprise cannot be computed. Put into plain words, the forgetting
686 factor is only applied when data are excessively surprising under the current belief,
687 signaling that the current generative model is inadequate. Inference of the volatility of
688 the environment can be implemented in a more principled manner, for example in using
689 a hierarchical model [51]. However, this simpler paradigm allows us to incorporate
690 some surprised-based adaptation without adding much complexity to the model.

691

692 *Observations.* When dealing with discrete state spaces, observations generated by the
693 environment can be received by the agent either as point-samples from the observation
694 distribution, or as the entire distribution. In the former case there is no ambiguity in the
695 observation itself (you either observe a nutritious berry or you do not), but there could
696 still be some ambiguity in how that observation relates to the hidden state (how likely is
697 a single berry-observation to have come from a high- vs low-density berry region). The
698 latter case allows for ambiguity to also be baked into the observation itself (e.g.,
699 observing a sound in a noisy environment). Since we treat noxious observations as the
700 incoming signals from peripheral afferent neurons, we expect there to be some
701 ambiguity in these observations. Thus, we treat observations as distributions (by setting
702 the `distr_obs` flag to `True`).

703

704 **Code availability**

705 Python code for all simulation results presented here are available online at:
706 <https://doi.org/10.5281/zenodo.17395215>. Additional results and pseudocode of the
707 active inference algorithm can be found in the Supplementary Material.

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