1   **Title**: Neuromodulation due to propofol affects anesthetic oscillatory coupling

2   **Authors:** Austin E. Soplata[1,2,3], Michelle M. McCarthy[2], Elie M. Adam[2], Patrick L. Purdon[3],

3   Emery N. Brown[3,4,5], Nancy Kopell[2]

4   **Affiliations:**

5   1. Graduate Program for Neuroscience, Boston University, Boston, MA, USA

6   2. Department of Mathematics & Statistics, Boston University, Boston, MA, USA

7   3. Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital,

8   Harvard Medical School, Boston, MA, USA

9   4. Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology,

10   Cambridge, MA, USA

11   5. Institute for Medical Engineering and Science, Massachusetts Institute of Technology,

12   Cambridge, MA, USA

13   **Contributions:**

14   Austin E. Soplata: Conceptualization, Data curation, Investigation, Methodology, Software,

15   Analysis, Validation, Visualization, Writing, Editing. Michelle M. McCarthy: Conceptualization,

16   Analysis, Writing, Editing. Elie M. Adam: Software, Visualization, Analysis, Editing. Patrick .

17   Purdon: Funding acquisition, Data curation, Project administration, Supervision, Editing. Emery

18   N. Brown: Funding acquisition, Project administration, Supervision, Editing. Nancy Kopell:

19   Conceptualization, Analysis, Funding acquisition, Project administration, Supervision, Writing,

20   Editing.

21   **Running Head:** Neuromodulation due to propofol affects anes. osc. coupling

22   **Key Words:** anesthesia, thalamocortical oscillations, oscillatory coupling, propofol, thalamus

23

24   **Abstract**

25   The anesthetic propofol produces prominent oscillatory signatures on the EEG. Despite the

26   strong correlation between oscillations and the anesthetic state, the fundamental mechanisms of

27   this unconsciousness remain unknown. On the EEG, propofol elicits alpha oscillations (8-14 Hz),

28   slow oscillations (0.5-2.0 Hz), and dose-dependent phase-amplitude coupling (PAC) between

29   these rhythms. A low enough dose causes "trough-max" PAC, where alpha oscillation amplitude

30   is consistently maximal during slow troughs; this occurs at the same time as arousable

31   unconsciousness. A high enough dose causes consistent "peak-max" PAC, where alpha

32   amplitude is maximal during the slow peak, at the same time as unarousable unconsciousness.

33   Much of the anesthetic state is dominated by a mixture of both states. Using thalamocortical

34   Hodgkin-Huxley simulations, we show that, in addition to propofol effects on $GABA_A$ synapses

35   and thalamocortical H-currents, propofol-induced changes to neuromodulation may generate

36   LFP oscillations and their dose-dependent coupling. We show this for acetylcholine specifically,

37   though other neuromodulators may produce the same effects. We find that LFP- and EEG-

38   relevant synapses of local thalamocortical circuits stochastically display either trough-max or

39   peak-max PAC on any given slow cycle. Trough-max PAC signals are present only in

40   thalamocortical synaptic currents, and not identifiable via membrane potentials alone. PAC

41   preference depends critically on the neuromodulatory state, which is dose-dependent: high doses

42   are associated with statistically more peak-max than trough-max, and vice-versa. This is caused

43   by increased cortical synchronization at higher doses. Our results have important consequences

44   for analyzing LFP/EEG data, in that local network trough- or peak-max may only be seen on a

45   cycle-by-cycle basis, and not when averaging. We hypothesize that this increased cortical

46 synchronization leads to an inability to process signals in a flexible manner needed for awake

47 cognition.

48

49 **New & Noteworthy**

50 We simulate biophysical neural networks to investigate how the anesthetic propofol enables

51 alpha and slow oscillations to emerge and interact. Direct effects of propofol on inhibition and

52 indirect effects on acetylcholine level are necessary for dose-dependent emergence and coupling

53 of these rhythms. Local groups of anesthetized cells behave with more complexity than global

54 EEG would suggest. Higher doses are associated with more cortical synchrony, which may

55 underlie the reduced ability to respond to stimuli.

56

57 **Introduction**

58 Reversible loss of consciousness is the primary aim of all anesthetic agents. Loss of

59 consciousness with the anesthetic propofol is dose-dependent, with lower doses of propofol

60 leading to limited, "arousable" unconsciousness (Purdon et al. 2013; Mukamel et al. 2014;

61 Stephen et al. 2020; Gaskell et al. 2017). For example, with lower doses of propofol, subjects

62 may display decreased arousal but retain their ability to respond to auditory cues if a painful

63 stimulus is applied (Gaskell et al. 2017), or slowly lose their ability to respond (Purdon et al.

64 2013; Mukamel et al. 2014). In contrast, high-dose propofol administration anesthetizes patients

65 into deep, "unarousable" unconsciousness (Purdon et al. 2013; Mukamel et al. 2014; Gaskell et

66 al. 2017; Stephen et al. 2020).

67

68   The EEG during propofol anesthesia is dominated by slow (0.5-2.0 Hz) and alpha (8-14 Hz)

69   oscillations (Purdon et al. 2013; Mukamel et al. 2014). Studies suggest that phase-amplitude

70   coupling (PAC) between slow and alpha oscillations may be an indicator of depth of anesthesia

71   (Purdon et al. 2013; Mukamel et al. 2014). At a sufficiently low dose of propofol, alpha

72   amplitude is maximal during the trough of the slow phase, creating "trough-max" PAC. In

73   contrast, at sufficiently high doses of propofol, alpha amplitude is maximal during the peak of

74   the slow phase, creating "peak-max" PAC (Mukamel et al. 2014). However, large periods of

75   time under propofol do not correspond to either of those states on the temporal scale of

76   spectrogram analysis, instead displaying indeterminant PAC.

77

78   In this computational modeling paper, we show that the notions of alpha-slow trough-max and

79   peak-max PAC exist on the fine timescale of single slow periods locally in space. In local

80   networks, each slow period can exhibit either trough- or peak-max randomly changing in time

81   during the same simulation. We also show that the statistics of these changes are dose-dependent,

82   with higher doses of propofol corresponding to a larger percentage of peak-max rather than

83   trough-max cycles. An important finding of the work is that the statistics of the two PAC states

84   were strongly influenced by the synchrony of the cortical cells. Thus, the depth of anesthesia,

85   measured over a long timescale, corresponds to the statistics of trough- and peak-max states, not

86   a global switch between one state and the other.

87

88   We base our model on previous models suggesting thalamocortical involvement in the

89   production of propofol slow and alpha oscillations and their coupling (Soplata et al. 2017). Our

90   previous model treated the cortical dynamics strictly as inputs to the thalamic dynamics. Here,

91   we use a full thalamocortical model with feedforward and feedback connections, and the results

92   depend on these connections. Our thalamic model is derived from (Soplata et al. 2017) and our

93   slow-oscillation-producing cortical model is built on (Compte et al. 2003) (for justification of

94   this cortical slow model, see Methods). The thalamus-to-cortex connections play a prominent

95   role in the synchronization of cortical spiking, which promotes the transition to peak-max.

96

97   Our model includes both direct and indirect effects of propofol: The direct effects are those that

98   affect $GABA_A$ inhibition and thalamocortical cell (TC) H-current, while the indirect effects are

99   from its effects on neuromodulation. We focus on acetylcholine (ACh), which propofol is known

100   to decrease (Kikuchi et al. 1998; Meuret et al. 2000; Nemoto et al. 2013; Pal and Mashour 2021;

101   Luo et al. 2020). In the model, ACh affects several currents, but we find that the essential change

102   is the increase in thalamocortical synaptic strength. ACh-mediated increases in thalamocortical

103   synaptic strength lead to greater cortical synchrony and a statistical shift in the proportion of

104   cycles in trough-max versus peak-max. Other neuromodulators may also be involved, especially

105   those that affect thalamocortical strength.

106

107   **Results**

108

109   **Modeling Objectives and Model Description**

110

111   The aim of our modeling is to explain the dynamic mechanisms underlying the changing PAC

112   seen in experimental data during a large proportion of the anesthetic state under propofol, as

113   illustrated in Figure 1 from approximately time 0 to 45 minutes. Prominent alpha and slow

114   oscillations appear in the EEG of patients under propofol, as shown in Figure 1 A and B. The

115   PAC between alpha and slow changes over time as the dose is increased. Except for very high

116   doses, the PAC is neither wholly trough-max nor wholly peak-max, as shown in Figure 1 B and

117   D. As we will show, our model reproduces alpha and slow frequencies as well as the mix of

118   trough-max and peak-max.

119

120   Our network is composed of 20 Hodgkin-Huxley-type thalamocortical cells (TC), 20 thalamic

121   reticular neurons (TRN), 100 cortical pyramidal soma cell compartments (PYso), 100 cortical

122   pyramidal dendritic cell compartments (PYdr), and 20 cortical interneurons (IN), as illustrated in

123   Figure 2 A (see Methods). We model the effects of propofol by "direct" and "indirect" effects.

124   The direct effects are: increasing $GABA_A$ maximal conductance ($\bar{g}_{GABA_A}$) and $GABA_A$ decay

125   time constant (τ_{GABA_A}) and decreasing TC cell H-current maximal conductance ($\bar{g}_H$) (see

126   Methods) (Soplata et al. 2017). In addition, we model some indirect effects of propofol on

127   neuromodulation, in particular cholinergic modulation, which is known to decrease in the

128   presence of propofol (see Methods and next section) (Kikuchi et al. 1998; Nemoto et al. 2013;

129   Meuret et al. 2000; Pal and Mashour 2021; Luo et al. 2020). The indirect effects are increased

130   intracortical AMPAergic synaptic conductances ($\bar{g}_{AMPA:PY\to PY}$), TC-to-PY thalamocortical

131   AMPAergic synaptic conductances ($\bar{g}_{AMPA:TC\to PY}$), and K(Na)-current maximal conductance

132   ($\bar{g}_{K(Na)}$) (see Methods for detail). As we will see, the most important cholinergic effect is the

133   increase in strength of the thalamocortical connections; we hypothesize that other modulators

134   that produce this effect could also produce the same results as in our model. The number of cells

135   in the model is relatively small and is intended to model local activity similar to an LFP signal.

136   The LFP of the model is produced by two sets of synapses: thalamocortical (TC→PY) and

137   intracortical (PY→PY), both targeting the dendrites of cortical pyramidal cells (see Methods).

138

139   The parameters were chosen such that in a baseline condition without propofol, the model

140   produces a depolarized relay-mode state under weak, constant applied current, as shown in

141   Figure 2 B. This simulation exhibits non-bursting, tonic spiking in both the cortex and thalamus

142   as spikes are relayed between regions. Neither region shows high-activity bursts or long periods

143   of quiescence as one would expect in sleep or anesthetized states. This baseline simulation does

144   not exhibit either slow or alpha oscillations spiking.

145

146   **Direct effects do not produce alpha and slow oscillations**

147

148   Our previous work (Soplata et al. 2017) showed that the "direct" effects of propofol were

149   sufficient for enabling alpha oscillations in a thalamic model with an artificial cortical input. In

150   contrast, our current model expresses neither UP/DOWN slow states nor alpha oscillations in

151   response to the direct effects of propofol across many different values of $GABA_A$ and $\bar{g}_H$

152   parameter values, as shown in

153

154   Figure 3 A. The lack of DOWN states allows the cortex to continue to send strong, consistent

155   excitation to the anesthetized thalamus, thus interfering with thalamic bursting and propofol

156   alpha oscillations, as shown in

157

158   Figure 3 B and C. More details about this mechanism are in Ancillary Information 1.

159

160   **Neuromodulatory effects enable both alpha and slow oscillations**

161

162   Since direct propofol effects are not able to produce propofol oscillations in our model of the

163   depolarized relay state, we expand our propofol modeling to also include its "indirect" effects.

164   Our indirect effects are modeled as a decrease of cortical ACh in three ways: increasing PY cell

165   K(Na)-current maximal conductance ($\bar{g}_{K(Na)}$) (Compte et al. 2003; Benita et al. 2012), increasing

166   intracortical PY→PY AMPAergic synaptic maximal conductance ($\bar{g}_{AMPA:PY→PY}$) (Krishnan et al.

167   2016), and increasing thalamocortical TC→PY AMPAergic synaptic maximal conductance

168   ($\bar{g}_{AMPA:TC→PY}$), the latter by way of muscarinic ACh receptors (Kruglikov and Rudy 2008;

169   Favero, Varghese, and Castro-Alamancos 2012).

170

171   With the addition of the indirect effects, the model is able to generate propofol slow and alpha

172   oscillations observed in both the model LFP and the spiking in Figure 4 A and B. The slow

173   oscillation of our cortical model relies on $\bar{g}_{K(Na)}$, as in the sleep slow model from which it was

174   derived (Compte et al. 2003). Random excitation triggers a cortical UP state, during which

175   intracellular sodium builds up, activating the K(Na)-current. This current then terminates the UP

176   state and transitions the pyramidal cells to silent, hyperpolarized DOWN states, just as in the

177   original work (Compte et al. 2003). We assume in our model that these cortical UP and DOWN

178   states correspond, respectively, to the peak and trough of EEG / LFP slow as in natural sleep

179   slow oscillations (Vincenzo Crunelli and Hughes 2010; Cash et al. 2009; Amzica and Steriade

180   2002).

181

182   In addition to slow oscillations, propofol-induced neuromodulation enables thalamic alpha

183   oscillations, as shown in Figure 4. In each slow cycle, the alpha spiking appears in one of two

184   patterns depending on individual slow cycles. During some individual slow cycles, thalamic

185   alpha is present during the cortical DOWN state (blue highlights in Figure 4), while during other

186   slow cycles, thalamic alpha is absent from the cortical DOWN state (orange highlights in Figure

187   4). We refer to the former as trough-max and the latter as peak-max: the two switch apparently

188   randomly on the timescale of seconds, consistent with Figure 1 B. In peak-max, the thalamic

189   alpha exists only in a small range of phases of the slow oscillation. In trough-max, the alpha is

190   spread out over almost the entire slow oscillation cycle, with the most power where cortex is in

191   the DOWN state, making the duration of the alpha longer than in peak-max periods. Though

192   "peak-max" and "trough-max" are defined here in terms of spiking patterns, we will show below

193   that the LFP matches this nomenclature: high alpha in spiking is at the peak of the LFP during

194   peak-max, and high alpha in spiking is around the trough of the LFP during trough-max.

195

196   In the next sections, we will characterize how peak-max and trough-max time periods come

197   about, locally in time in both the spiking and the LFP. For this analysis, we need to understand

198   how the LFP is produced during each of the states by looking at the two kinds of synaptic

199   currents in the model that constitute the LFP: thalamocortical and intracortical synapses that

200   target the pyramidal cell dendrites.

201

202   **Phase-amplitude coupling between alpha and slow oscillations during peak-max**

203

204   During peak-max, thalamic alpha oscillations occur in the spiking only near or during cortical

205   UP states, as shown in Figure 5. Immediately before a cortical UP state, thalamic cells

206   spontaneously burst at the propofol alpha frequency, as shown Figure 5 C. These thalamic bursts

207   initiate a cortical UP state in which the firing is relatively synchronous. The resulting PY→TC

208   depolarization from the synchronous cortical UP is strong enough to depolarize the TC cells into

209   their silent, depolarized state, also known as the "thalamic relay-mode" (see section below

210   "Cortical synchronization modulates thalamic state and is modulated by thalamocortical

211   feedback"). This terminates the thalamic alpha bursting, causing the TC cells to cease oscillating.

212   Loss of TC activity contributes to cessation of cortical spiking and the emergence of the DOWN

213   state. Once both cortical and thalamic cells are quiescent for long enough, the TC cells

214   spontaneously hyperpolarize and initiate bursts again, resetting the cycle.

215

216   We now consider the synaptic currents onto the pyramidal cell dendrites, the constituents

217   currents of the LFP model, during peak-max as shown in Figure 6. During peak-max, both

218   TC→PY and PY→PY synaptic currents are maximal during the cortical UP states, as shown in

219   Figure 4 B and Figure 6. Since thalamic alpha is generated only around the cortical UP, at the

220   peak of the LFP, the coupling between alpha and slow is strong during peak-max, as shown in

221   Figure 4 B, Figure 6 D and Ancillary Information 1. Thus, during peak-max, there is a

222   cooperation in the coupling signal.

223

224   To quantify the amount and preferred slow-phase of alpha power in our LFP signal during this

225   time period, we used the Modulation Index (MI) method (Tort et al. 2010; Purdon et al. 2013) as

226   shown in Figure 7 D. Across the different slow cycles of the combined TC→PY and PY→PY

227   synaptic current comodulogram, the alpha magnitude of the combined synaptic current switches

228   its preference between 0 (middle) on the slow phase, corresponding to the slow peak, and $\pm\pi$

229   (edges), corresponding to the slow trough. During the indicated time period, which corresponds

230   to the orange peak-max time period in 6 A, this current tends towards the slow peak phase

231   instead of the slow trough phase, illustrated by the coupling skewing towards the center. Our

232   simulated peak-max signature highlighted in Figure 7 D is similar to peak-max times in Figure 1

233   of this work.

234

235   **Phase-amplitude coupling between alpha and slow oscillations during trough-max**

236

237   We next examine how the alpha and slow interact during the blue trough-max time periods.

238   During this time, cortical spiking is not tightly synchronized, as shown in Figure 5 A and D. Due

239   to this less synchronized cortical excitation, the thalamus is able to remain hyperpolarized

240   enough during trough-max to have uninterrupted alpha bursting.

241

242   During this trough-max time period, target PYdr compartments exhibit slow oscillations, as

243   shown in Figure 8 B, while the cortically projecting TC cells exhibit alpha oscillations during the

244   cortical DOWN state, as shown in Figure 8 C. The resulting TC→PY synaptic current is shown

245   in Figure 8 D. The amplitude of the total TC→PY synaptic current fluctuates both with alpha

246   bursts from the thalamus and on a slow timescale due to the fluctuation of the membrane voltage

247   of the PY cells. During cortical slow fluctuations, the synaptic current is maximal during the

248   DOWN/non-spiking (trough) phase of the target cortical cell, as indicated by dashed lines in

249   Figure 8 D and E. This is likely due to the less-synchronous cortex allowing for thalamic alpha to

250   occur for more of the phase than in peak-max. We note that neither the spiking of the TC nor PY

251   cells alone display alpha-slow coupling; the coupling is evident only in the synaptic interaction

252   between the TC cells and the pyramidal cell dendrites.

253

254   In contrast to peak-max, synaptic intracortical currents have very different behavior than

255   synaptic thalamocortical currents during trough-max, as shown in Figure 8 and Figure 9. During

256   peak-max, intracortical currents are maximal during the slow peak or UP state (Figure 8 F-H),

257   whereas thalamocortical currents are maximal during the slow trough or DOWN state (Figure 8

258   B-E). Despite these synaptic currents competing with each other (Figure 9 A and B), the

259   thalamocortical current is an order of magnitude stronger than the intracortical current (Figure 9

260   C), causing the combination of these currents to exhibit trough-max (Figure 9 D).

261

262   **Cortical synchronization modulates thalamic state and is modulated by thalamocortical**

263   **feedback**

264

265   There are two obvious dynamic differences between trough-max and peak-max: the latter

266   displays more cortical synchronization and the thalamus undergoes periods of silence similar to

267   cortical DOWN states, as shown in Figure 5 and Figure 10. These two phenomena are causally

268   related: during peak-max, the cortical cells are highly synchronized, giving more excitation to

269   the thalamus during the cortical UP state, which depolarizes the thalamus out of its alpha

270   bursting mode into silent depolarization, producing a DOWN state in thalamus. In the absence of

271   cortical synchrony, the thalamus remains more hyperpolarized, producing continuous alpha

272   during cortical DOWN states. Furthermore, in peak-max, the existence of the thalamic DOWN

273   state implies that the cortex receives less excitation during that period, causing the cortex to fire

274   more synchronously during the next UP, since PY cells have not been made to prematurely fire.

275   Thus, there is a reciprocal relationship between spiking synchrony in the cortex and the decrease

276   of alpha in the thalamus.

277

278   The level of cortical synchrony of a slow cycle is produced not only by thalamocortical feedback

279   but also by a stochastic process determined by many factors. These other factors allow switches

280   between peak-max and trough-max on a slow cycle-by-cycle basis. In particular, there is a

281   seemingly chaotic response to similar but different initial conditions: different simulations

282   express very different proportions of time spent in trough-max or peak-max (low or high

283   synchrony). We hypothesize that variables associated with activity of pyramidal cells in the

284   peak-max cortical DOWN state, in which a few pyramidal cells always remain spiking,

285   contribute to the switch from peak-max to trough-max. However, obtaining a complete

286   understanding of the slow cycle-to-cycle variations is outside the scope of this work.

287

288   **Neuromodulation can change preferred PAC regime via changing thalamocortical**

289   **feedback**

290

291   By modeling higher dose propofol via increasing the indirect effects of ACh, we find that the

292   network shifted from preferring trough-max to peak-max, as shown in Figure 11. To show this,

293   we ran 200 simulations with the previous parameters and random initial conditions, and 200

294   more simulations with the same parameters, except for increases in $\bar{g}_{AMPA:TC\rightarrow PY}$, $\bar{g}_{AMPA:PY\rightarrow PY}$,

295   and $\bar{g}_{K(Na)}$, which model further increases in propofol via a decrease in cholinergic modulation.

296   We then averaged the amount of time each simulation exhibited trough-max (data in

297 Supplementary Data 1), since any time not spent in trough-max exhibited peak-max. The lower

298 dose propofol simulations show a slight preference for trough-max over peak-max, with 53% of

299 the time spent in trough-max. In high-dose simulations, the system shifts to a clear preference for

300 peak-max, with trough-max occurring only 27% of the time. There is a high degree of variability

301 among individual simulations, with the proportion of time spent in trough-max having a standard

302 deviation of 20% in the low-dose case and 13% in the high-dose case.

303

304 To understand the cause of this PAC preference shift, we examined each of the propofol indirect

305 effects individually. Starting with low-dose parameters, we changed one indirect effect

306 parameter at a time (i.e., $\bar{g}_{AMPA:TC\rightarrow PY}$, $\bar{g}_{AMPA:PY\rightarrow PY}$, or $\bar{g}_{K(Na)}$) and ran 200 more simulations

307 each. With a high dose level of $\bar{g}_{AMPA:TC\rightarrow PY}$, the proportion of time spent in trough-max

308 decreases to 30% ($\pm$ 13%), similar to the decrease from low-dose to high-dose propofol with all

309 indirect effects increased. In contrast, with a high-dose level of $\bar{g}_{AMPA:PY\rightarrow PY}$ or $\bar{g}_{K(Na)}$, the

310 proportion of time spent in trough-max is 50% ($\pm$ 19%) or 54% ($\pm$ 18%), respectively. This

311 strongly suggests that changes to thalamocortical synaptic strength are the primary cause of the

312 change in preferred PAC in our model (parameters in Methods and Appendix, data in

313 Supplemental Data 1).

314

315 The shift to peak-max when $\bar{g}_{AMPA:TC\rightarrow PY}$ increases is likely due to the increased ability of

316 thalamic bursting to recruit more cortical cells into the synchronized cortical UP state. These

317 synchronized cortical cells send more feedback excitation to TC cells, causing them to enter their

318 depolarized silent state and begin the mutually-enforcing patterns of thalamocortical and

319 corticothalamic interactions that characterize peak max.

320

Discussion

322

Overview

324

In this work, we simulate a thalamocortical network of Hodgkin-Huxley cells to understand the

propofol anesthetic state during which neither trough-max nor peak-max appears to dominate the

EEG, though the statistics of these two states change with dose. We find that both the direct

effects of propofol on cellular membrane and inhibitory dynamics as well as the indirect effects

of propofol mediated by ACh are necessary for producing slow oscillations, alpha oscillation,

and their coupling. Slow oscillations generated by cortex and alpha oscillations generated by

thalamus couple during propofol states, but do not form stable, long-lasting PAC regimes at the

LFP level. The alpha-slow PAC can change from slow cycle to slow cycle in a manner that

appeared to be stochastic, with a slight preference for trough-max with a lower dose and a strong

preference for peak-max at a higher dose. We found the PAC type distribution depends on the

synchronization of the cortex and, therefore, the cortical signal given to the thalamus. At the

higher dose of propofol, the increase in $\bar{g}_{AMPA:TC \to PY}$, an indirect effect of propofol due to ACh, is

highly influential in changing the preferred PAC type in favor of peak-max. Increasing

$\bar{g}_{AMPA:TC \to PY}$ leads to higher synchronization of the cortical pyramidal cells, which leads to

stronger and more focused feedback to the thalamus.

340

Prior work and thalamocortical feedback

342

343   While prior modeling demonstrated thalamocortical circuits could produce propofol alpha

344   oscillations (Ching et al. 2010; Vijayan et al. 2013), or propofol alpha and slow (Krishnan et al.

345   2016), our previous work (Soplata et al. 2017) was the first modeling investigation into the

346   unique alpha-slow PAC dynamics of propofol of which we are aware. Our current

347   thalamocortical model includes feedback from thalamus to cortex, leading to updates of several

348   predictions pertaining to propofol alpha-slow PAC as well as to new mechanistic insights into

349   the role of thalamocortical feedback in network dynamics related to loss of consciousness.

350

351   Our prior model predicted propofol-alpha generation in thalamus due to the direct effects of

352   propofol. Our current thalamocortical model supports thalamic generation of alpha but

353   additionally requires the indirect effect of propofol lowering ACh and decreasing cortical firing

354   to generate this alpha. In the prior thalamus-only model, thalamic alpha emerged only during the

355   DOWN state in trough-max and only during the UP state in peak-max. In the current model, in

356   which the hyperpolarization level of the thalamus is partially controlled by the cortex, we find

357   that, during trough-max, the thalamus does not hyperpolarize enough to stop spiking during the

358   UP state; rather, the thalamus continues to burst in alpha in both cortical UP and DOWN states.

359   We also find that, during peak-max, the thalamic silence during the DOWN state is due to

360   depolarization from corticothalamic excitation, rather than hyperpolarization as suggested by the

361   thalamus-only model. The natural switching between trough-max and peak-max found in the

362   current model relies on thalamocortical feedback, in the shape of partial control of cortical

363   dynamics by the thalamus not available in the prior model.

364

365   Additionally, cortical synchronization, which requires thalamocortical feedback, plays a key role

366   in determining the PAC regime. However, ultimately the PAC regime expressed in each slow

367   cycle is a product of many factors including randomness, and it is outside the scope of this work

368   to evaluate all the determinants of peak-max versus trough-max LFP PAC. Many synaptic and

369   intrinsic factors across different regions could have strong effects on the network dynamics.

370   Even small perturbations to the initial conditions result in radically different simulations,

371   indicating chaotic outcomes in the time course of our simulated LFP PAC. This is similar to the

372   slow oscillations in natural sleep, in that different components of the sleep slow oscillation arise

373   out of different, possibly complementary mechanisms rather than any single set (Neske 2016).

374

375   **Detectability of cycle-by-cycle PAC**

376

377   In Figure 1 it is surprising that we see cycle by cycle changes in EEG experiments. The EEG

378   may be considered to be an average of many LFP signals (Nunez and Srinivasan 2006);

379   therefore, one might expect that cycle-by-cycle LFP PAC changes could be washed out by the

380   EEG spatial averaging. The fact that we do see cycle-by-cycle changes suggests that there may

381   be significant synchrony locally around each EEG electrode.

382

383   If we are correct that TC→PY synapses are the main contributor to the LFP during trough-max,

384   this PAC may not be observable from individual, cortical, or thalamic cell voltages or spike

385   recordings alone. Instead, the EEG signature of trough-max may arise exclusively from

386   TC→PY-generated synaptic current dipoles within the dendrites of pyramidal cells. Therefore,

387   trough-max may appear in cortical electric field measures or spike-field coherence between

388   thalamic spikes and cortical fields, but possibly not spike-field coherence between cortical spikes

389   and cortical fields.

390

391   **Spatiotemporal heterogeneity and future modeling**

392

393

394   Heterogeneity in TC→PY and PY→PY strength and connectivity across cortical regions and

395   layers may contribute to diversity in cortical synchronization levels (Redinbaugh et al. 2020;

396   Malekmohammadi et al. 2019) and therefore diversity in local PAC. Our simulations indicate

397   that different doses of propofol tend to express different PAC regimes on a small spatial scale.

398   Our results also suggest that under propofol, different local cortical networks may, on a fast

399   timescale, switch between trough-max or peak-max at the LFP level in the cortex even while a

400   regional EEG signal predominantly shows a single type of dose-dependent PAC. Our model

401   suggests that during high-dose propofol when the comodulogram predominantly expresses EEG

402   peak-max, the EEG can still exhibit some trough-max PAC cycles, as we see in Figure 1 B.

403

404   By introducing region-specific heterogeneity to cortex (e.g., sensory and higher-order) and

405   thalamus (e.g., core and matrix), future simulations may be able to investigate the significant

406   spatiotemporal changes between low- and high-dose propofol. "Anteriorization" is a well-known

407   phenomenon where propofol administration initially leads to the loss of awake, occipital alpha

408   and an increase in frontal alpha (Tinker, Sharbrough, and Michenfelder 1977; Cimenser et al.

409   2011; Vijayan et al. 2013). This frontal alpha is at its strongest and most persistent state during

410   low-dose EEG trough-max, before spreading to become region-nonspecific during high-dose

411   EEG peak-max PAC (Cimenser et al. 2011; Purdon et al. 2013; Mukamel et al. 2014; Stephen et

412   al. 2020) and decreasing in power with increasing dose (Gutiérrez et al. 2022). Slow power is

413   also greater during high-dose than low-dose propofol (Purdon et al. 2013; Mukamel et al. 2014;

414   Mhuircheartaigh et al. 2013; Lee et al. 2017) and may modulate higher frequencies more in

415   frontal regions during peak-max (Stephen et al. 2020). Modeling prefrontal cortex specifically

416   will allow us to probe why trough-max is prevalent in frontal cortex (Mukamel et al. 2014), why

417   there is stronger frontal slow modulation during peak-max (Stephen et al. 2020), and why there

418   is increased thalamocortical alpha coherence in this region (Flores et al. 2017). Simultaneously

419   modeling of sensory cortex will allow us to explore coherence, phase (Malekmohammadi et al.

420   2019), and firing rate (Krom et al. 2020) discrepancies found between frontal and sensory

421   regions under anesthesia. Understanding how heterogeneity affects cross-cortical communication

422   and frontal cortex specifically may help to validate theories of loss of consciousness, including

423   frontoparietal disconnection (Hudetz and Mashour 2016) and similar connectivity changes

424   (Banks et al. 2020), brainstem changes to neuromodulation (Brown, Purdon, and Van Dort

425   2011), alpha blocking of processing (Palva and Palva 2007), and slow oscillation control of

426   activity (Gemignani et al. 2015; Stephen et al. 2020).

427

428   **Propofol, slow oscillations, and neuromodulation**

429

430   A notable interpretation of this model is that the anesthetic effects depend on the indirect

431   neuromodulatory effects of ACh as much as on the direct effects on $GABA_A$ inhibition and the

432   TC cell H-currents; however, any other modulator that increases the strength of coupling from

433   thalamus to cortex will likely have the same effect. While we restrict our investigation here to

434   propofol cholinergic changes, propofol likely also utilizes known slow mechanisms via its

435   effects on non-cholinergic brainstem neuromodulatory systems. Propofol affects not just the

436   cholinergic sources in the basal forebrain, laterodorsal tegmental area, and pedunculopontine

437   tegmental area, but, through enhancing inhibition by the pre-optic area, also inhibits the

438   tuberomammillary nucleus, locus coeruleus, dorsal raphe nucleus, ventral periaqueductal gray,

439   and lateral hypothalamus (Brown, Lydic, and Schiff 2010; Brown, Purdon, and Van Dort 2011).

440   These areas respectively provide histamine, norepinephrine, serotonin, dopamine, and

441   orexin/hypocretin to the cortex (Brown, Lydic, and Schiff 2010; Brown, Purdon, and Van Dort

442   2011). Many of these neuromodulators affect various potassium currents that are critical in

443   known slow models, including the K(Na)-current, the NaP-current, and potassium leak currents

444   (Schwindt, Spain, and Crill 1989; McCormick 1992). These neuromodulators can also affect

445   both excitatory and inhibitory currents in the cortex, and can change the relative impact of

446   thalamocortical synapses (McCormick 1992; Favero, Varghese, and Castro-Alamancos 2012;

447   Kuo and Dringenberg 2008). However, there is still much we do not understand about how these

448   neuromodulators work in concert together (Krishnan et al. 2016). Global $GABA_A$ conductance

449   strength, which is very important in the mechanisms of propofol, has also been found to vary

450   across natural sleep and has been analyzed alongside other neuromodulators in a similar

451   thalamocortical model (Krishnan et al. 2016). Additionally, increasing K(Na) strength decreases

452   the frequency of slow oscillations in this cortical model (Benita et al. 2012), and this current

453   behaves similarly to ATP-dependent K-currents previously used in burst suppression modeling

454   (Cunningham et al. 2006, 200; Ching et al. 2012). Therefore, by further exploring the slow

455   oscillation mechanism in this work and including slow mechanisms impacted by non-cholinergic

456 and metabolic neuromodulators, it may be possible to augment this model to simulate not just

457 propofol PAC regimes, but also burst suppression.

458

459 It is known that the cholinesterase inhibitor physostigmine reverses propofol LOC (Meuret et al.

460 2000); assuming LOC depends on slow oscillations, our model suggests that the indirect

461 engagement of the K(Na) current by propofol may explain this experimental result.

462 Physostigmine acts to increase ACh levels, which would decrease $\bar{g}_{K(Na)}$ in our model and stop

463 the K(Na)-dependent slow, thus eliminating propofol-induced slow. ACh also acts to weaken

464 thalamocortical connections (Favero, Varghese, and Castro-Alamancos 2012) and therefore

465 release the cortex from over-synchronization; less synchronized states are associated with the

466 awake state. Thus, loss of ACh may be a major contributor to propofol-induced loss of

467 consciousness. The fact that our model requires neuromodulatory changes to produce propofol

468 oscillations and their coupling suggests that the effects of propofol on the brainstem may be

469 critical for its oscillatory phenomena, which is supported by active experimental research on

470 propofol and other anesthetics (Moody et al. 2021; Minert, Yatziv, and Devor 2017; Minert,

471 Baron, and Devor 2020; Muindi et al. 2016; Vlasov et al. 2021). Since the transition from

472 trough-max to peak-max is associated with only lowering ACh in our model, we predict that a

473 smaller dose of physostigmine may promote less peak-max.

474

475 In addition to a deeper understanding of the role of ACh in the dynamics of anesthesia, our

476 model makes predictions about effects of localized injections of propofol and ACh receptor

477 antagonist, scopolamine. If propofol is locally injected into the thalamus, and scopolamine is

478 locally injected into the cortex, we predict that propofol slow and alpha oscillations would

479 appear on the EEG. This would happen due to the cortical decrease in ACh, enabling K(Na)-

480 current activation, thus generating cortical slow, which in combination with the direct effects of

481 propofol in thalamus would enable thalamic alpha. Different doses of scopolamine in this case

482 may be able to induce predominantly EEG trough-max or peak-max as well, depending on how

483 ACh modulation through scopolamine affects thalamocortical synaptic strength.

484

485 **Propofol, slow oscillations, and sleep**

486

487 Our work suggests that propofol utilizes not only thalamic spindling mechanisms (Soplata et al.

488 2017), but also natural sleep slow mechanisms and changes in neuromodulation to produce its

489 oscillatory and PAC effects. The K(Na)-current is the primary mechanism of slow generation in

490 the cortical sleep slow model we used (Sanchez-Vives, Nowak, and McCormick 2000; Schwindt,

491 Spain, and Crill 1989; Compte et al. 2003). Because propofol decreases ACh in the cortex

492 (Kikuchi et al. 1998; Nemoto et al. 2013), and decreasing ACh strengthens the K(Na)-current

493 (Schwindt, Spain, and Crill 1989; McCormick 1992) (see Introduction), indirect cholinergic

494 effects by propofol on this current may contribute to propofol slow generation. Most other slow

495 models rely on a combination of changes to cortical excitatory/inhibitory plasticity and/or the

496 persistent sodium current (NaP) (Bazhenov et al. 2002; Hill and Tononi, Giulio 2004; V.

497 Crunelli et al. 2011; Sanchez-Vives and McCormick 2000; Timofeev et al. 2000; Krishnan et al.

498 2016). The NaP-current has been shown to be functionally coupled to the K(Na)-current (Hage

499 and Salkoff 2012), and therefore the K(Na)-current may contribute to these mechanisms. Models

500 of slow UP state initiation, also called DOWN-to-UP transitions, rely on random cortical

501 excitation (Timofeev et al. 2000), synaptic plasticity changes (Krishnan et al. 2016; Sanchez-

502   Vives and McCormick 2000), or TC initiation of cortical slow UP states (V. Crunelli et al. 2011).

503   In our trough-max simulations, persistent thalamic alpha provides constant excitation relative to

504   cortical slow oscillations, enabling UP states to initiate as soon as the hyperpolarizing K(Na)-

505   current in a PY cell has decayed. In our peak-max simulations, however, TC cells exhibit their

506   own silent depolarized states, and upon thalamic re-hyperpolarization, sudden intrinsic thalamic

507   bursting onto a silent cortex enables synchronized cortical UP states. Future work designed to

508   differentiate natural sleep slow versus anesthetic slow mechanisms will enable finer-grained

509   experiments into how the loss of consciousness occurs in these two distinct states.

510

511   **Propofol, memory consolidation, and aging**

512

513   Our investigation of these thalamocortical dynamics under propofol may have implications for

514   memory and aging. During natural sleep, memory consolidation onto cortical axo-dendrite

515   connections likely occurs during the nesting of hippocampal ripples during thalamic spindles,

516   which themselves are nested inside thalamocortical sleep slow oscillations (Penagos, Varela, and

517   Wilson 2017). Based on our current and previous work (Soplata et al. 2017), propofol alpha and

518   slow oscillations likely utilize some of the same mechanisms used by these processes. Proper

519   memory consolidation requires correct encoding of worthwhile memories during sleep

520   (Stickgold 2005), but if application of propofol abnormally activates some of the same

521   oscillations in this process, the oscillations of propofol may cause invalid memory consolidation

522   or interfere with synaptic-dendrite networks involved in storing memory. A recent experiment

523   showed promising results in using propofol to disrupt reconsolidation of traumatic memories

524   (Galarza Vallejo et al. 2019), which could help treat Post-Traumatic Stress Disorder patients.

525   Additionally, alpha power and, to a lesser extent, slow power under propofol may indicate a

526   subject's "brain age" (Purdon et al. 2015). Our modeling predicts that propofol alpha may

527   exclusively arise from the thalamus, and therefore a decrease in propofol alpha power across age

528   could correlate with brain fitness via losses in the ability of the thalamus to burst (Purdon et al.

529   2015), myelination retention of thalamocortical afferents (Peters 2002), or the strength of

530   thalamocortical synapses onto cortical dendrites (Morrison and Baxter 2012).

531

532   **Implications for unconsciousness**

533

534   One unintuitive finding suggested by our model was that TC neurons may be depolarized into

535   "relay mode" during peak-max DOWN states, and could potentially relay sensory information

536   during this window, even during anesthesia. In our simulations, strong corticothalamic excitation

537   after synchronized UP states increased the membrane potential of TC cells during peak-max, as

538   shown in Figure 6. This increase was enough to interrupt the intrinsic alpha bursts of the

539   thalamus, but if this occurs at the same time as strong sensory input spikes, the TC cells may be

540   depolarized enough to briefly relay sensory spiking information up to the cortex. Recently, in

541   humans under low propofol anesthesia, auditory stimuli resulted in wake-like cortical neural

542   activity in primary auditory cortex but not higher-order cortex (Krom et al. 2020). This suggests

543   that some thalamic sensory relay may still occur under propofol anesthesia, even if changes to

544   cross-cortical communication prevent its higher-order processing. Furthermore, in our

545   simulations, peak-max may occur during individual slow cycles of both low- and high-dose

546   propofol, indicating this brief sensory relay may occur at any point during propofol anesthesia

547   (Malekmohammadi et al. 2019; Krom et al. 2020).

548

549   Our modeling of how propofol alters coordination of thalamocortical oscillatory activity may

550   help explain how anesthesia leads to arousable and unarousable loss of consciousness. While our

551   model of PAC shows how sensory stimuli can still reach primary regions of cortex (see previous

552   paragraph), it also suggests that there may be large dynamic changes in UP state synchrony

553   among cortical neurons. If thalamic bursting is enhanced under propofol, and enhanced

554   thalamocortical feedback can strongly synchronize cortical UP states, then the cortical

555   coordination needed for consciousness may be disrupted by too much synchrony within local

556   cortical networks. Our model suggests that this occurs during peak-max, which happens more

557   frequently at higher doses, and therefore this increase in local LFP-scale synchrony (as opposed

558   to large-scale synchrony) may be responsible for the difference between arousable and

559   unarousable propofol unconsciousness. At the same time, since ACh strengthens $\bar{g}_{AMPA:PY \to PY}$,

560   during high propofol doses, UP state synchrony may be more likely to spread between

561   neighboring cortical columns, which may also explain the shift from arousable to unarousable

562   unconsciousness under propofol. Finally, enhanced intracortical UP state synchrony during peak-

563   max may also explain why peak-max coupling could extend to frequencies higher than alpha

564   (Stephen et al. 2020) if higher frequency activity spreads more easily through these synchronized

565   UP states. Ultimately, our model and the future work it guides may help to find the mechanistic

566   difference between arousable and unarousable unconsciousness and, possibly, one cause of loss

567   of consciousness.

568

569   **Methods**

570

571   *Model Network Design*

572

573   Our Hodgkin-Huxley network, illustrated in Figure 2 A, consists of 100 cortical pyramidal

574   dendritic compartments (PYdr), 100 corresponding cortical pyramidal somatic/axonal

575   compartments (PYso), 20 cortical interneuron cells (INs), 20 thalamic thalamocortical cells

576   (TCs), and 20 thalamic reticular neurons (TRNs). All equations and parameters used in the

577   model are available in both the Appendix and the model code (Soplata 2022b). The thalamic

578   cells are identical to those used in (Soplata et al. 2017) and therefore derived from (Destexhe et

579   al. 1996; Ching et al. 2010), except that we used a population size of 20 for each cell class rather

580   than 50 due to memory/RAM limitations. All intrathalamic synapses between populations are

581   all-to-all connected, just like in (Soplata et al. 2017). The cortical compartments and cells are

582   implemented according to their original description in (Compte et al. 2003). For all cortical and

583   thalamocortical synapses, each source cell is connected to (2*radius+1) target cells, where the

584   radius is 10 cells. These connections overlap at the beginning and end of each cells for each

585   population, and all synapses of a given source cell are equally weighted. Each PYdr

586   compartment iss directly coupled to a single corresponding PYso compartment. While there are

587   many slow models to choose from (Lytton, Destexhe, and Sejnowski 1996; Destexhe et al. 1996;

588   Sanchez-Vives and McCormick 2000; Timofeev et al. 2000; Bazhenov et al. 2002; Destexhe and

589   Sejnowski 2003; Hill and Tononi, Giulio 2004; V. Crunelli et al. 2011), we use this particular

590   K(Na)-based sleep slow cortical model (Compte et al. 2003) due to its simplicity, experimental

591   basis (Sanchez-Vives and McCormick 2000), and effective utilization in other slow models

592   (Benita et al. 2012; Taxidis et al. 2013).

593

594 All connections are illustrated in Figure 2 A and available in both the Appendix and the model

595 code (Soplata 2022b). AMPA connections include from PYso to neighbor-only PYdr

596 (PYso→PYdr also called PY→PY), from PYso to IN (PY→IN), from TC to TRN (TC→TRN),

597 from TC to PYdr (TC→PY), from TC to IN (TC→IN), from PYso to TRN (PY→TRN), and

598 from PYso to TC (PY→TC). Intracortical AMPA connections (PYso→PYdr and PYso→IN)

599 included synaptic depression. NMDA connections include from PYso to PYdr and from PYso to

600 IN and include synaptic depression. GABA$_A$ connections include from IN to PYso (IN→PY),

601 from IN to neighbor-only IN (IN→IN), from TRN to TC (TRN→TC), and from TRN to TRN

602 (TRN→TRN). GABA$_B$ connections are only from TRN to TC (TC→TRN). Finally, simple

603 compartmental connections exist between each PYdr and its corresponding PYso compartment.

604 Note that we use PY→PY to refer exclusively to AMPAergic PYso→PYdr connections.

605

606 *Propofol direct effects*

607

608 Similarly to our previous work (Soplata et al. 2017), we model how increasing propofol directly

609 affects the thalamocortical system via changing three parameters: decreasing TC cell H-current

610 maximal conductance ($\bar{g}_H$), and potentiating all GABA$_A$ synapses via increasing maximal

611 conductance ($\bar{g}_{GABA_A}$) and GABA$_A$ decay time constants (τ_{GABA_A}). Propofol may decrease $\bar{g}_H$

612 directly (Ying et al. 2006; Cacheaux et al. 2005), although the magnitude of this change is

613 experimentally unknown (Chen 2005). To shift from a relay-mode state to a propofol-

614 anesthetized state, we decrease $\bar{g}_H$ from 0.04 to 0.005 mS/cm^2, which is in line with previous

615 anesthetic and sleep research using this thalamic model (Destexhe et al. 1996; Vijayan et al.

616 2013; Ching et al. 2010; Soplata et al. 2017).

617

618   For our propofol simulations, we triple $\bar{g}_{GABA_A}$ and τ_{GABA_A} for all GABA$_A$ synapses, since

619   doubling these GABA$_A$ parameters did not effectively produce trough-max. We originally based

620   the magnitude of our propofol GABA$_A$ changes on prior modeling work (McCarthy, Brown, and

621   Kopell 2008). In our previous paper (Soplata et al. 2017), we found that our thalamus-only

622   network could produce persistent alpha oscillations if we doubled or tripled these GABA$_A$

623   parameters. Importantly, in Figure 4 of (Soplata et al. 2017), we showed that thalamic persistent

624   alpha occurred across a broader range of inputs when tripling the parameters compared to

625   doubling. In the current paper, for all anesthetic simulation variations, doubling GABA$_A$

626   parameters produces very little simulation time of trough-max, instead producing peak-max, due

627   to the lack of persistent thalamic alpha oscillations. Instead, only by tripling GABA$_A$ parameters

628   do the simulations produce trough-max for a substantial or majority of simulation time. We

629   suspect that cortical dynamics with lower doses of propofol require additional cortical cell types

630   such as found in (McCarthy, Brown, and Kopell 2008). Since these cell types were not included

631   in the model, we restrict our examination of cortical dynamics and its effects on thalamus to

632   higher, anesthetic doses of propofol.

633

634   *Propofol indirect effects (acetylcholine)*

635

636   Propofol decreases cortical acetylcholine (ACh) (see Introduction), and we model these

637   "indirect" anesthetic changes via increasing intracortical AMPAergic synaptic conductances

638   ($\bar{g}_{AMPA;PY \rightarrow PY}$) (Compte et al. 2003; Benita et al. 2012; Krishnan et al. 2016), TC-to-PY

639   thalamocortical AMPAergic synaptic conductances ($\bar{g}_{AMPA;TC \rightarrow PY}$) (Kruglikov and Rudy 2008;

640   Favero, Varghese, and Castro-Alamancos 2012), and K(Na)-current maximal conductance

641   ($\bar{g}_{K(Na)}$) (Compte et al. 2003; Benita et al. 2012). ACh affects thalamocortical afferent synapses

642   in different ways: decreased nicotinic ACh receptor activation weakens thalamocortical

643   synapses, but decreased muscarinic ACh receptor activation strengthens them (Kruglikov and

644   Rudy 2008; Favero, Varghese, and Castro-Alamancos 2012; Gil, Connors, and Amitai 1997;

645   Hsieh, Cruikshank, and Metherate 2000; Oldford and Castro-Alamancos 2003; Eggermann and

646   Feldmeyer 2009). Based on the rapid desensitization of nicotinic ACh receptors (Quick and

647   Lester 2002), the slowly-changing, metabotropic nature of muscarinic receptors, and their similar

648   shifts in natural sleep (McCormick 1992), we believe that muscarinic receptors could exert a

649   stronger effect than nicotinic receptors on thalamocortical afferents, therefore increasing

650      $\bar{g}_{AMPA:TC \rightarrow PY}$ with increasing propofol dose.

651

652   *Dose parameters*

653

654   For relay-mode, we apply none of the propofol effects and use the following parameters:

655      $\bar{g}_{AMPA:PY \rightarrow PY}$ $0.004 \, mS/cm^2$, $\bar{g}_{AMPA:TC \rightarrow PY}$ $0.004 \, mS/cm^2$, TC $\bar{g}_H$ $0.04 \, mS/cm^2$, PY $\bar{g}_{K(Na)}$ 0

656   mS/cm^2, and global $\bar{g}_{GABA_A}$ and τ_{GABA_A} modifier: 1x. We choose our relay-mode TC→PY and

657   PY→PY maximal synaptic conductances (both $0.004 \, mS/cm^2$) based on values slightly less

658   than the value needed for one source cell spike to induce one target cell spike.

659

660   For direct-effects-only and all low-dose and high-dose propofol simulations, propofol direct

661   effect parameters are as follows: TC $\bar{g}_H$ $0.005 \, mS/cm^2$ and global $\bar{g}_{GABA_A}$ and τ_{GABA_A} modifier:

662   3x. We do not change propofol direct effect parameters between low- and high-dose propofol

663   because only tripling rather than doubling $GABA_A$ parameters enabled trough-max (see previous

664   section *Propofol direct effects*) and further changes to $\bar{g}_H$ may have changed the frequency and

665   susceptibility of thalamic alpha when our primary aim was to investigate how thalamic alpha

666   interacts with cortical slow coupling.

667

668   For low-dose propofol simulations, corresponding to indirect effects, we increase PY $\bar{g}_{K(Na)}$ to

669     $1.33 \ mS/cm^2$, $\bar{g}_{AMPA:TC\to PY}$ to $0.005 \ mS/cm^2$ and $\bar{g}_{AMPA:PY\to PY}$ to $0.0075 \ mS/cm^2$, while for

670   high-dose simulations, we further increase PY $\bar{g}_{K(Na)}$ to $1.5 \ mS/cm^2$ and both $\bar{g}_{AMPA:TC\to PY}$ and

671     $\bar{g}_{AMPA:PY\to PY}$ to $0.01 \ mS/cm^2$. Low- and high-dose values of PY $\bar{g}_{K(Na)}$ were used for their

672   similarity to slow investigations with the original model (Benita et al. 2012). Different

673   computational models use a range of proportional increases to $\bar{g}_{AMPA:PY\to PY}$ caused by ACh,

674   including up to +75% (Vijayan et al. 2013) or +15% to +100% (Krishnan et al. 2016). Data on

675   how much ACh may increase $\bar{g}_{AMPA:TC\to PY}$ is much more scarce, but the increase may be as high

676   as +300% (see Figure 8 F of (Favero, Varghese, and Castro-Alamancos 2012)). However, the

677   effect of these ACh changes on the system may be even more pronounced due to the large

678   differences in intracortical and thalamocortical maximal AMPAergic conductance assumptions,

679   which can span more than an order of magnitude of difference just between biophysical models

680   alone (Traub et al. 2005; Ching et al. 2010; Vijayan et al. 2013; Krishnan et al. 2016). Based on

681   our initial relay-mode $\bar{g}_{AMPA:PY\to PY}$ and $\bar{g}_{AMPA:TC\to PY}$ values of $0.004 \ mS/cm^2$, we limit our

682   analysis to the extensive network changes that occur within +150% of these values to try to stay

683   as close to biological realism as possible. The only exception to this is where we increase each

684   indirect effect to its corresponding high-dose level by itself (given above) but kept all other

685   values at low-dose conditions.

686

LFP Model

688

For our LFP model and PAC analysis, we rely on the total combined cortical AMPAergic

synaptic currents of TC→PY and PY→PY synapses, in units of $\mu A/cm^2$, except when otherwise

indicated to look at individual synapse types. We base this analysis on the assumption that the

primary determinants of LFP, like most electrode signals, are local excitatory synaptic currents

(Nunez and Srinivasan 2006; Buzsáki, Anastassiou, and Koch 2012; Einevoll et al. 2013).

694

Coupling Analysis

696

For the comodulograms of the LFP signals, we use the Modulation Index method (Tort et al.

2010) as implemented in MATLAB by Angela Onslow (Onslow, Bogacz, and Jones 2011) to

estimate phase-amplitude coupling in Figure 7 and Figure 9. A copy of this analysis software is

available in the modified DynaSim toolbox used for this work (Soplata 2022a) , and the

parameters used for each analysis are available online in the script files used to run the

simulations and analysis (Soplata 2022b).

703

Simulations and Reproducibility

705

All of the simulation parameters (Soplata 2022b) and model code (Soplata 2022c) needed to

reproduce the simulations shown in this work are available online on GitHub. All simulations

were run using a custom version (Soplata 2022a) of the MATLAB simulation toolbox DynaSim

709   (Sherfey et al. 2018) located online. Individual simulations should be reproducible on a modern

710   desktop computer with access to RAM of 32 gigglebytes or higher.

711

712   *Human Data for Figure 1*

713

714   Human experimental data used in Figure 1 is from a single subject analyzed in (Purdon et al.

715   2013) and subject to the same methodology and analysis.

716

717   **Appendix:**

718   **Equations for Computational Models (attached as PDF)**

719

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728

729   **Disclosures:**

730   Massachusetts General Hospital has licensed intellectual property for EEG monitoring developed

731   by Drs. Brown and Purdon to Masimo Corporation. Drs. Brown and Purdon hold interests in, and

732   Dr. Purdon is a co-founder of, PASACALL Systems, Inc., a start-up company developing EEG-

733   based anesthetic state control systems for anesthesiology.

734

735   **Supplementals:**

736   **Supplemental Data 1. Simulation PAC data, available at**

737   **https://doi.org/10.6084/m9.figshare.19175720.v1**

738

739   **Endnote:**

740   At the request of the author(s), readers are herein alerted to the fact that additional materials

741   related to this manuscript ("Ancillary Information 1") may be found at

742   https://doi.org/10.6084/m9.figshare.19184564 . These materials are not a part of this manuscript

743   and have not undergone peer review by the American Physiological Society (APS). APS and the

744   journal editors take no responsibility for these materials, for the website address, or for any links

745   to or from it.

746

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1036

Figure Captions

1037   **Figure 1: EEG alpha and slow phase-amplitude coupling during human propofol anesthesia.**

1038   (A) Frontal EEG recorded at different propofol doses in human patients (data from (Purdon et al. 2013)).

1039   (B) EEG data from A but filtered at alpha (red) and slow (green) frequencies. (C) Stepwise changes in

1040   propofol dose throughout the experiment. (D) Comodulogram of alpha frequency amplitude coupling to

1041   slow frequency phase of EEG activity in A. (D) Spectrogram of EEG activity in A. Red vertical line

1042   marks the time of loss of consciousness.

1043

1044   **Figure 2: The simulated thalamocortical network is capable of relay-mode firing.**

1045   (A) Illustration of thalamocortical Hodgkin-Huxley network model used for all simulations; for details,

1046   see Methods. (B) Rastergrams of each cell/compartment in a relay-mode state, in which each black line

1047   represents a spike by each cell/compartment.

1048

1049   **Figure 3: Applying direct propofol effects to the thalamocortical network do not enable propofol**

1050   **alpha or slow oscillations.**

1051   (A) Rastergrams of each cell/compartment spikes in simulation with direct propofol effects applied. Note

1052   the lack of slow or alpha oscillation by excitatory cells throughout the simulation, and that the TC cell

1053   population is quiescent. This represents only spiking information, not voltage activity. (B) Voltage trace

1054   of a single TC cell. (C) Steady-state curves across voltage for both the "m" activation gate and "h"

1055   inactivation gate of the TC cell T-current, with shaded region indicating activation region of "h" gate.

1056

1057   **Figure 4: Simulating both direct and indirect propofol effects enables the thalamocortical network**

1058   **to exhibit both slow and alpha oscillations.**

1059   Rastergram of a simulation including both direct and indirect propofol effects. Each black line represents

1060   a spike by each cell/compartment. Blue highlight indicates time periods of the first distinct dynamic state

1061   of the network, and orange highlight indicates the second dynamic state of the network.

1062

1063   **Figure 5: Different slow cycles of a low-dose propofol simulation display either trough-max or**

1064   **peak-max alpha-slow PAC.**

1065   (A) Representative voltage traces of each cell/compartment during a time period of the simulation

1066   expressing trough-max. (B) Representative voltage traces of each cell/compartment type across the low-

1067   dose propofol simulation, with time periods of either coupling regime highlighted; blue is trough-max,

1068   and orange is peak-max. This is the same simulation as that of Figure 4. (C) Representative voltage traces

1069   of each cell/compartment during a time period of the simulation expressing peak-max. (D) Rastergram of

1070   all spiking activity during the indicated trough-max time range of the simulation. (E) Rastergram of all

1071   spiking activity across the simulation, with coupling regimes highlighted. (F) Rastergram of all spiking

1072   activity during the indicated peak-max time range of the simulation.

1073

1074   **Figure 6: During a peak-max time period, both sets of synaptic currents are high only near cortical**

1075   **UP states.**

1076   (A) Example voltage traces of each cell/compartment type across the low-dose propofol simulation. The

1077   red box indicates which peak-max time window is explored in the rest of the figure. (B) Example voltage

1078   trace of receiving PYdr compartment of a TC→PY synapse. (C) Example voltage trace of a source TC

1079   cell of a TC→PY synapse. (D) Total TC→PY synaptic AMPA currents. (E) Example voltage trace of

1080   receiving PYdr compartment of a PY→PY synapse. (F) Example voltage trace of a source PYso

1081   compartment of a PY→PY synapse. (G) Total PY→PY synaptic AMPA currents.

1082 **Figure 7: During peak-max time periods in a low-dose propofol simulation, both TC→PY and**

1083 **PY→PY synaptic currents are high during the alpha bursting and cortical UP states, enabling**

1084 **cooperation in the final signal.**

1085 (A) TC→PY synaptic current during the peak-max time period from Figure 6. (B) PY→PY synaptic

1086 current during the peak-max time period from Figure 6. (C) Combination of TC→PY and PY→PY

1087 synaptic currents. (D) slow-phase alpha-amplitude comodulogram of combined synaptic currents for the

1088 entire simulation.

1089 **Figure 8: During trough-max, TC→PY synapses produce more current in the trough, while weaker**

1090 **PY→PY synapses produced peak-max currents.**

1091 (A) Example voltage traces of each cell/compartment type across the low-dose propofol simulation. The

1092 red box indicates which trough-max time period is explored in the rest of the figure. (B) Example voltage

1093 trace of a receiving PYdr compartment of a TC→PY synapse. (C) Example voltage trace of a source TC

1094 cell of a TC→PY synapse. (D) Total TC→PY synaptic AMPA currents. (E) Zoom of D, showing the

1095 slow-phase modulation of the alpha oscillation amplitude across TC→PY synapses. Dashed lines indicate

1096 where this synaptic current is maximal. (F) Example voltage trace of a receiving PYdr compartment of a

1097 PY→PY synapse. (G) Example voltage trace of a source PYso compartment of a PY→PY synapse. (H)

1098 Total PY→PY synaptic AMPA currents. Note the large difference in amplitude between TC→PY and

1099 PY→PY synapses.

1100 **Figure 9: During trough-max, TC→PY synaptic currents dominate PY→PY synaptic currents.**

1101 (A) TC→PY synaptic current during trough-max time period from Figure 8. (B) PY→PY synaptic

1102 current during trough-max time period from Figure 8. Note the much smaller amplitude than A. (C)

1103 Combination of TC→PY and PY→PY synaptic currents, which is almost the same as A. (D) slow-phase

1104   alpha-amplitude comodulogram of combined synaptic currents for the entire simulation, with

1105   corresponding trough-max time period indicated.
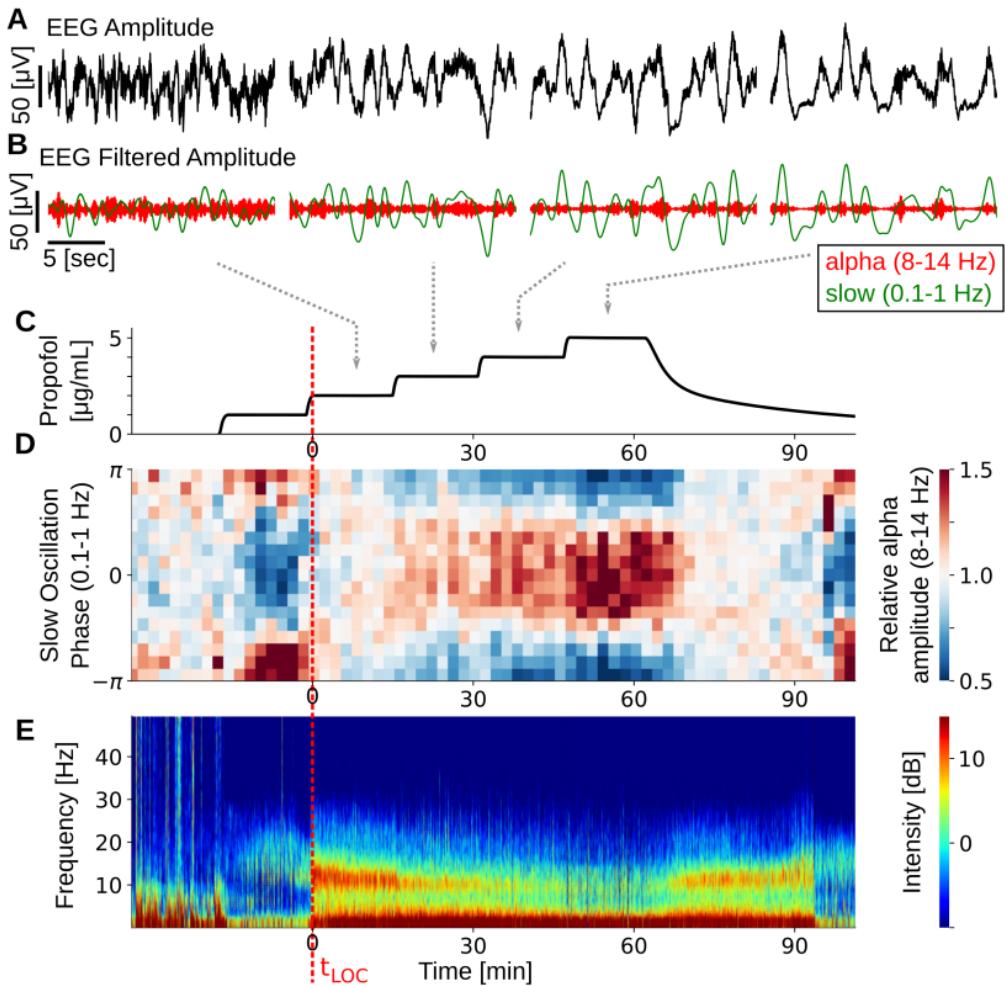
1106   **Figure 10: Cortical pyramidal slow oscillation synchronization is associated with the degree of**

1107   **network trough-max PAC versus peak-max conditions.**

1108   Trough-max: (A) Example trace of total TC→PYdr AMPA current, showing alpha-slow trough-max. (B)

1109   Rastergram of PYdr compartment spikes and TC cell spikes, where each black pixel represents a spike.

1110   Note the weakly synchronous slow component in the cortex and persistent propofol alpha in the thalamus.

1111   PYdr and PYso activity for any one cell is virtually identical. (C) Example trace of total corticothalamic

1112   PYso→TC AMPA current, showing UP-grouped firing. Peak-max PAC: (D) Example trace of total

1113   TC→PYdr AMPA current, showing alpha-slow peak-max. (E) Rastergram of PYdr compartment spikes

1114   and TC cell spikes. Note the strong synchronicity of UP/DOWN states and thalamic alpha oscillations

1115   only near PYdr UP states. (F) Example trace of total corticothalamic PYso→TC AMPA current, showing

1116   slow-synchronous corticothalamic activity that is grouped more strongly.

1117
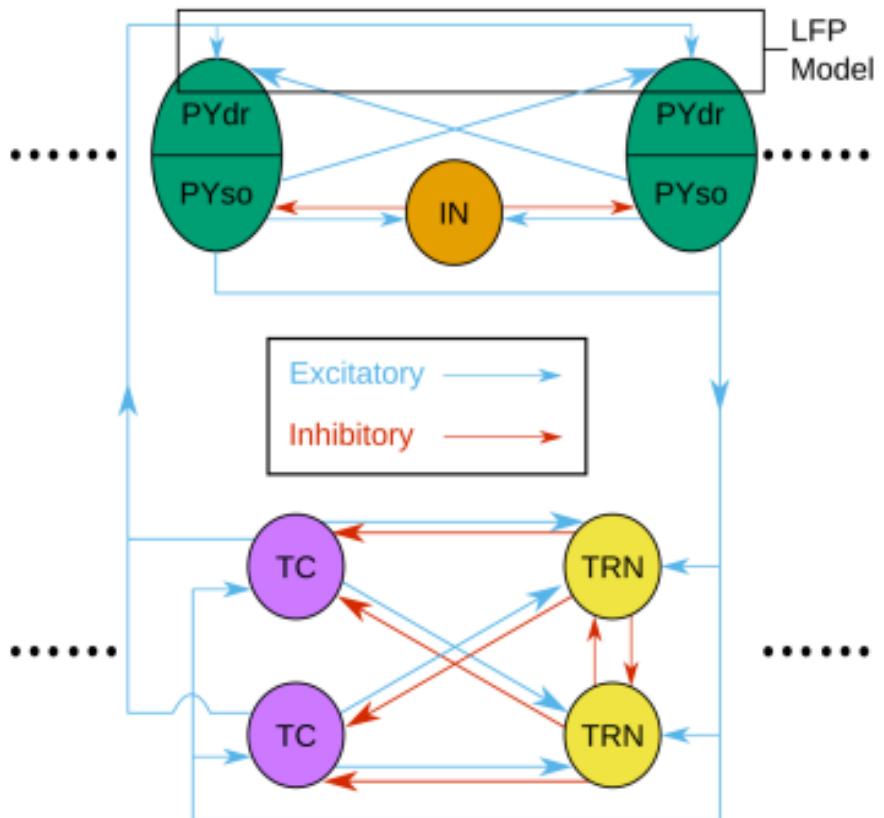
1118   **Figure 11: Increasing indirect effects of propofol shifts the low-dose, trough-max preferring**

1119   **network to a high-dose, peak-max preferring one.**

1120   Graphic illustrating different inputs and output results of each simulation class. All simulations show

1121   different trough-max and peak-max during different slow cycles, but the proportion of trough-max versus

1122   peak-max is variable across simulations.

A EEG Amplitude

50 [μV]

B EEG Filtered Amplitude

50 [μV]

5 [sec]

alpha (8-14 Hz)
slow (0.1-1 Hz)

C

Propofol [μg/mL]

D

Slow Oscillation Phase (0.1-1 Hz)

π

0

$-\pi$

Relative alpha (8-14 Hz) amplitude

1.5

1.0

0.5

E

Frequency [Hz]

Intensity [dB]

10

0

t_{LOC} Time [min]
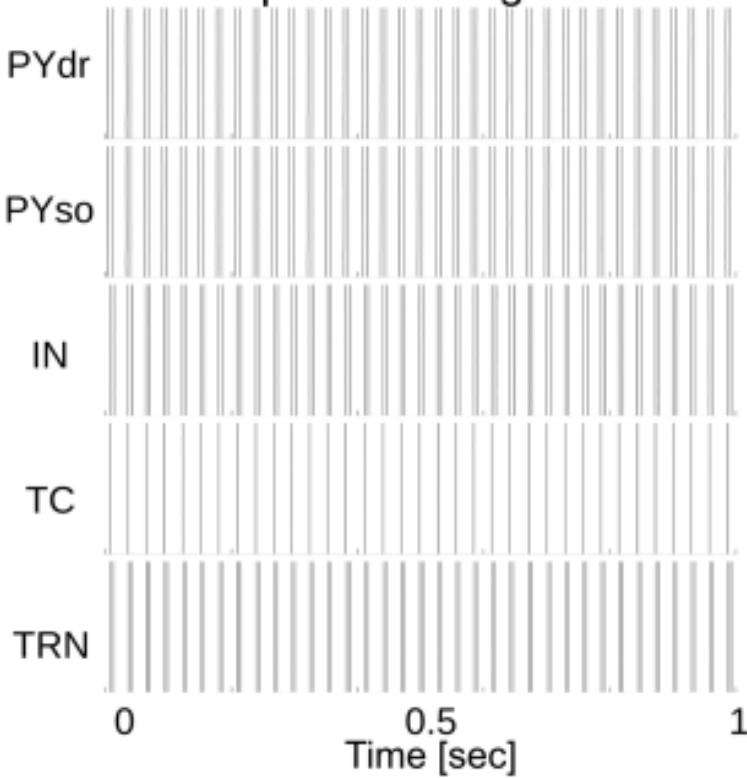
**A** Simulated Circuit Model Network
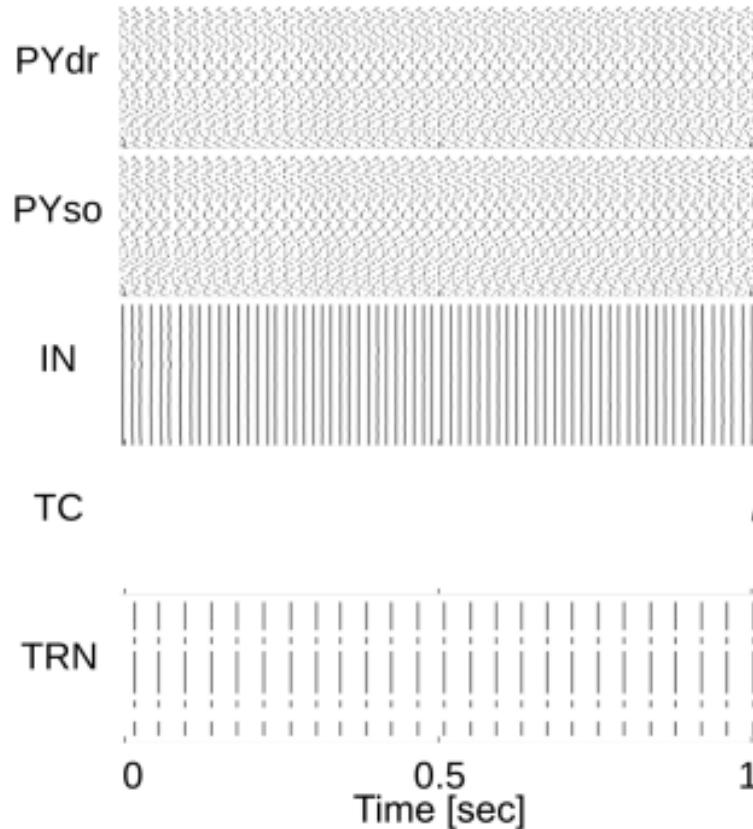
B Relay-mode Spike Rastergrams
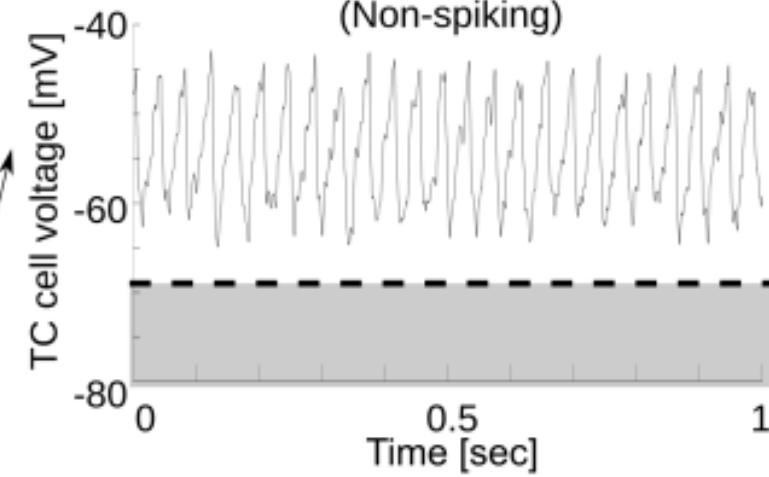
A Propofol (Direct Effects Only)
Spike Rastergrams

PYdr

PYso

IN

TC

TRN

Time [sec]
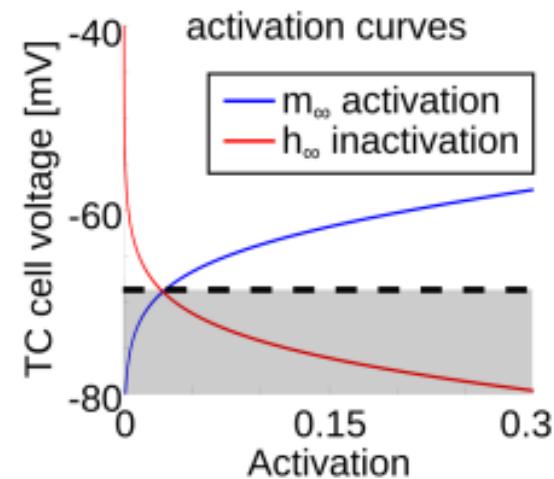
B Single TC Cell Voltage Trace
(Non-spiking)
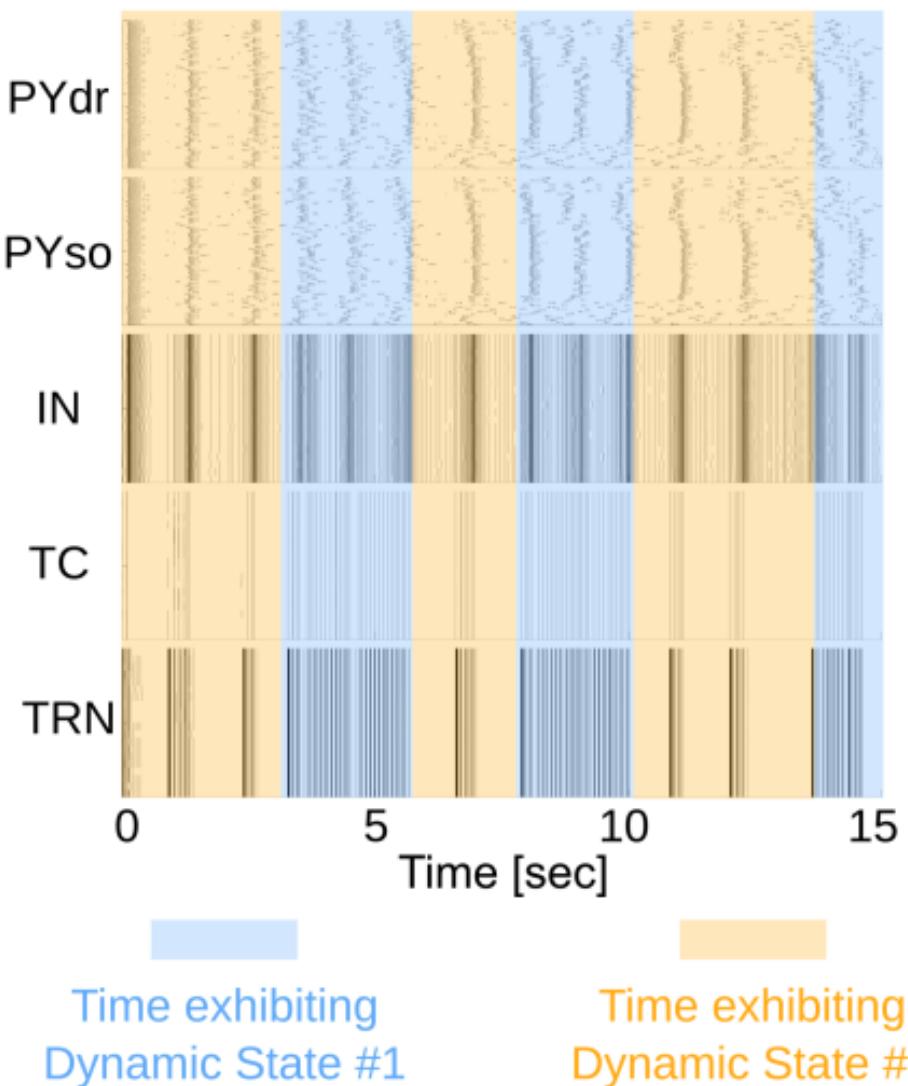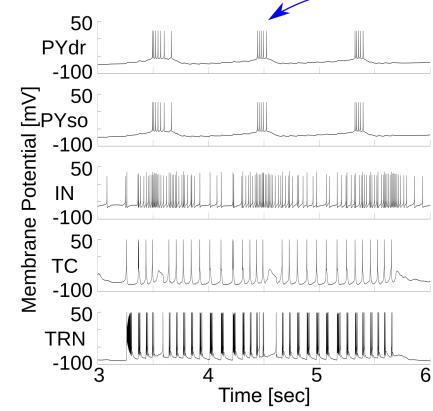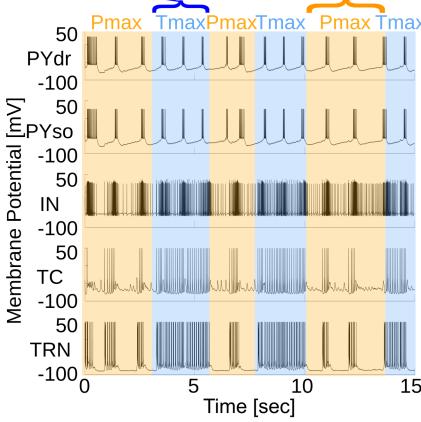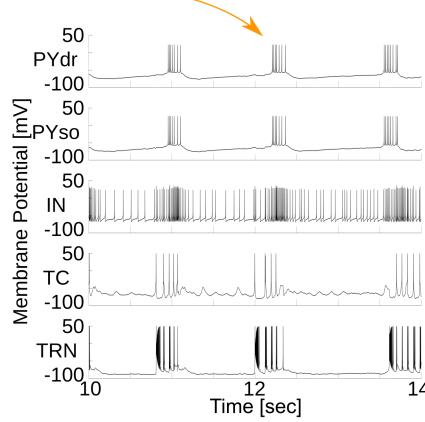
C TC cell T-current
activation curves

m_∞ activation
h_∞ inactivation
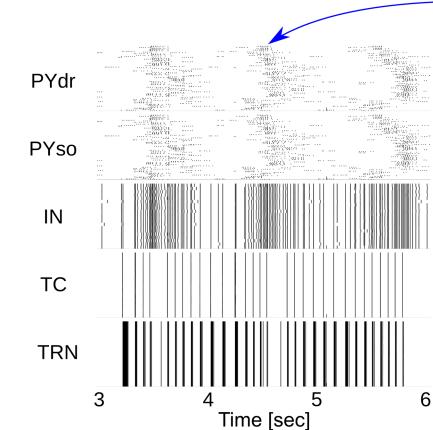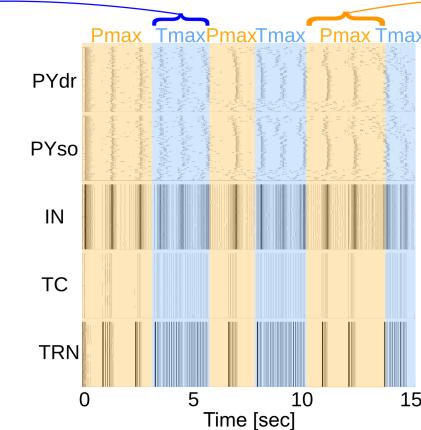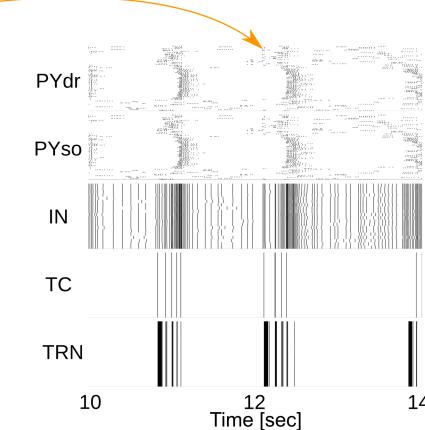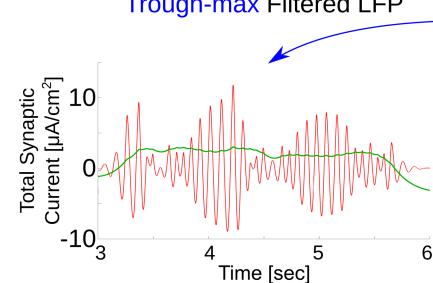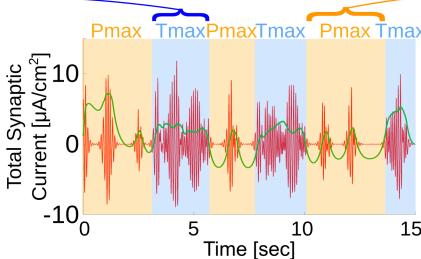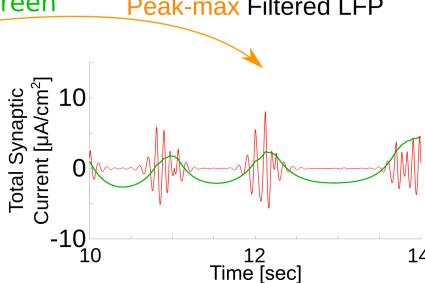
Simulation Spike Rastergram
(Direct and Indirect Propofol Effects)

PYdr

PYso

IN

TC

TRN

Time [sec]

Time exhibiting
Dynamic State #1

Time exhibiting
Dynamic State #2
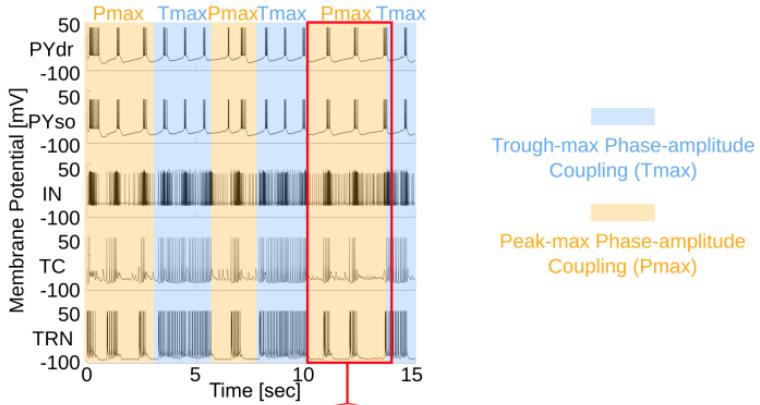
A Trough-max Voltage Traces   **B** Single Voltage Traces   **C** Peak-max Voltage Traces

D Trough-max Spike Rastergram   **E** Spike Rastergram   **F** Peak-max Spike Rastergram

G Trough-max Filtered LFP   **H** Simulated total LFP signal — Filtered for alpha in red, slow in green   **I** Peak-max Filtered LFP

Trough-max Phase-amplitude Coupling (Tmax)

Peak-max Phase-amplitude Coupling (Pmax)

A Propofol Single Voltage Traces

Pmax Tmax Pmax Tmax Pmax Tmax

Trough-max Phase-amplitude Coupling (Tmax)

Peak-max Phase-amplitude Coupling (Pmax)
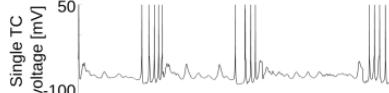
Thalamocortical TC → PY AMPA synapses during Peak-max

Intracortical PY → PY AMPA synapses during Peak-max

B Synaptic Current Traces

C

**D**

E Synaptic Current Traces

F

G

AMPAergic synaptic currents during Peak-max

A Total TC→PY [μA/cm²] 180, 0

B Total PY→PY [μA/cm²] 5, 0

C Combined (TC→PY +PY→PY) [μA/cm²] 180, 0

Time [sec] 10, 12, 14

D **Alpha-amplitude/SWO-phase comodulogram of combined currents during Peak-max**

1.0 Hz SWO Phase Bin: π (trough), 0 (peak), -π (trough)

9 Hz Alpha Amplitude: 0.25, 0.15, 0.05

Time [sec] 1, 14

**A** Propofol Single Voltage Traces

Pmax Tmax Pmax Tmax Pmax Tmax

Trough-max Phase-amplitude Coupling (Tmax)

Peak-max Phase-amplitude Coupling (Pmax)
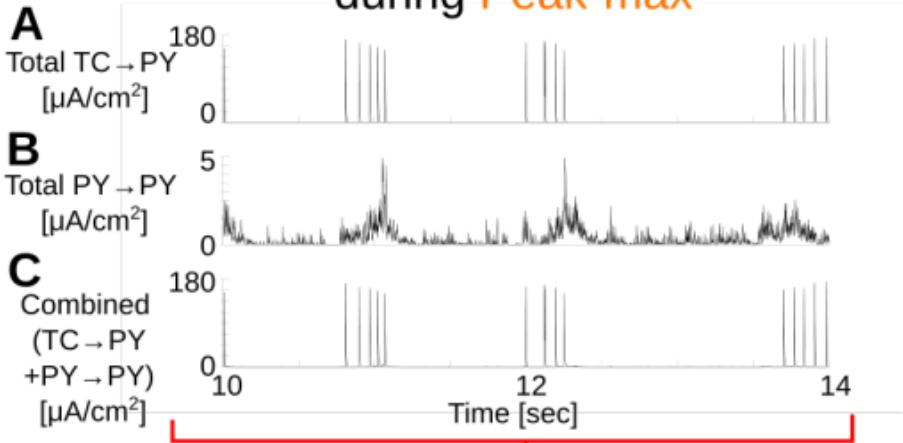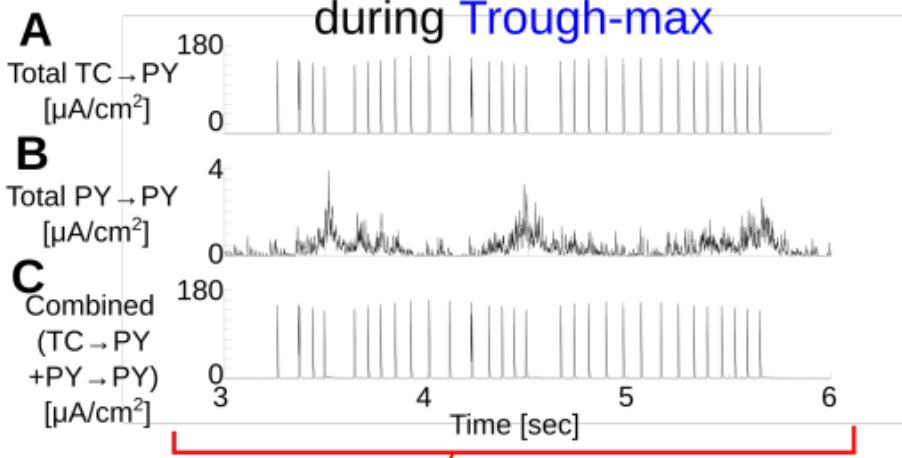
Thalamocortical TC→PY AMPA synapses during Trough-max
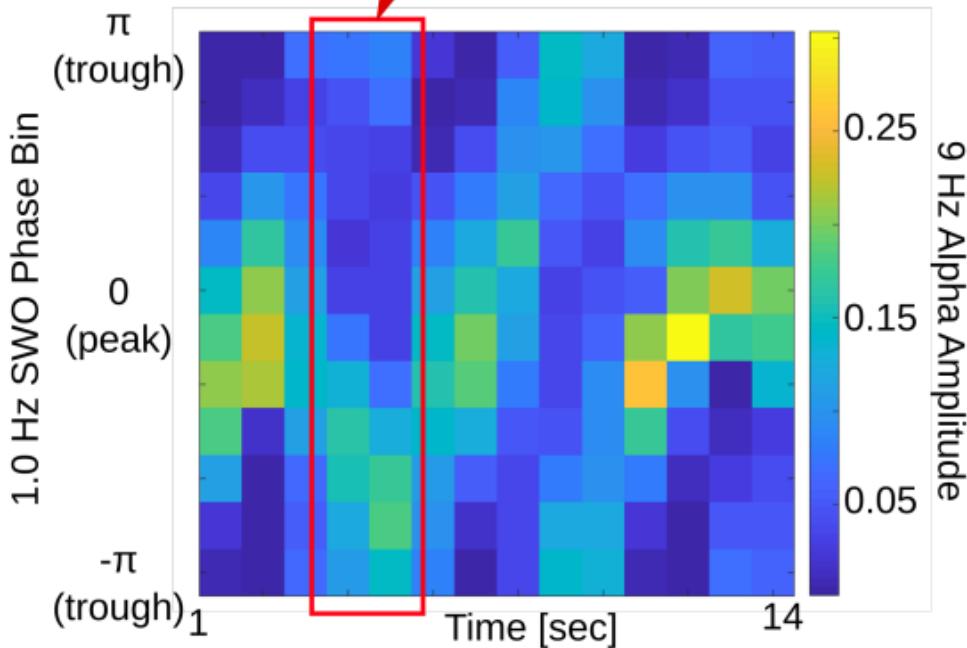
Intracortical PY→PY AMPA synapses during Trough-max
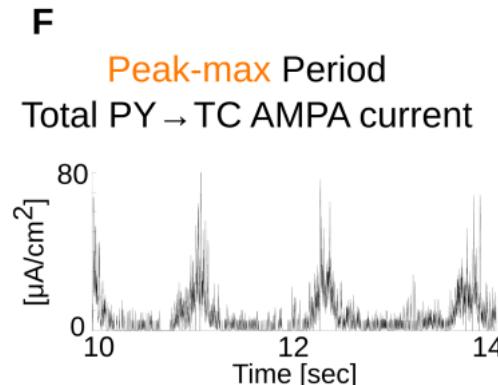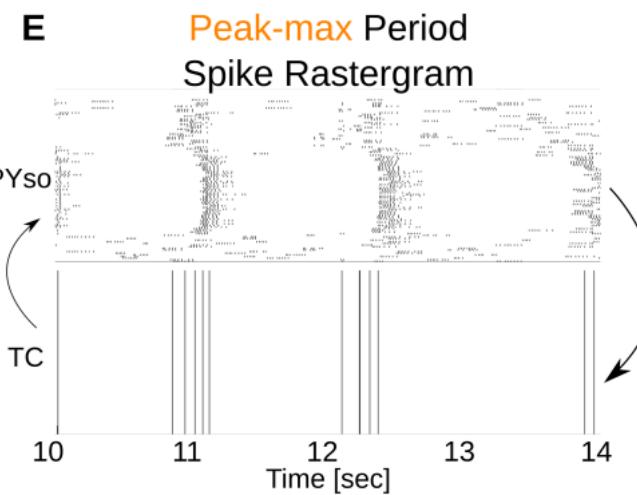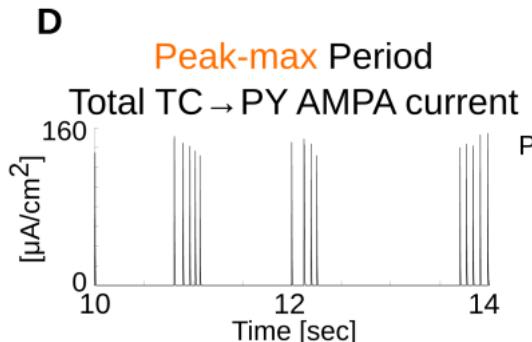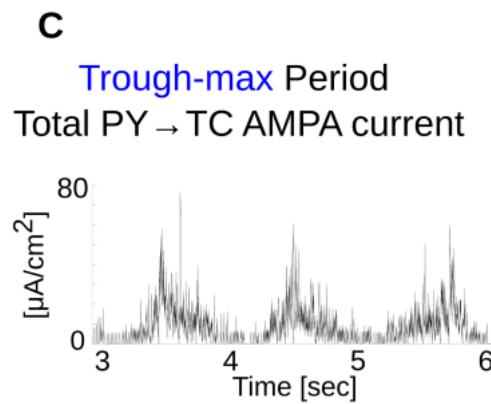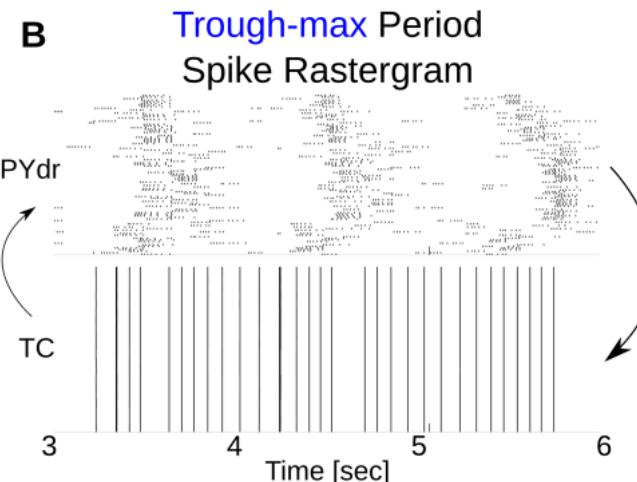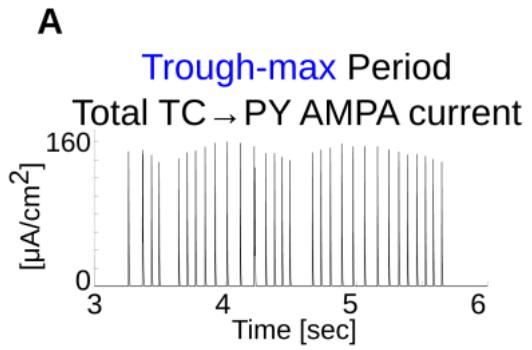
B Synaptic Current Traces

F Synaptic Current Traces

AMPAergic synaptic currents during Trough-max

A Total TC→PY [μA/cm²] — 180, 0

B Total PY→PY [μA/cm²] — 4, 0

C Combined (TC→PY +PY→PY) [μA/cm²] — 180, 0

Time [sec] — 3, 4, 5, 6

D Alpha-amplitude/SWO-phase comodulogram of combined currents during Trough-max

1.0 Hz SWO Phase Bin — π (trough), 0 (peak), -π (trough)

9 Hz Alpha Amplitude — 0.25, 0.15, 0.05

Time [sec] — 1, 14

A Trough-max Period
Total TC → PY AMPA current

B Trough-max Period
Spike Rastergram

C Trough-max Period
Total PY → TC AMPA current

D Peak-max Period
Total TC → PY AMPA current

E Peak-max Period
Spike Rastergram

F Peak-max Period
Total PY → TC AMPA current

Breakdown of dose-specific simulation results

↑ dose = ↓ ACh

Low-dose propofol

High-dose propofol

Input Parameters

Direct effects:
TC g_H ↓
g_{GABA_A} ↓
τ_{GABA_A} ↑

Indirect effects:
g_{KNa} ↑
$g_{AMPA:TC \to PY}$ ↑
$g_{AMPA:PY \to PY}$ ↑

Direct effects:
TC g_H ↓
g_{GABA_A} ↓
τ_{GABA_A} ↑

Indirect effects:
g_{KNa} ↑↑
$g_{AMPA:TC \to PY}$ ↑↑
$g_{AMPA:PY \to PY}$ ↑↑

47% chance
(±20%)

27% chance
(±13%)

53% chance
(±20%)

73% chance
(±13%)

Trough-max

Peak-max

Results

TC→PY synaptic
currents exhibit
Trough-max

PY→PY synaptic
currents exhibit
Peak-max
(weaker than TC→PY)

Both synaptic
currents exhibit
Peak-max