Thalamic generation of propofol phase amplitude coupling

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Introduction

- The intraveneous anesthetic **propofol** exhibits dose-dependent phase-amplitude coupling (PAC) between Slow Wave Oscillation (SWO, 0.1-1.5 Hz) **phase** and alpha (9-15 Hz) **amplitude** in human EEG [5]
- At low doses, alpha-amplitude is maximum at the "trough" or DOWN state of the SWO, aka "trough-max"
- At high doses, alpha-amplitude is maximum at the "peak" or UP state of the SWO, aka "peak-max"
- Propofol is a $GABA_A$ agonist [1] and hyperpolarization-activated cation current (H-current) suppressor [6]; both mechanisms are important in thalamocortical sleep oscillations including spindles (8-14 Hz) and endogenous SWO [3]
- We hypothesized that the thalamus can produce this PAC by propofol dynamically hyperpolarizing the network, enabling the thalamus to exhibit alpha when the appropriate SWO phase enters a fixed region of thalamic alpha oscillation

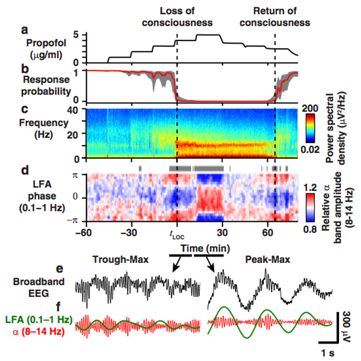

Figure 1: Propofol's loss of patient responsiveness, increase in alpha and SWO power, and shifting of phase-amplitude coupling states; reproduced with permission from Figure 1 of [5]

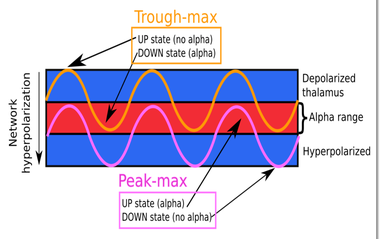

Figure 2: Our hypothesis: in trough-max, the DOWN state enters the more hyperpolarized region of thalamic excitation where the thalamus produces intrisic alpha oscillations. In peak-max, the DOWN is too hyperpolarized to spike, but the UP state can enter the region of thalamic excitation that enables alpha oscillations.

Methods

- All simulations were networks of 50 Hodgkin-Huxley-style TC (thalamocortical relay) and 50 RE (reticular nucleus) cells built on [3,4]
- We simulated different doses of propofol by ↑ synaptic maximal conductance $\bar{g}_{GABA_A}$ and synaptic decay constant τ_{GABA_A}, in addition to ↓ maximal conductance for the intrinsic H-current $\bar{g}_H$
- We modeled the cortical SWO inputs to the thalamus by comparing simulations with and without
  - 1. Poisson 12 Hz cortical spiking AMPA input
  - 2. Changesin background excitation level ($\frac{\mu A}{cm^2}$)

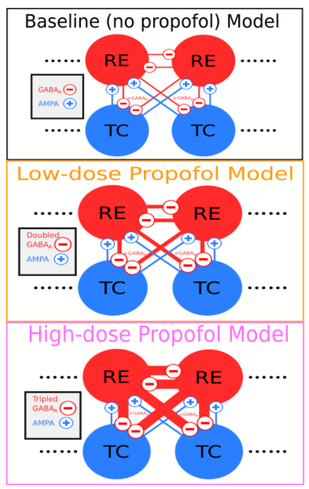

Figure 3: Illustration of thalamic circuits, where dose indicates level of $GABA_A$ potentiation.

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Results

Without propofol, there is NO thalamic sustained alpha

- Did not find any intrinsic alpha oscillation region (red) across the plane of the maximal H-current conductance and background excitation dimensions
- Lack of intrinsic alpha oscillation ⇒ propofol's effects on baseline excitation and g_h levels are NOT sufficient to enable PAC

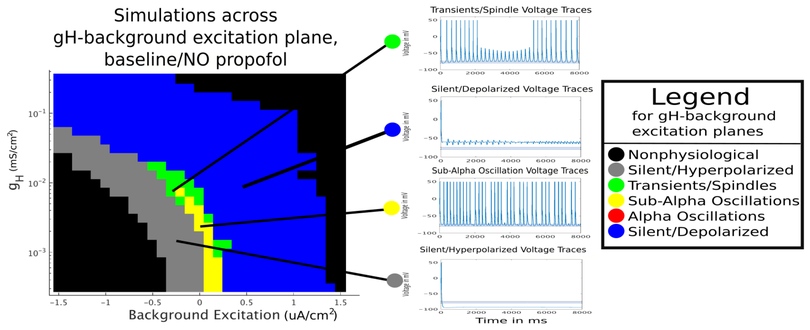


Figure 4: g_H-background excitation plane of behavior of the thalamic network under baseline/no propofol. Each pixel represents a single simulation. Voltage traces of the first TC cell in example simulations are shown for four different behaviors. Note the lack of red, or sustained alpha oscillation. Also shown: legend for simulation behavior classification in g_H-background excitation planes.

Under propofol, there IS thalamic sustained alpha

- Under high-dose propofol, modeled as tripled $GABA_A$ potentiation, DO find a large region exhibiting *sustained* alpha oscillations (red simulations in figure) at steady-state.
- Fundamental mechanism for propofol alpha oscillations:
  - ↑ in RE→TC inhibition ⇒ ↑ TC cell T-current deinactivation (h_T) ⇒ TC cell T-current "burst"

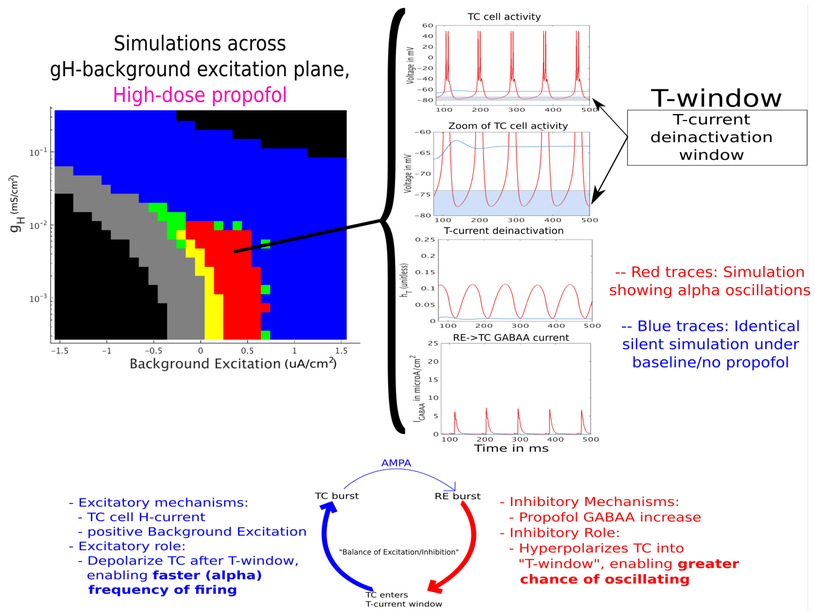
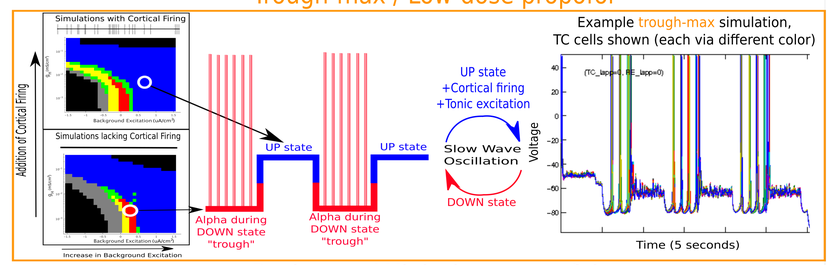


Figure 5: g_H-background excitation plane of behavior of the thalamic network under high-dose propofol. Note the large swath of red, indicating sustained alpha oscillations by the network. Intrinsic dynamics like T-current deinactivation h_T are shown for a single cell in a single alpha oscillating simulation, alongside h_T activation curves.

Thalamus produces trough-max and peak-max PAC

- We can model SWO UP states in the thalamus by introducing 1. cortical spiking and 2. an increase in background excitation. DOWN states are defined by the absence of these.
- By simulating UP and DOWN states across 1. different levels of propofol and 2. overall background excitation, the thalamic network can produce trough-max and peak-max.
  - In trough-max, the thalamus alpha-oscillates during DOWN states, and is silent/depolarized during UP states.
  - In peak-max, the thalamus alpha-oscillates during UP states, and is silent/hyperpolarized during DOWN states.



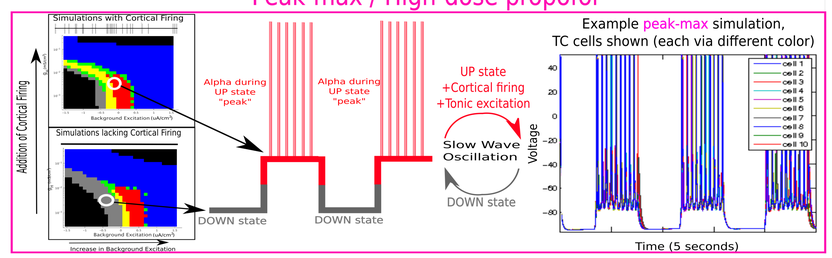


Figure 6: Cartoons of trough-max and peak-max behaviors, where either the UP or the DOWN parts of an example SWO are points on, respectively, the g_H-background excitation simulation planes with and without cortical firing. To the right are traces from actual simulations illustrating the appropriate PAC.

Conclusions

- The thalamic network could only produce alpha oscillations when propofol $GABA_A$ potentiation was included. Our initial hypothesis, that hyperpolarization could push the network into a fixed thalamic alpha oscillation range, was incorrect.
- This alpha oscillation comes from more T-current bursts, caused by greater TC cell T-current deinactivation, h_T, caused by ↑ $GABA_A$ potentiation of RE→TC inhibition.
- By modeling the SWO UP states as increases in background excitation and cortical firing, the thalamic network is capable of expressing the full range of propofol PAC, including trough-max and peak-max.
- Therefore, propofol can take advantage of thalamic sleep oscillation mechanisms in order to produce oscillations and act as anesthesia.

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Conflicts of Interest

1. EB: F. Consultant Masimo
2. PP: inventor on patents pending on anesthetic brain monitoring that have been licensed by MGH to Masimo Corporation, and has received speaker's honoraria from Masimo Corporation