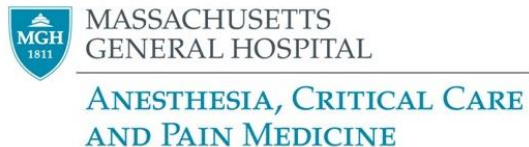


Dynamics of propofol anesthesia in the thalamocortical loop

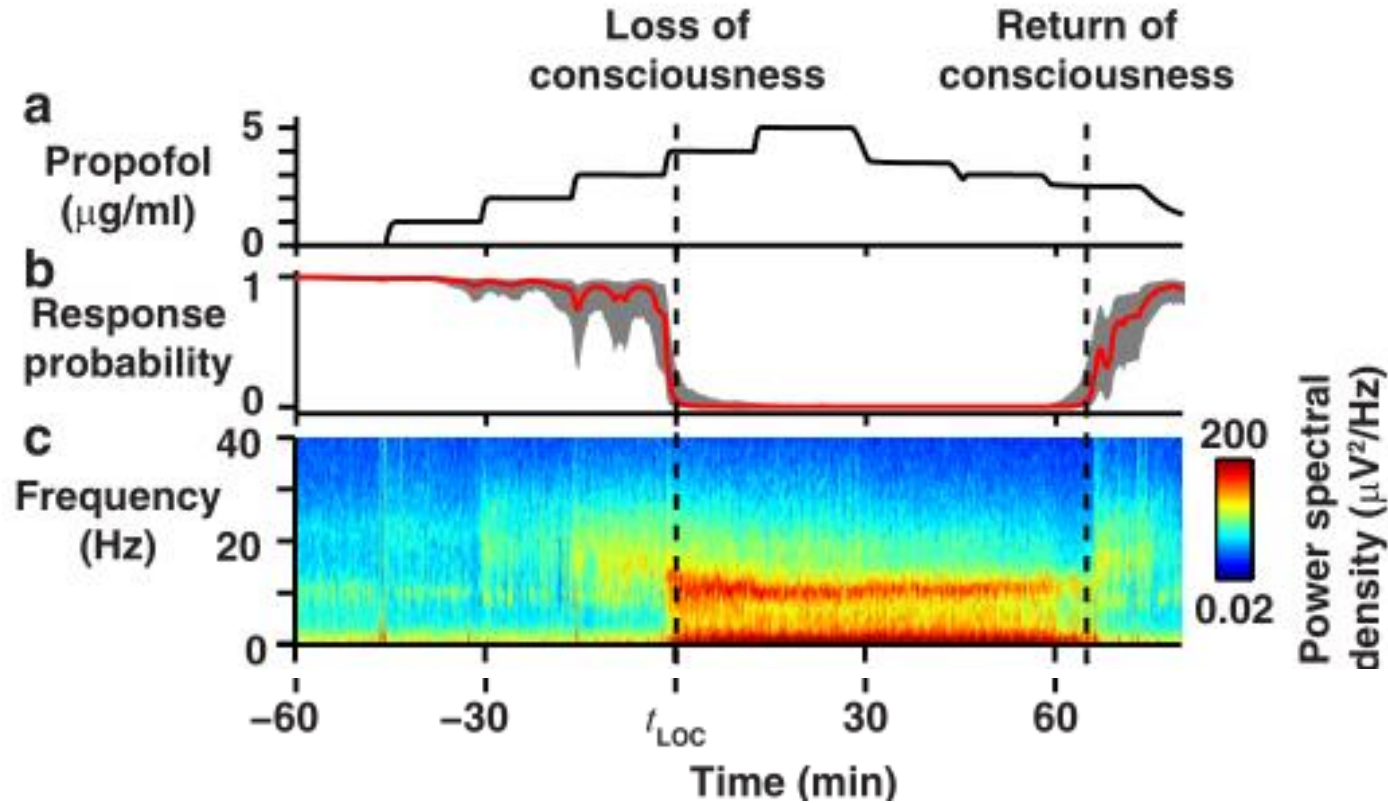
Austin E. Soplata, PhD

Post-doc in Emery Brown lab at MGH/HMS/MIT,

Collaboration with Nancy Kopell lab at BU



EEG oscillations under propofol anesthesia



- What causes **Alpha Oscillations (8-14 Hz)** in propofol anesthesia?

Image from (Mukamel et al., 2014)

Propofol alpha is same frequency as Thalamic Sleep Spindles (8-16 Hz)

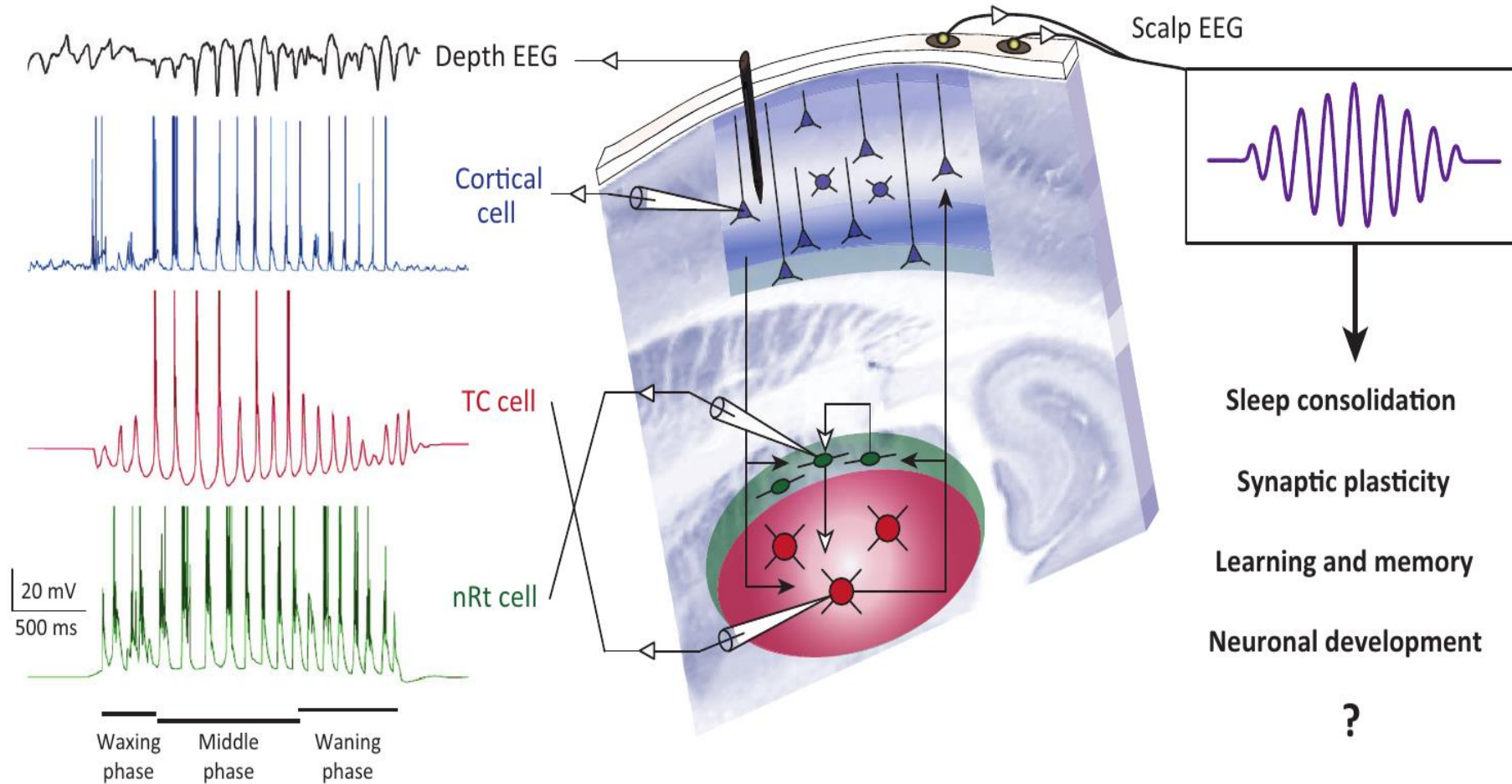
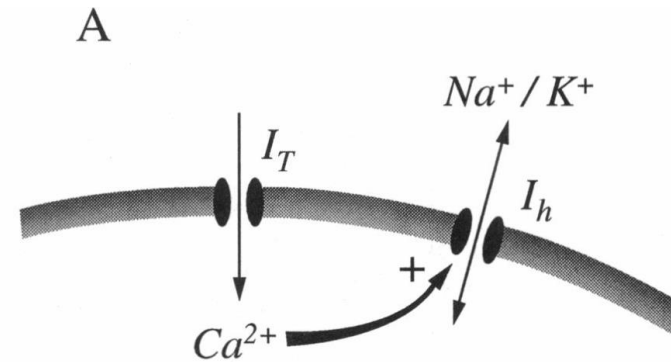
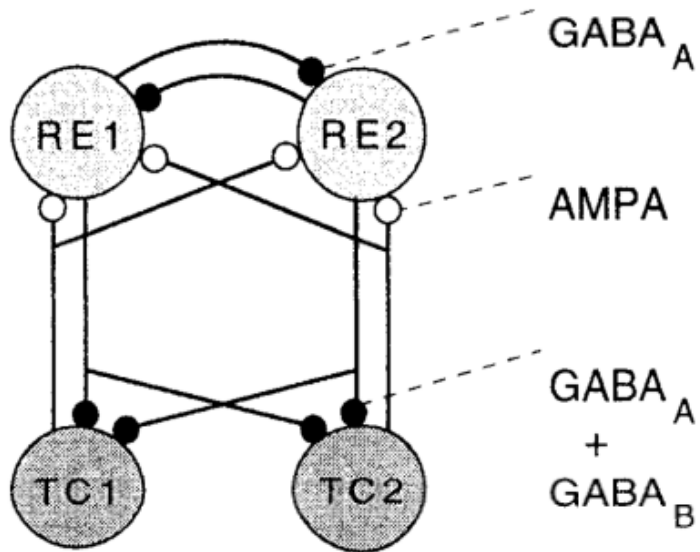


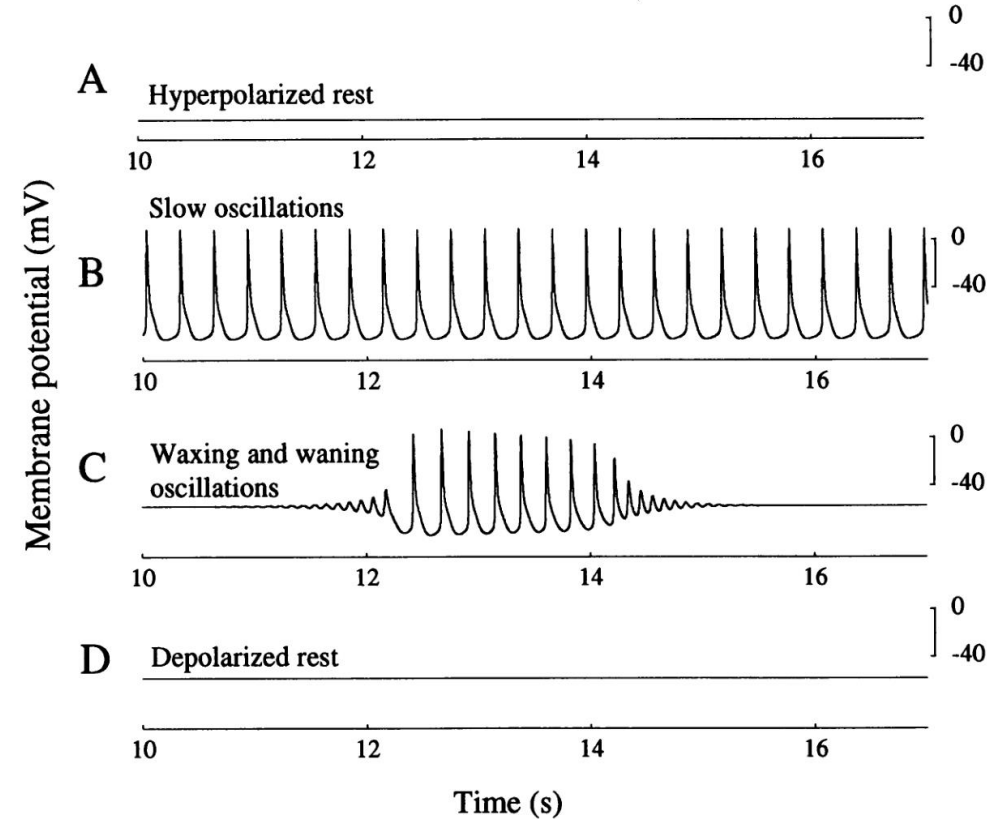
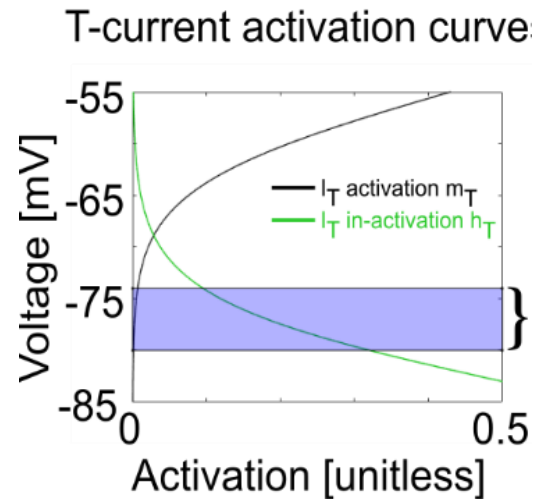
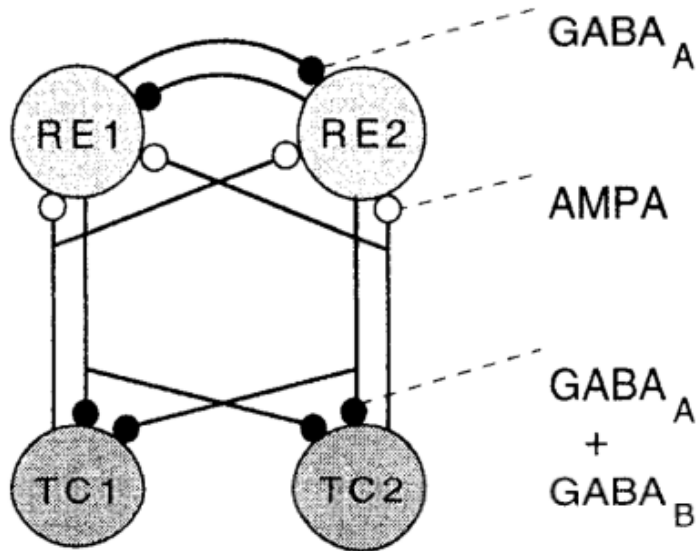
Image from (Astori et al., 2013)

1996: Computer Models of Thalamic Spindles



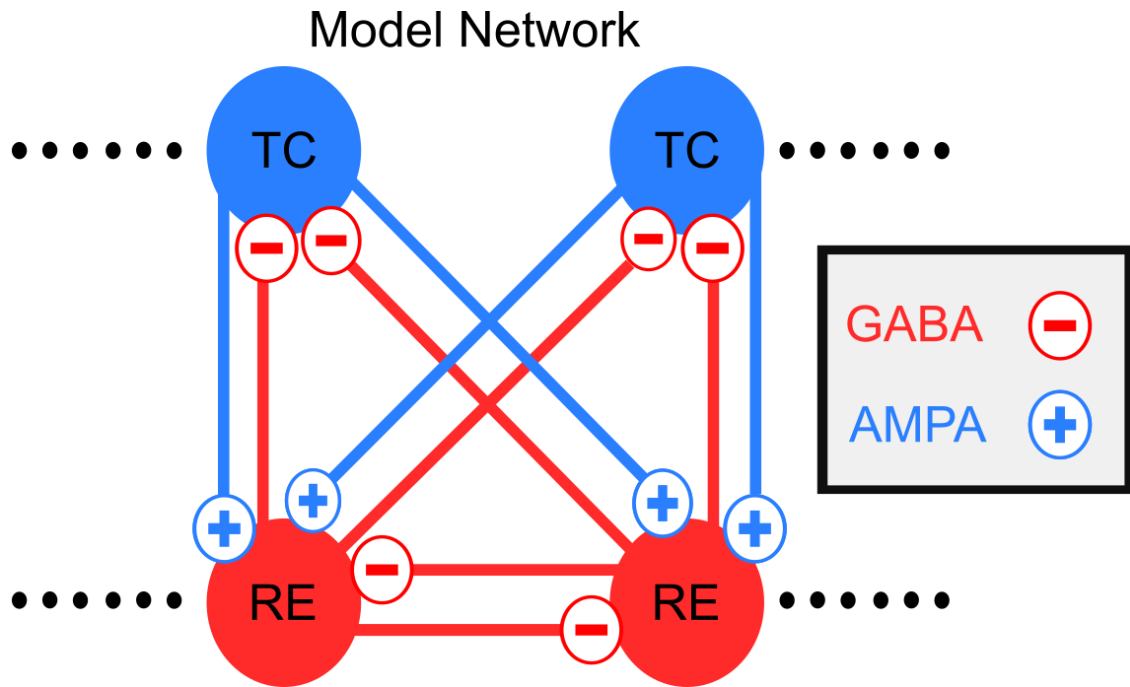
$$C_m \dot{V}_T = -g_L(V_T - E_L) - I_T - I_h + I_{KL} - I_{Na} - I_K - I_{GABA_A T} - I_{GABA_B} \quad (1)$$

Hyperpolarized TC Cell T-current and H-current



$$C_m \dot{V}_T = -g_L(V_T - E_L) - I_T - I_h + I_{KL} - I_{Na} - I_K - I_{GABA_A T} - I_{GABA_B} \quad (1)$$

Our Thalamic Circuit

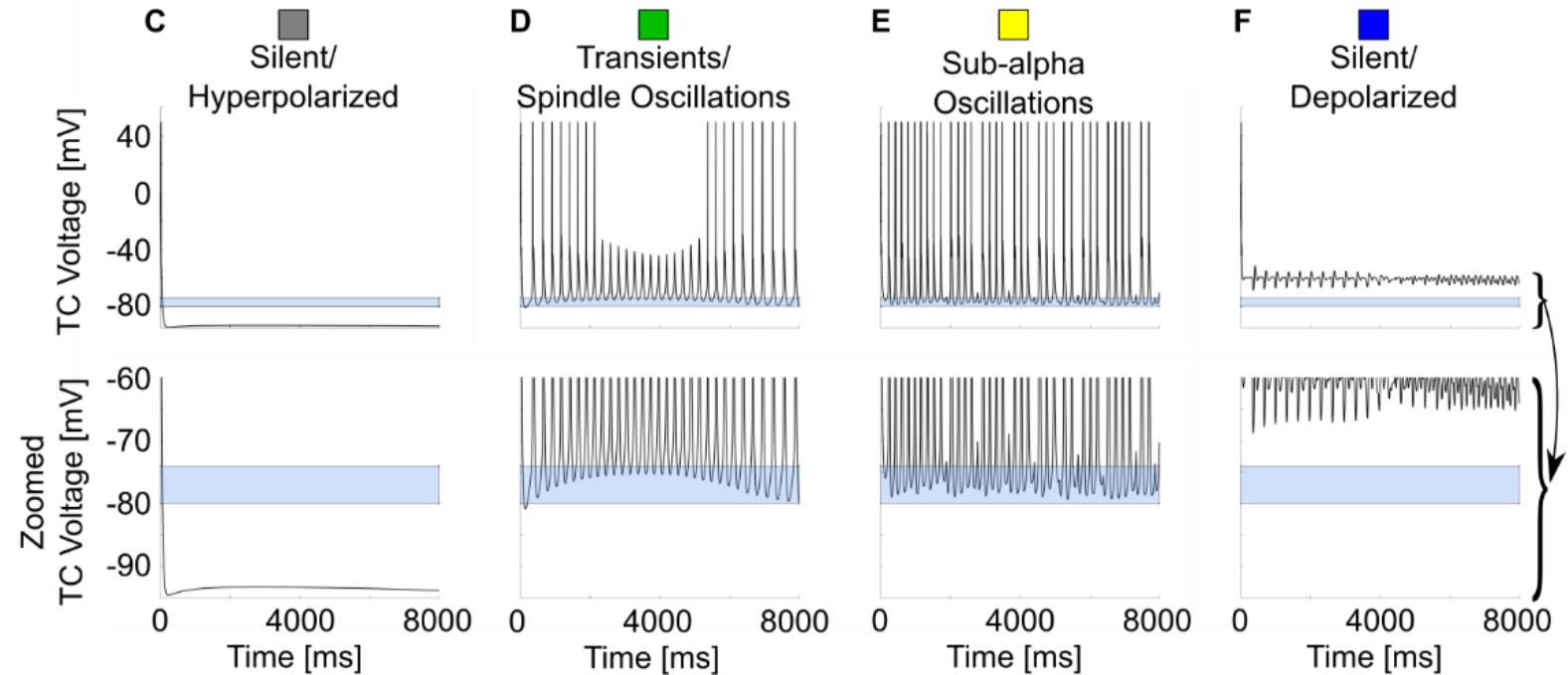
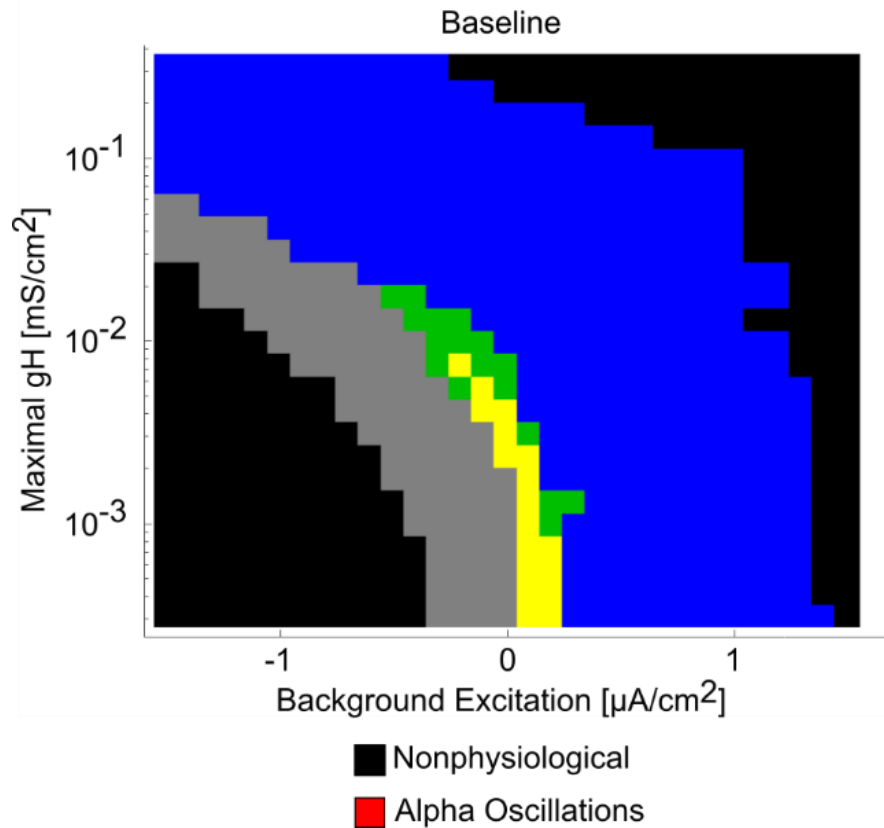


Propofol direct effects

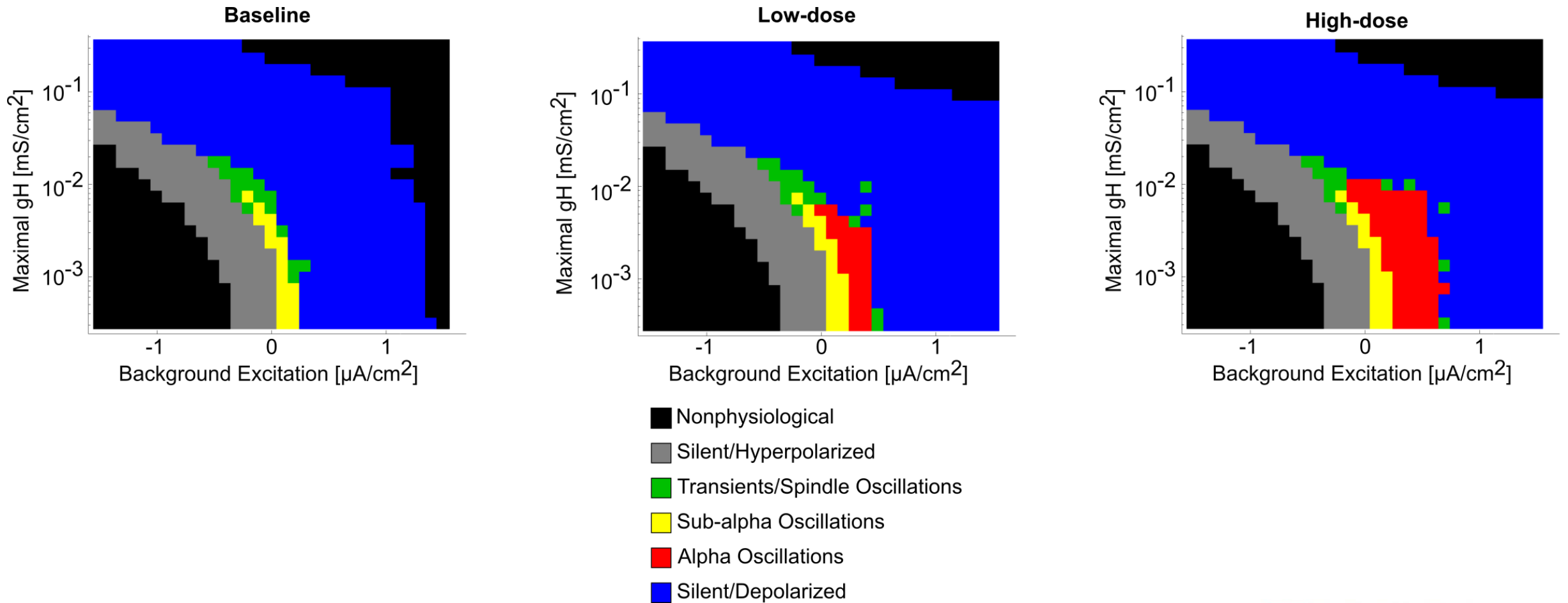
- Increases \bar{g}_{GABA_A} (“strength of inhibition”)
- Increases τ_{GABA_A} (“how long inhibition lasts”)
- Decreases \bar{g}_H (TC cell H-current strength)
- Decreases Background Excitation

All remaining images from (Soplata et al., 2017) or unpublished,
Unless otherwise indicated

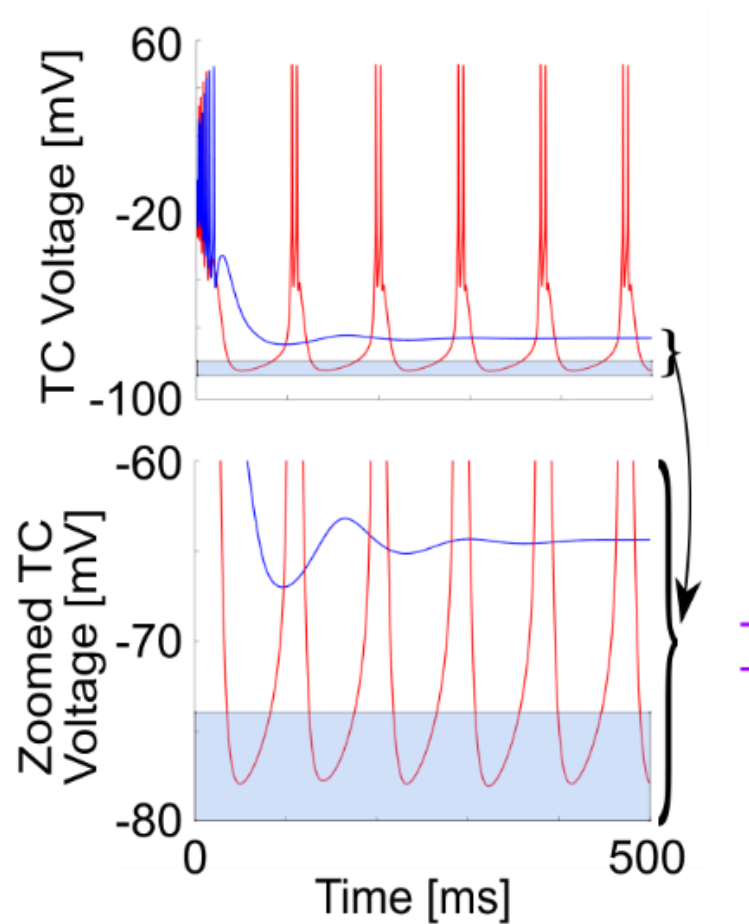
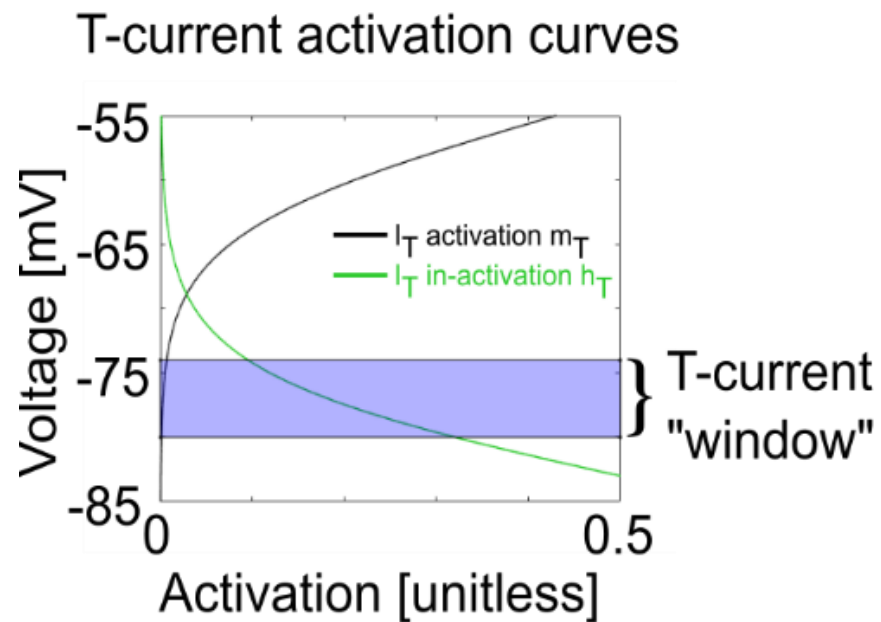
Can we get propofol-like alpha without GABA enhancement? **No!**



Propofol dose affects the likelihood of alpha



Enhanced GABA_A inhibition enables alpha



— Baseline Silent/Depolarization
— High-dose Sustained Alpha

Alpha activity does occur in rat cortex and higher-order thalamus LFP (shown) under propofol

E

preLORR (~7 min after start)



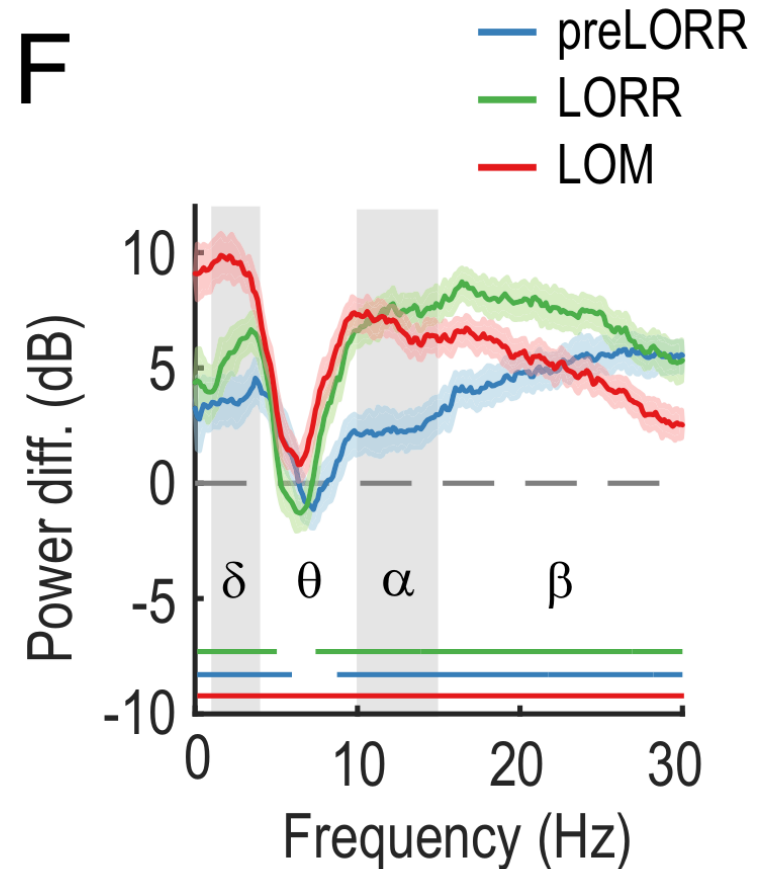
LORR (~10 min)



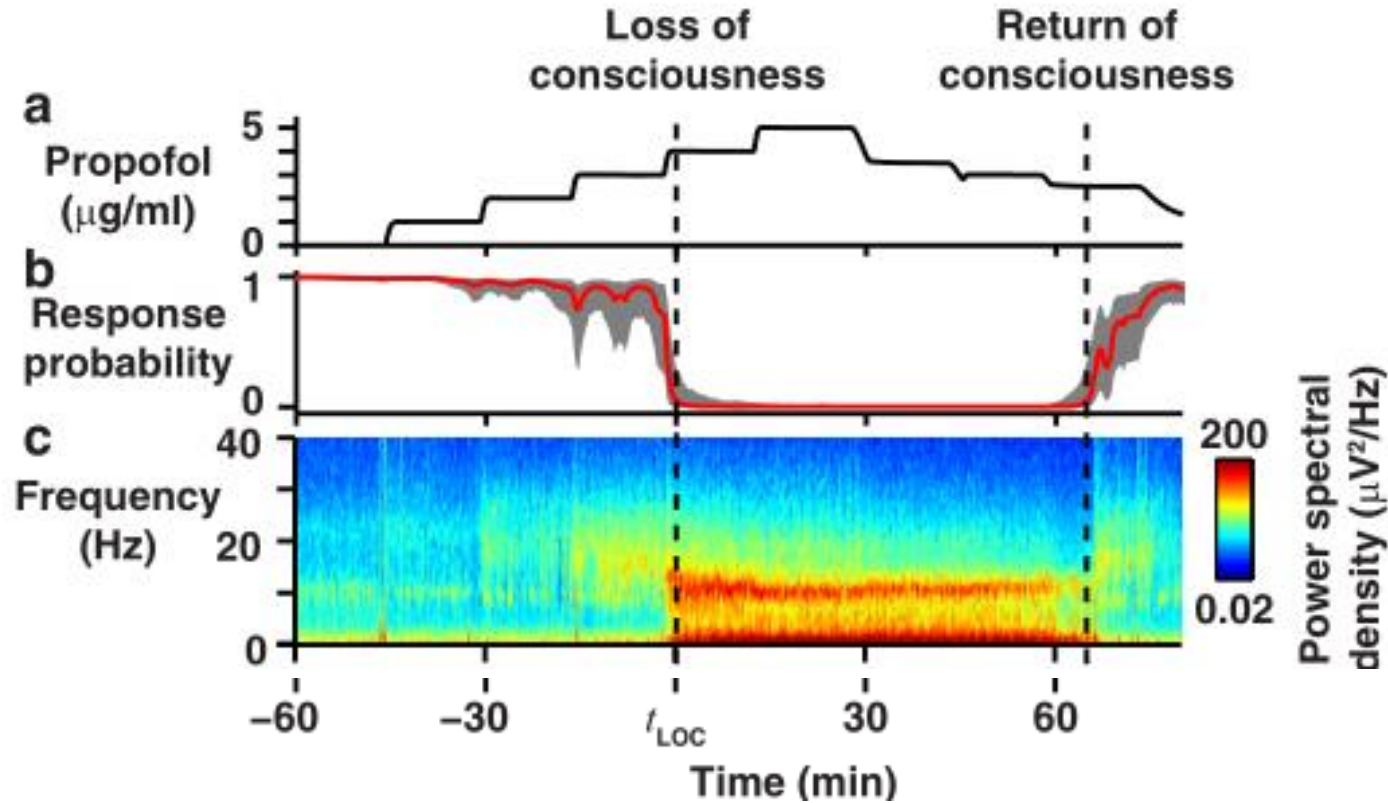
LOM (~13 min)



F



EEG oscillations under propofol anesthesia

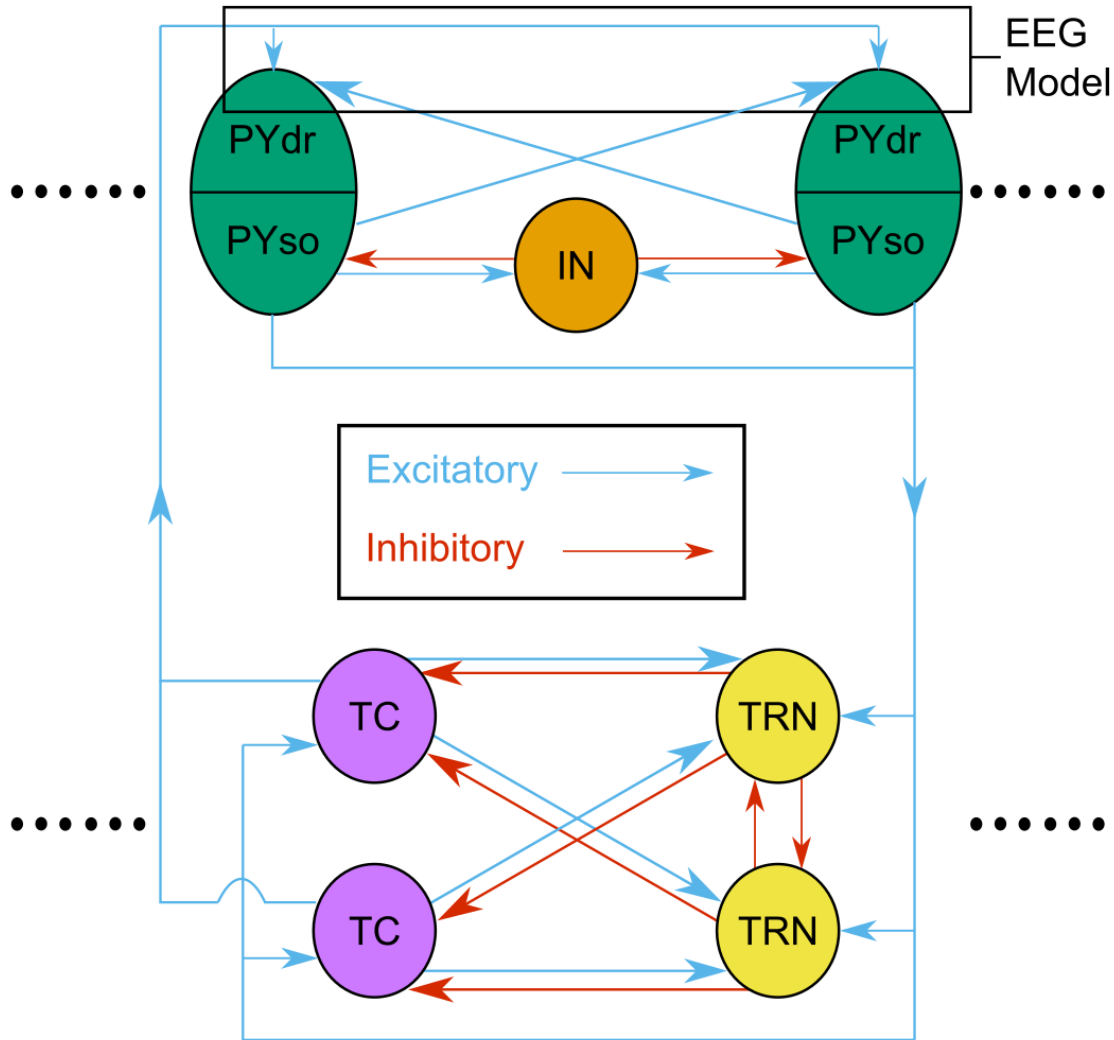


- What causes Alpha Oscillations (8-14 Hz) in propofol anesthesia?
- What causes Slow Wave Oscillations (SWO, 0.1-2 Hz) in propofol anesthesia?

Image from (Mukamel et al., 2014)

Thalamocortical Circuit

Simulated Circuit Model Network



Cortical Slow Wave Mechanism:
K(Na)-current

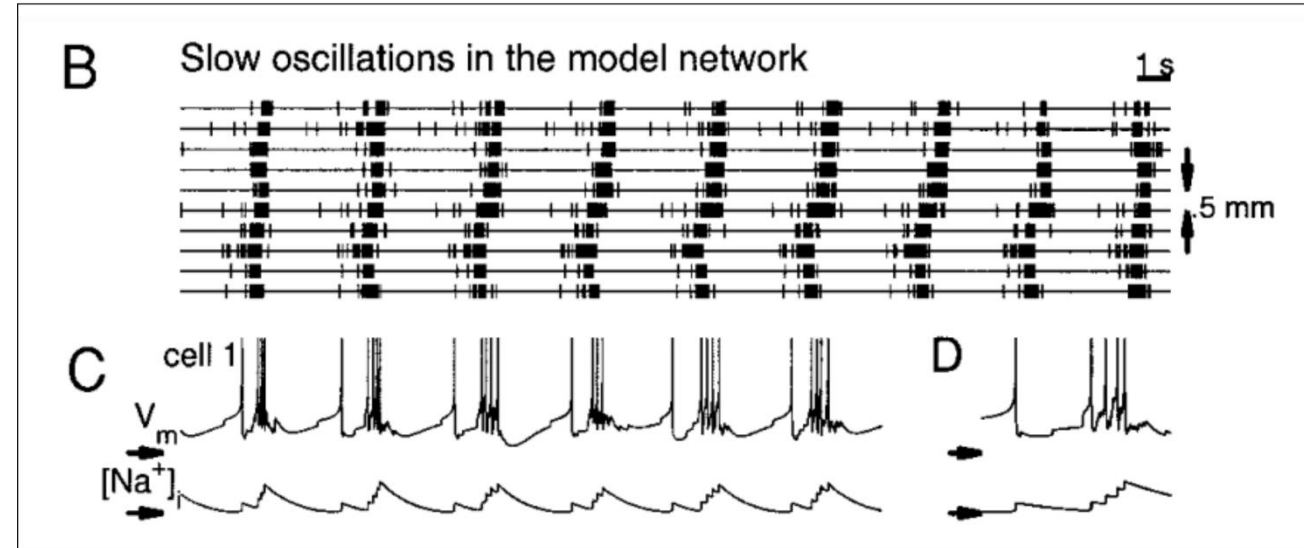
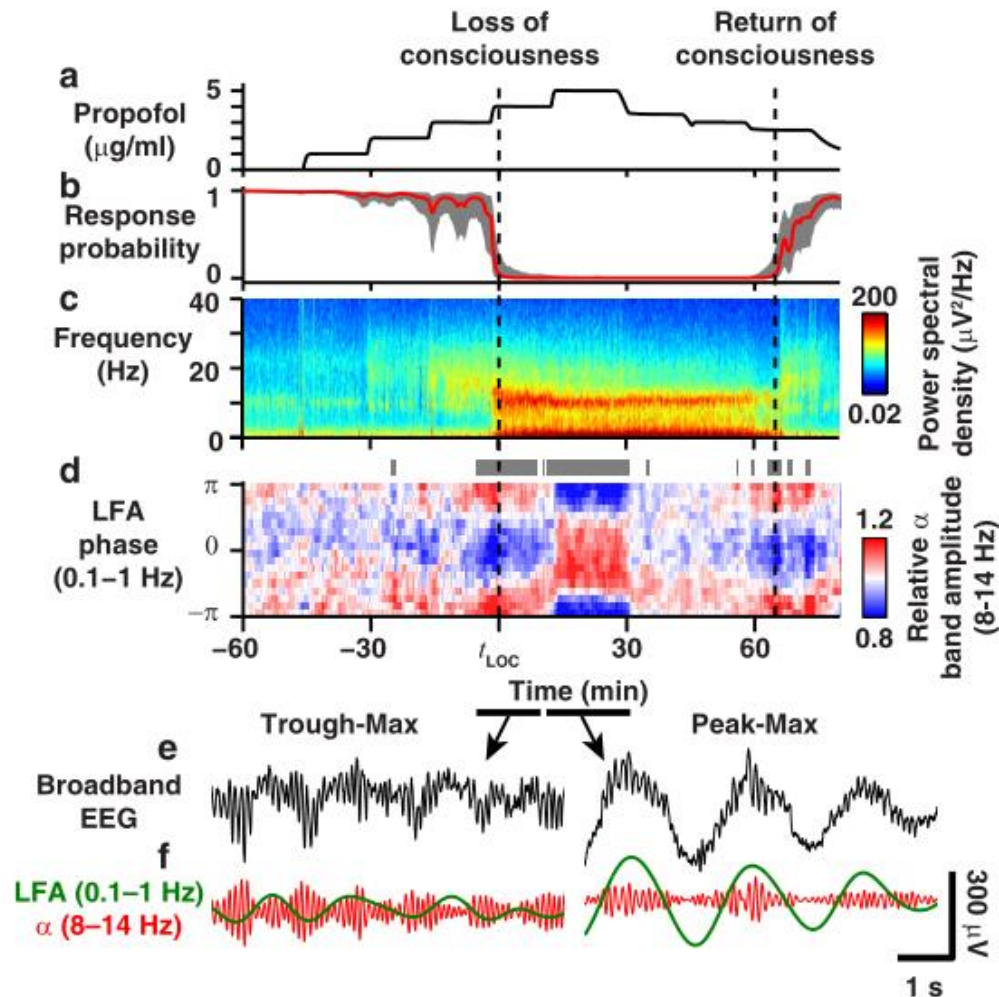


Image from (Compte et al., 2003)

EEG oscillations under propofol anesthesia

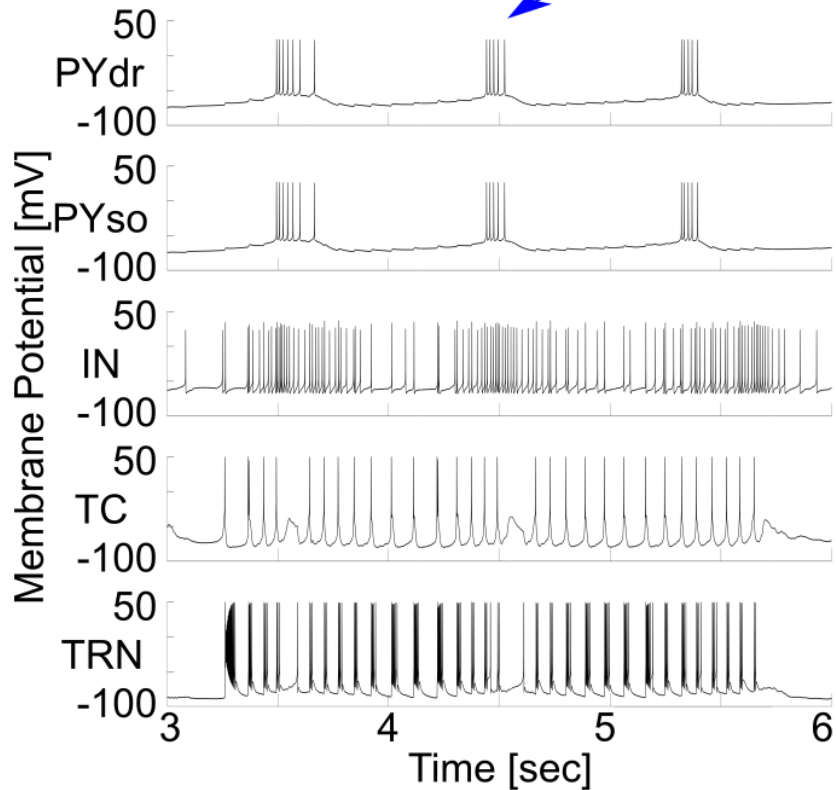


- What causes Alpha Oscillations (8-14 Hz) in propofol anesthesia?
- What causes Slow Wave Oscillations (SWO, 0.1-2 Hz) in propofol anesthesia?
- What causes **Trough-max** and **Peak-max** Phase-Amplitude Coupling between alpha and SWO?

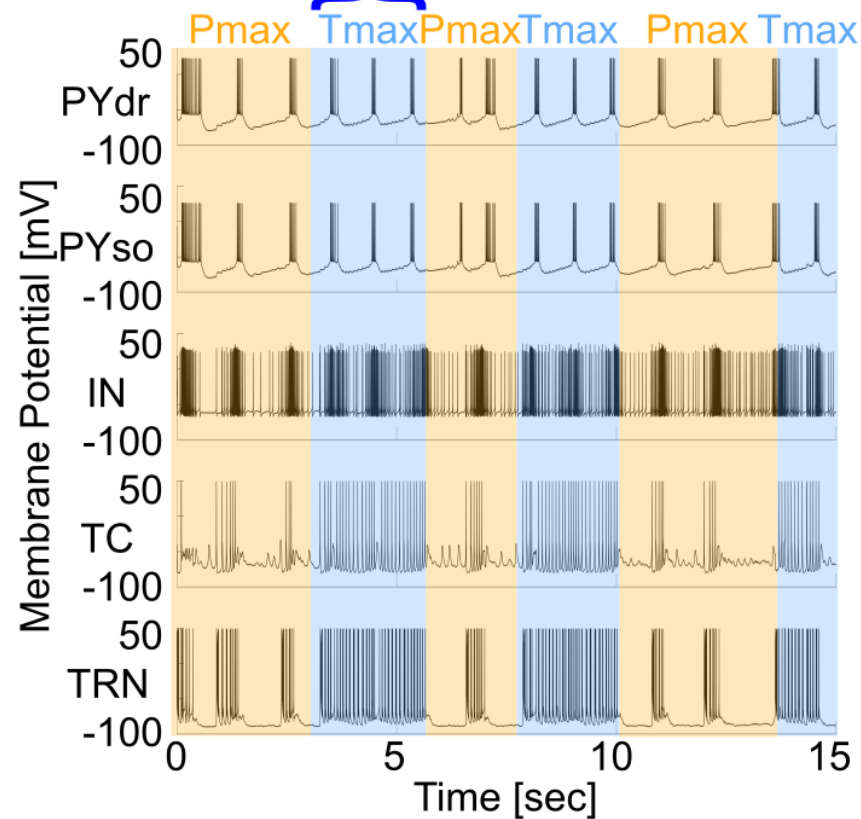
Image from (Mukamel et al., 2014)

Trough-max and Peak-max can occur on different SWO cycles

A Trough-max Voltage Traces



B Low-dose Single Voltage Traces

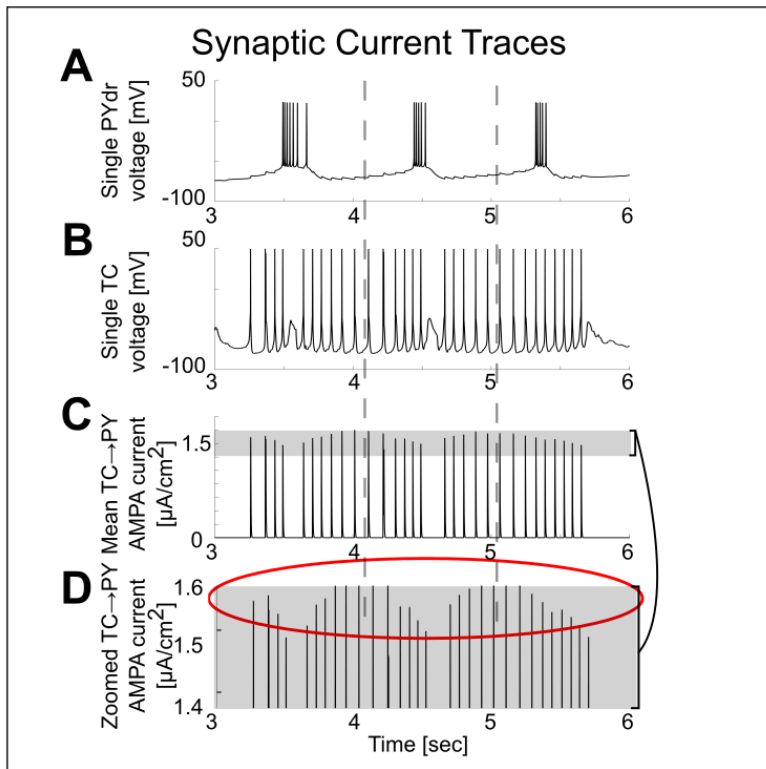


- Cycle-by-cycle variation in coupling driven by

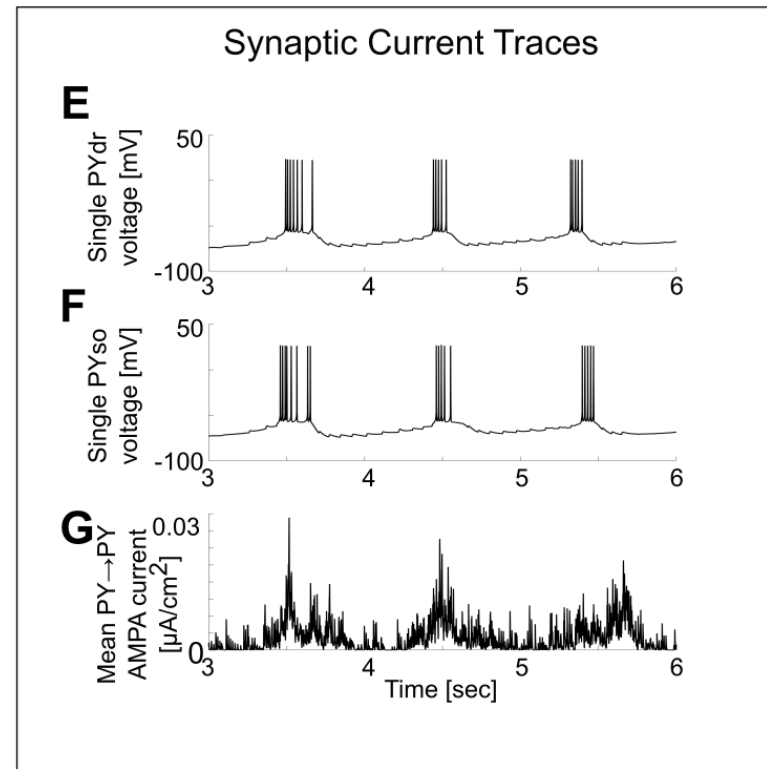
- Randomness
- Degree of cortical synchronization

Trough-max occurs at TC->PY synaptic currents

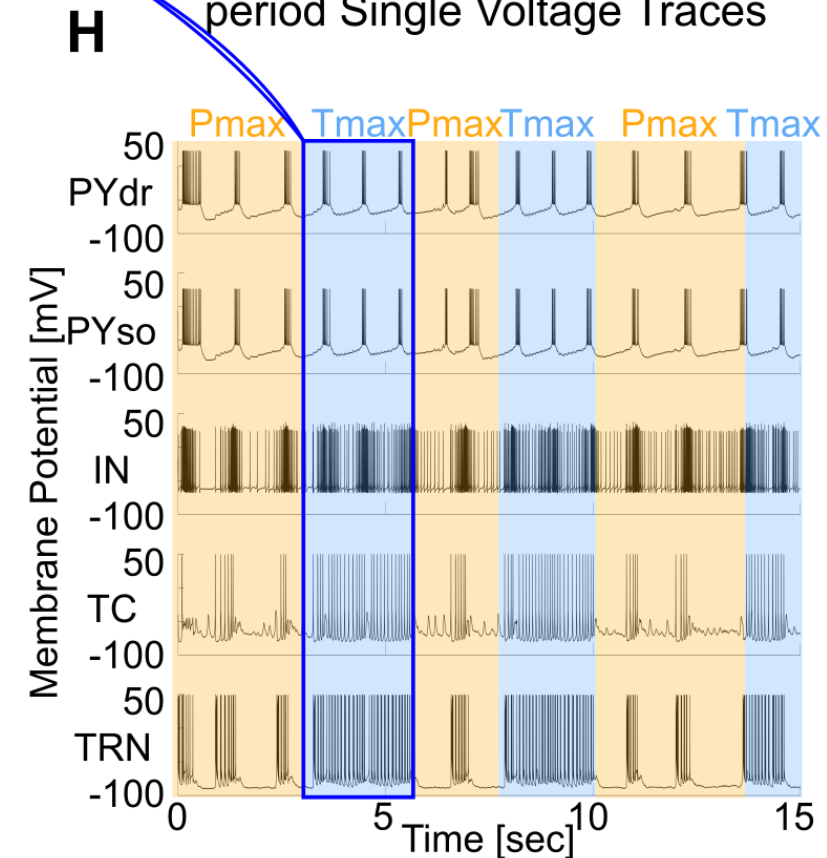
Thalamocortical TC→PY AMPA synapses during Low-dose Propofol Trough-max PAC



Intracortical PY→PY AMPA synapses during Low-dose Propofol Trough-max PAC

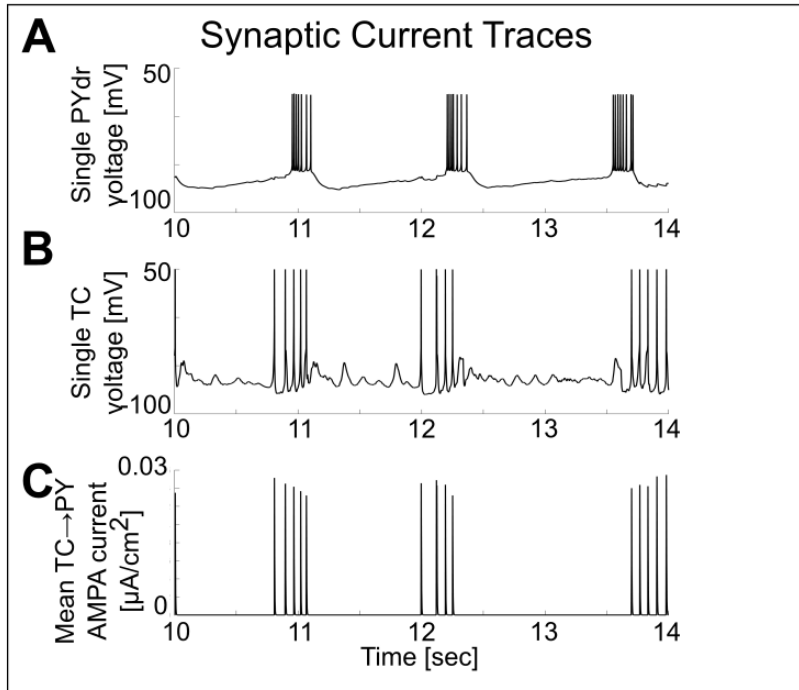


Low-dose Propofol Trough-max period Single Voltage Traces

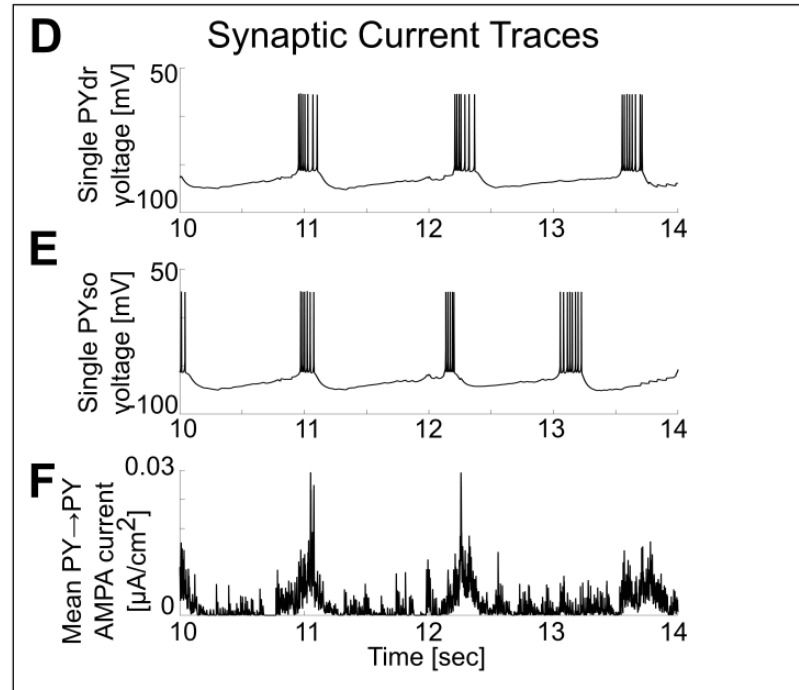


Peak-max occurs at all cortical synaptic currents

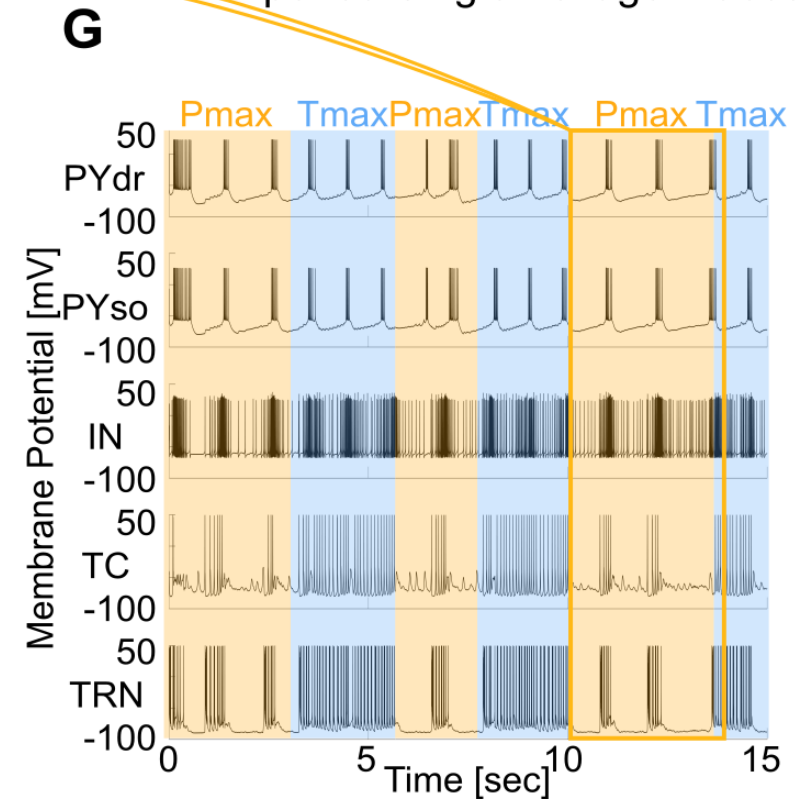
Thalamocortical TC→PY AMPA synapses during Low-dose Propofol Peak-max PAC



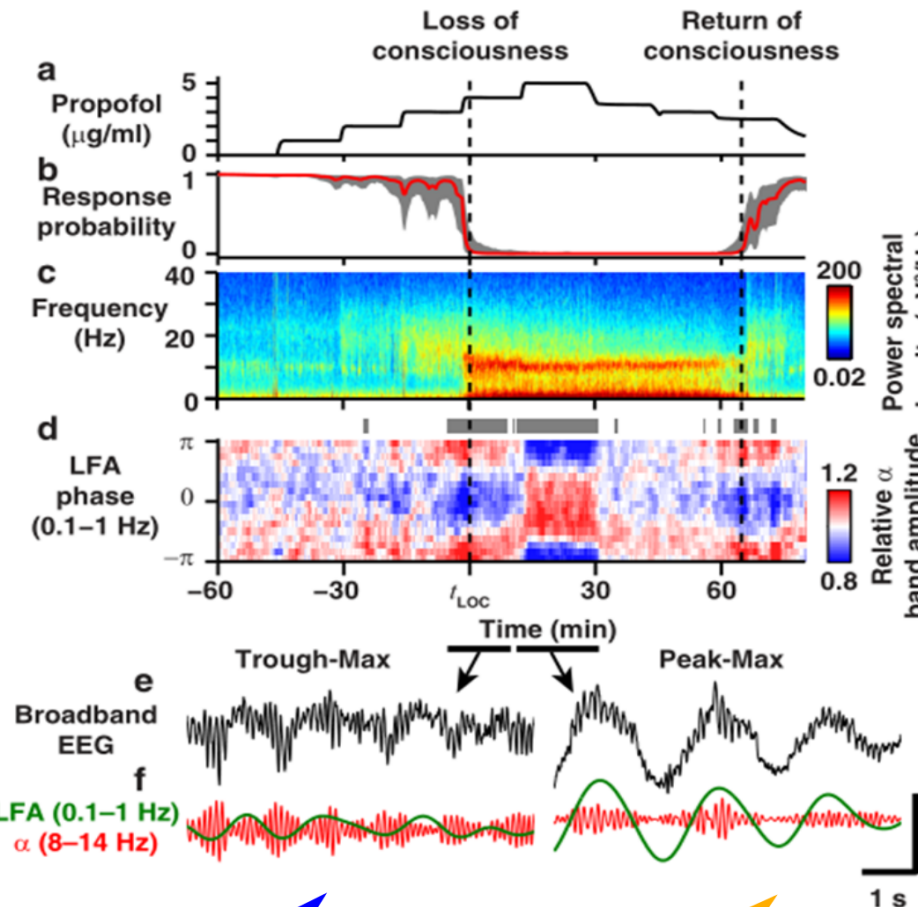
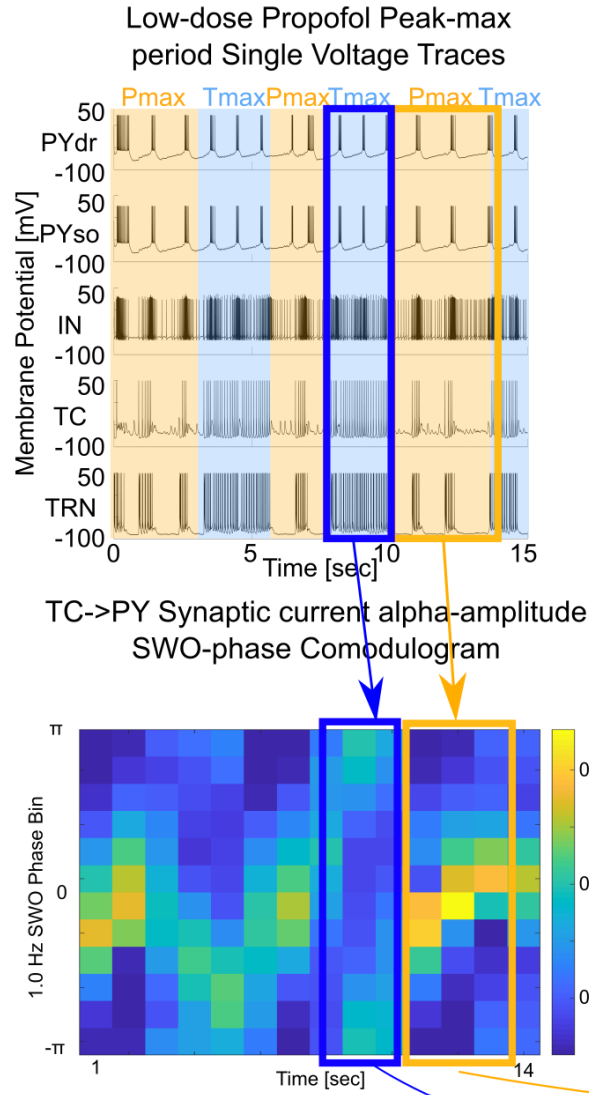
Intracortical PY→PY AMPA synapses during Low-dose Propofol Peak-max PAC



Low-dose Propofol Peak-max period Single Voltage Traces



Model coupling resembles experimental data



Proportion of Trough/Peak-max depends on dose-dependent acetylcholine (ACh)

- Propofol Direct Effects:
 - Increases GABA-A
 - Decreases \bar{g}_H
- Propofol INDIRECT Effects:
 - Decreases ACh, causing:
 - Increased K(Na)-current strength
 - Increased PY→PY excitatory AMPA strength
 - nAChRs decrease TC→PY excitatory AMPA strength
 - mAChRs increase TC→PY excitatory AMPA strength

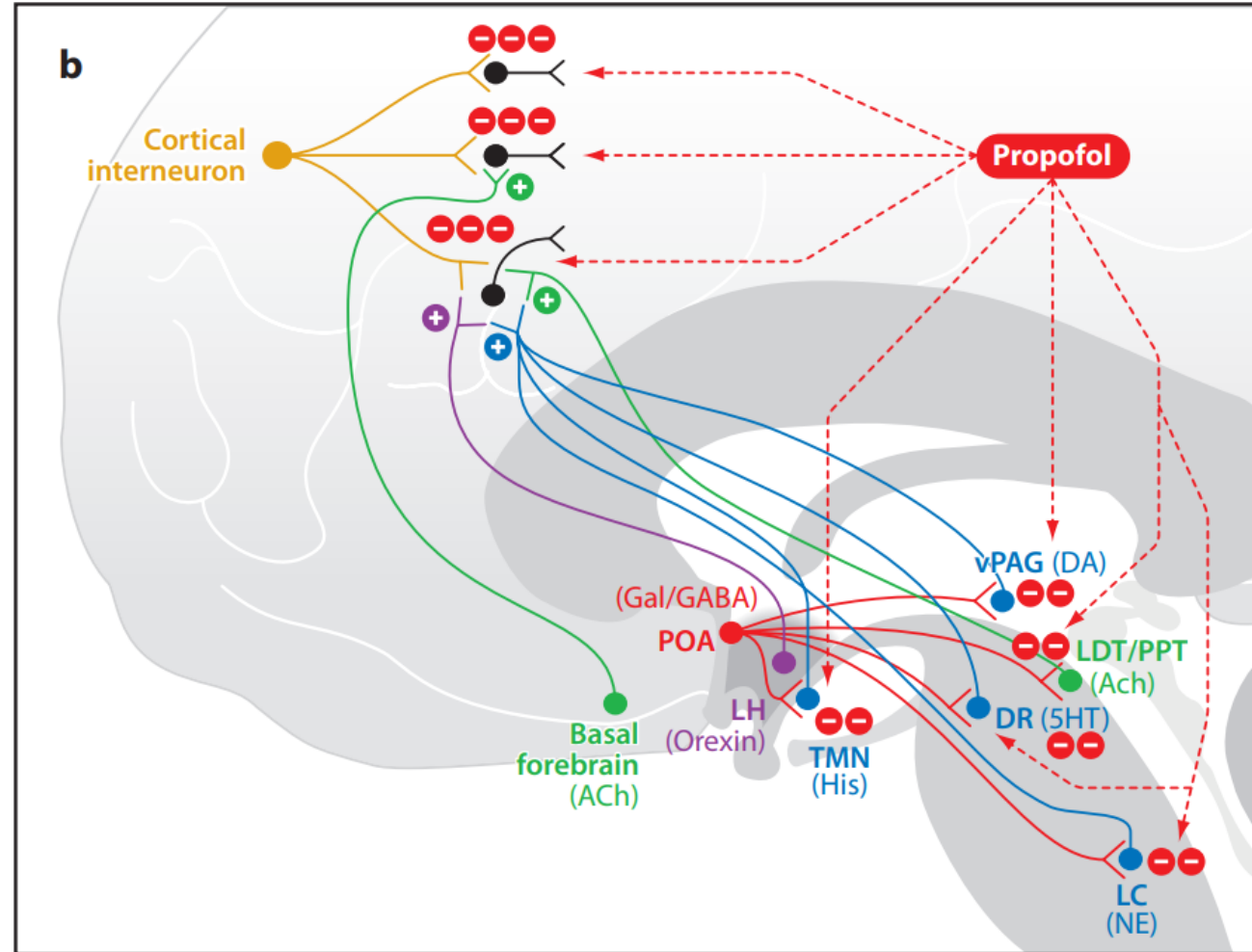


Image from (Brown et al., 2010)



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ANESTHESIA, CRITICAL CARE
AND PAIN MEDICINE

Conclusions

- Thalamus produces Sleep Spindles (8-16 Hz) via TC cell/RE cell interactions
- Propofol **Alpha Oscillations** likely come from thalamic Sleep Spindle mechanisms under enhanced GABA-A inhibition
- Propofol **Alpha** occurs at different **Slow Wave phases** depending on propofol dose (**Trough-** and **Peak-max**)
- Short-term coupling: thalamocortical synapses can exhibit **Trough-** or **Peak-max** depending on immediate cortical synchronization
- Long-term coupling: Acetylcholine effects on thalamocortical synapses bias system to either **Trough-** or **Peak-max**
- Email me at austin.soplata@gmail.com !



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Cycle-by-cycle coupling depends on cortical synchronization and feedback

