Thalamocortical phase-amplitude coupling under propofol anesthesia

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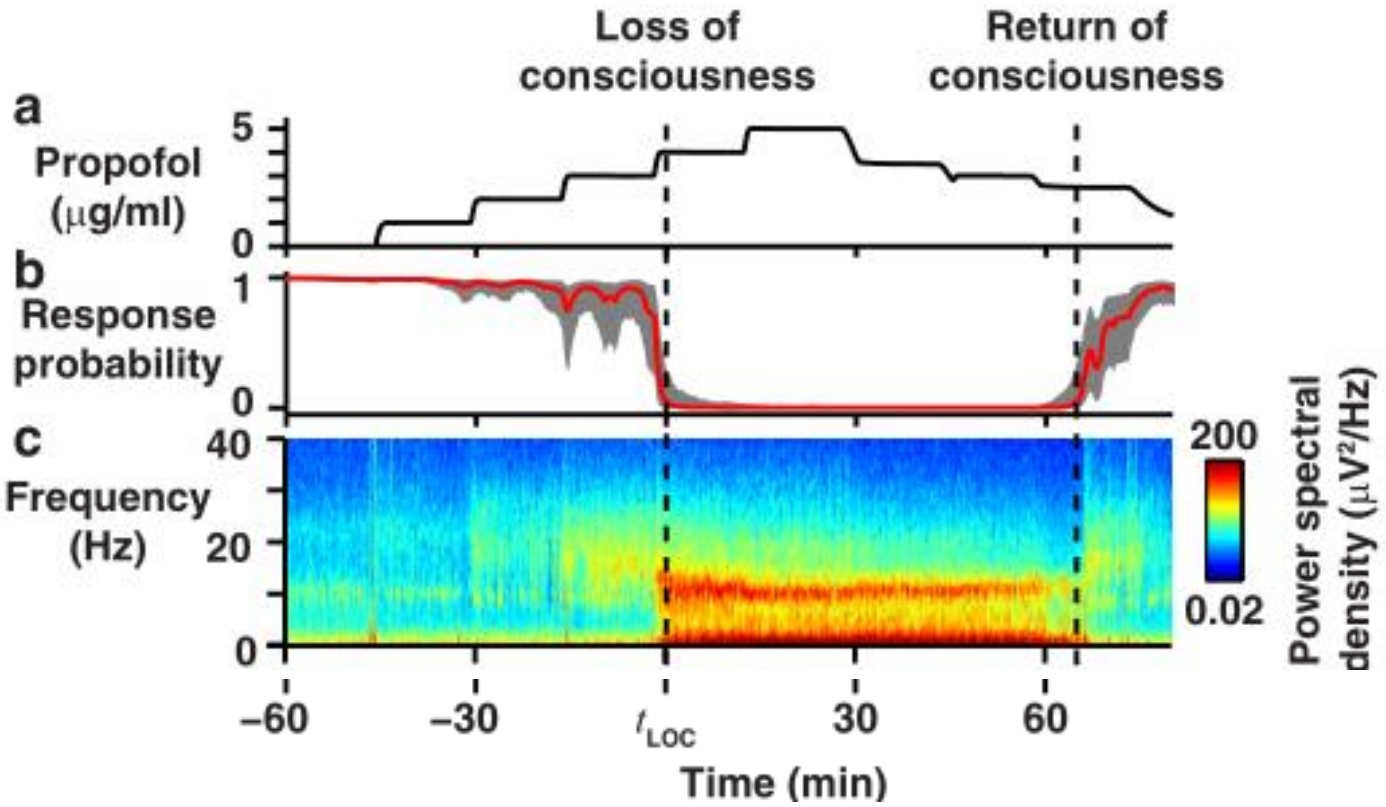
Collaboration with Nancy Kopell lab at BU

20 April 2022

Understanding propofol anesthesia via EEG oscillations



- How can functionally significant propofol coupling occur in a dose-dependent manner?
  - What causes Alpha Oscillations (8-14 Hz) in propofol anesthesia?
  - What causes Slow Wave Oscillations (SWO, 0.5-2 Hz) in propofol anesthesia?
  - What causes Trough-max and Peak-max Phase-Amplitude Coupling between alpha and SWO?

Image from (Mukamel et al., 2014)

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

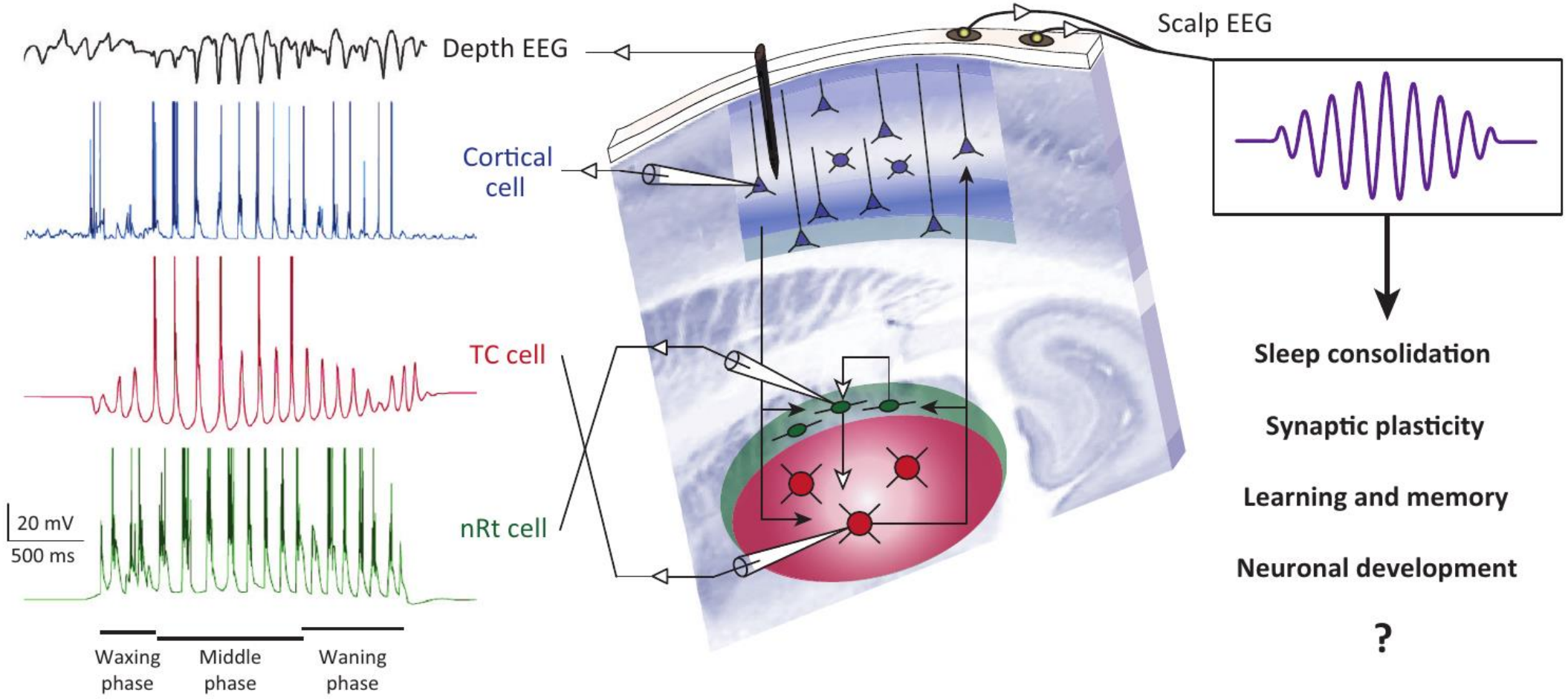
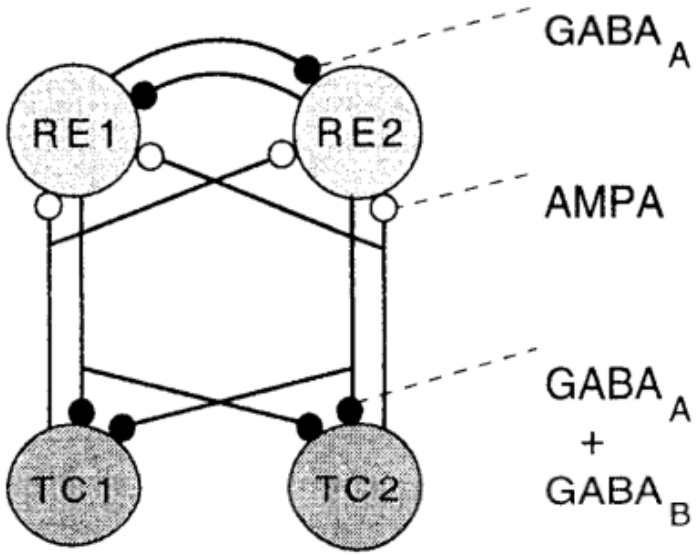
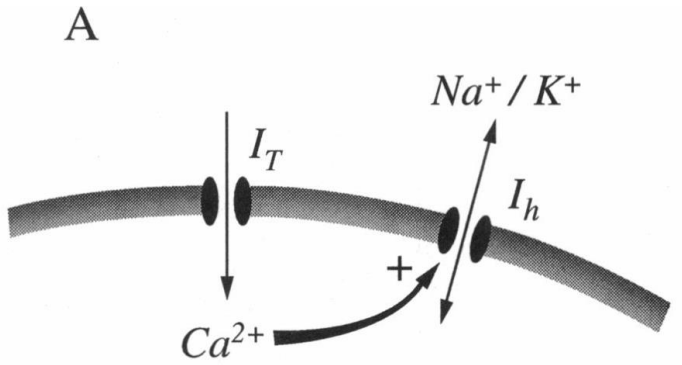


Image from (Astori et al., 2013)

Destexhe Model of Thalamic Spindles

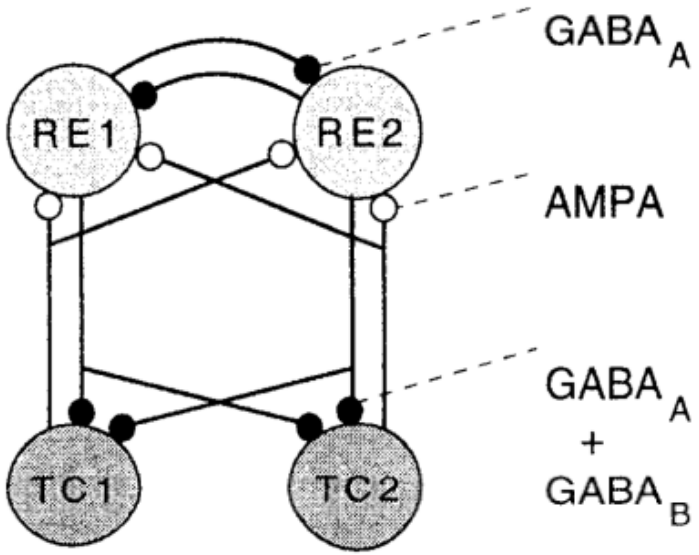


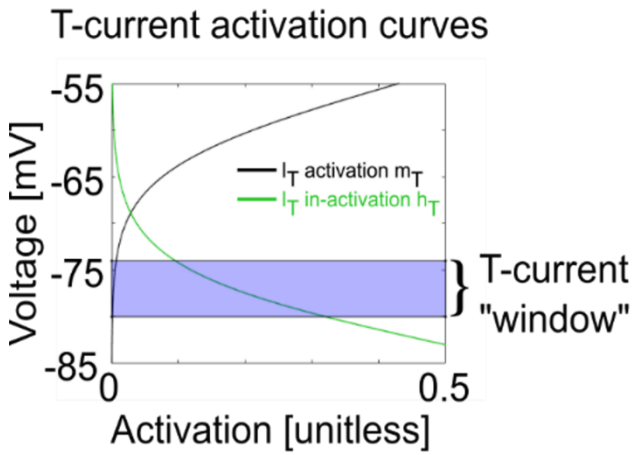


$$C_m \dot{V}_T = -g_L(V_T - E_L) - I_T - I_h - I_{KL} - I_{Na} - I_K - I_{GABA_AT} - I_{GABA_B} \quad (1)$$

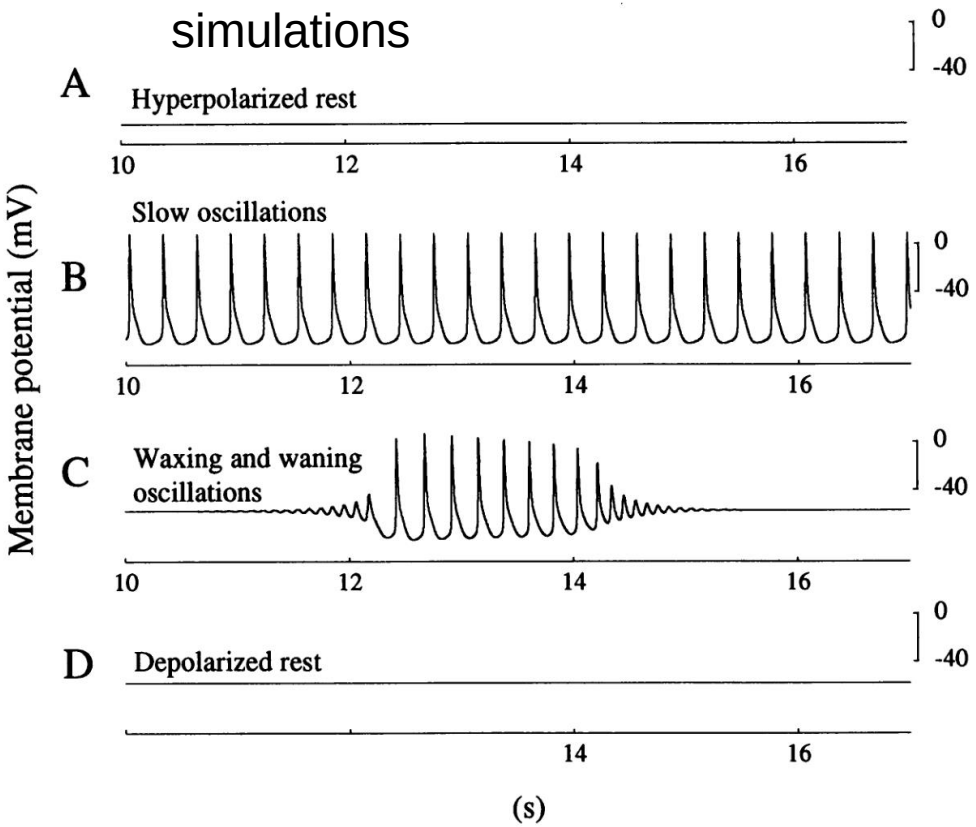
Images from (Destexhe et al., 1996 and 1993)

Destexhe Model of Thalamic Spindles





Different H-current simulations



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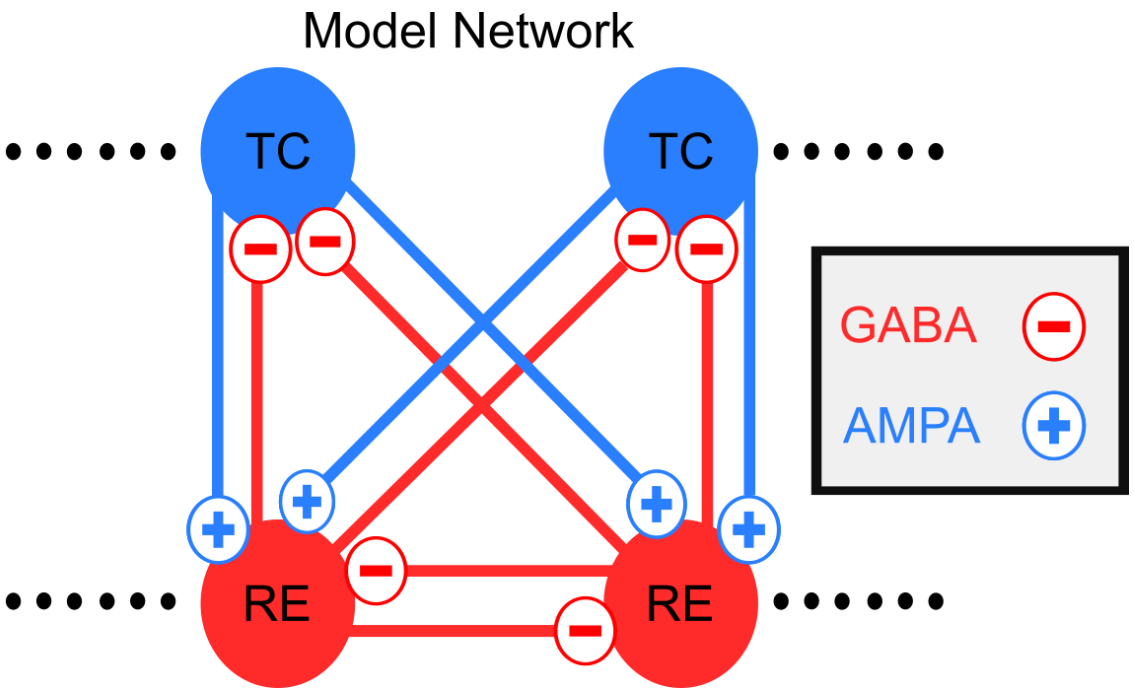
Images from (Destexhe et al., 1996 and 1993)

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

Images hereon from (Soplata et al., 2017), unless otherwise indicated

frontiers in Neuroinformatics

METHODS
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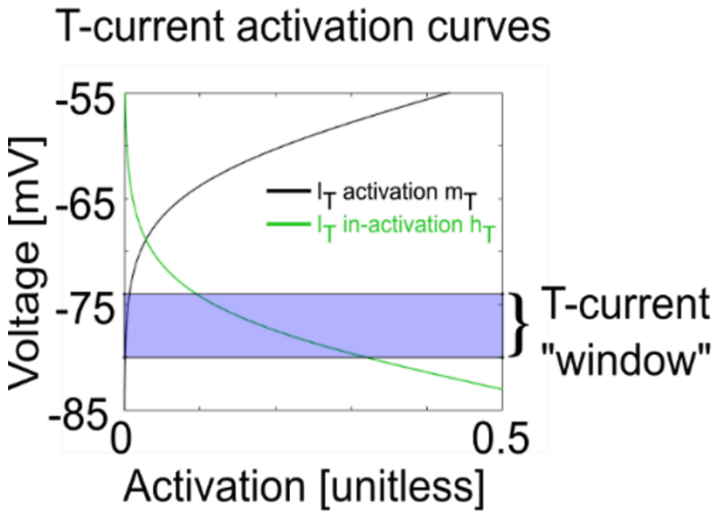
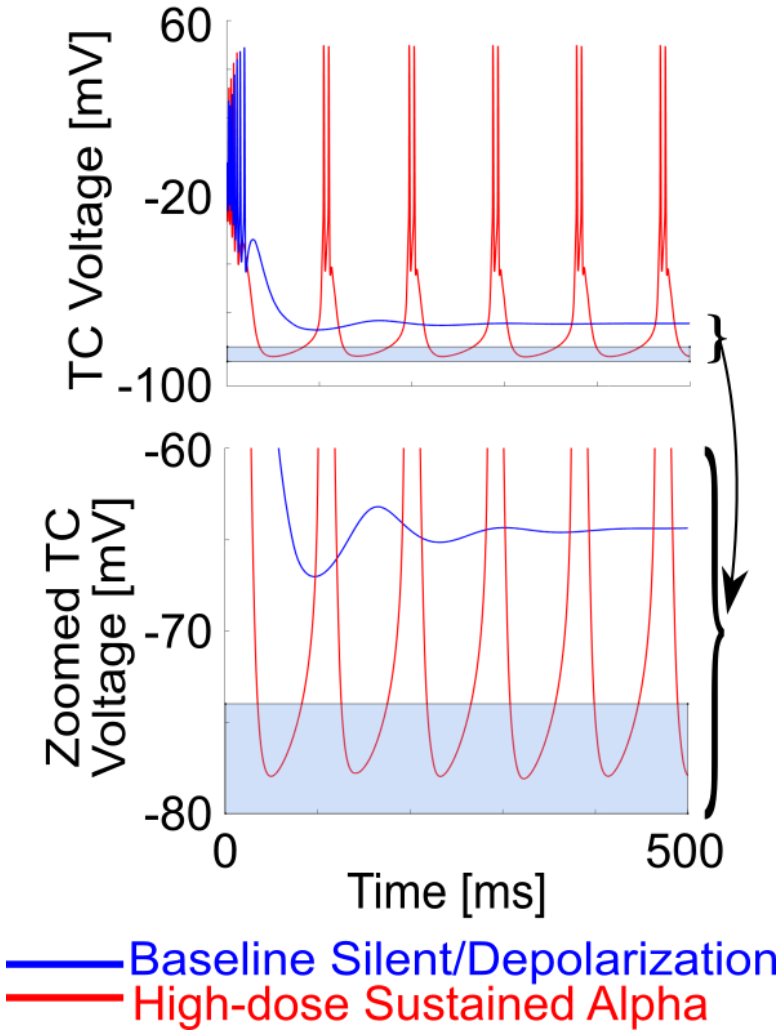
DynaSim: A MATLAB Toolbox for Neural Modeling and Simulation

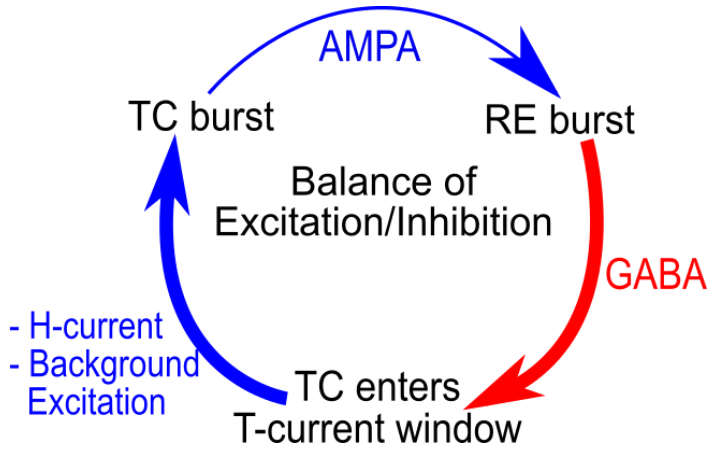
Jason S. Sherfey[1,2], Austin E. Soplata[3], Salva Ardid[1], Erik A. Roberts[4], David A. Stanley[1], Benjamin R. Pittman-Polletta[1] and Nancy J. Kopell[1]*

- Easy vectorization of ODEs
- Plug-and-play mechanism functionality like NEURON MOD files
- Built-in parameter grid search and batch job submission on clusters/HPC

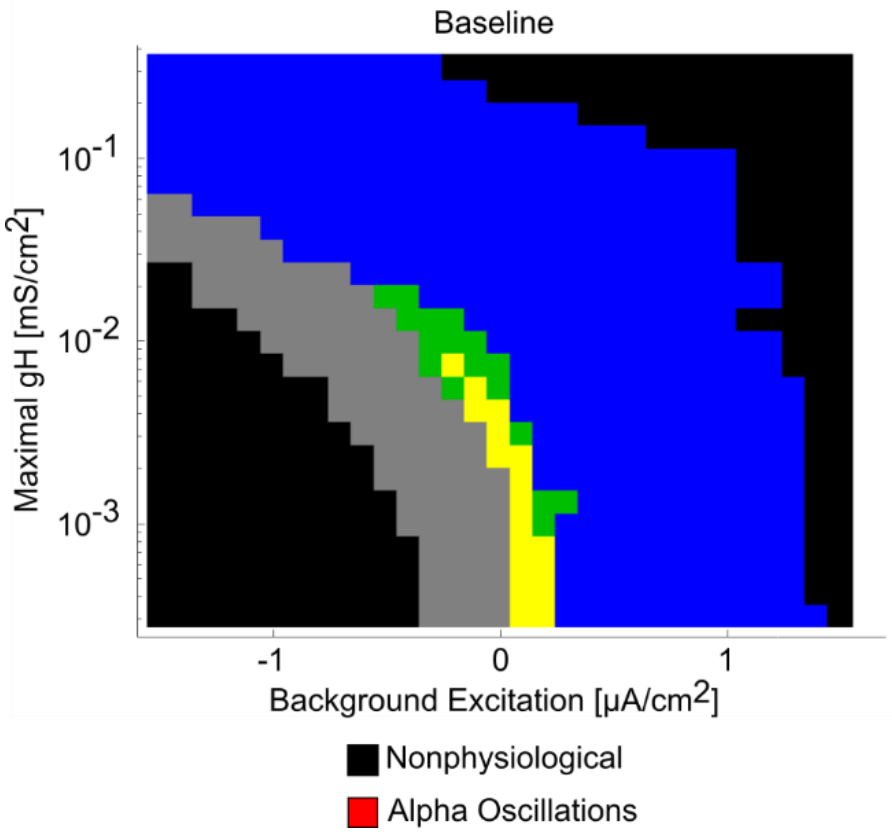
Enhanced $GABA_A$ inhibition enables Alpha

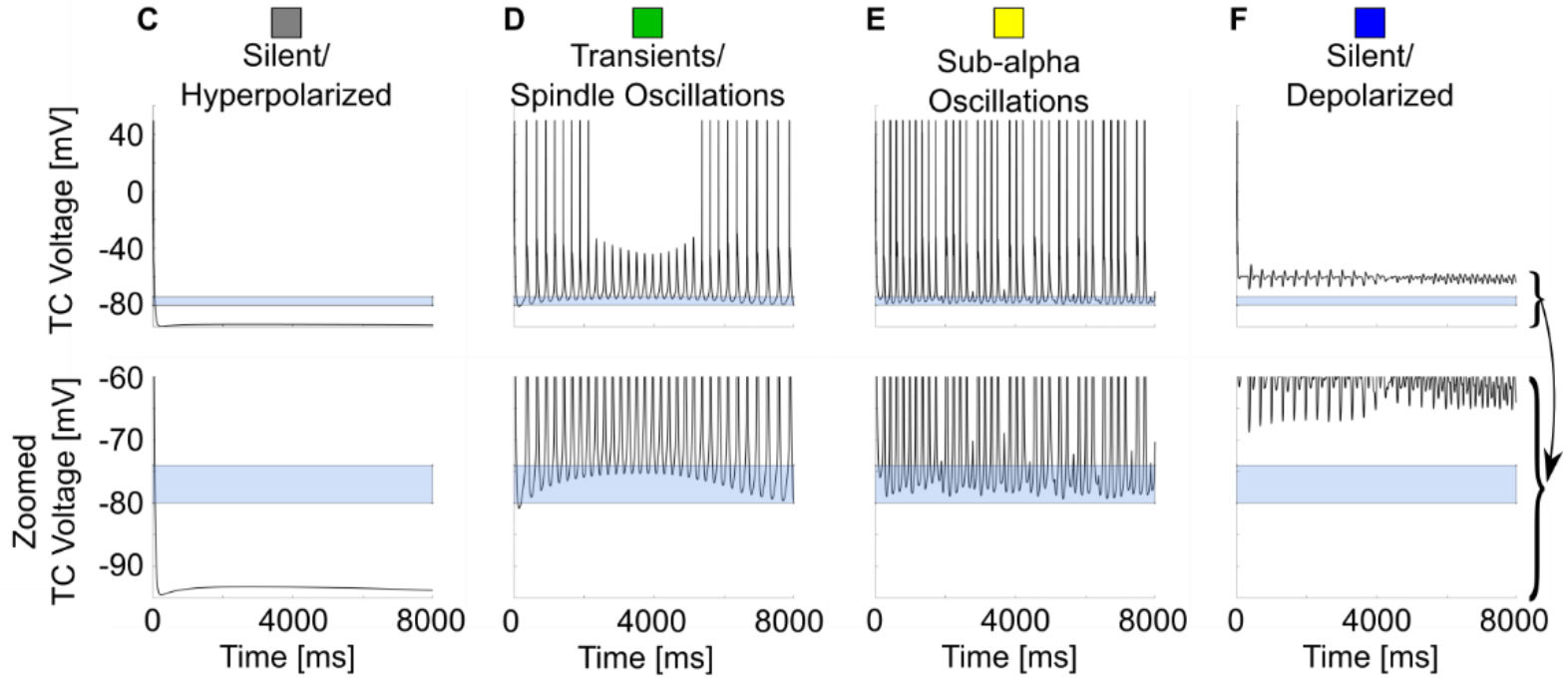




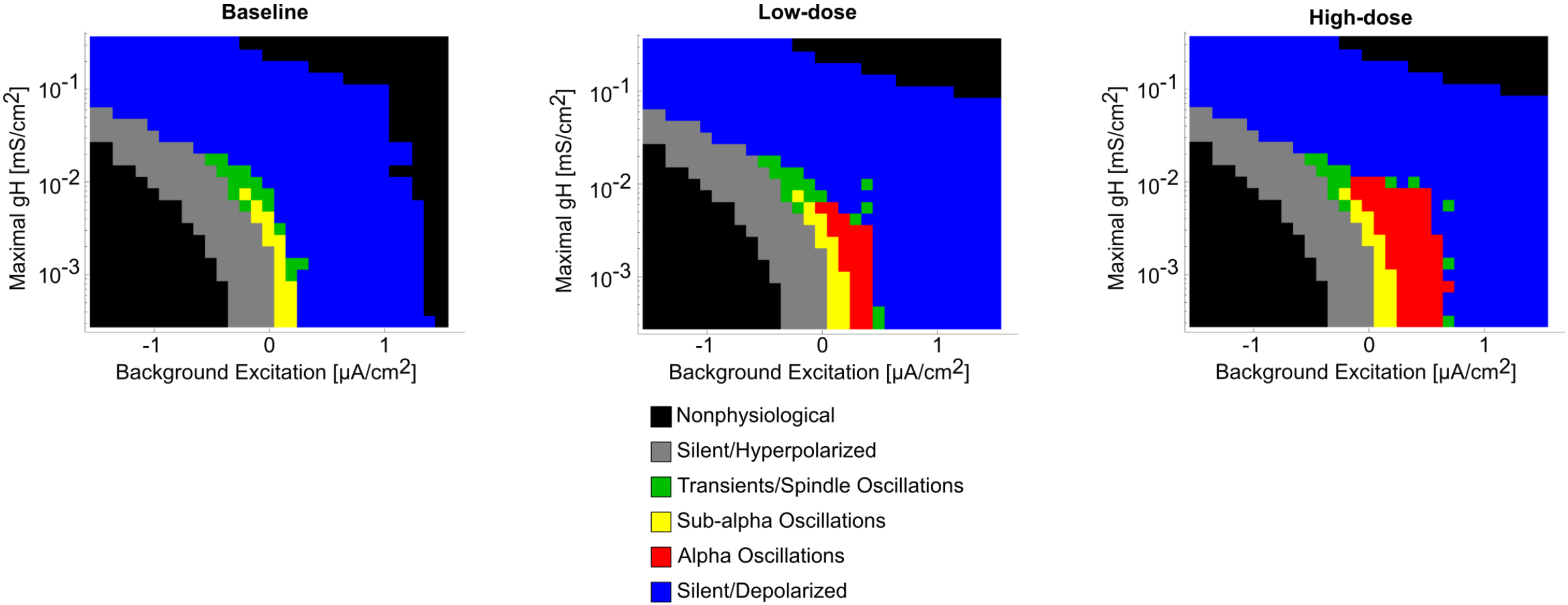


Can we get propofol-like Alpha without GABA enhancement? **No!**

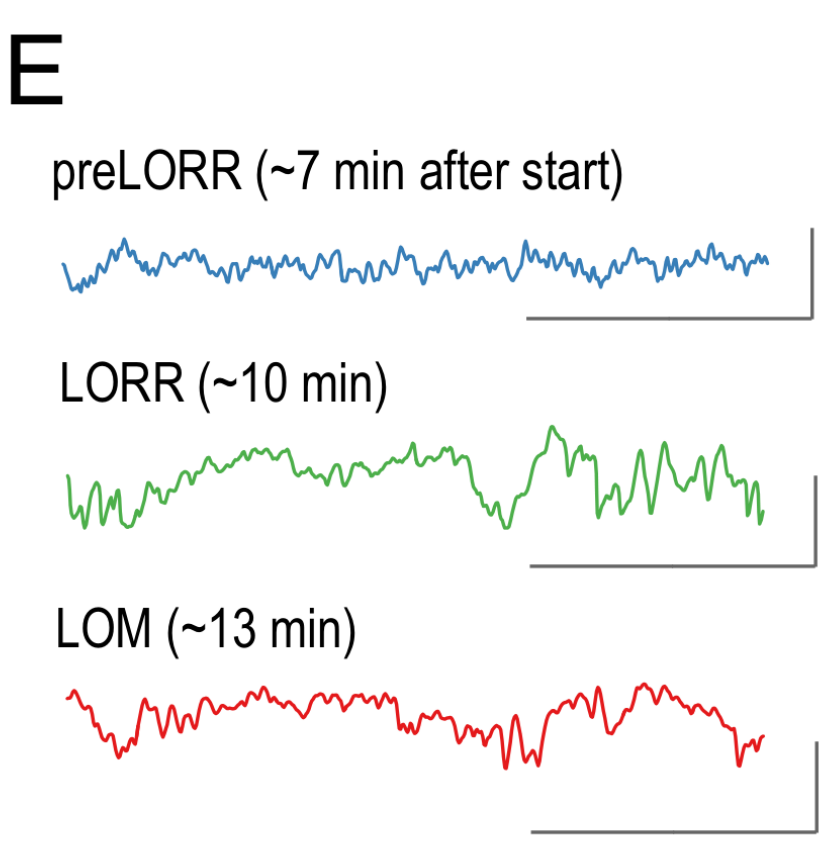




Propofol changes to GABA-A **and H-current** affect the likelihood of Alpha



Experimental evidence: Propofol Alpha occurs in rat cortex and higher-order thalamus LFP



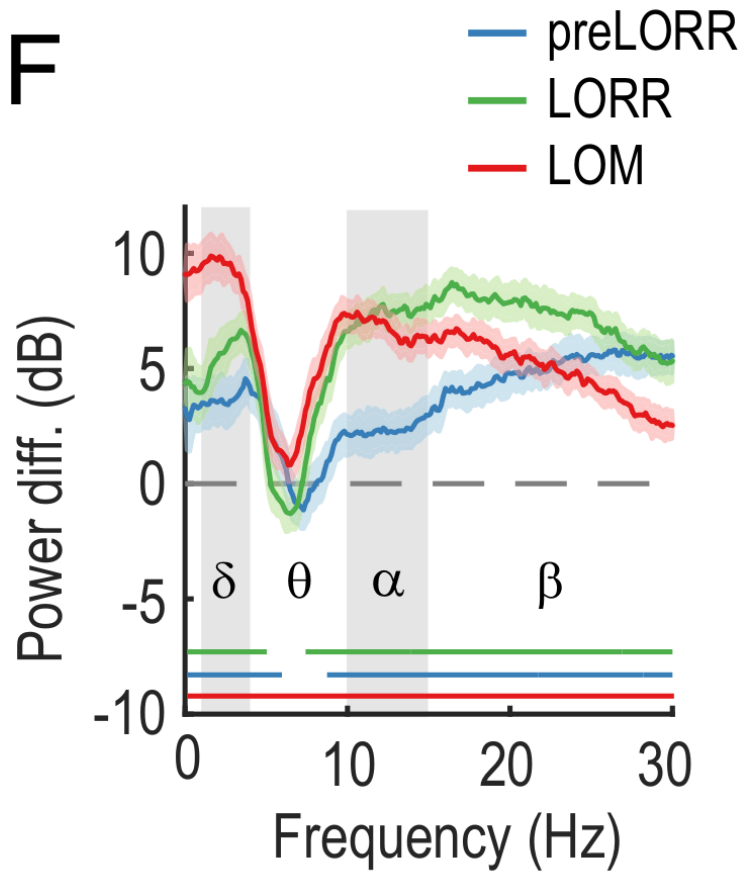


Image from (Flores et al., 2017)

Understanding propofol anesthesia via EEG oscillations

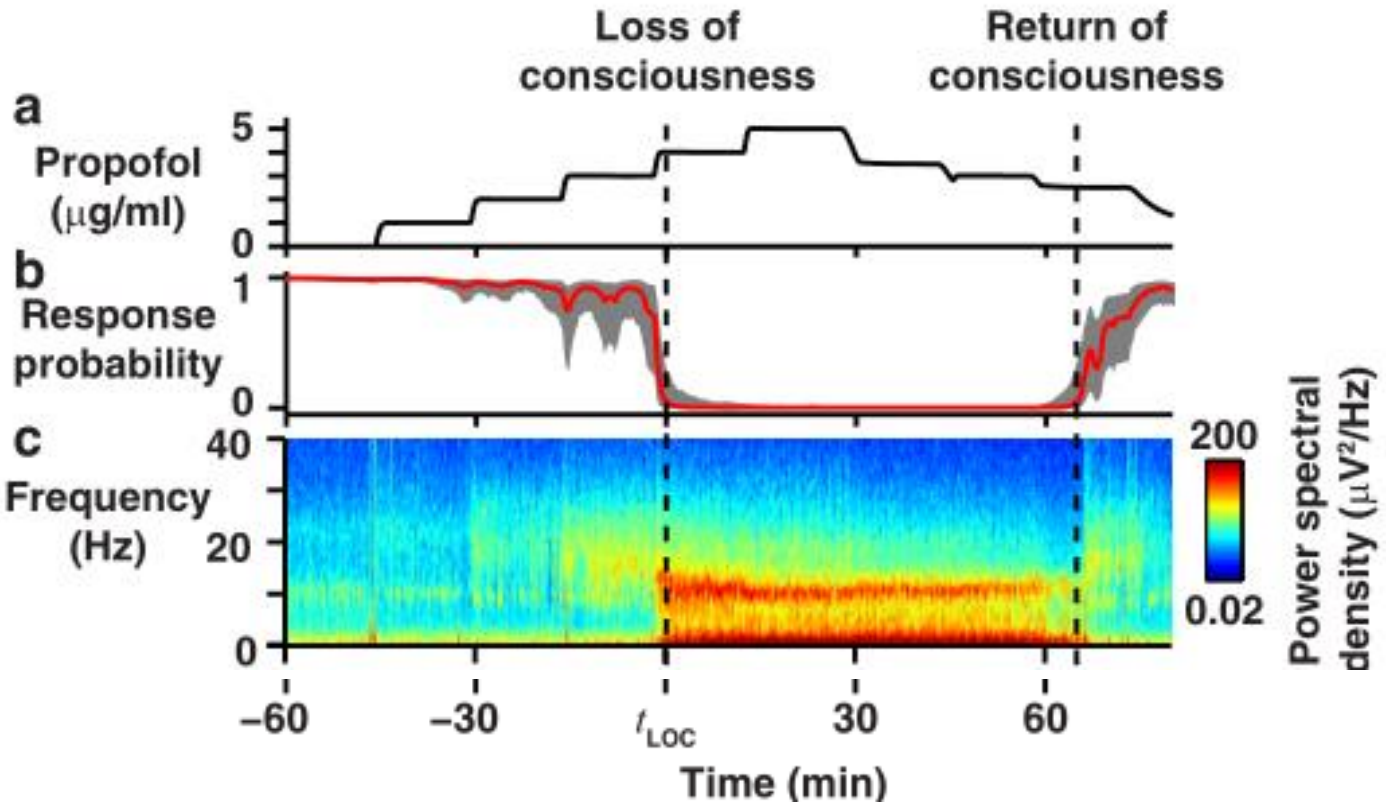


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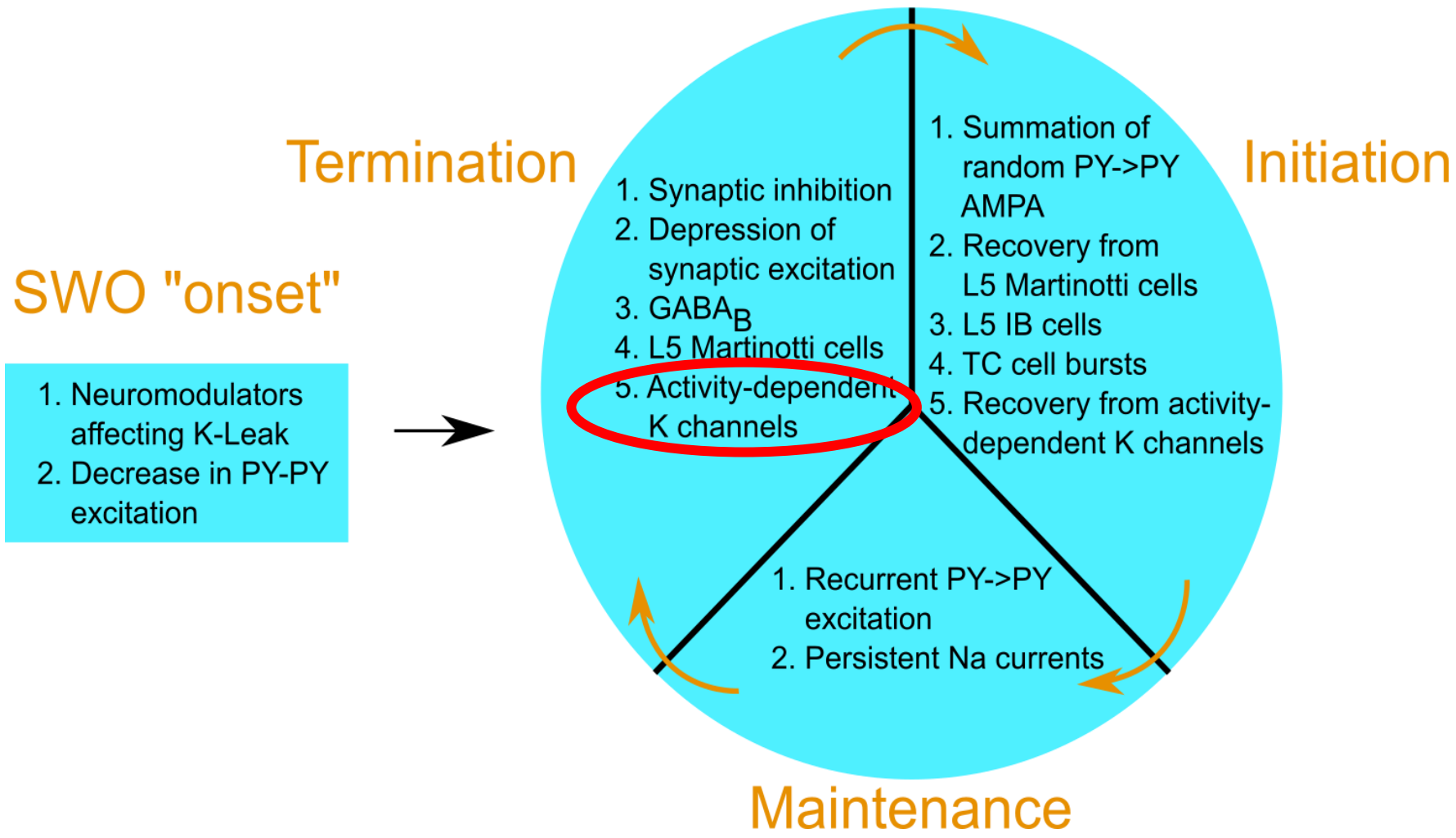
Image from (Mukamel et al., 2014)

Slow Wave Oscillation Mechanisms



Cortical Slow Wave Mechanism: K(Na)-current

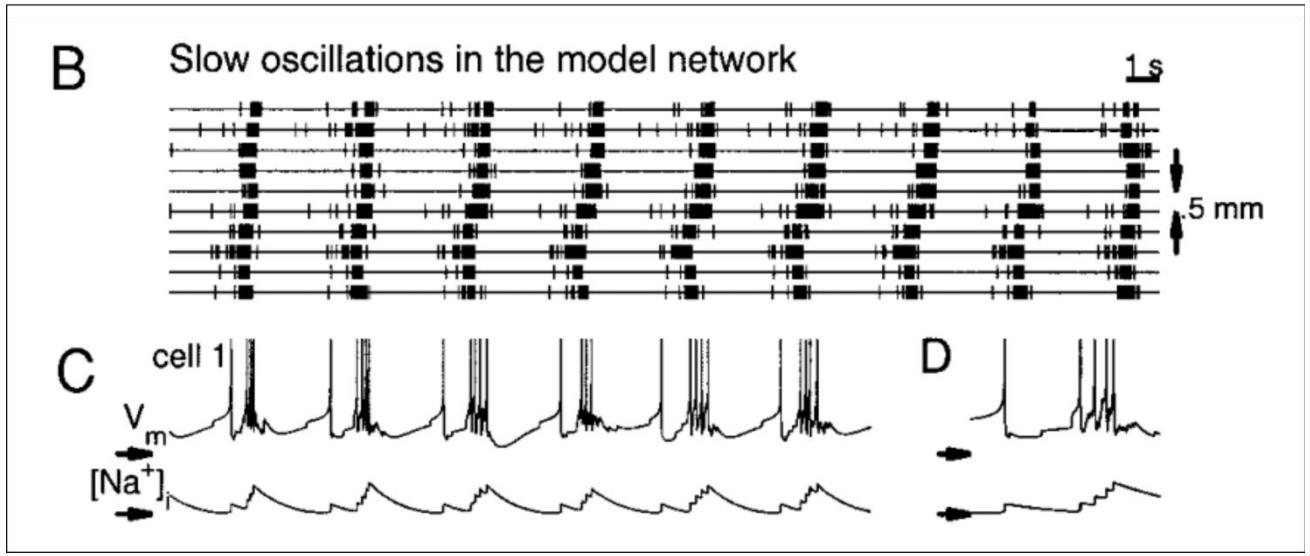


Image from (Compte et al., 2003)

Slow K(Na) cycle:

1. Random excitation triggers cortical PY UP state
2. Internal [Na+] builds up
3. High [Na+] triggers hyperpolarizing K(Na)-current
4. K(Na)-current terminates PY UP state and forces DOWN state
5. Internal [Na+] decays, disabling K(Na)-current

Simulated Circuit Model Network

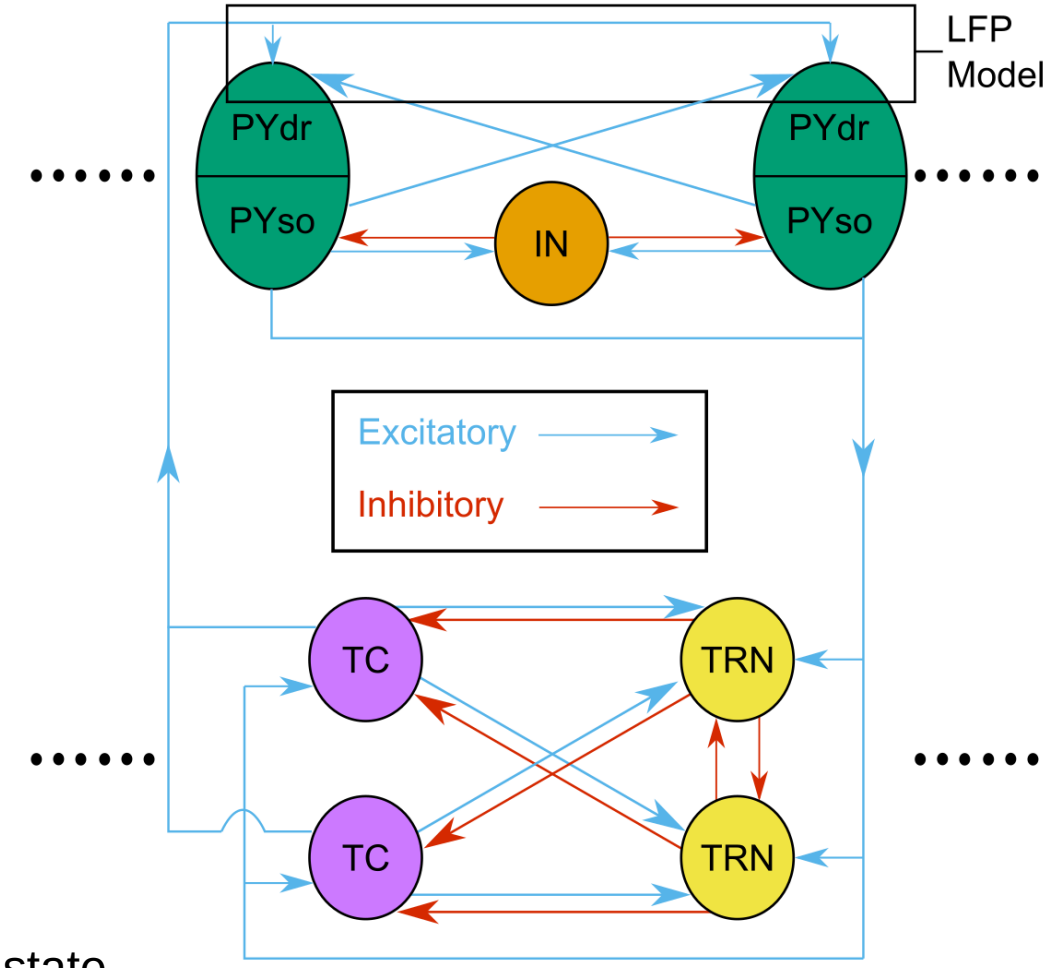


Image from (Soplata et al., 2022)

Understanding propofol anesthesia via EEG oscillations

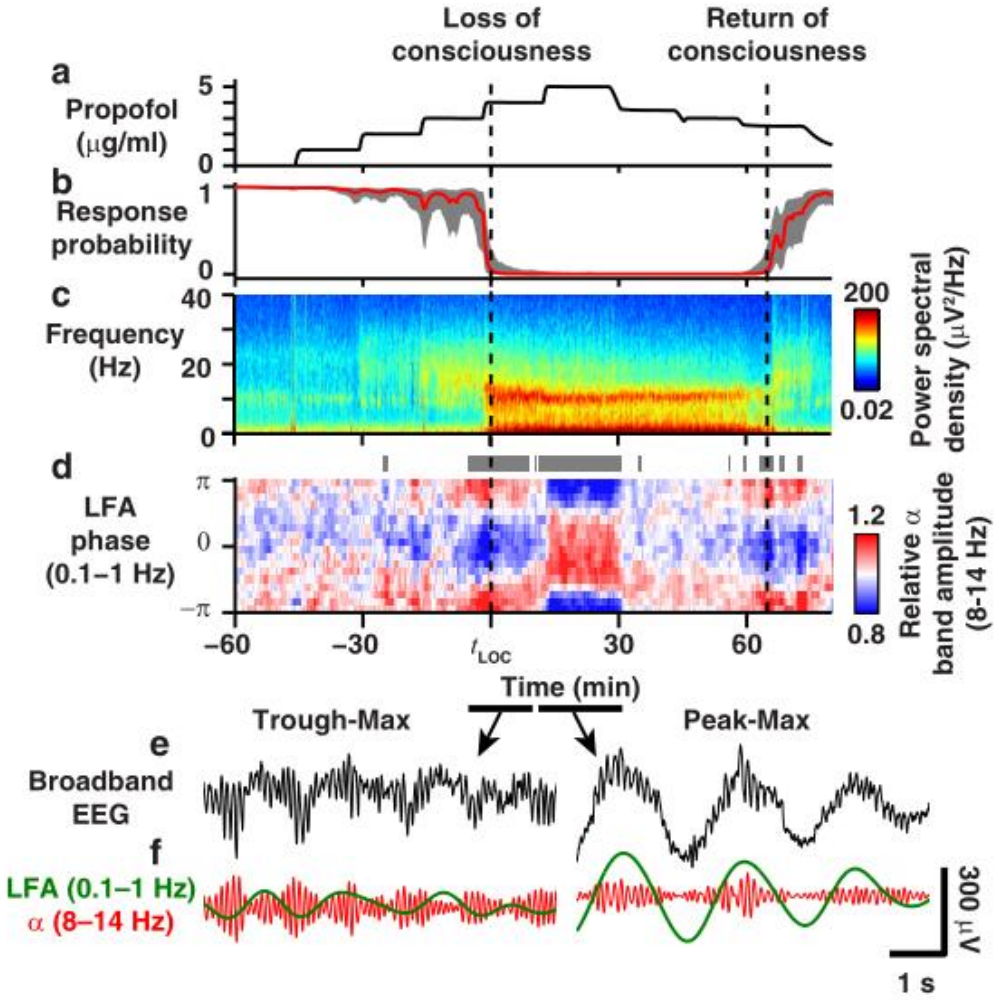


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Image from (Mukamel et al., 2014)

Propofol GABA-A and H-current effects were insufficient -- Need ACh!

- Propofol Direct Effects:
  - Potentiates GABA-A
  - Decreases H-current strength

- Propofol INDIRECT Effects:
  - Decreases ACh, causing:
    - Increased **K(Na)-current** strength
    - Synaptic effects, which I'll get to later

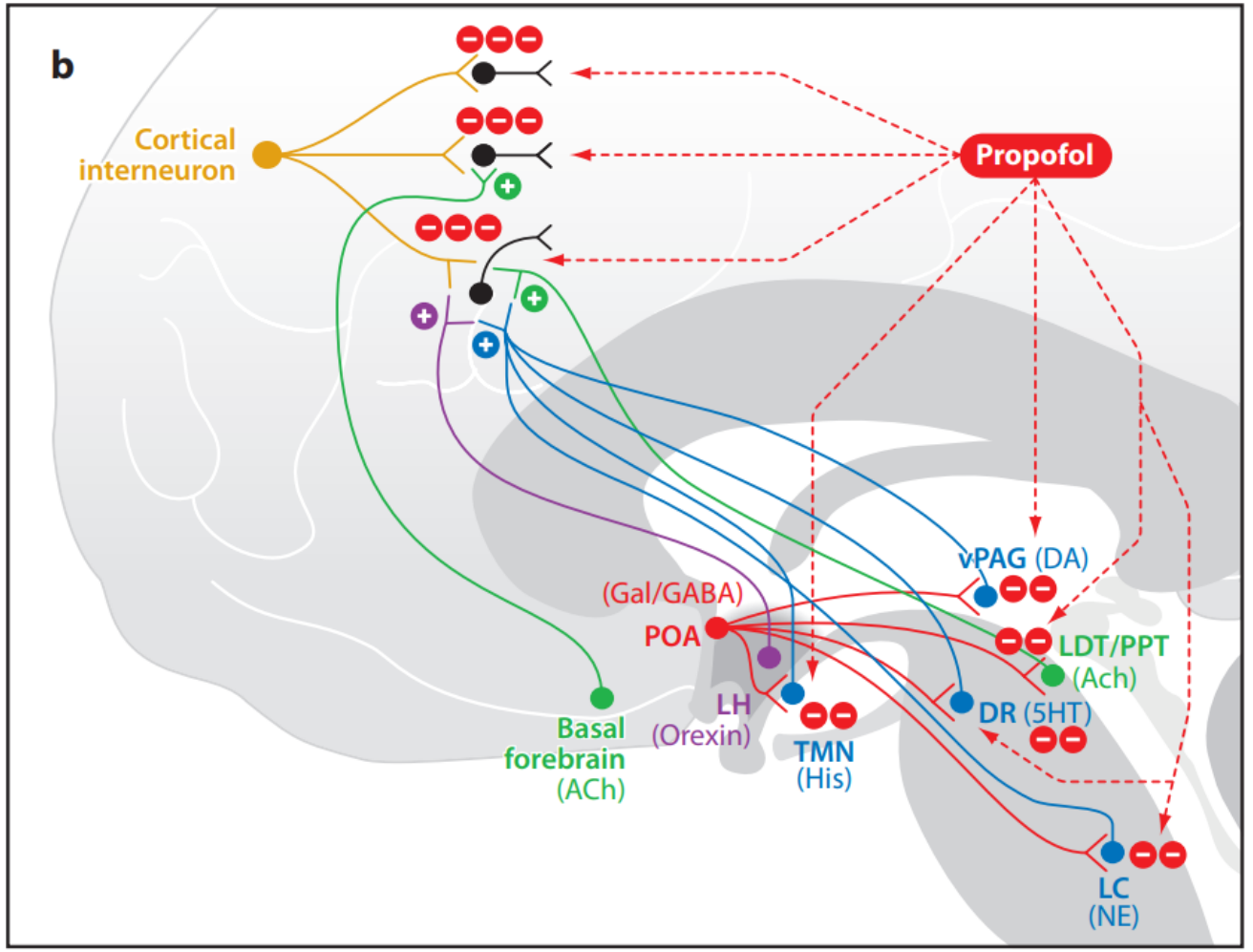
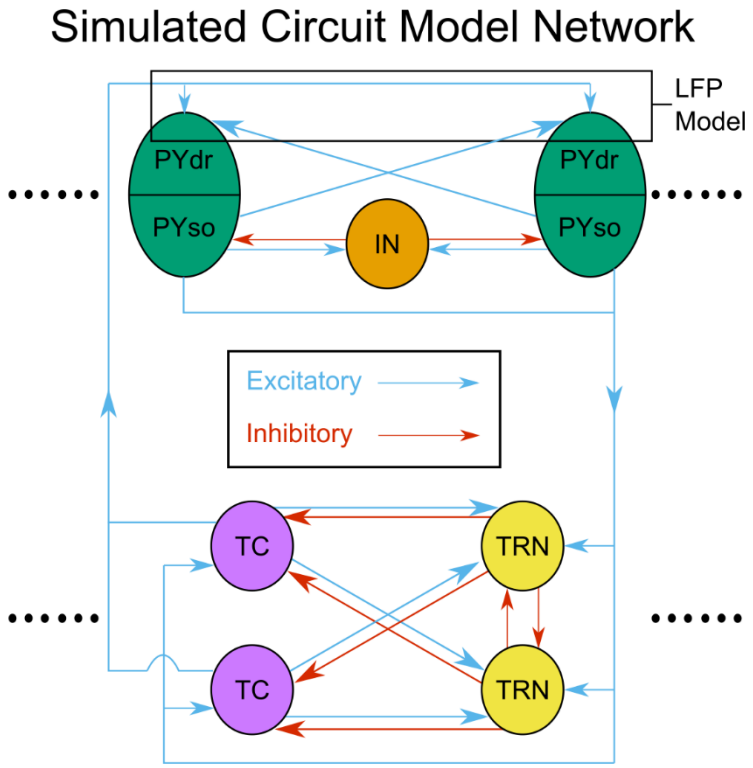
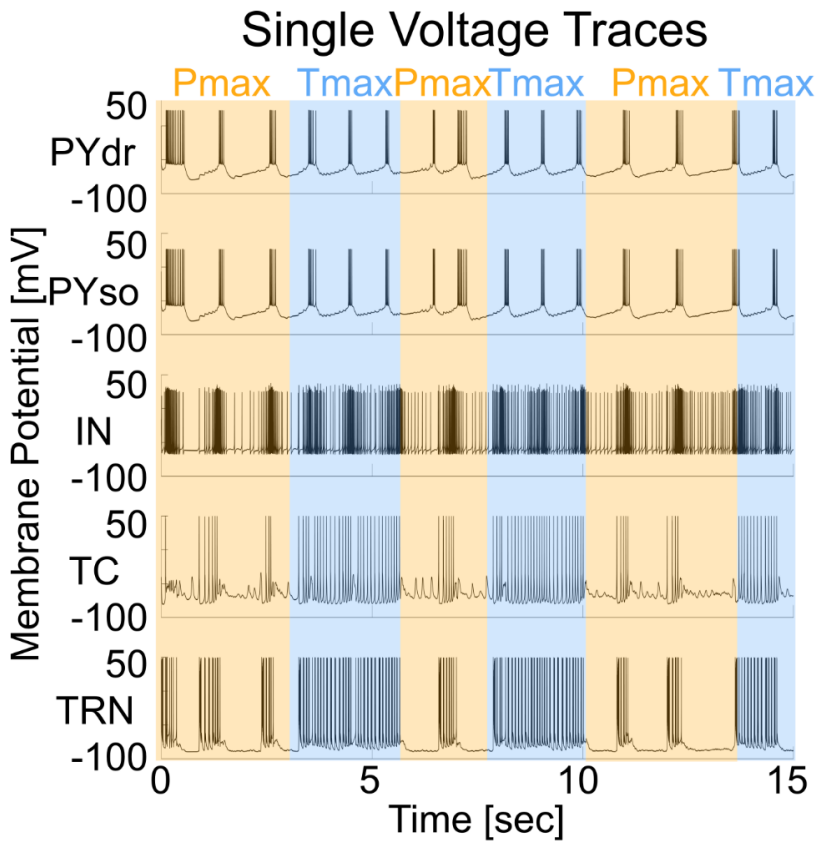
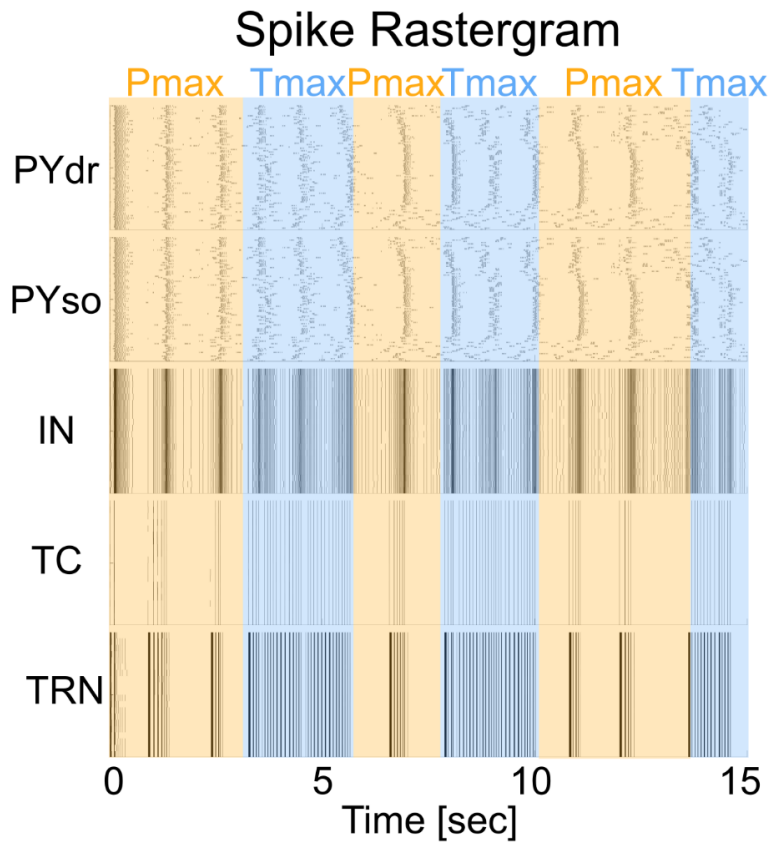


Image from (Brown et al., 2011)

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







Trough-max Phase-amplitude Coupling (Tmax)

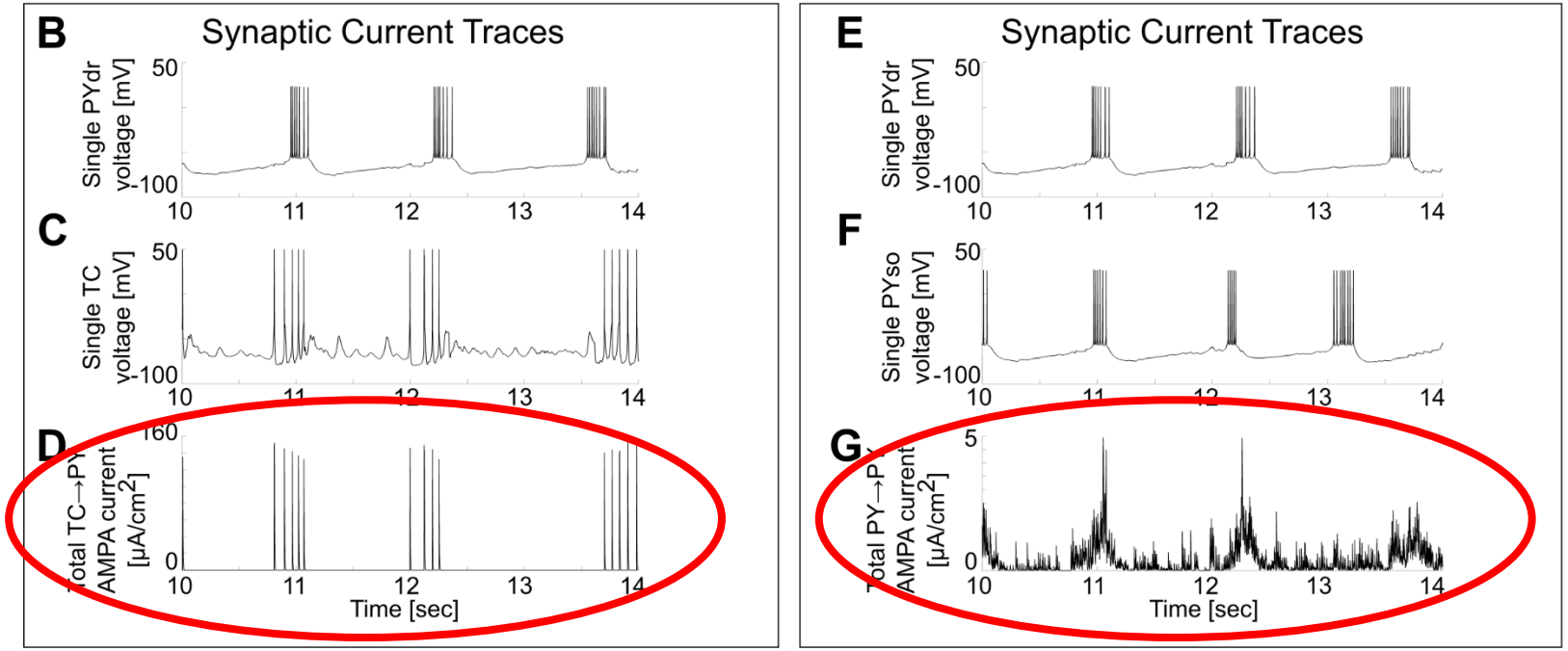
Peak-max Phase-amplitude Coupling (Pmax)

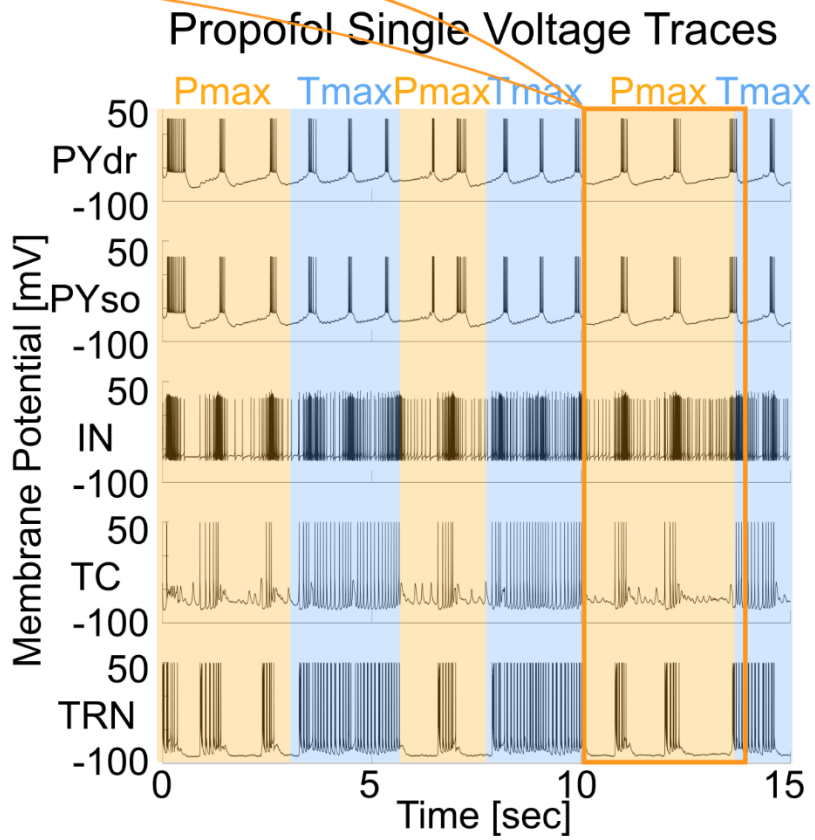
Images hereon from (Soplata et al., 2022), unless otherwise indicated

Peak-max occurs at all cortical synaptic currents

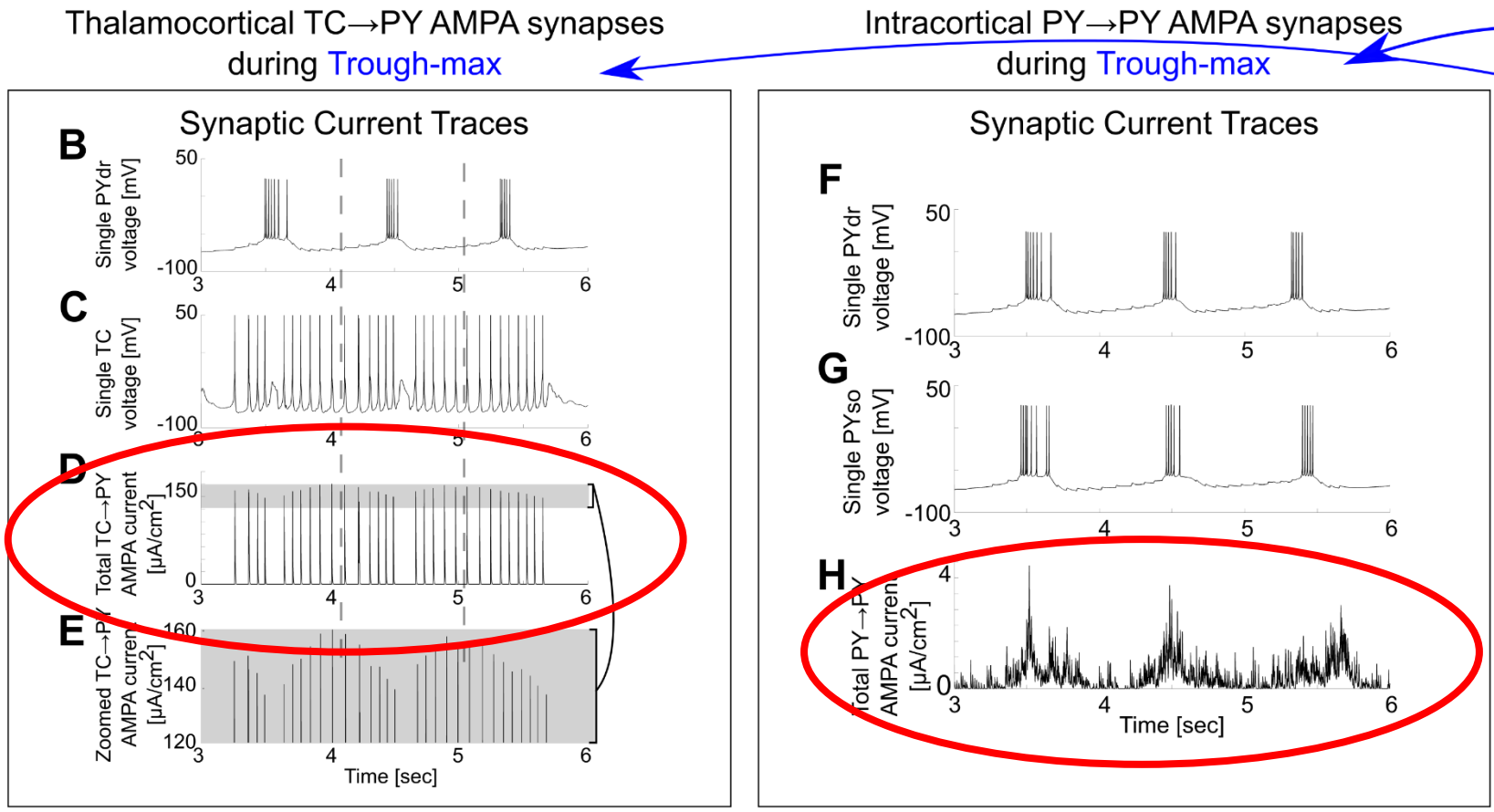
Thalamocortical TC→PY AMPA synapses during Peak-max

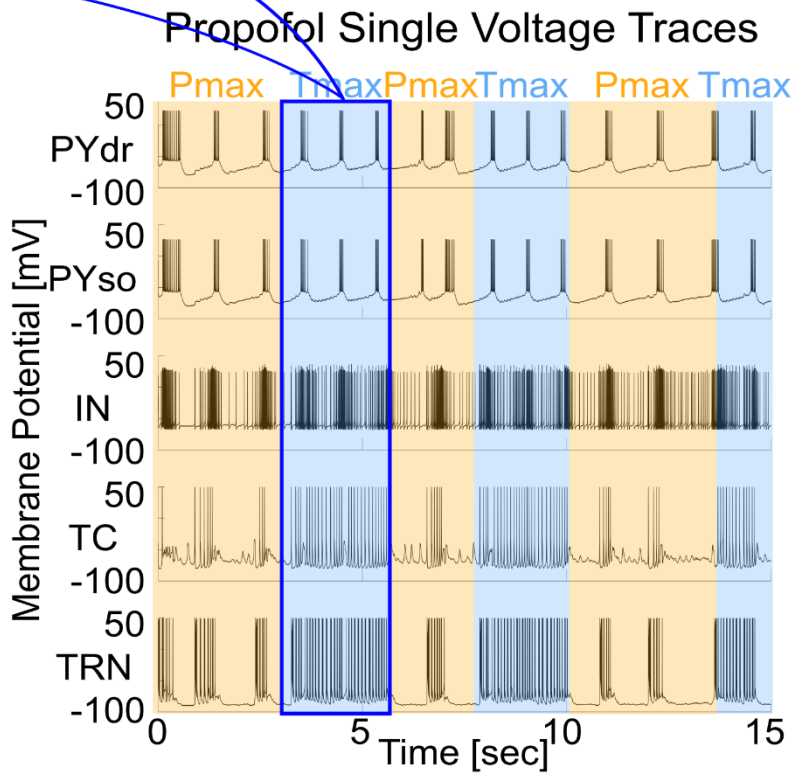
Intracortical PY→PY AMPA synapses during Peak-max





Trough-max occurs at TC->PY synaptic currents





Model coupling resembles experimental data, but at much faster different timescale

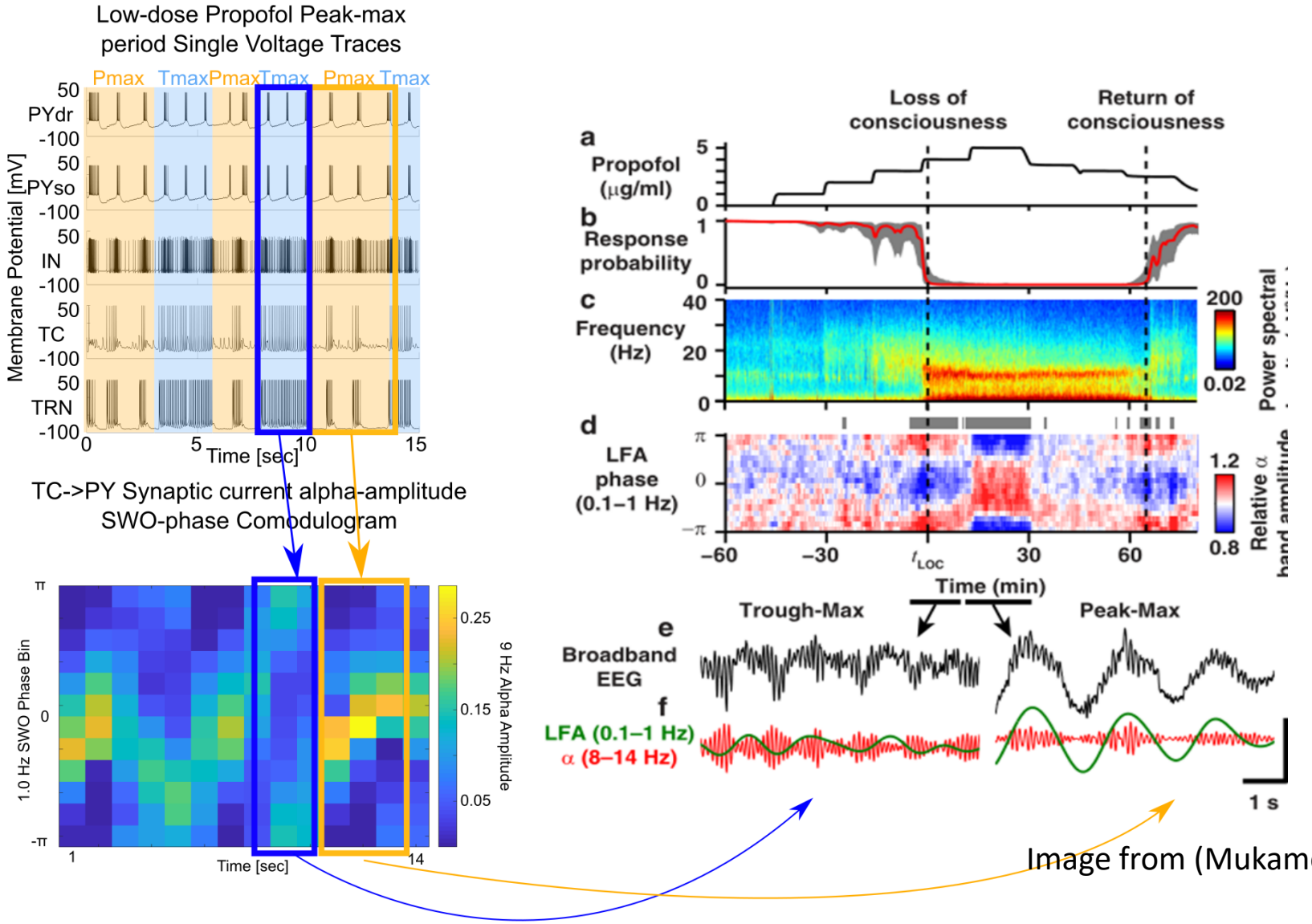
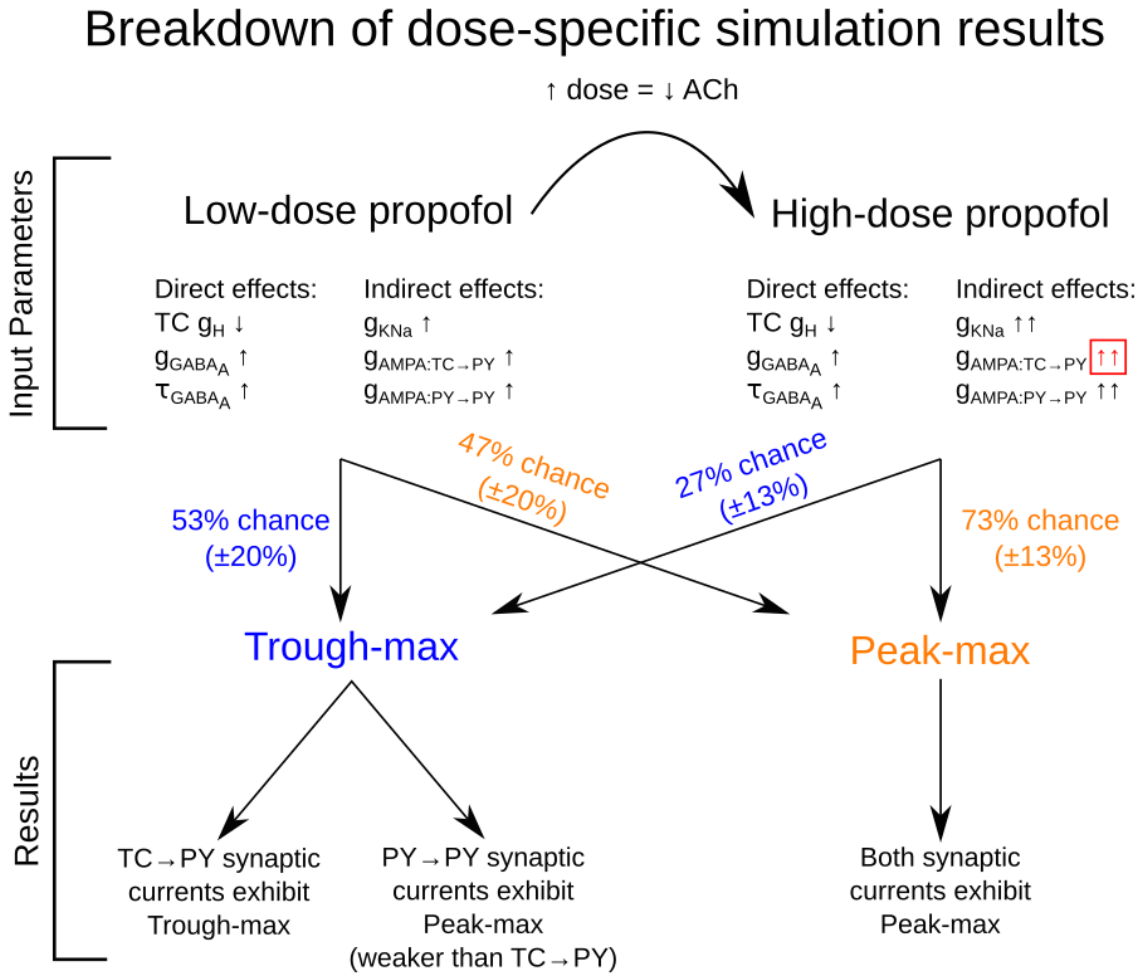


Image from (Mukamel et al., 2014)

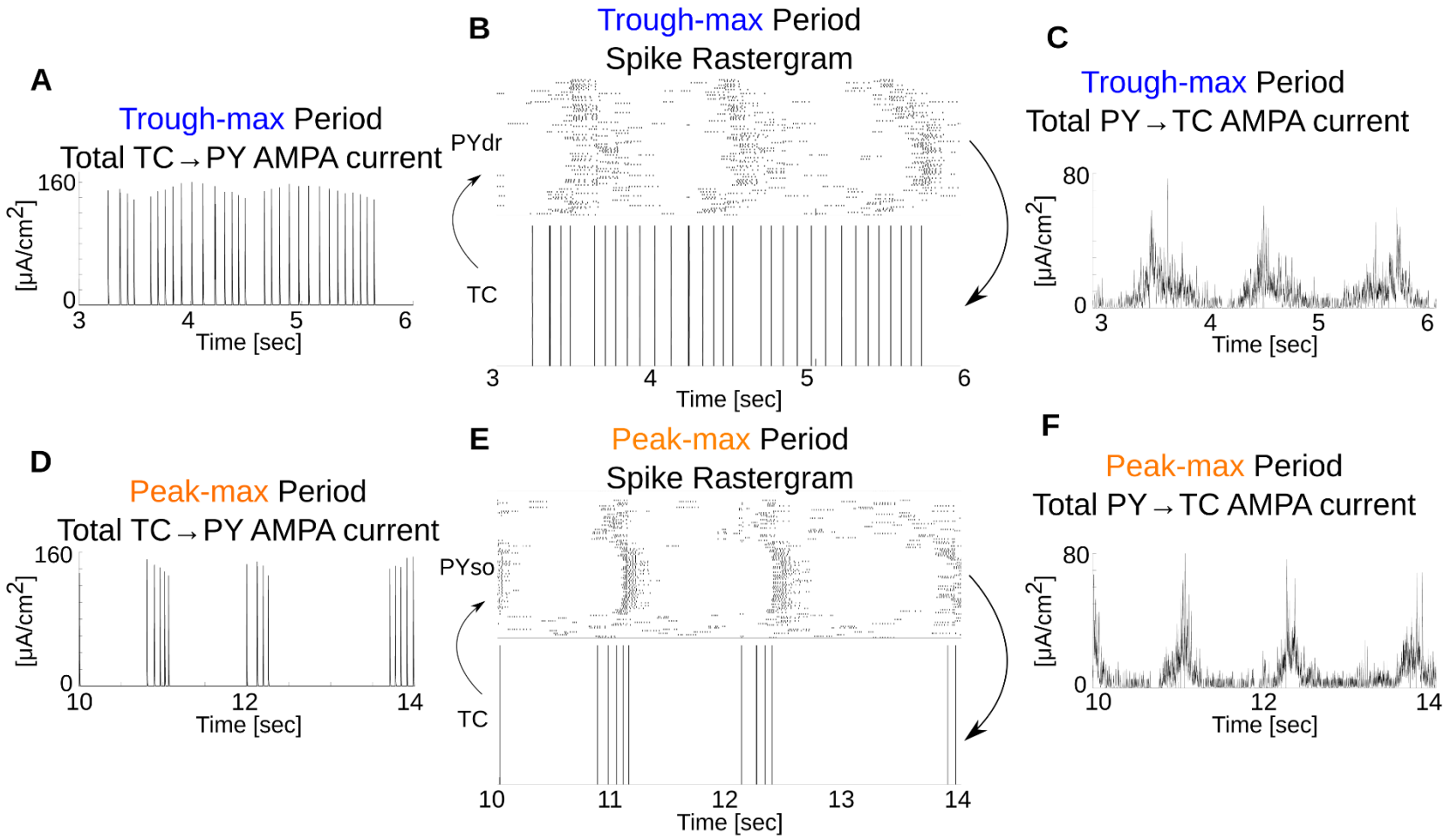
Dose-dependent ACh changes increase chance of Peak-max coupling

- Propofol Direct Effects:
  - Potentiates GABA-A
  - Decreases H-current strength

- 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



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



Conclusions

- In prior EEG experiments, Propofol Alpha amplitude is differentially coupled to Slow Wave phases: Trough-max at low dose / sedation, while Peak-max at high doses / deep unconsciousness.

- Propofol Alpha Oscillations may arise from thalamus due to effects on GABA-A and H-current.

- In local cortical networks, Trough-max vs Peak-max coupling may fluctuate very quickly, across individual Slow cycles.

- Decreasing ACh led to our local networks exhibiting more Peak-max than Trough-max due to **increased cortical firing synchronization**. Implications:
  - Peak-max preference may indicate too much cortical synchronization for local processing and long-range communication in deeper anesthesia.
  - May explain why age-related ACh decline correlates with increased anesthesia sensitivity
  - May explain why ACh agonism can reverse propofol anesthesia (e.g. physostigmine)
- Questions? Email me at austin.soplata@gmail.com! Website QR code:

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Additional figures