Computational modeling of cortical transition to slow wave oscillations modulated by K-ATP current

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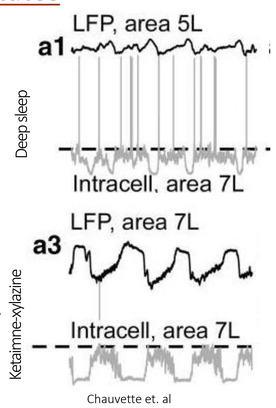
Introduction: The occurrence of slow wave oscillations is modulated by neuron metabolism.

Slow wave oscillations (SWO) occur in unconscious states

During **states of unconsciousness**, networks of neurons in the brain demonstrate **periods of high-frequency activity interspersed with periods of quiescence** which gives rise to slow wave oscillations (SWO).



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What mechanisms underlie the generation of slow wave oscillations observed under anesthesia?

Activity dependant ATP-modulated potassium (K_{ATP}) current has been implicated in SWO generation

In-vitro studies demonstrate that slow wave oscillations may be a consequence of interactions between neuronal **network-mediated mechanisms** and neuronal **metabolism-related mechanisms**. (2)

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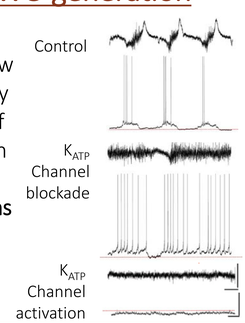
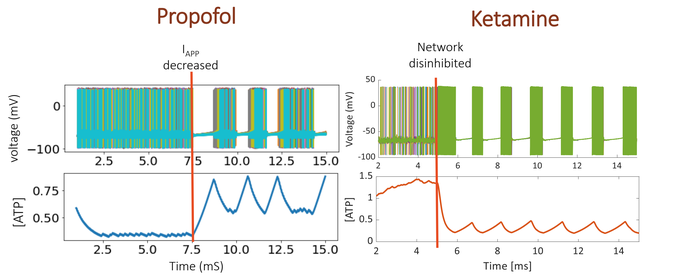


Networks oscillate at high and low excitation states



SWO occur at both high and low I_{APP}, but not at mid-ranges.

How are up- and down-states initiated when the K-ATP current is present?

METHOD: Hodgkin-Huxley based modeling

Neurons:

The change in neuron voltage (V_m) over time is modeled by:

$$C\frac{dV_m}{dt} = -I_{Na} - I_K - I_{K_{ATP}} - I_{leak} - I_{AMPA} - I_{GABA} + I_{app}$$

C=capacitance
$I_{Na}, I_K, I_{K_{ATP}}, I_{leak}$= membrane currents
I_{AMPA}, I_{GABA}= synaptic current
I_{app}= applied current

K_{ATP} current:

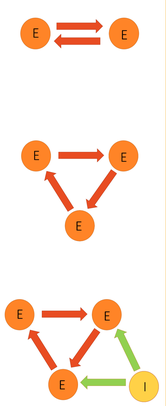
We add the additional K_{ATP} current [3]:

$$\frac{d[Na^+]_i}{dt} = FI_{Na,i} - 3K_m[Na^+]_i^3[ATP]_i$$

$$\frac{d[ATP]_i}{dt} = K_{prod}([ATP]_{max} - [ATP]_i) - K_m[Na^+]_i^3[ATP]_i$$

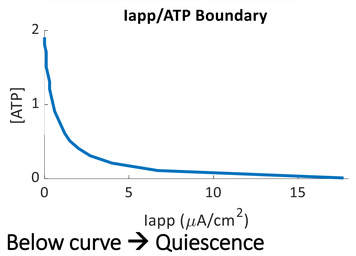
$[Na]$ = Sodium concentration
$[ATP]$ = ATP concentration
F= surface factor
K_m = kinetic constant of NaK-ATPase
K_{prod} = rate of ATP production
$[ATP]_{max}$ = max ATP concentration

Networks:

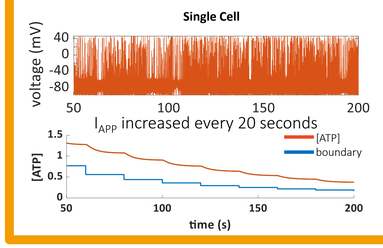


RESULTS

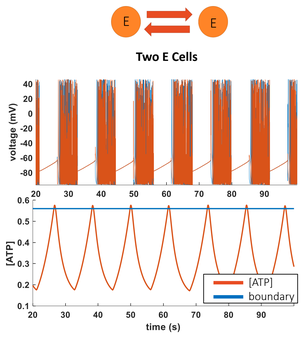
Single Cell: no ATP-mediated oscillations



Below curve → Quiescence
Above curve → Spontaneous spiking

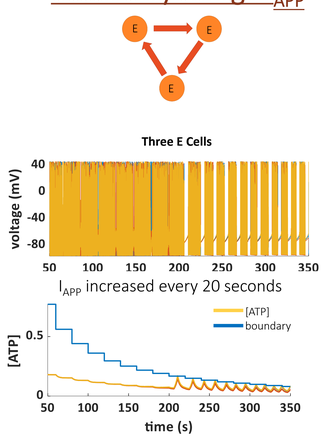


Synaptic connections allow ATP-mediated oscillations



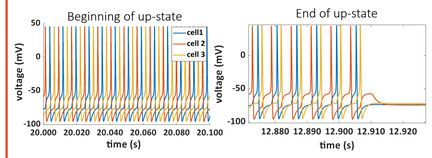
- Synaptic activity continues even when neurons are below boundary, due to excitatory input from network
- Oscillations occur across full range of I_{APP} (0-11 μA/cm^2)

Three excitatory cells: SWO occur only at high I_{APP}



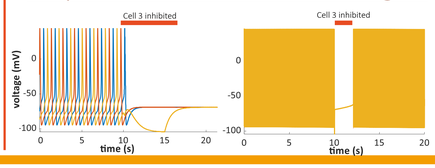
- ATP below the boundary is necessary but not sufficient for SWO

High I_{APP} stops cell due to shifts in phases of action potentials

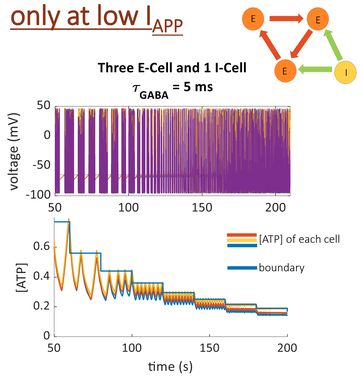


- Cell cannot respond to synaptic input during refractory period
- When one cell stops, all cells stop
- Phase-shift also occurs with 2-cells
- Open question: What causes phase shift only at high I_{APP} for three cells but at all I_{APP} for 2 cells?

Stop one cell -> down state begins

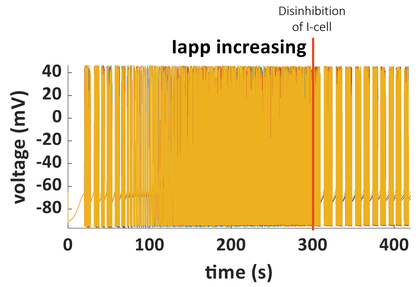


With inhibition, SWO appear only at low I_{APP}



- With inhibition, there are always down-states
- As I_{APP} increases, the frequency of oscillations increase
- This occurs over a range of τ_{GABA}
  - High τ_{GABA} applicable to propofol

Anesthesia-mediated SWO can be explained by 3-cell model



- Propofol SWO may be due to loss of cortical excitation (lowered I_{APP}).
- Ketamine SWO may come about from disinhibition

CONCLUSION: Hypothesized SWO transition

1. **During up-state**, cells spike, and **ATP levels decay (ATP level is activity dependent)**
2. Individual neurons **require excitation from interacting E-cells** to spike when ATP levels cross the boundary
3. **Changes in phase relationships** during the up-state, causes some cells to stop responding to synaptic excitation, and hence stop spiking.
4. **Down state caused** if a sufficient number of E-cells drop out, reducing synaptic excitation such that all activity stops
5. **Up-state resumes** when **ATP level has recovered** adequately and some neurons can spike independently, activating the others

FUTURE DIRECTIONS

- What is the origin of the phase shift?
  - Why can the two cell network oscillate at all levels of I_{APP}?
  - What determines the timescale of an upstate?
  - How does the anatomy of large networks affect phase shifts?
- Is there any mechanism other than shift of phases to produce down state?

ACKNOWLEDGEMENTS

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CITATIONS

Chauvette, S., Crochet, S., Volgushev, M., & Timofeev, I. (2011). Properties of slow oscillation during slow-wave sleep and anesthesia in cats. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *31*(42), 14998–15008. doi:10.1523/JNEUROSCI.2339-11.2011

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