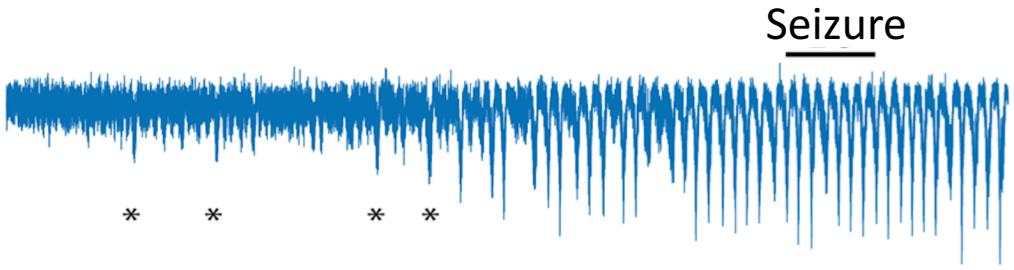
Ion dynamics in epileptic brain: the role of intracellular chloride for seizure initiation



Anatoly Buchin, Anton Chizhov, Gilles Huberfeld, Richard Miles and Boris Gutkin

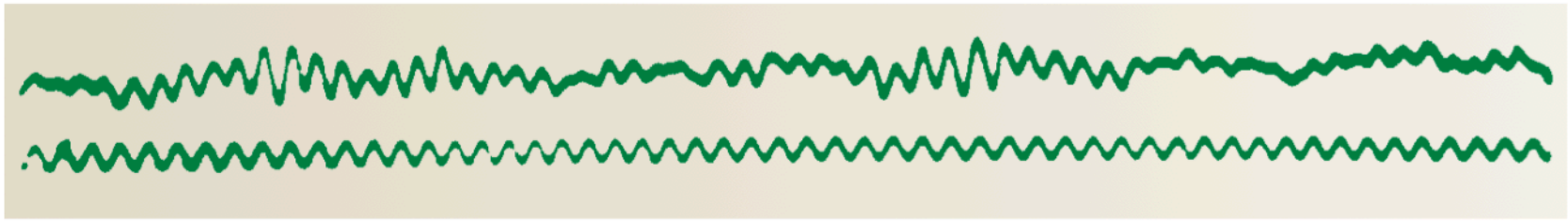
UNIVERSITY of WASHINGTON

HIGHER SCHOOL OF ECONOMICS

GNT

Ioffe Institute

Oscillations in the brain



Berger 1929

0.01 Hz Ultraslow	5-30 Hz Alpha-beta	40-80 Hz Gamma	250 – 600 Hz High Frequency
Cortex	Visual cortex	Prefrontal cortex Hippocampus	Hippocampus

Oscillations during epilepsy

- **Epilepsy** is a group of neurological diseases characterized by epileptic seizures
- **Epileptic seizure** is a brief episode of symptoms due to abnormal synchronous neuronal activity in the brain

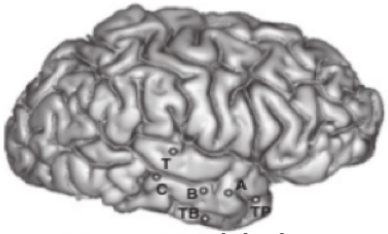
- "Seizure frequency" 4-10 Hz
- ~50% of epileptic patients have the **temporal lobe epilepsy**
  (adult patients)
- ~40% of patients do not respond to the pharmacological treatment

Seizures *in vivo* and *in vitro*

Gilles Huberfeld

in vivo

Intracranial recordings

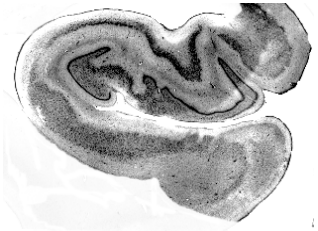


temporal lobe

seizure initiation

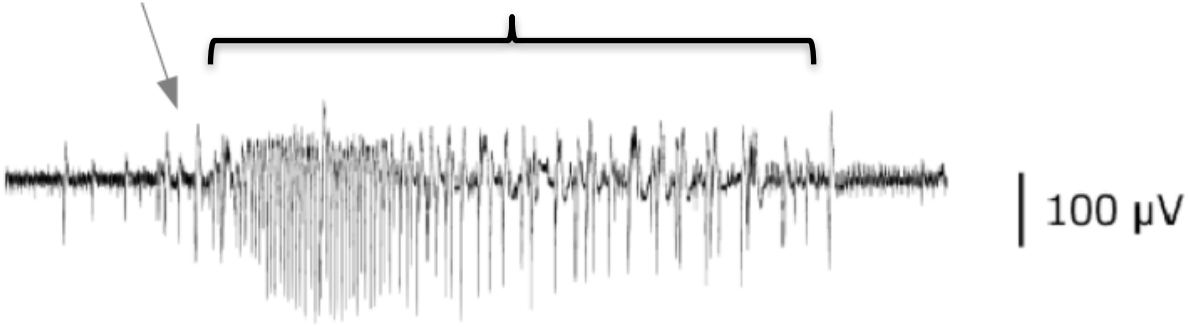
Ictal discharge

in vitro



K^+_{Ext}

8 mM



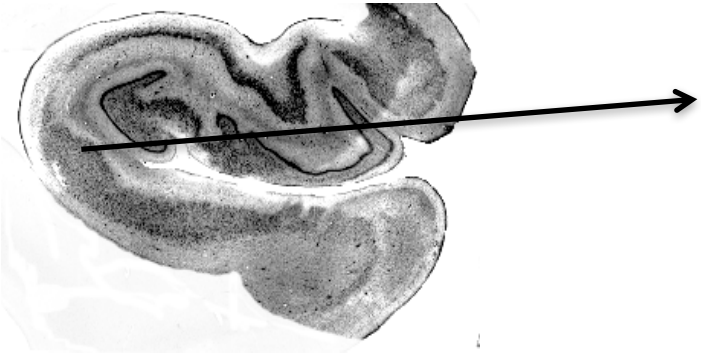
Extracellular recordings **in vitro**

Huberfeld et al. 2011

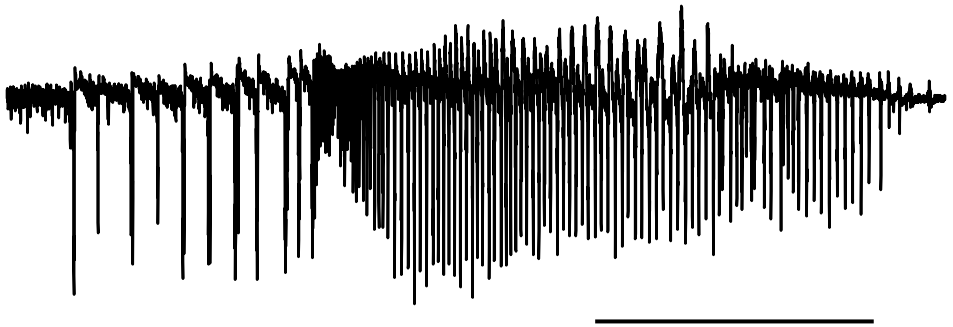
Question

- What are the mechanisms responsible for ictal discharge initiation?

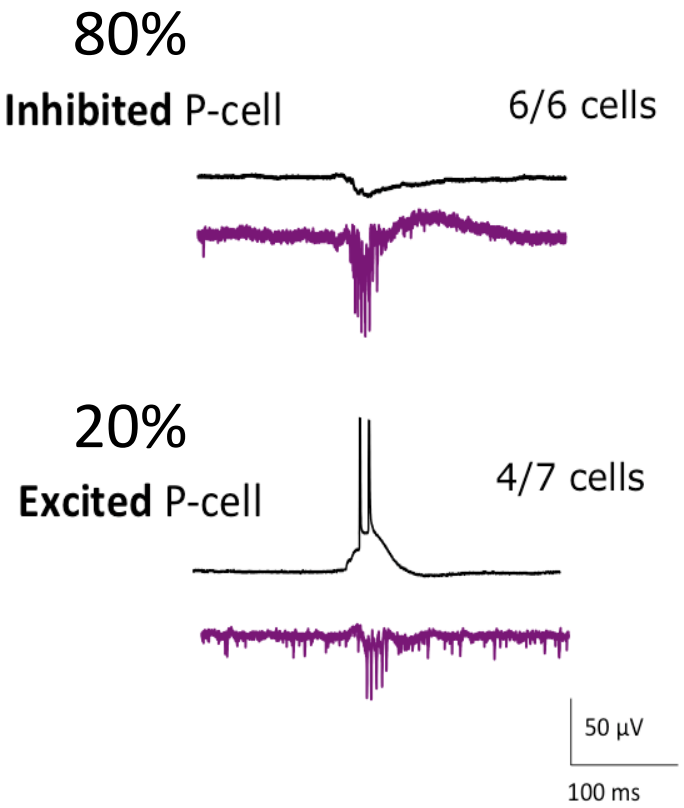
Human subiculum



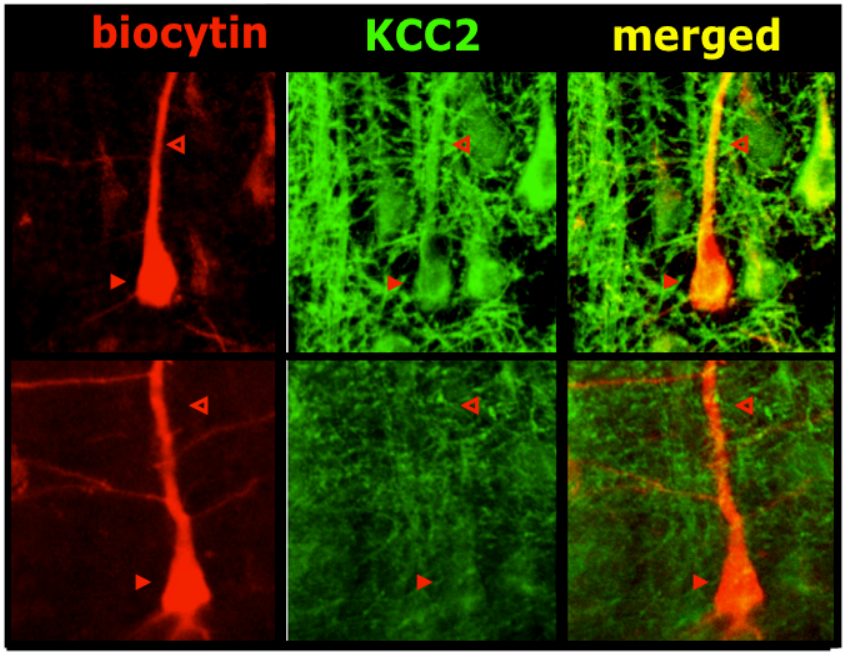
Ictal discharge



Absence of KCC2 leads to depolarizing GABA responses

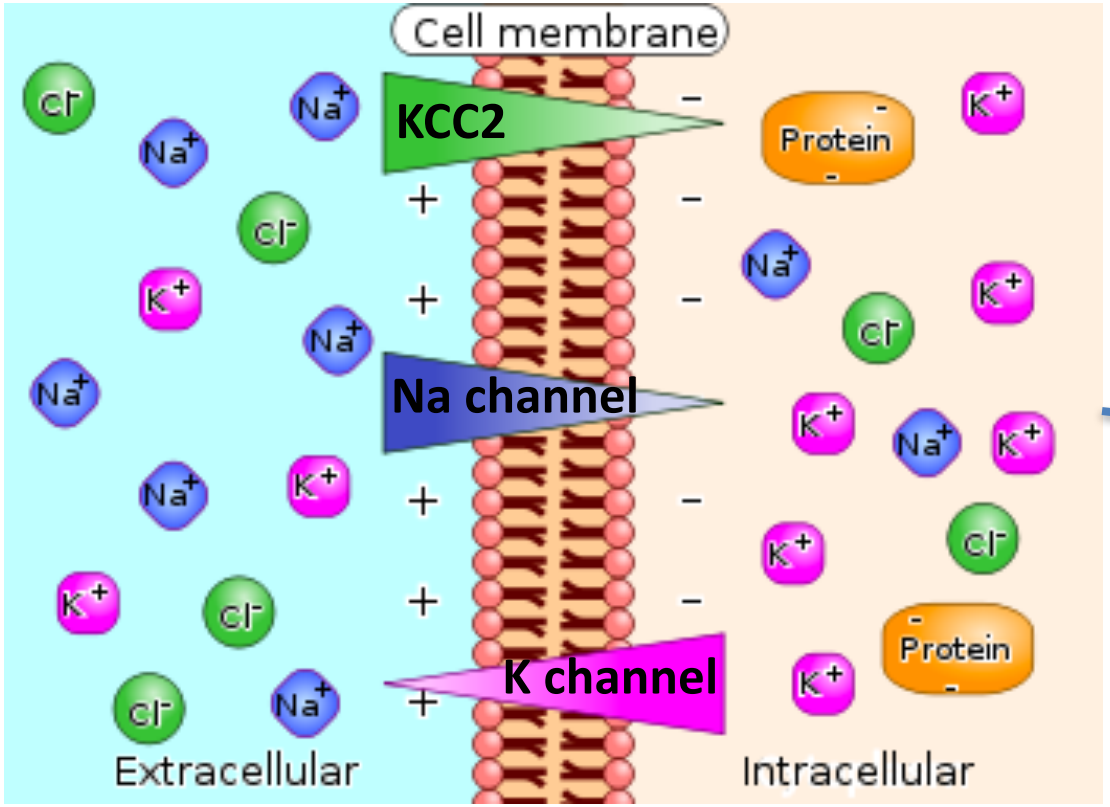


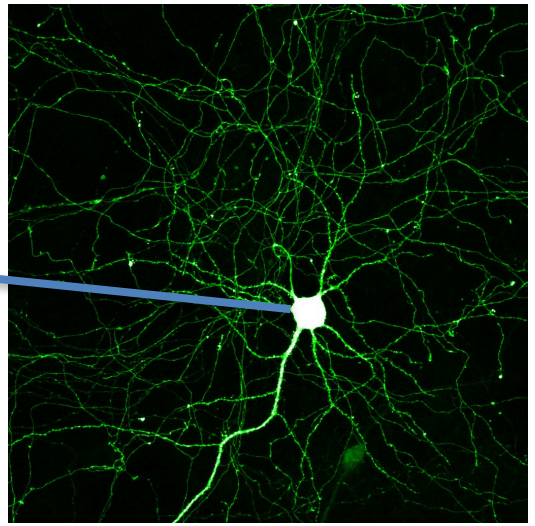
KCC2 – Kation Chloride Cotransporter 2



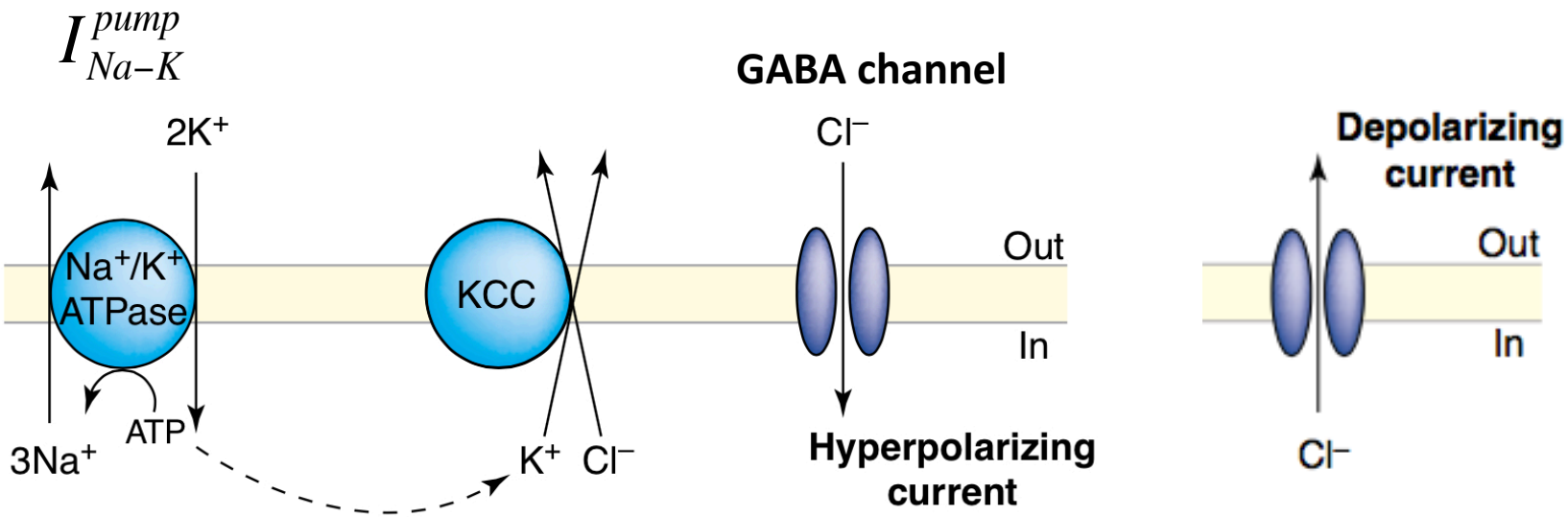
Huberfeld et al. 2007

Reminder: ion concentration inside and outside of a neuron





KCC2 maintains the intracellular chloride level



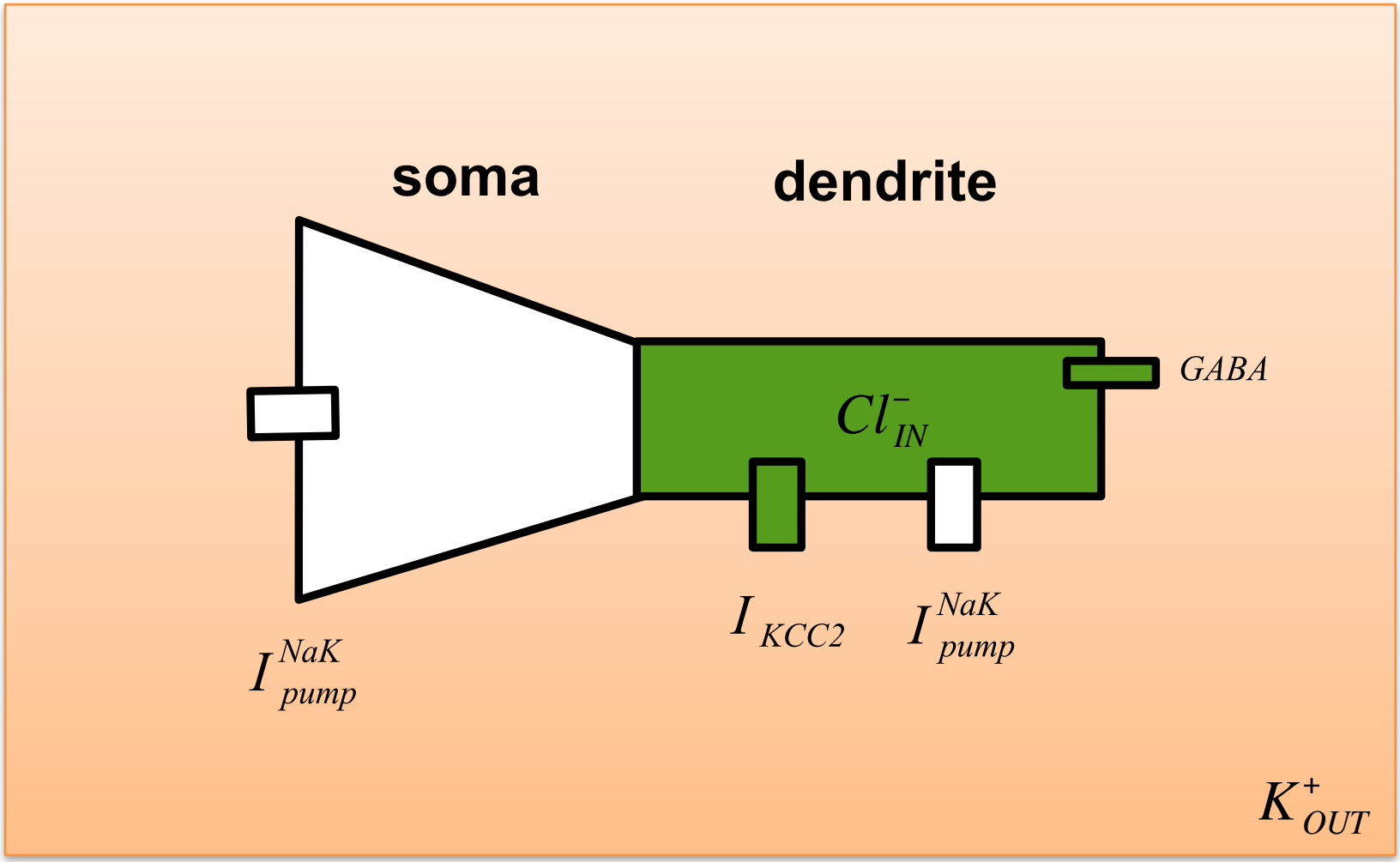
$$I_{KCC2} = \frac{I_{\max}(V_K - V_{Cl})}{(V_K - V_{Cl}) + V_{1/2}}$$

$$I_{GABA} = g_{GABA}[V - V_{GABA}(Cl^-_{IN})]$$

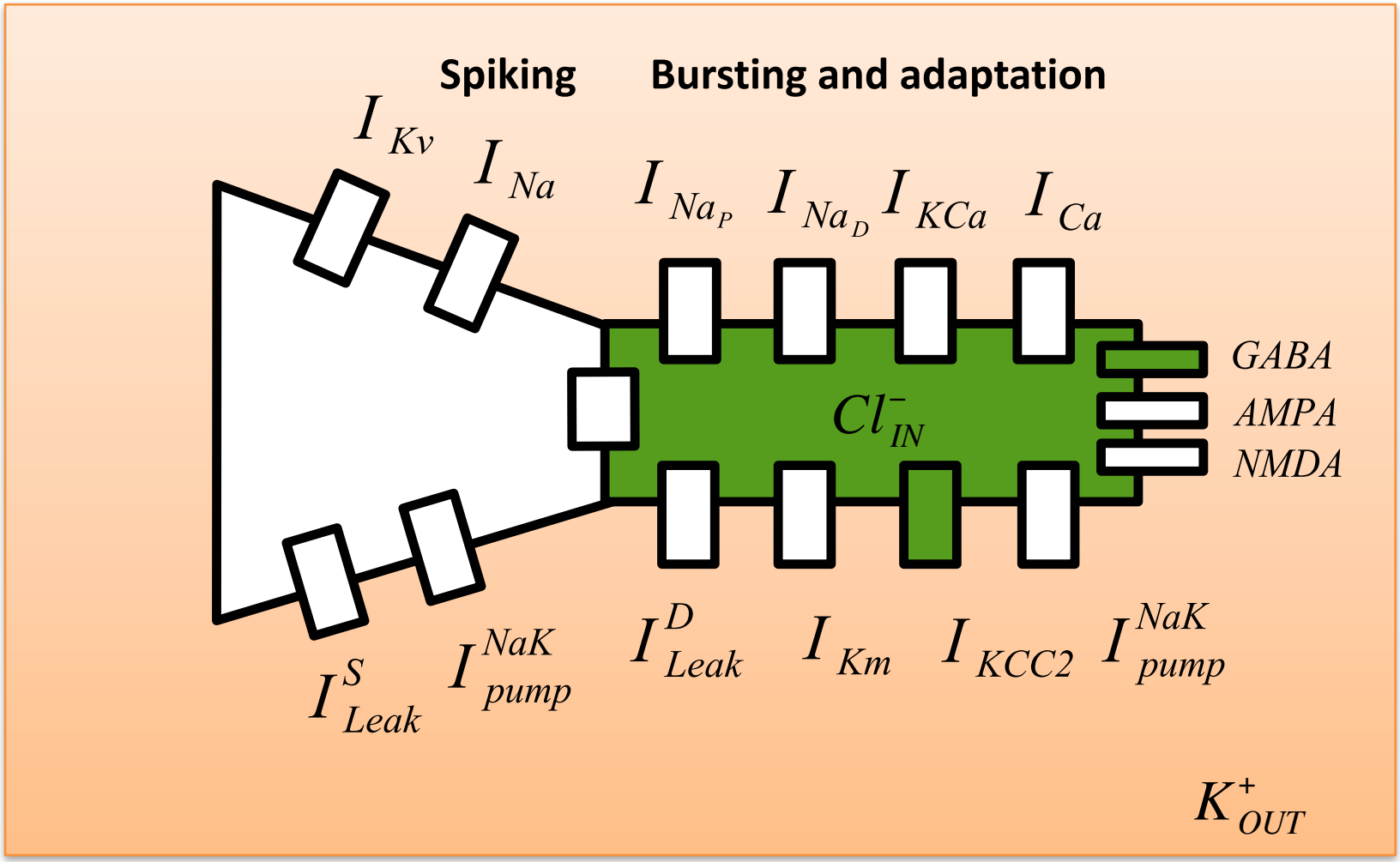
Payne et al. 2003

How does the KCC2 affect the single neuron excitability?

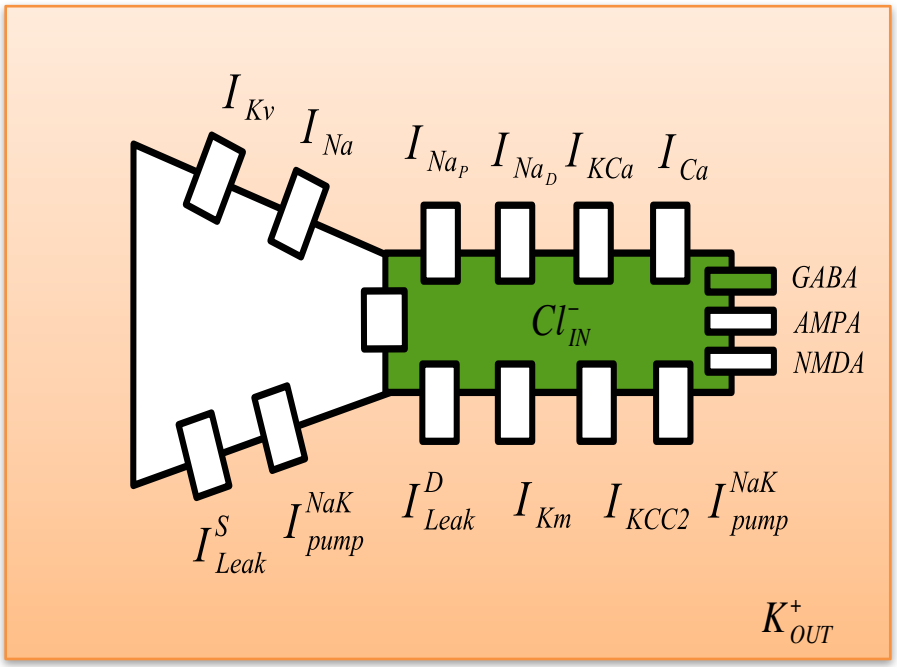
Pyramidal cell model: ion mechanisms



Pyramidal cell model: intrinsic and synaptic currents



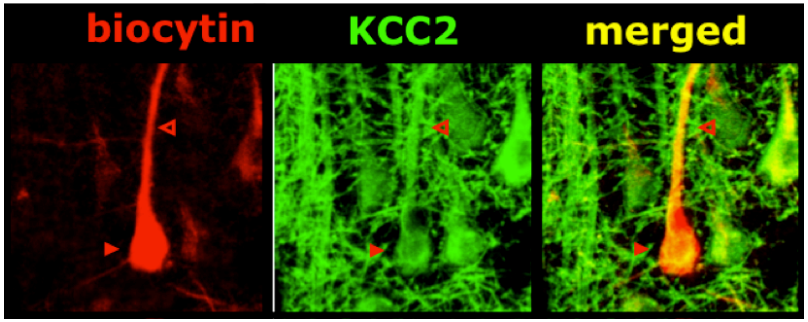
Model: KCC2(+) cell



$$\frac{dCl^-_{IN}}{dt} = I_{GABA} + I_{Cl} + I_{KCC2}$$

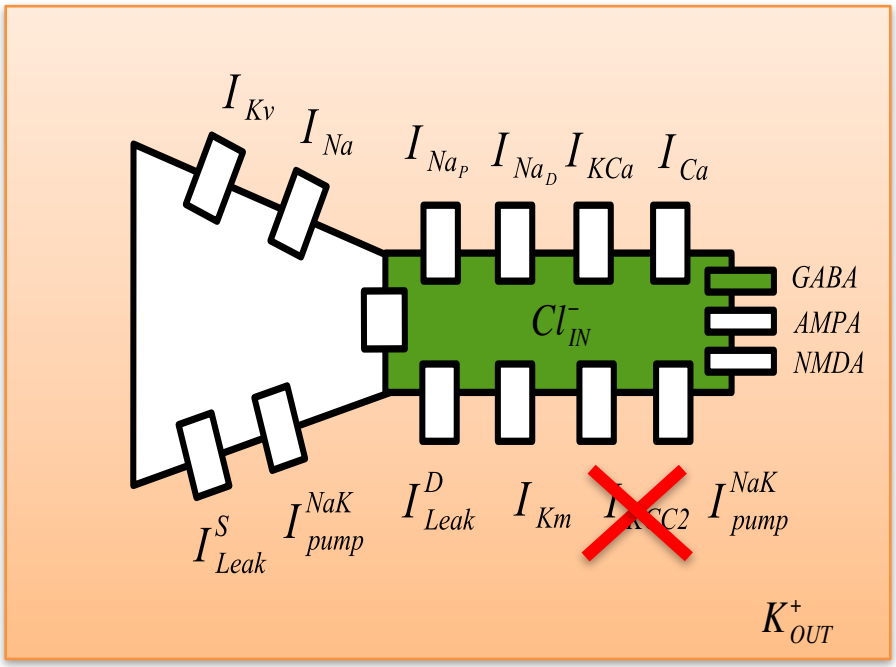
Chloride concentration

$$Cl^-_{IN} = 3.5mM$$



Huberfeld et al. 2007

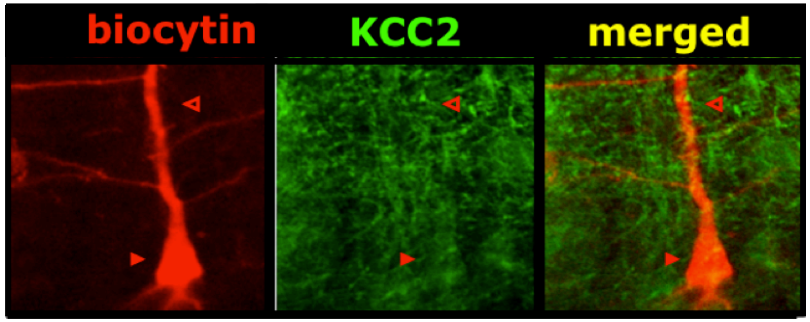
Model: KCC2(-) cell



$$\frac{dCl^-_{IN}}{dt} = I_{GABA} + I_{Cl} + I_{KCC2}$$

Chloride concentration

$$Cl^-_{IN} = 11.3mM$$



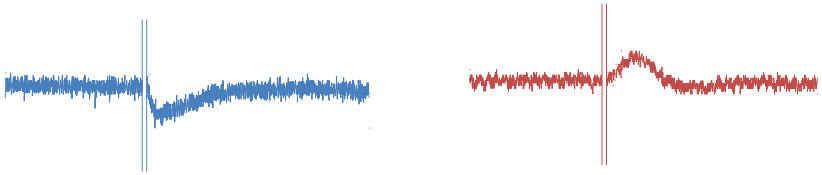
Huberfeld et al. 2007

Model validation: response to the GABA stimulation

$$I_{GABA} = g_{GABA}[V - V_{GABA}]$$

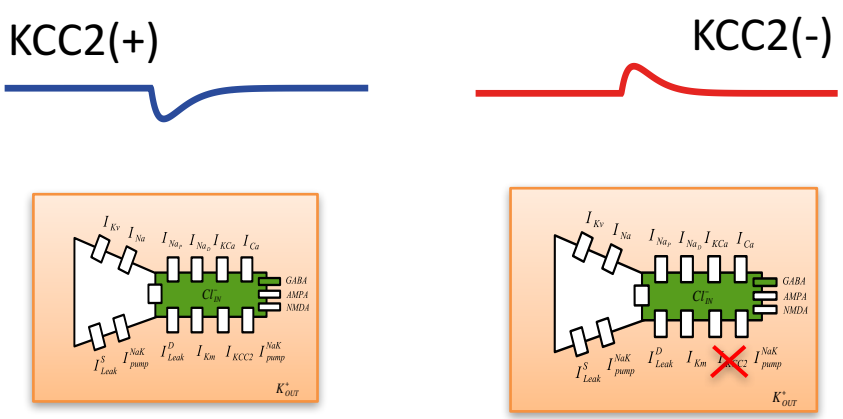
$$V_{GABA} = \frac{RT}{F}\ln\left(\frac{Cl^-_{IN} + 4HCO_{3IN}}{Cl^-_{OUT} + 4HCO_{3OUT}}\right)$$

Experiment



Model

KCC2(+) KCC2(-)



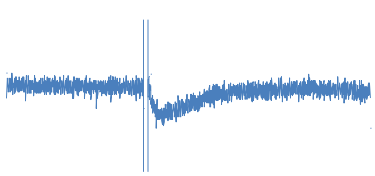
Model validation: response to the GABA stimulation

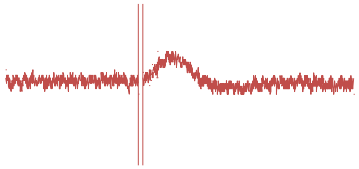
$V_{GABA} = -78mV$

$V_{GABA} = -56mV$

$$V_{GABA} = \frac{RT}{F}\ln\left(\frac{Cl^-_{IN} + 4HCO_{3IN}}{Cl^-_{OUT} + 4HCO_{3OUT}}\right)$$

Experiment

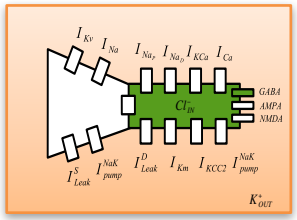


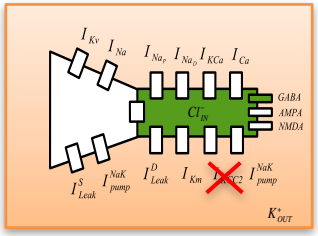


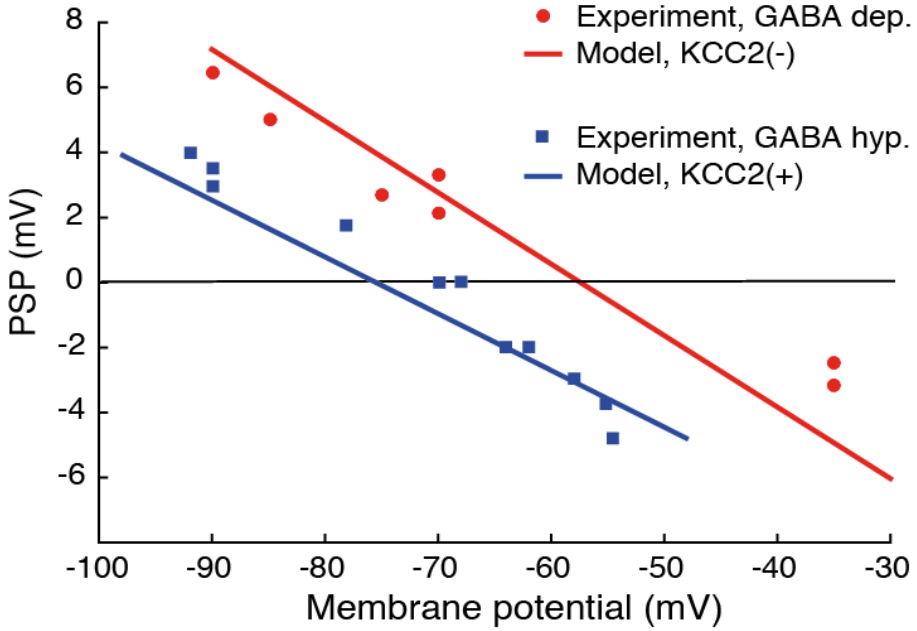
Model

KCC2(+)

KCC2(-)

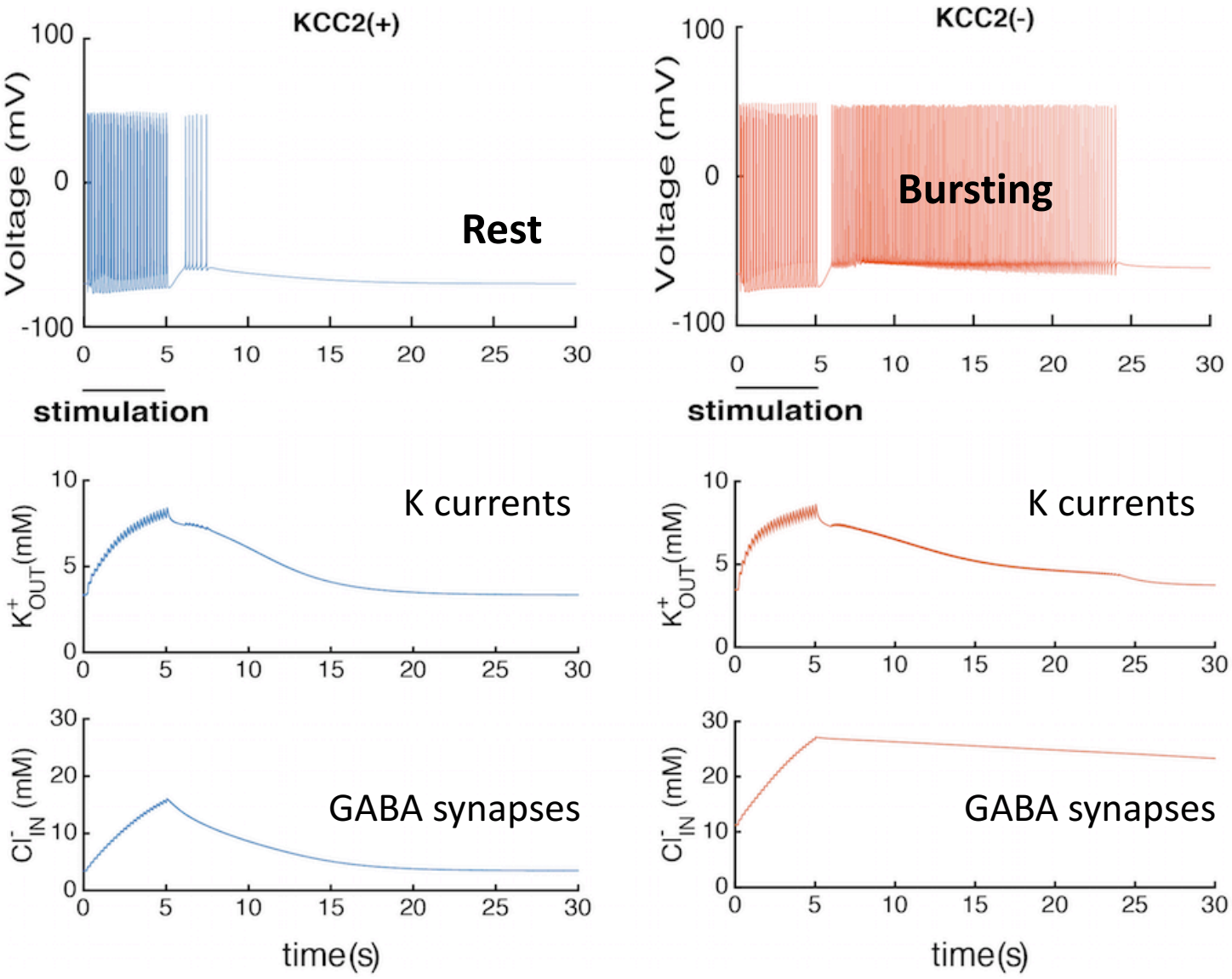




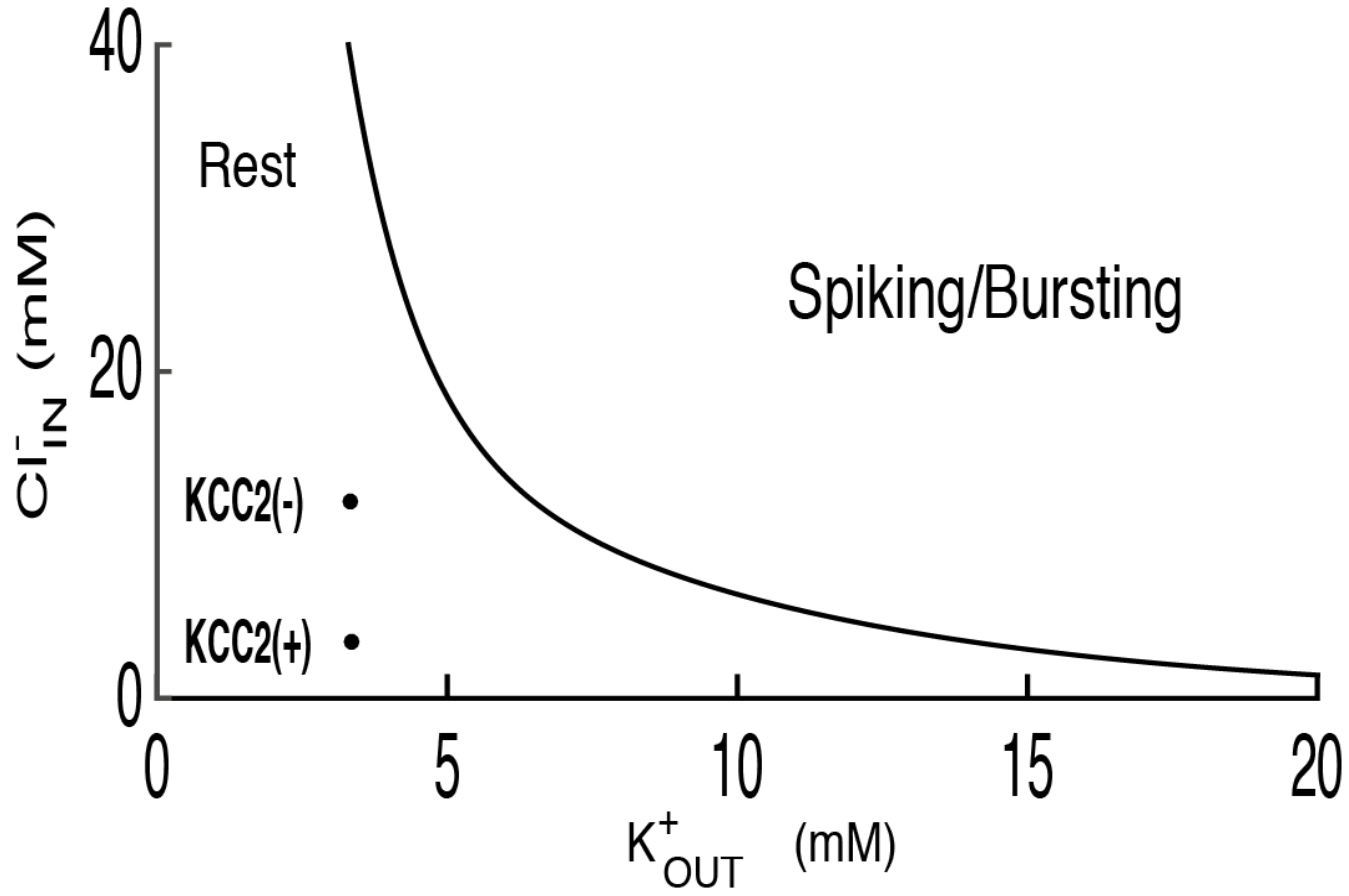


Cohen et al. 2002

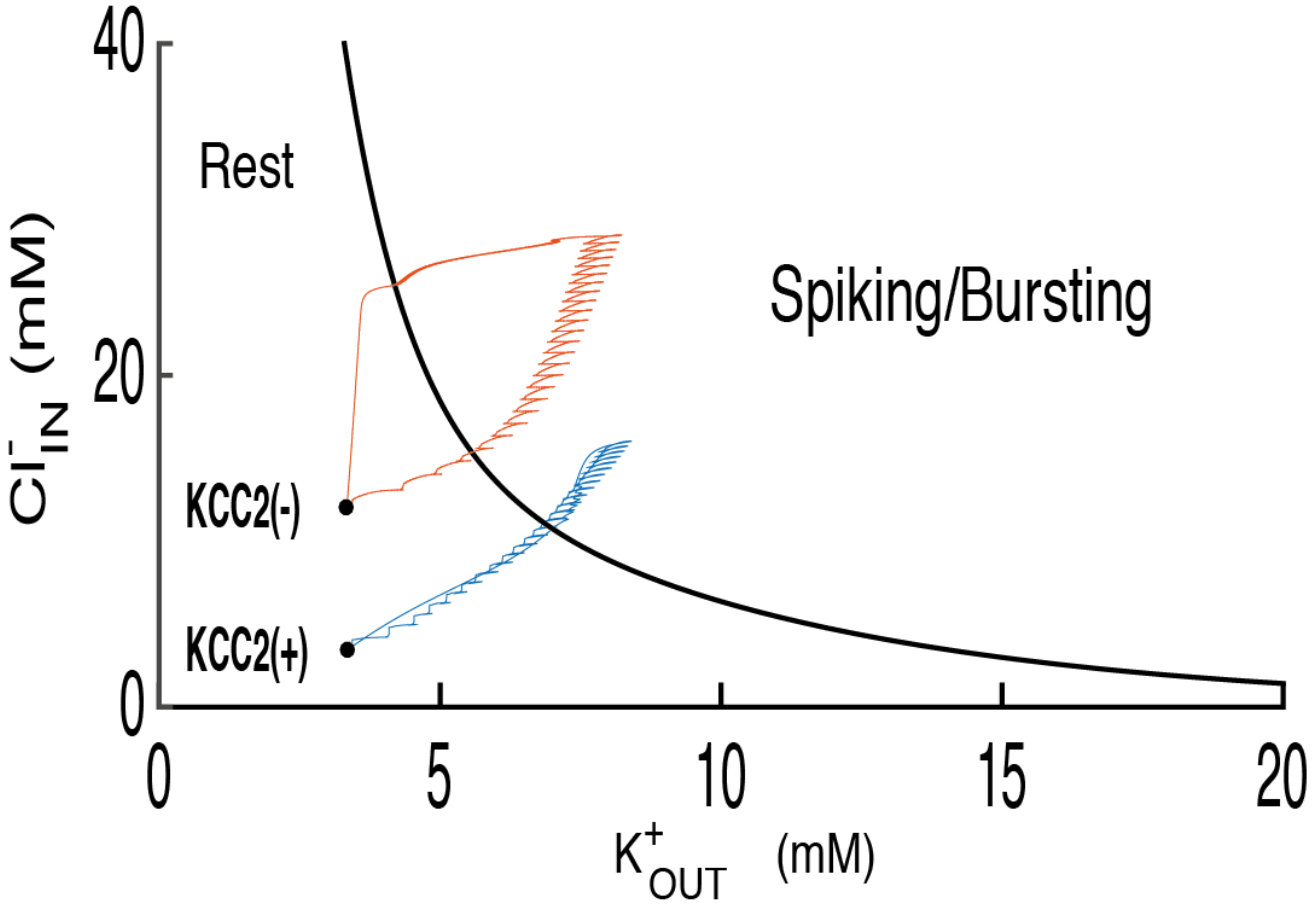
KCC2(-) pathology promotes bursting behavior



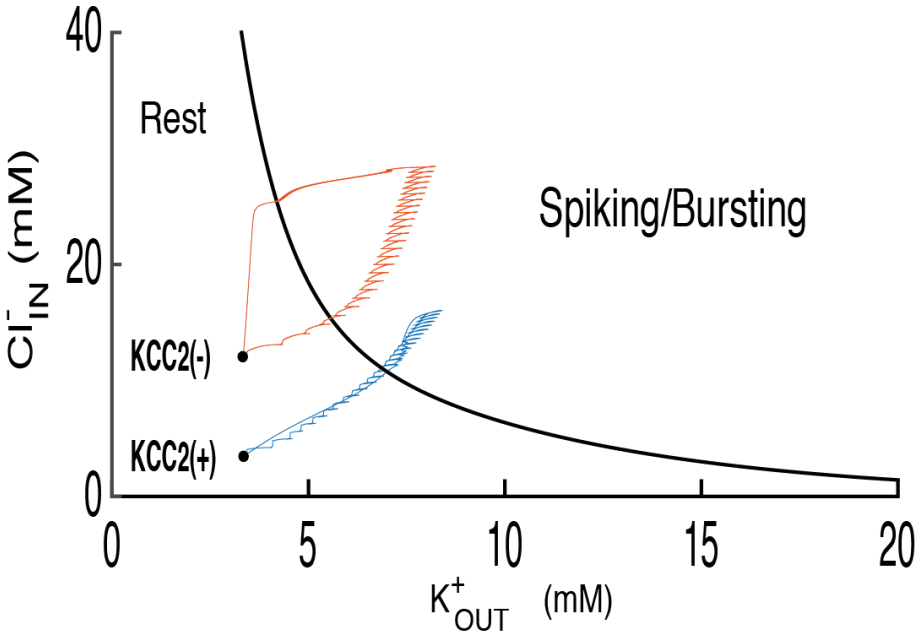
Pyramidal cell model analysis

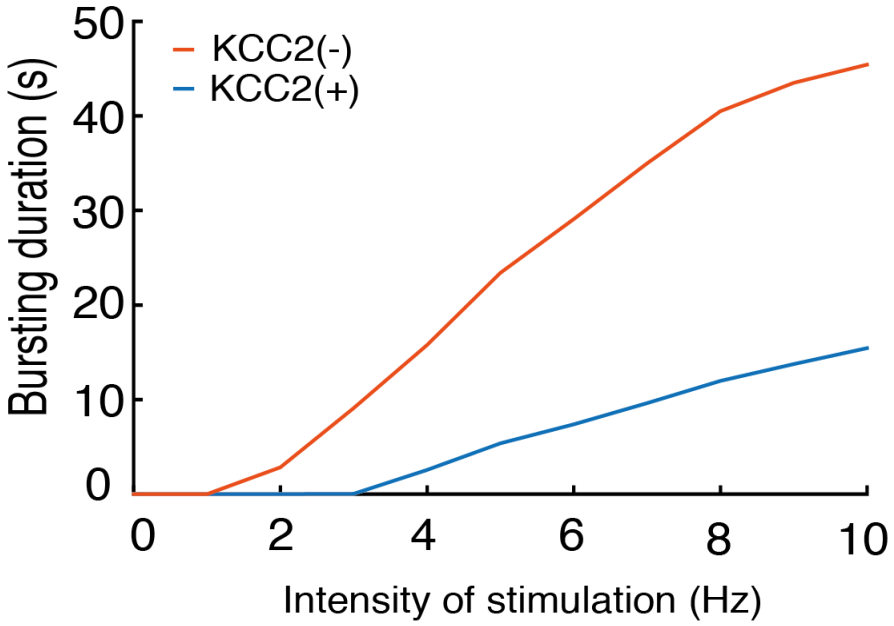


Potassium and chloride dynamics during synaptic stimulation

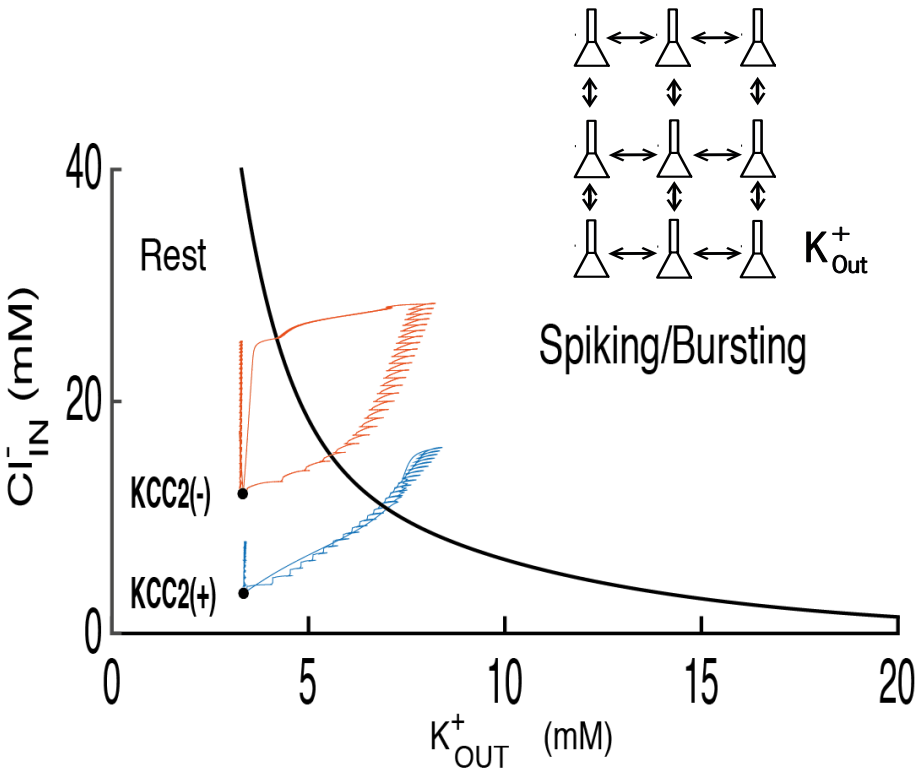


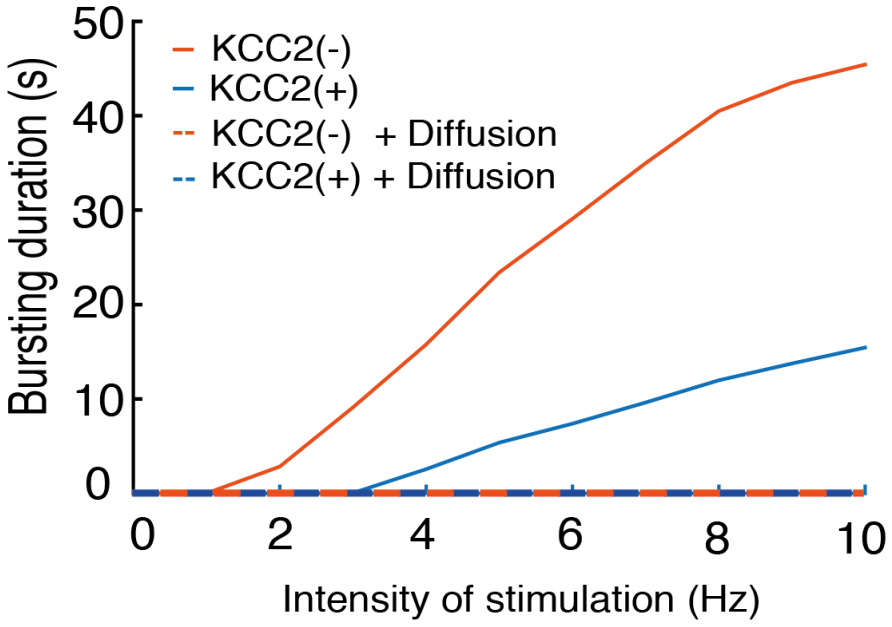
Lack of KCC2 increases bursting duration





Potassium diffusion eliminates bursting

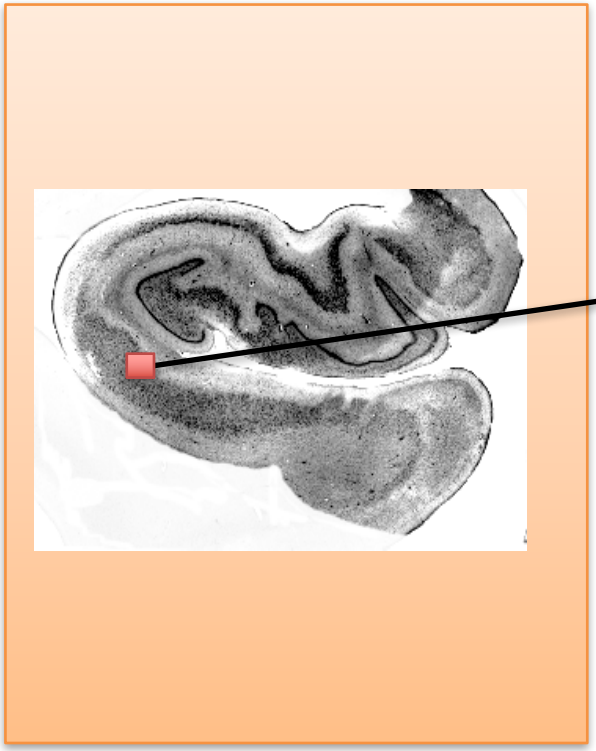




How does KCC2 affect the excitability on the network level?

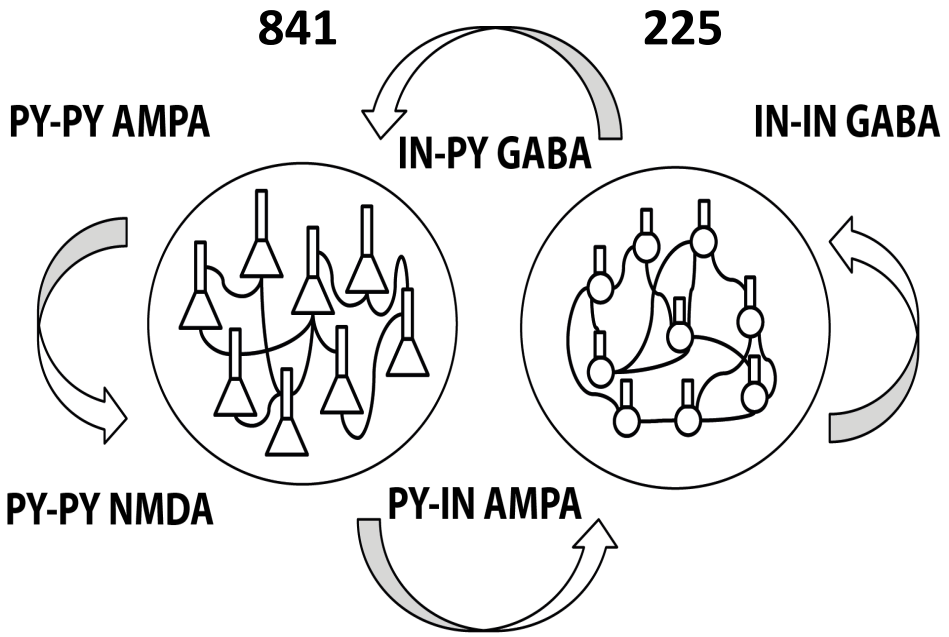
KCC2(+) subiculum circuit: synaptic structure

Subiculum slice



$$K^{+}_{bath} = 8mM$$

Subiculum connectivity in mice



Sparse random connections

Peng et al. 2014

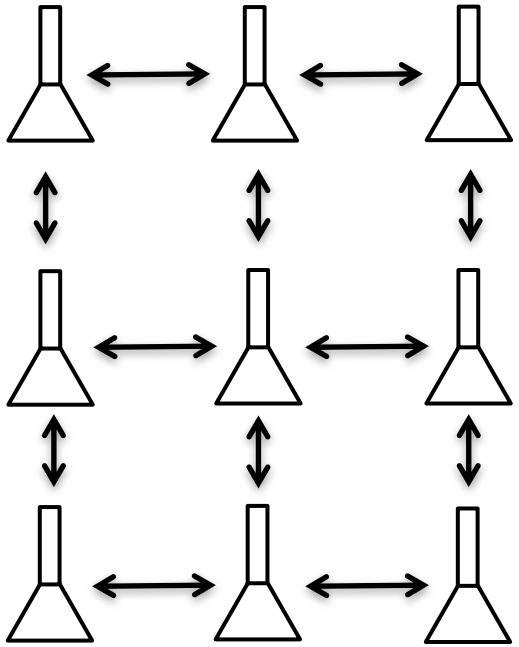
Potassium dynamics

Reaction-diffusion of potassium

$$\frac{\partial K^+_{OUT}}{\partial t} = R + \varepsilon\left(\frac{\partial^2 K^+_{OUT}}{\partial x^2} + \frac{\partial^2 K^+_{OUT}}{\partial y^2}\right)$$

$$R = \frac{k_K}{Fd}\left(I_K + I^{NaK}_{pump} - I_{KCC2}\right) + G$$

Diffusion in the network



Potassium and chloride dynamics

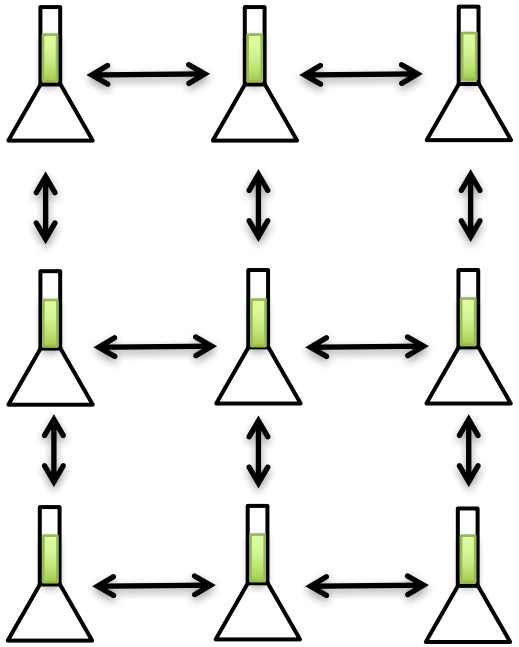
Reaction-diffusion of potassium

$$\frac{\partial K^+_{OUT}}{\partial t} = R + \varepsilon\left(\frac{\partial^2 K^+_{OUT}}{\partial x^2} + \frac{\partial^2 K^+_{OUT}}{\partial y^2}\right)$$

Intracellular chloride

$$\frac{dCl^-_{IN}}{dt} = \frac{k_{Cl}}{F}\left(I_{GABA} + I^{Cl}_{L} - I_{KCC2}\right)$$

Diffusion in the network



Potassium and chloride dynamics + bath solution

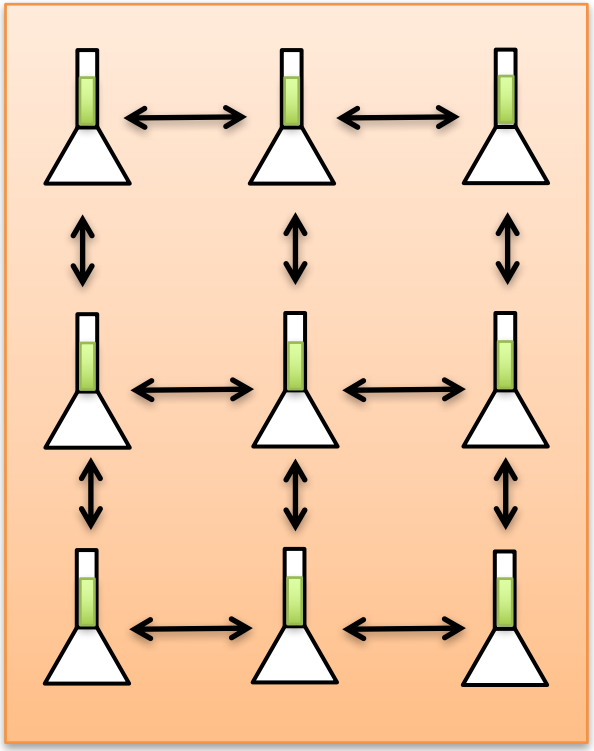
Reaction-diffusion of potassium

$$\frac{\partial K^+_{OUT}}{\partial t} = R + \varepsilon\left(\frac{\partial^2 K^+_{OUT}}{\partial x^2} + \frac{\partial^2 K^+_{OUT}}{\partial y^2}\right) + \frac{\varepsilon_{bath}}{\Delta x^2}\left(K^+_{bath} - K^+_{OUT}\right)$$

Intracellular chloride

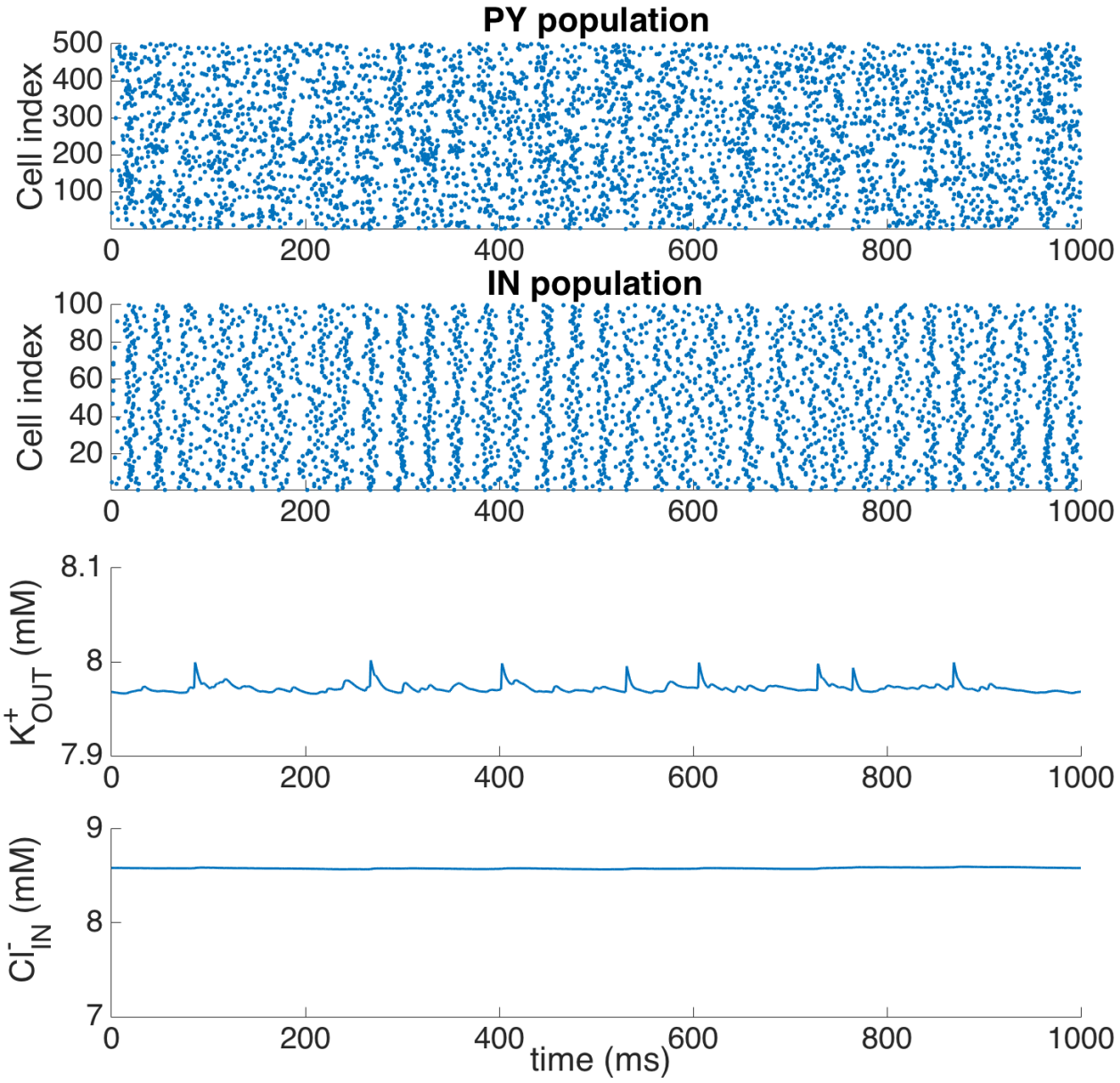
$$\frac{dCl^-_{IN}}{dt} = \frac{k_{Cl}}{F}\left(I_{GABA} + I^{Cl}_{L} - I_{KCC2}\right)$$

Diffusion in the network



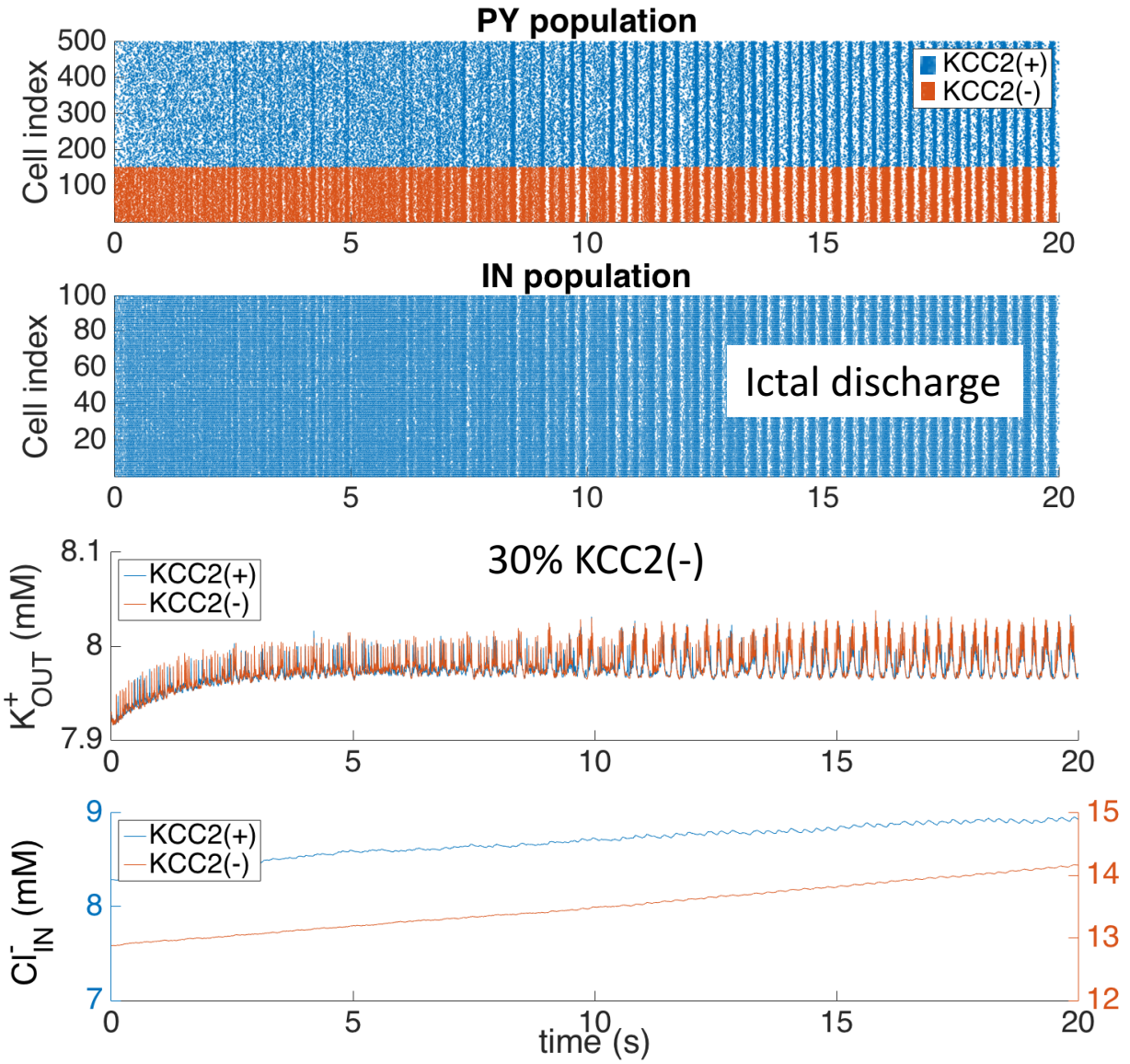
K^+_{bath}

KCC2(+) circuit: stable ion concentrations during network oscillations

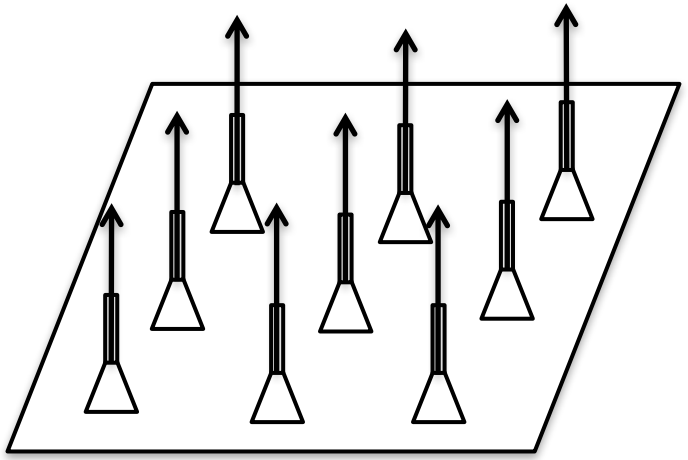


K^+_{bath}

KCC2(-) circuit: addition of KCC2(-) cells lead to the ictal discharge



Local field potential model

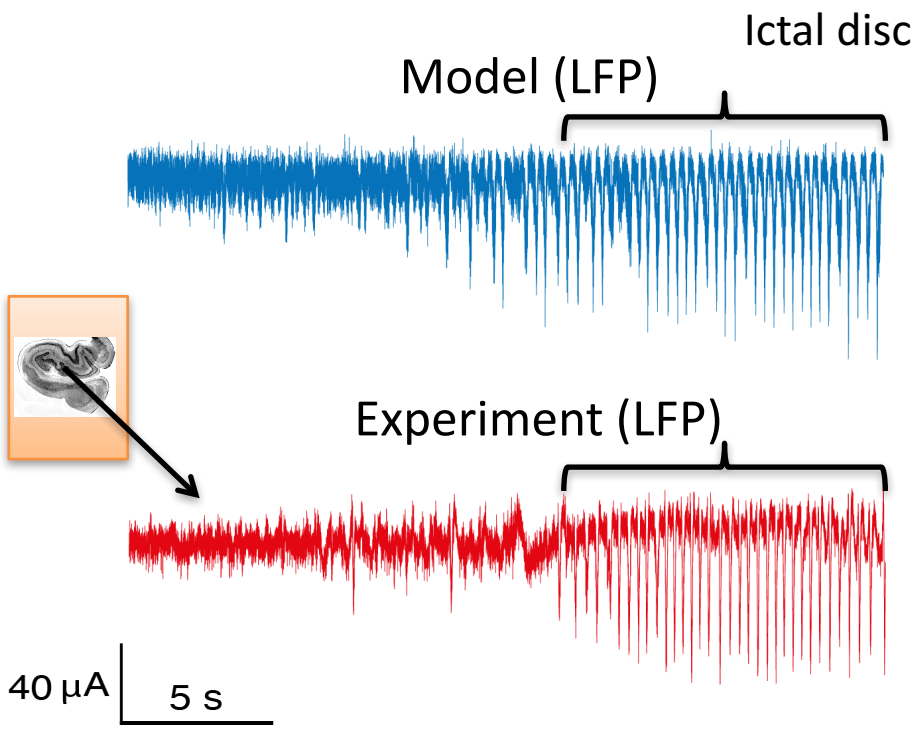


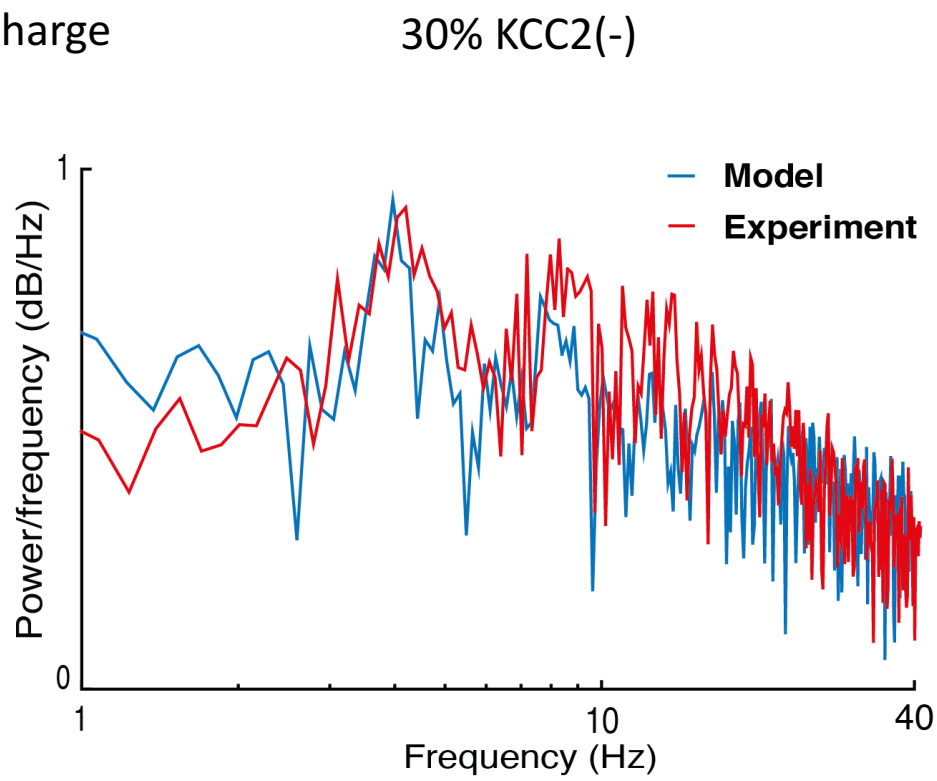
$$\varphi_i \sim (V_S - V_D)$$

$$= \sum_{i=1}^{N} \varphi_i = LFP$$

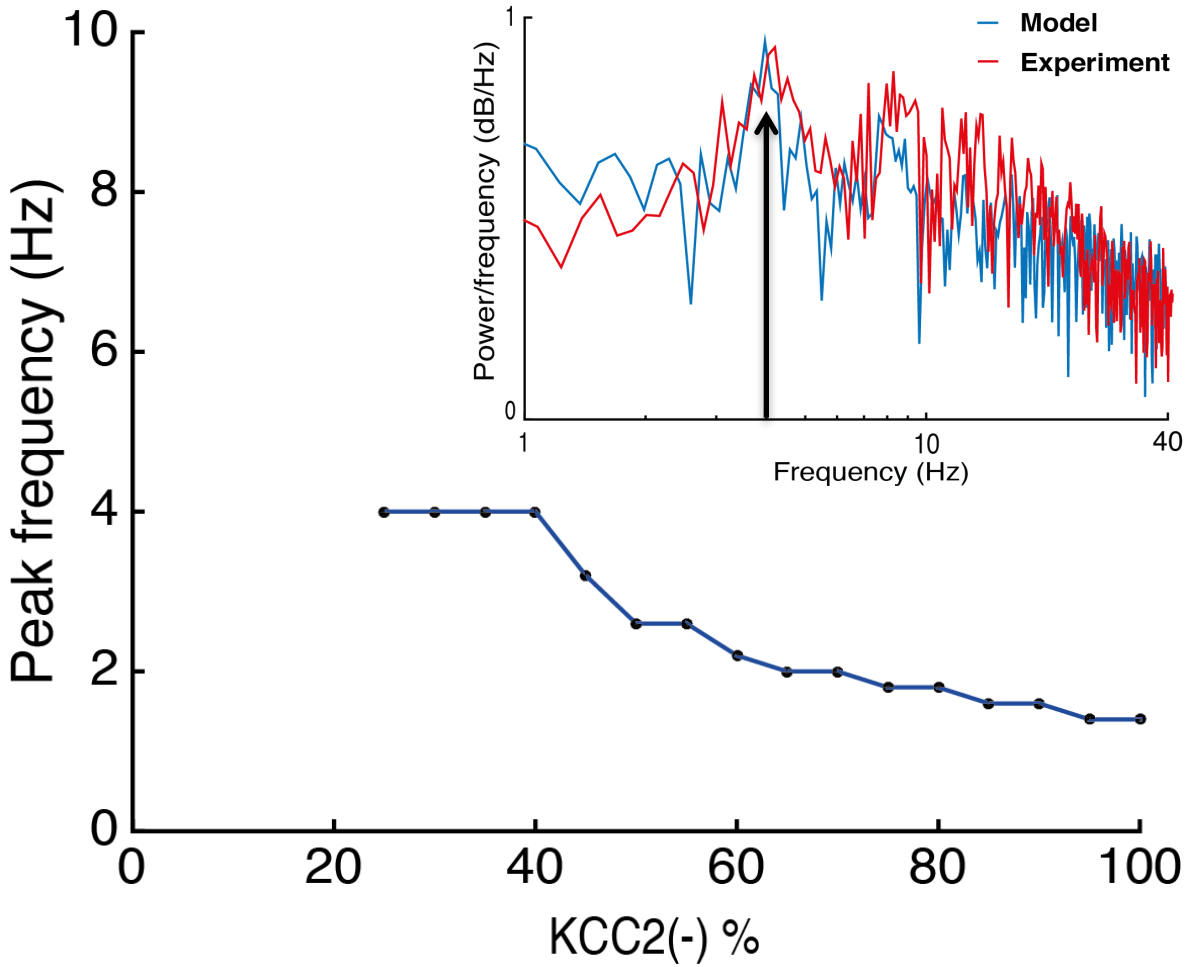
Chizhov et al. 2015

KCC2(-) circuit: oscillations during the ictal discharge

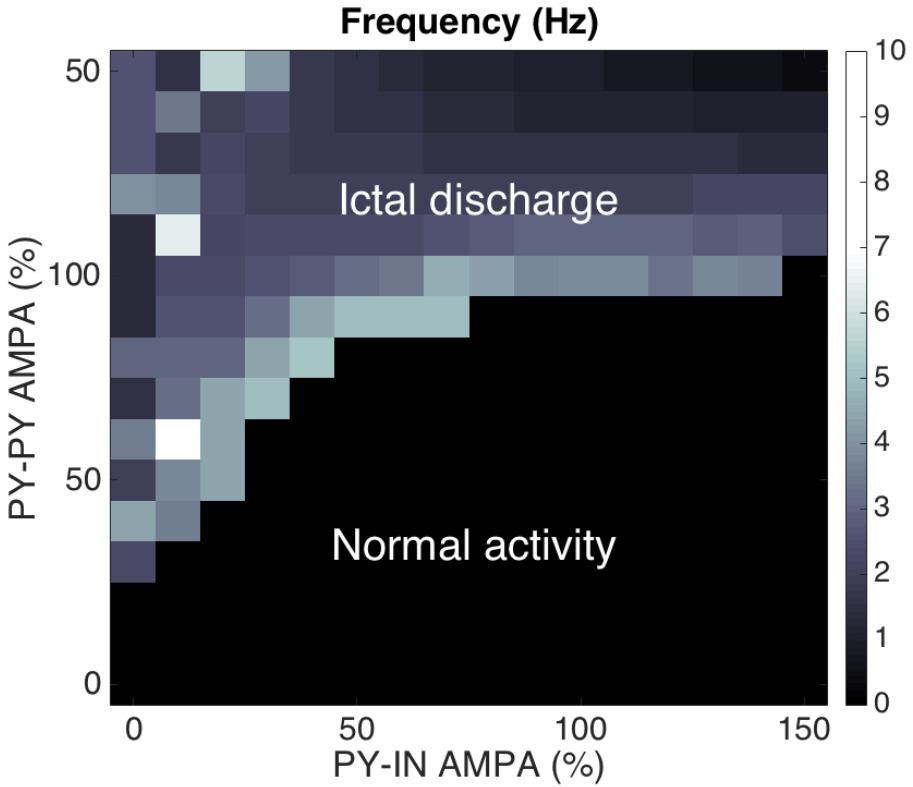


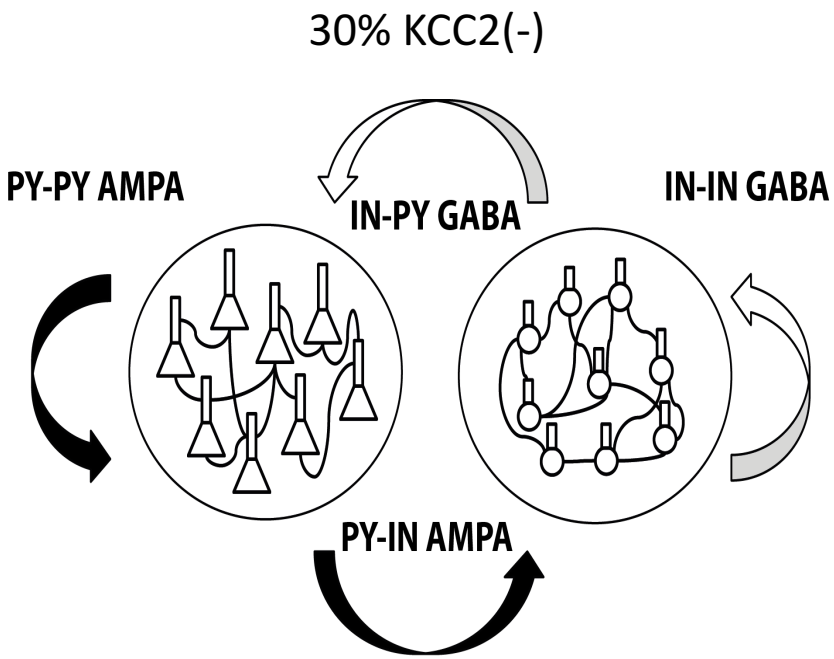


Critical fraction of KCC2(-) cells is required to initiate an ictal discharge

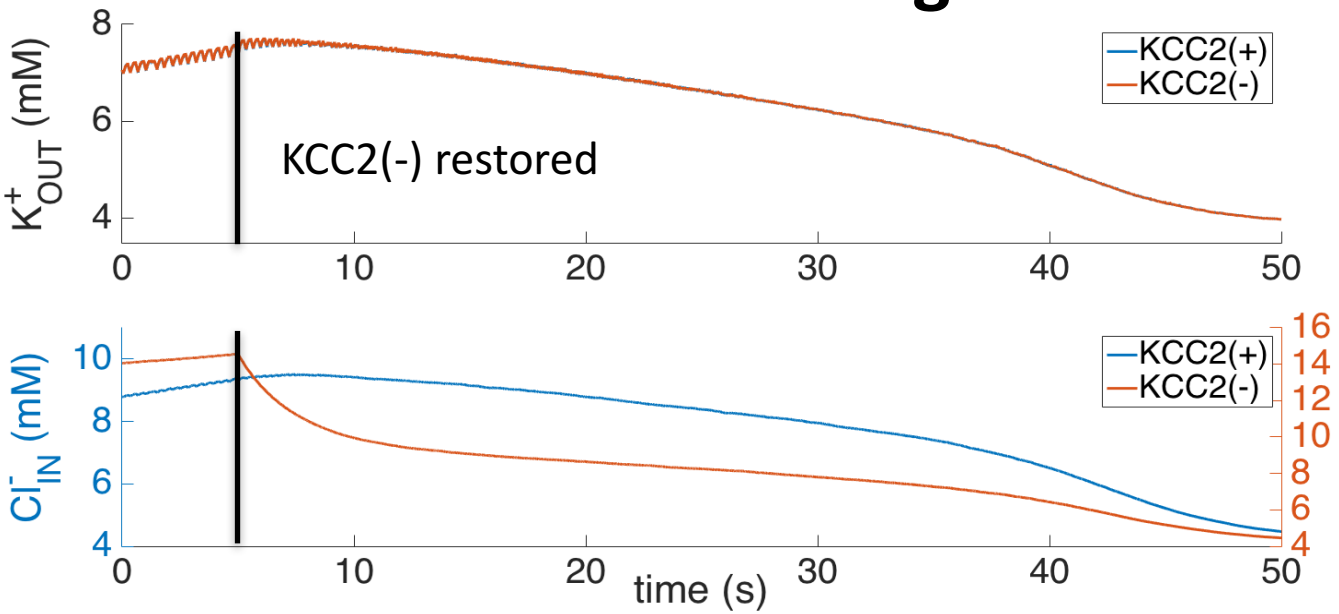


KCC2(-) pathology depends on synaptic connectivity

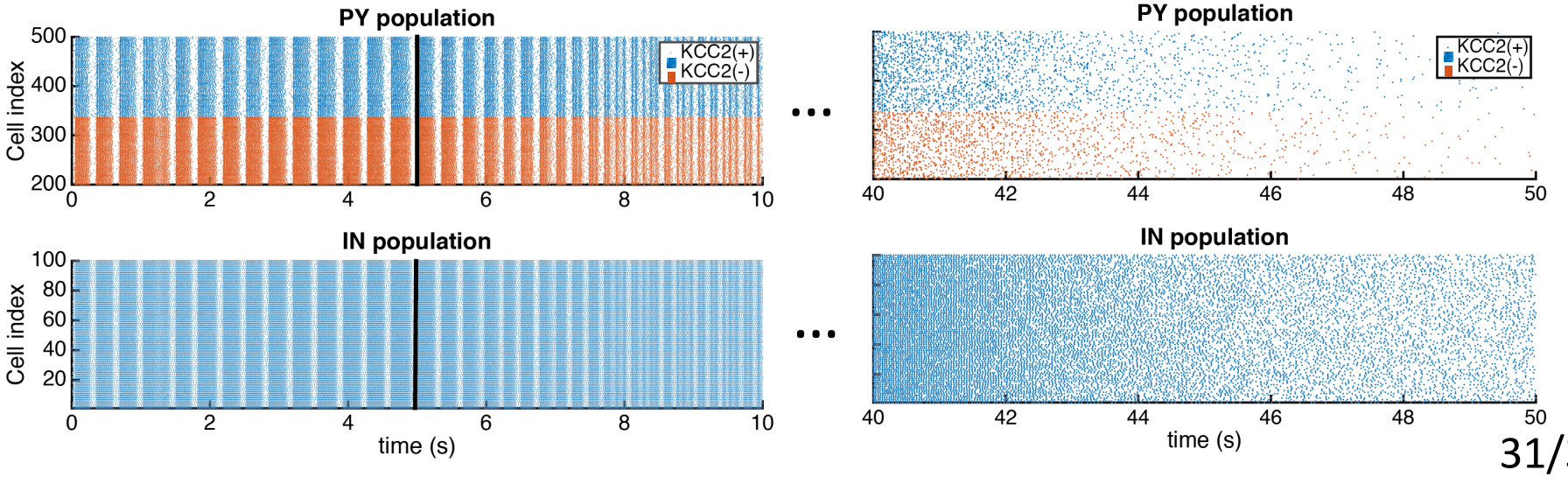




Restoration of KCC2(-) eliminates the ictal discharge



40% KCC2(-)

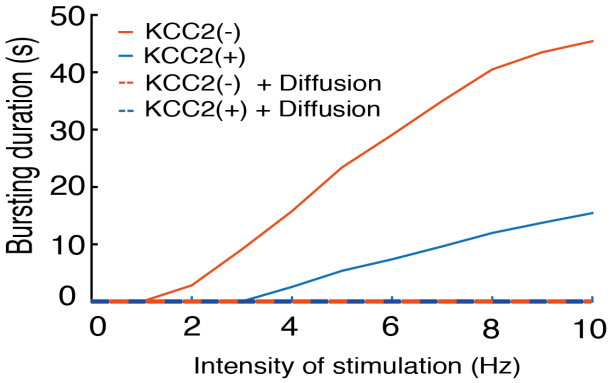


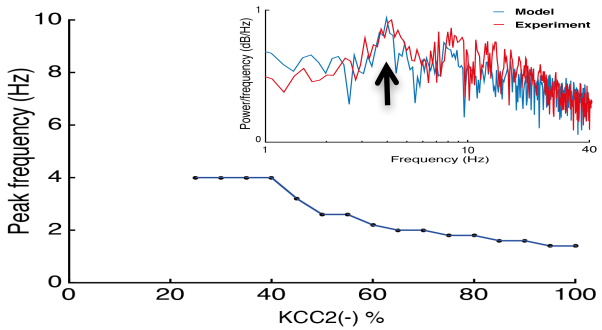
Conclusions

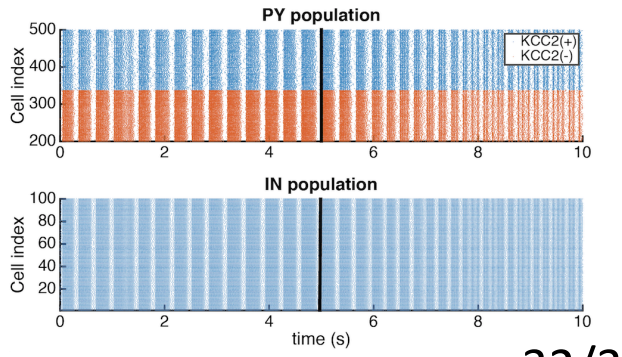
- KCC2(-) pathology leads to the depolarizing GABA reversal potential due to Cl^-_{IN} accumulation and increased susceptibility to bursting

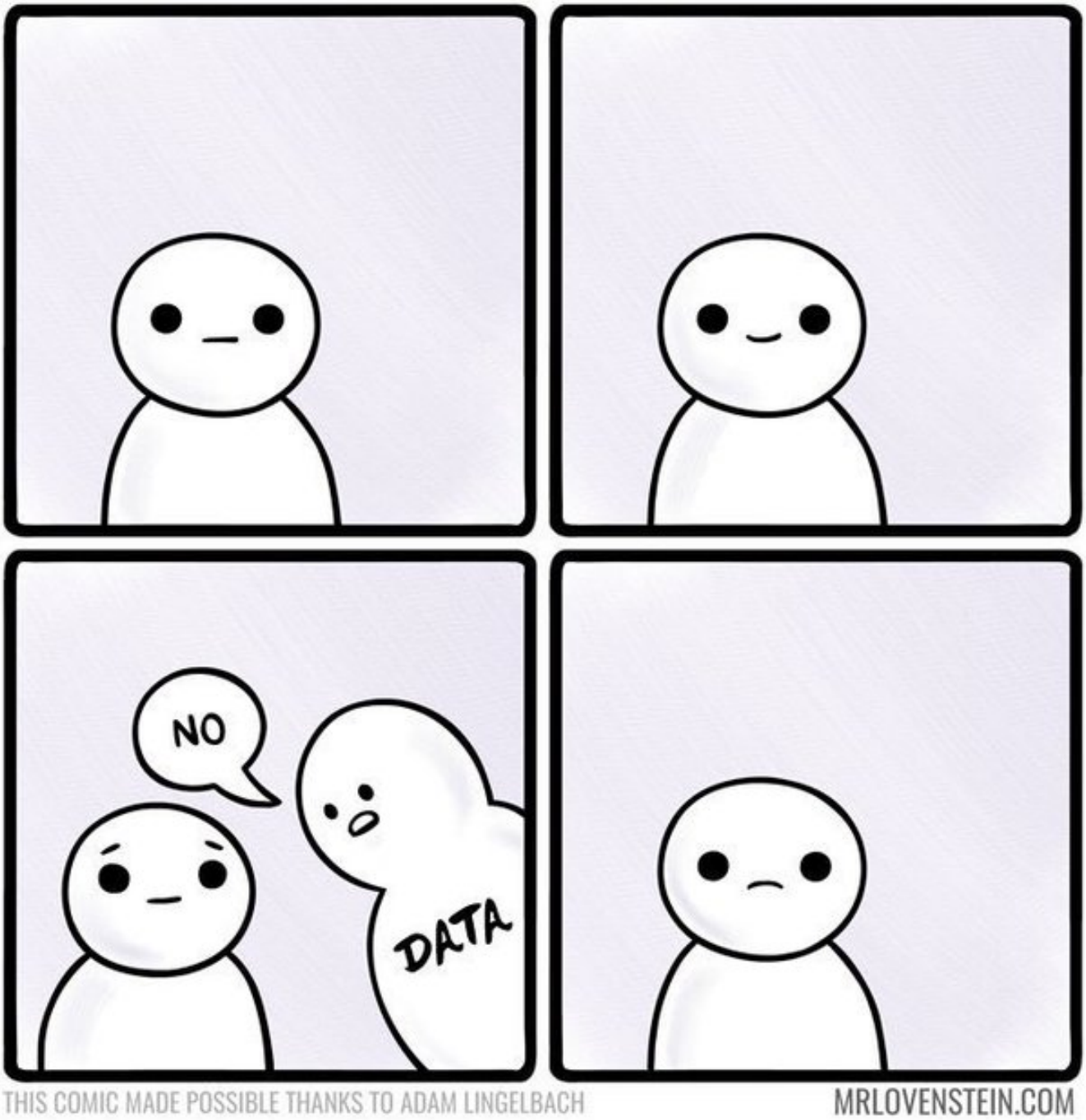
- There is a critical amount of KCC2(-) pyramidal cells in the network required for seizure initiation

- Restoration of KCC2(-) function restores the excitation-inhibition eliminates seizure





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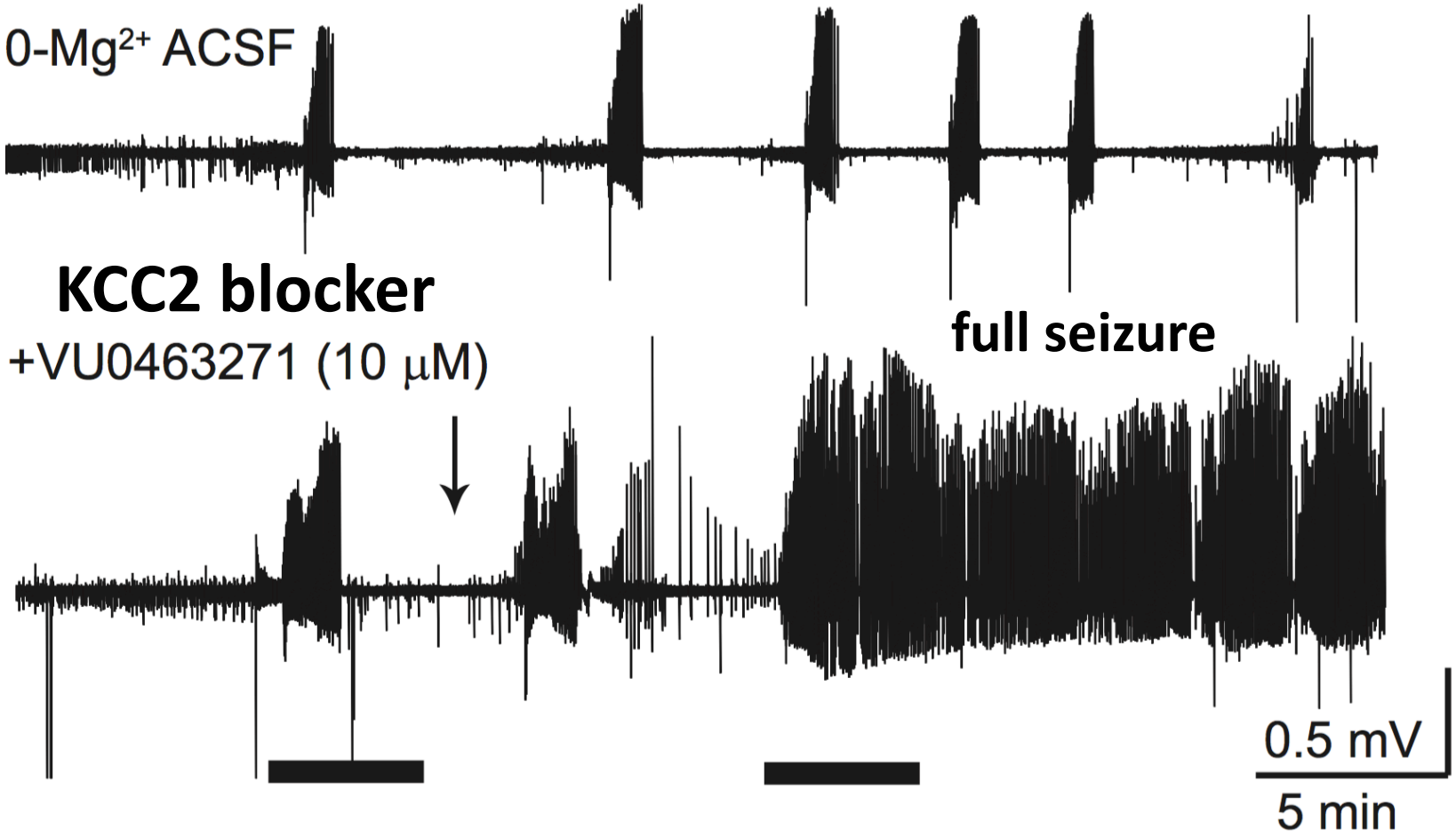
Evidence for the crucial role of KCC2



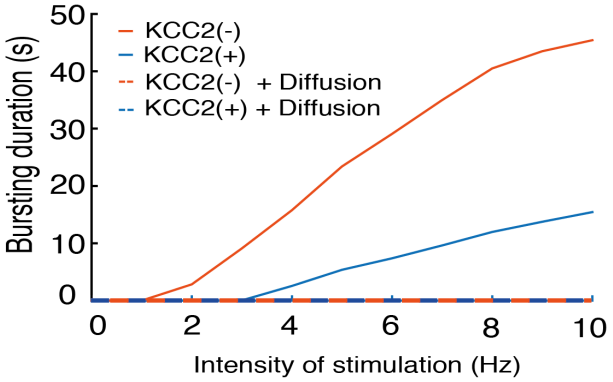
Sivakumaran et al 2015

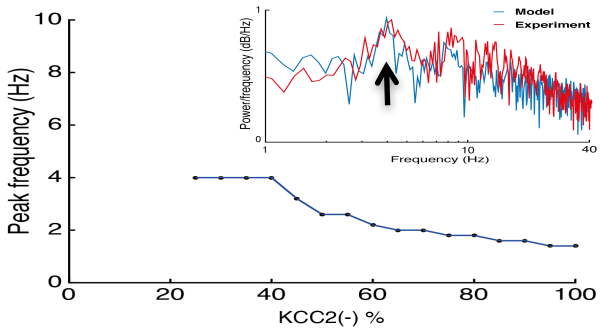
Conclusions

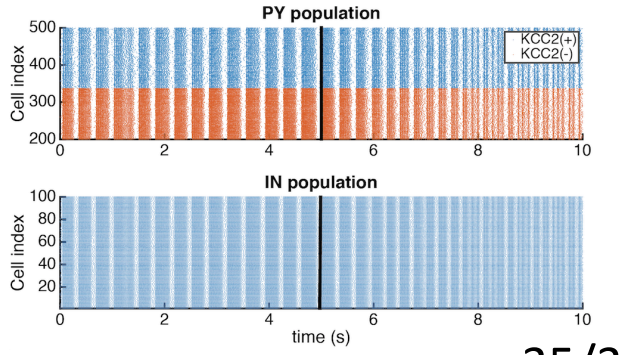
- KCC2(-) pathology leads to the depolarizing GABA reversal potential due to Cl^-_{IN} accumulation and increased susceptibility to bursting

- There is a critical amount of KCC2(-) pyramidal cells in the network required for seizure initiation

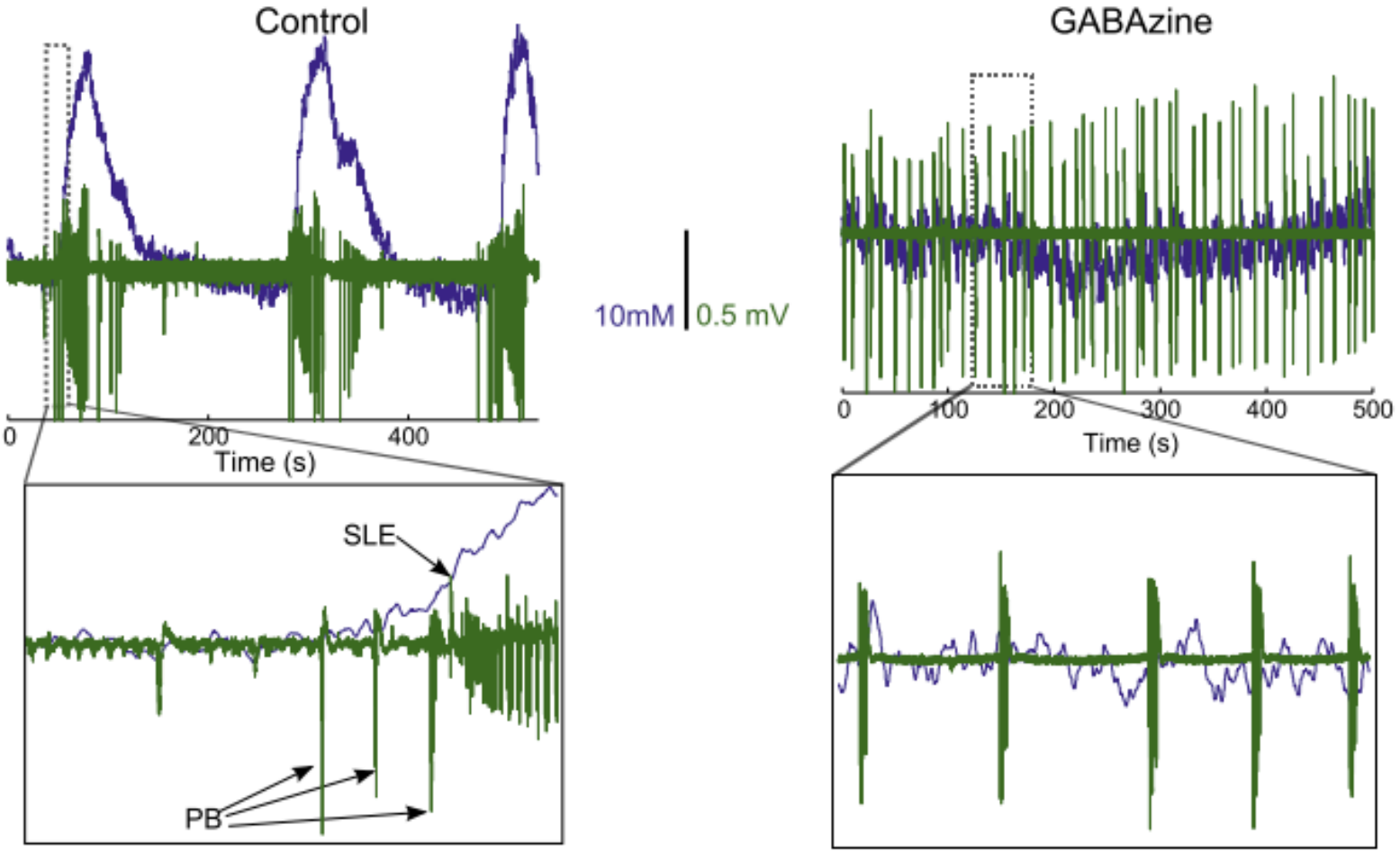
- Restoration of KCC2(-) function restores the excitation-inhibition balance







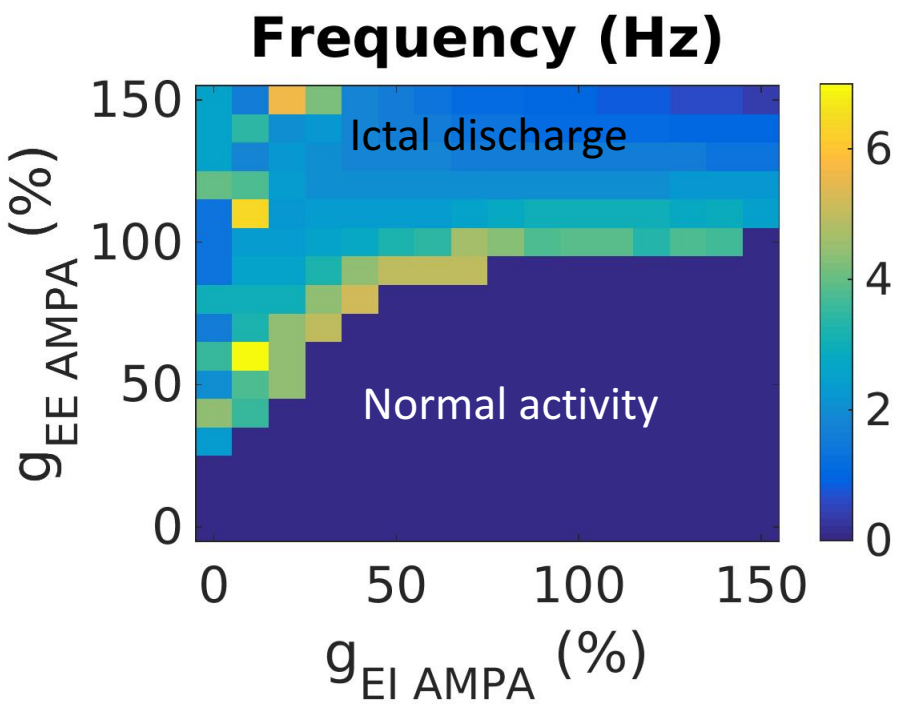
Chloride accumulation before ictal discharge initiation



Lillis et al. 2013

Difference between KCC2(+) and KCC2(-) excitability in the network

30% KCC2(-)



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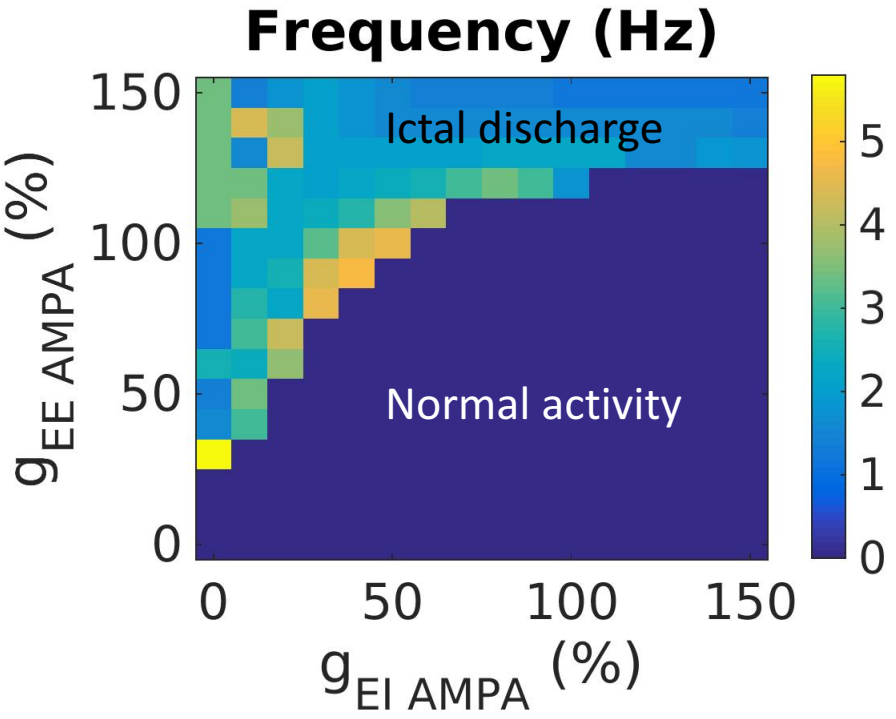
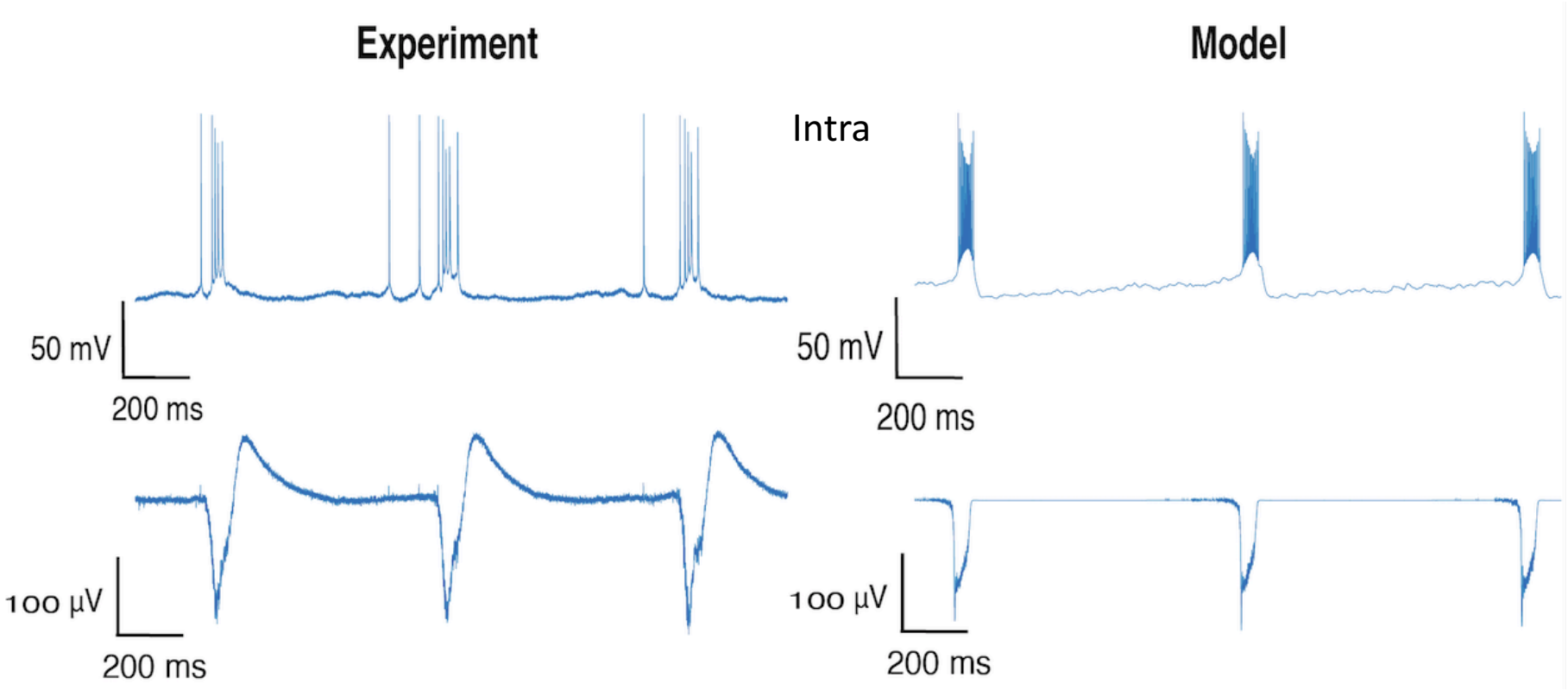
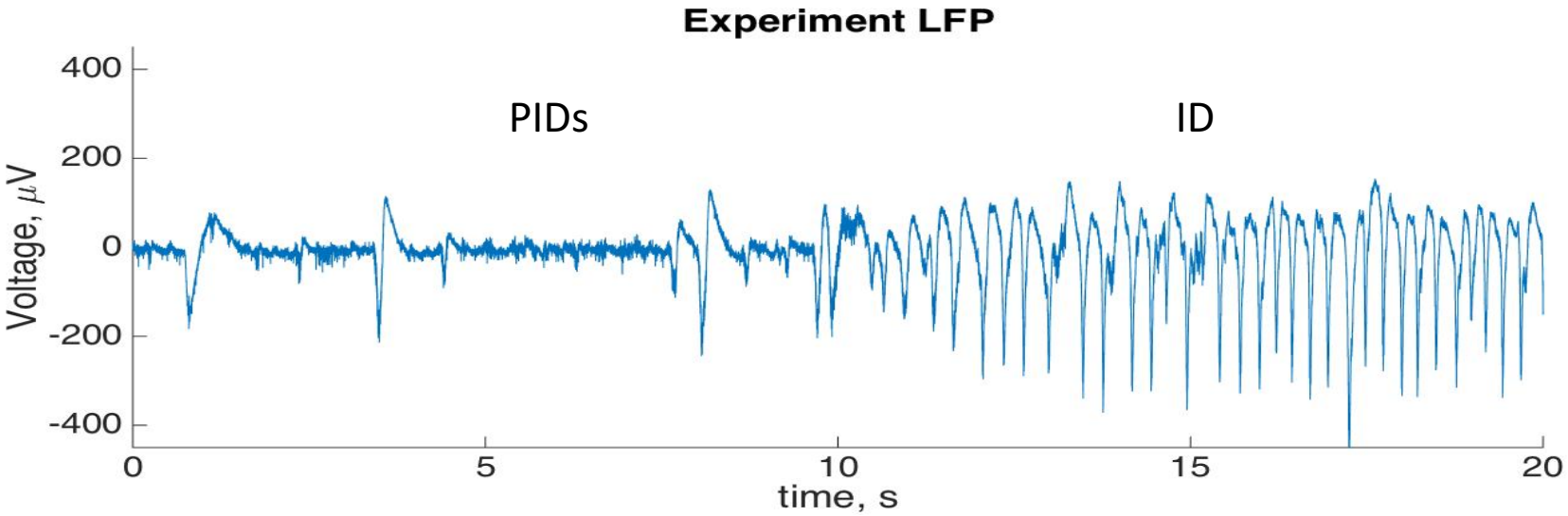
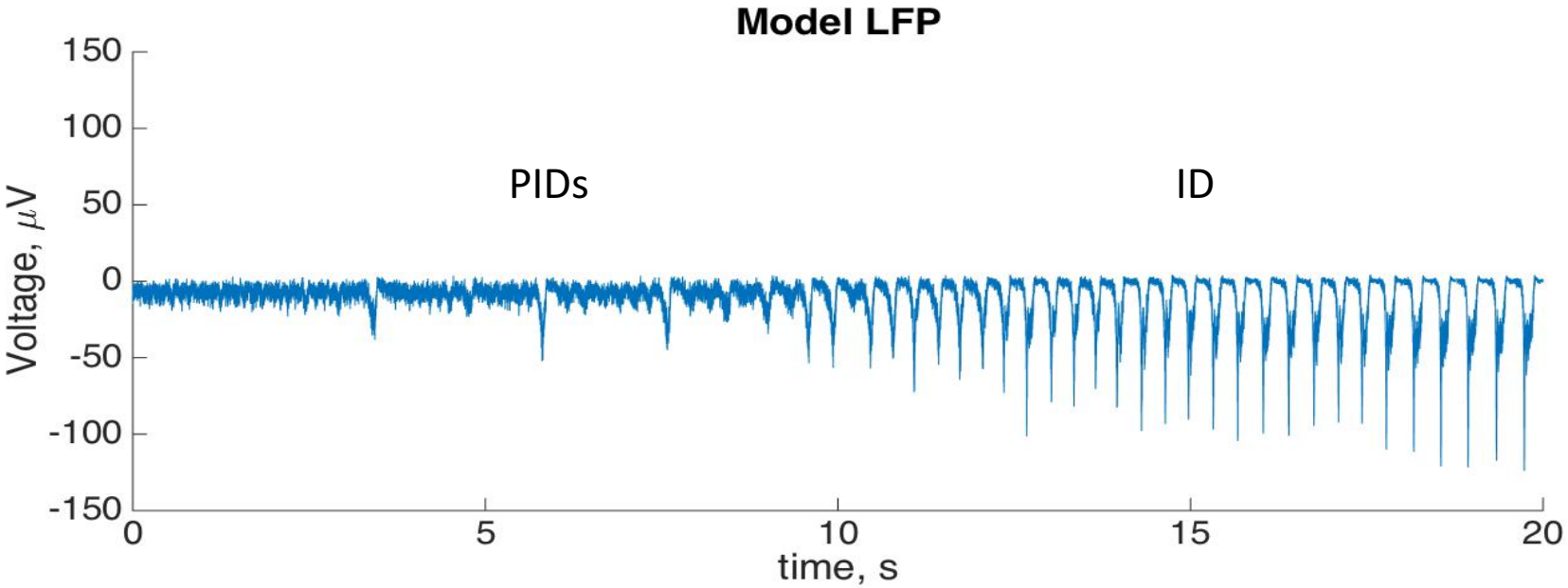


Blockade of inhibition leads to the development of population burst



Transition to seizure in slice experiment and model





LFP and pyramidal cell activity in slice experiment and model