

Multi scale dynamics in retinal waves

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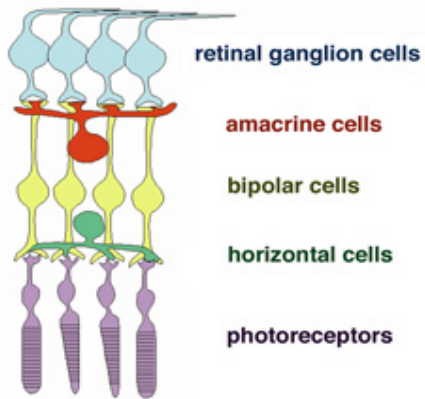
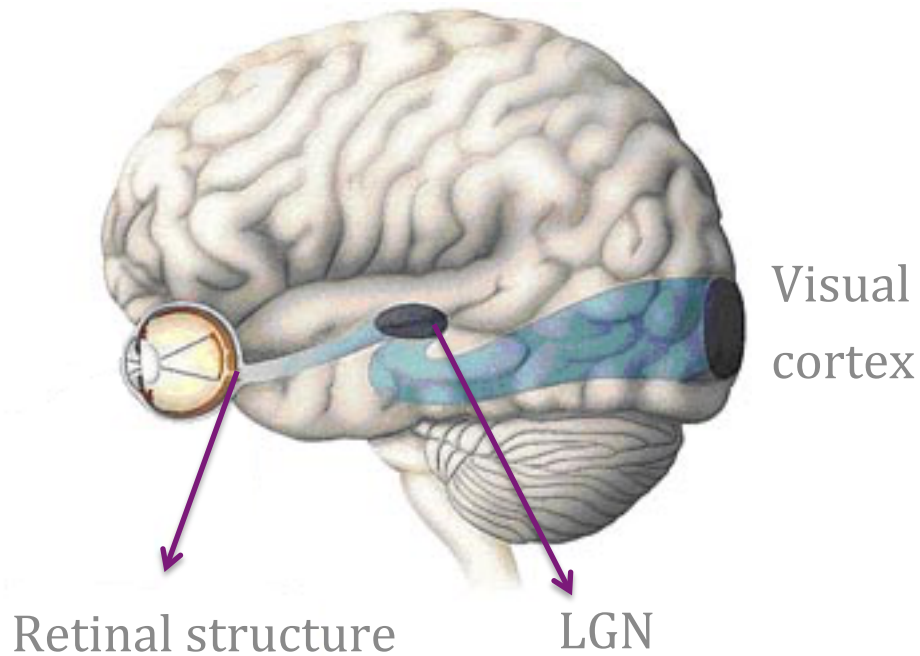
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Visual system and retinal waves



Visual system and retinal waves

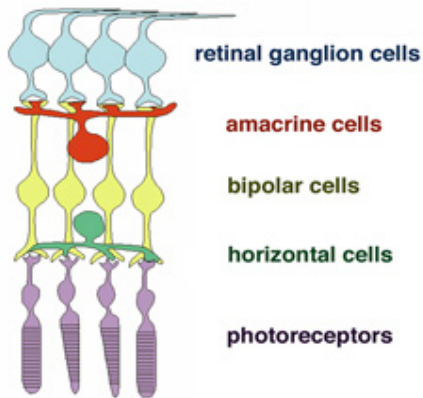
Spontaneous spatio-temporal “waves”
during development

- Disappear short after birth

Visual
cortex

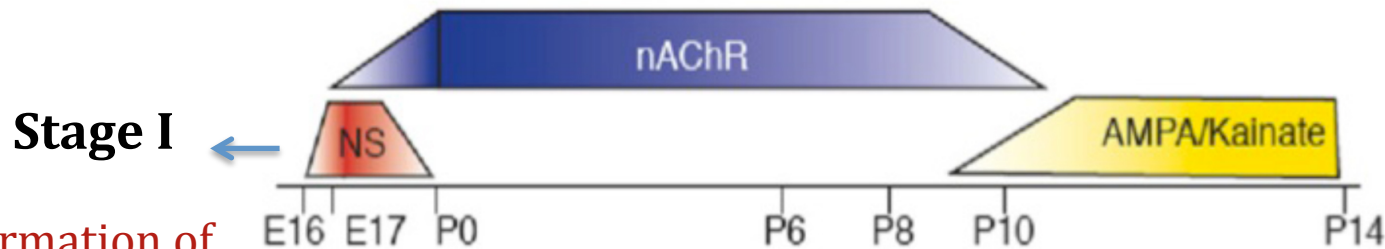
Retinal structure

LGN



*Spatio-Temporal evolution of a
retinal wave in mice during
development, Maccione et al. 2014*

Stages of Retinal Waves During Development



- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

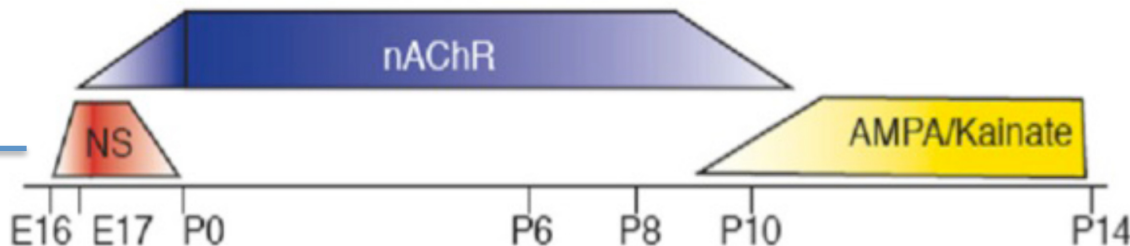
Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)



Stage I



- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

Stages of Retinal Waves During Development

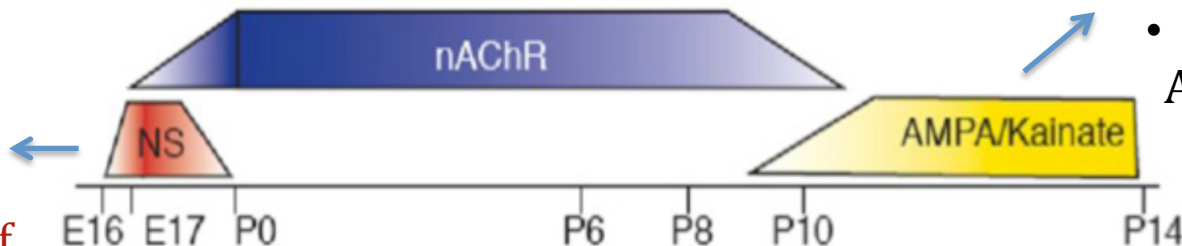
Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors

Stage I



- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

Stages of Retinal Waves During Development

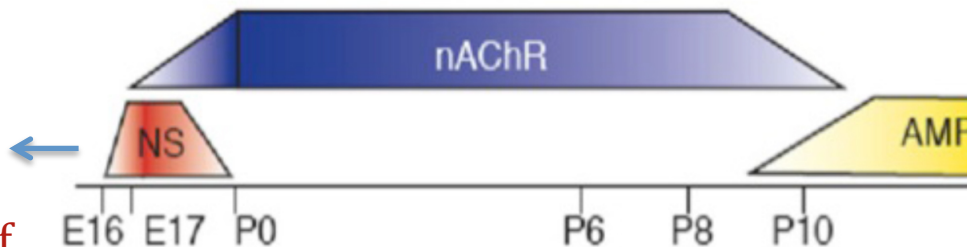
Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

Stage III

See the nice work of
Hannah Choi & al
Journal of
Neurophysiology 2014 on
All cells intrinsic bursting.

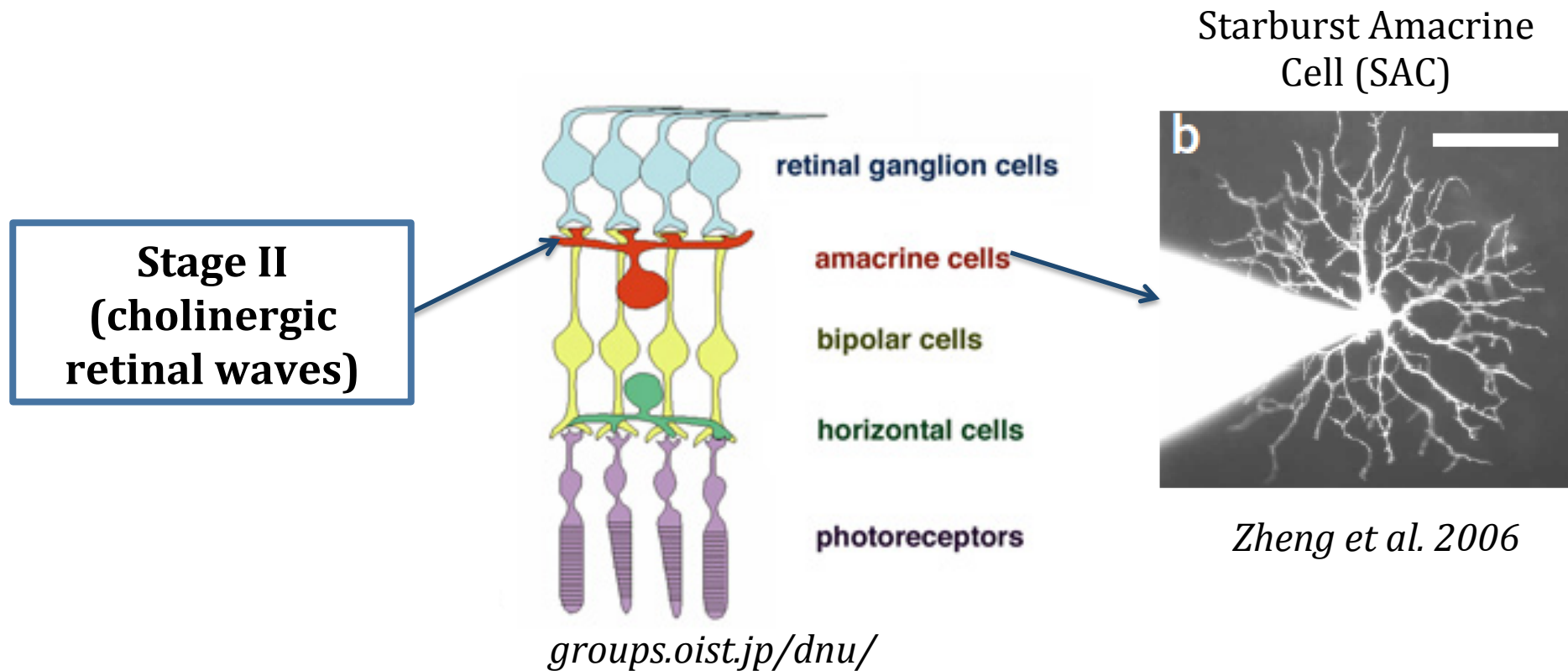
Stage I



- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

Focus on stage II retinal waves

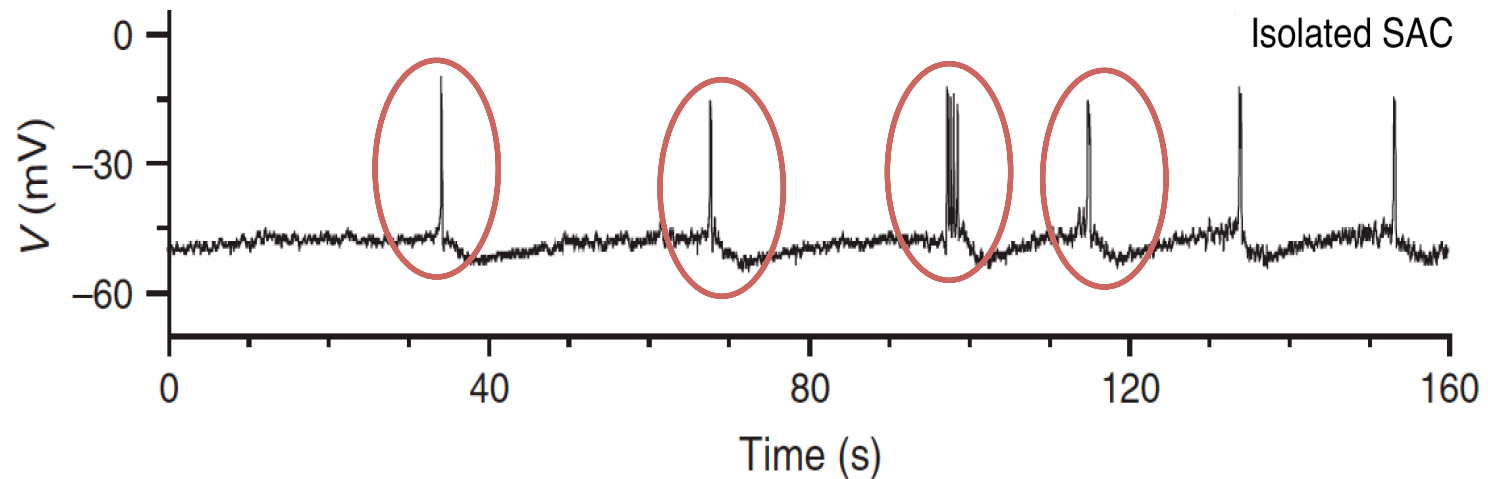
Stage II retinal waves are well studied experimentally and there is already existing work on their modeling



Experiments for the emergence of retinal waves

Retinal waves require three components:

i) Spontaneous bursting activity

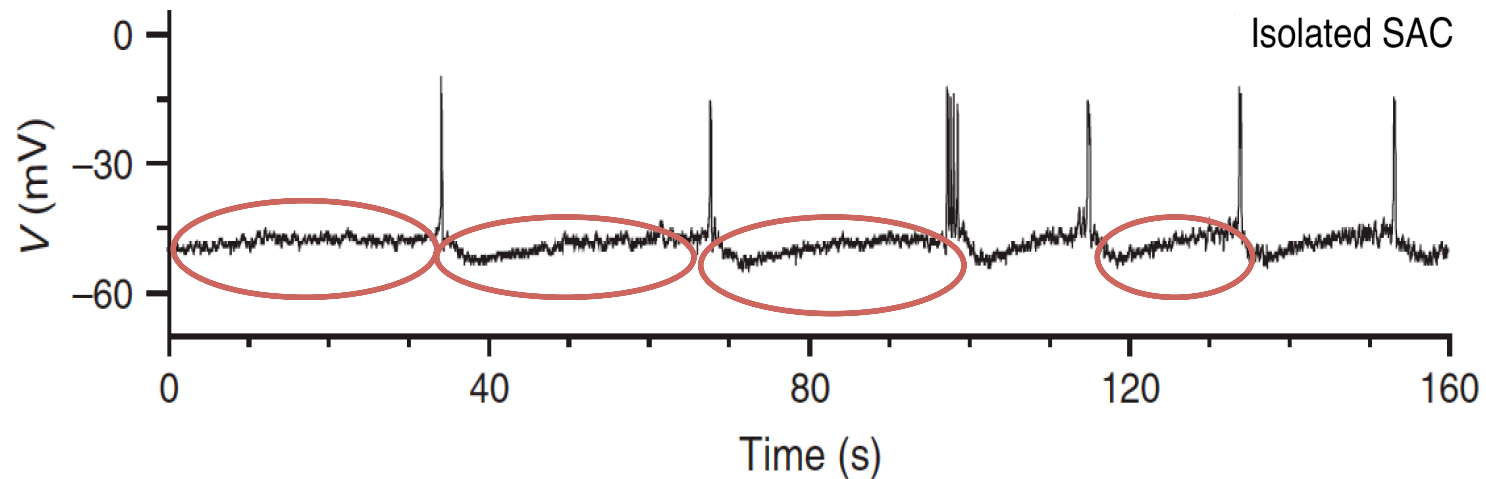


Experiment for isolated neurons,
Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)

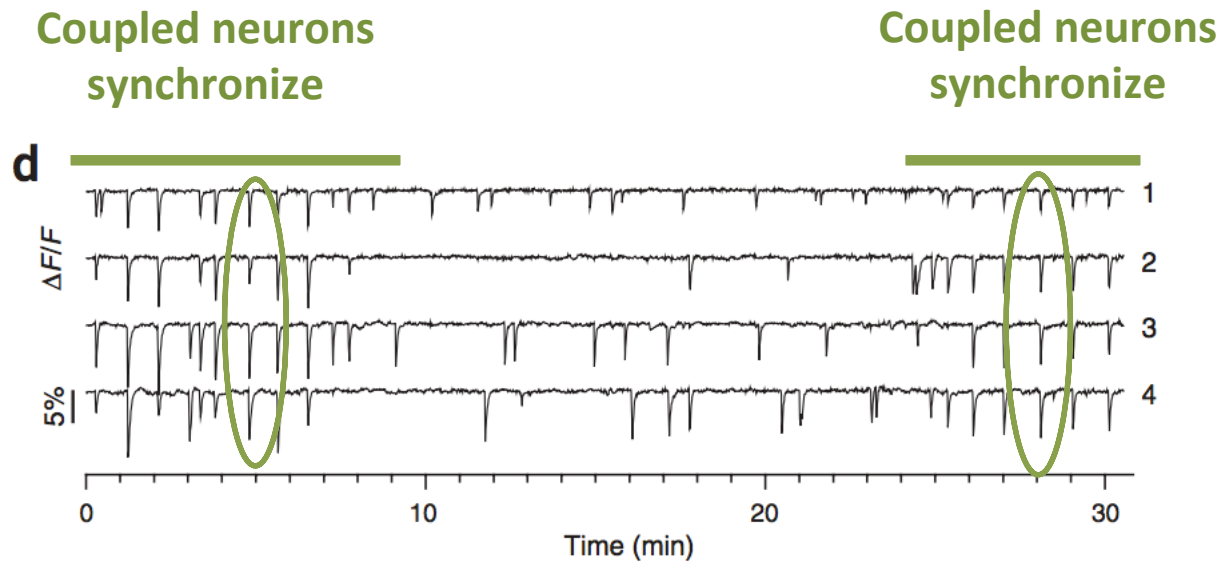


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Experiments for the emergence of retinal waves

Retinal waves require three components:

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- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)
- iii) Coupling (through Acetylcholine neurotransmitter)

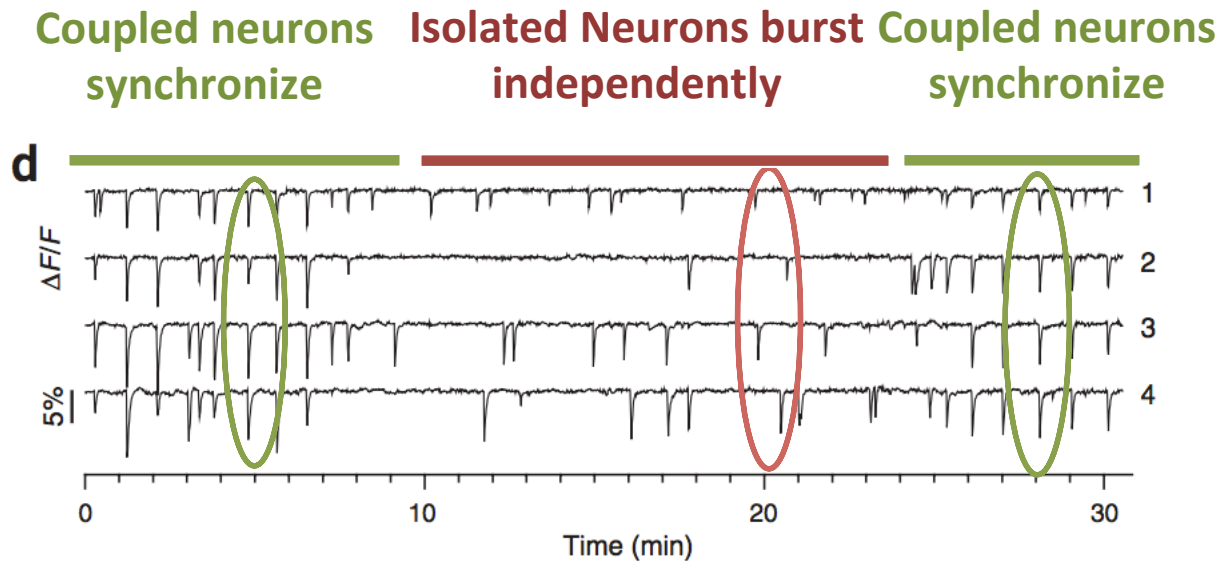


Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

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Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

Several models of stage II retinal waves have been proposed already:

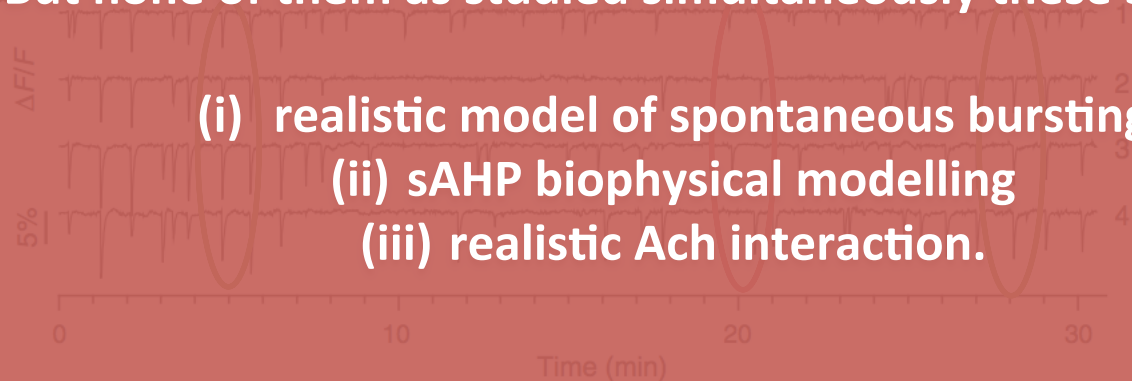
ii) Refractory mechanism (slow After HyperPolarisation- sAHP)

iii) Coupling (through Acetylcholine neurotransmitter)

- Feller et al Neuron, 1997.
- Eglon et al, J. Neuroscience 2000.
- Godfrey & Swindale. PLoS Comput Biol, 2007.
- Hennig et al, J. Neuroscience, 2009
- Lansdell et al, PLoS Computational Biology, 2014.

But none of them as studied simultaneously these 3 aspects:

- (i) realistic model of spontaneous bursting
- (ii) sAHP biophysical modelling
- (iii) realistic Ach interaction.



Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

Why study retinal waves?

Motivations:

- Retinal waves instruct **the shaping of the visual system**
 - Retina structuration
 - Retinotopy
 - Binocularity
- Understanding the mechanisms that generate them may help to **control them pharmacologically**.
- Using modelling to find **generic organizing principles**, explain **experiments** and propose new ones.
- Interesting **physical/mathematical** problem.

Why study retinal waves?

Strategy:

To propose a model (i) sufficiently close from biophysics to explain and propose experiments and (ii) sufficiently well posed mathematically to analyse its dynamics upon varying biophysical parameters (conductances).

- Modelling one cell bursting
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

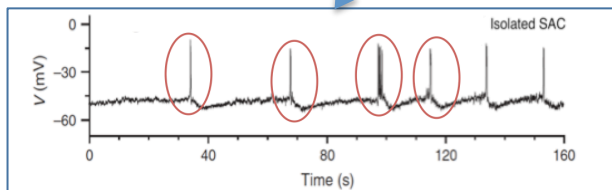
A network model for stage II retinal waves

Membrane potential dynamics

$$C_m \frac{\partial V}{\partial t} = -g_L^M(V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N(V - V_K)$$

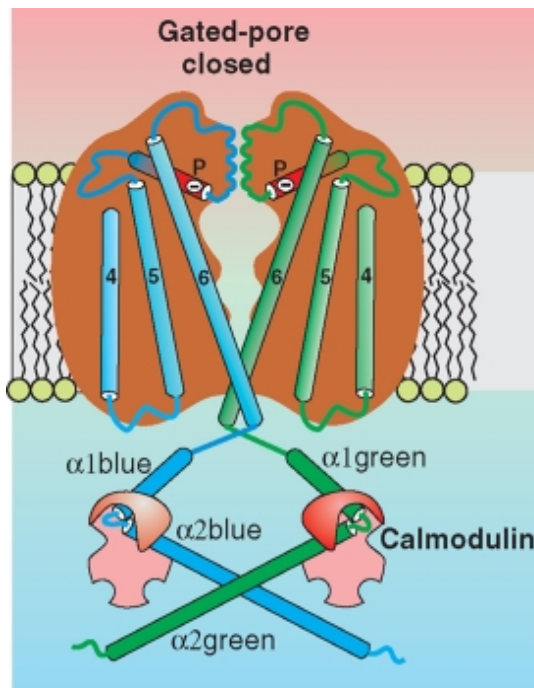
$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

**Morris-Lecar &
Fast K⁺ channels**

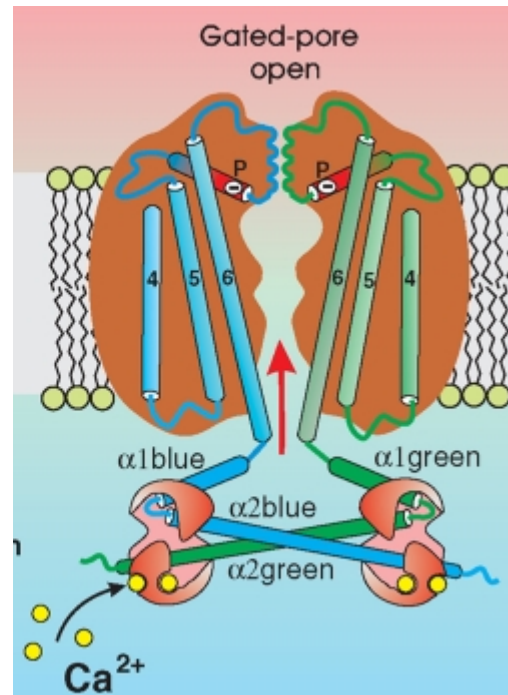


sAHP current

- **Definition**
 - Slow After Hyperpolarisation Current
 - Calcium-dependent slow potassium channels
- **Mechanism**
 - Model SK-like channels (Abel et al. 2004)
 - Gating Mechanism: **Four** ions Ca^{2+} bind to Calmodulin (CaM)



Closed



Open

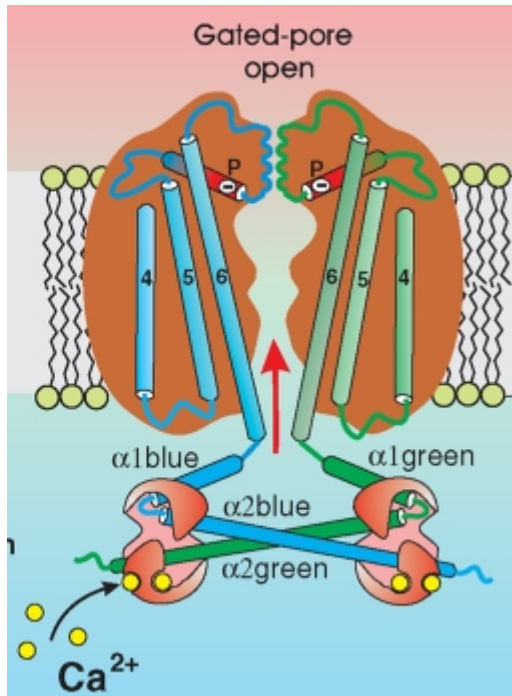
*Calcium gated
potassium
channel*

*superhimik.livejournal.
com/*

sAHP current

- Four Ca^{2+} ions bound to calmodulin open the channel
- I_{sAHP} current depends on gating variable R as follows:

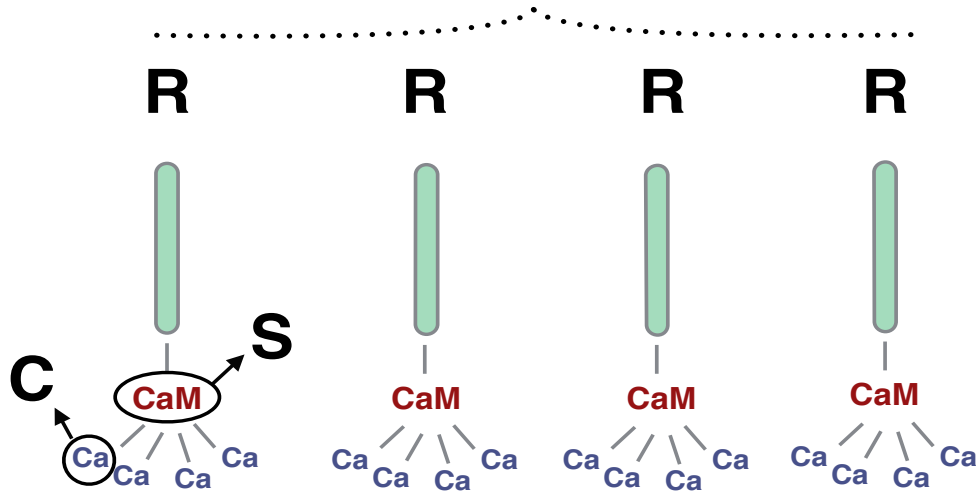
$$I_{sAHP} = g_{sAHP}^m R^4 (V - V_K) \quad (\text{Hennig et al. 2009})$$



The conductance is proportional to the fourth power of R because four terminals are needed to open the channel.

Set of equations for sAHP current

Activated Ca-gated K⁺ channel



Gating mechanism

All 4 subunits R of the channel are bound to activate the channel



Saturated Calmodulin molecule (CaM) bind to each channel subunit



4 Calcium ions bound to each saturated Calmodulin complex S

Set of equations for sAHP current

Activated
Ca-gated K⁺ channel

$$\tau_R \frac{dR}{dt} = a_R S(1 - R) - R$$

R : Probability that one terminal of the channel is open

$$\tau_S \frac{dS}{dt} = -S + a_S C^4(1 - S)$$

S : Fraction of saturated calmodulin concentration (CaM)

$$\tau_{Ca} \frac{dC}{dt} = -a_R \frac{C}{H_x} + C_o + \delta_{Ca} I_{Ca}(V)$$

C : Intracellular Calcium concentration

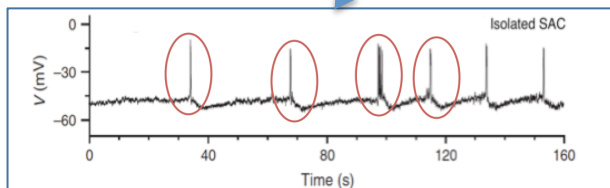
A network model for stage II retinal waves

Membrane potential dynamics

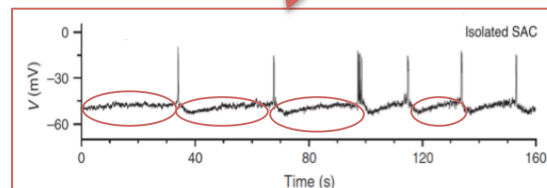
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V) (N_\infty(V) - N)$$

**Morris-Lecar &
Fast K⁺ channels**



**sAHP current
Refractory
mechanism**



SACs Network

Model synaptic interactions

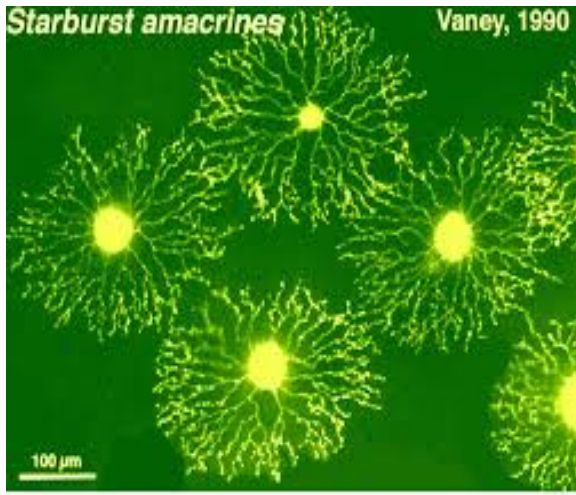
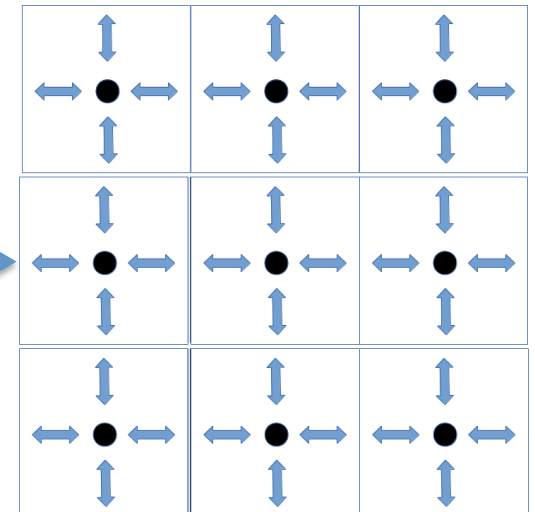
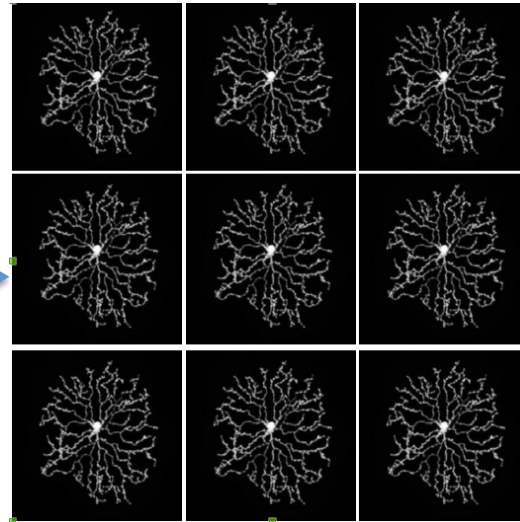


Fig 7. Starburst amacrine cells are stained with lucifer yellow in whole-mount rabbit retina.



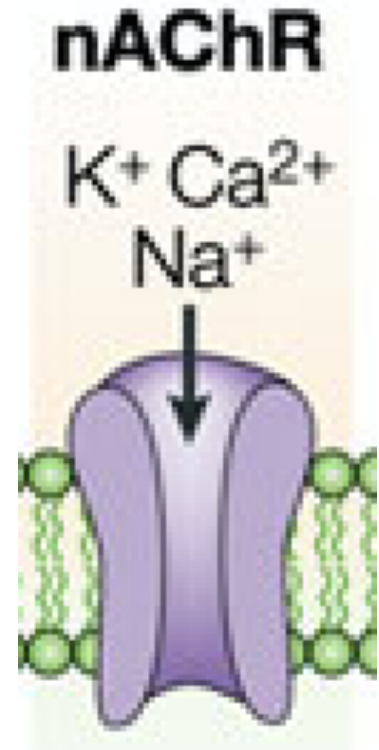
SACs realistic
connections

SACs on a lattice

SACs become points on
a lattice

Acetylcholine current

- Molecular nicotinic receptors (nAChR)
- Two molecules of acetylcholine bind to open a nicotinic channel
- The nicotinic conductance depends on the second power of the acetylcholine neurotransmitter concentration A

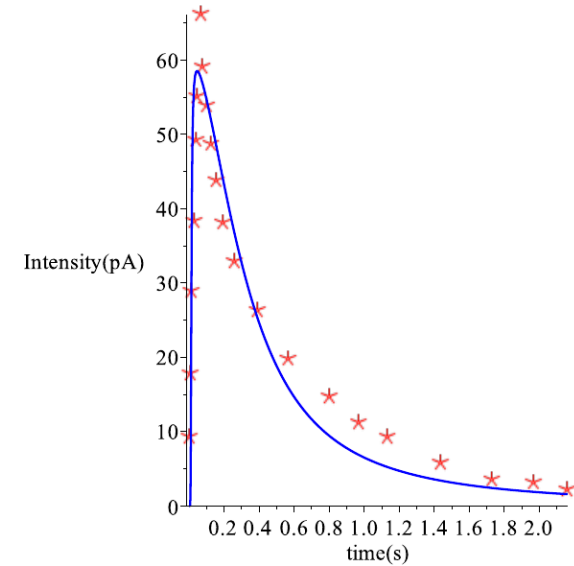
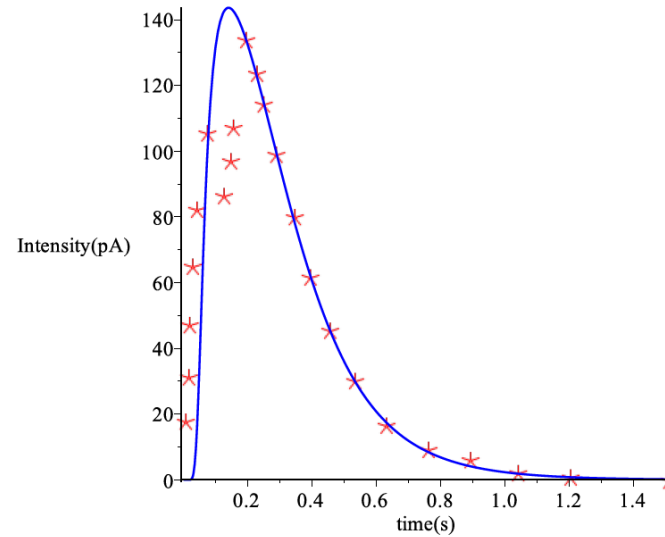
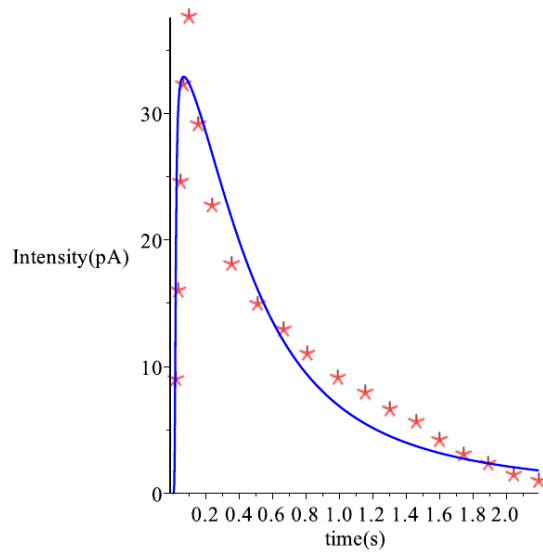


$$g_{Ach} = g_{Ach}^m \frac{A^2}{K_d^2 + A^2}$$

Acetylcholine current

$$\frac{\partial A}{\partial t} = \beta_{Ach} T_{Ach} (V) - \frac{A}{\tau_{Ach}}$$

A: Extracellular Acetylcholine concentration



Experimental fits from Zhou et al. 2004, Neuron

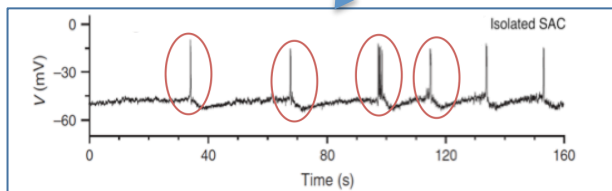
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Membrane potential dynamics

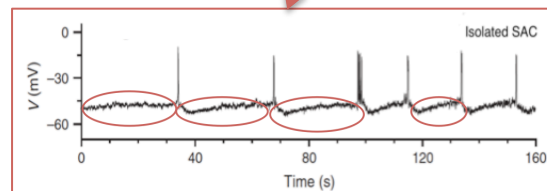
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach} (A_j) (V_i - V_{Ach})$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V) (N_\infty(V) - N)$$

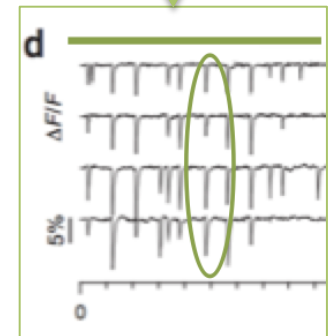
**Morris-Lecar &
Fast K⁺ channels**



**sAHP current
Refractory
mechanism**



**Ach current
Network
effect**



A network model for stage II retinal waves

$$\left\{ \begin{array}{lcl} C_m \frac{dV_i}{dt} & = & -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\ & & - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k \in \mathcal{B}_i})(V_i - V_A) \\ \tau_N \frac{dN_i}{dt} & = & \Lambda(V_i)(N_\infty(V_i) - N_i) \\ \tau_C \frac{dC_i}{dt} & = & -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\ \tau_S \frac{dS_i}{dt} & = & \alpha_S(1 - S_i)C_i^4 - S_i \\ \tau_R \frac{dR_i}{dt} & = & \alpha_R S_i(1 - R_i) - R_i \\ \frac{dA_i}{dt} & = & -\mu A_i + \beta_A T_A(V_i), \end{array} \right.$$

A network model for stage II retinal waves

N neurons, 6 N equations

$$\left\{ \begin{array}{l} C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\ \quad - G_{SAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k \in \mathcal{N}})(V_i - V_A) \\ \tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i) \\ \tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\ \tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i)C_i^4 - S_i \\ \tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i \\ \frac{dA_i}{dt} = -\mu A_i + \beta_A T_A(V_i), \end{array} \right.$$

~ 20 parameters per neuron

(But neurons are assumed identical)

A network model for stage II retinal waves

N neurons, 6 N equations

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~ 20 parameters per neuron
(But neurons are assumed identical)

Time scale separation

Fast V, N . $\tau_L = 11$ ms, $\tau_N = 5$ ms.

Medium C, A . $\tau_C = 2$ s, $\tau_A = 1.86$ s.

Slow S, R . $\tau_R = \tau_S = 44$ s.

Fast time scale

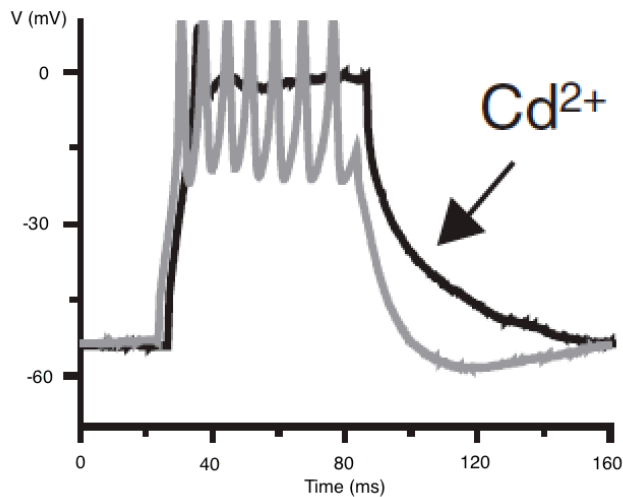
Morris-Lecar model with fast dynamics, in the presence of a slow external current

$$\begin{cases} \frac{dV}{dt_f} &= -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) + I_{\text{ext}} \\ \frac{dN}{dt_f} &= \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \end{cases}$$

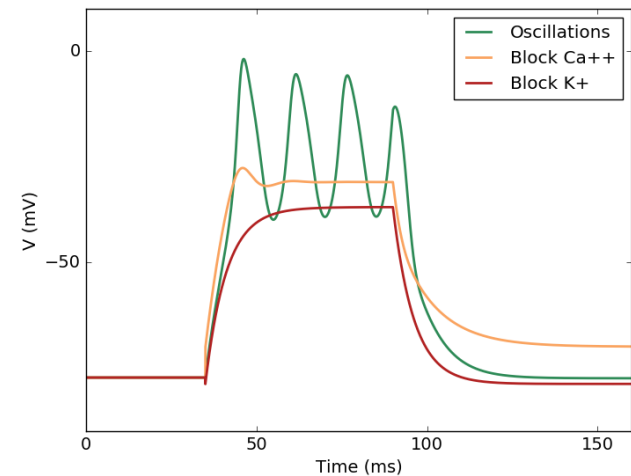
Fast time scale

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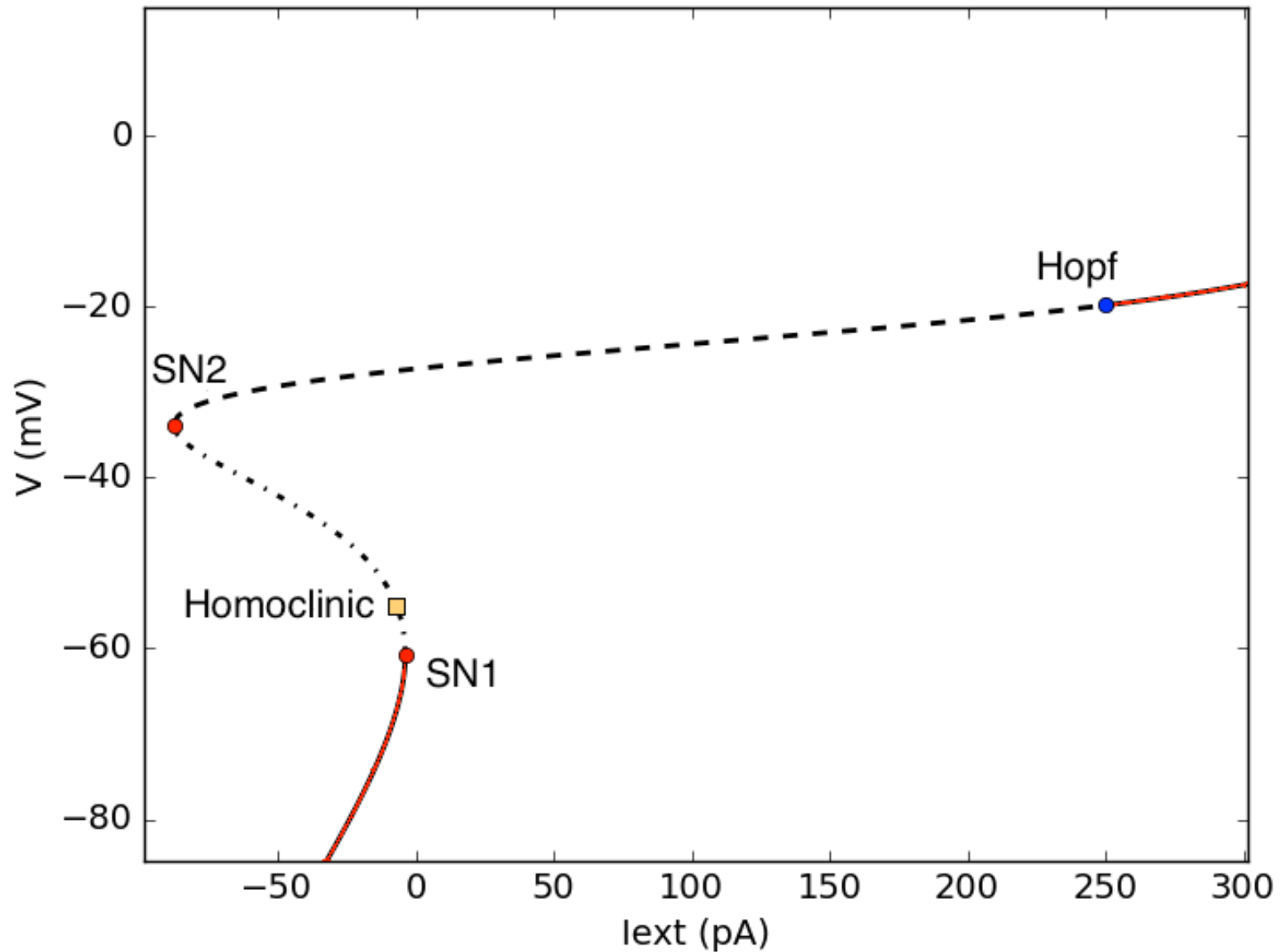


**Experiment by Zheng et al. 2006,
Nature**

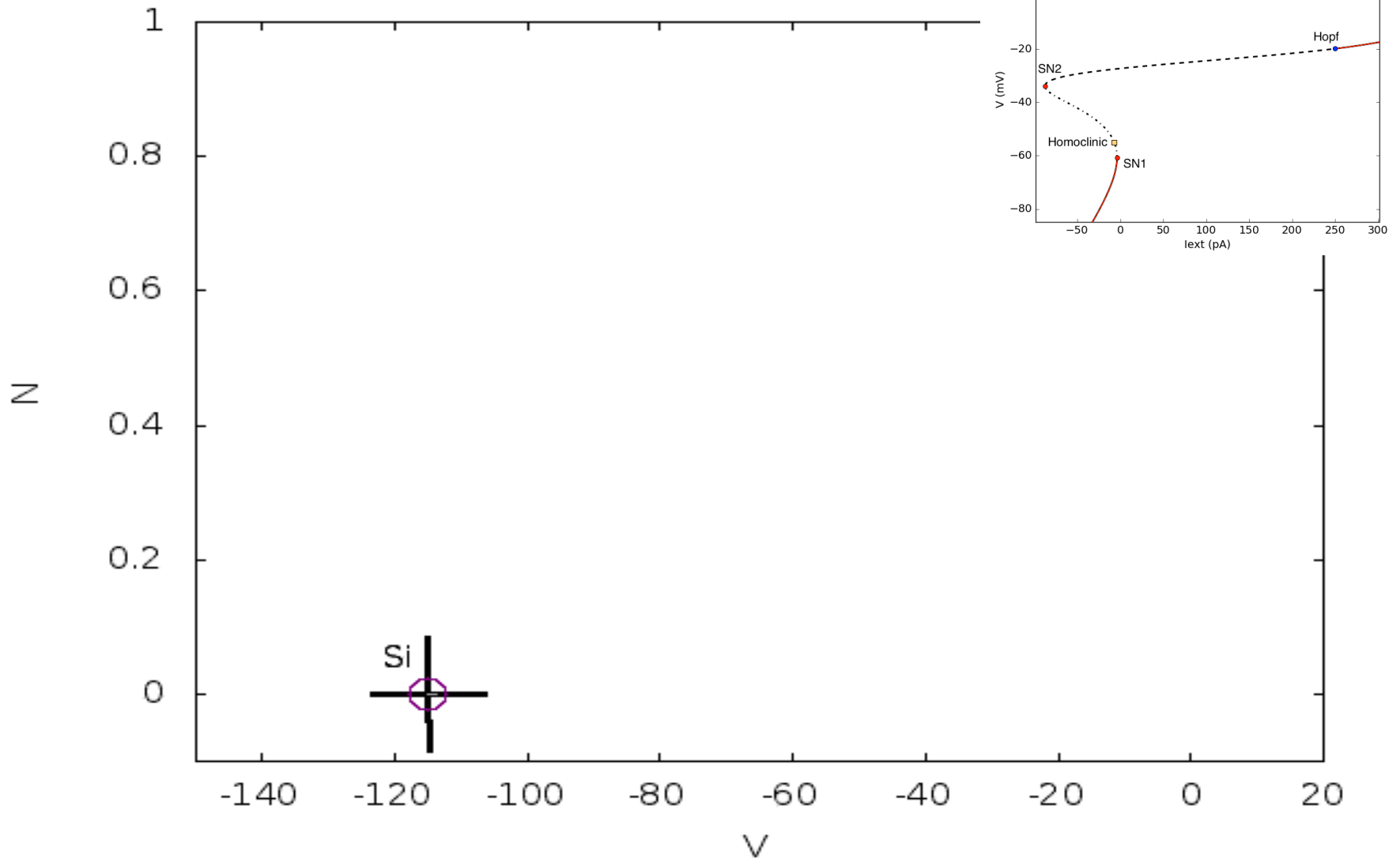


**Model. Tuning parameters V1, V2,
V3 ,V4 from ML adjusted to
reproduce the experiment**

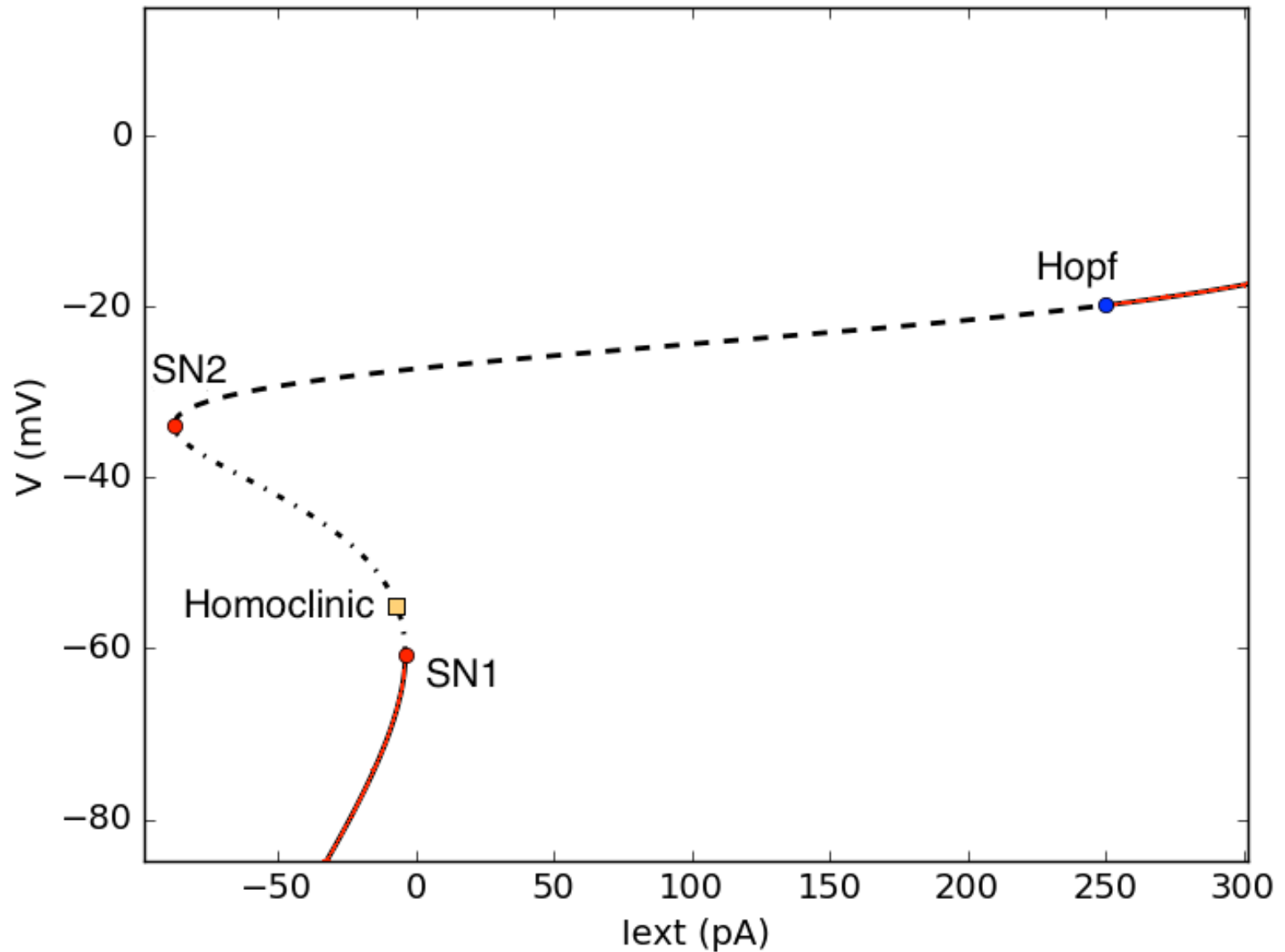
Bifurcation diagram of M-L model



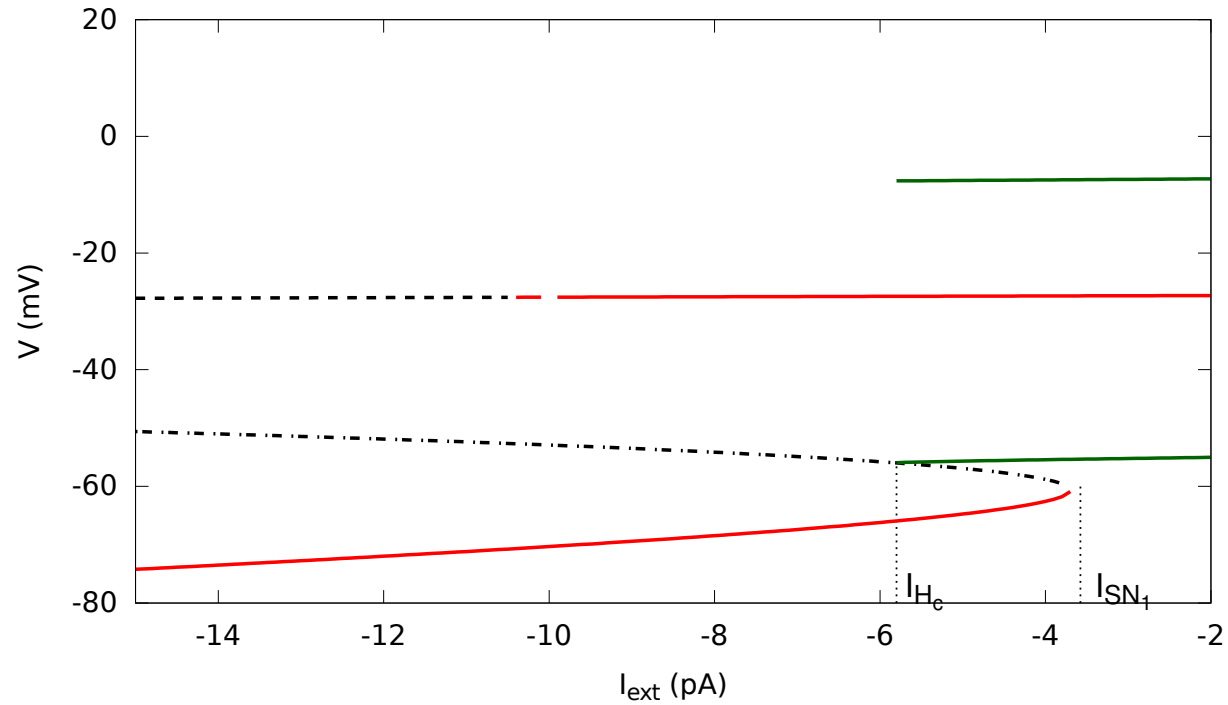
Bifurcation diagram of M-L model



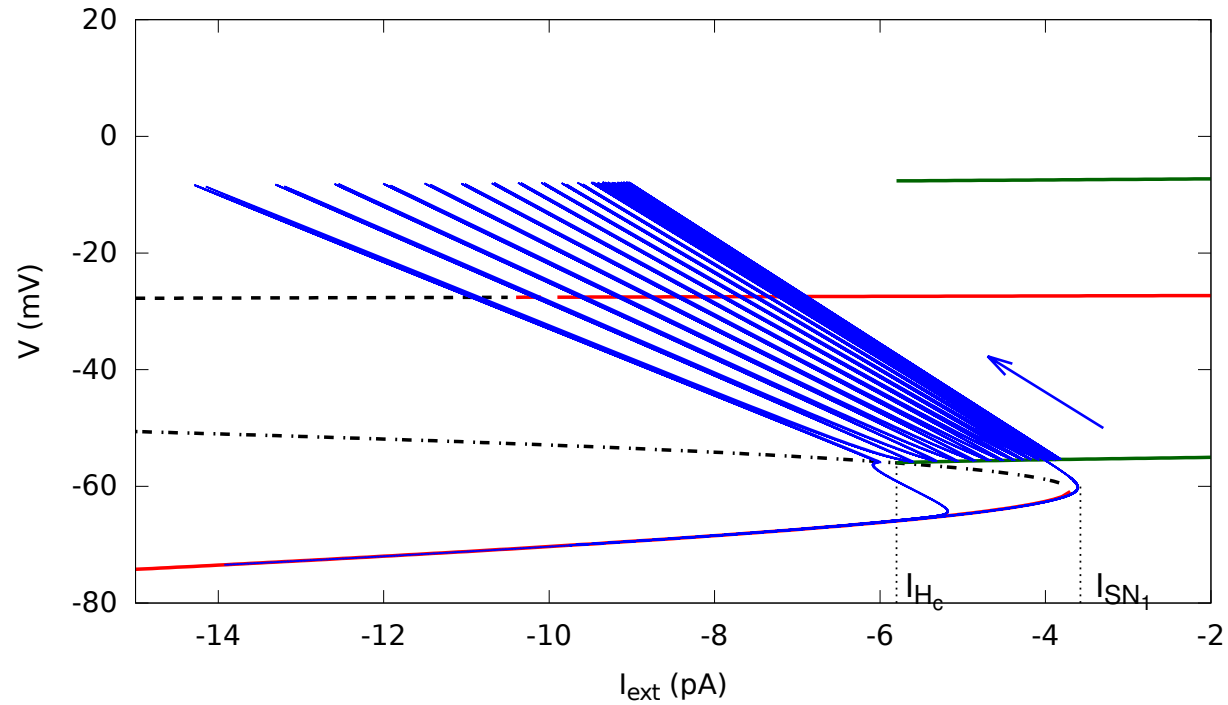
Bifurcation diagram of M-L model



The mechanism of bursting

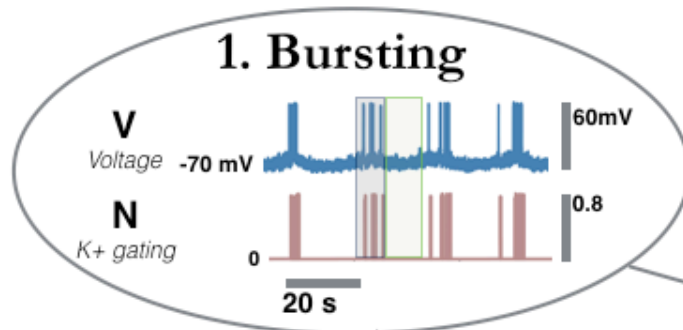


The mechanism of bursting

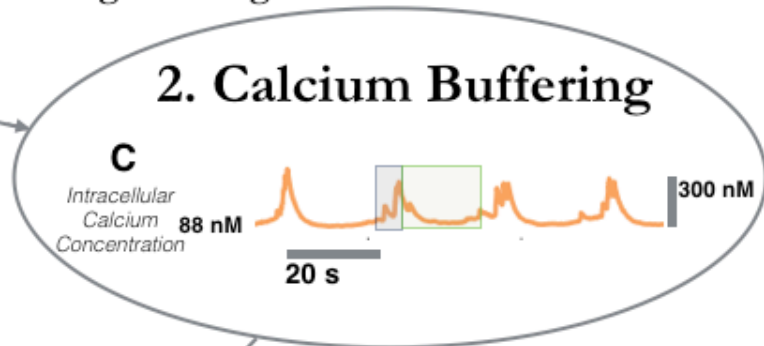


Spontaneous Bursting Mechanism of SACs

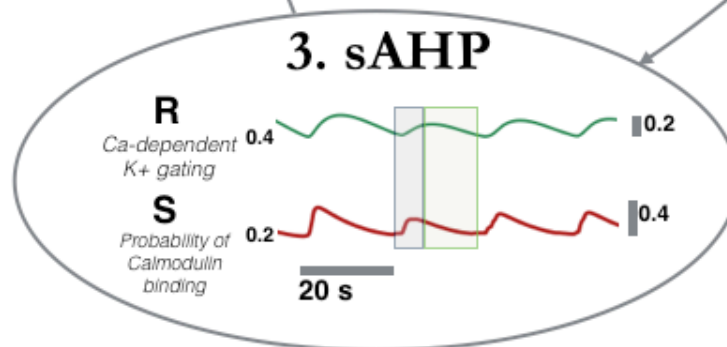
Bursting
 sAHP



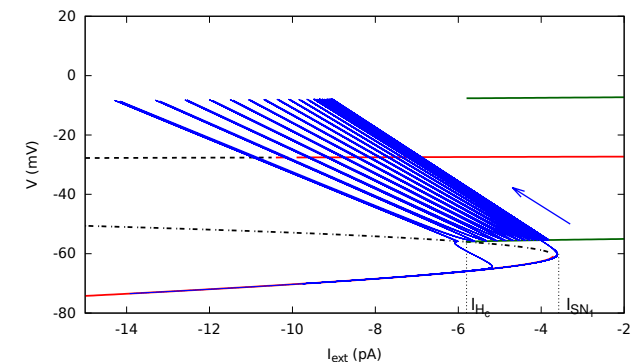
Increase of Calcium load during bursting



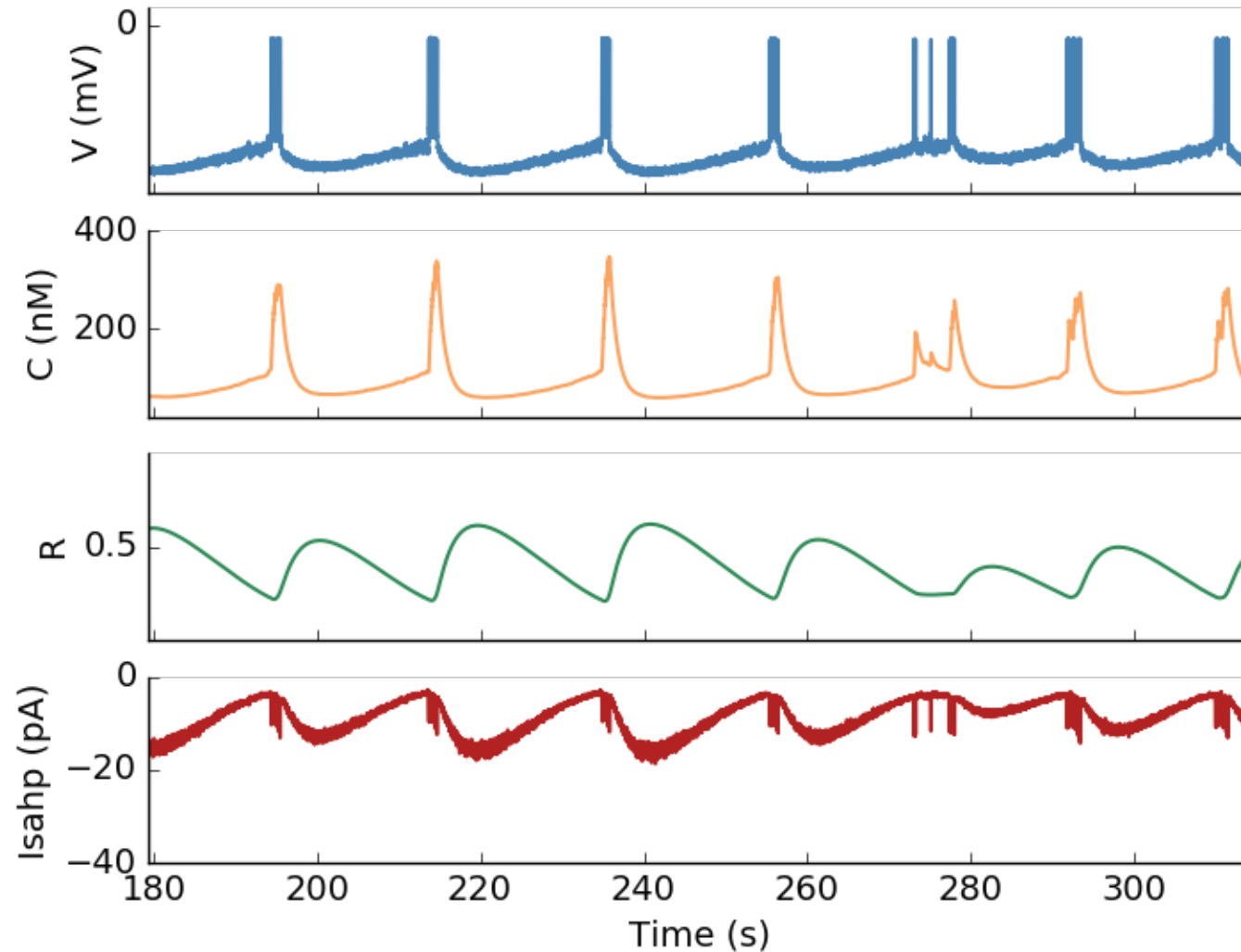
Bursting starts again when the Calcium load is low enough



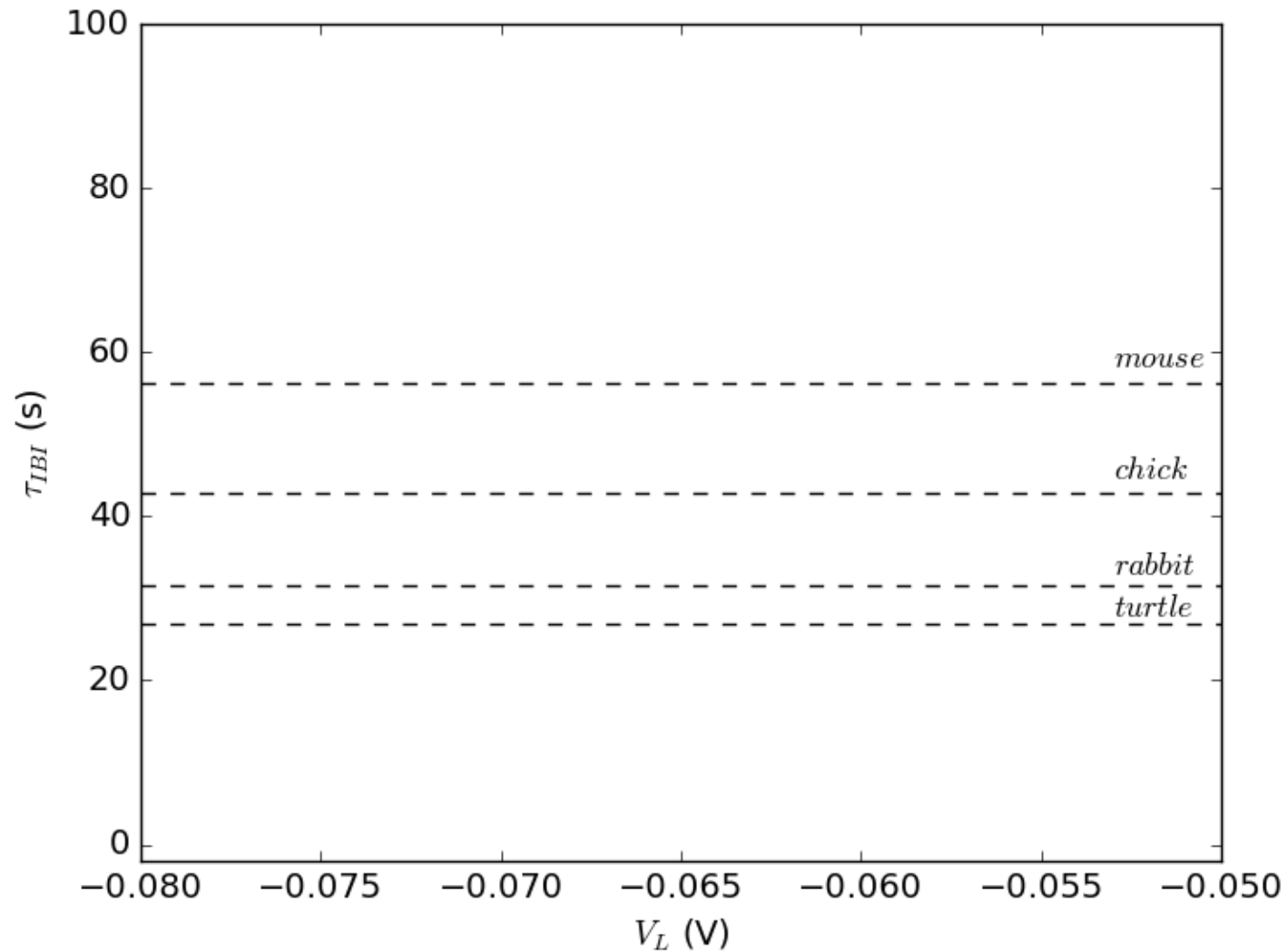
Calcium controls the sAHP phase.
Voltage is low and Calcium starts offloading



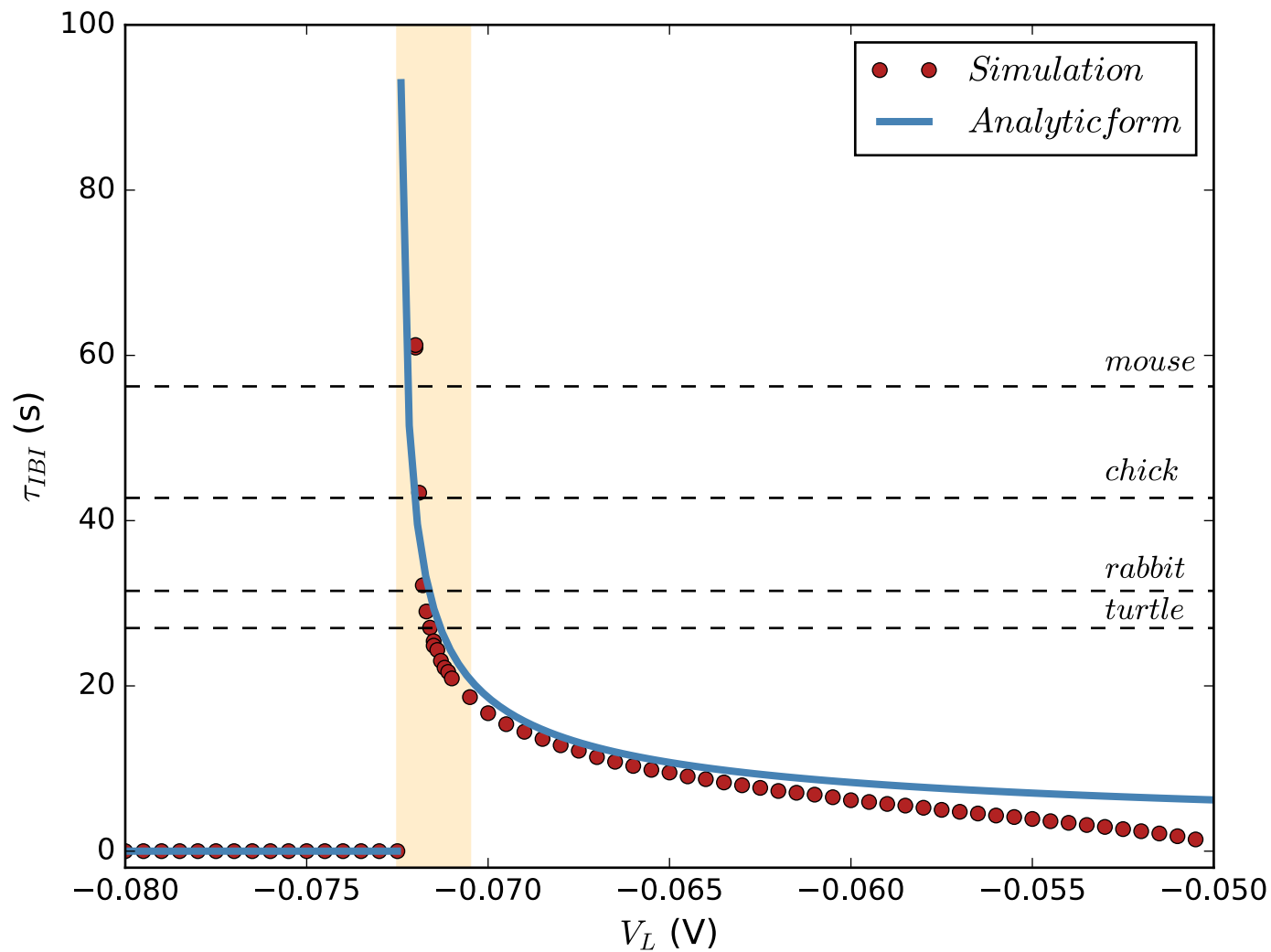
Reproduce Individual SACs bursting dynamics



Explain variable bursting period across species

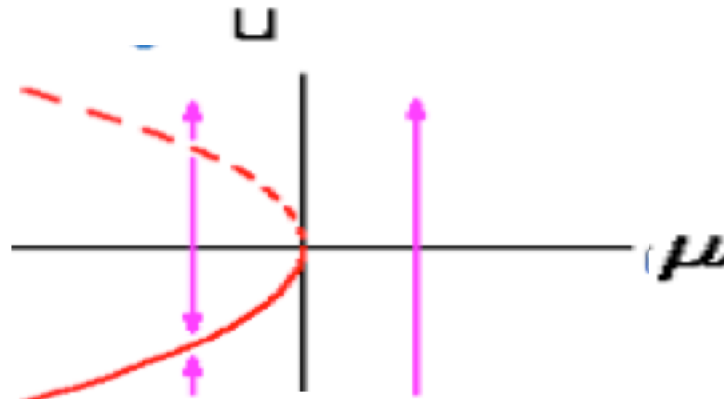


Explain variable bursting period across species

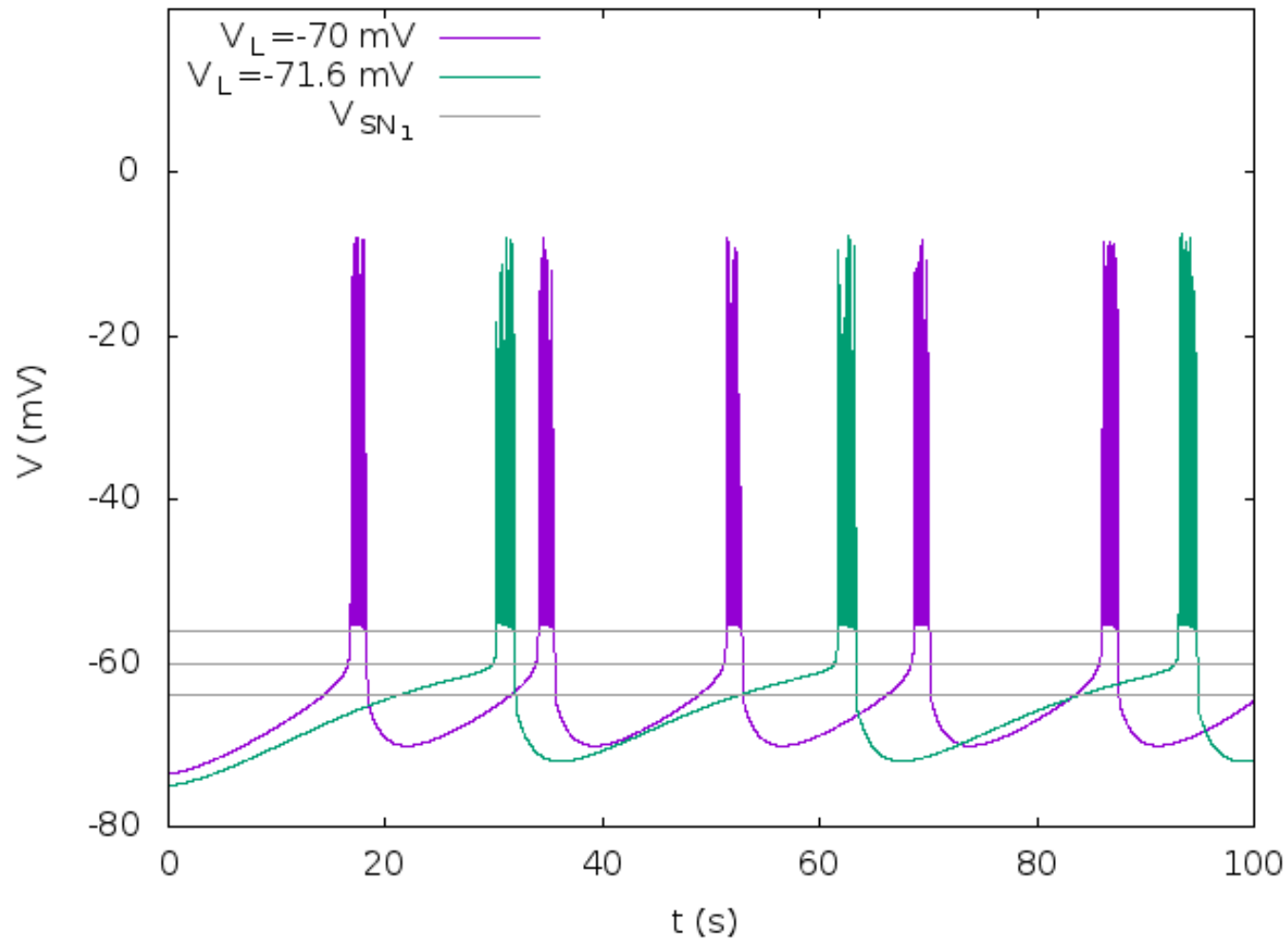


Explain variable bursting period across species

saddle-node bifurcation



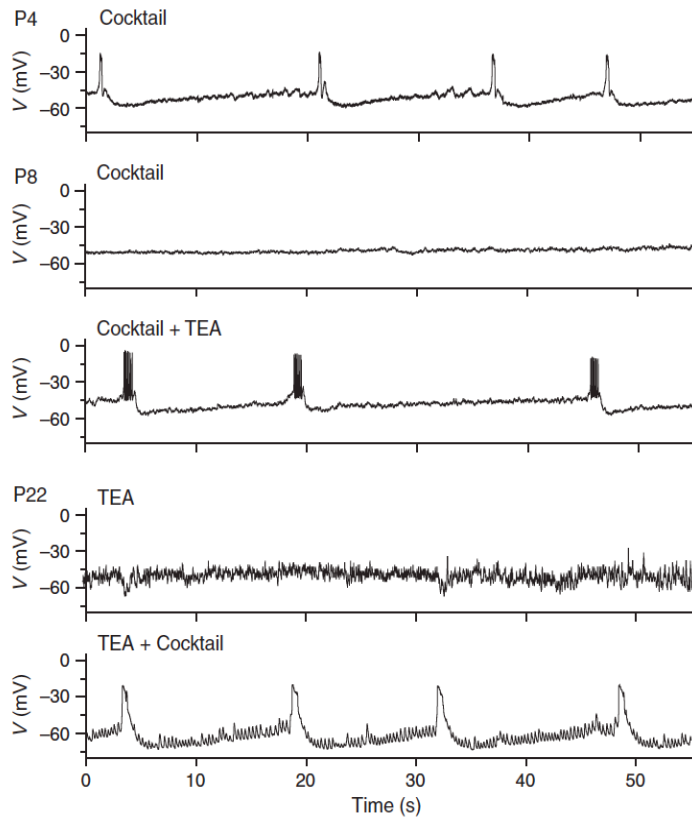
Explain variable bursting period across species



Predict the role of Kv3 channels in the loss of SACs excitability

A

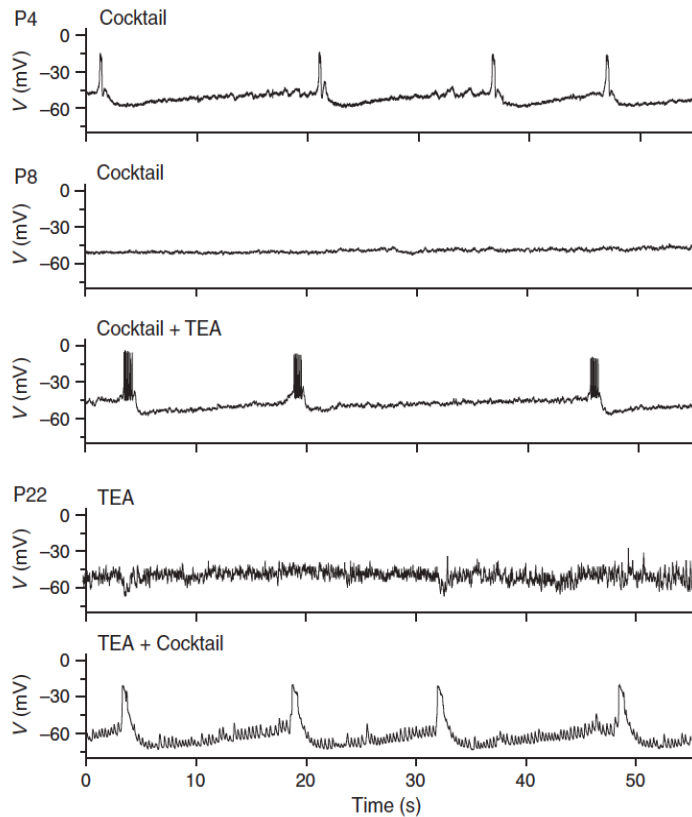
Experiment (Zheng et al. 2006)



Predict the role of Kv3 channels in the loss of SACs excitability

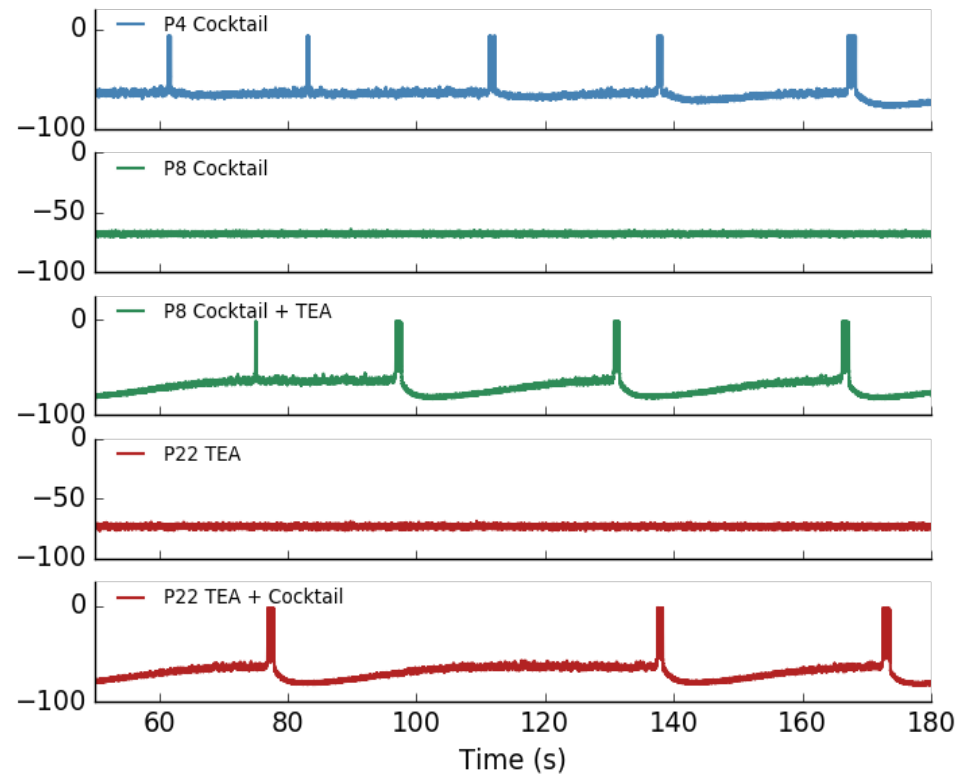
A

Experiment (Zheng et al. 2006)



B

Model



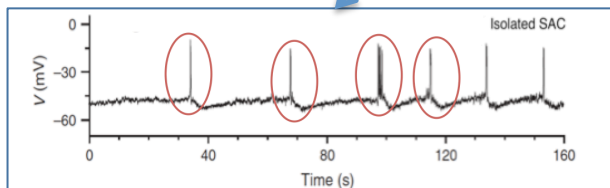
A network model for stage II retinal waves

Morris-Lecar

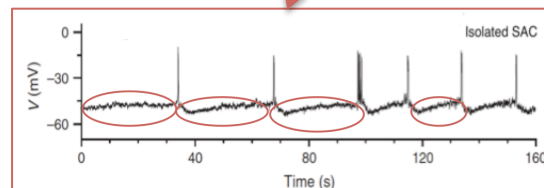
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach} (A_j) (V_i - V_{Ach})$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V) (N_\infty(V) - N)$$

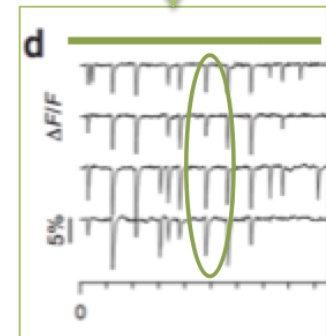
**Morris-Lecar &
Fast K⁺ channels
(kV3)**



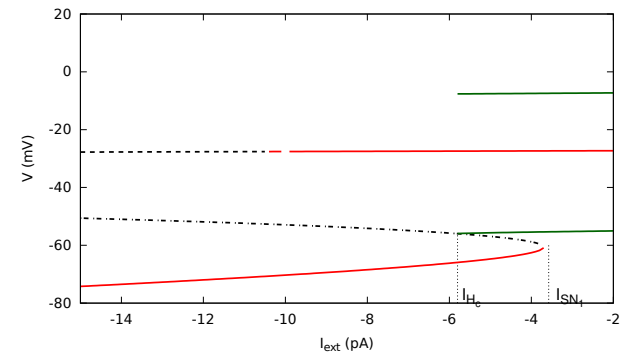
**sAHP current
Refractory
mechanism**



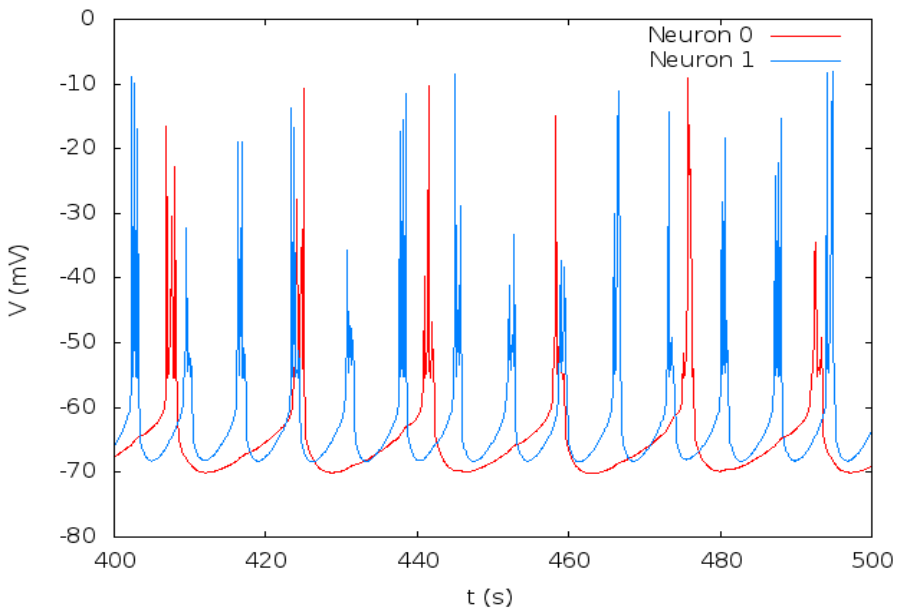
**Ach current
Network
effect**



Coupling 2 cells

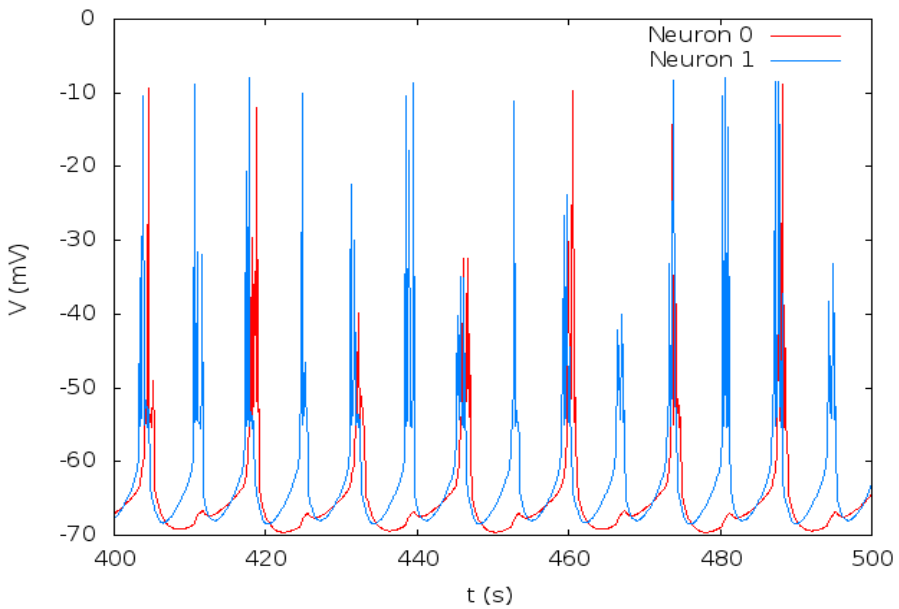


Coupling 2 cells

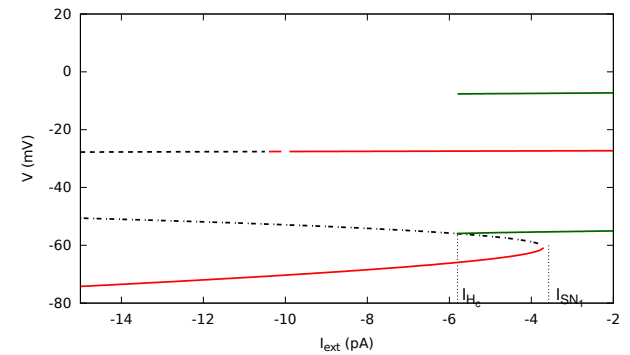


Gach: synaptic conductance

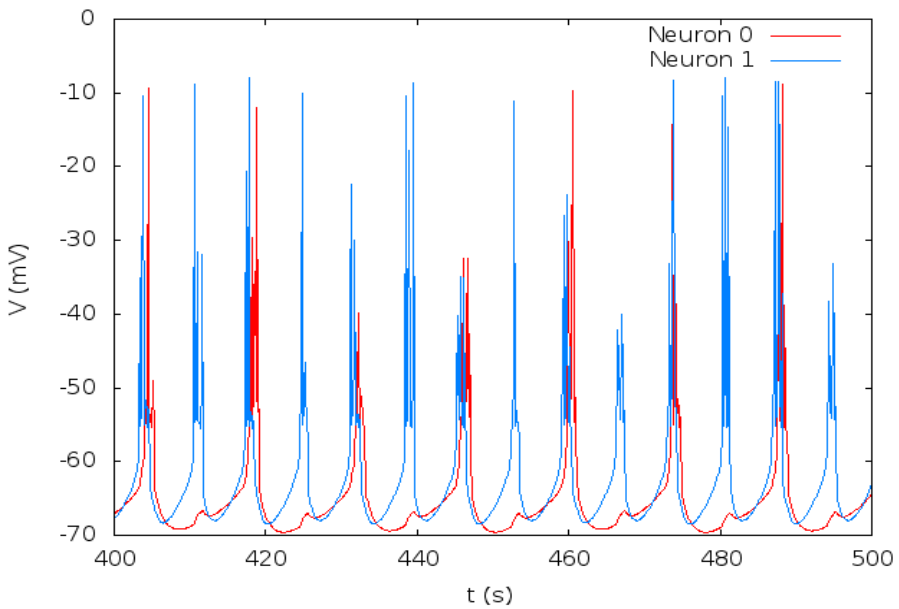
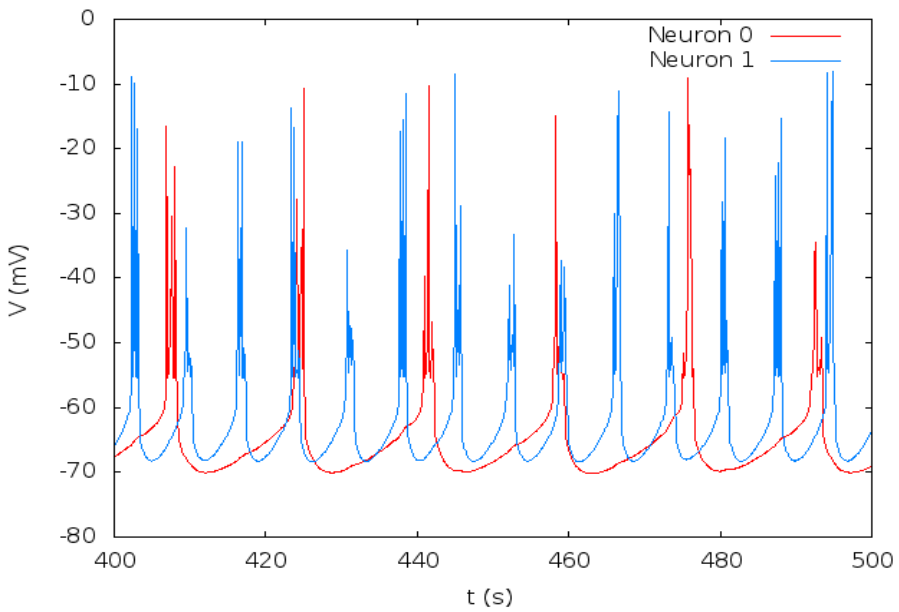
$G_{ach} = 0.05$ nS



$G_{ach} = 0.15$ nS

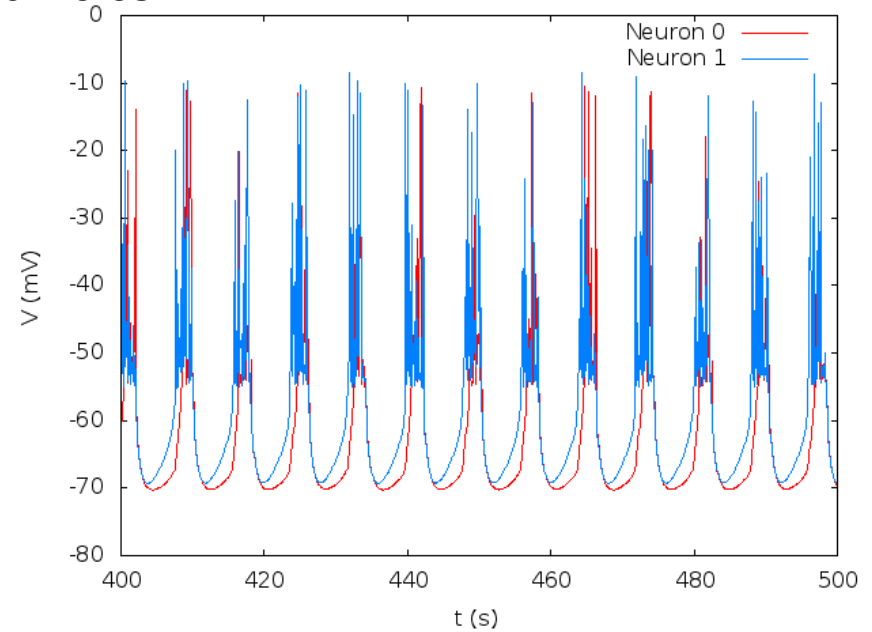


Coupling 2 cells



G_{ach} : synaptic conductance

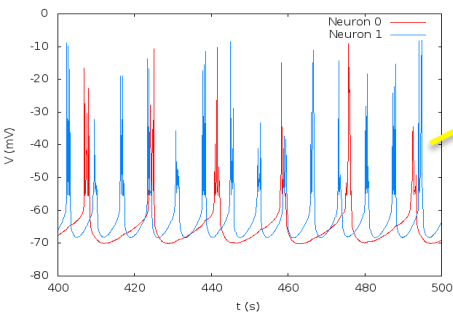
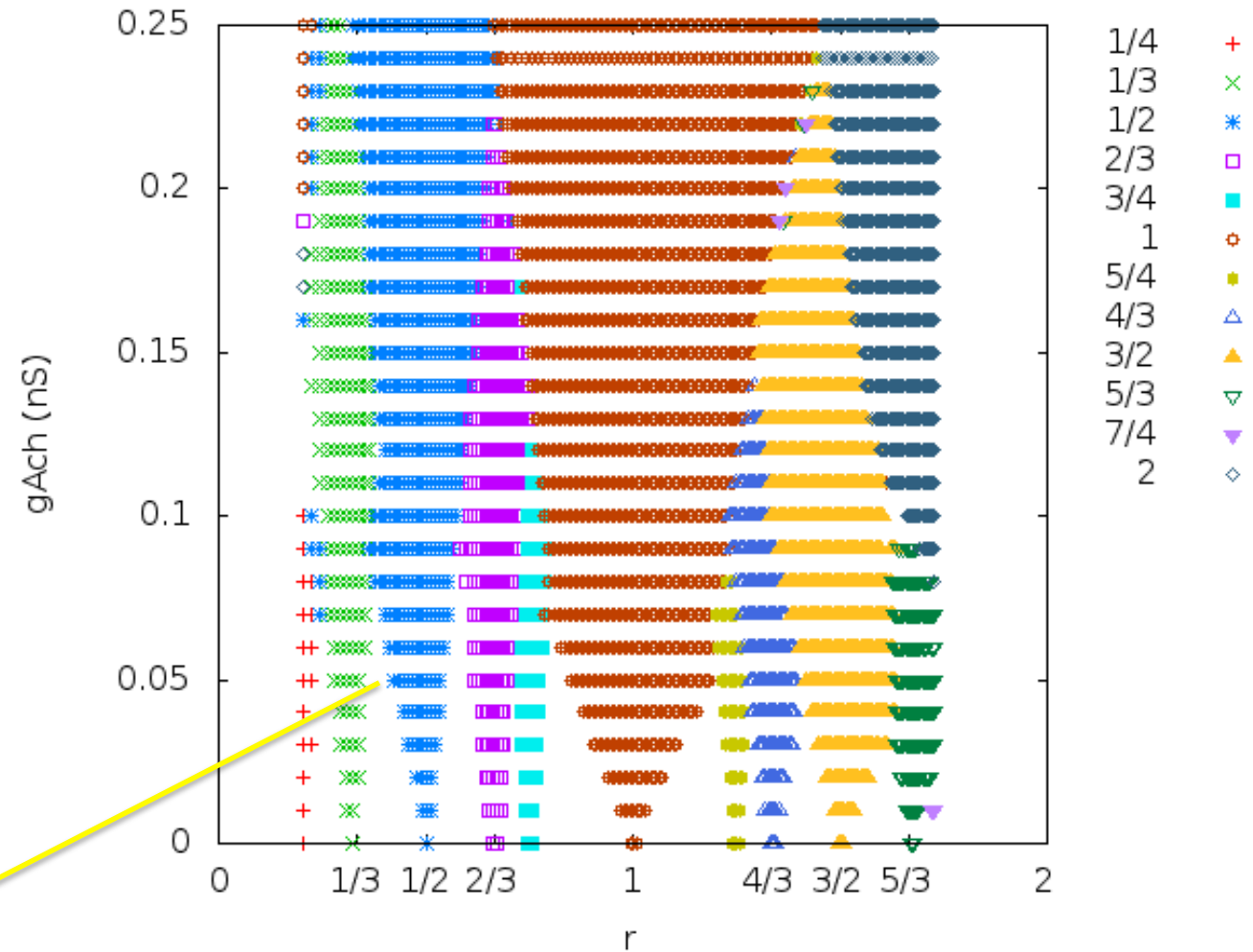
$G_{ach}=0.05$



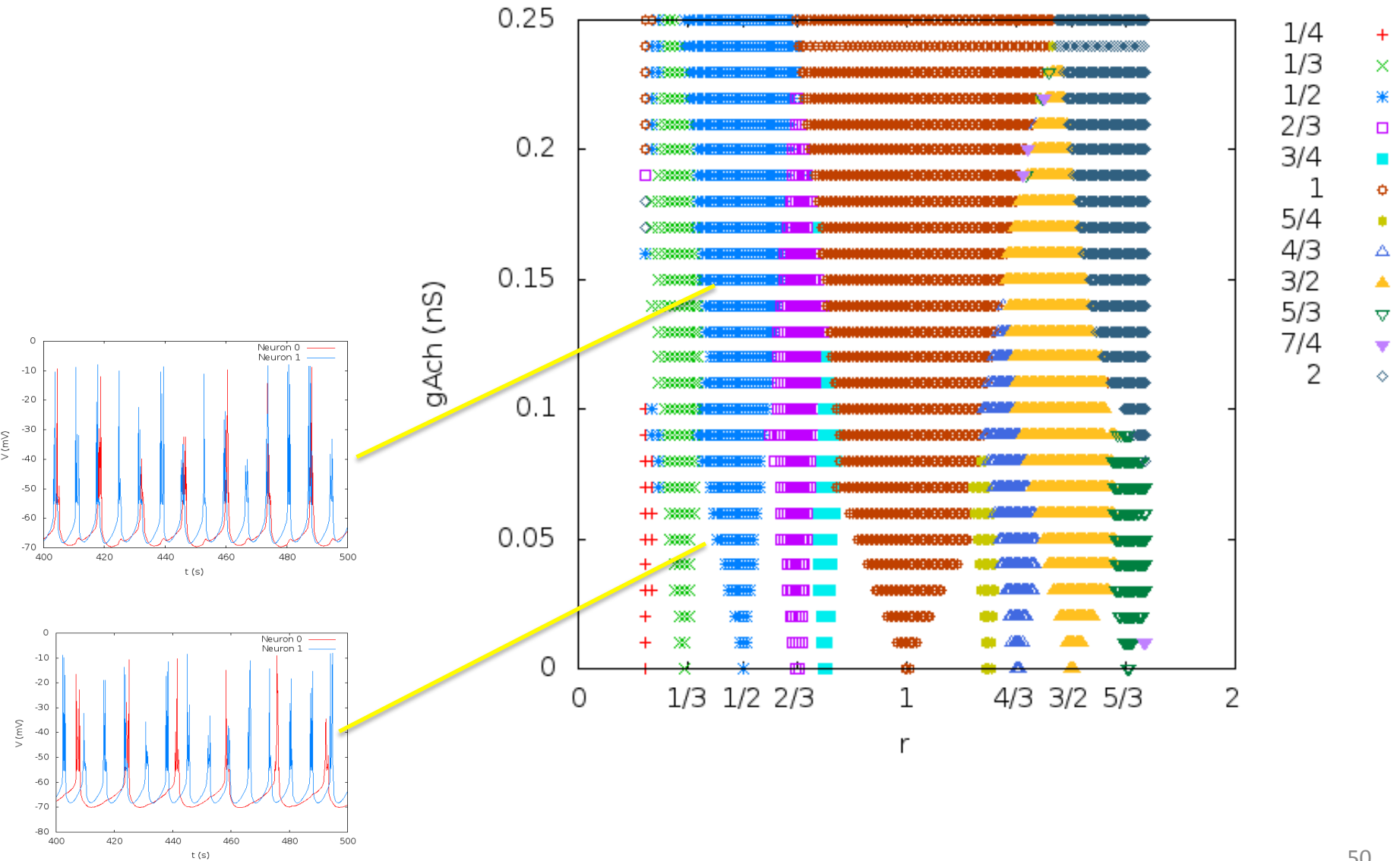
$G_{ach}=0.15$

$G_{ach}=0.5$ nS

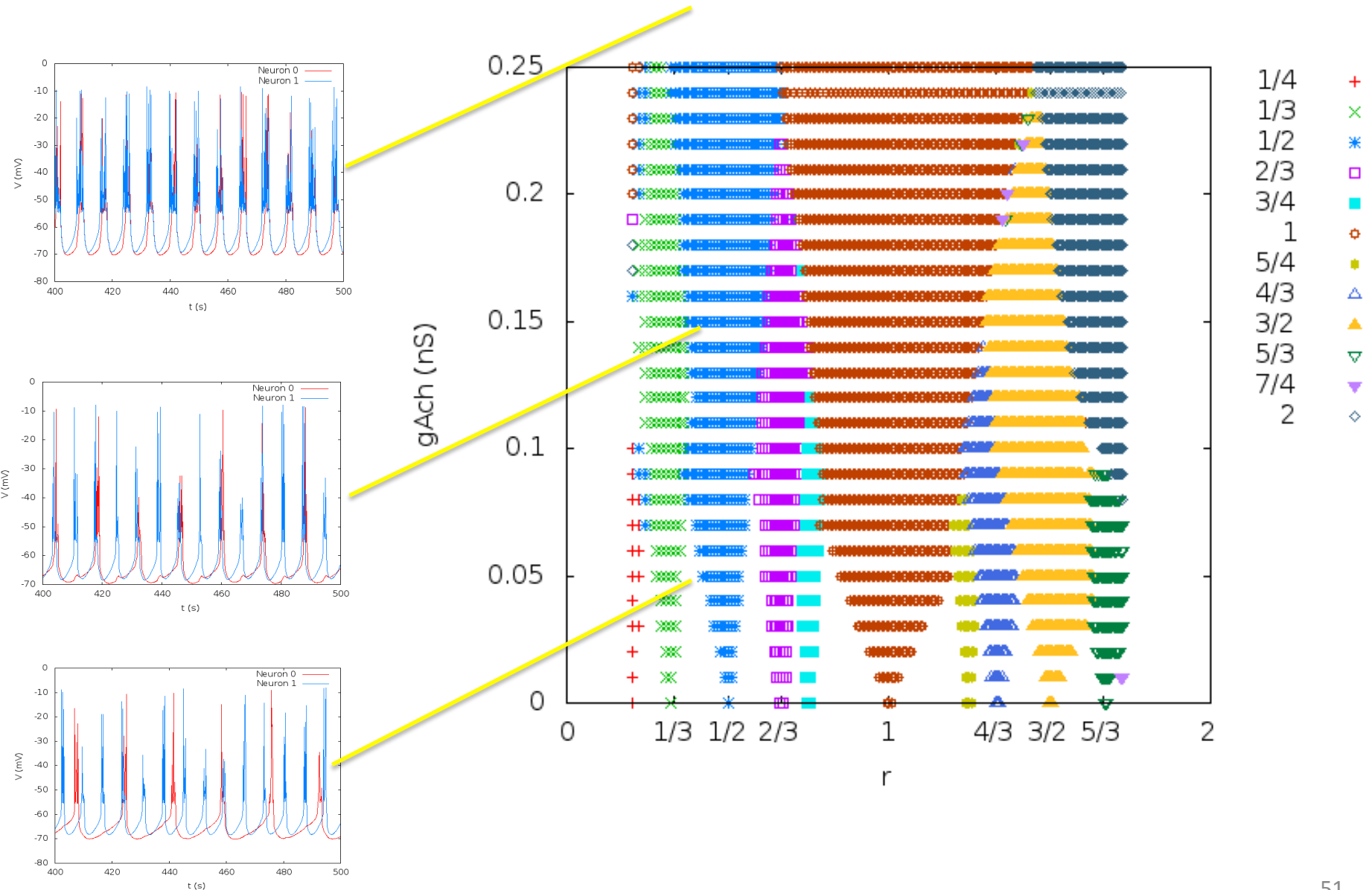
Synchrony: Arnold tongues



Synchrony: Arnold tongues



Synchrony: Arnold tongues



SACs Network

Model synaptic interactions

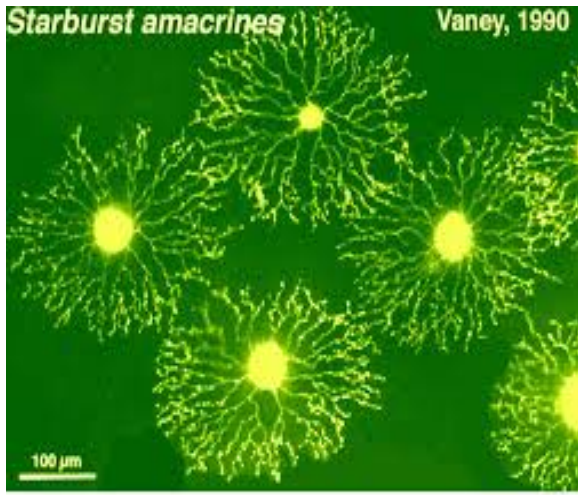
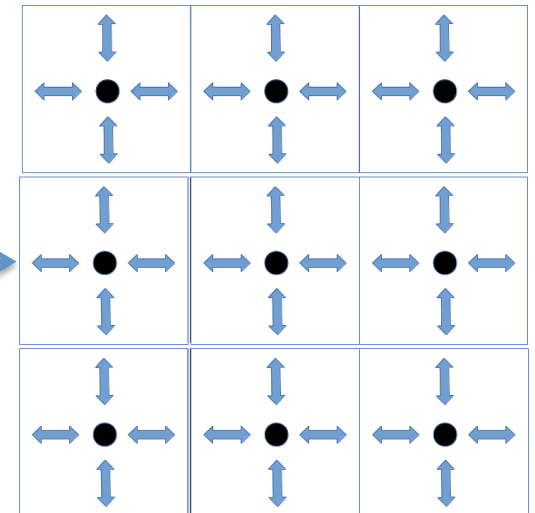
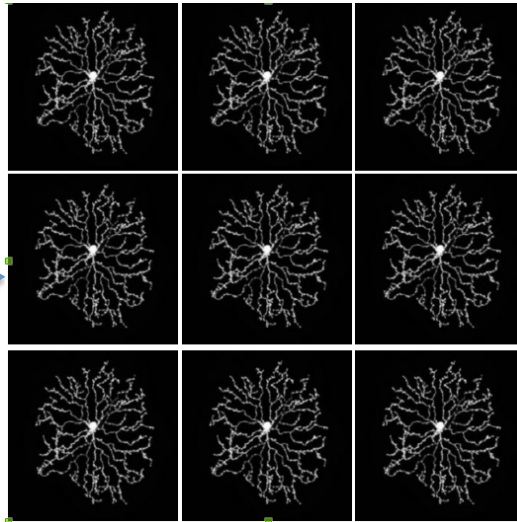


Fig 7. Starburst amacrine cells are stained with lucifer yellow in whole-mount rabbit retina.

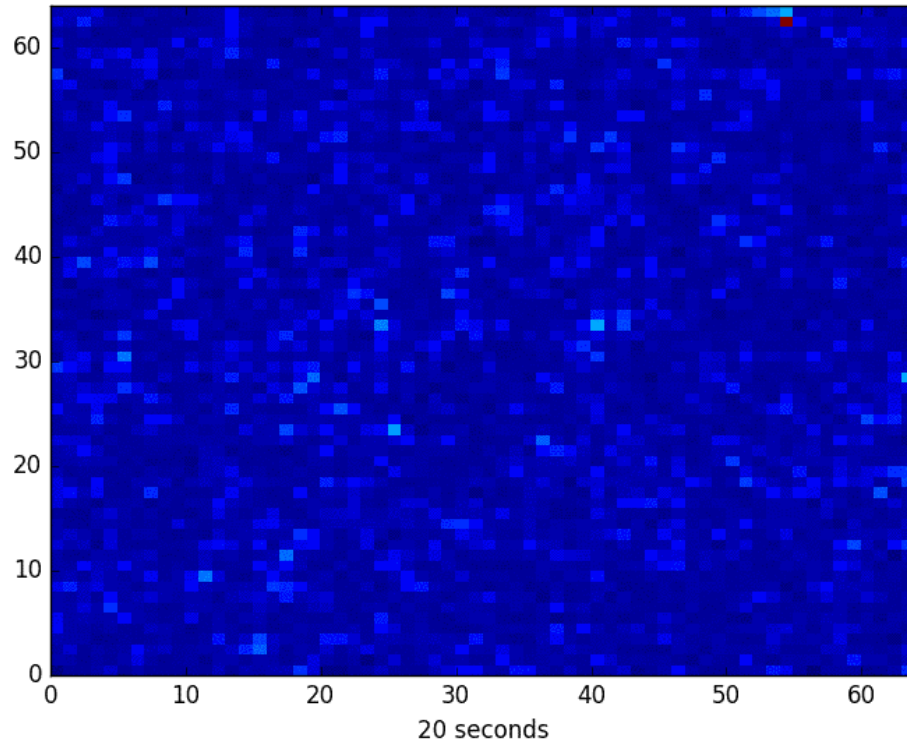


SACs realistic
connections

SACs on a lattice

SACs become points on
a lattice

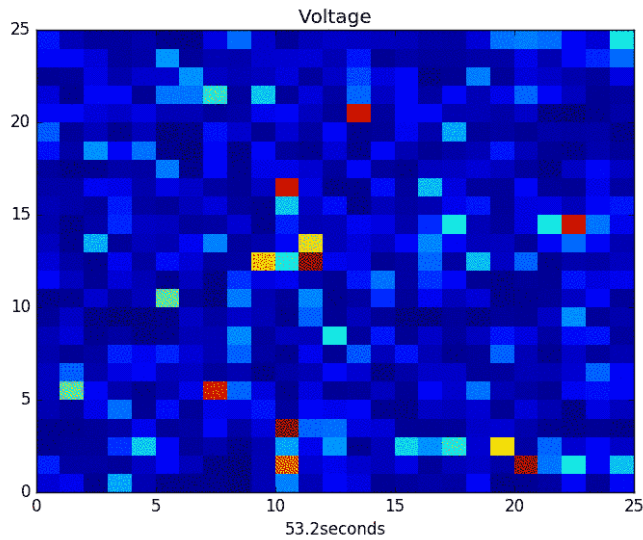
Reproduce coupled SACs dynamics in stage II retinal waves



Network of SACs : Simulated Voltage

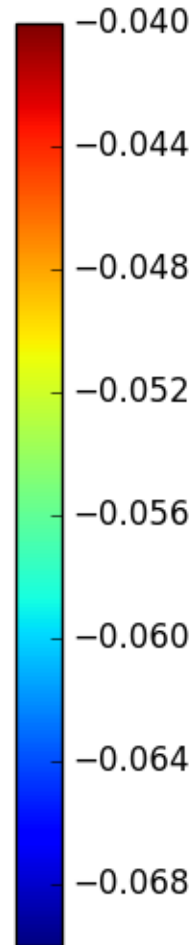
Isolated Neurons

$g_{ach}=0.126 \text{ nS}$



$g_{ach}=0.168 \text{ nS}$

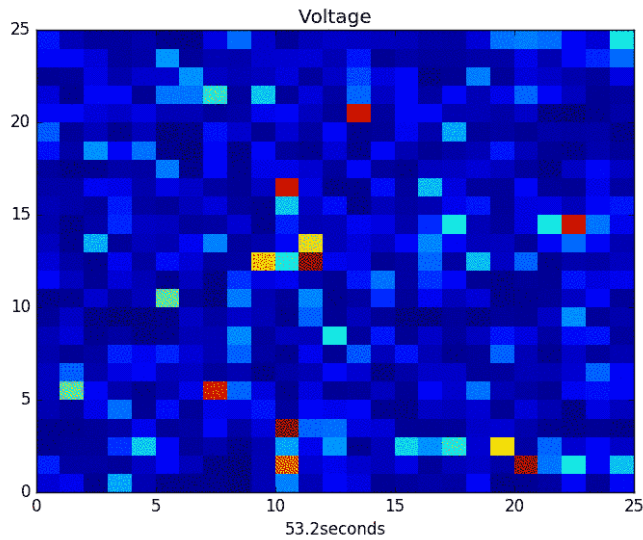
$g_{ach}=0.21 \text{ nS}$



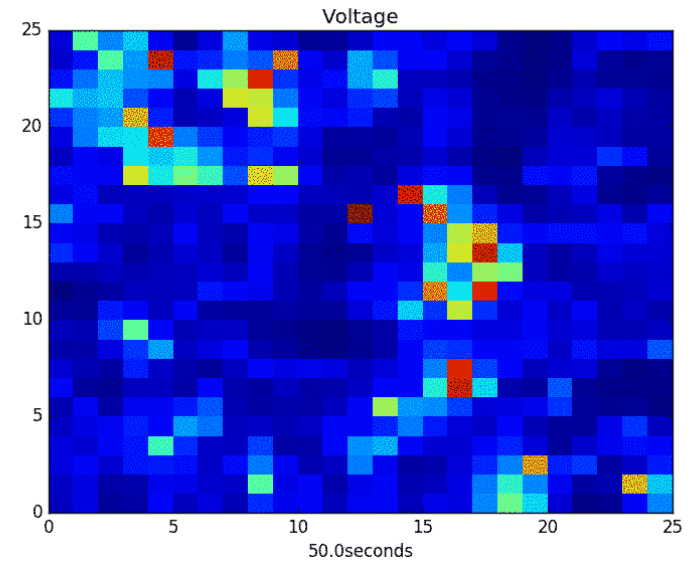
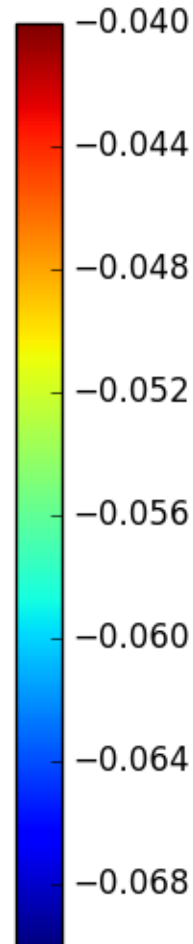
Network of SACs : Simulated Voltage

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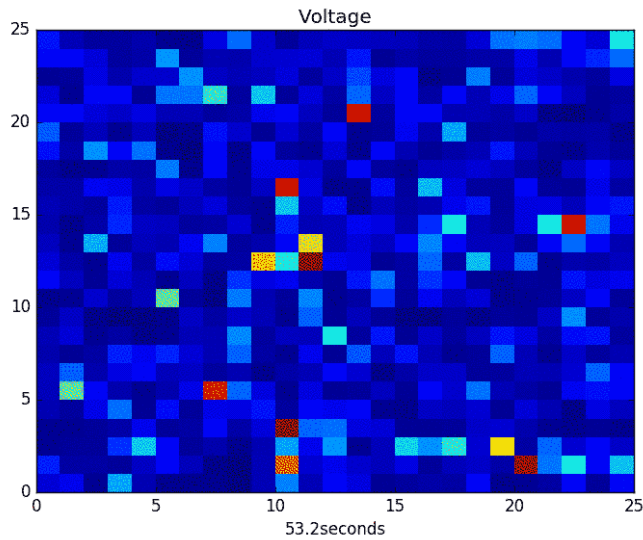


$g_{ach}=0.21 \text{ nS}$

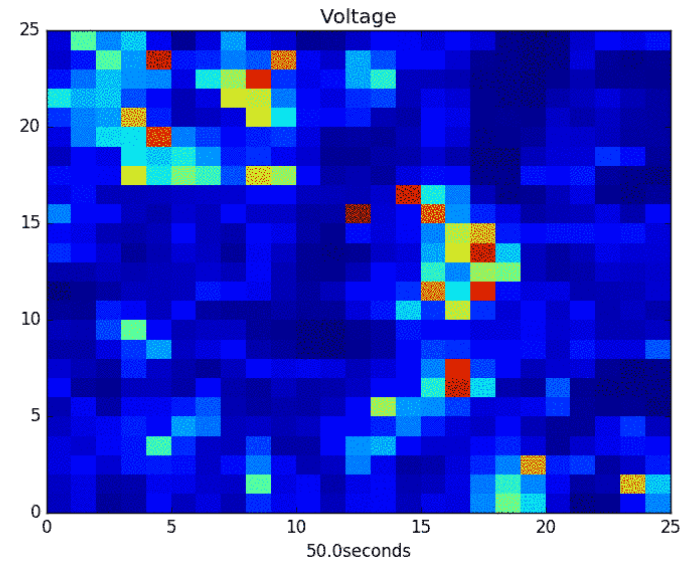
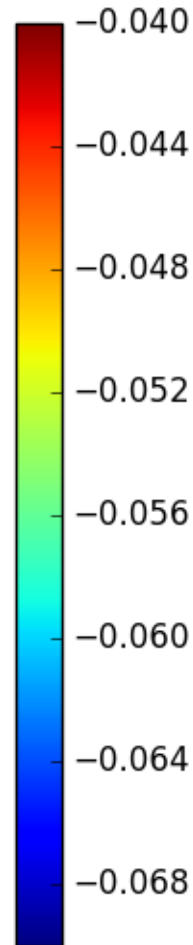
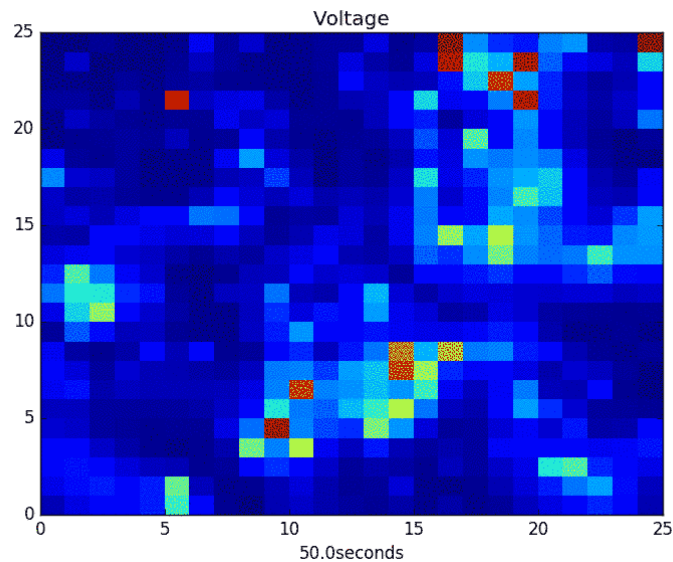
Network of SACs : Simulated Voltage

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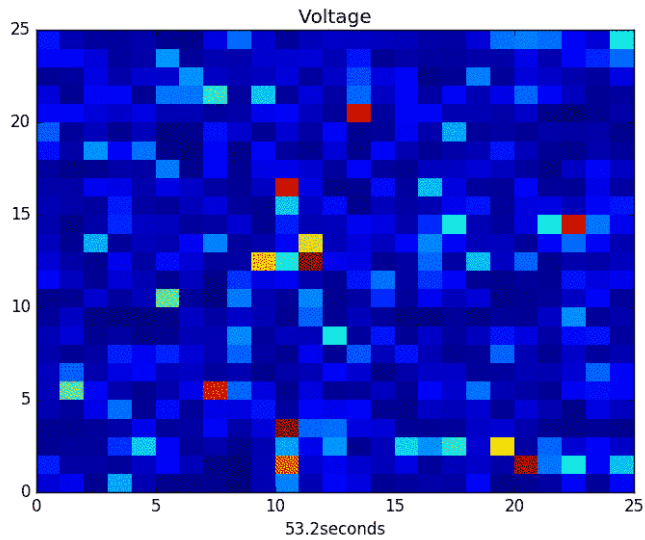


$g_{ach}=0.21 \text{ nS}$

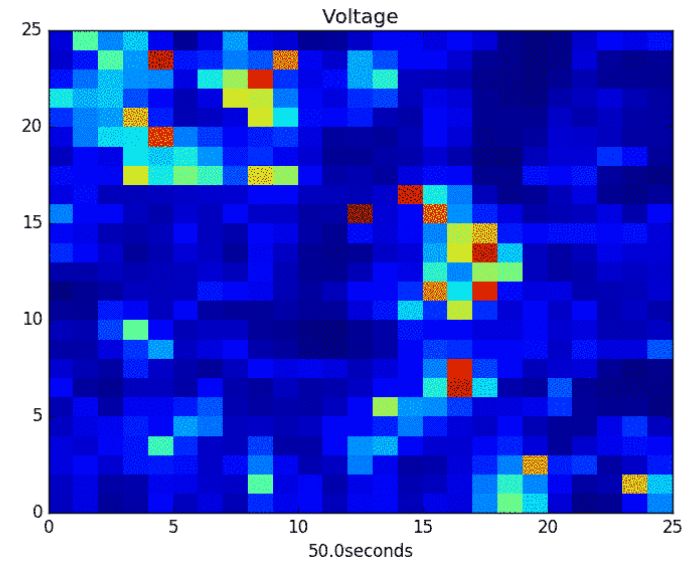
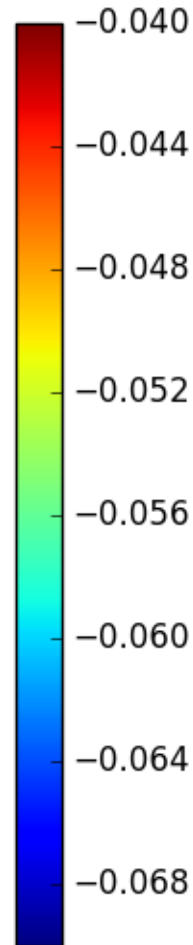
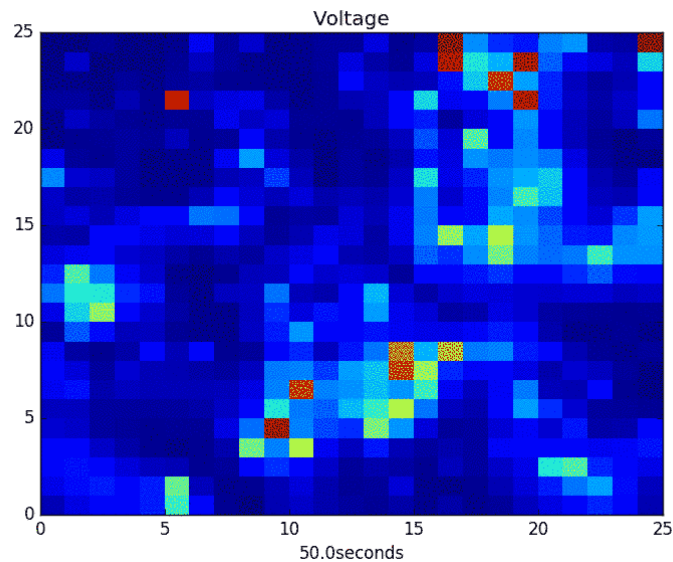
Network of SACs : Simulated Voltage

Isolated Neurons

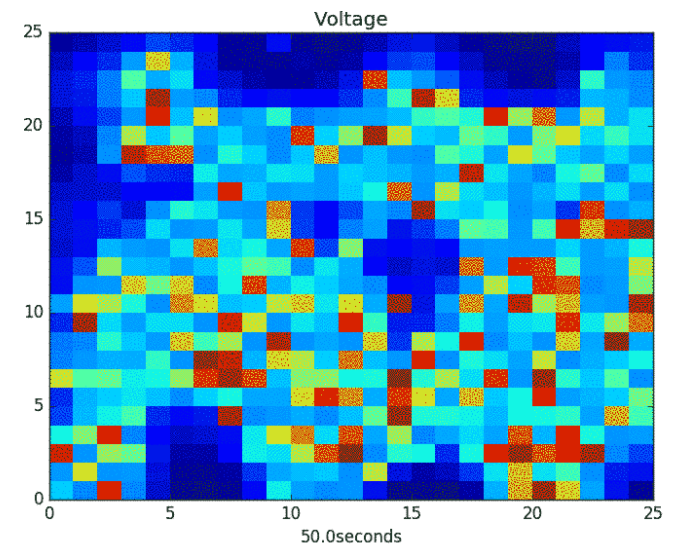
$g_{ach}=0.126$ nS



$g_{ach}=0.168$ nS

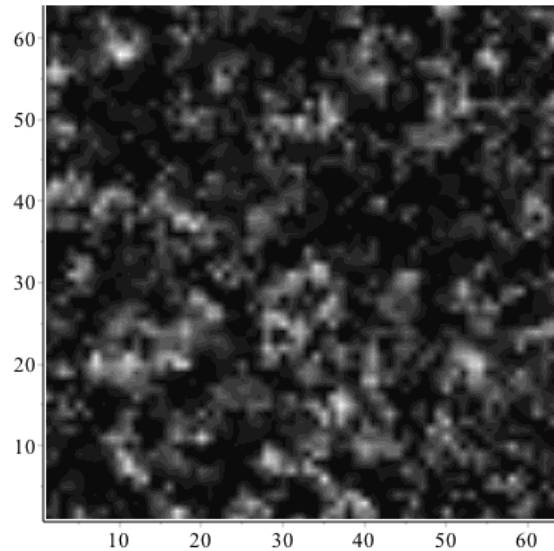


$g_{ach}=0.21$ nS

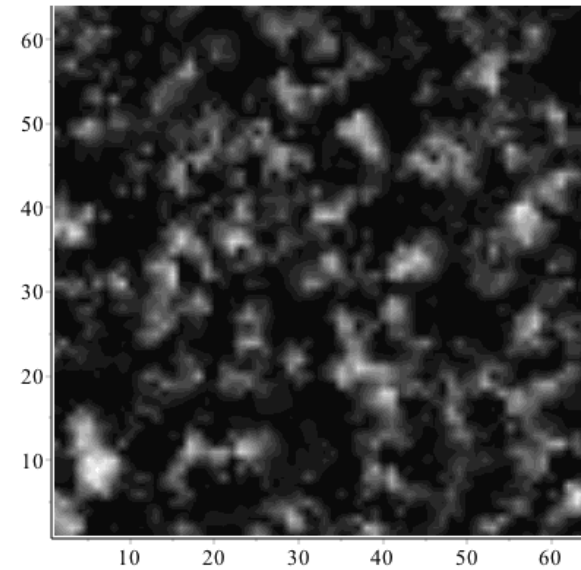


Network of SACs : Simulated Calcium Concentration

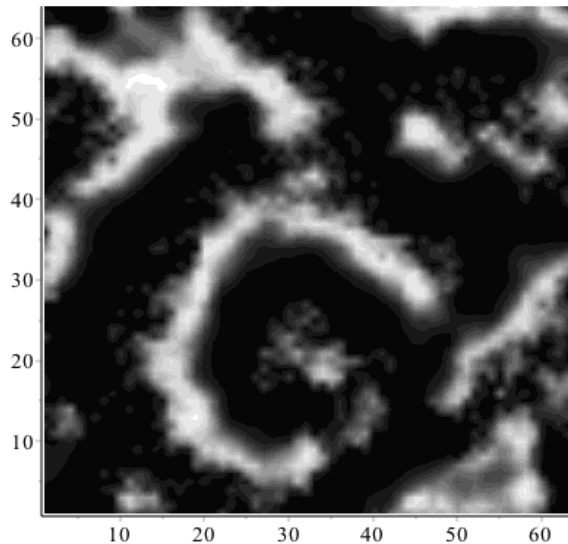
$g_{ach}=0.102$ nS



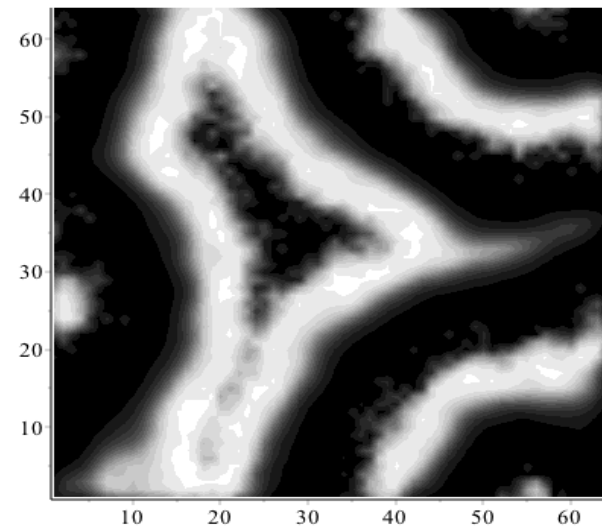
$g_{ach}=0.126$ nS



$g_{ach}=0.168$ nS



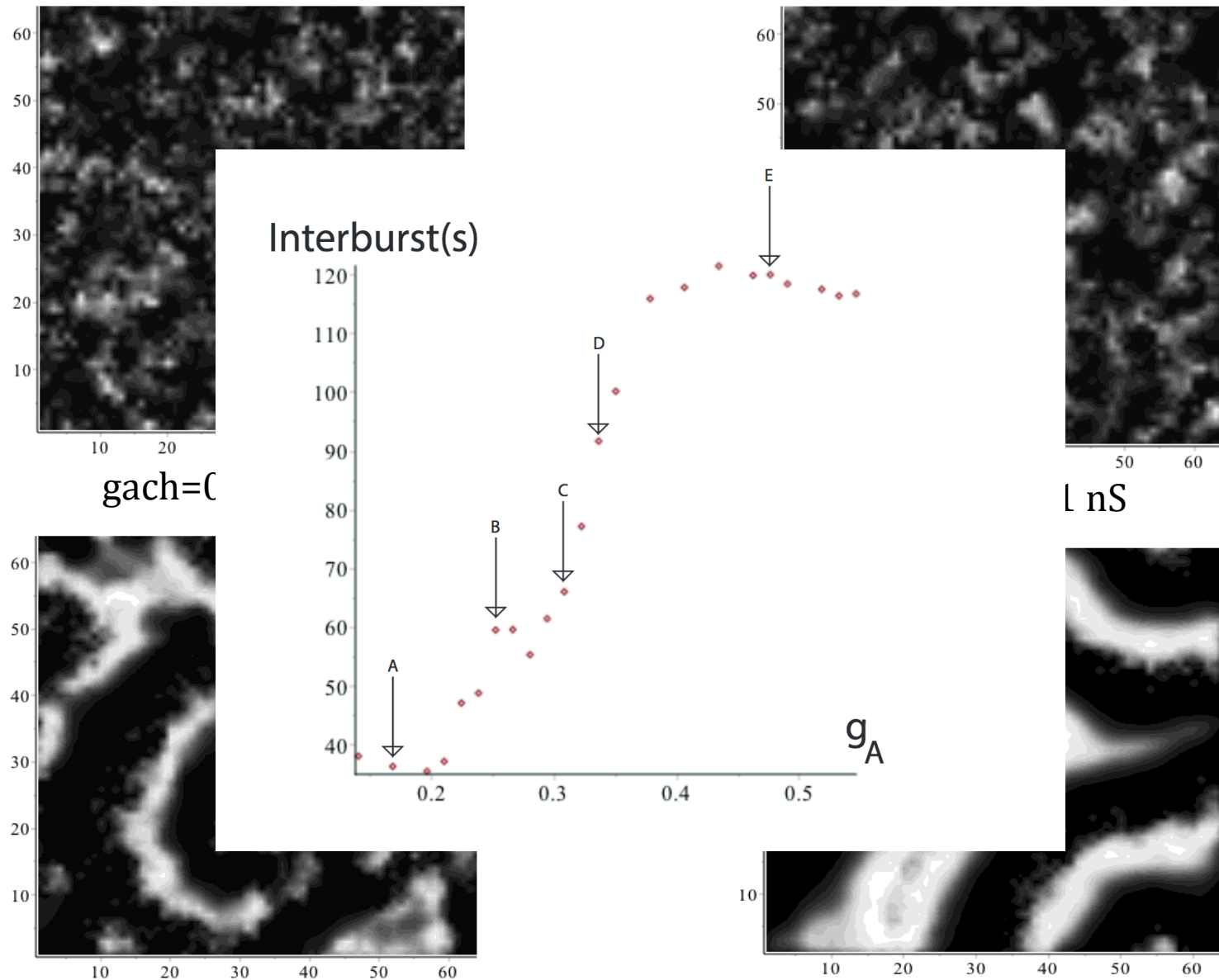
$g_{ach}=0.21$ nS



Network of SACs : Simulated Calcium Concentration

$g_{ach}=0.102 \text{ nS}$

$g_{ach}=0.126 \text{ nS}$

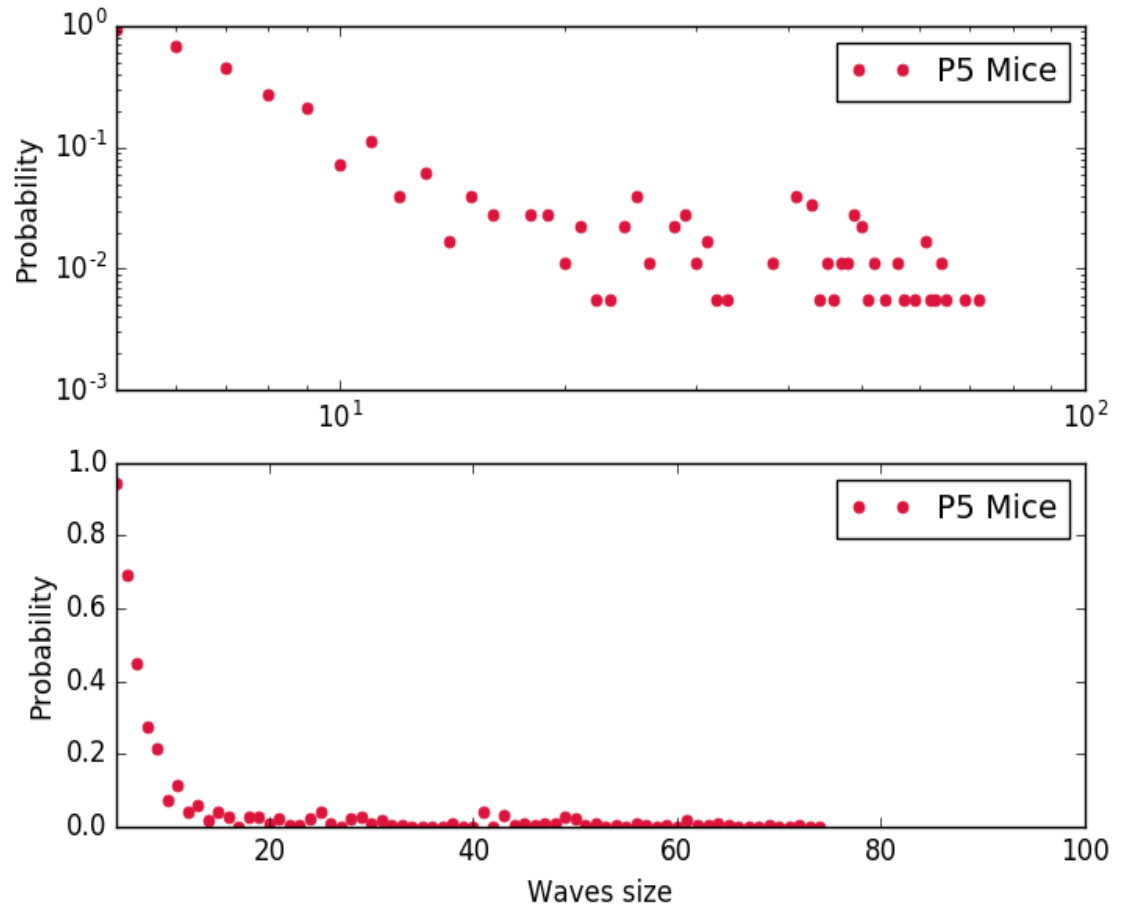


N-neuron model

- There is a **competition** between 2 mechanisms:
 - Period variability which tends to desynchronise
 - Acetylcholine which tends to synchronise
- There is an intermediate regime of coupling, where **variability** is maximum
- Therefore there is a wide repertoire of patterns
 - **Weak coupling** leads to small **localised activity**
 - **Moderate coupling** leads to **propagating patterns**
 - **Strong coupling** leads to **complete synchrony** of neurons

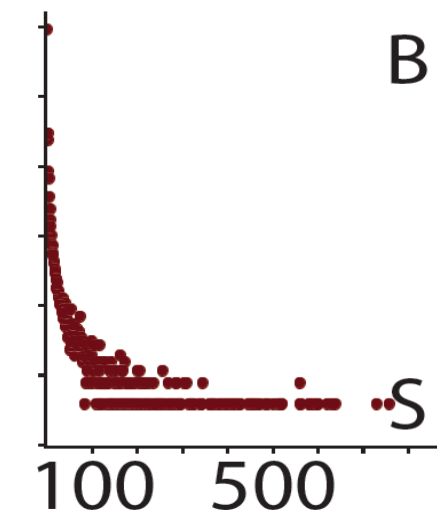
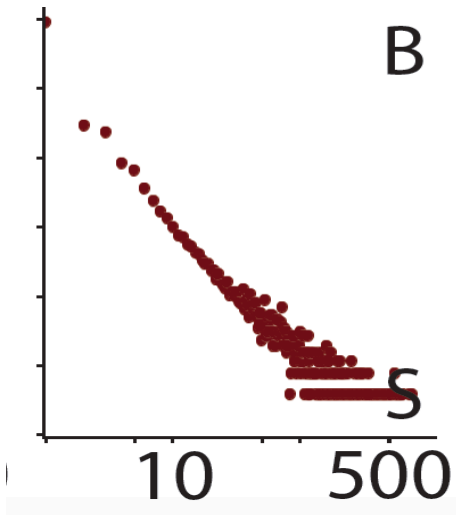
Experimentally varying Ach conductance

Experiment

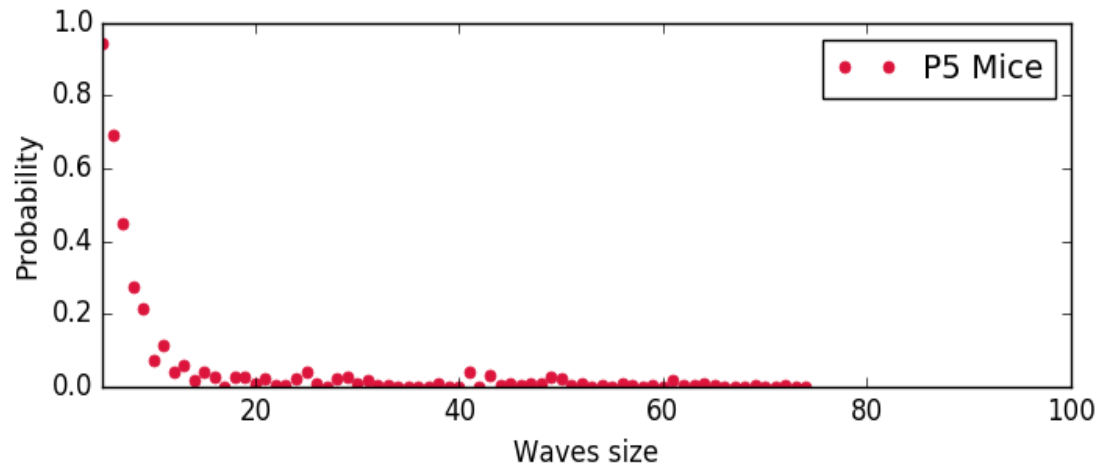
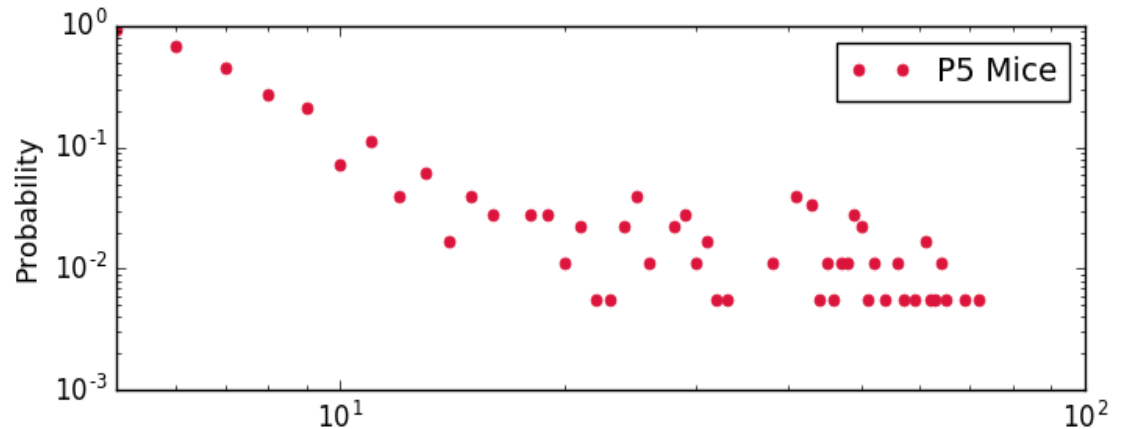


Experimentally varying Ach conductance

Model



Experiment



Transport equation

Assume:

Transport equation

Assume:

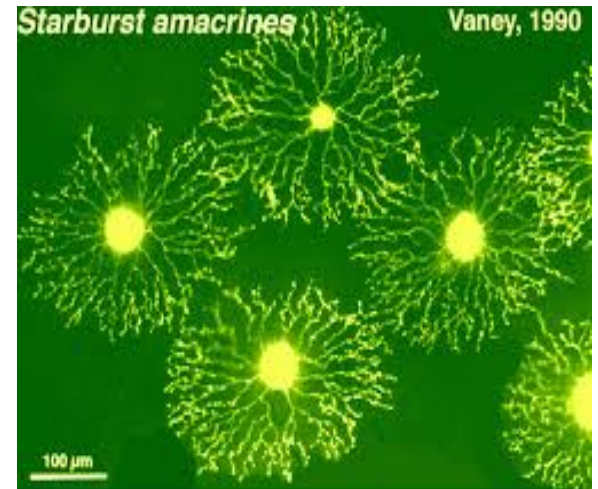
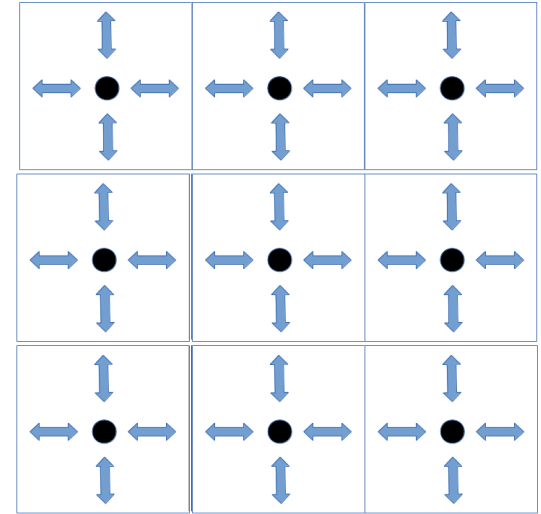


Fig. 7. Starburst amacrine cells are stained with Lucifer yellow in whole-mount rabbit retina.

Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;



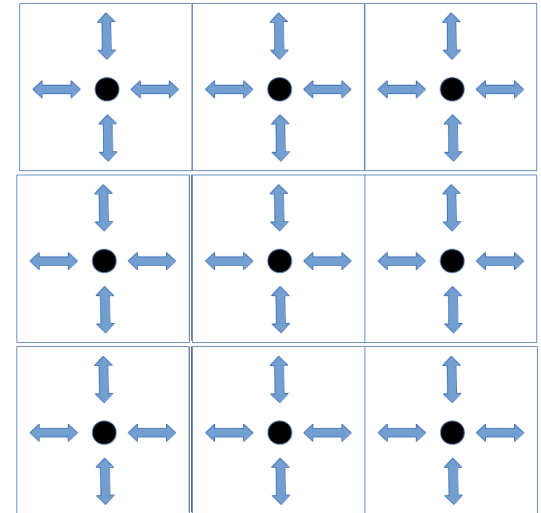
Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;

Oh ! Yes !!! This a reaction diffusion model !!

Lansdell et al, Plos Com Bio, 2014



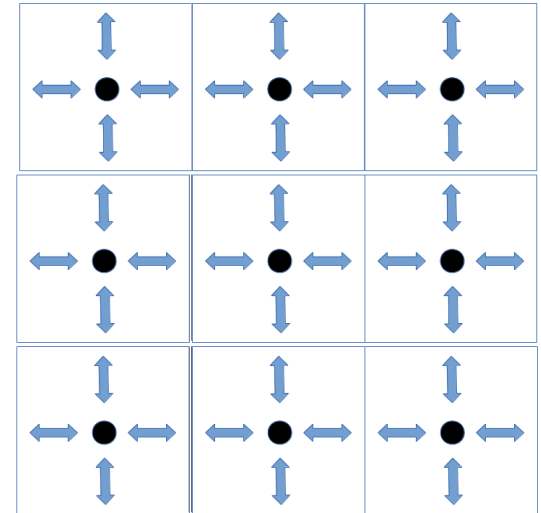
Transport equation

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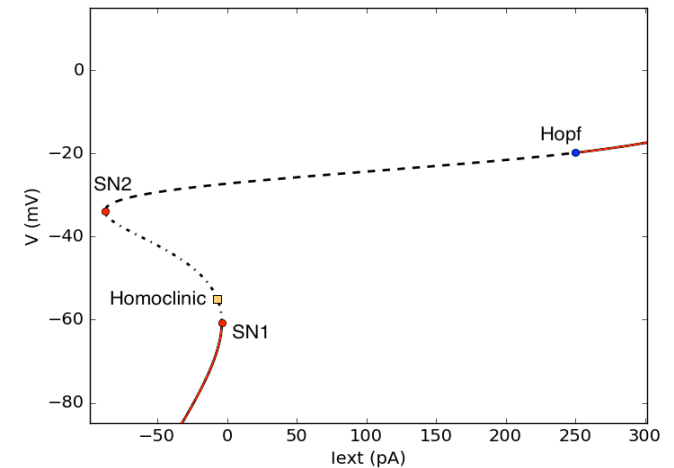


*Assume free
diffusion of Ach*

Transport equation

Assume:

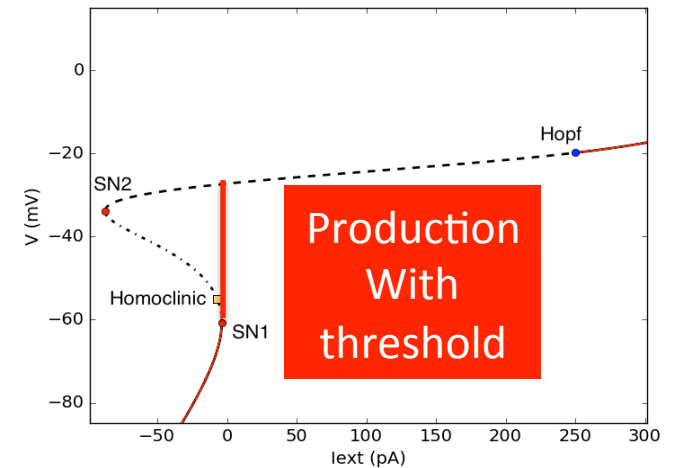
- Nearest neighbours interaction;
- State variable are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



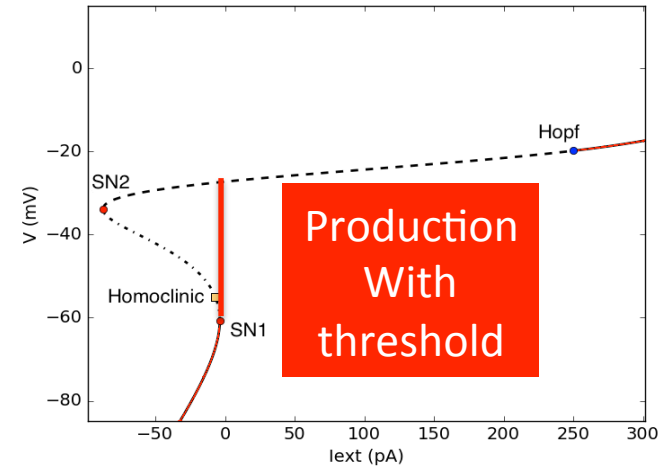
Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;
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- Ach production is maximum in the bursting state.

Transport of Ach conductance.

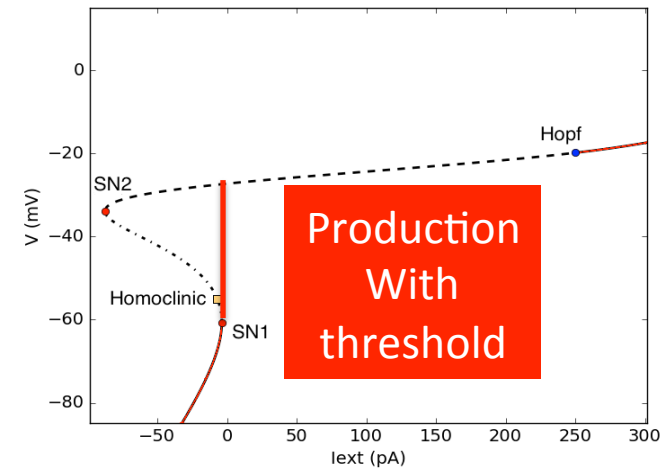
$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)] + a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]$$



Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



Transport of Ach conductance.

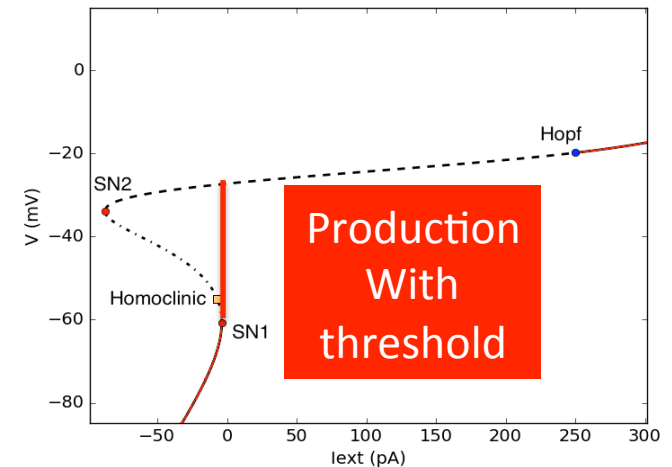
Local production

$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)] + a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]$$

Transport equation

Assume:

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Transport of Ach conductance.

Local production

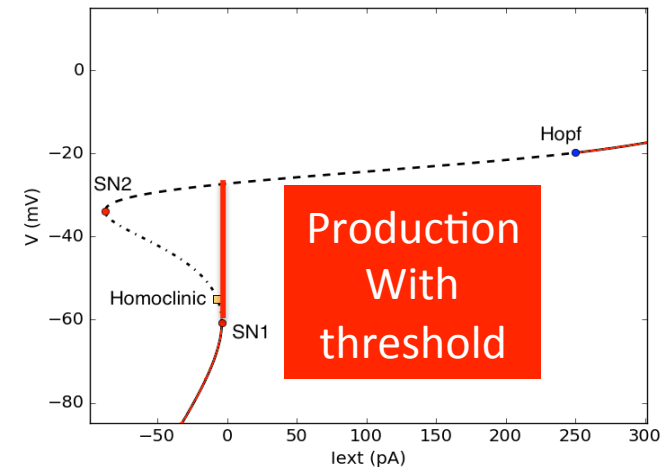
$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)] + a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]$$

Transport

Transport equation

Assume:

- Nearest neighbours interaction;
- State variable are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



Transport of Ach conductance.

$$\frac{\partial \Gamma}{\partial t} = \underbrace{-\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)]}_{\text{Local production}} + \underbrace{a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]}_{\text{Transport}}$$

Singular diffusion with R dependent threshold

Transport equation

- How do wave propagate (ballistic, normal diffusion, anomalous ?)
- How do wave stop ?
- What determines the wave scale ? The wave distribution ?
- When do we have power laws in the wave distribution ?

The diagram shows the transport equation with two terms circled in red. Above the first term is a red box labeled "Local production", and below the second term is a red box labeled "Transport".

$$\frac{\partial \Gamma}{\partial t} = \underbrace{-\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)]}_{\text{Local production}} + \underbrace{a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]}_{\text{Transport}}$$

Conclusion

- **Biophysical model of stage II retinal waves relevant at:**
 - The cells scale (bursting, experimental match and predictions)
 - The network scale (waves propagation)
 - The developmental level (evolution of ionic channels and synapses).
- **Theoretical description via bifurcation theory**
 - Bursting
 - Interburst variability
 - Waves patterns
- **Next step: reactivating waves in adults.**

Thanks 😊