

# Multi scale dynamics in retinal waves

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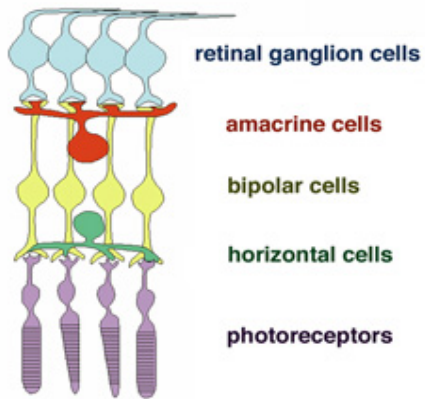
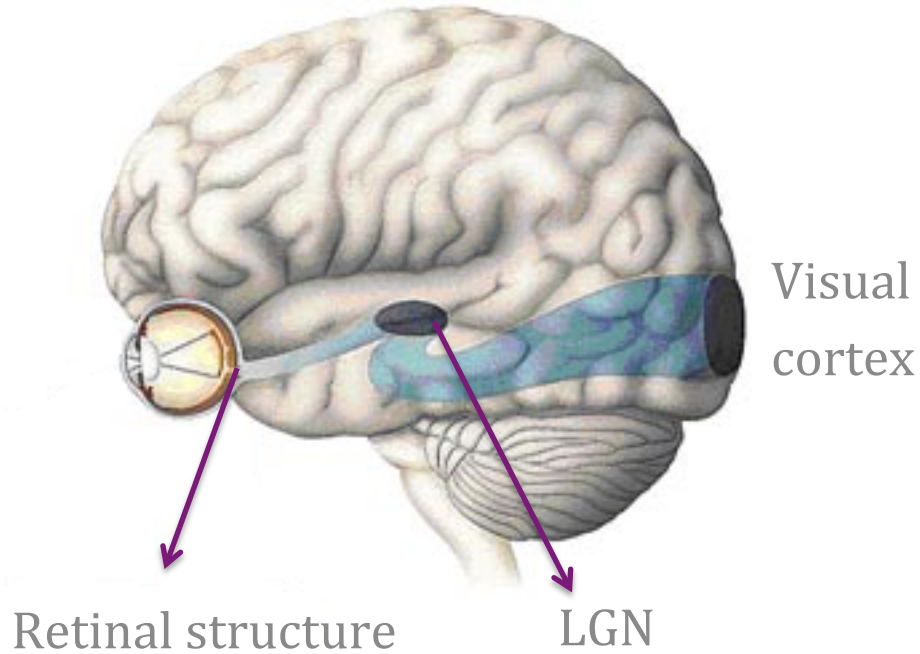
O. Marre, Institut de la Vision, Paris

S. Picaud, Institut de la Vision, Paris

B. Cessac, Biovision team, INRIA, Sophia Antipolis



# Visual system and retinal waves

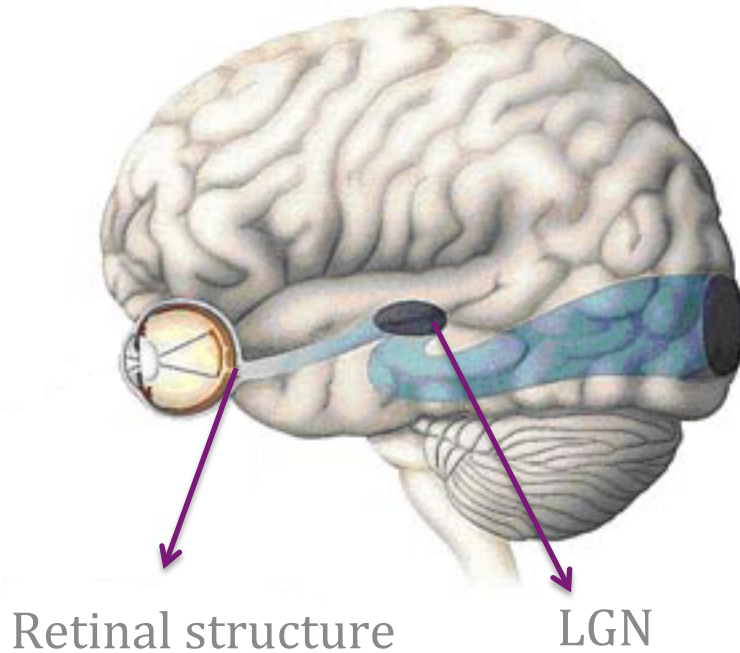


# Visual system and retinal waves

Spontaneous spatio-temporal “waves”  
during development

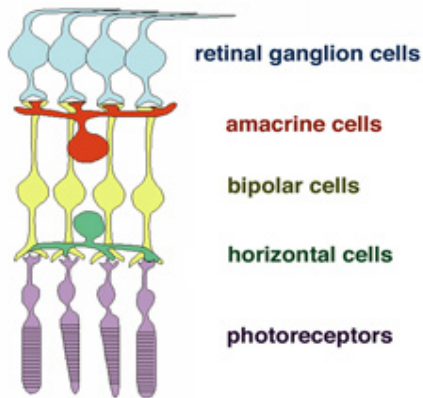
- Disappear short after birth

Visual  
cortex



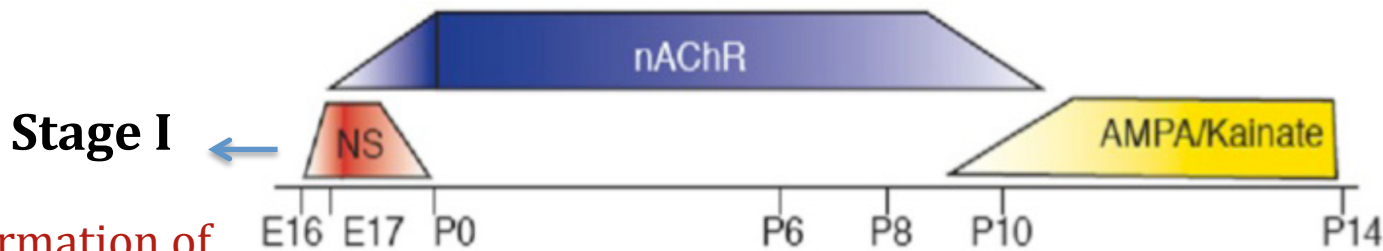
Retinal structure

LGN



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

# Stages of Retinal Waves During Development



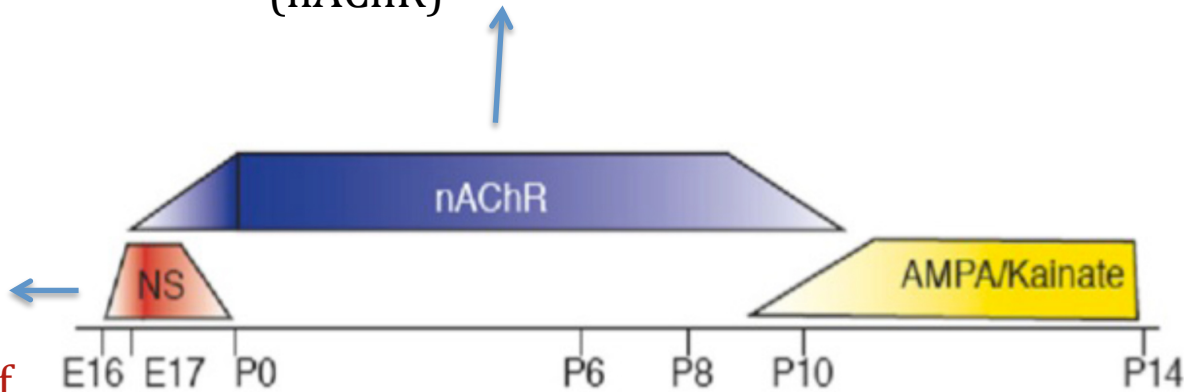
- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

# 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

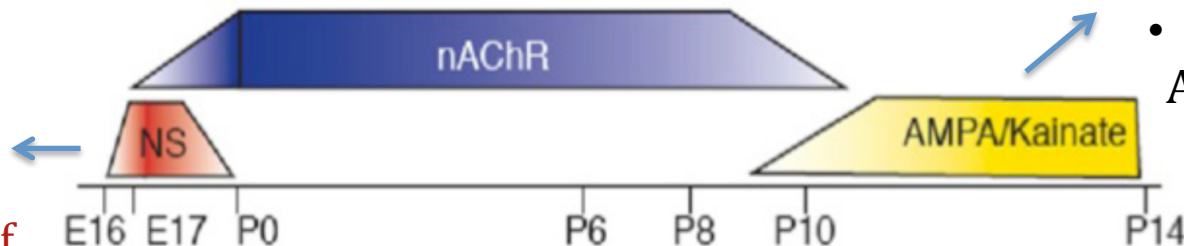
## Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

## Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors

## Stage I

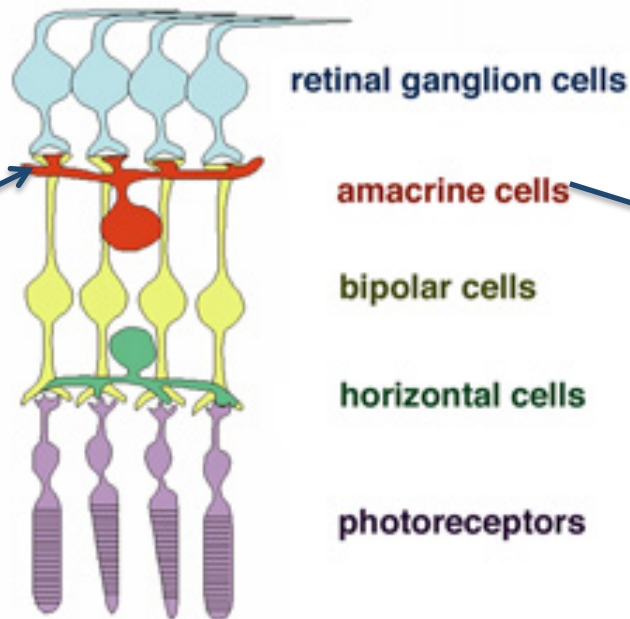


- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

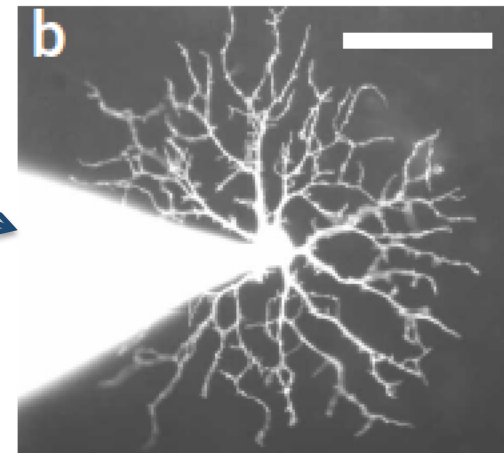
# Focus on stage II retinal waves

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

**Stage II  
(cholinergic  
retinal waves)**



Starburst Amacrine Cell (SAC)



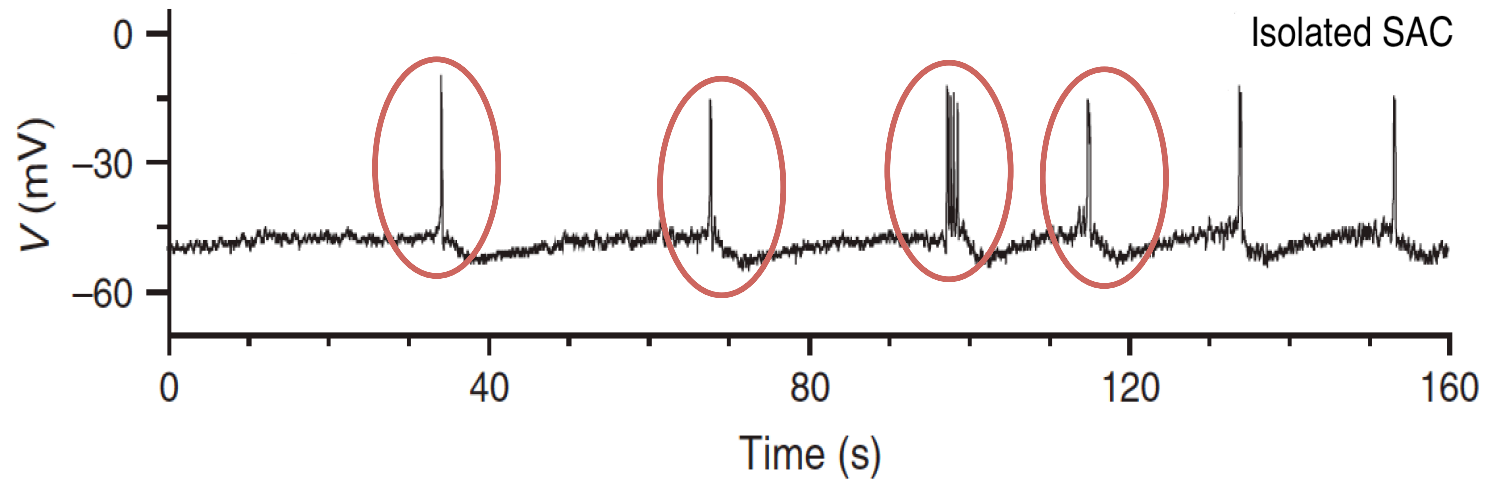
*Zheng et al. 2006*

*groups.oist.jp/dnu/*

# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity



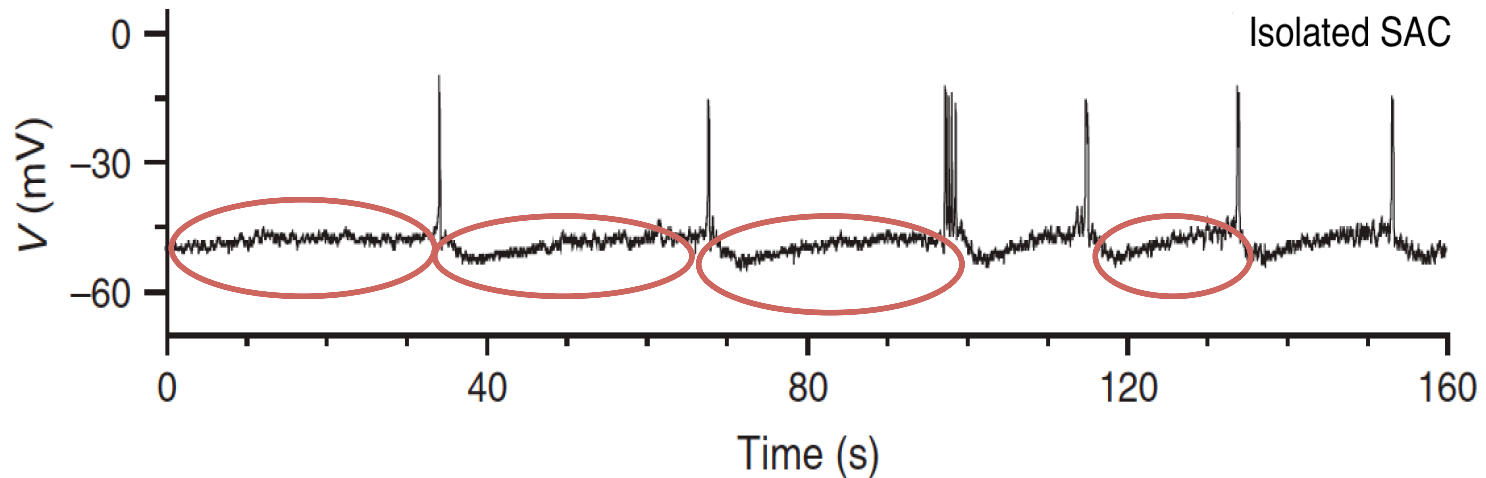
Experiment for isolated neurons,  
Zheng et al., 2006, Nature



# Experiments for the emergence of retinal waves

Retinal waves require three components:

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

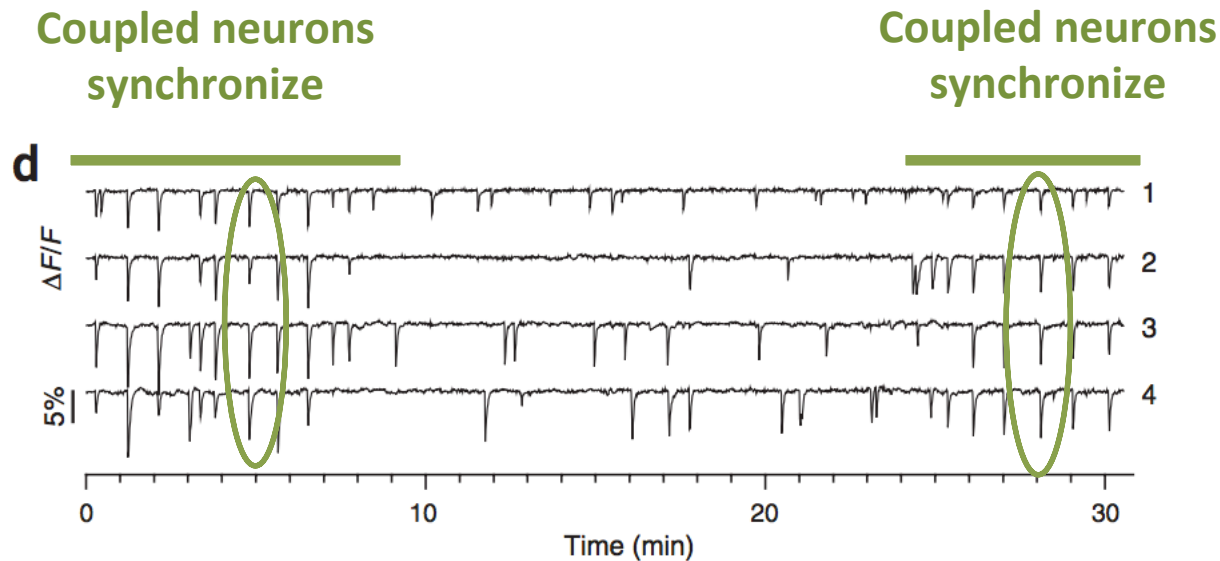


Experiment for isolated neurons,  
Zheng et al., 2006, Nature

# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
- ii) Refractory mechanism (slow After HyperPolarisation- sAHP)
- iii) Coupling (through Acetylcholine neurotransmitter)

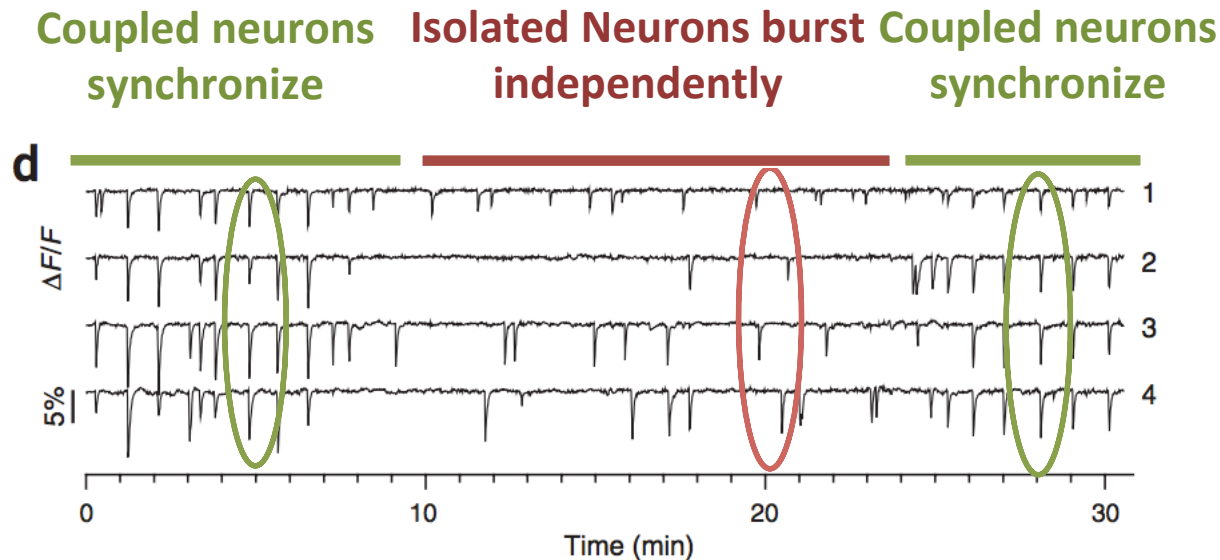


Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

# Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity
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- iii) Coupling (through Acetylcholine neurotransmitter)



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 sufficiently close from biophysics to explain and propose experiments and sufficiently well posed mathematically to analyse its dynamics upon varying biophysical parameters (conductances).*

- Simplify as much as possible but not more
- Fix as many parameters as possible from biophysics
- Behaviour must be robust to some parameters variations (physiology) and sensitive to others (development).

# Why study retinal waves?

## Strategy:

*To propose a model sufficiently close from biophysics to explain and propose experiments and 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.

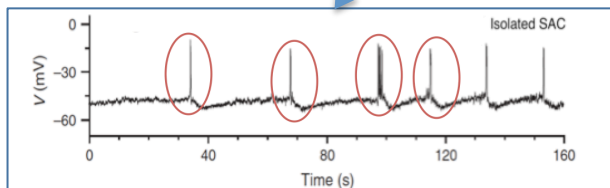
# A network model for stage II retinal waves

## Membrane potential dynamics

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

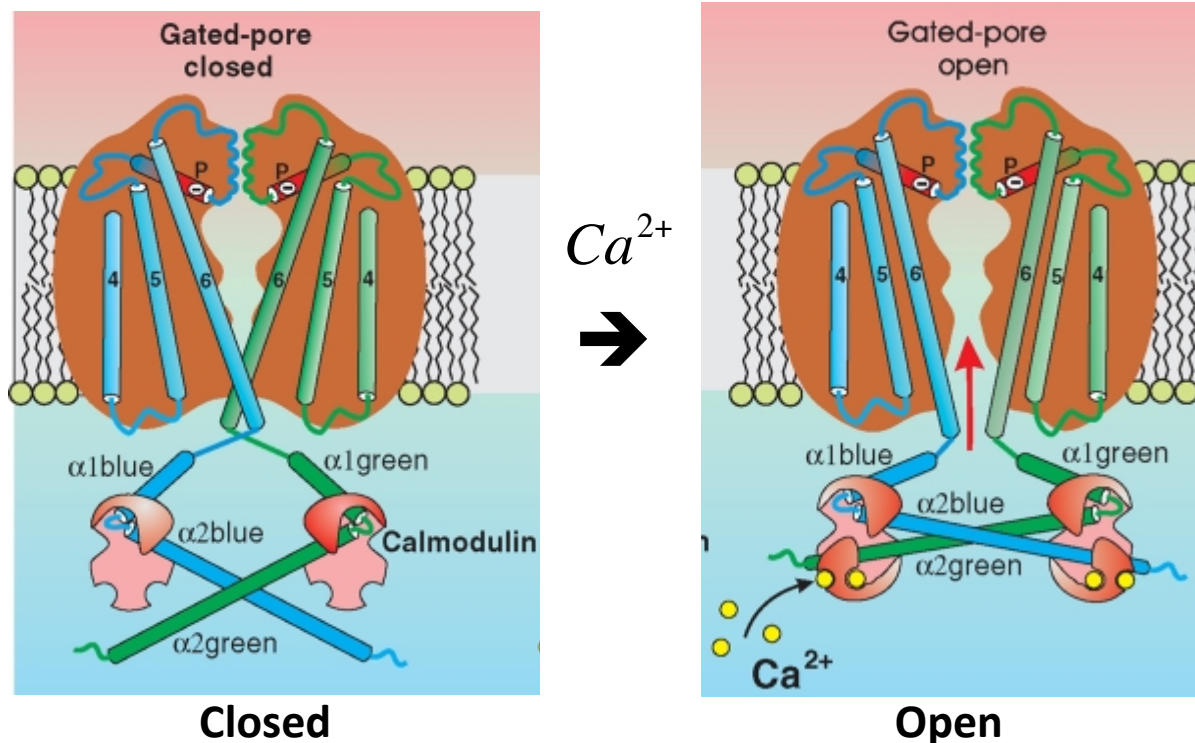
$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

## Morris-Lecar & Fast K<sup>+</sup> 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)



*Calcium gated  
potassium  
channel*

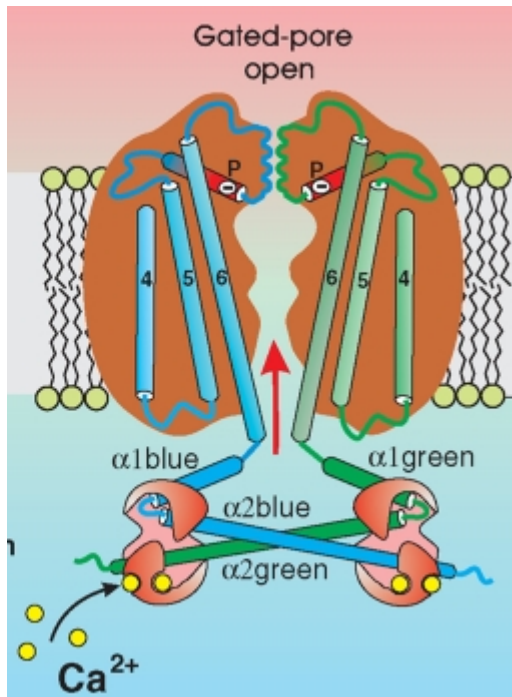
*superhimik.livejournal.  
com/*



# sAHP current

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

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



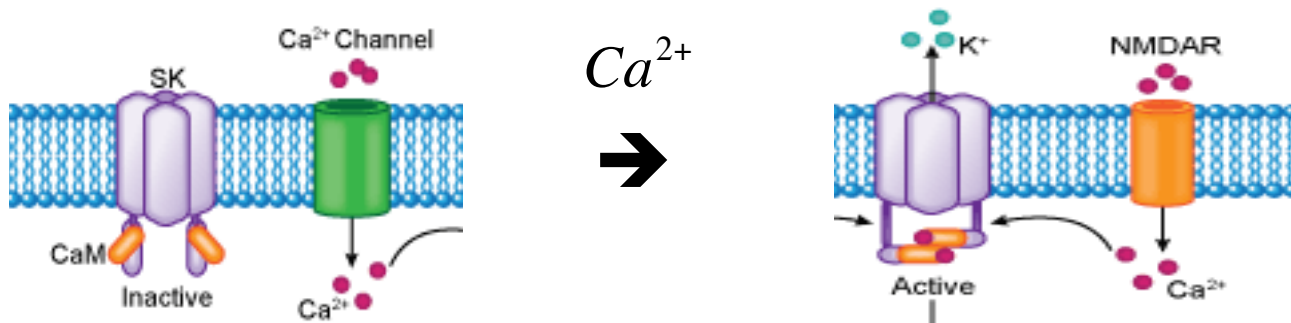
*The conductance is proportional to the fourth power of R because four terminals are needed to open the channel.*

*superhimik.livejournal.com/*

# Set of equations for sAHP current

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

**R** : Probability that one terminal of the channel is open



*Calcium gated potassium  
channel*

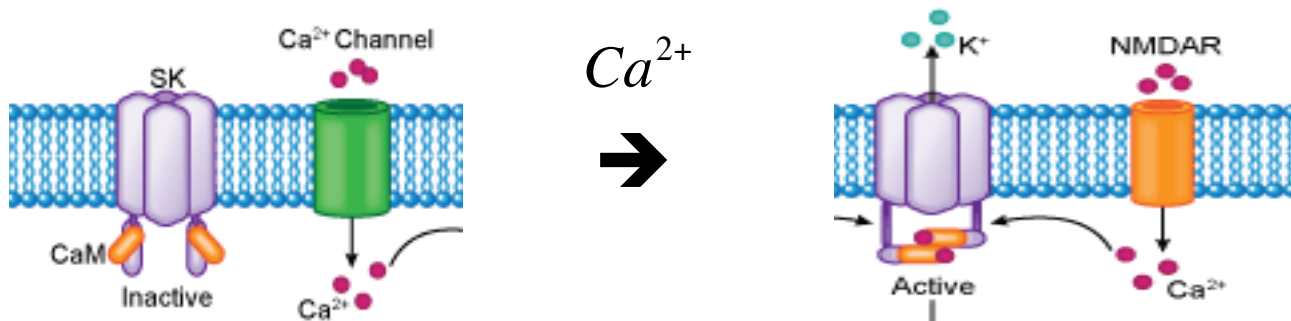
# Set of equations for sAHP current

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

**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)



*Calcium gated potassium  
channel*

# Set of equations for sAHP current

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

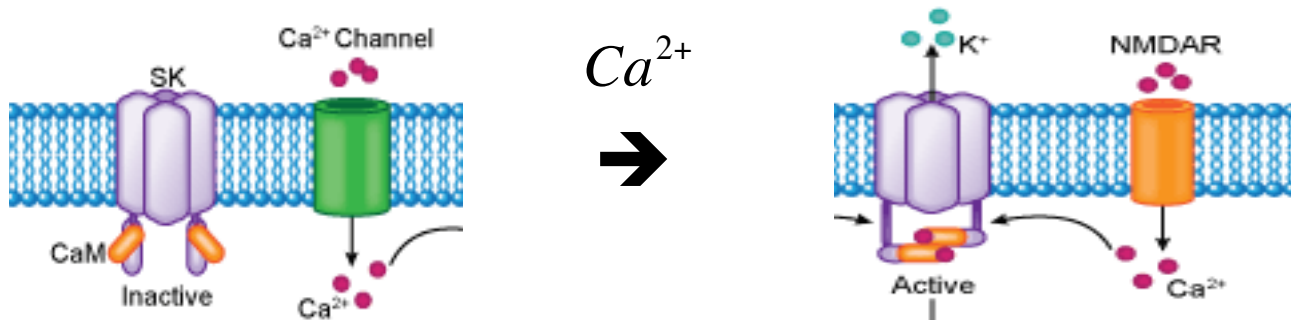
**R** : Probability that one terminal of the channel is open

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

**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



*Calcium gated potassium channel*

## Set of equations for sAHP current

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

**R** : Probability that one terminal of the channel is open

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

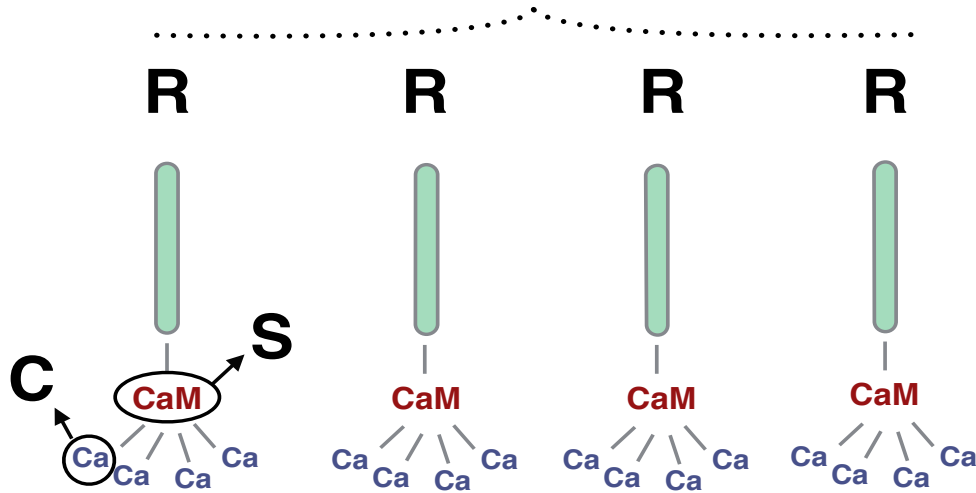
**S** : Fraction of saturated calmodulin concentration (CaM)

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

**C** : Intracellular Calcium concentration

# Set of equations for sAHP current

## Activated Ca-gated K<sup>+</sup> 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<sup>+</sup> 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

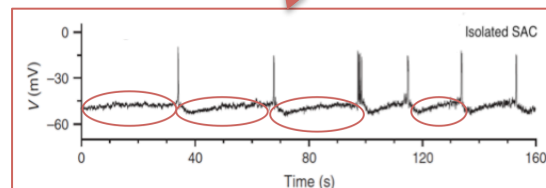
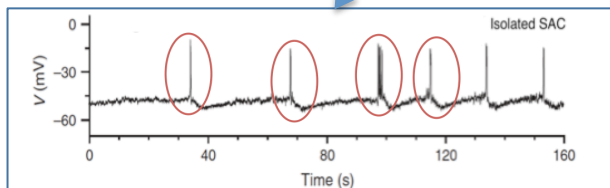
## Membrane potential dynamics

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

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

**Morris-Lecar &  
Fast K<sup>+</sup> channels**

**sAHP current  
Refractory  
mechanism**

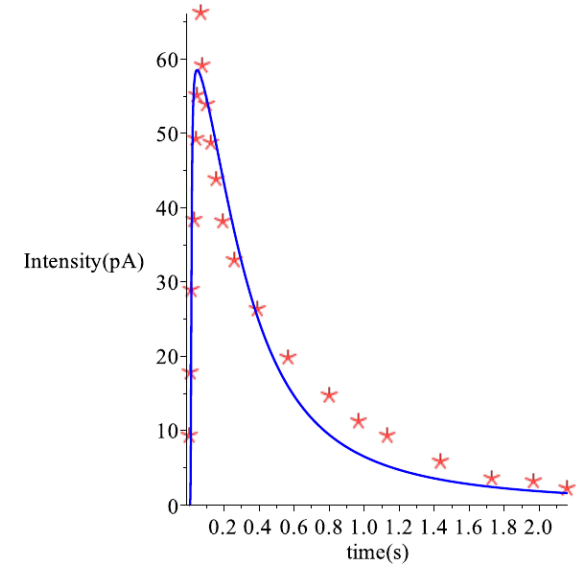
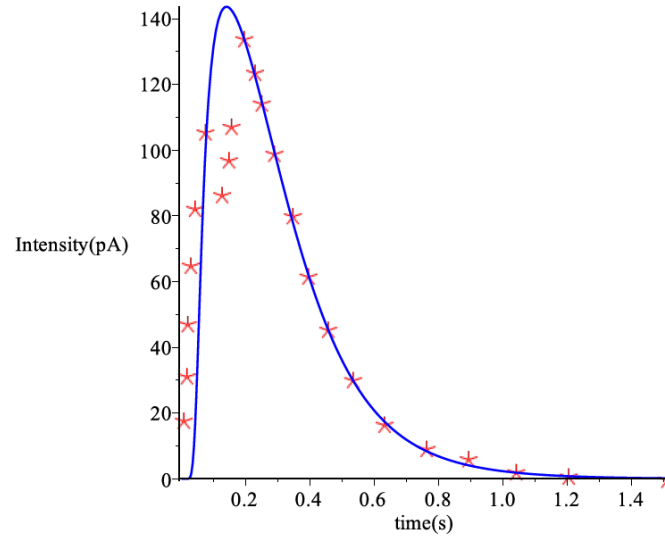
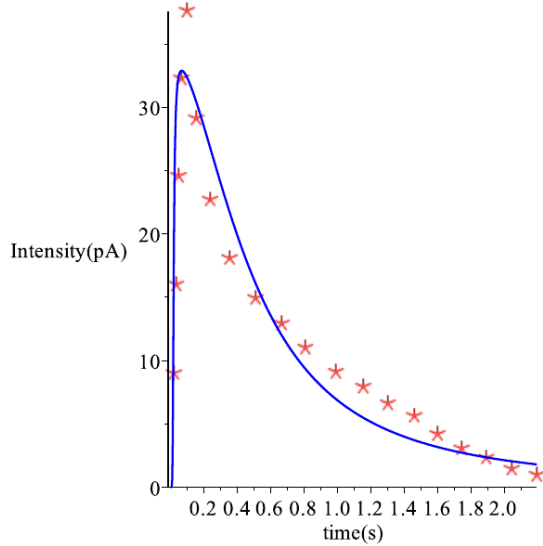




# Acetylcholine current

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

**A: Extracellular Acetylcholine concentration**



Experimental fits from Zhou et al. 2004, Neuron

# SACs Network

## Model synaptic interactions

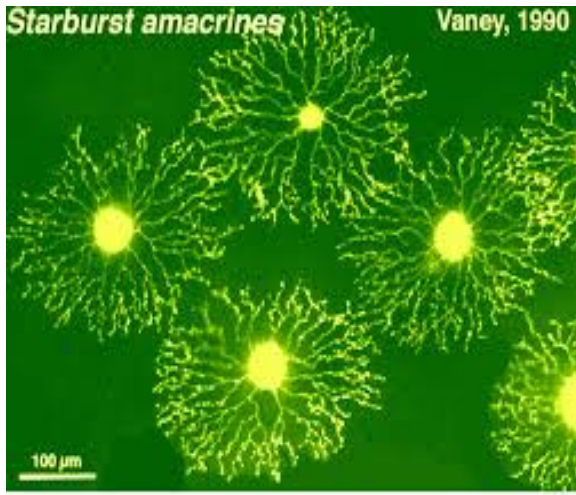
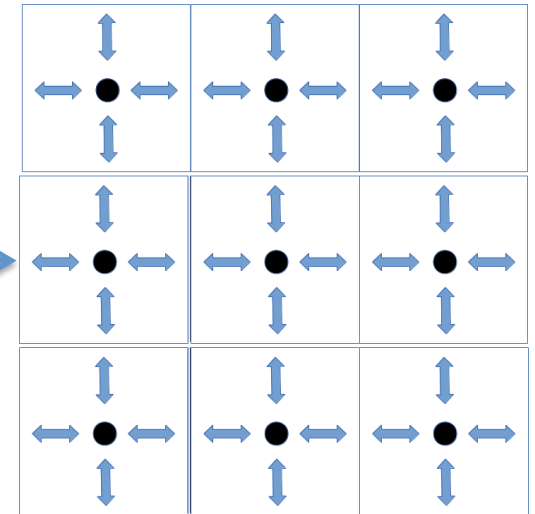
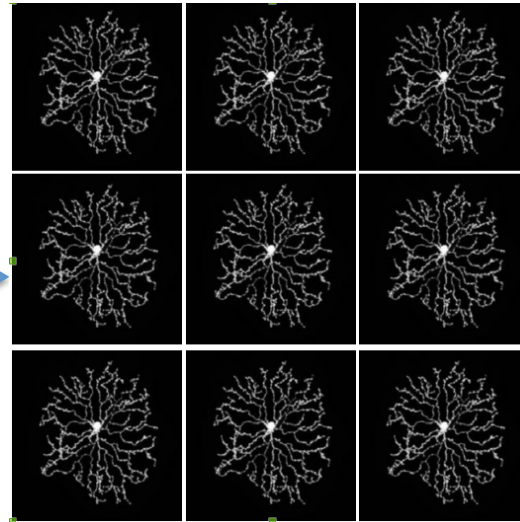


Fig 7. Starburst amacrine cells are stained with lucifer yellow in whole-mount rabbit retina.



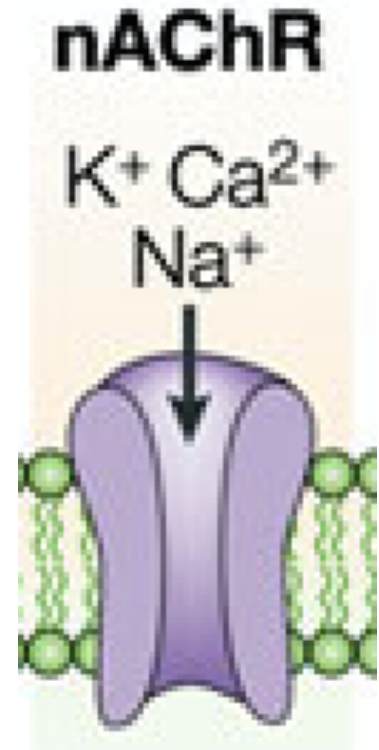
SACs realistic connections

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  $A$



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

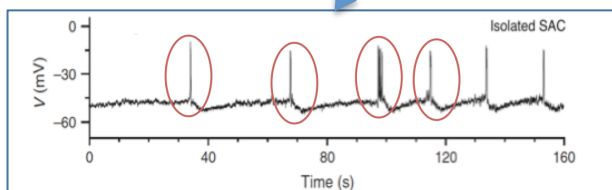
# A network model for stage II retinal waves

## Membrane potential dynamics

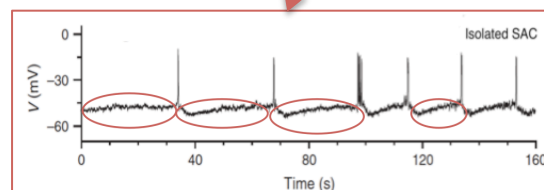
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach} (A_j) (V_i - V_{Ach})$$

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

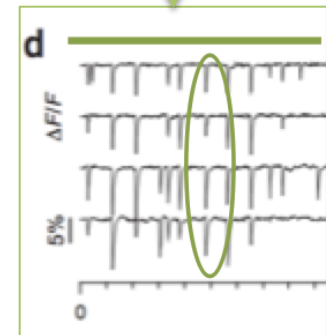
**Morris-Lecar &  
Fast K<sup>+</sup> channels**



**sAHP current  
Refractory  
mechanism**



**Ach current  
Network  
effect**



# A network model for stage II retinal waves

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

# A network model for stage II retinal waves

N neurons, 6 N equations

$$\left\{ \begin{array}{l}
 C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
 \quad - G_{SAPD}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k \in \mathcal{N}})(V_i - V_A) \\
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 \end{array} \right.$$

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

Time scale separation

# A network model for stage II retinal waves

N neurons, 6 N equations

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

~ 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**

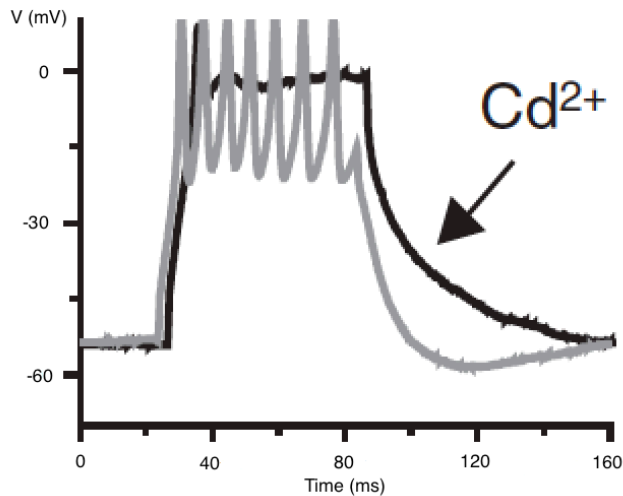
$$\begin{cases} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) + I_{\text{ext}} \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \end{cases}$$



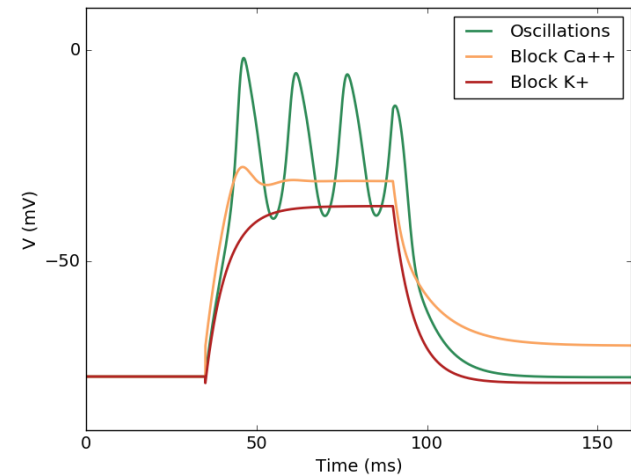
# Fast time scale

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

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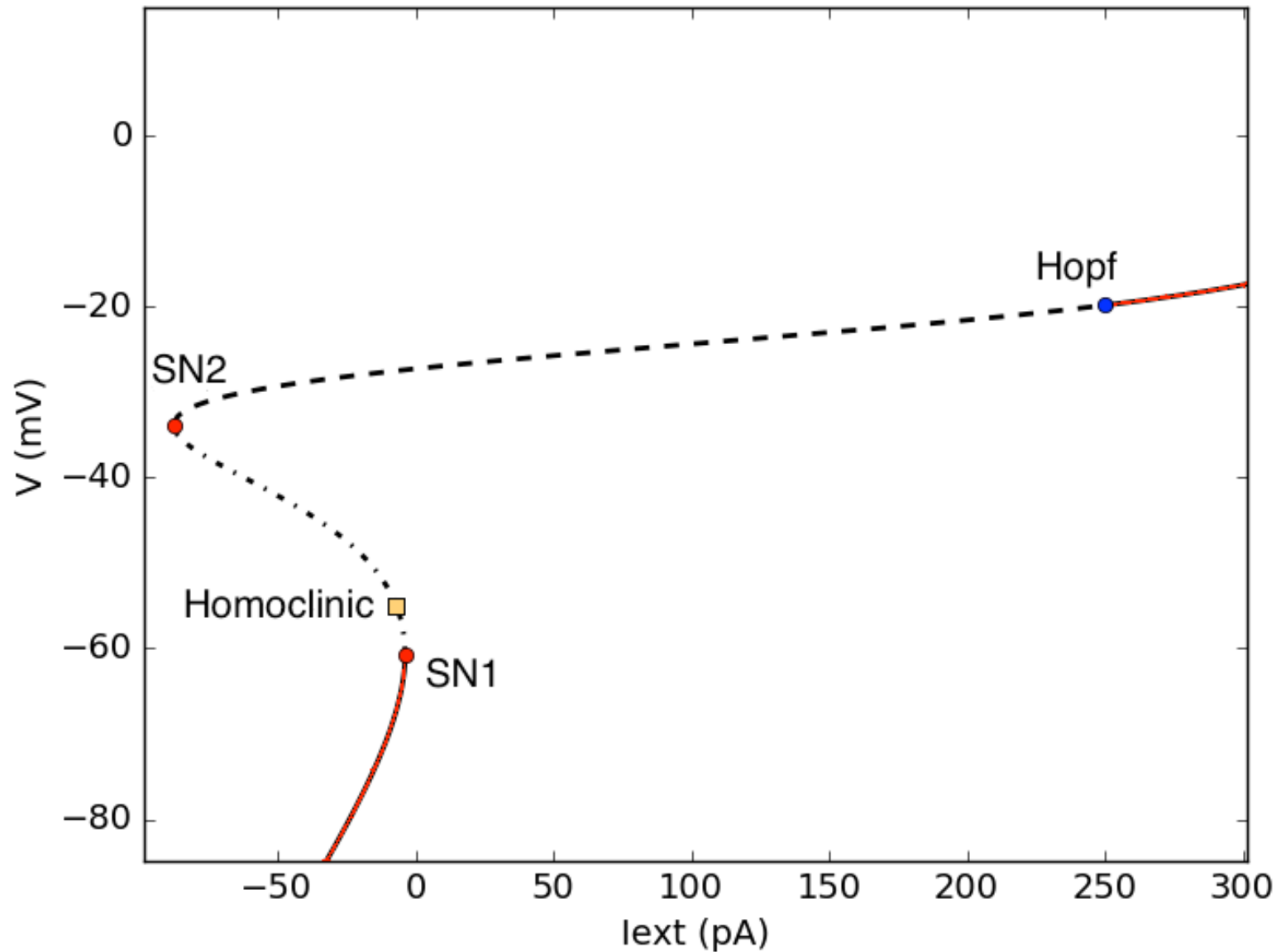


Experiment by Zheng et al. 2006,  
Nature

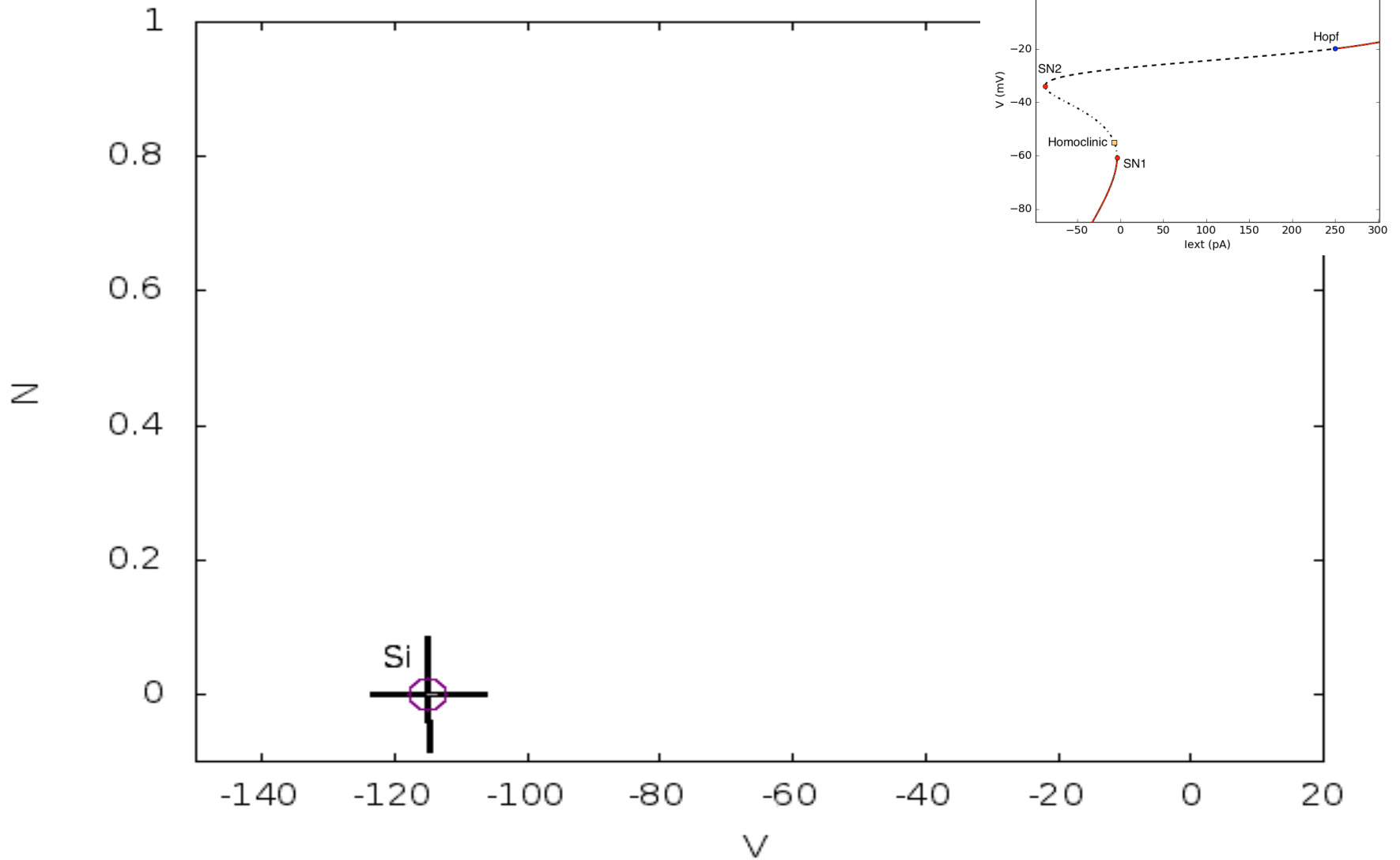


Model. Tuning parameters V1, V2,  
V3, V4 from ML adjusted to  
reproduce the experiment

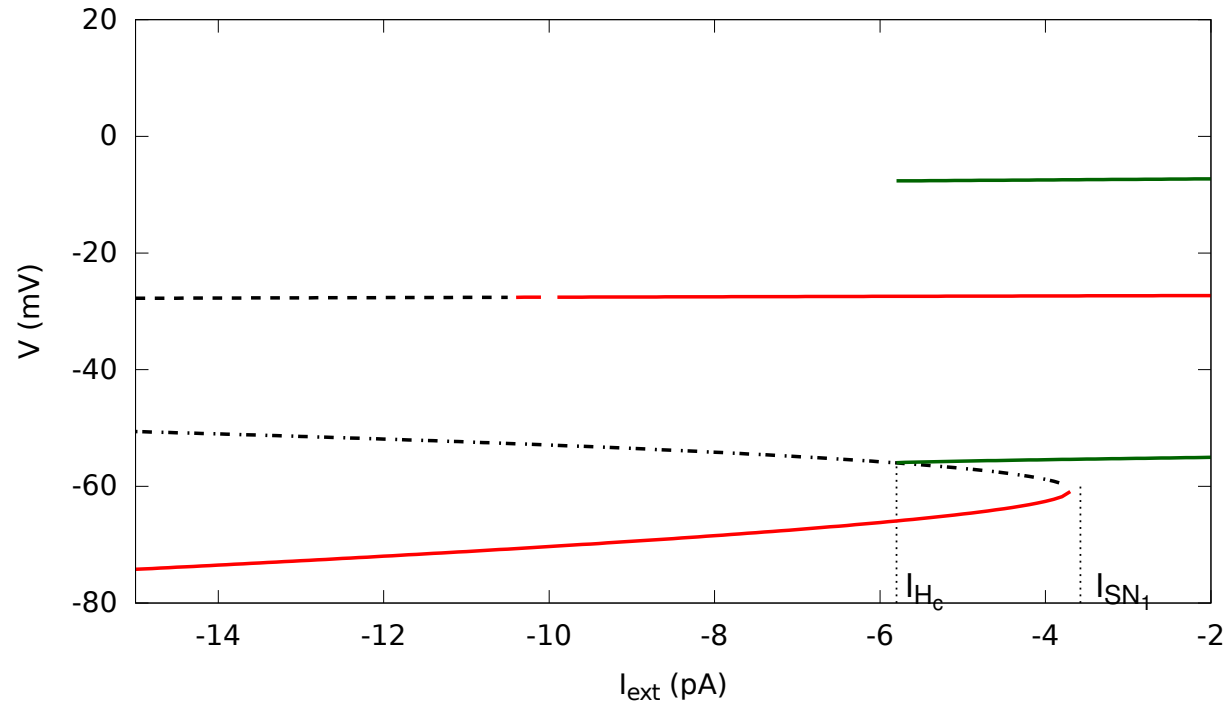
# Bifurcation diagram of M-L model



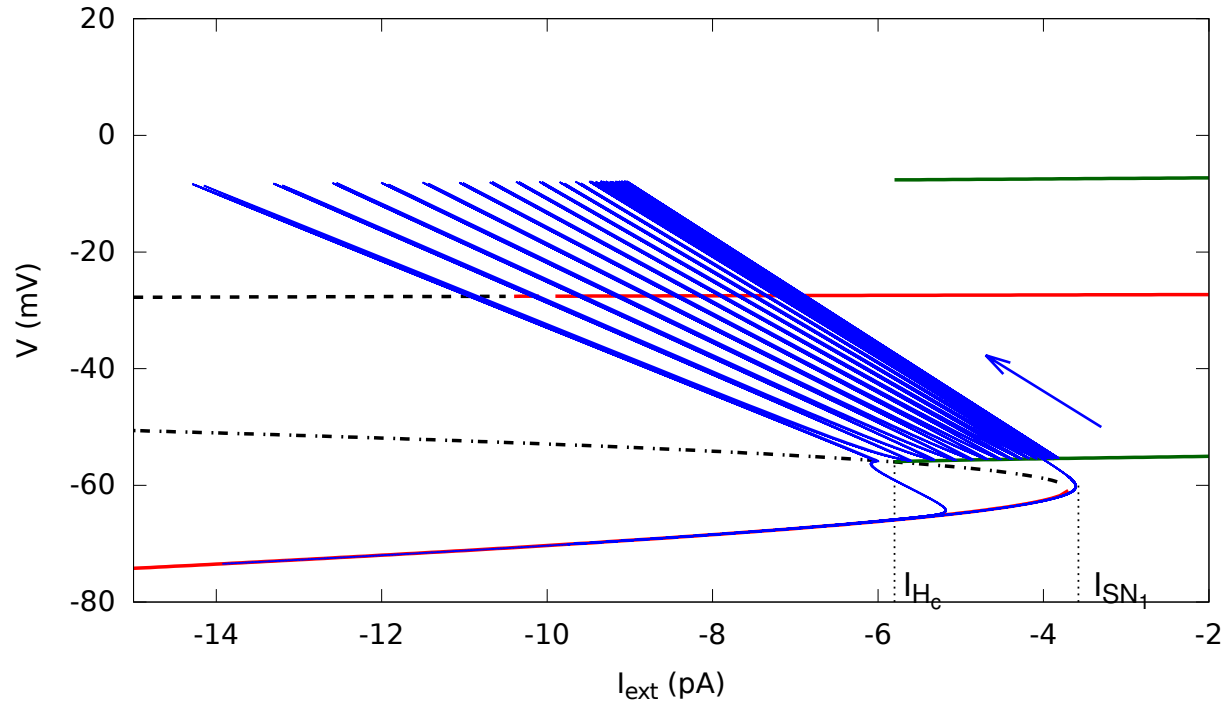
# Bifurcation diagram of M-L model



# The mechanism of bursting

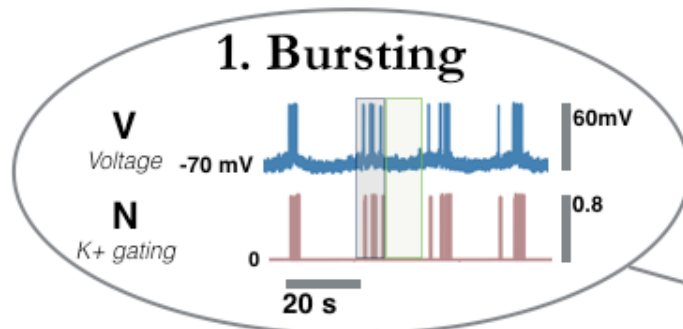


# The mechanism of bursting

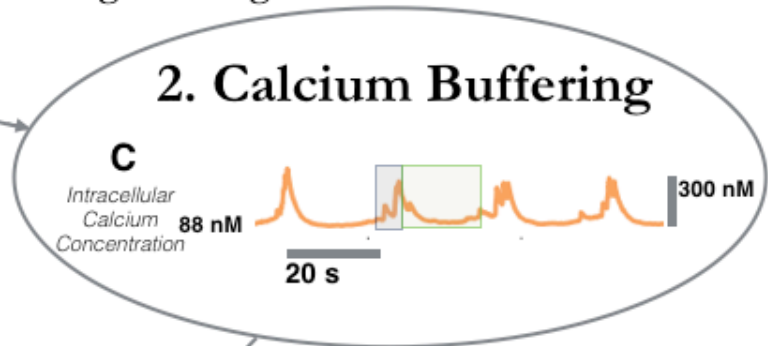


# Spontaneous Bursting Mechanism of SACs

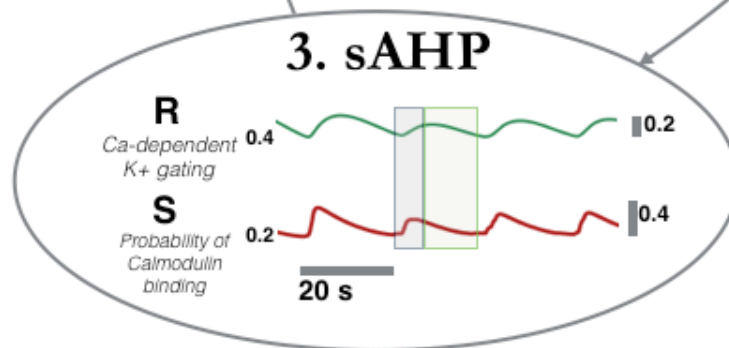
■ Bursting  
■ sAHP



Increase of Calcium load during bursting

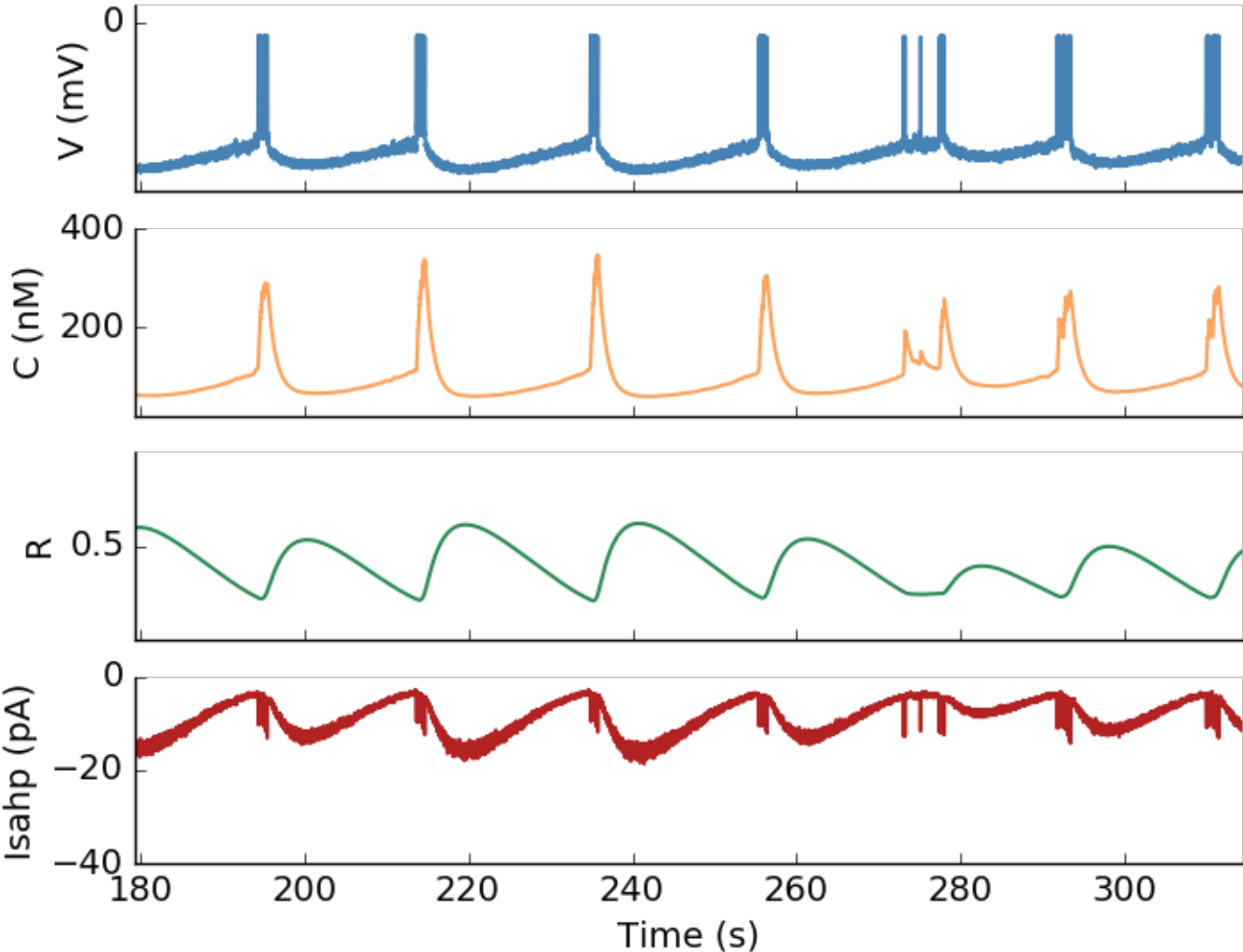


Bursting starts again when the Calcium load is low enough

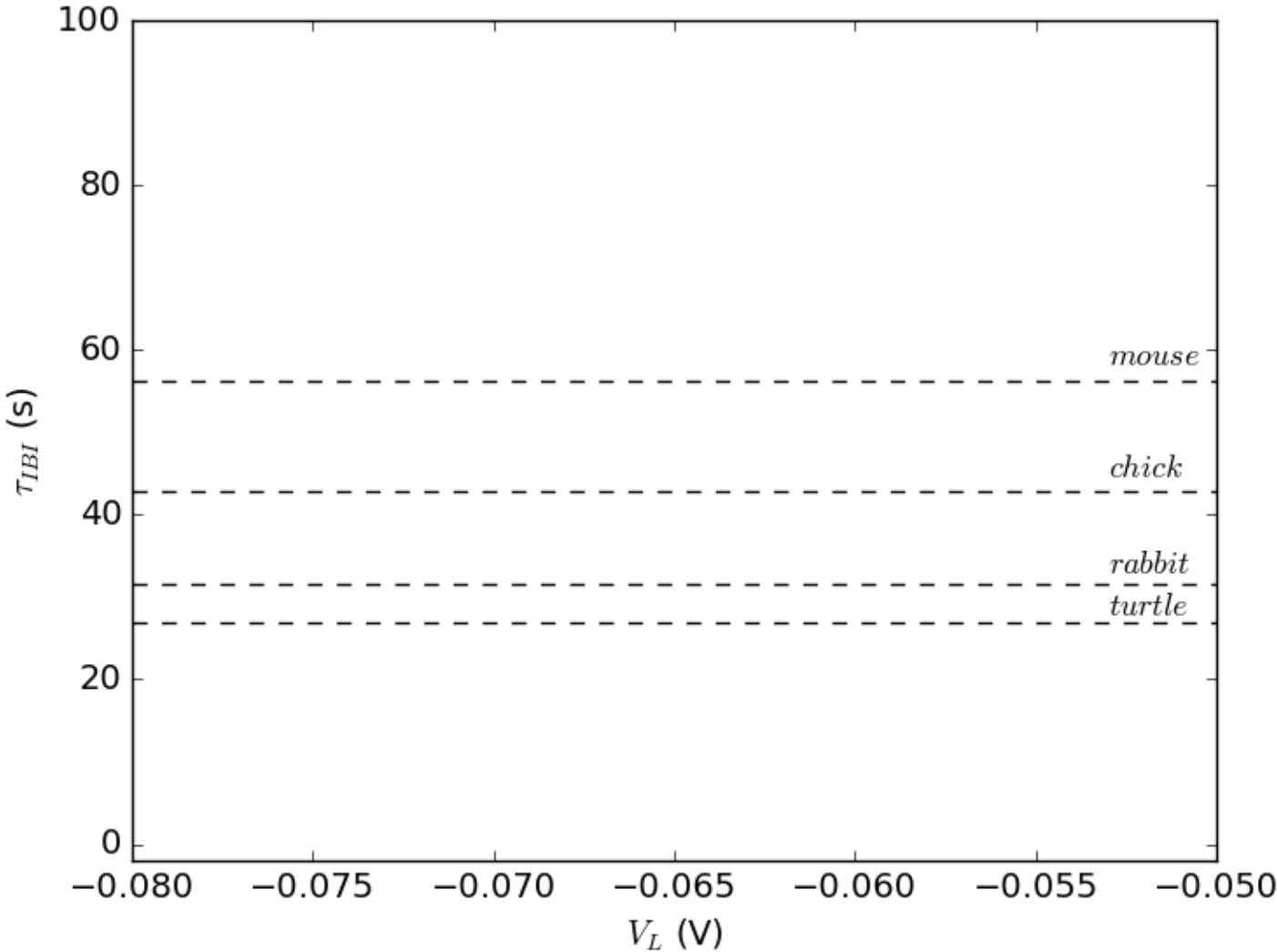


Calcium controls the sAHP phase. Voltage is low and Calcium starts offloading

# Reproduce Individual SACs bursting dynamics

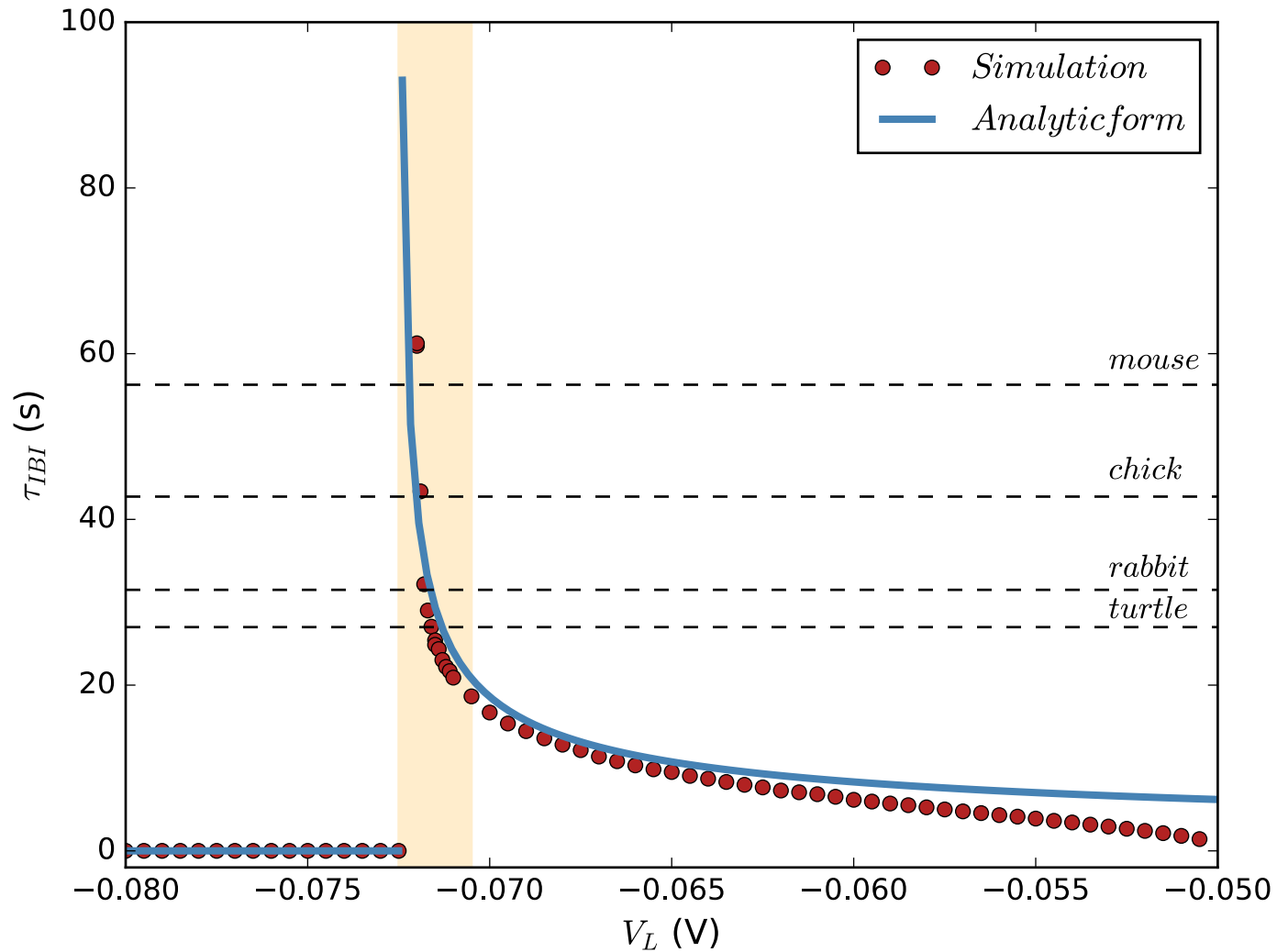


# Explain variable bursting period across species



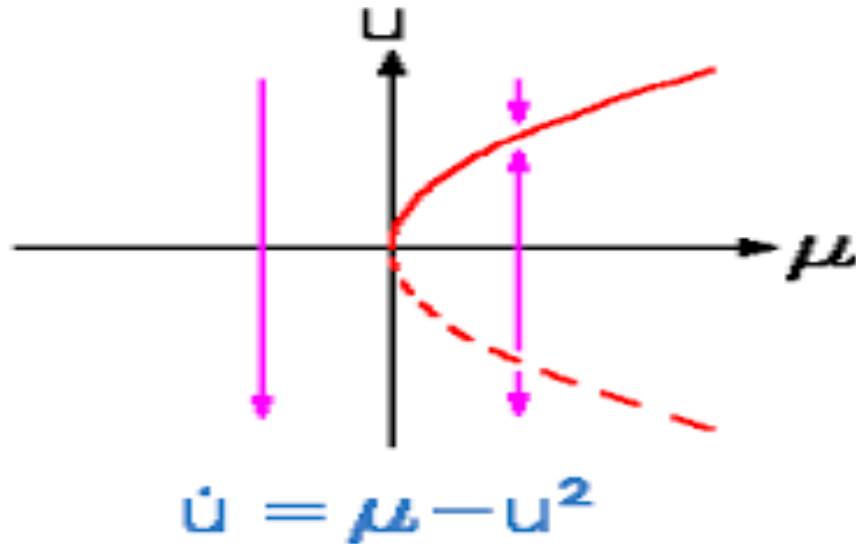


# Explain variable bursting period across species

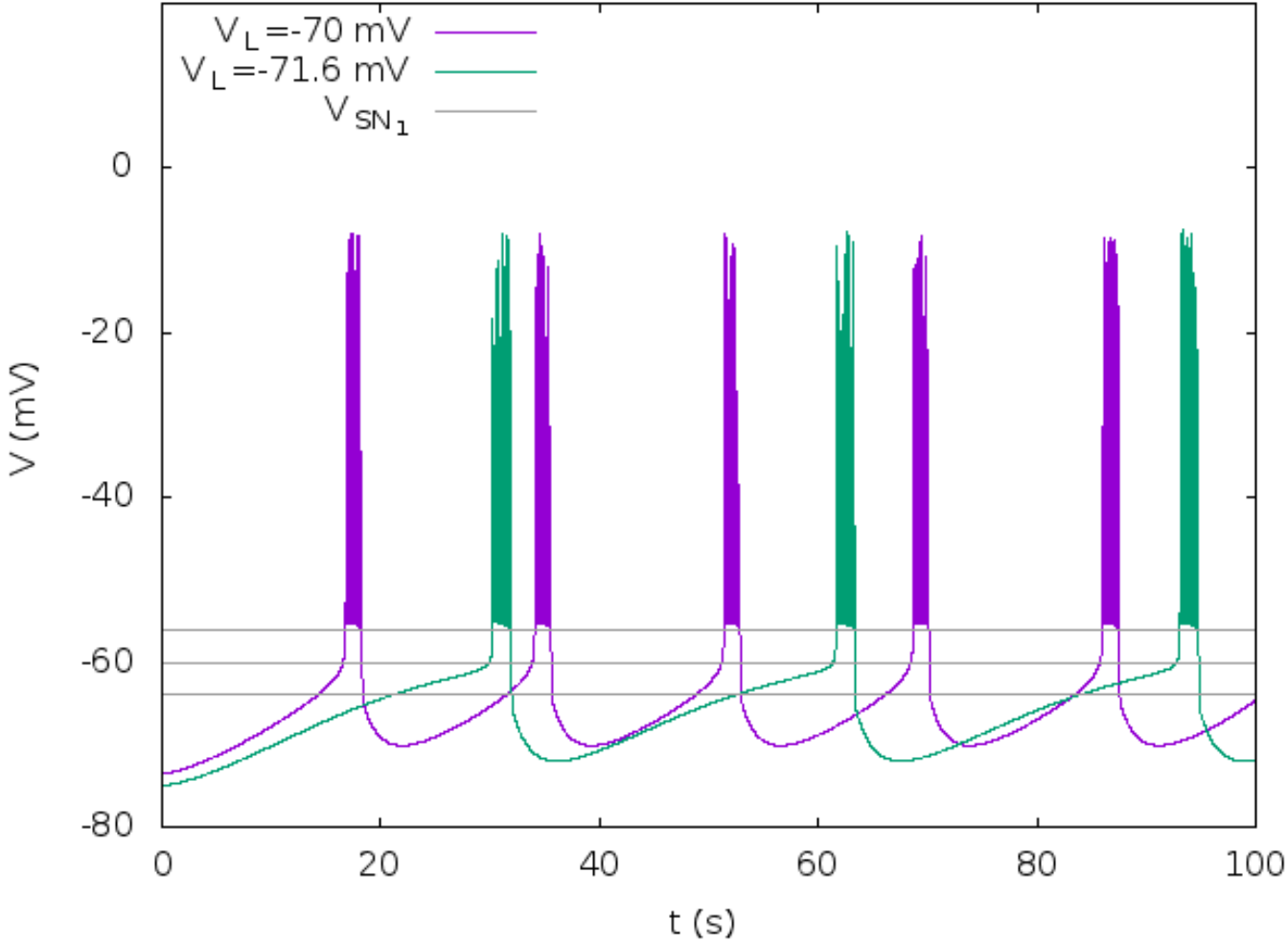


# Explain variable bursting period across species

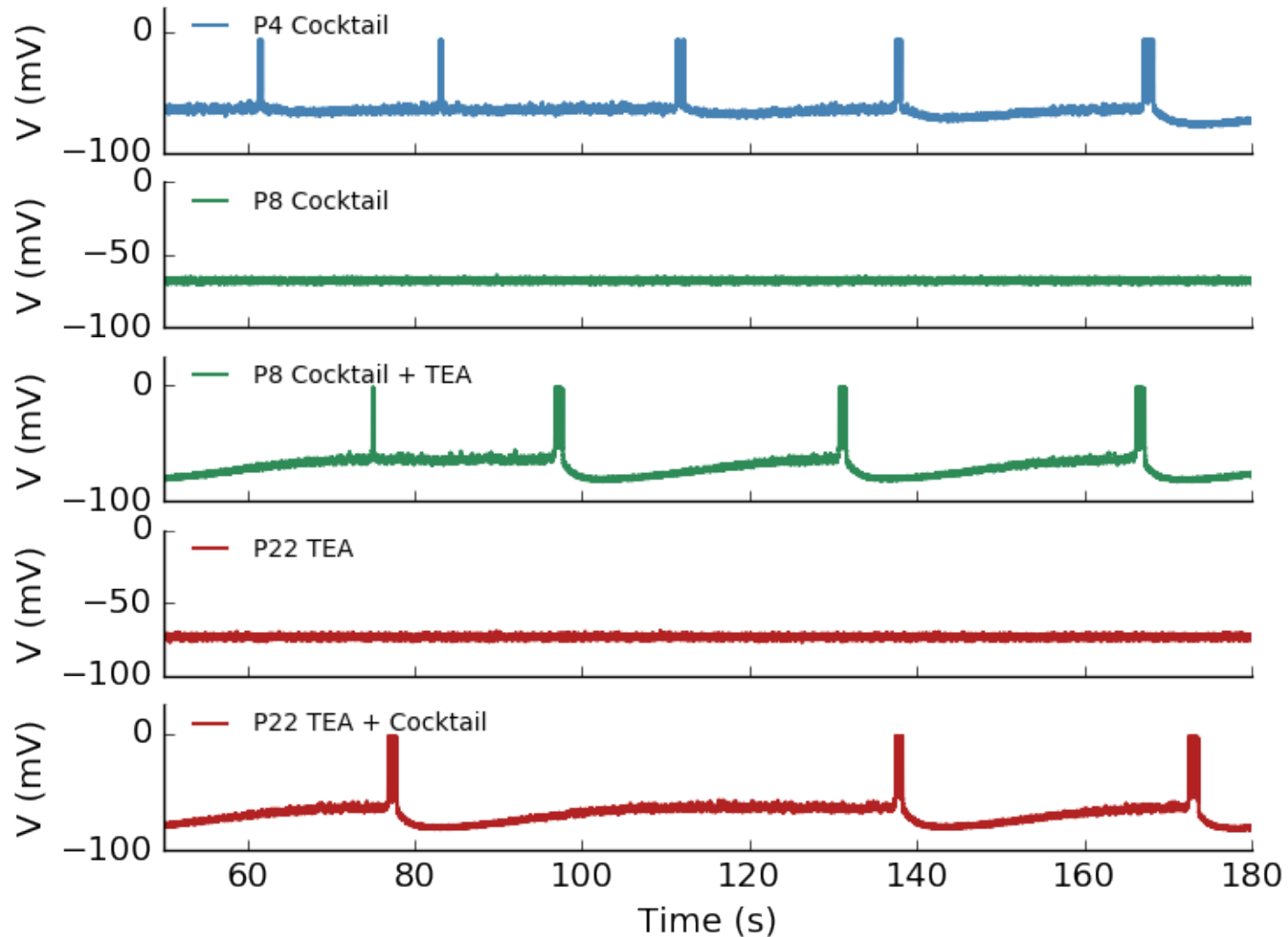
saddle-node bifurcation



# Explain variable bursting period across species



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



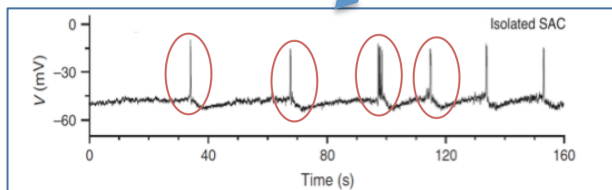
# A network model for stage II retinal waves

## Morris-Lecar

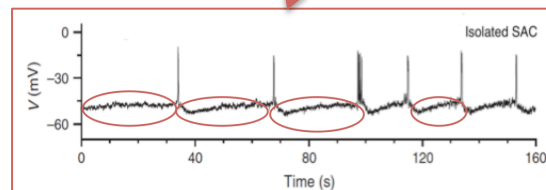
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach} (A_j) (V_i - V_{Ach})$$

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

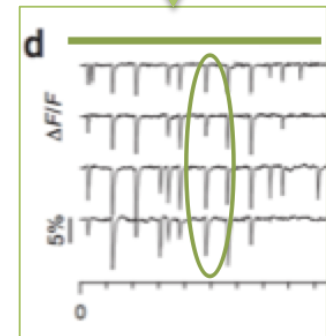
**Morris-Lecar &  
Fast K<sup>+</sup> channels  
(kV3)**



**sAHP current  
Refractory  
mechanism**

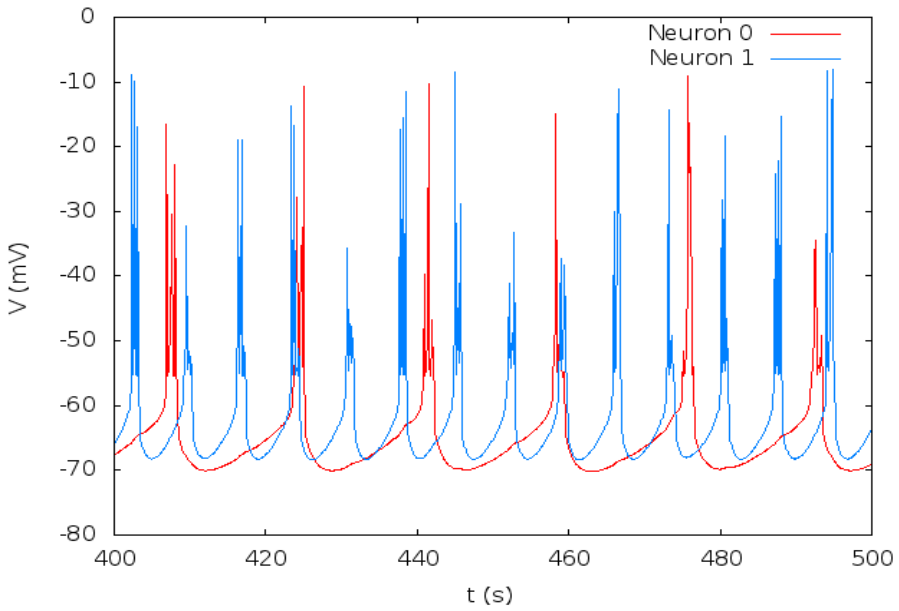


**Ach current  
Network  
effect**



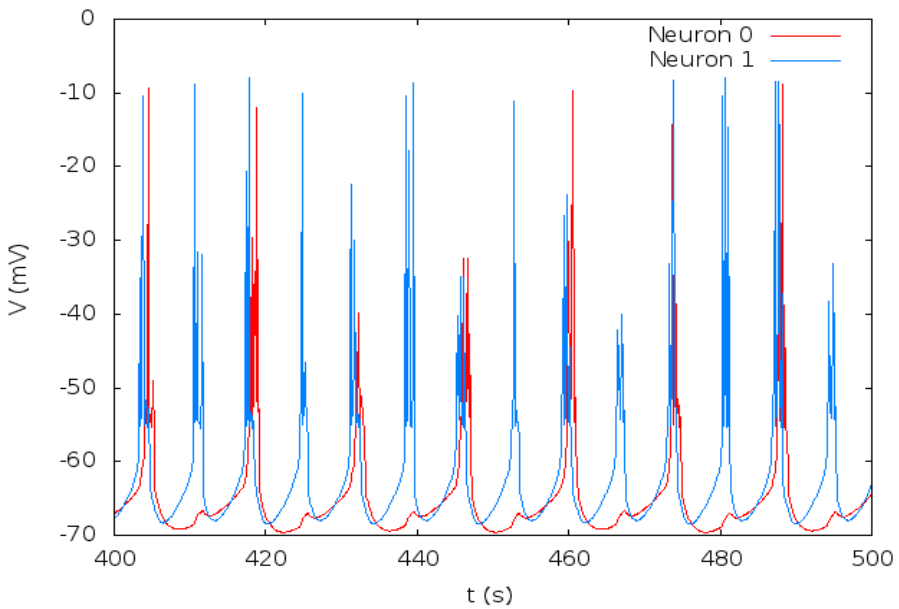
# Coupling 2 cells

# Coupling 2 cells



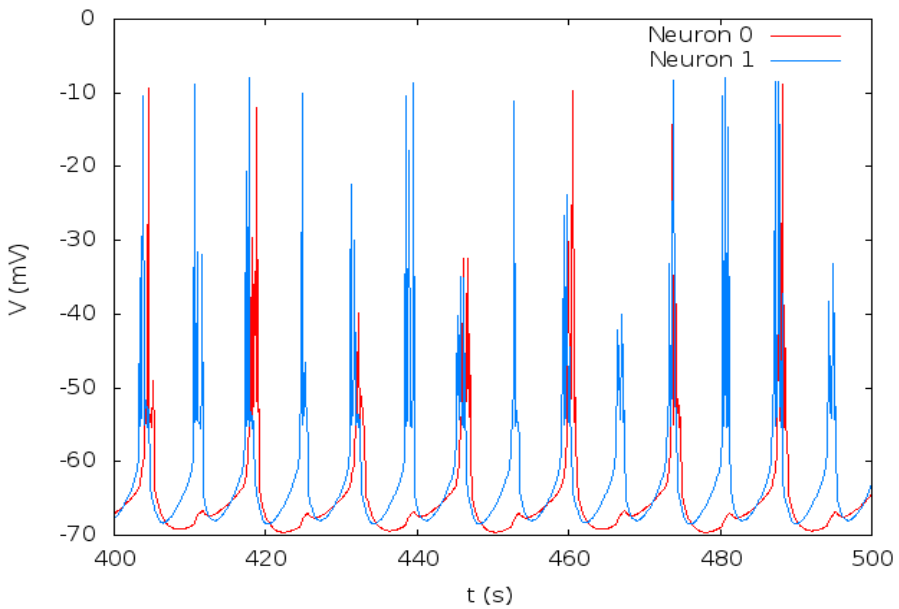
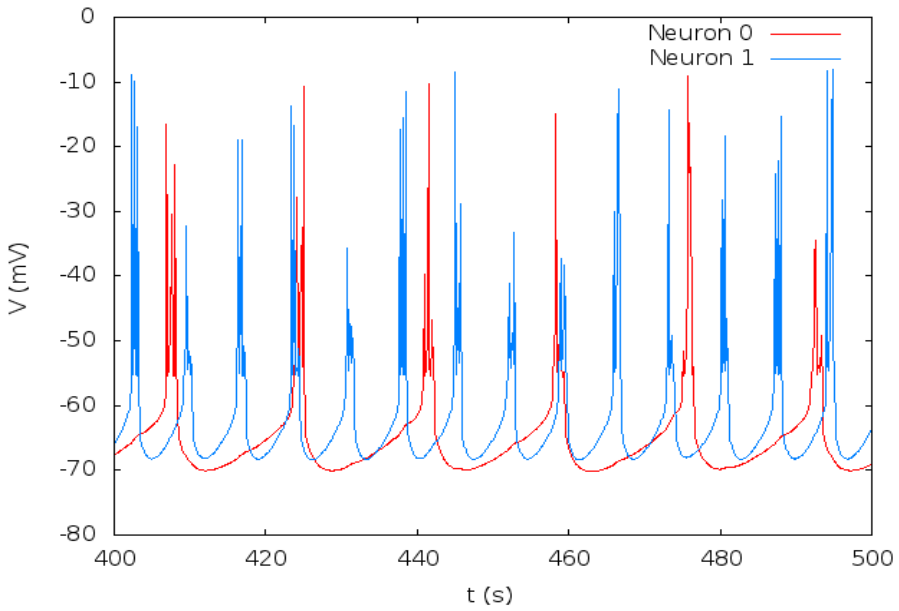
Gach: synaptic conductance

Gach=0.05



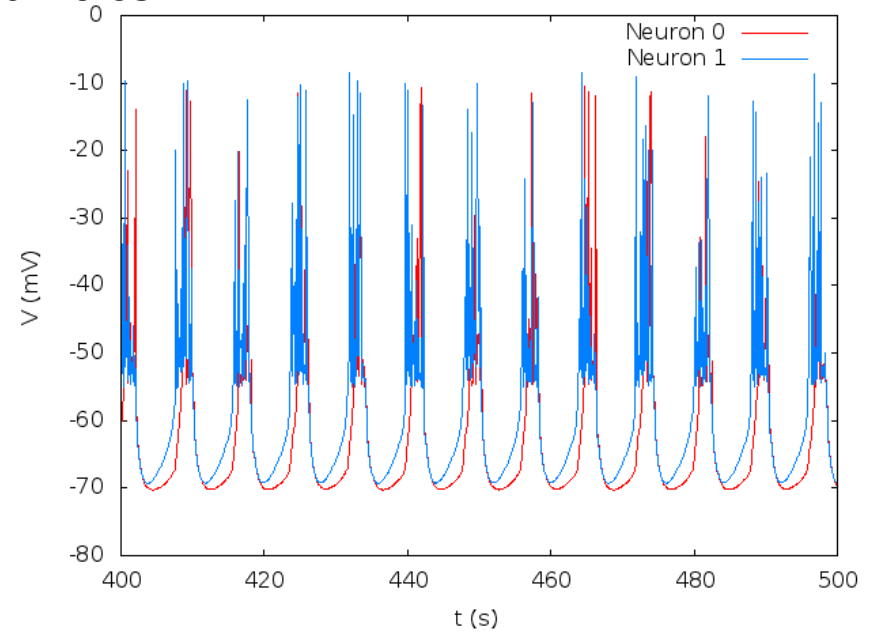
Gach=0.15

# Coupling 2 cells



Gach: synaptic conductance

Gach=0.05

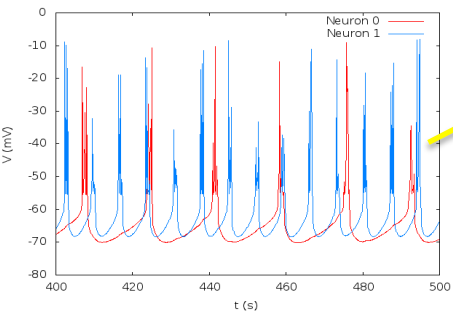
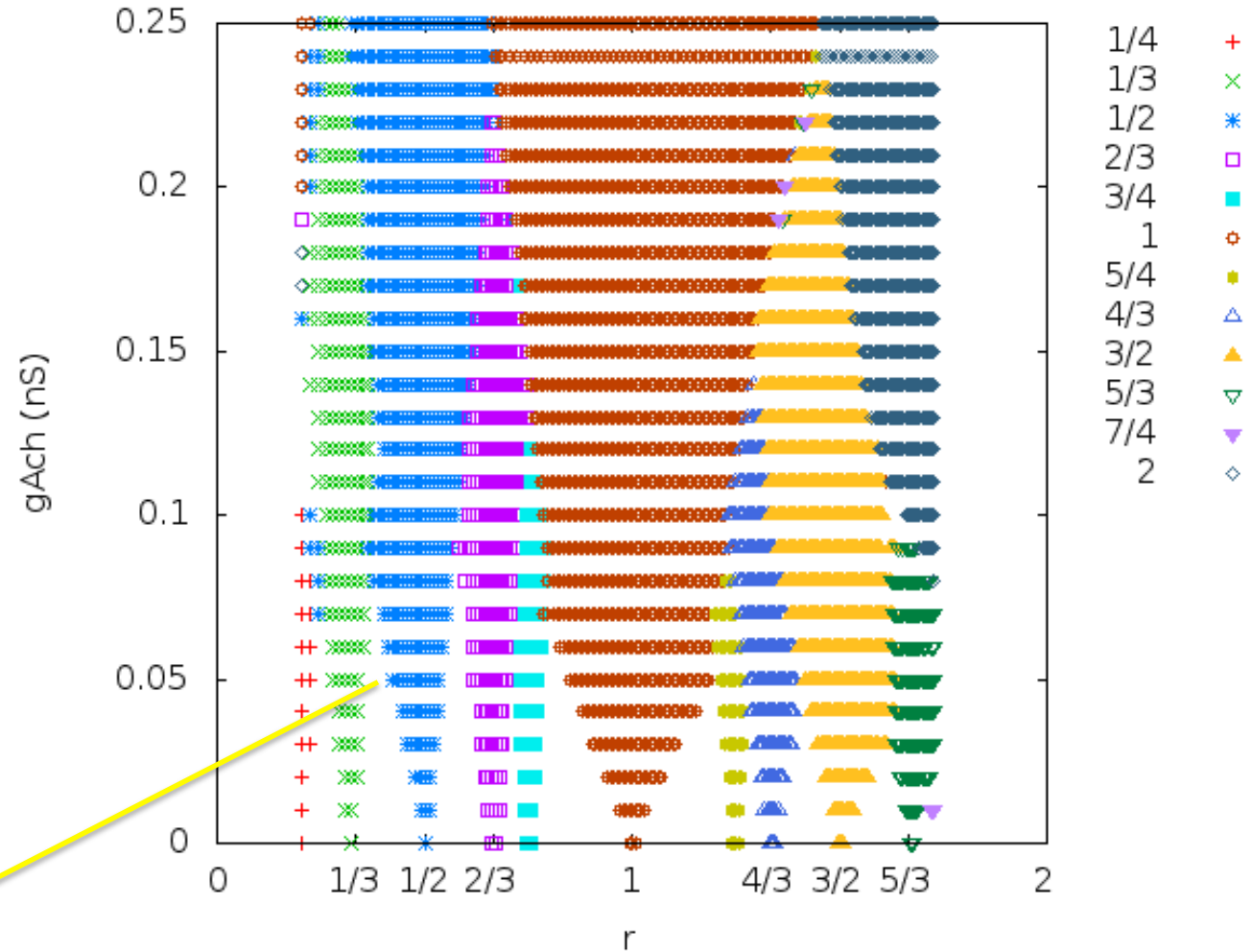


Gach=0.15

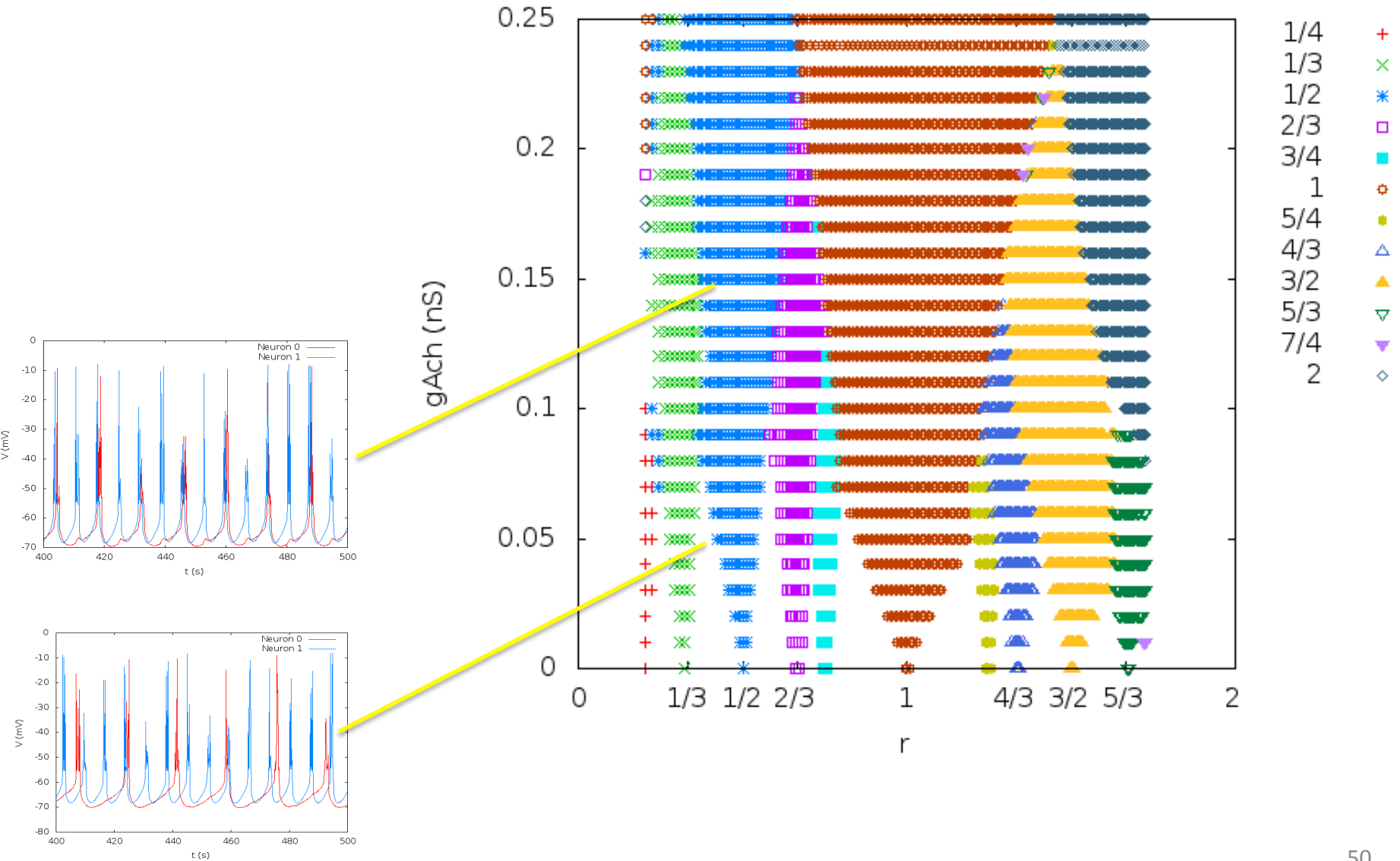
Gach=0.5



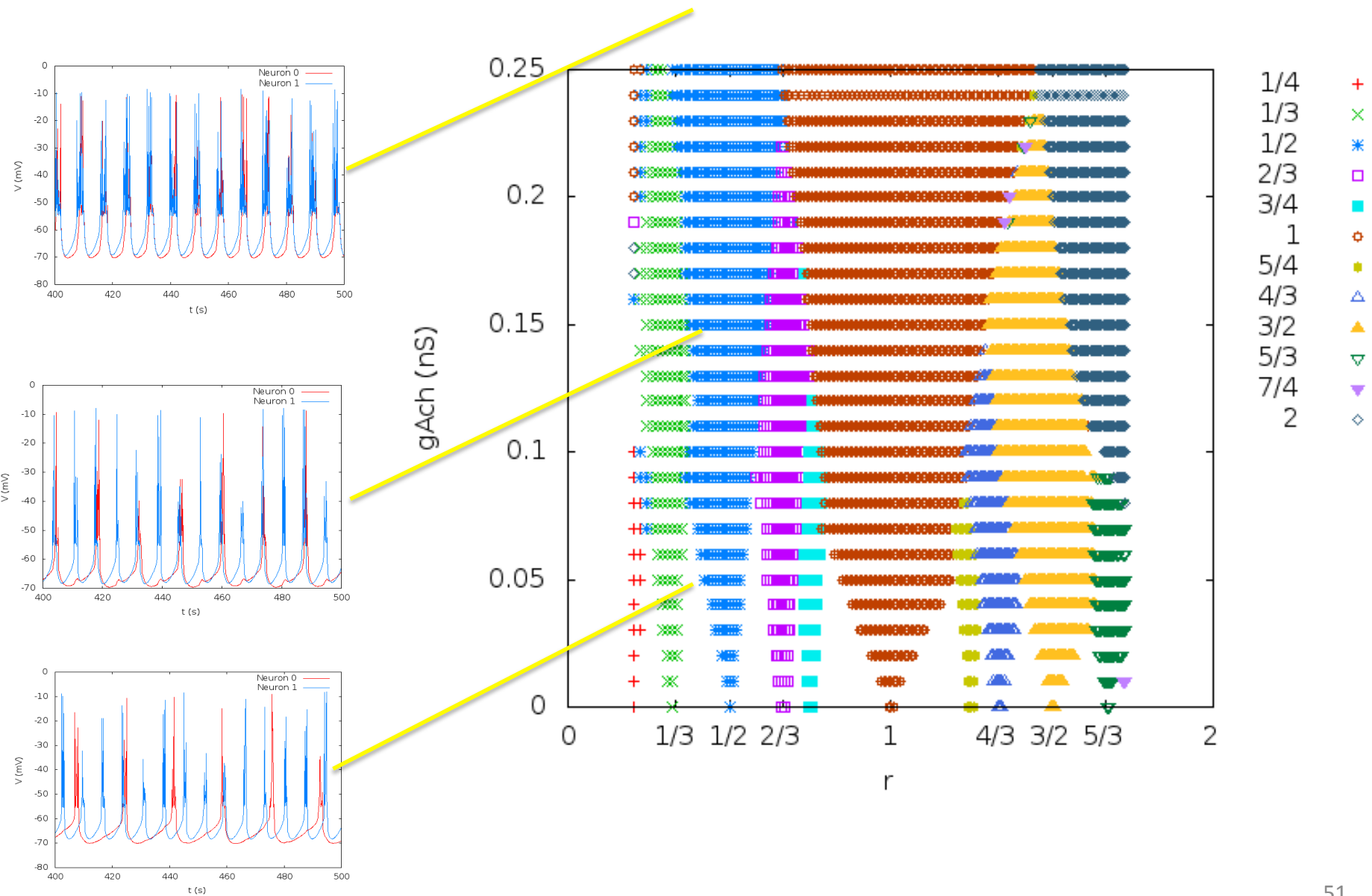
# Synchrony: Arnold tongues



# Synchrony: Arnold tongues



# Synchrony: Arnold tongues



# SACs Network

## Model synaptic interactions

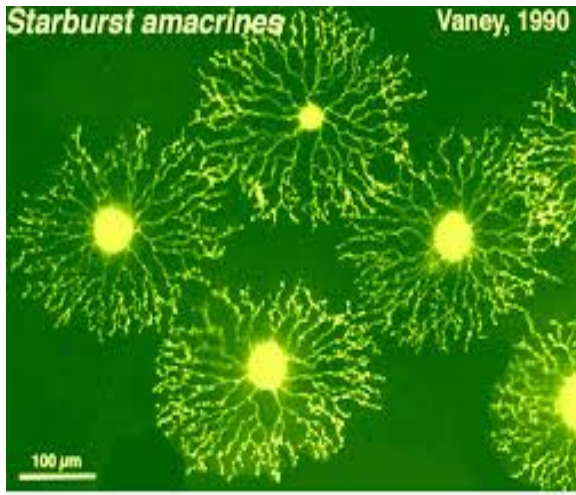
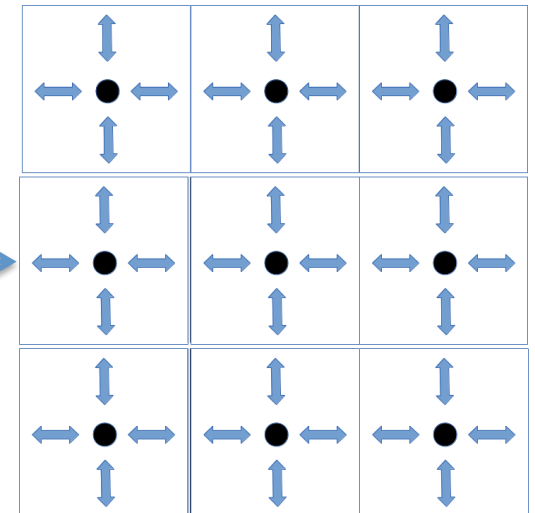
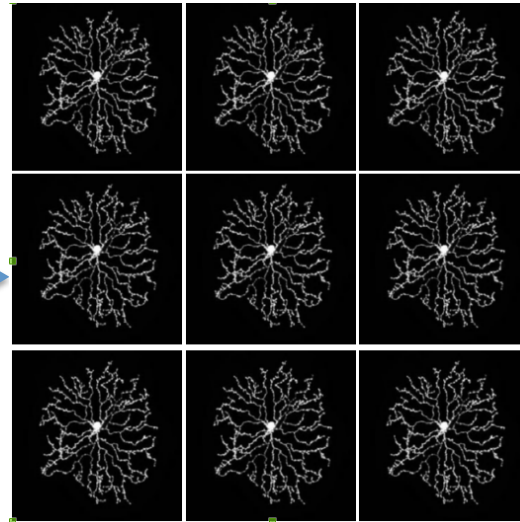


Fig 7. Starburst amacrine cells are stained with lucifer yellow in whole-mount rabbit retina.

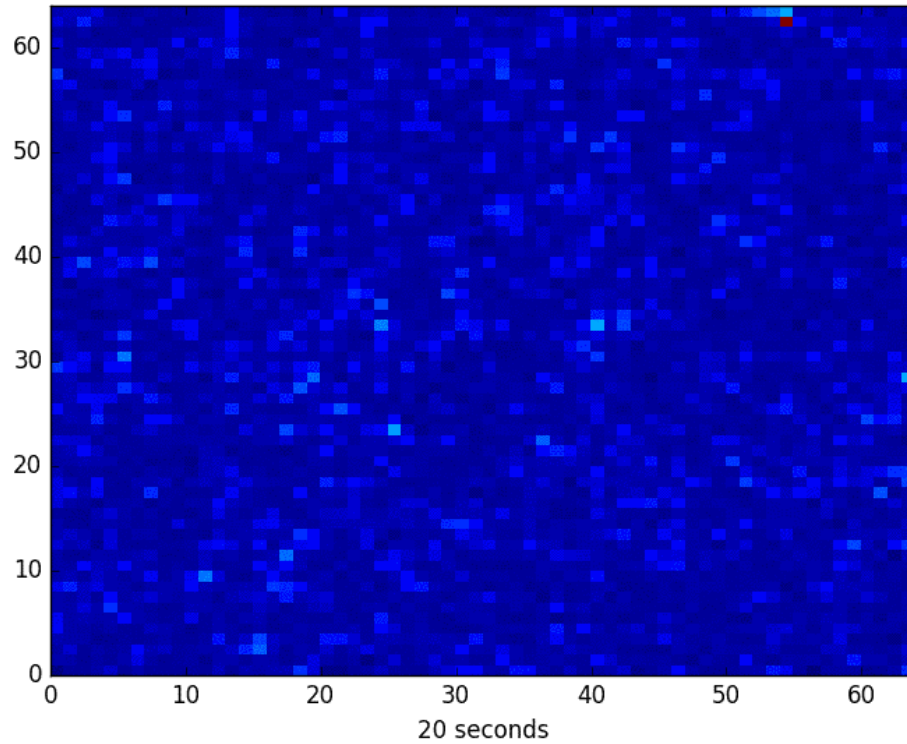


SACs realistic connections

SACs on a lattice

SACs become points on a lattice

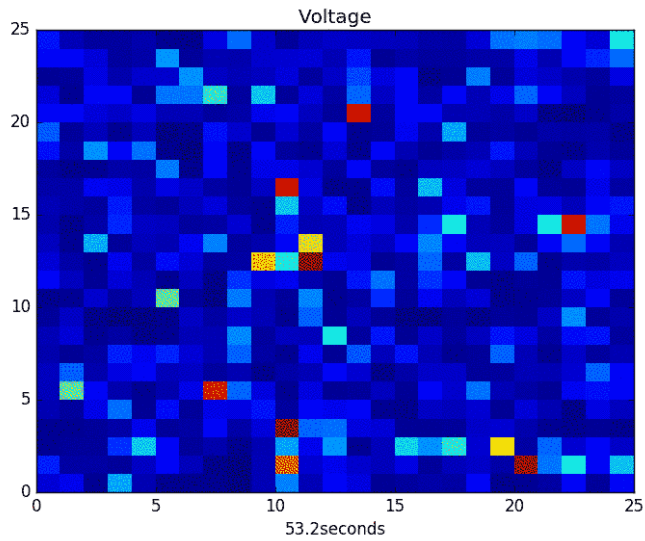
# Reproduce coupled SACs dynamics in stage II retinal waves



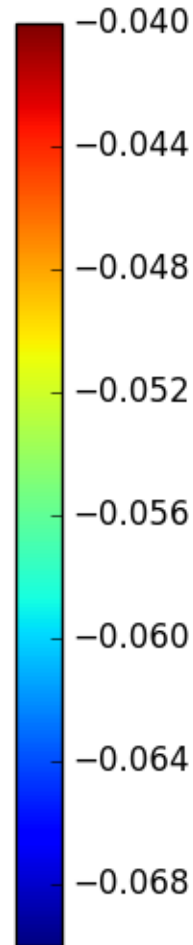
# Network of SACs : Simulated Voltage

Isolated Neurons

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



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

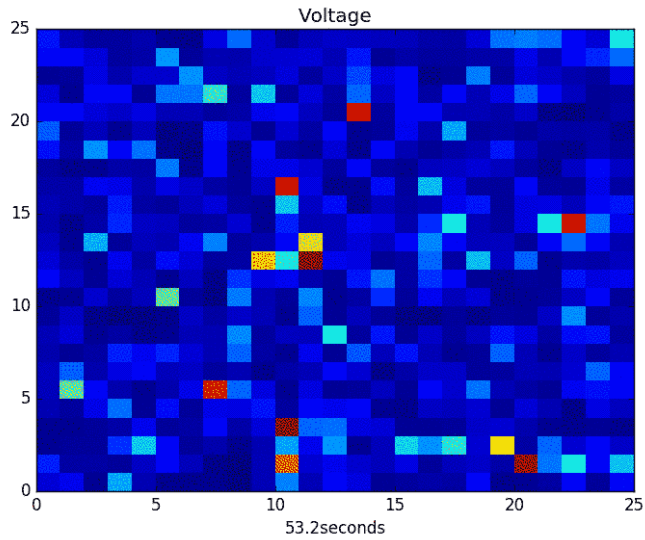


$g_{ach}=0.21 \text{ nS}$

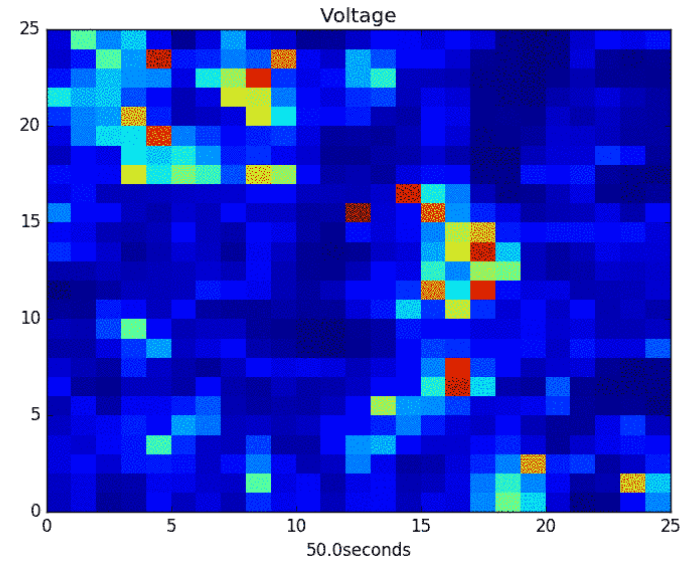
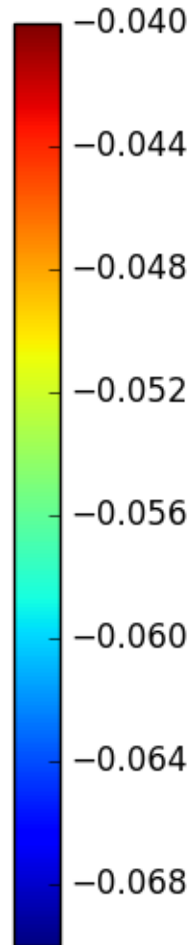
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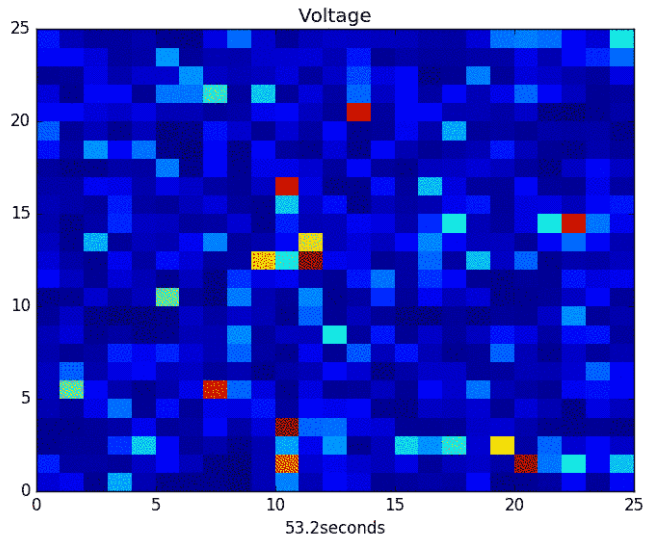


$g_{ach}=0.21 \text{ nS}$

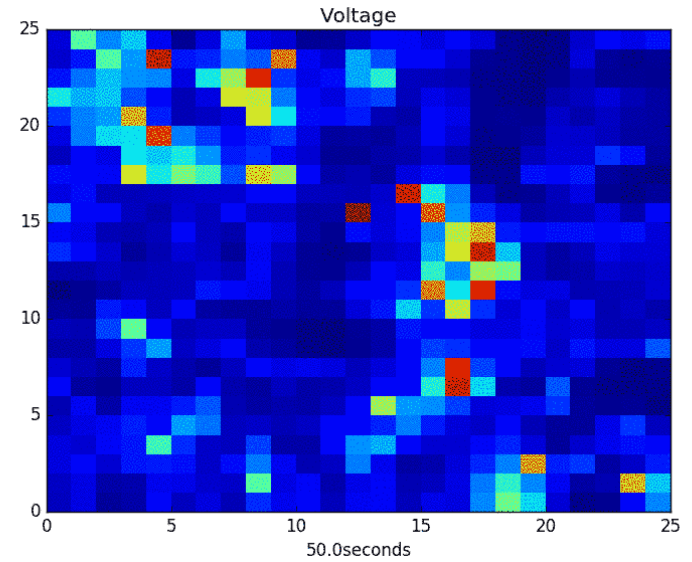
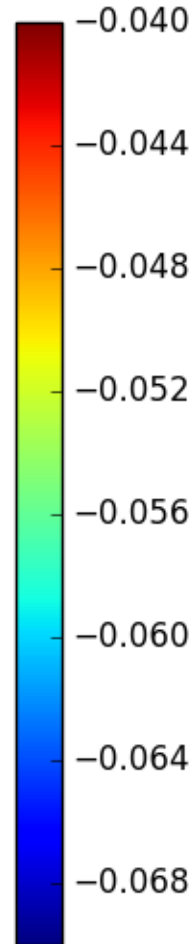
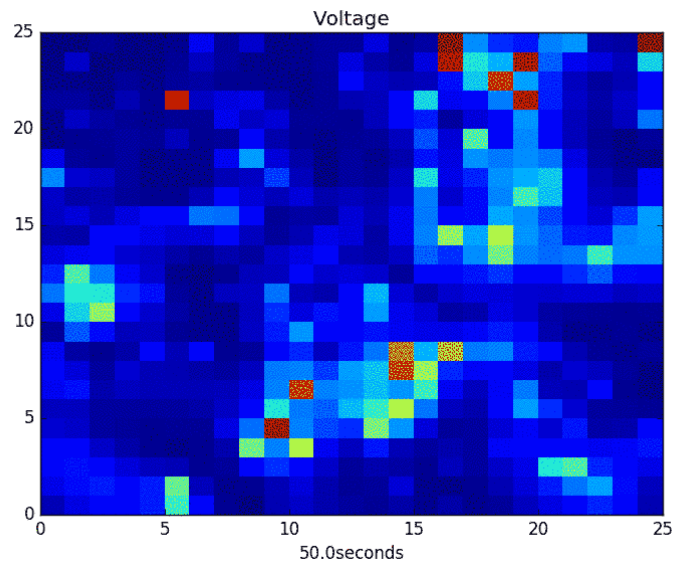
# Network of SACs : Simulated Voltage

Isolated Neurons

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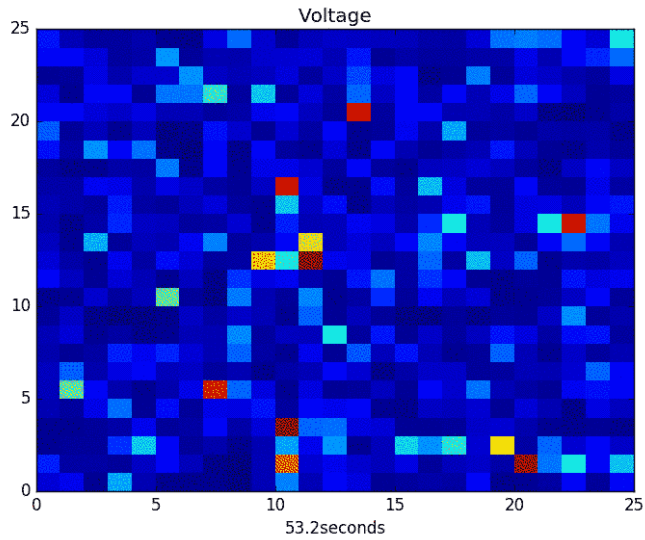
$g_{ach}=0.21 \text{ nS}$



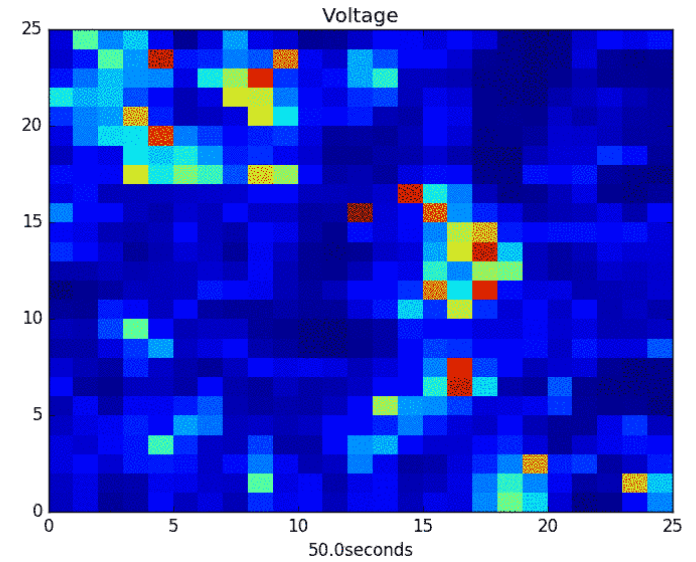
# Network of SACs : Simulated Voltage

Isolated Neurons

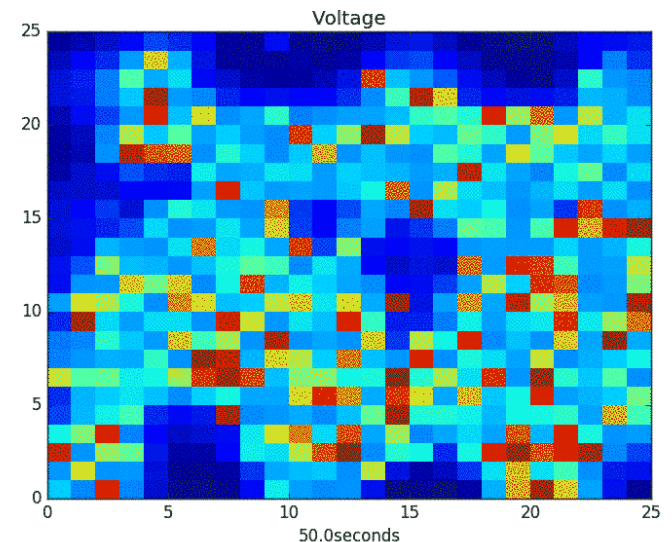
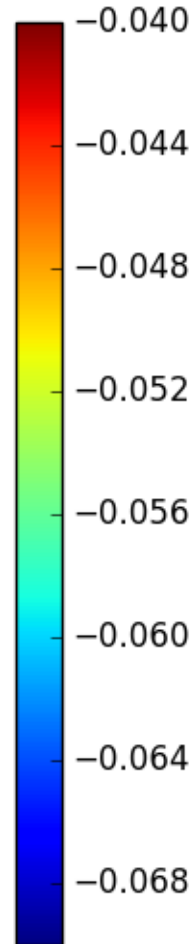
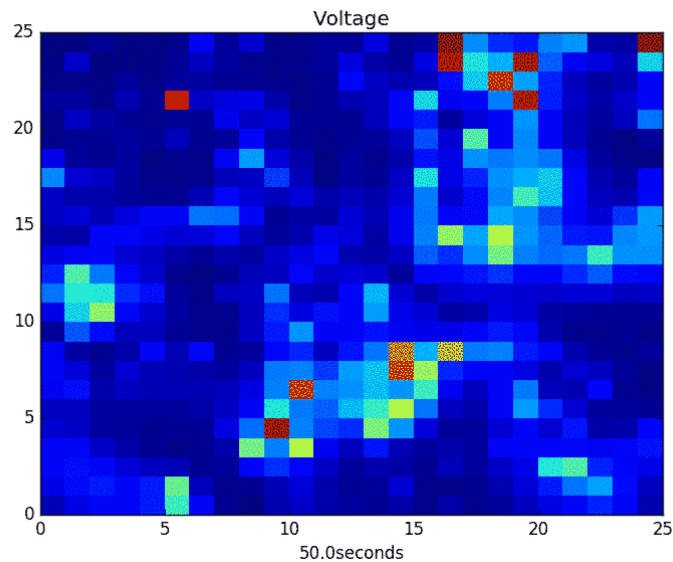
$g_{ach}=0.126 \text{ nS}$



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

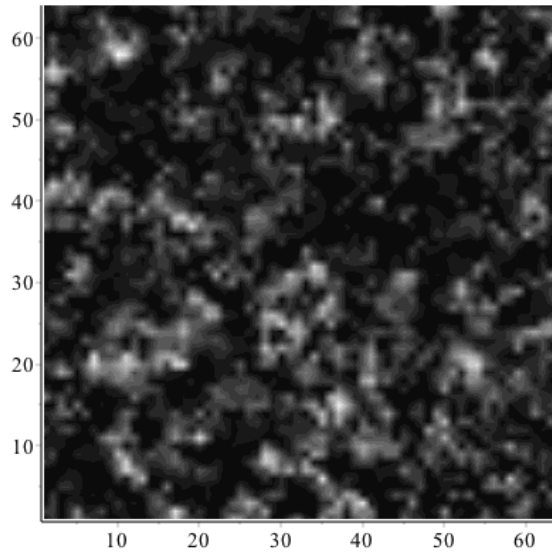


$g_{ach}=0.21 \text{ nS}$

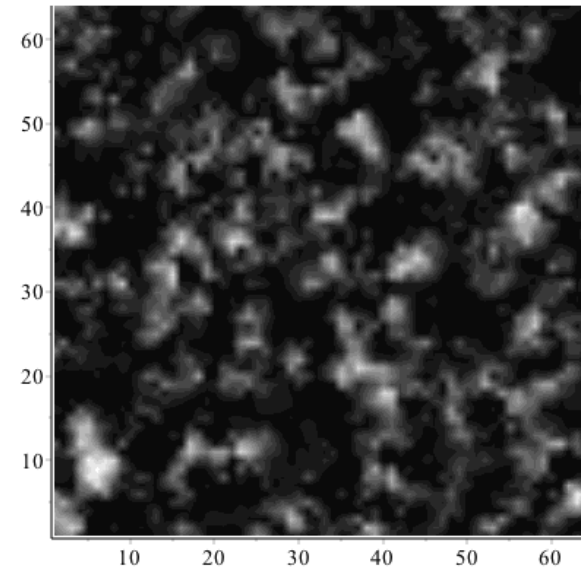


# Network of SACs : Simulated Calcium Concentration

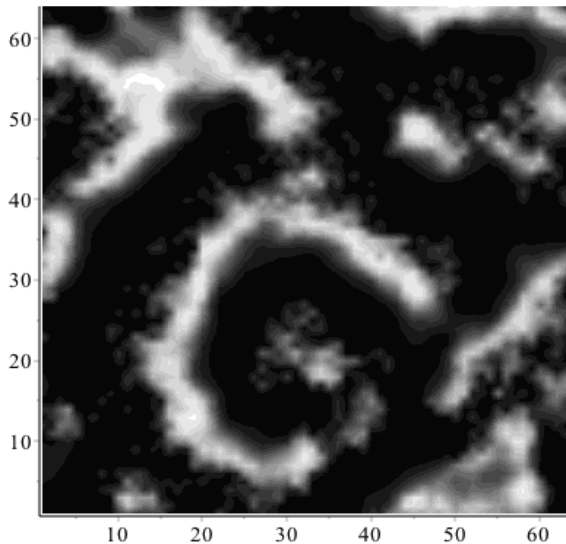
$g_{ach}=0.102$  nS



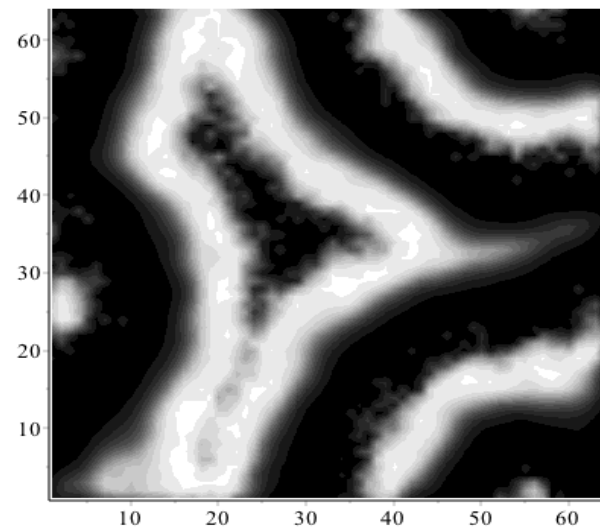
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



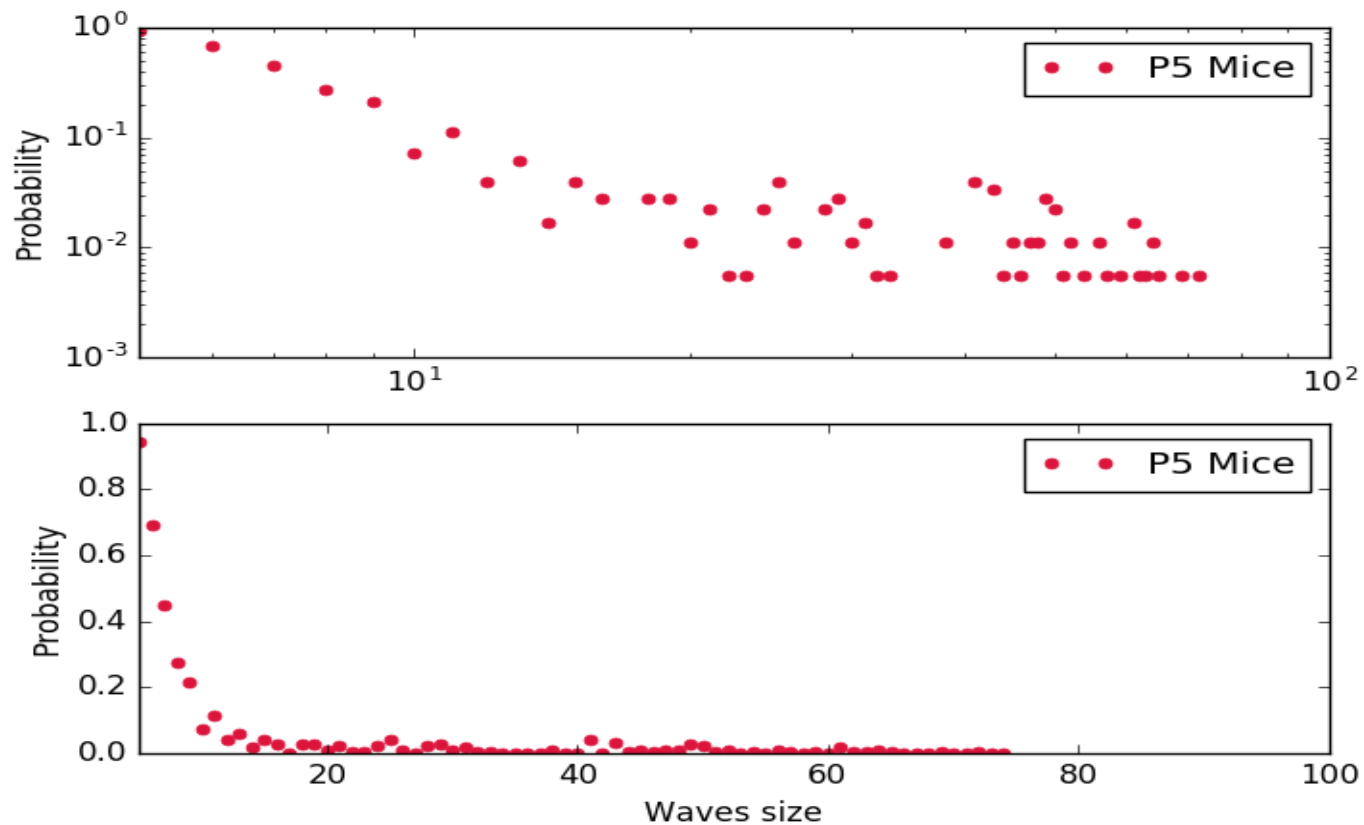
$g_{ach}=0.21$  nS



# N-neuron model

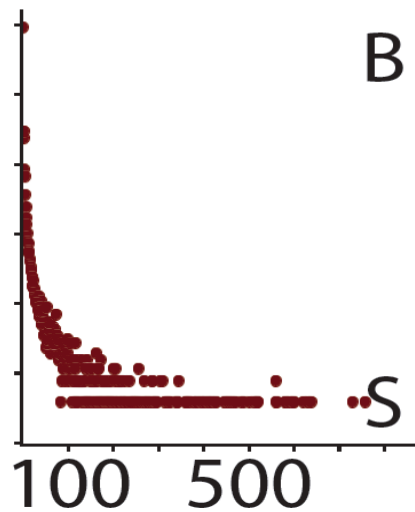
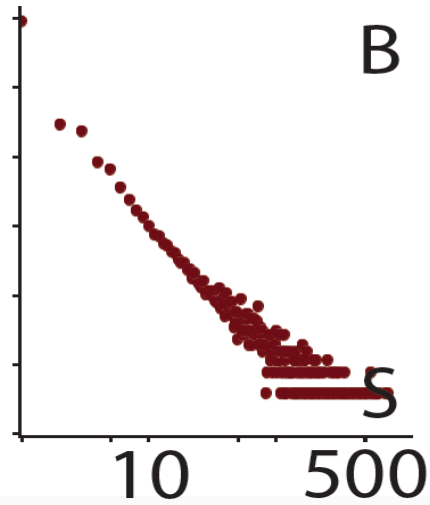
- There is a **competition** between 2 mechanisms:
  - **Period variability** which tends **to desynchronise**
  - **Acetylcholine** which tends **to synchronise**
- There is an intermediate regime of coupling, where **variability** is maximum
- Therefore there is a wide repertoire of patterns
  - **Weak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

# Experimentally varying Ach conductance

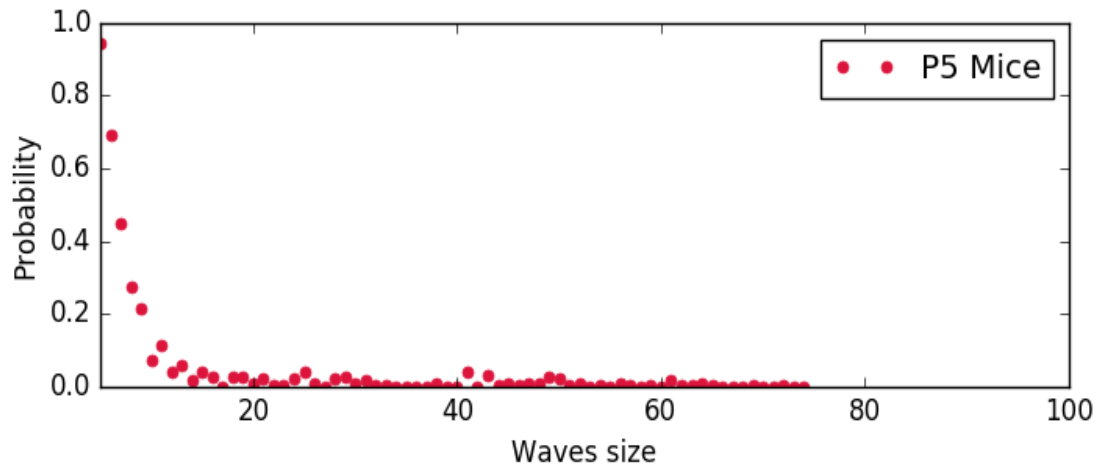
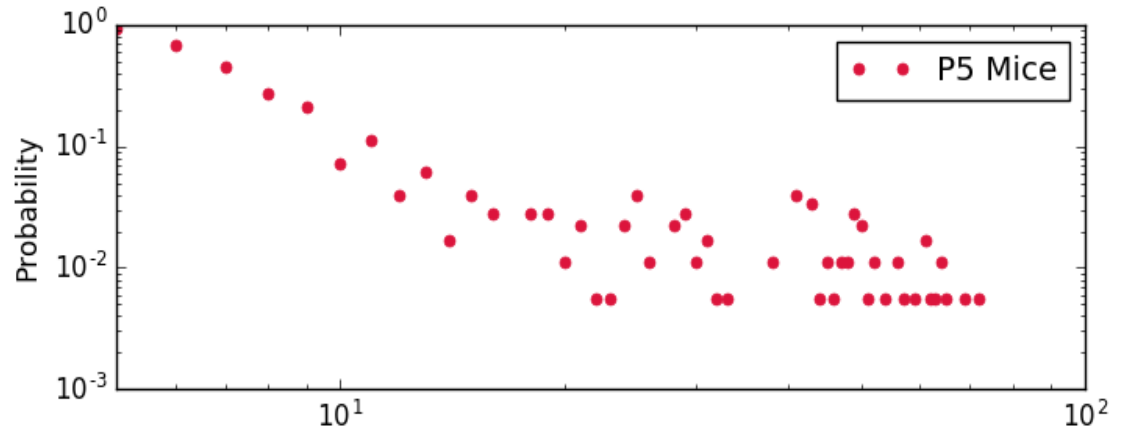


# Experimentally varying Ach conductance

Model



Experiment



# Transport equation

**Assume:**

# Transport equation

Assume:

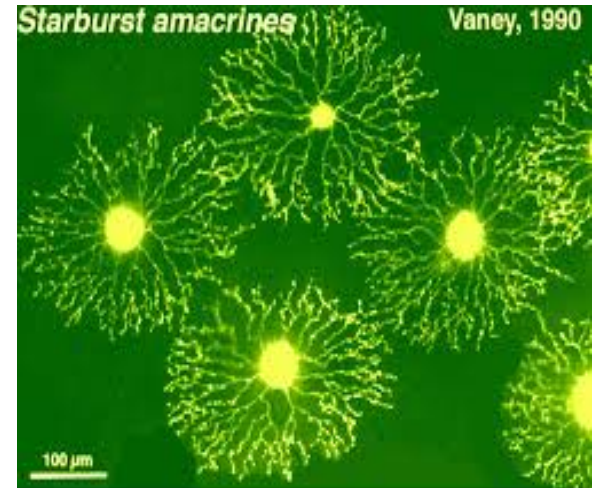
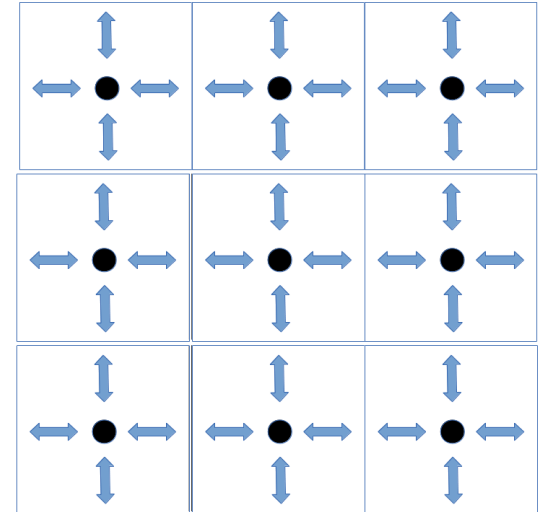


Fig. 7. Starburst amacrine cells as stained with Lucifer yellow in whole-mount rabbit retina.

# Transport equation

## Assume:

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





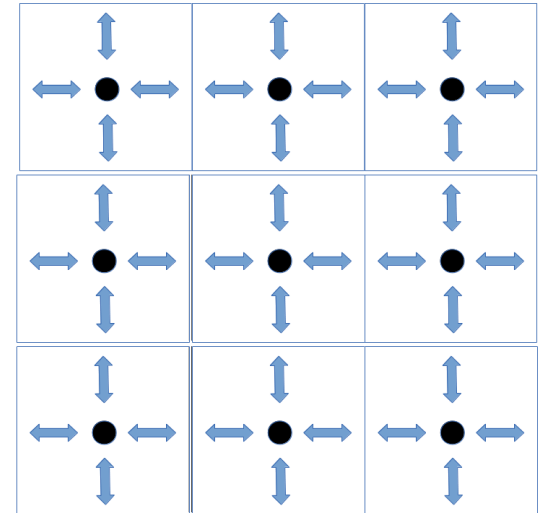
# Transport equation

## Assume:

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

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

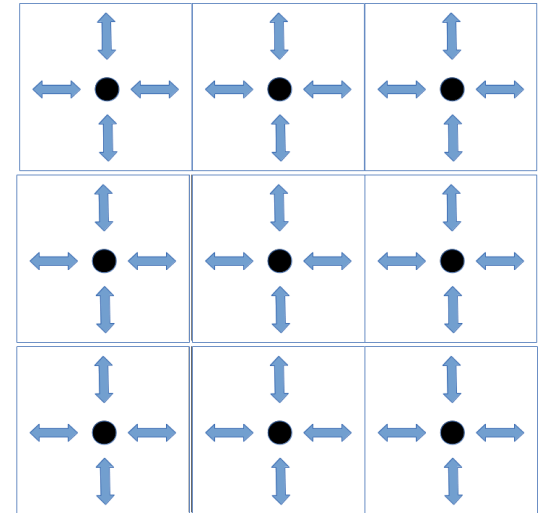
Lansdell et al, Plos Com Bio, 2014



# Transport equation

## Assume:

- Nearest neighbours interaction;
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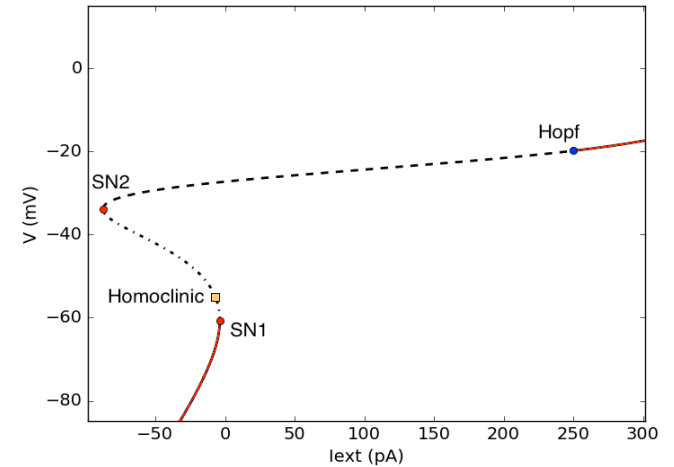


*No free diffusion  
of Ach*

# Transport equation

## Assume:

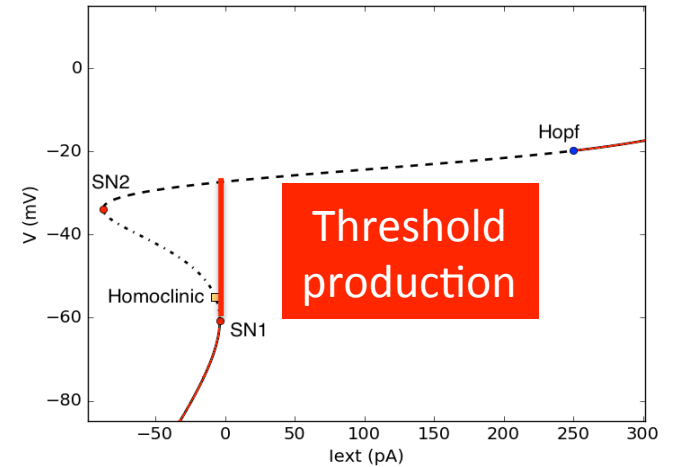
- Nearest neighbours interaction;
- State variables are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



# 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.



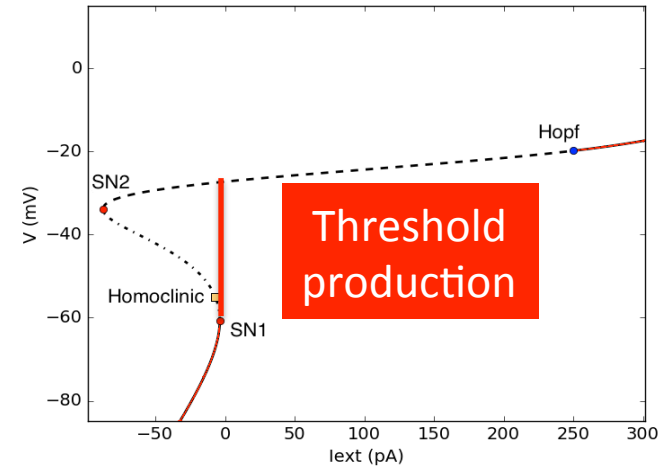
# Transport equation

## Assume:

- Nearest neighbours interaction;
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- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.

## Transport of Ach conductance.

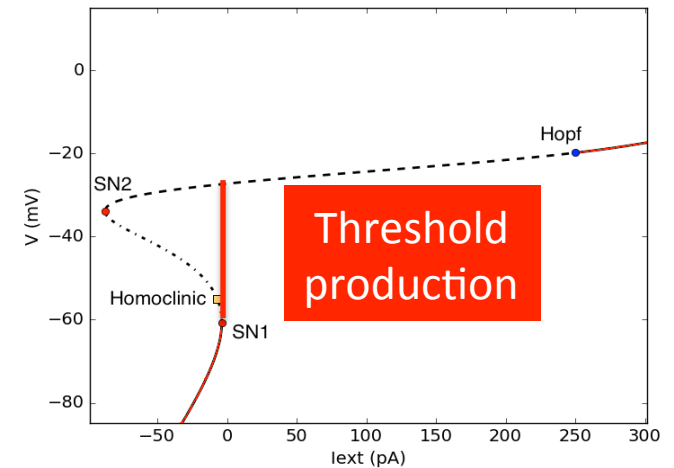
$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)] + a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]$$



# Transport equation

## Assume:

- Nearest neighbours interaction;
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## Transport of Ach conductance.

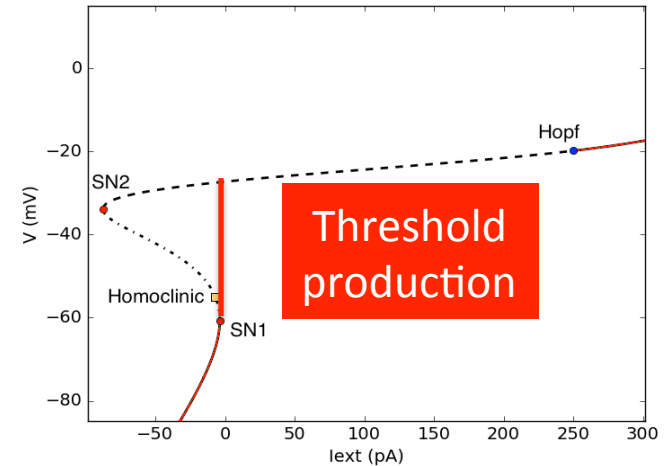
Local production

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

# Transport equation

## Assume:

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## Transport of Ach conductance.

Local production

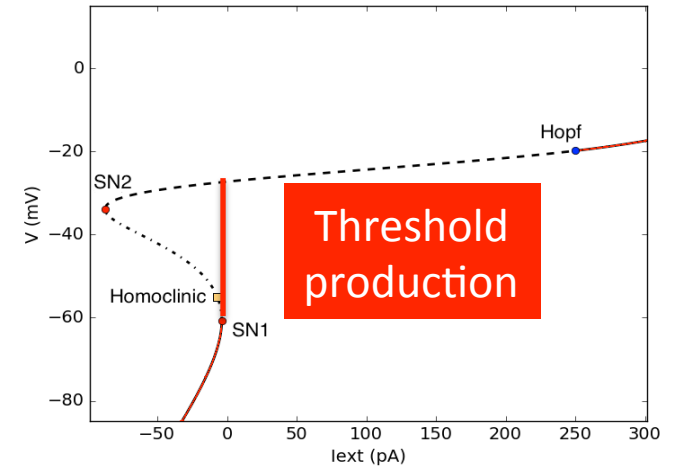
$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H[\Gamma - \Gamma_c(R)] - a^2\Omega\Delta H[\Gamma - \Gamma_c(R)]$$

Transport

# Transport equation

## Assume:

- Nearest neighbours interaction;
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- 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

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 ?

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

# 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 😊