

# Retinal waves: experiments and theory

**D. Karvouniari, Biovision team, INRIA, Sophia Antipolis**

L. Gil, INLN, Sophia Antipolis

O. Marre, Institut de la Vision, Paris


S. Picaud, Institut de la Vision, Paris

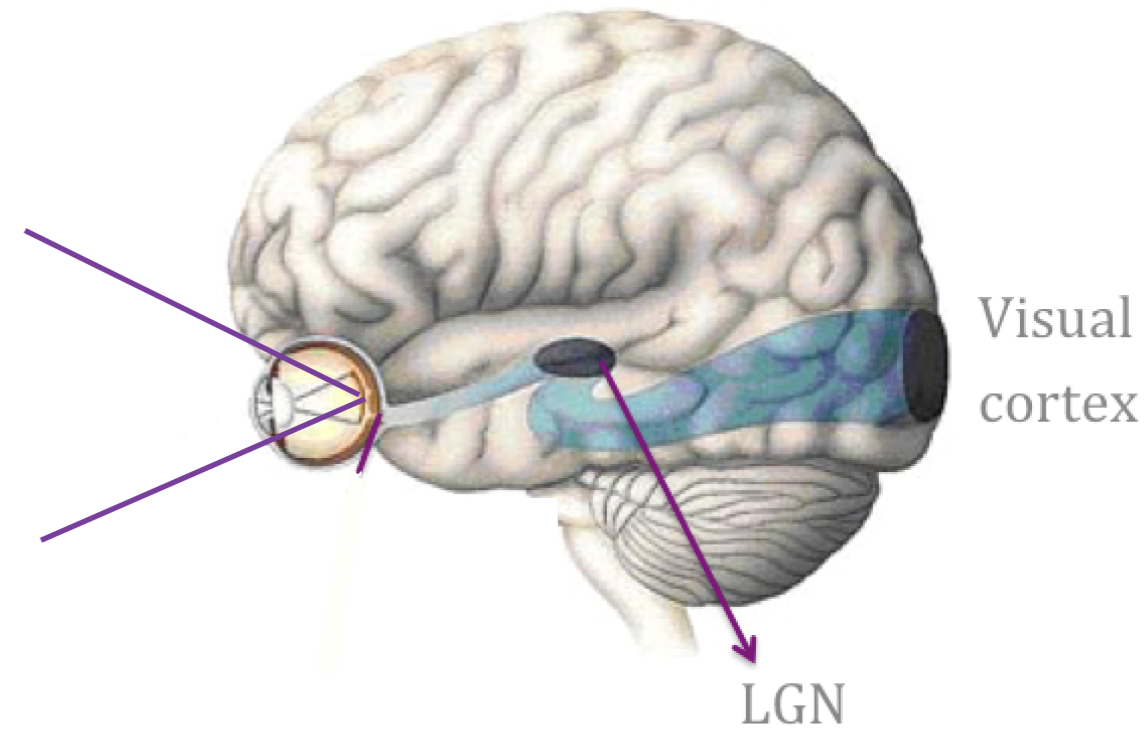
B. Cessac, Biovision team, INRIA, Sophia Antipolis

Acknowledgement: M. Hennig, E. Sernagor.



# The structure of the adult retina

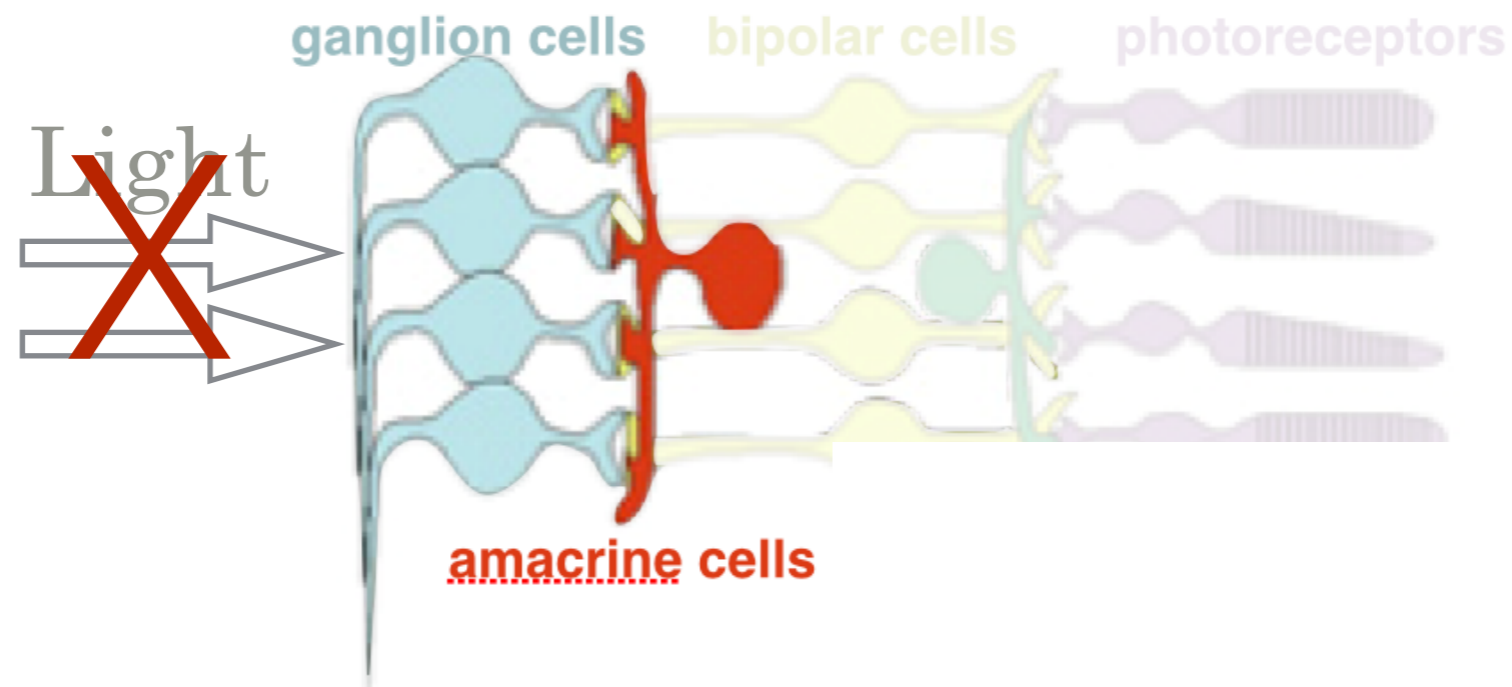
Light  






# The structure of the retina during development

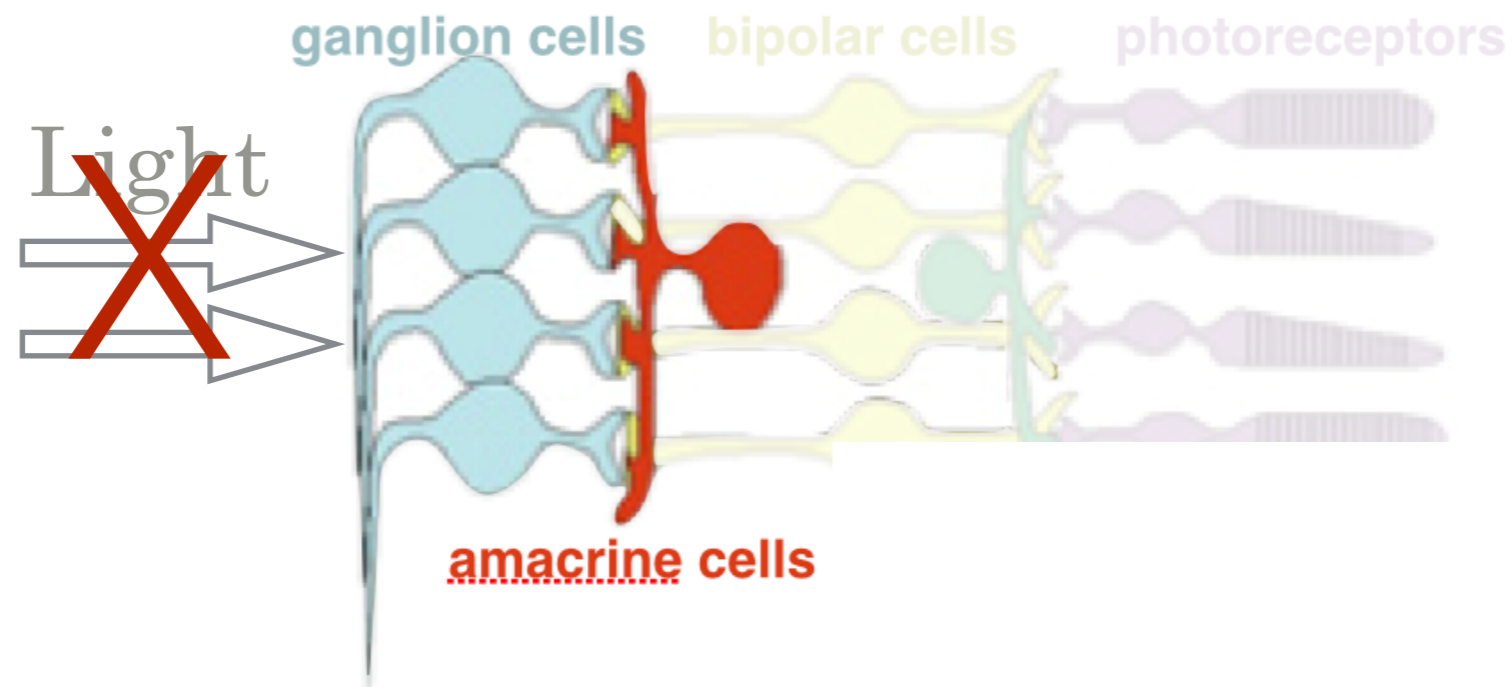
Retina's layered structure is shaped during development





# The structure of the retina during development

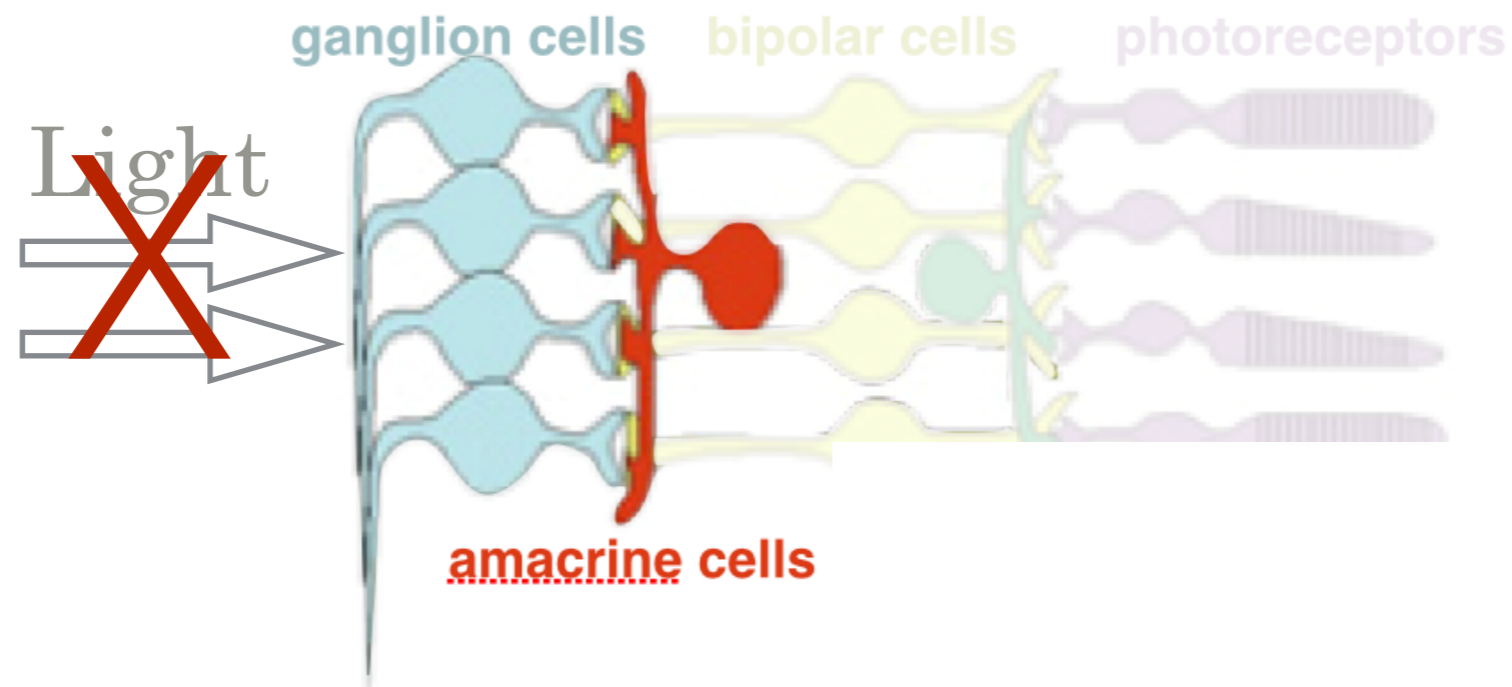
Retina's layered structure is shaped during development



But How?

# The structure of the retina during development

Retina's layered structure is shaped during development

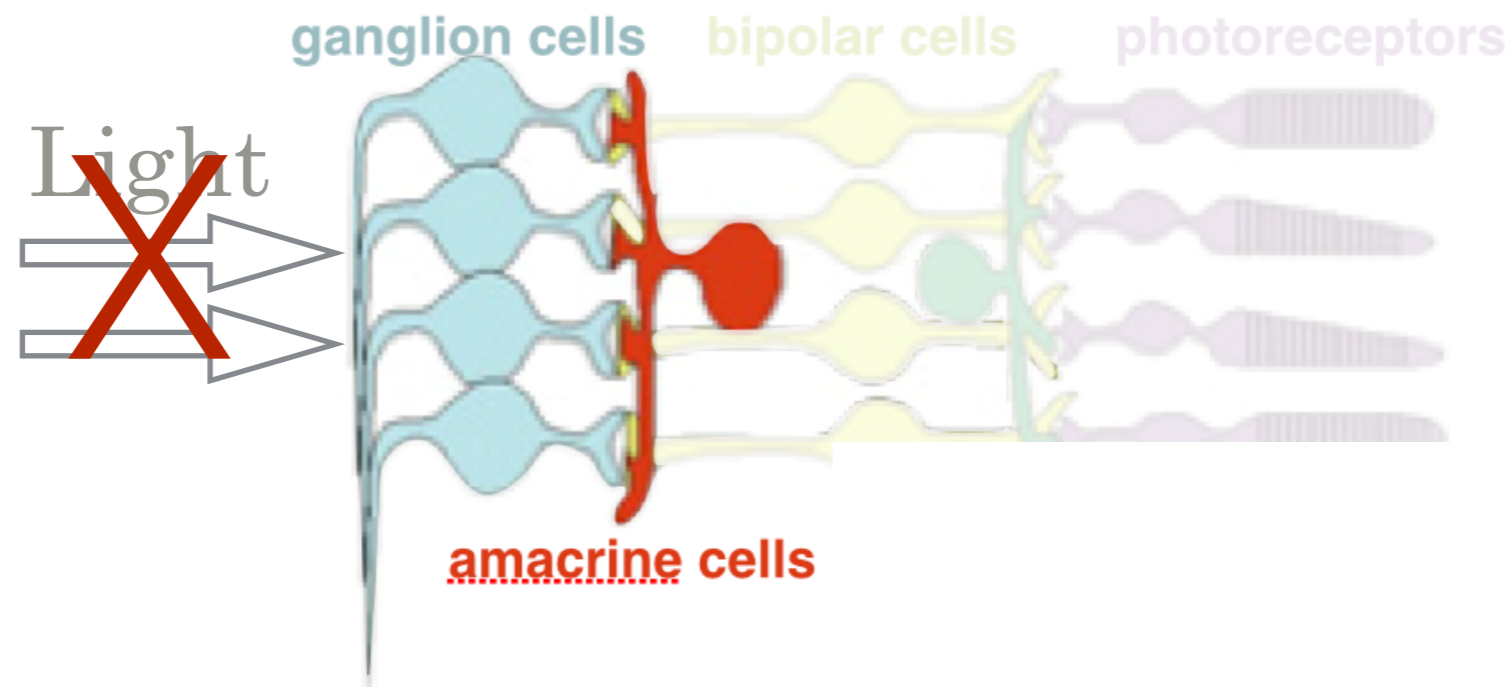


But How?



# The structure of the retina during development

Retina's layered structure is shaped during development



But How?



**Retinal waves!**

# What are Retinal waves?

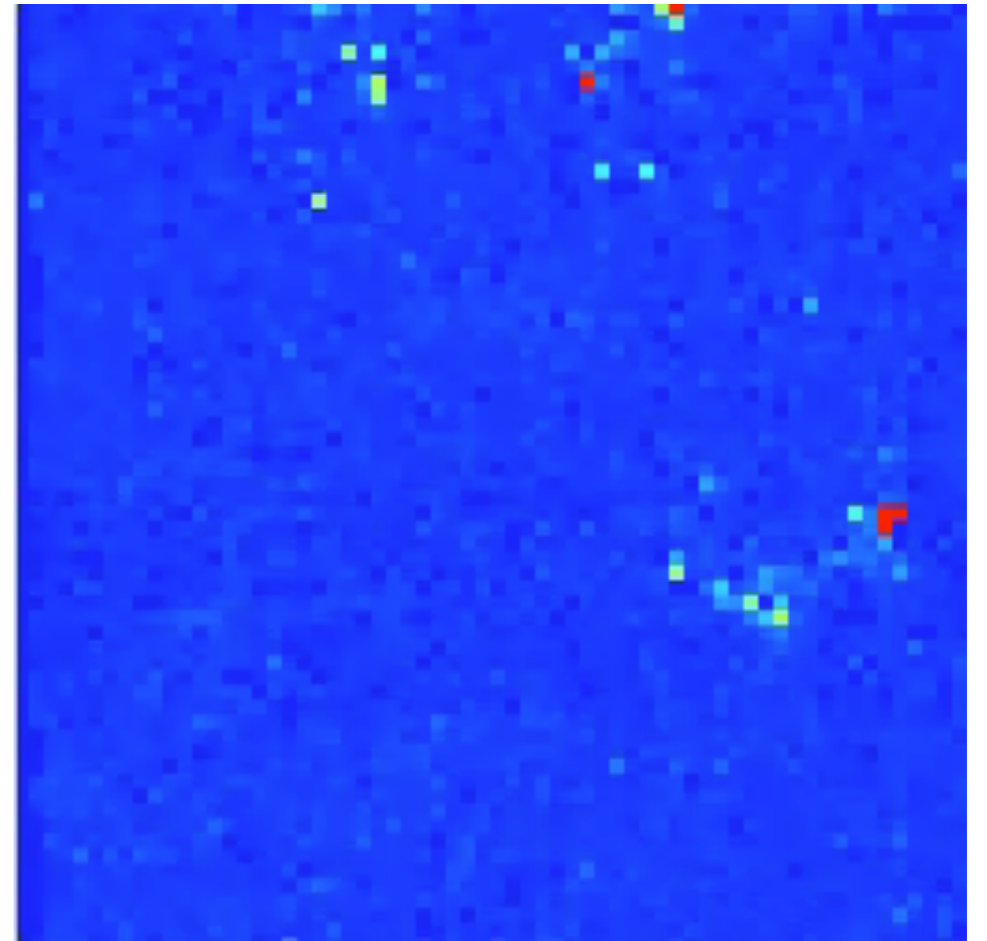
# What are Retinal waves?

Spontaneous spatio-temporal waves during development

Disappear short after birth when vision is functional

# What are Retinal waves?

Spontaneous spatio-temporal waves during development  
Disappear short after birth when vision is functional



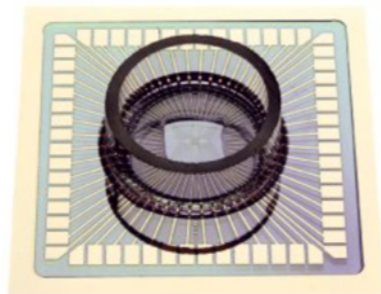
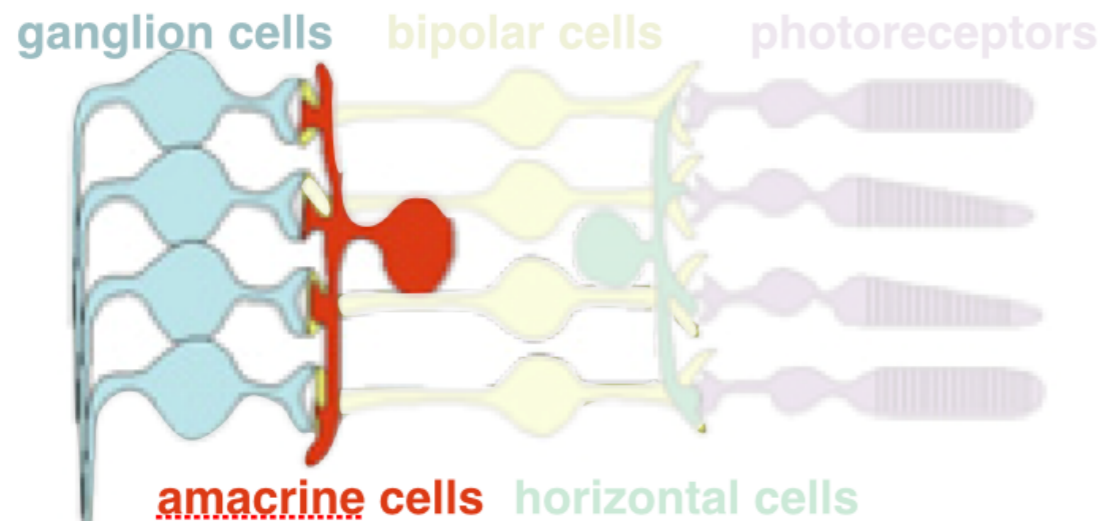
*(Maccione et al. 2014)*

*MEA recording of the voltage from a P11 mouse retina in the presence of 10  $\mu$ M bicuculline.*

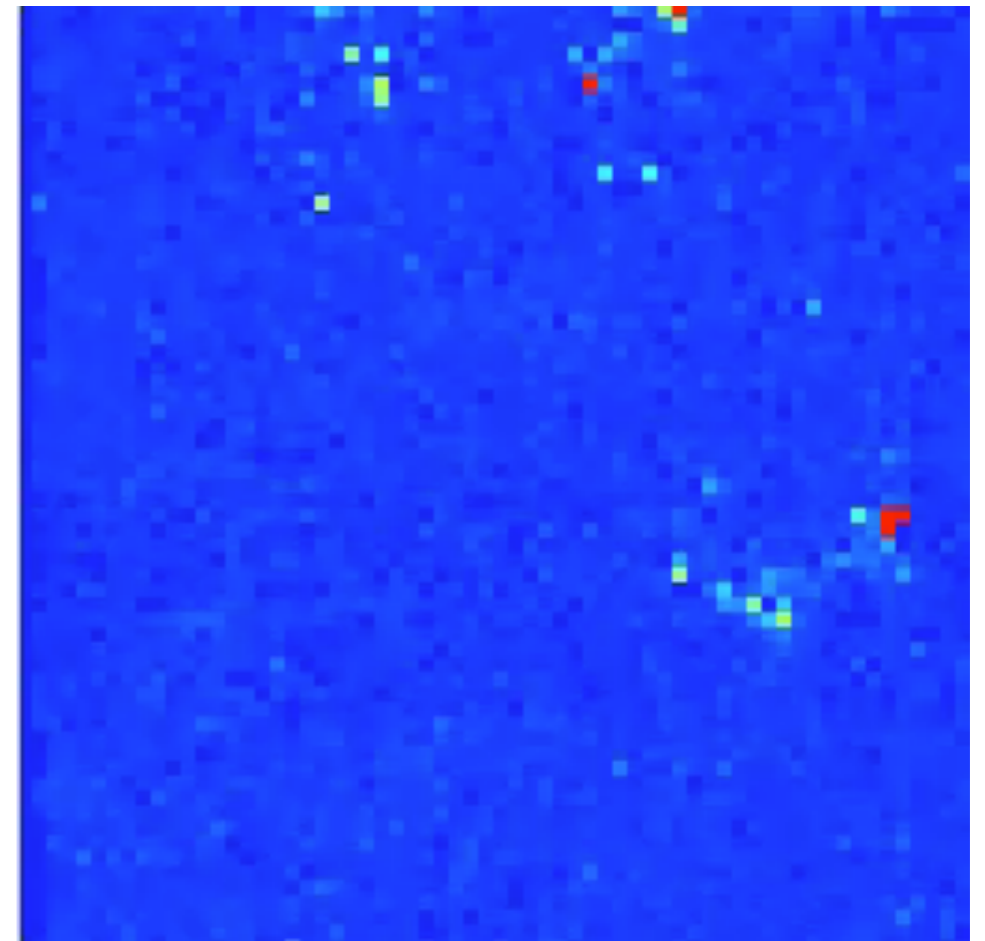
# What are Retinal waves?

Spontaneous spatio-temporal waves during development  
Disappear short after birth when vision is functional

## Recordings from the retina



Multi-electrode array (MEA)



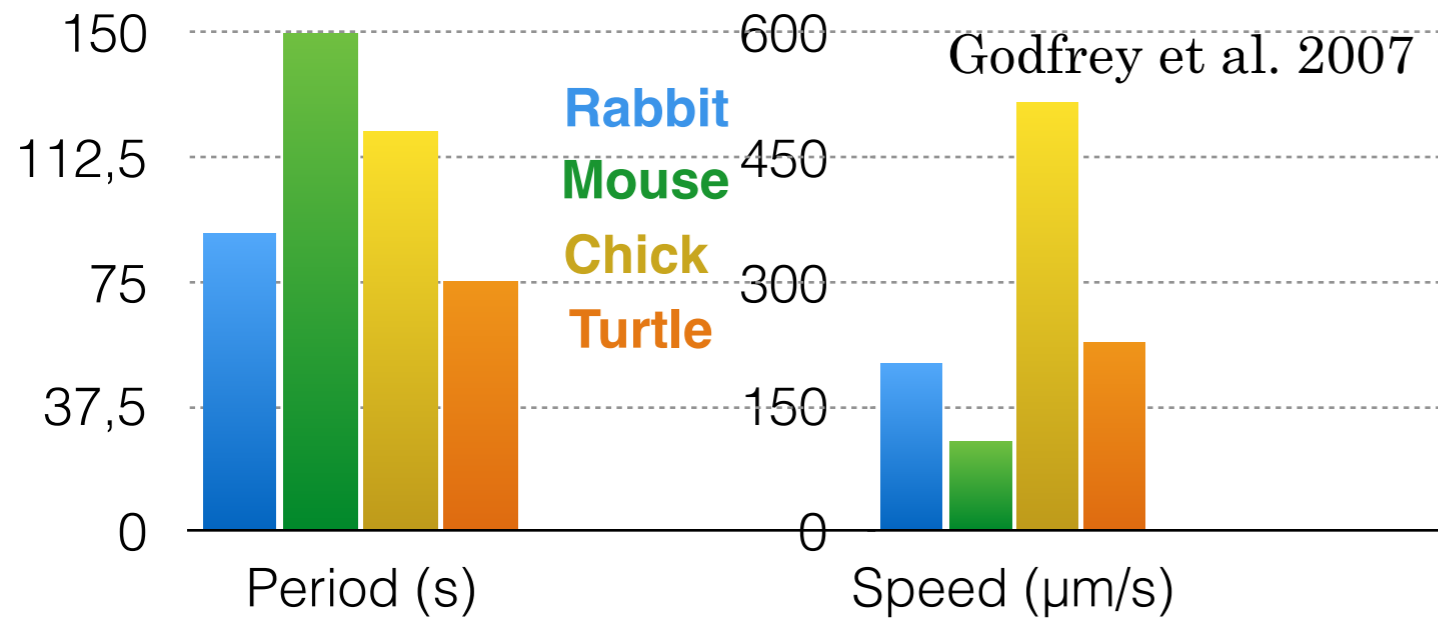
MEA recording of the voltage from a P11 mouse retina in the presence of 10  $\mu$ M bicuculline.



# Variability within retinal waves

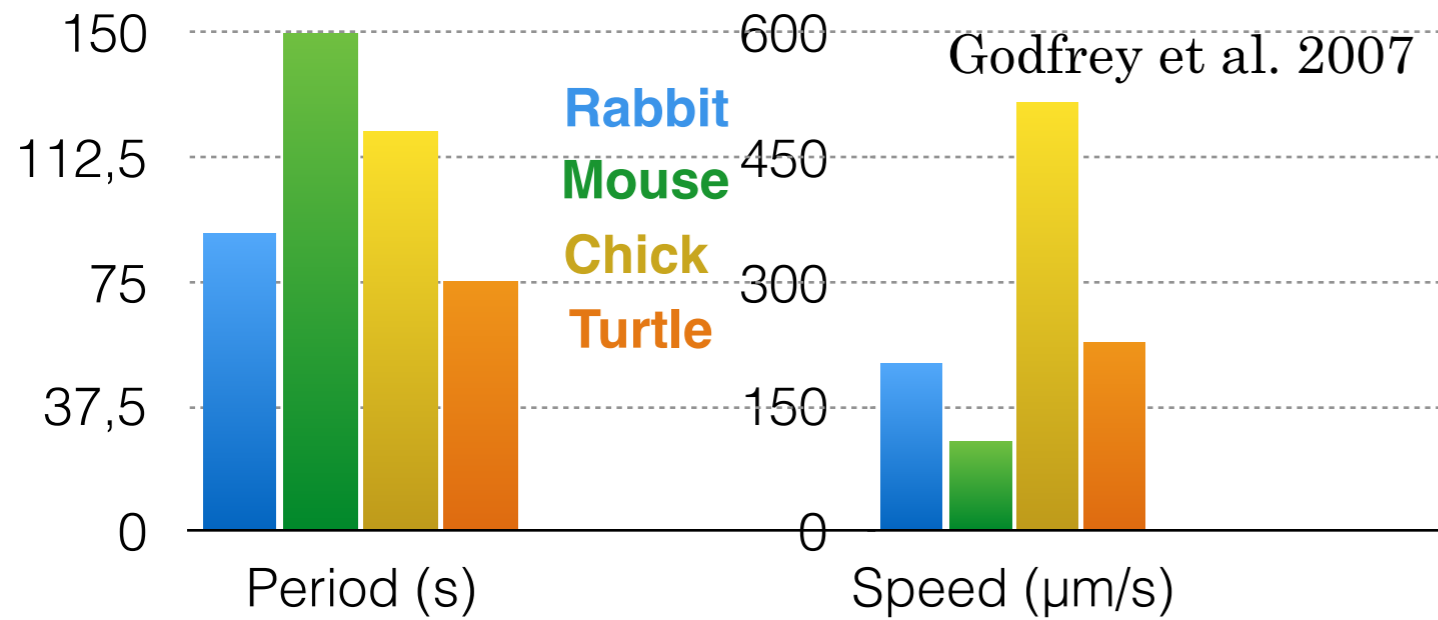
# Variability within retinal waves

## i) Across species

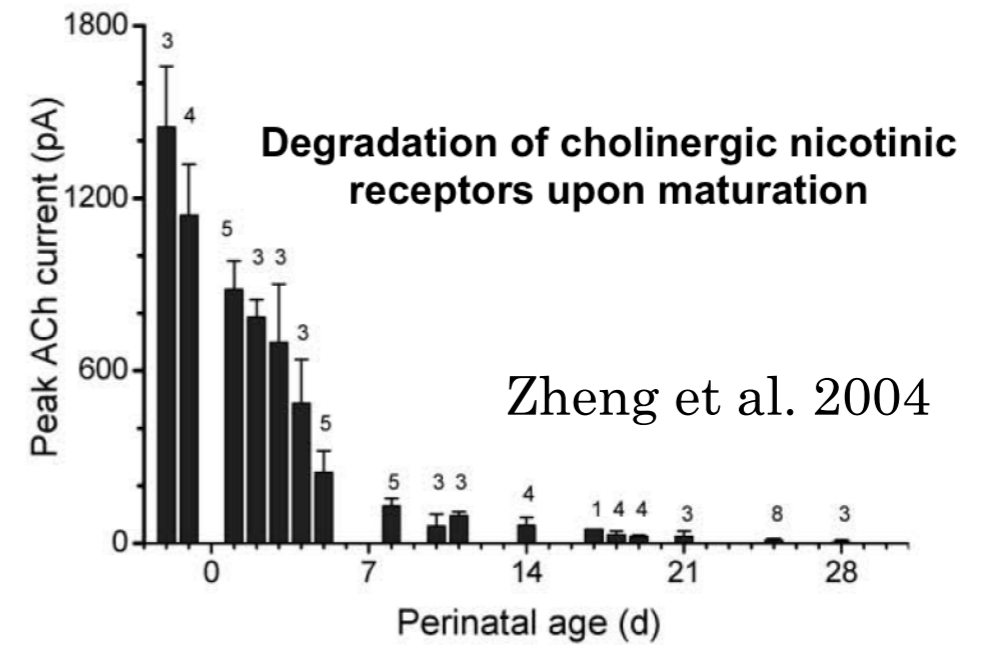


# Variability within retinal waves

## i) Across species

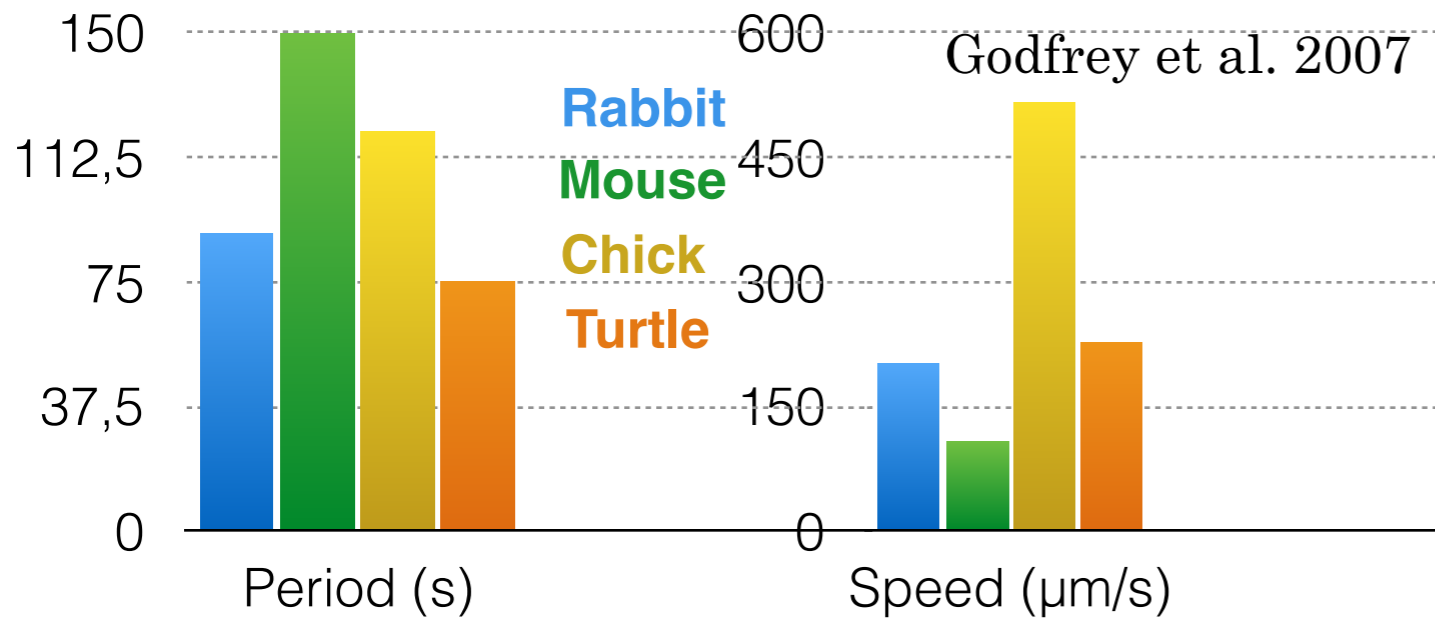


## ii) Development

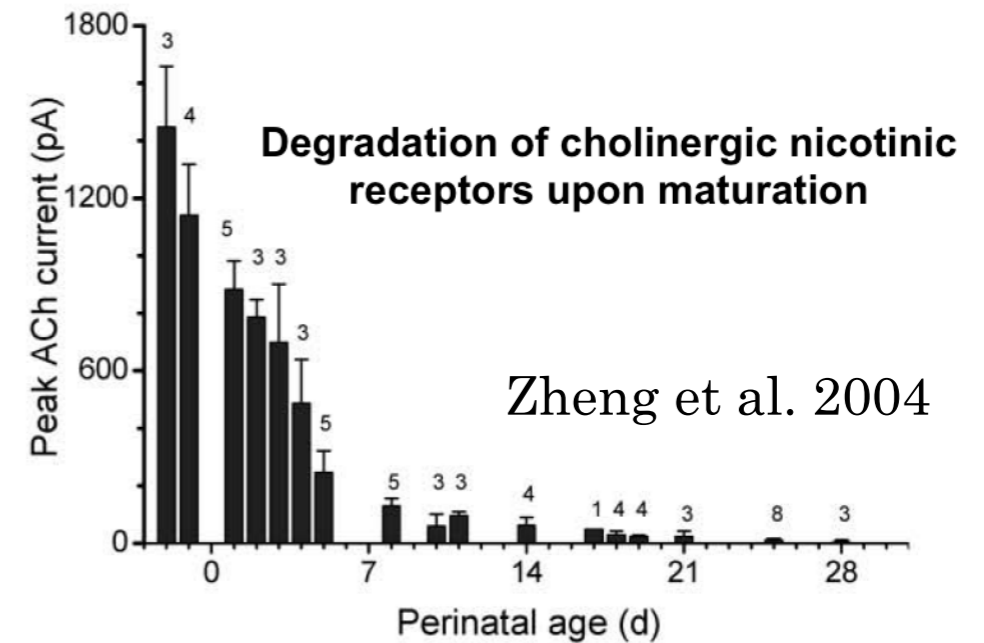


# Variability within retinal waves

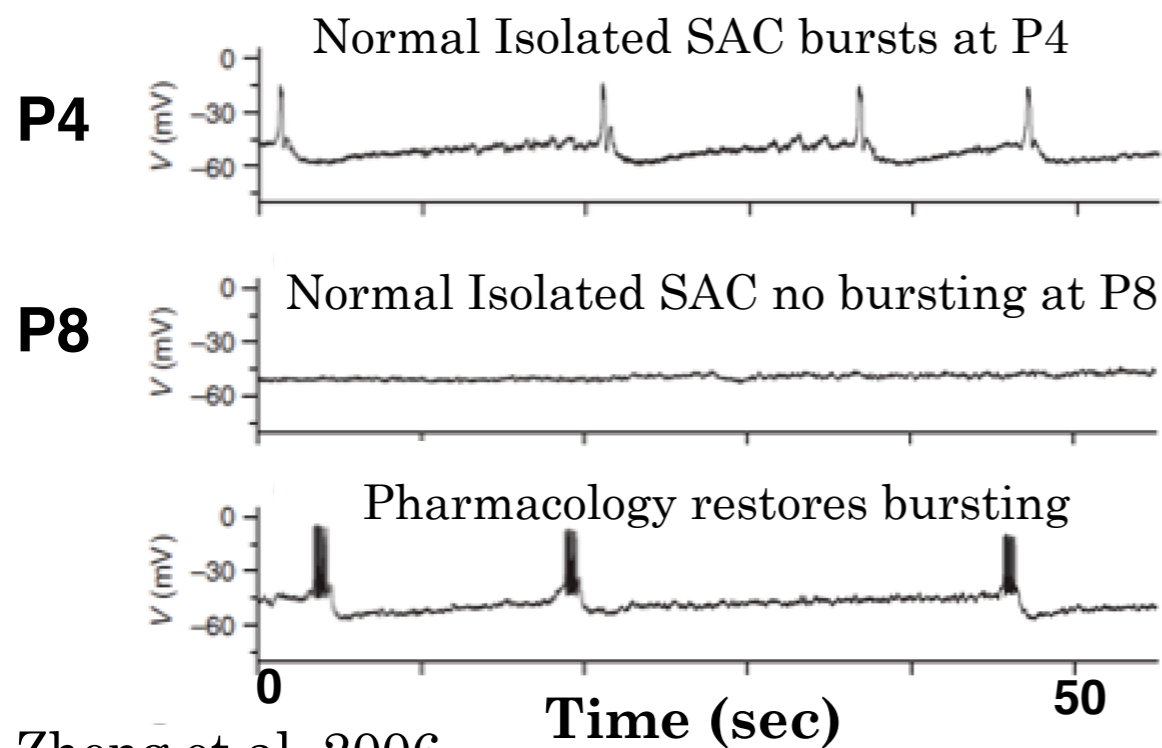
## i) Across species



## ii) Development

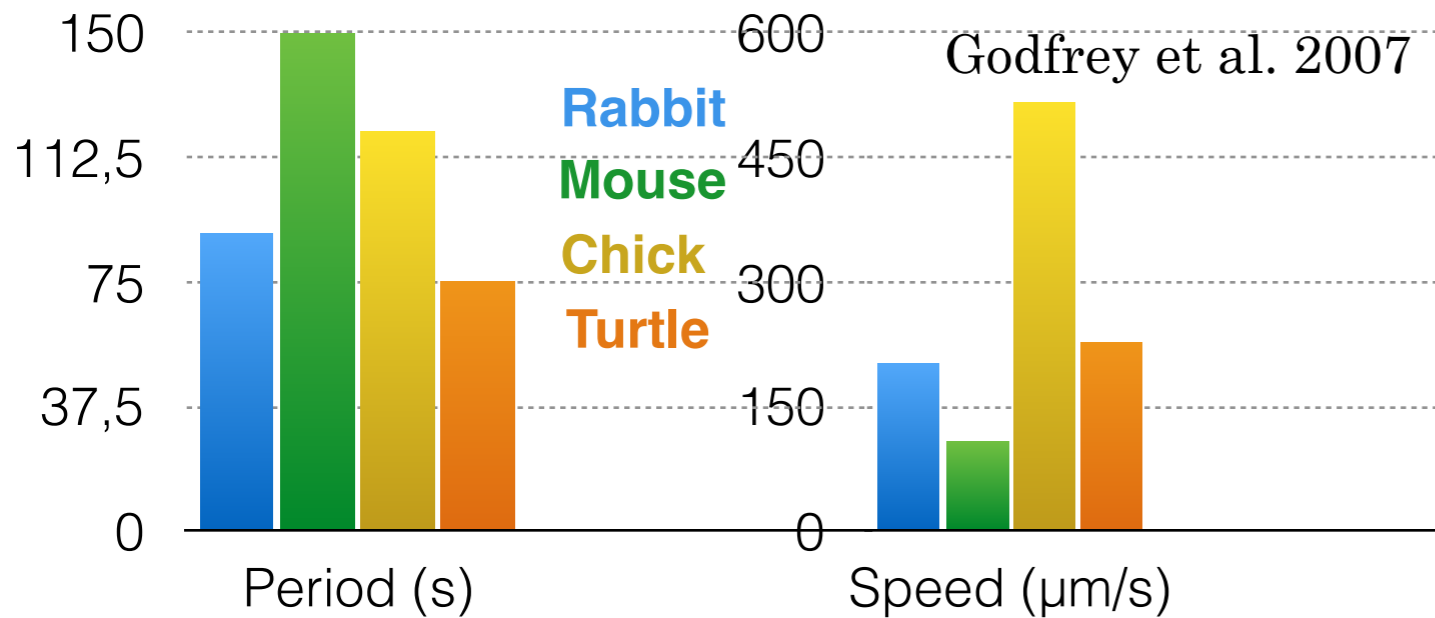


## iii) Pharmacology

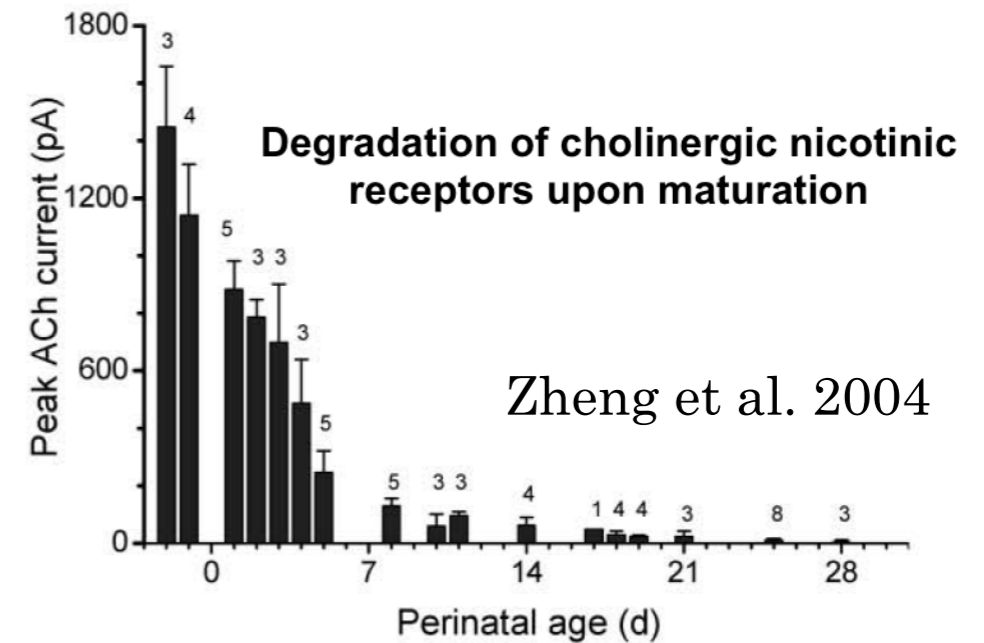


# Variability within retinal waves

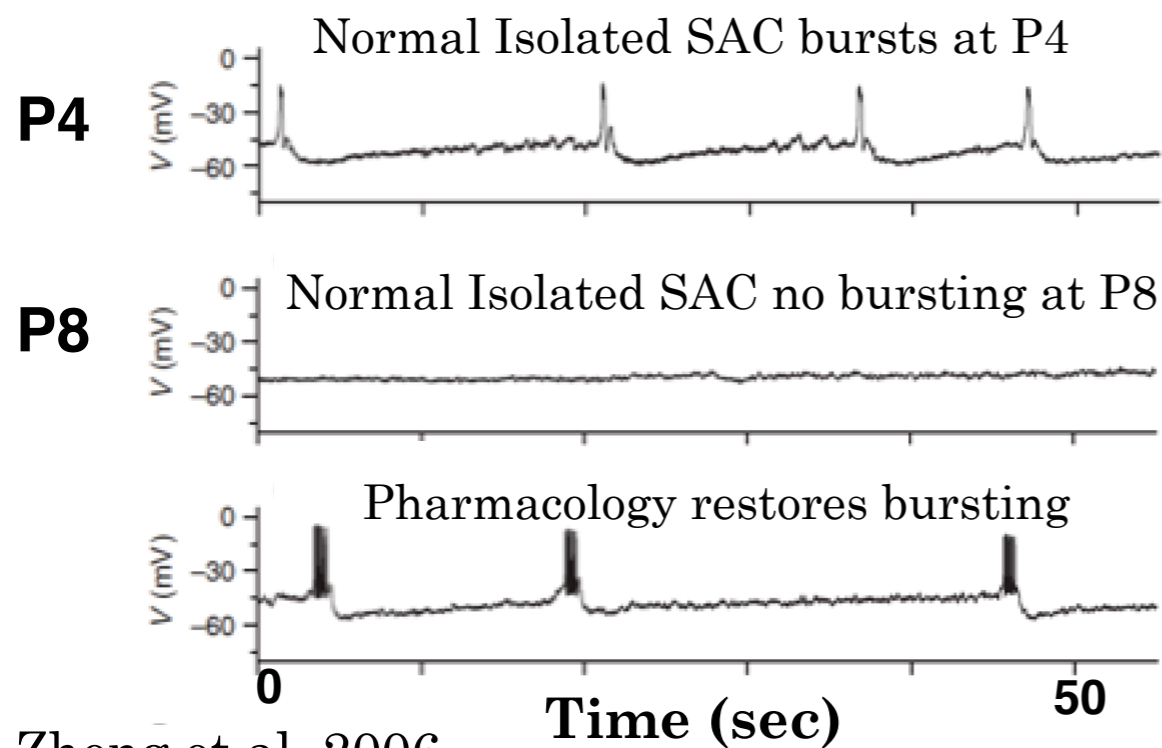
## i) Across species



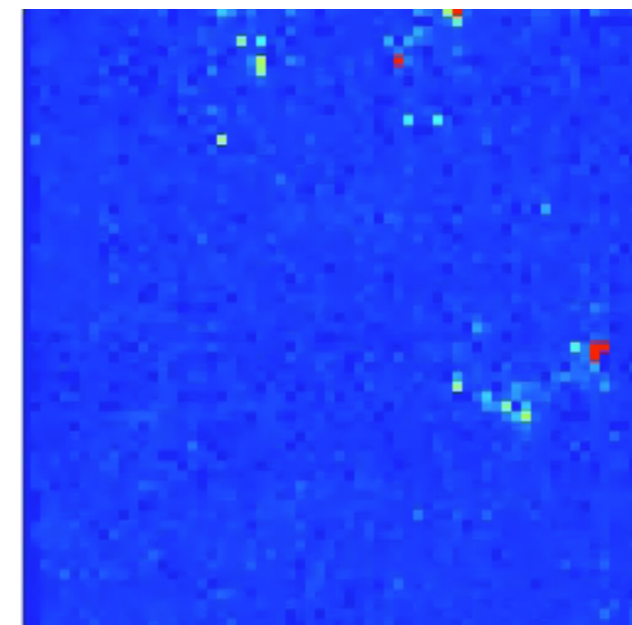
## ii) Development



## iii) Pharmacology



## iv) Spatial Variability



Waves have variable shapes due to a refractory mechanism which controls their borders.

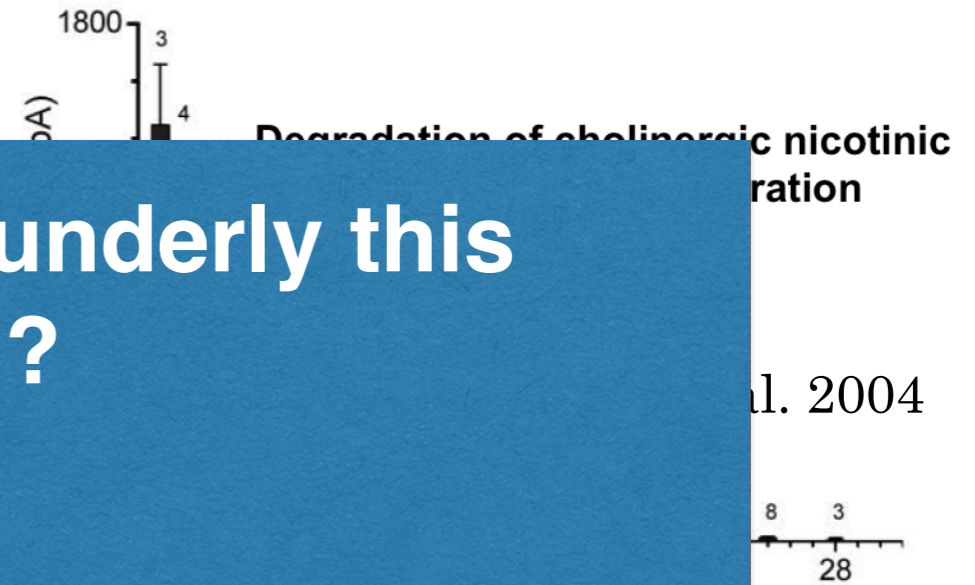
Maccione et al. 2014

# Variability within retinal waves

## i) Across species



## ii) Development



Which mechanisms underly this variability ?

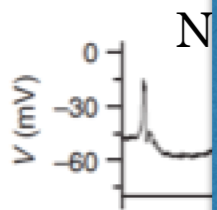
Randomness ?

Genetics ?

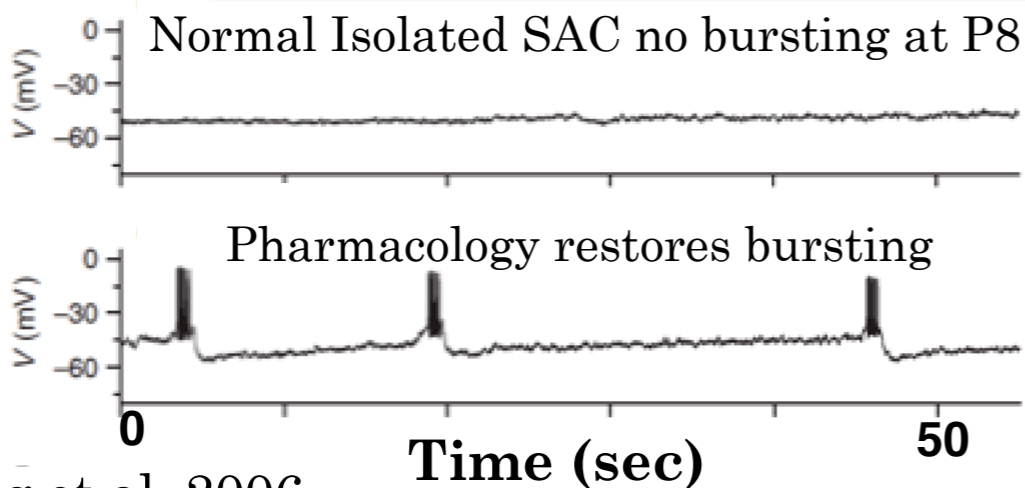
Non linear dynamics ?

## iii)

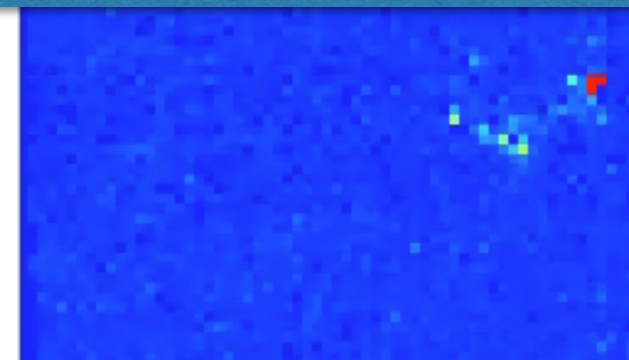
P4



P8



Zheng et al. 2006



Maccione et al. 2014

ability

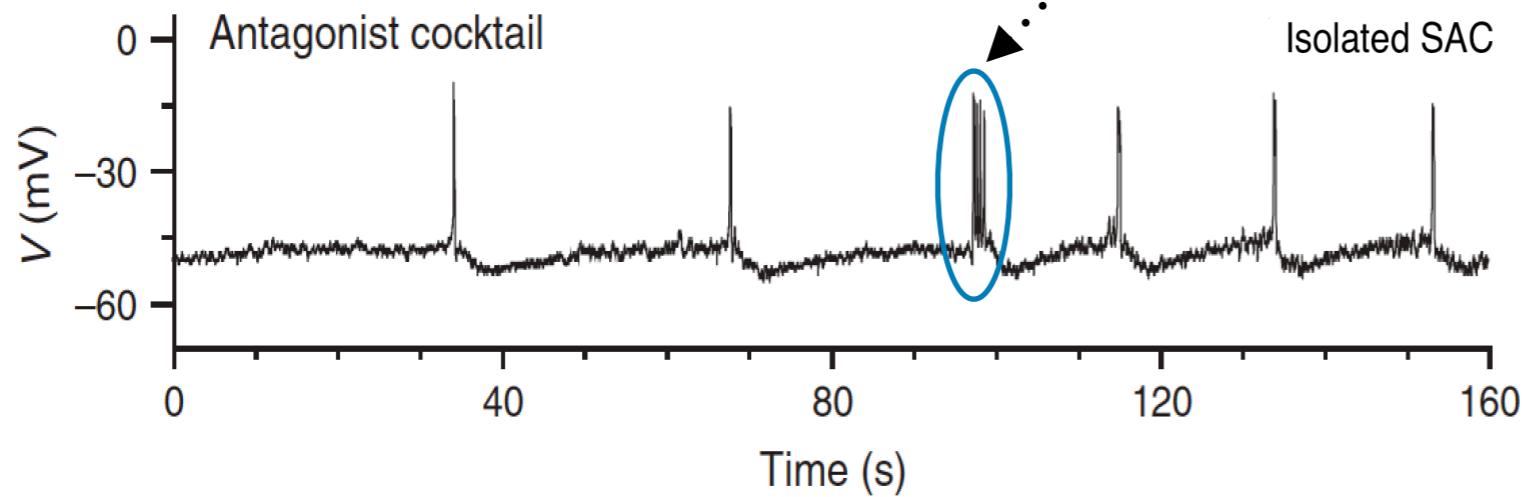
have variable shapes due to a refractory mechanism which controls their borders.

# Cellular mechanisms of SACs bursting



# Cellular mechanisms of SACs bursting

## A. Spontaneous Fast oscillations

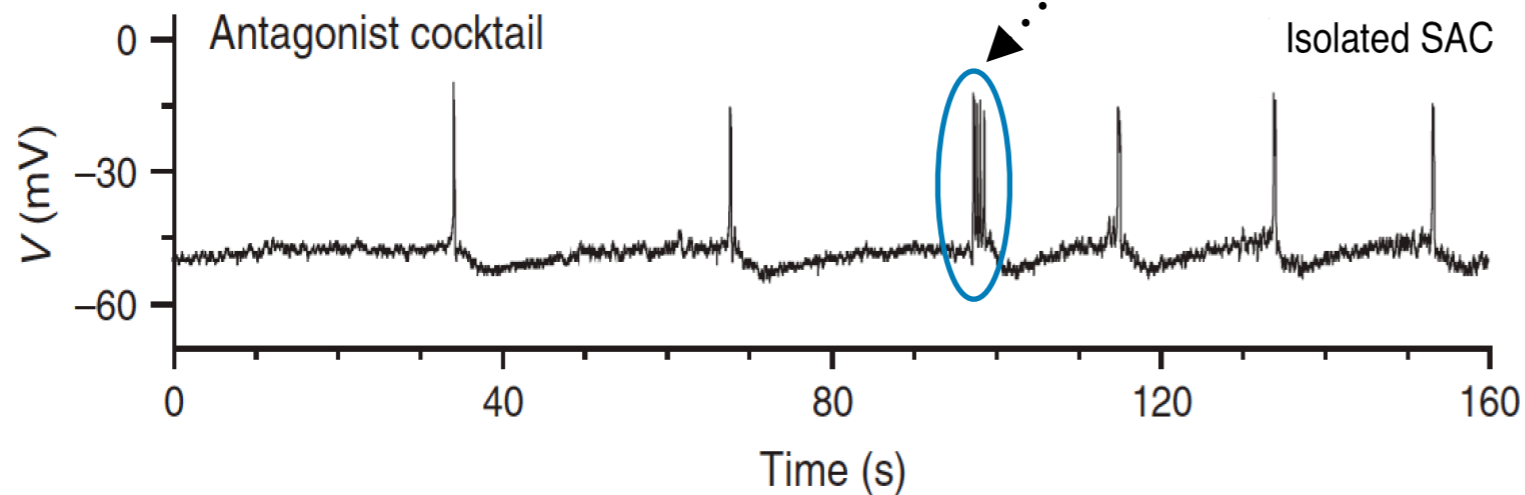


Generated mainly by  
fast voltage-gated  
Ca<sup>2+</sup> channels

Zheng et al. 2006

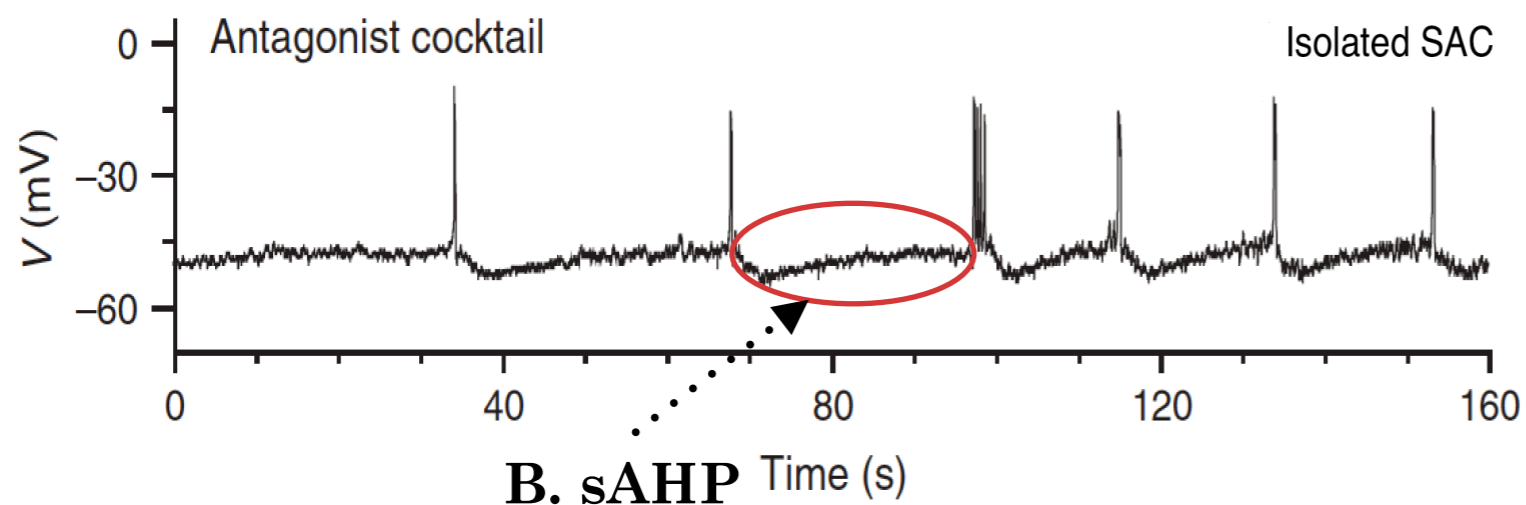
# Cellular mechanisms of SACs bursting

## A. Spontaneous Fast oscillations



Generated mainly by  
fast voltage-gated  
Ca<sup>2+</sup> channels

Zheng et al. 2006



Generated mainly by  
slow Ca<sup>2+</sup>-gated K<sup>+</sup>  
channels

Zheng et al. 2006

**B. sAHP**  
(slow AfterHyperpolarization)

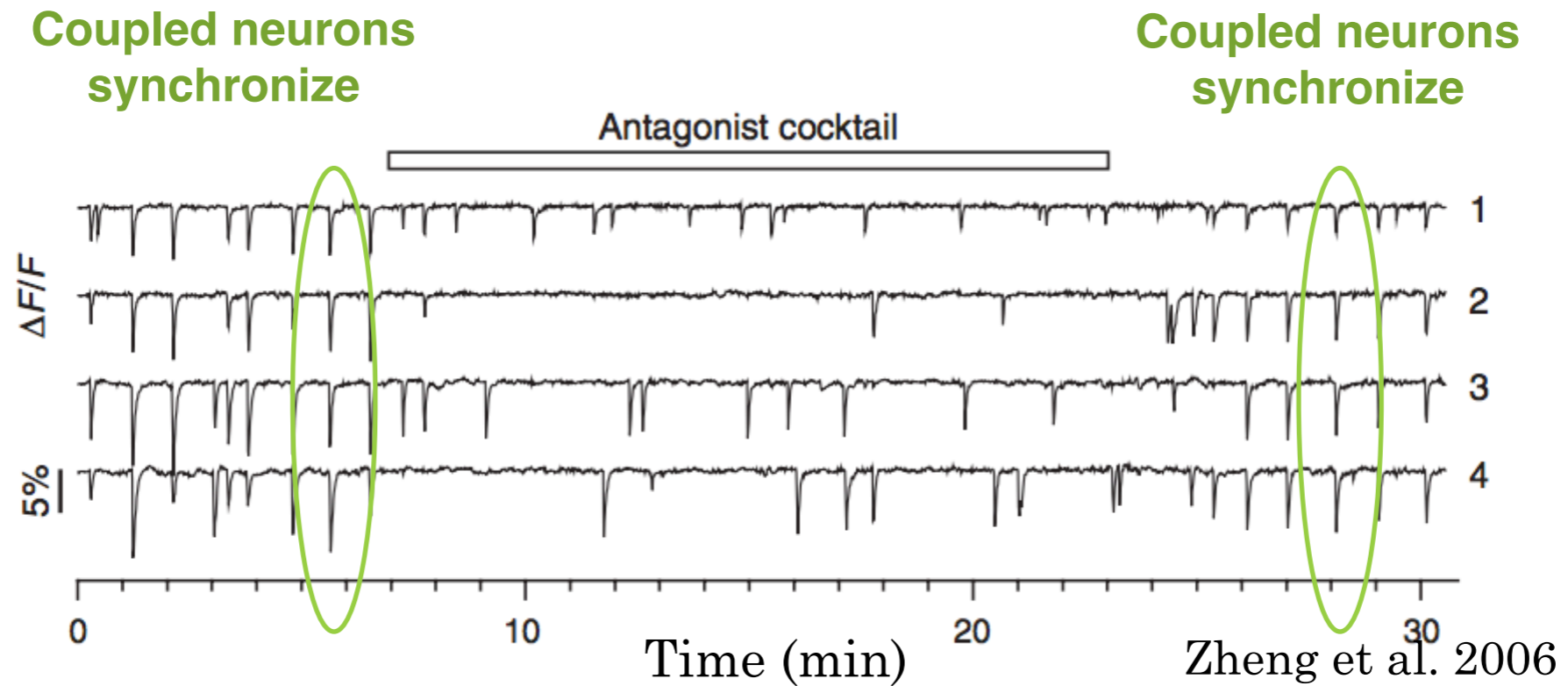
# Cellular mechanisms of stage II retinal waves

# Cellular mechanisms of stage II retinal waves

## C. Synchrony through Acetylcholine

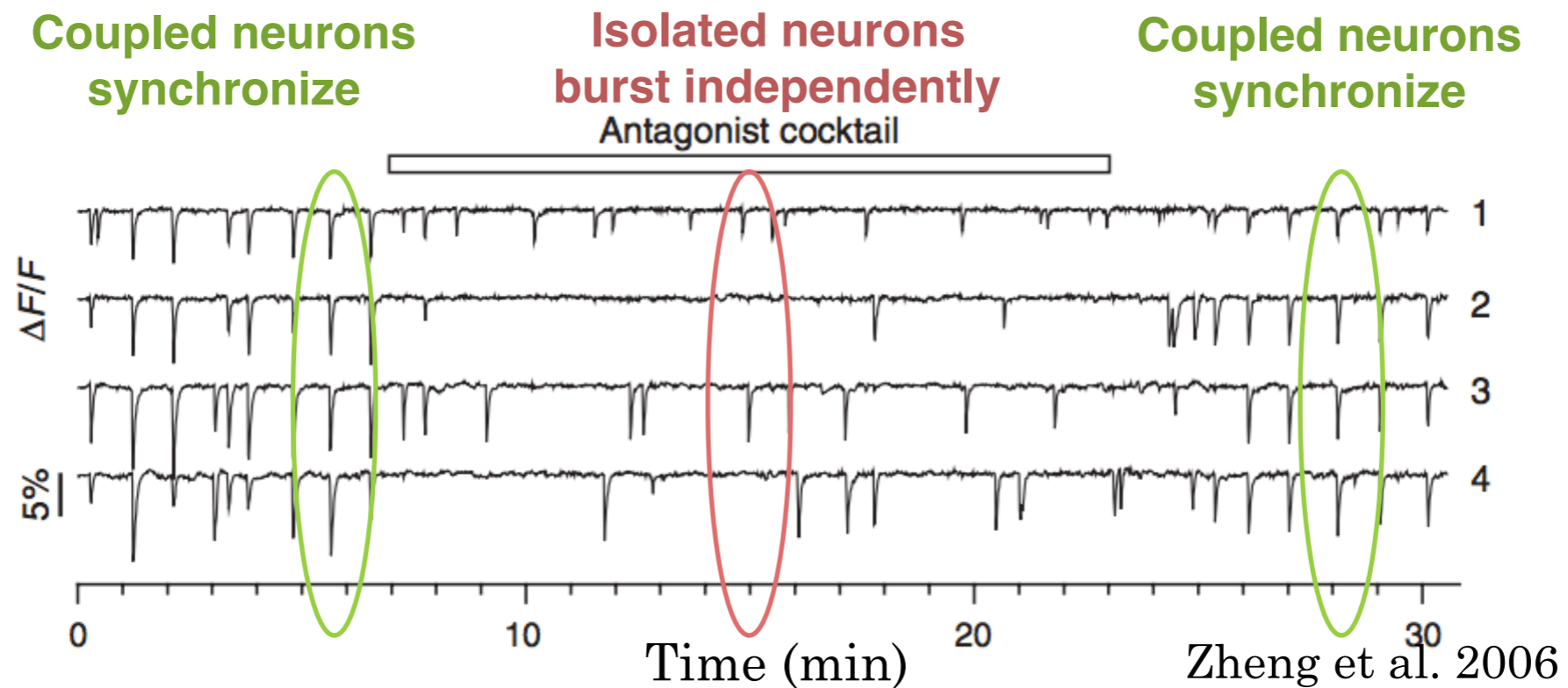
# Cellular mechanisms of stage II retinal waves

## C. Synchrony through Acetylcholine



# Cellular mechanisms of stage II retinal waves

## C. Synchrony through Acetylcholine



**Mutual excitatory connections between SACs through Acetylcholine**

# 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

$$C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) - G_{sAHP}(P_i)(V_i - V_K) - G_i(\{A_j\}_{j \in \mathcal{N}_i})(V_i - V_A)$$

~ 20 parameters per neuron

**Tuned to match experimental records.**

$$\tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i)$$

$$\tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C)$$

$$\tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i)C_i^4 - S_i$$

$$\tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i$$

$$\frac{dA_i}{dt} = -\mu A_i + \beta_A T_A(V_i),$$

# A network model for stage II retinal waves

N neurons, 6 N equations

$$C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) - G_{sAHP}(P_i)(V_i - V_K) - G_i(\{A_j\}_{j \neq i})(V_i - V_A)$$

~ 20 parameters per neuron

Tuned to match experimental records.

$$\tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i)$$

$$\tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C)$$

Time scale separation

$$\tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i)C_i^4 - S_i$$

$$\tau_R \frac{dR_i}{dt} = \dots$$

$$\frac{dA_i}{dt} = \dots$$

**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.

# 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

$$C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\ - G_{\text{AHP}}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k \in \mathcal{B}_i})(V_i - V_A) \\ + I(R_i, A_j)$$

$$\tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i)$$

$$\tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C)$$

$$\tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i) C_i^4 - S_i \\ I(R_i, A_j)$$

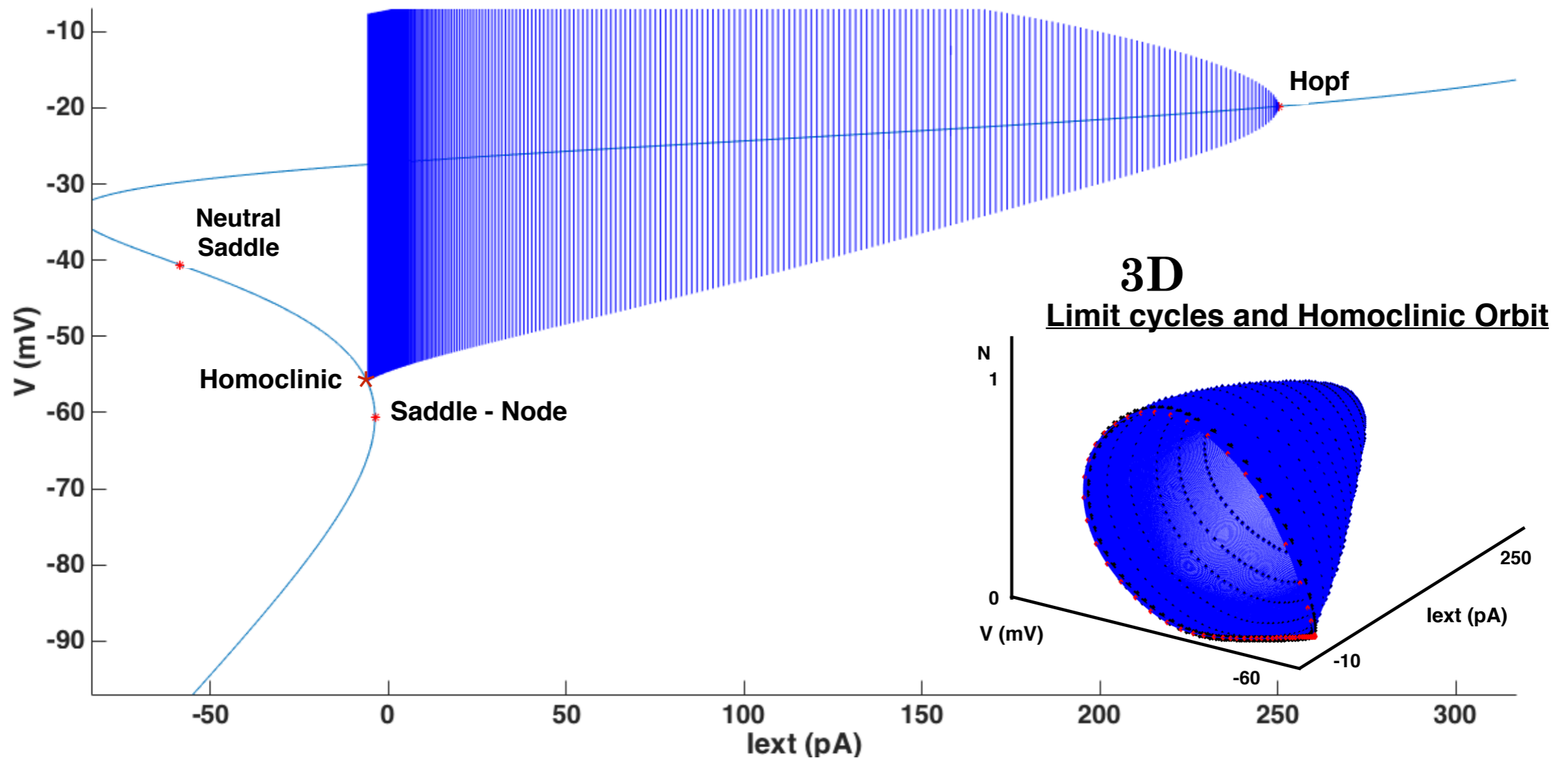
$$\tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i$$

$$\frac{dA_j}{dt} = -\mu A_j + \beta_A T_A(V_i),$$

# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

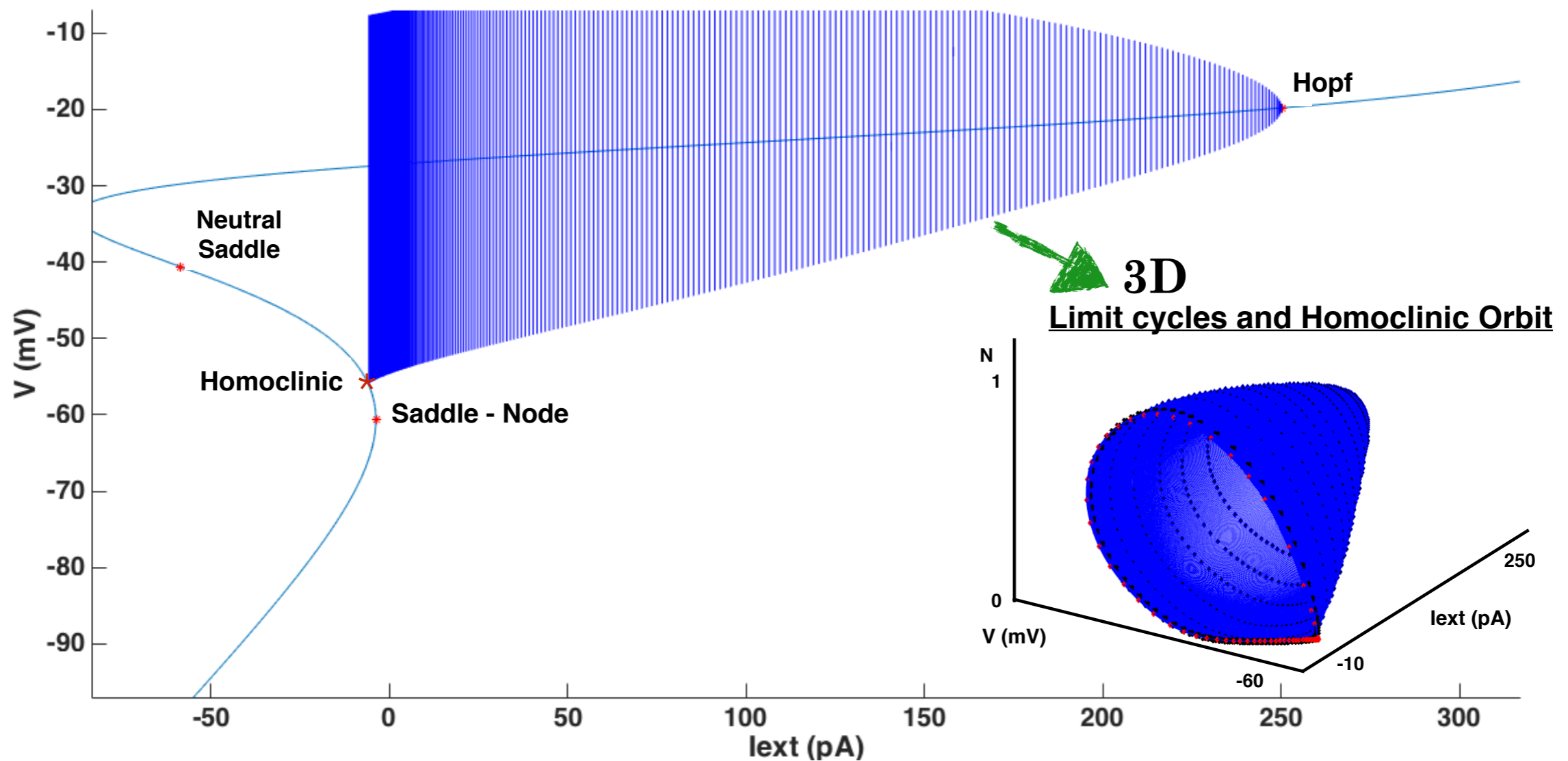
I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

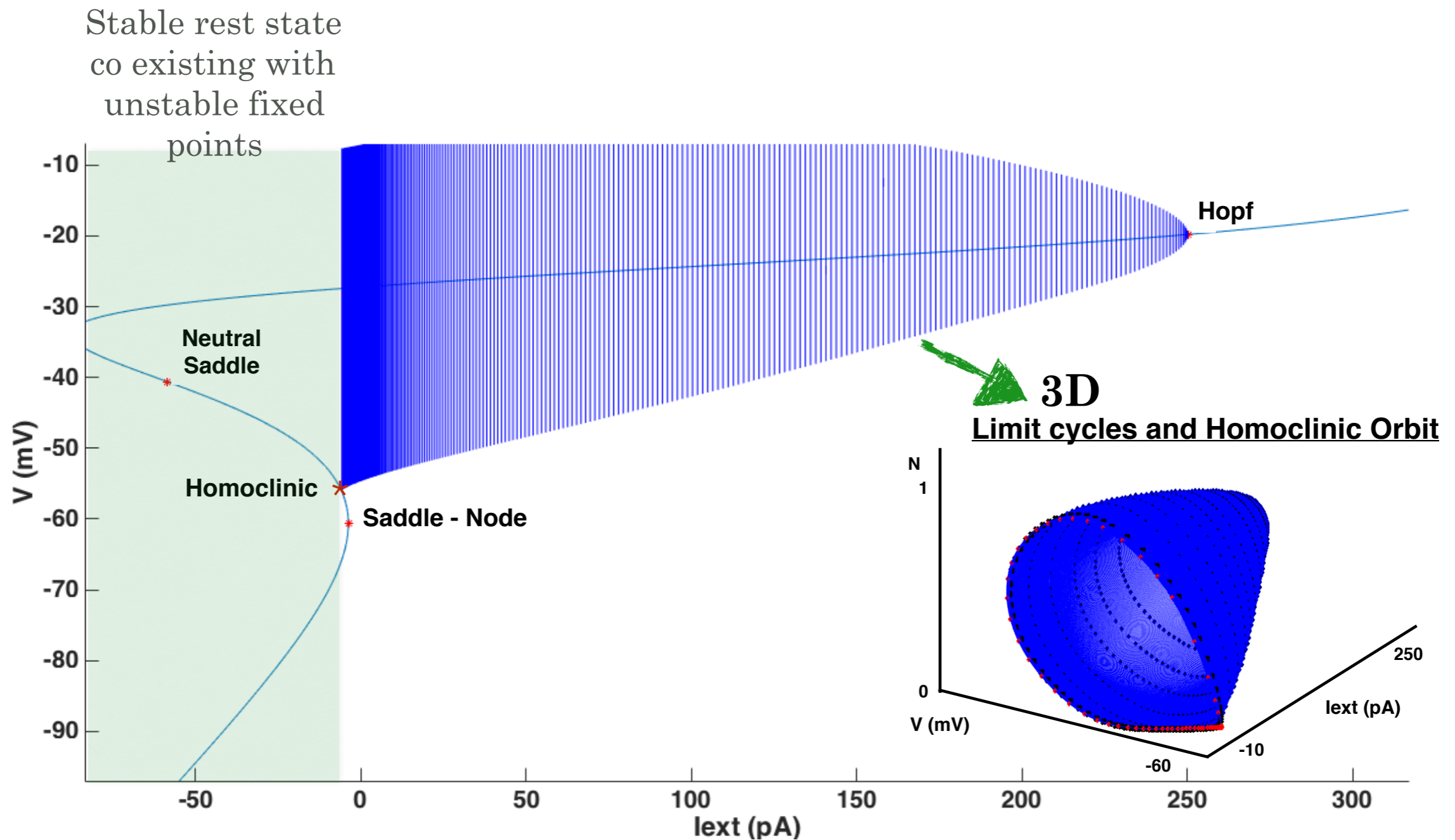
I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

## I. The SACs repertoire of dynamics upon a varying current

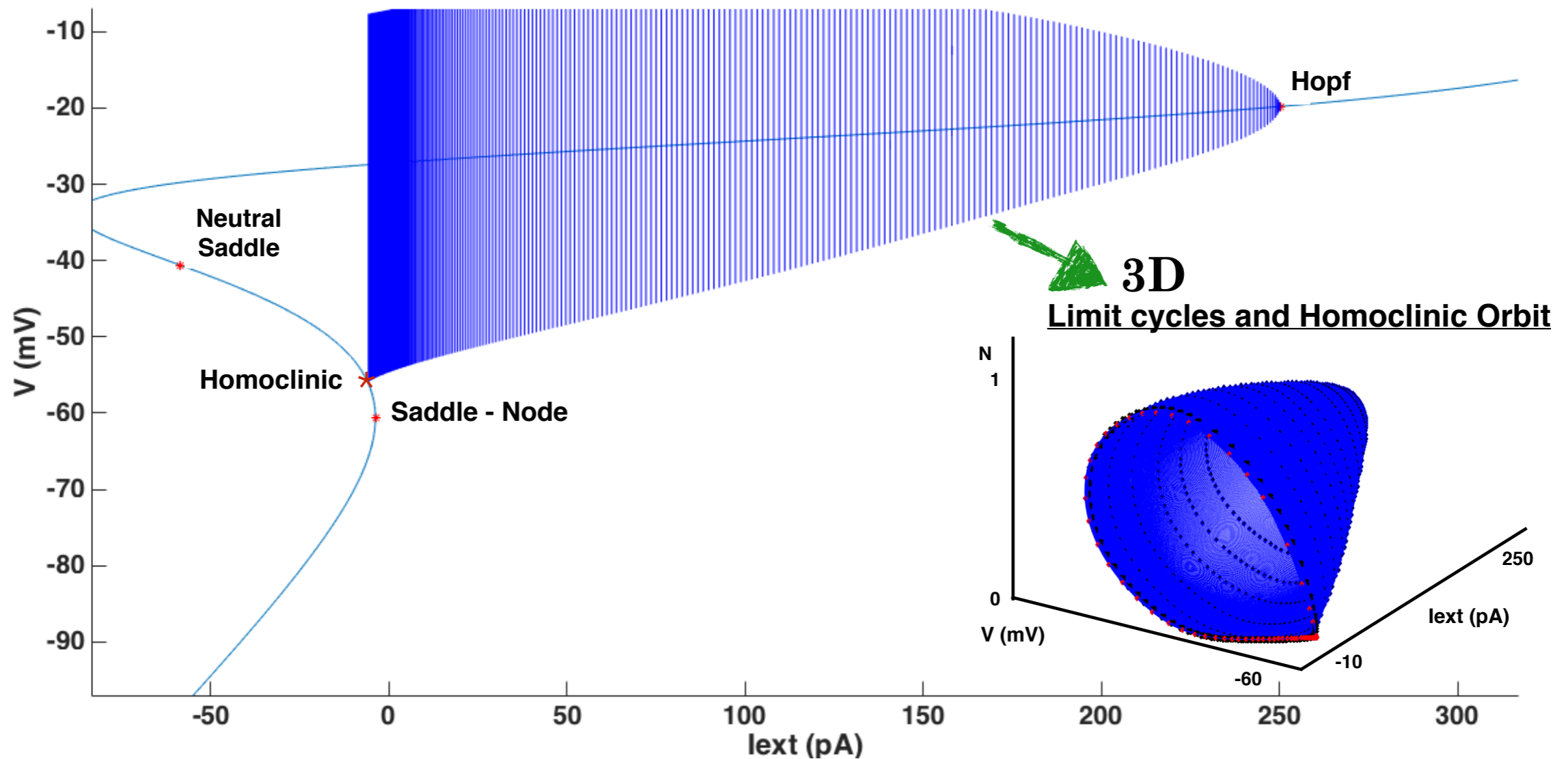




# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

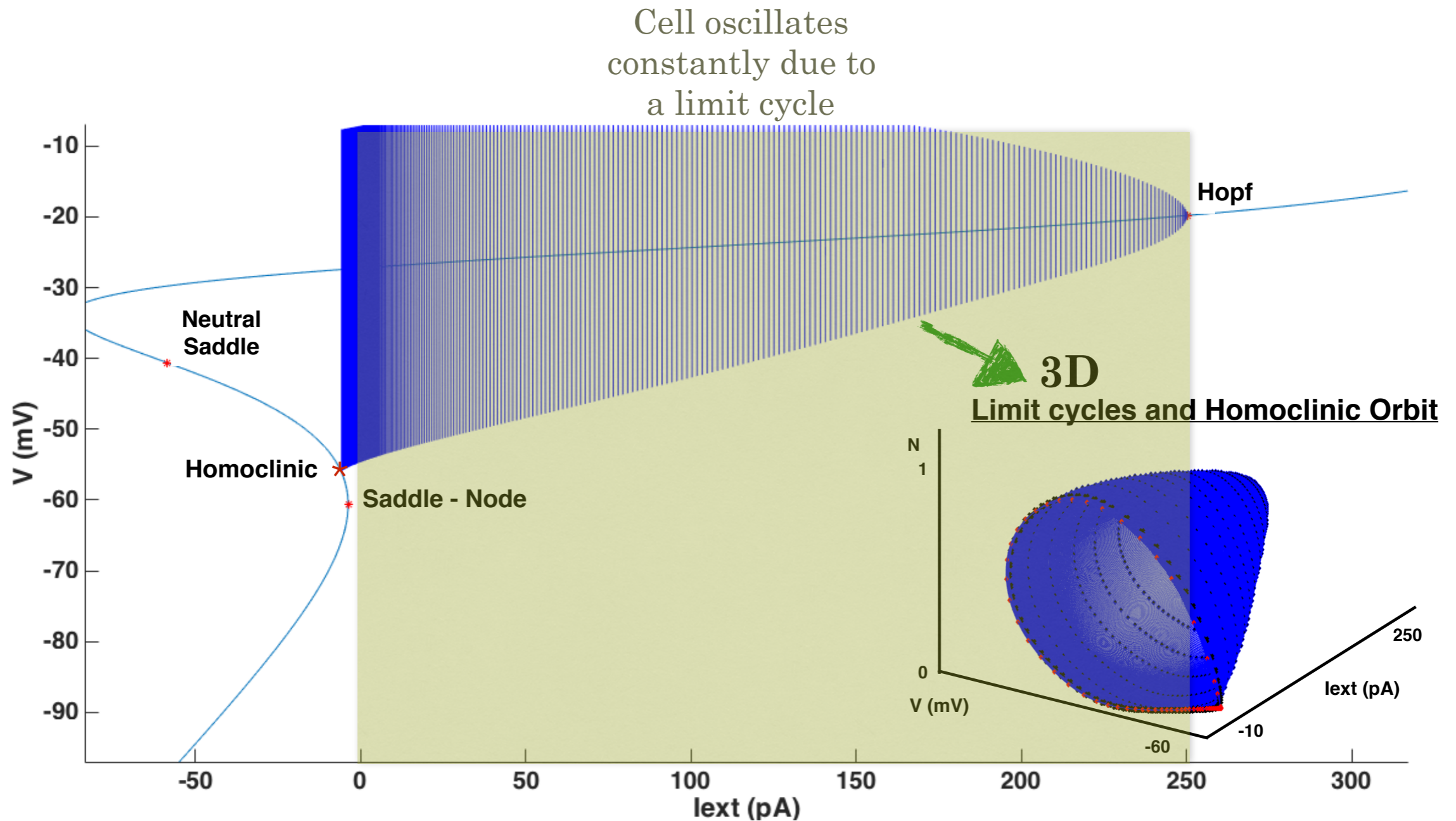
I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

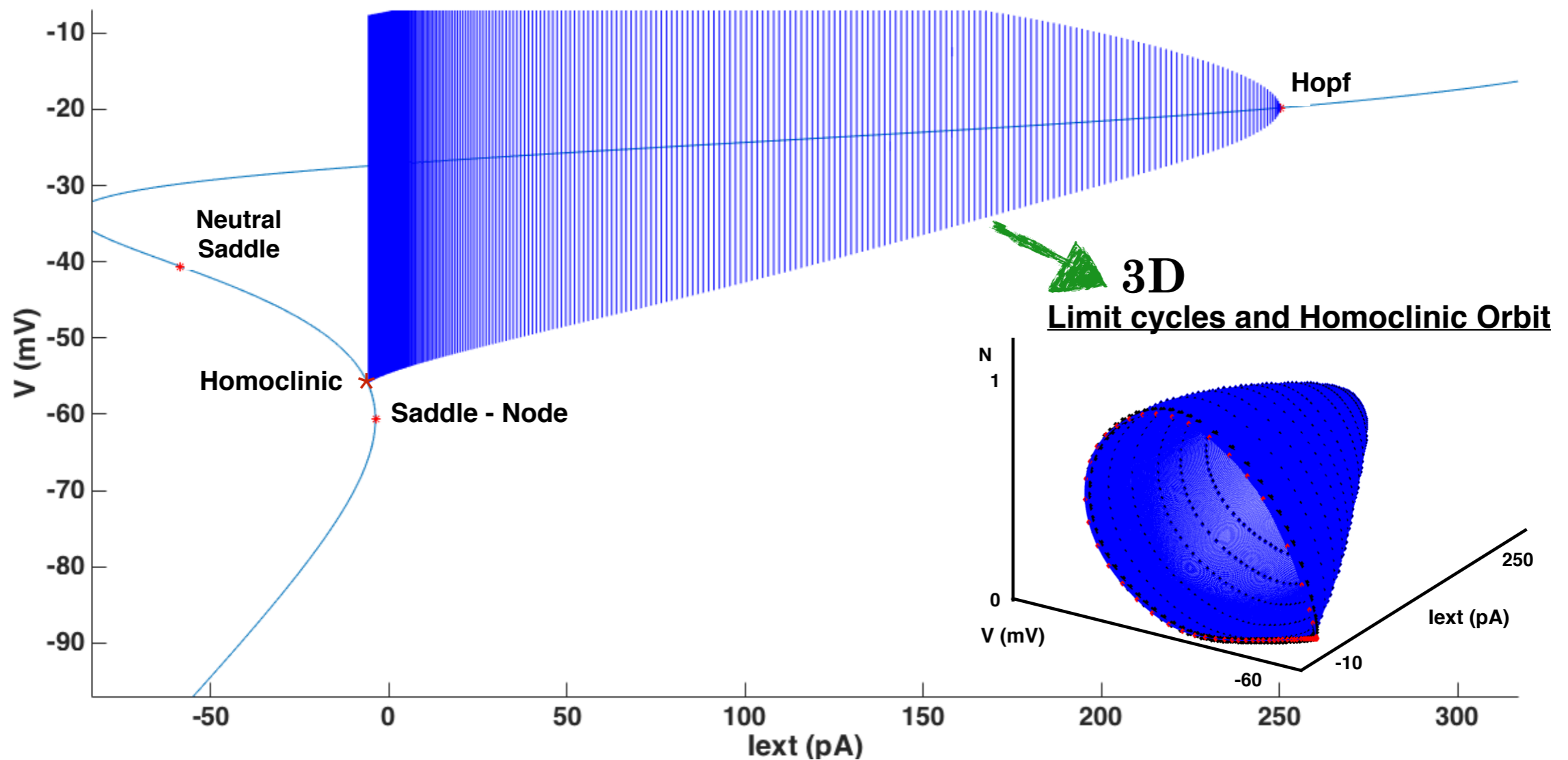
## I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

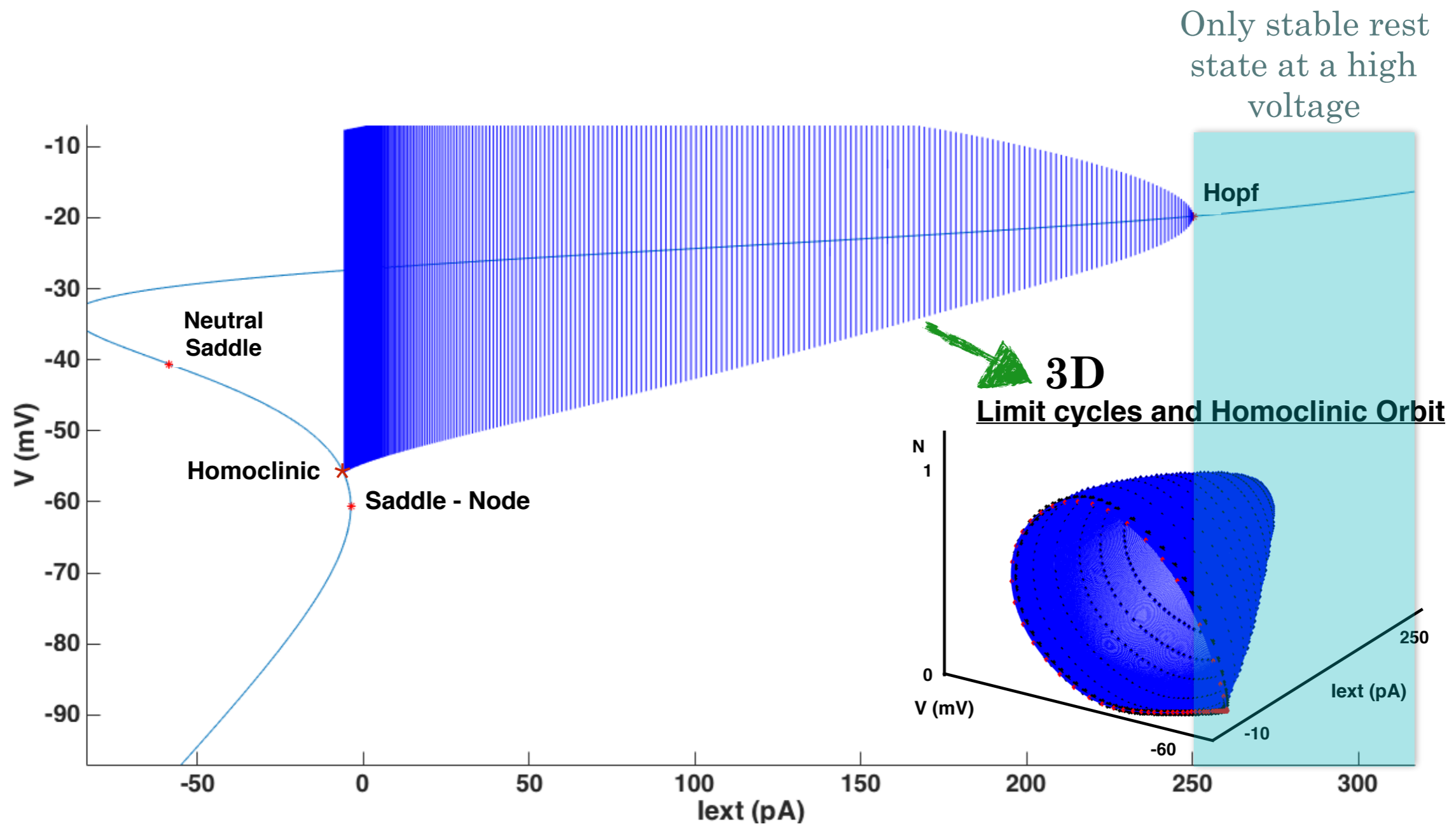
I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

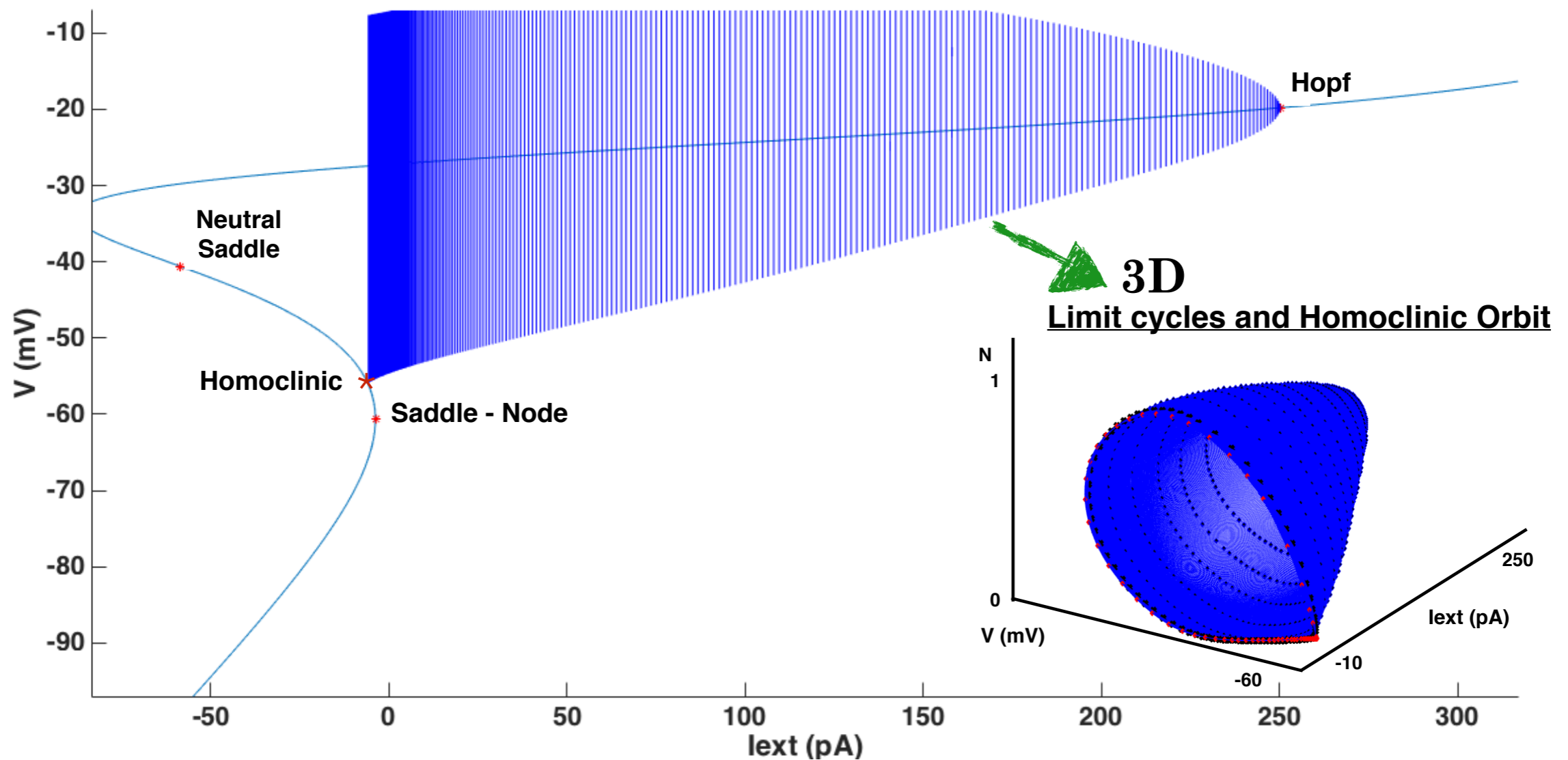
## I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

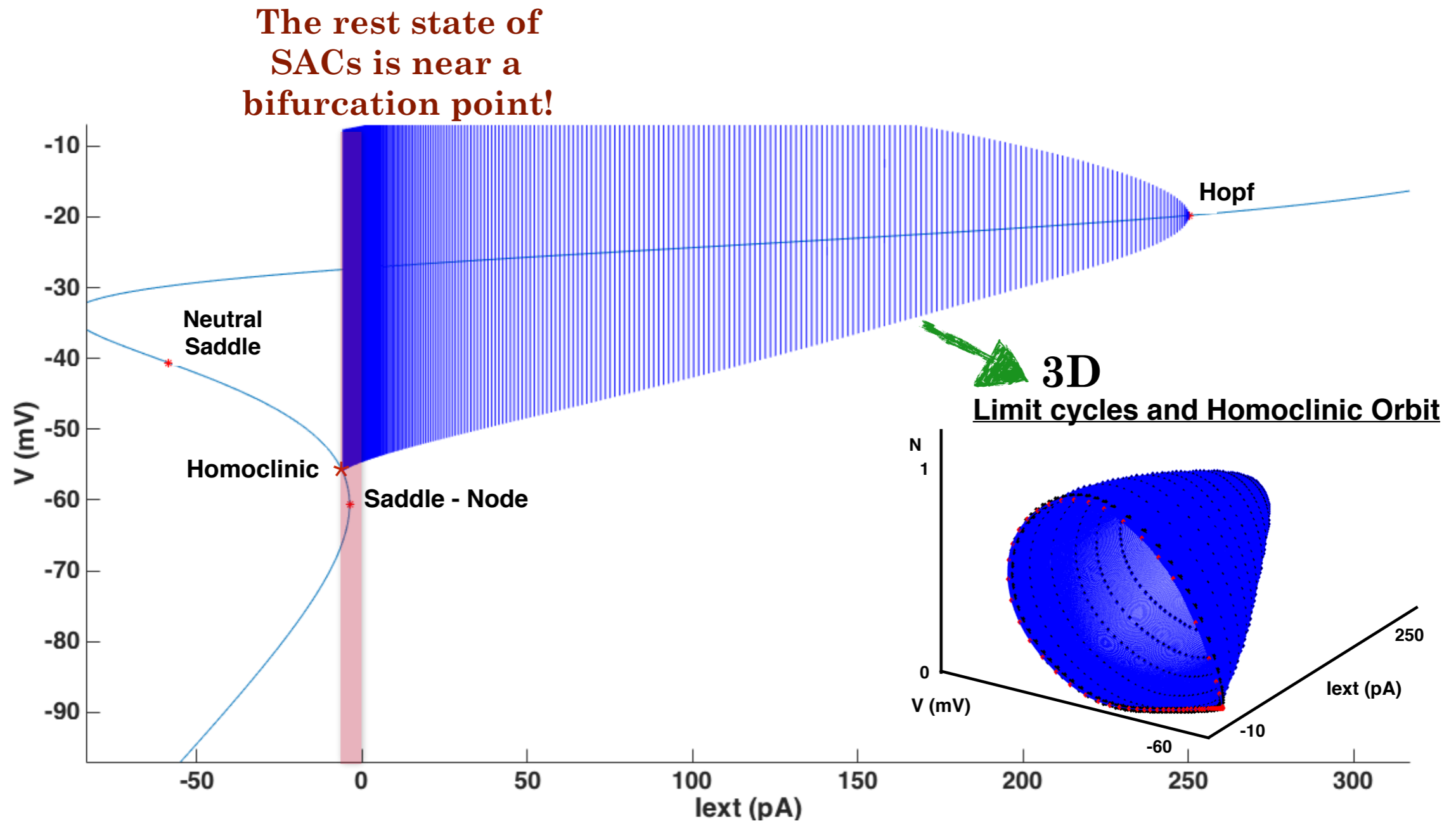
I. The SACs repertoire of dynamics upon a varying current



# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

I. The SACs repertoire of dynamics upon a varying current



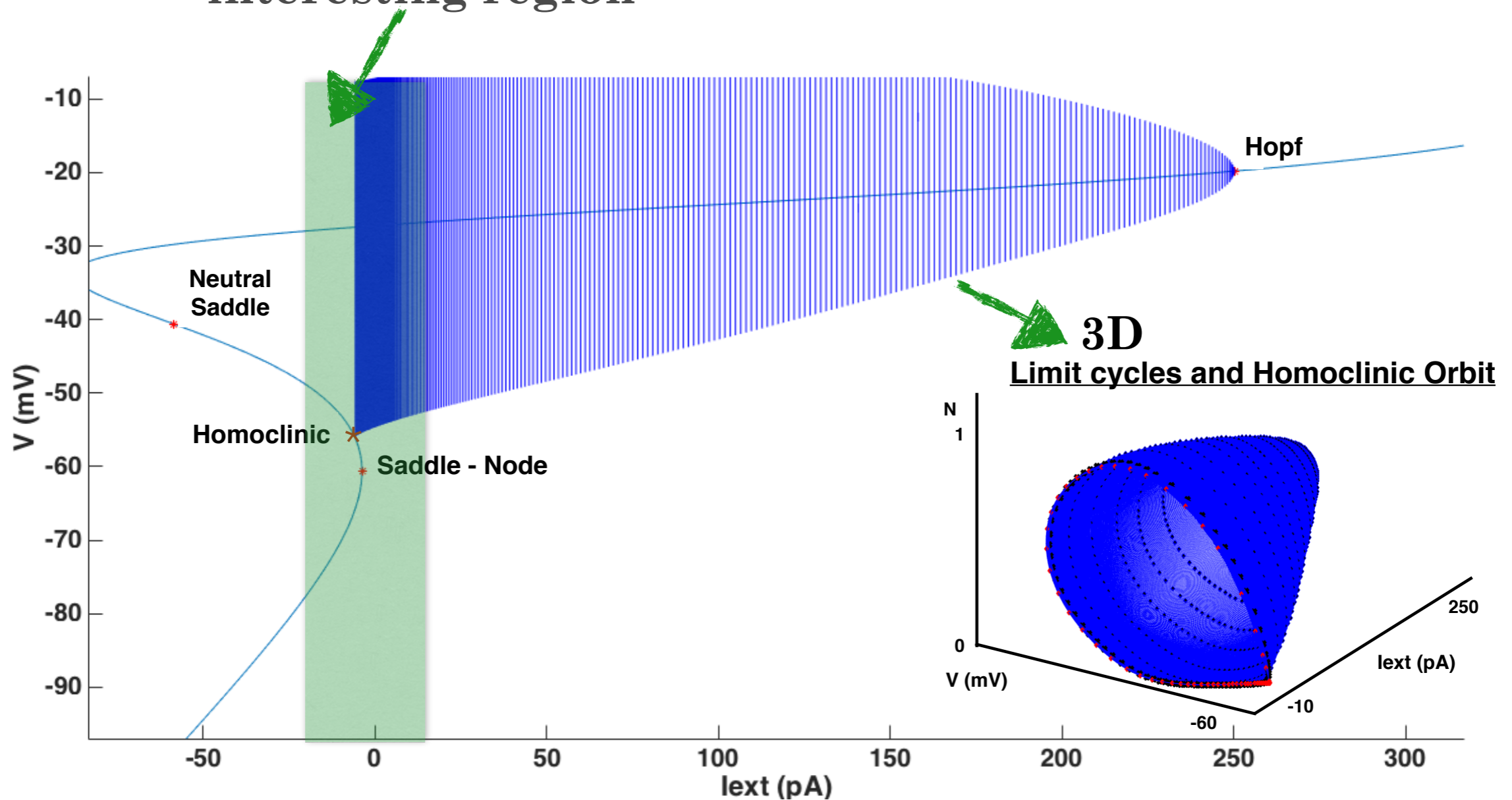


# Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

## I. The SACs repertoire of dynamics upon a varying current

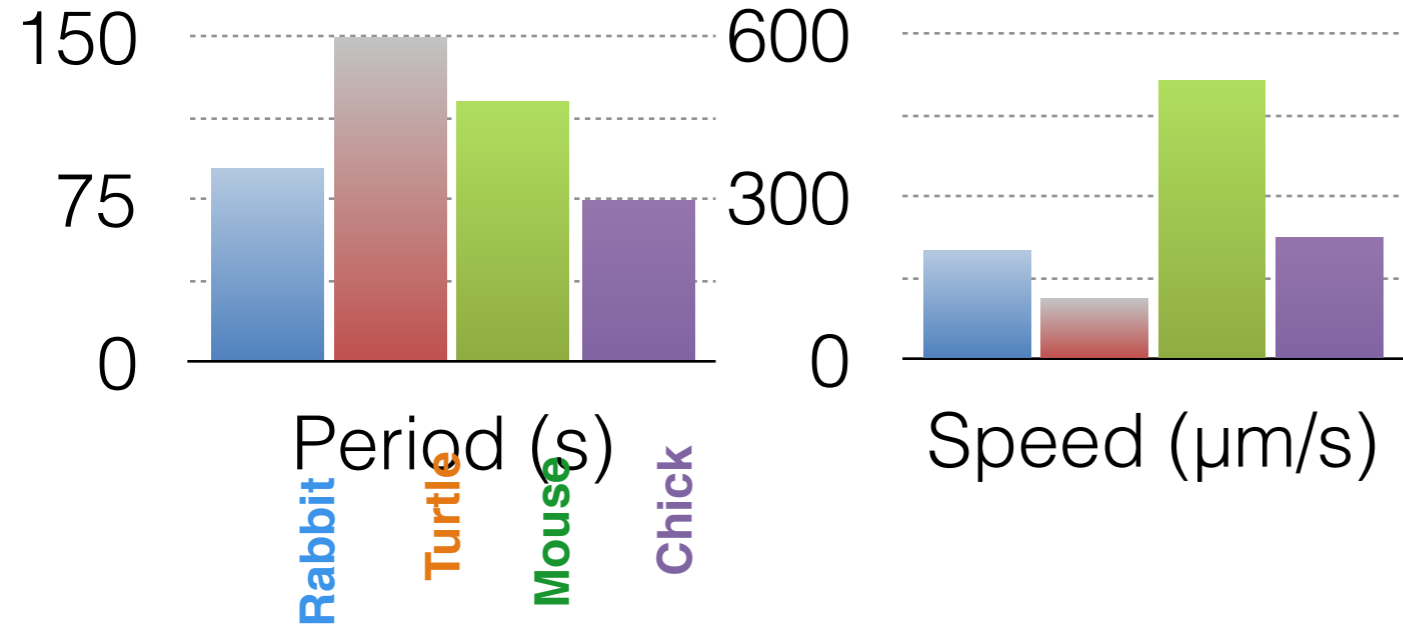
Zoom in this interesting region



# Variability within retinal waves

i) Across species

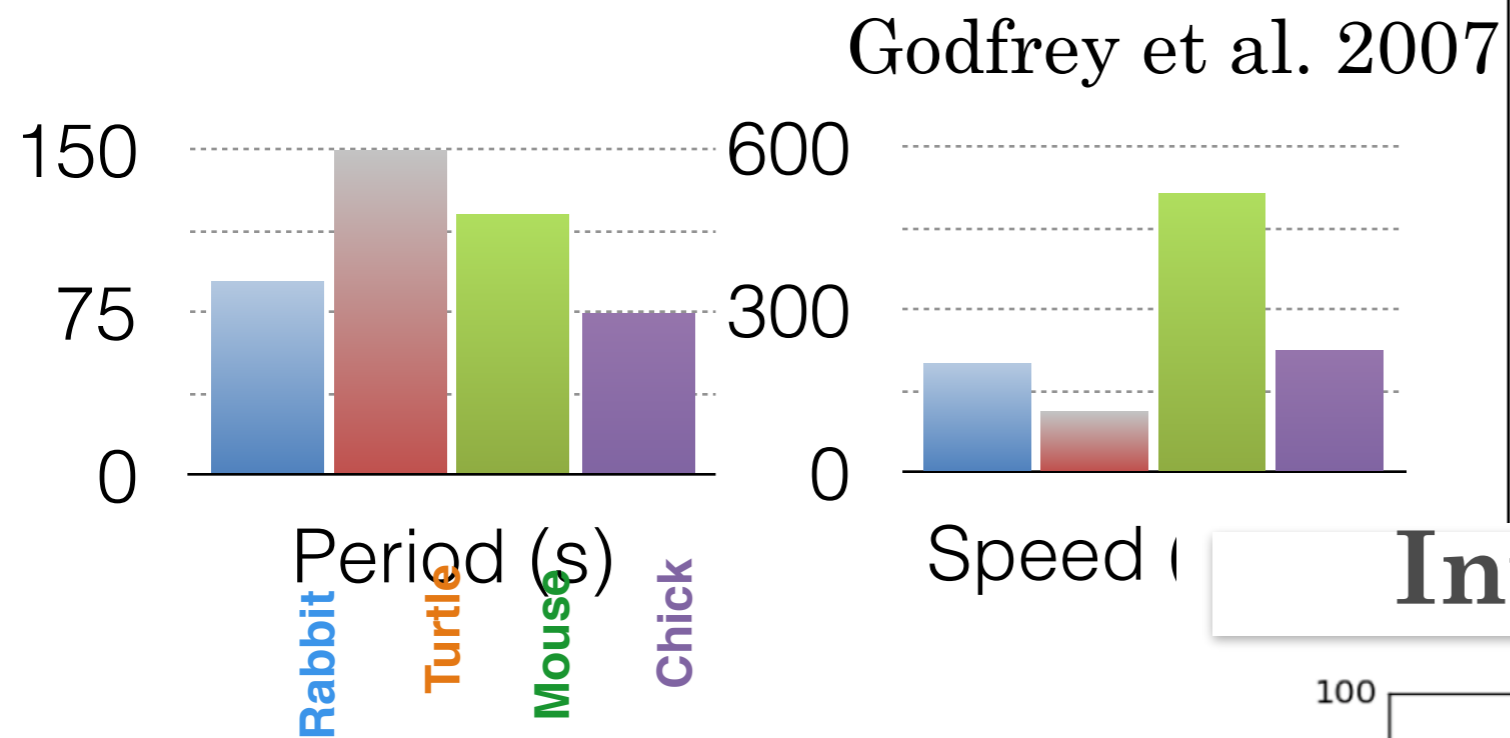
Godfrey et al. 2007



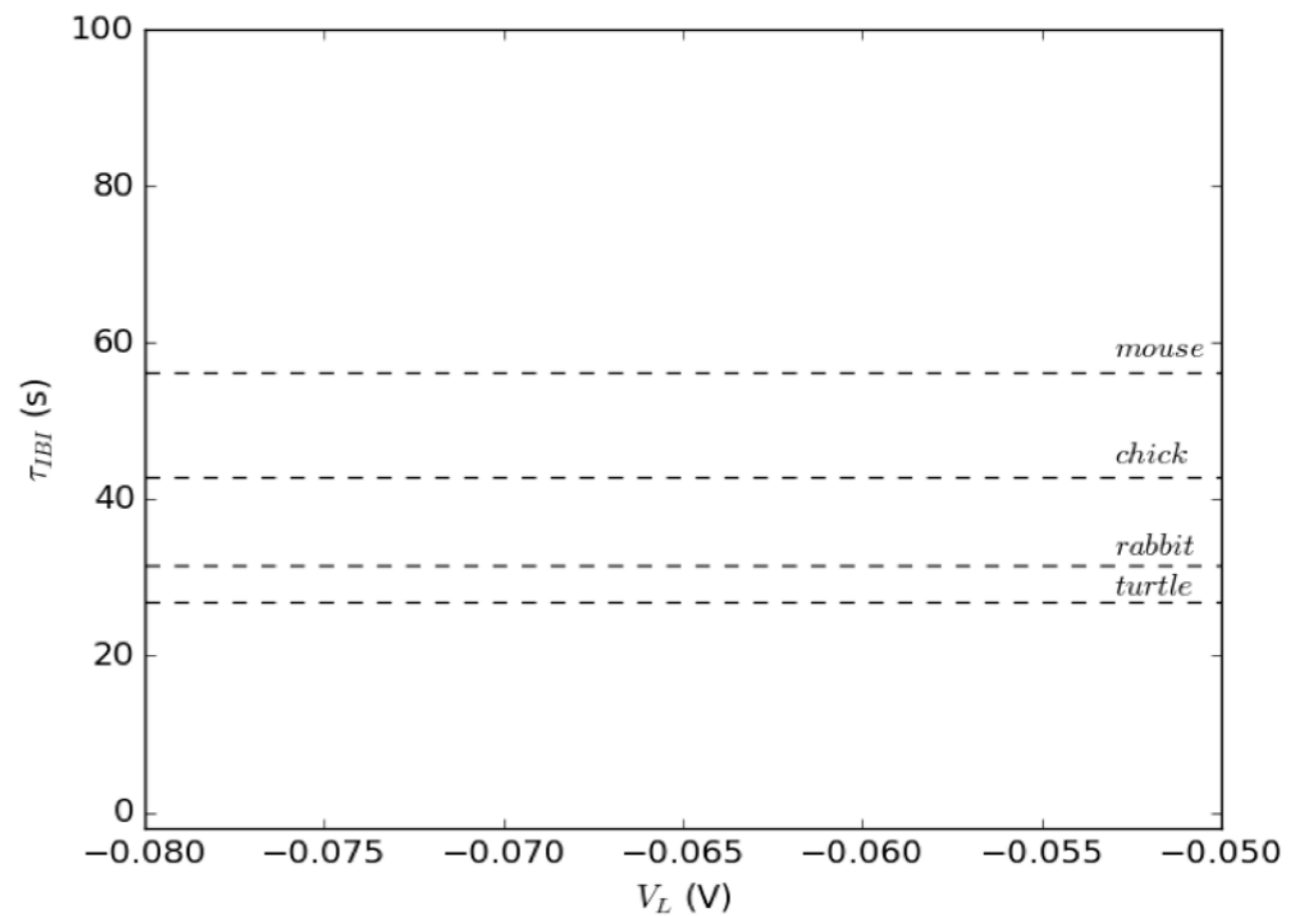


# Variability within retinal waves

## i) Across species

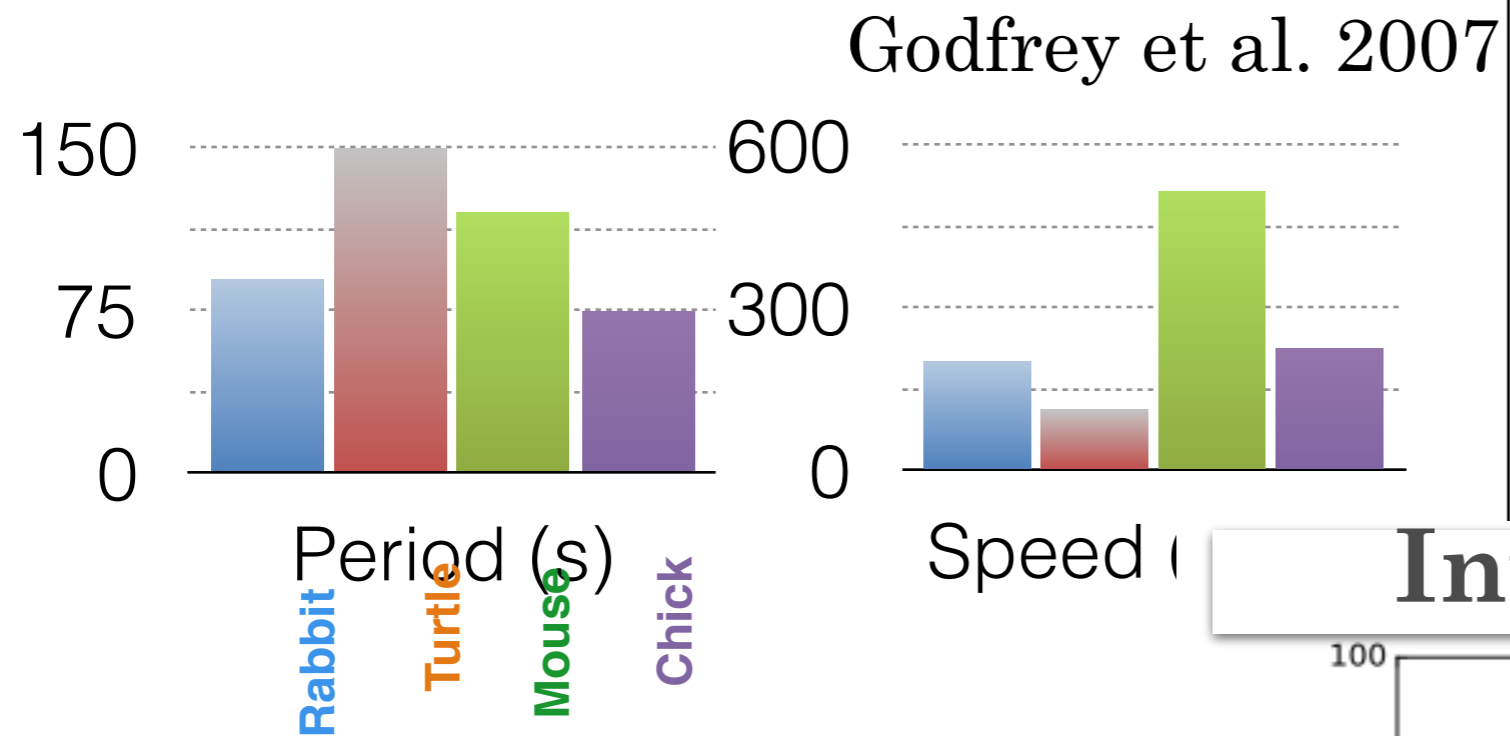


## Interburst intervals

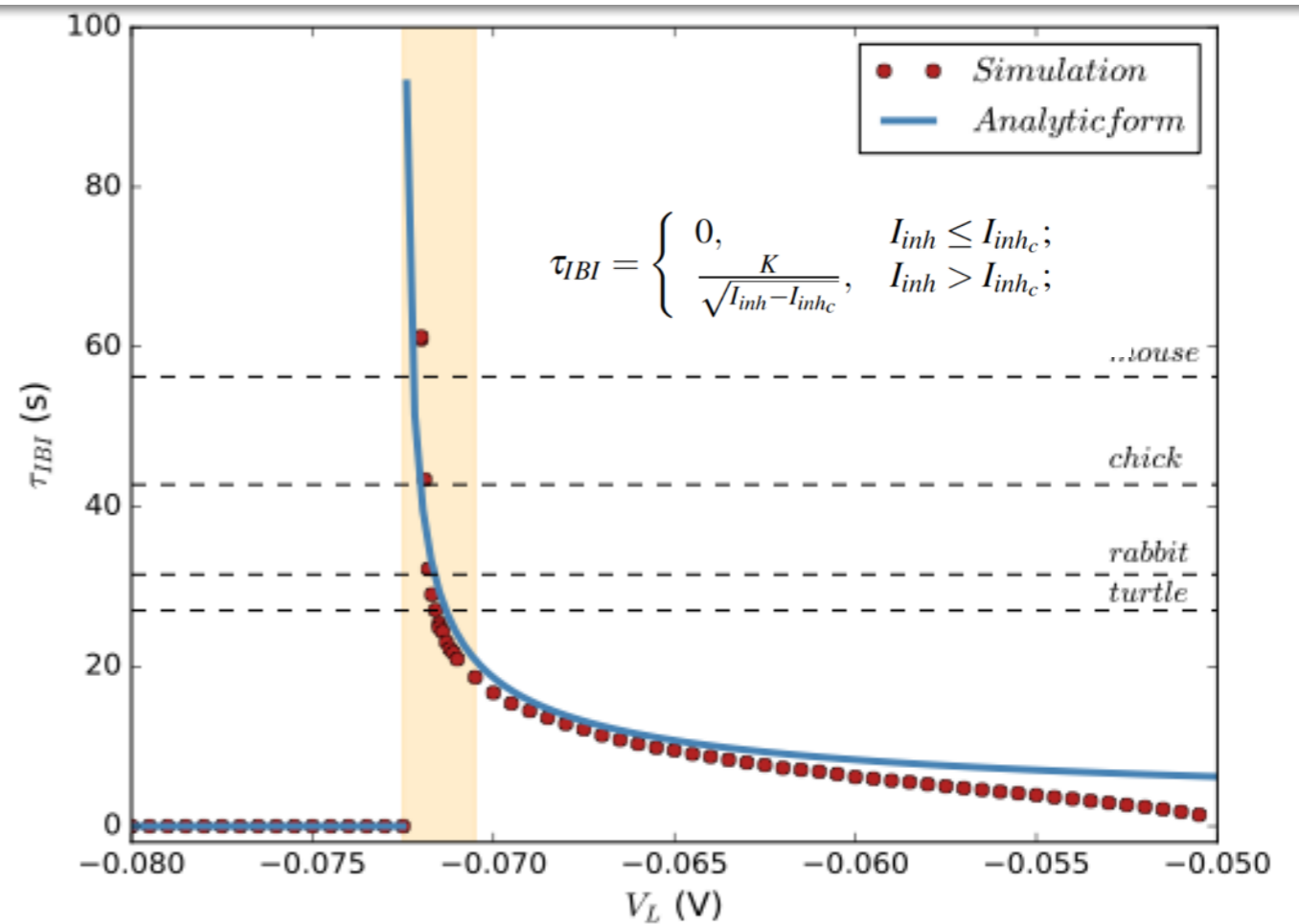


# Variability within retinal waves

## i) Across species



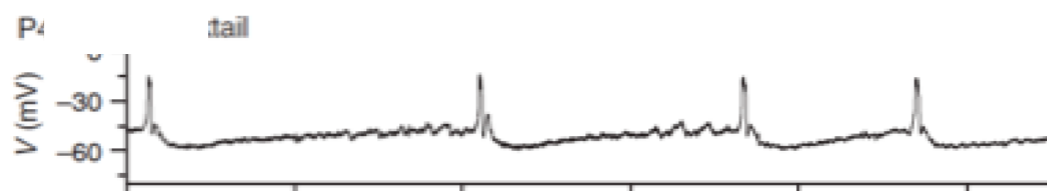
## Interburst intervals



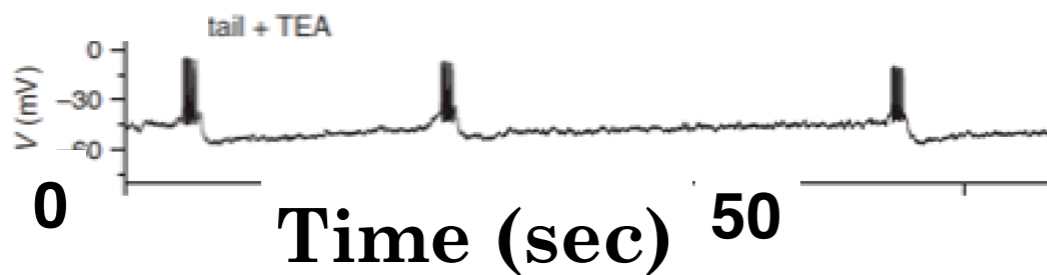
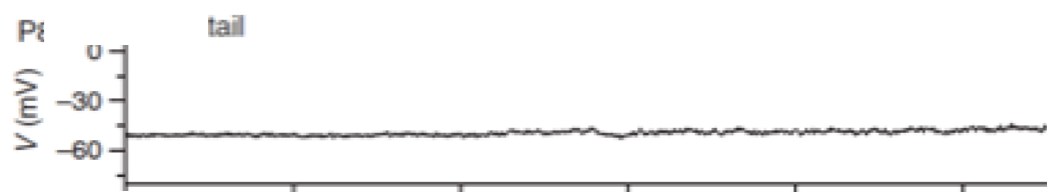
# Variability within retinal waves

## iii) Pharmacology

**P4**

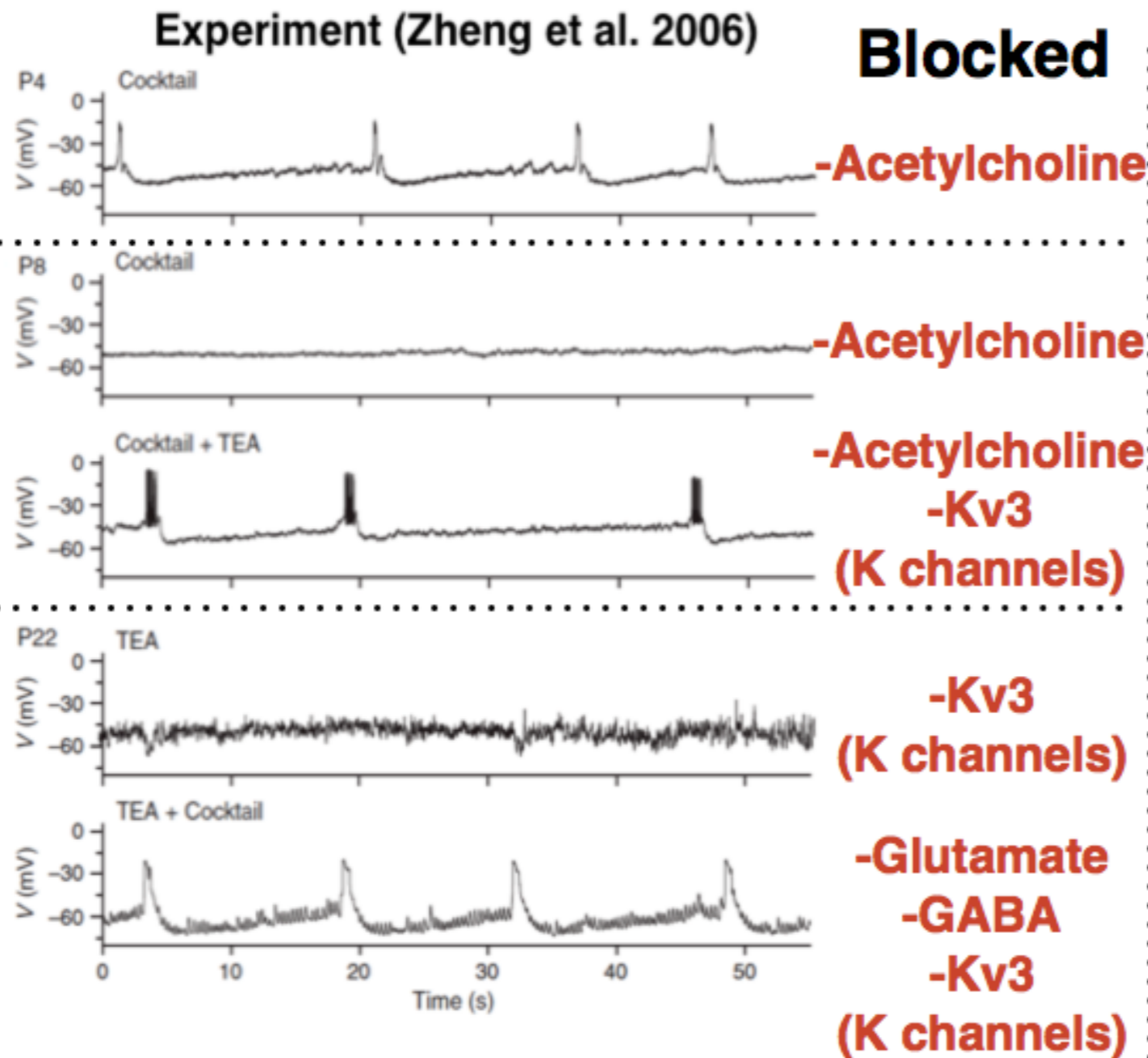


**P8**



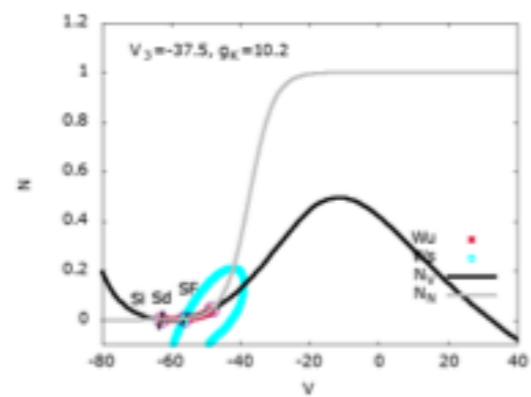
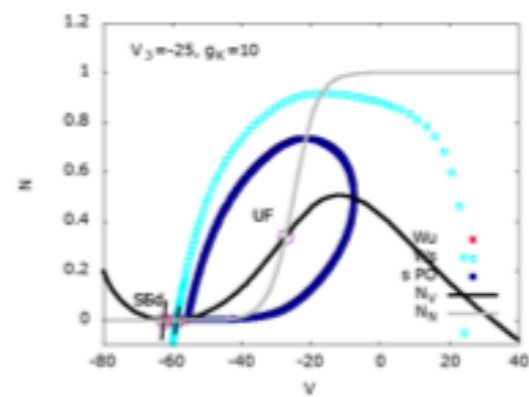
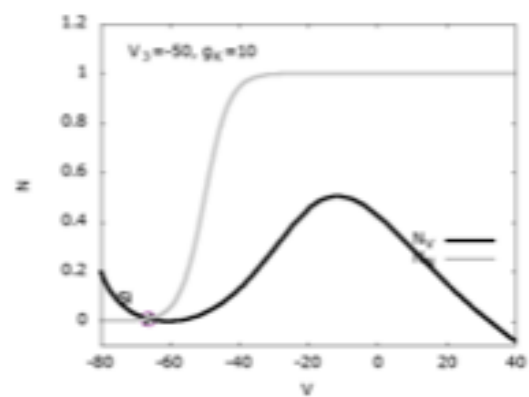
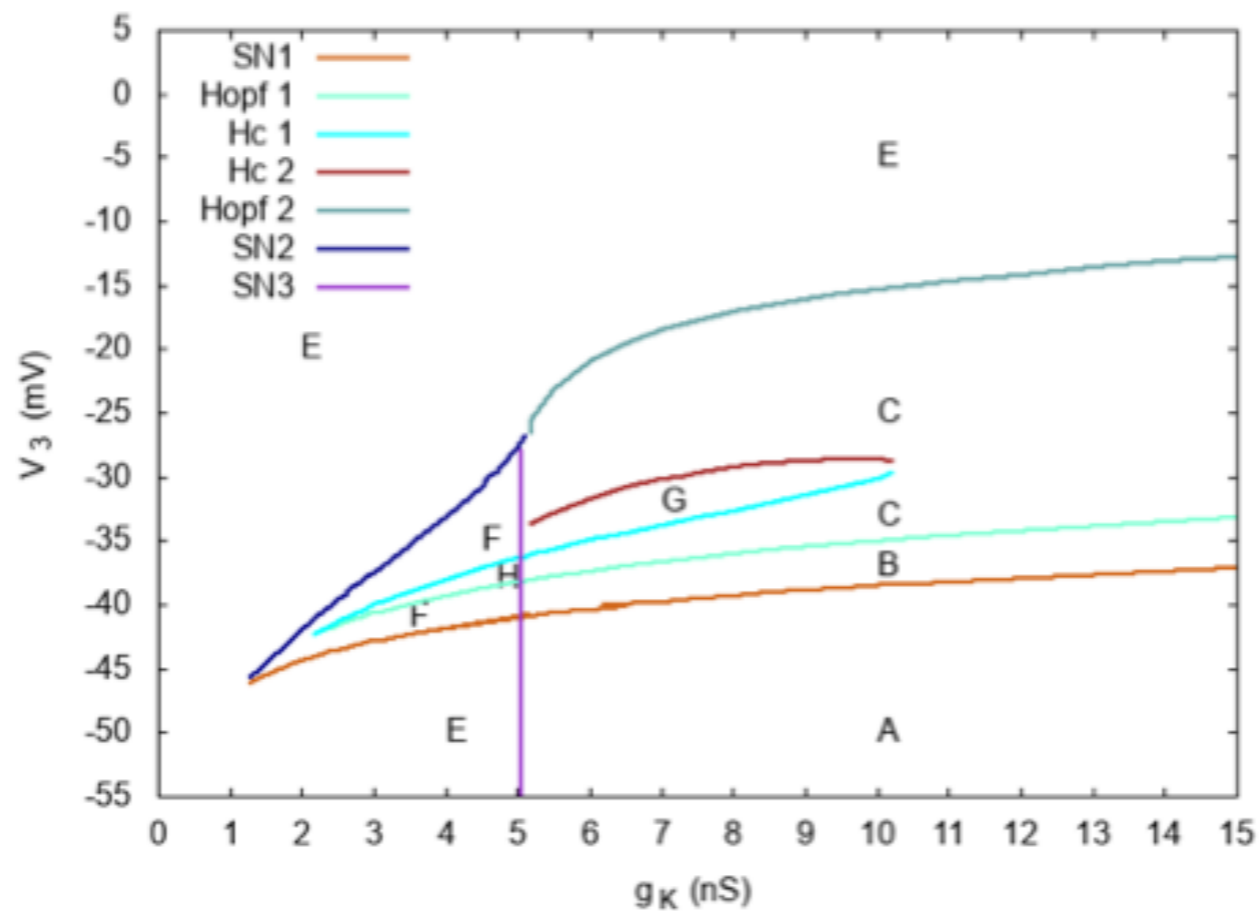
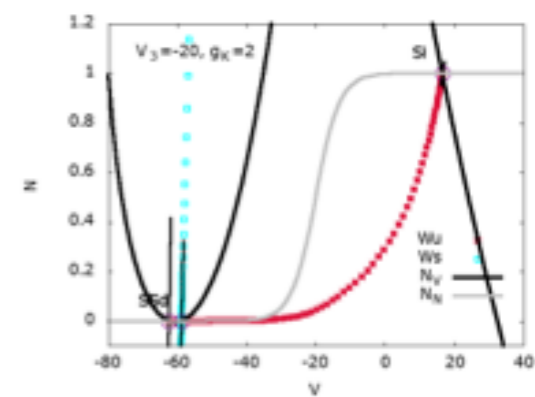
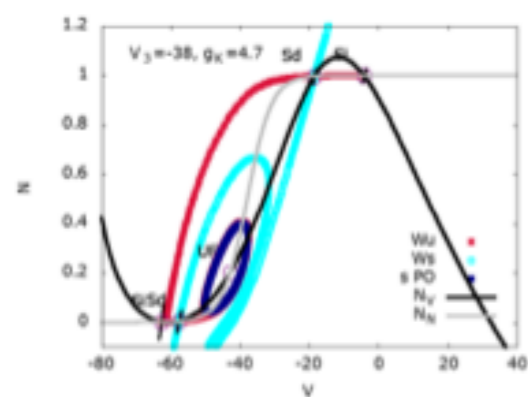
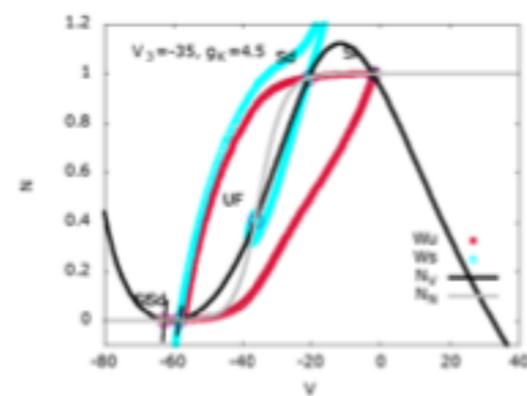
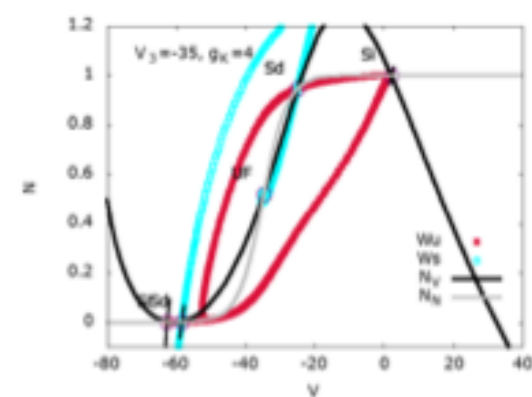
# How do SACs lose their excitability?

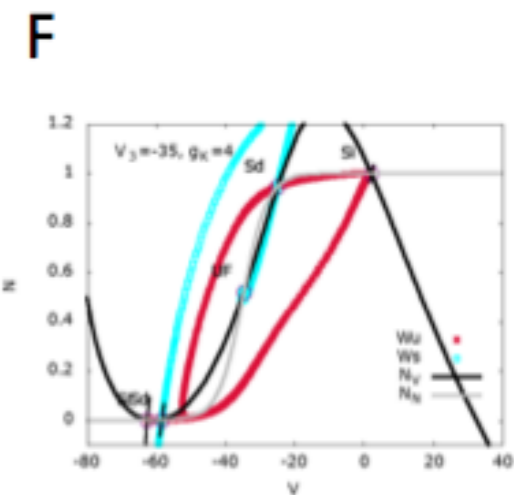
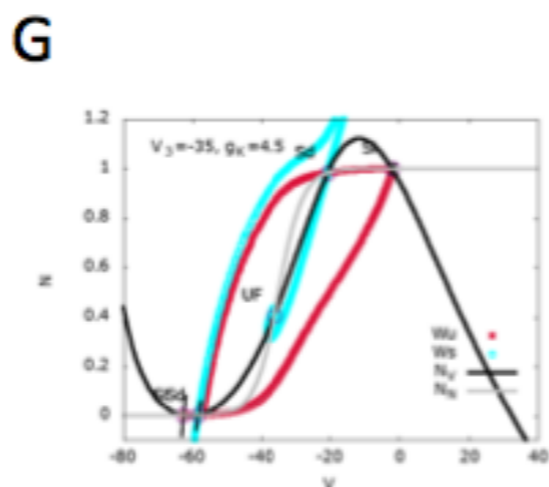
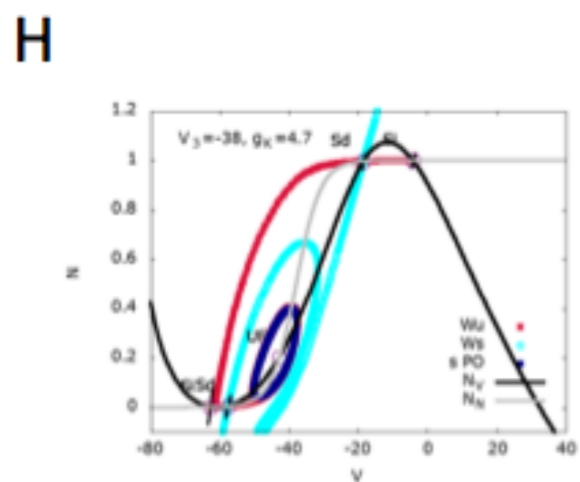
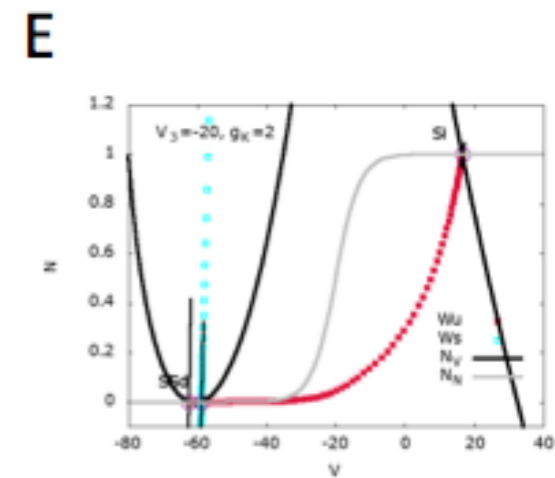
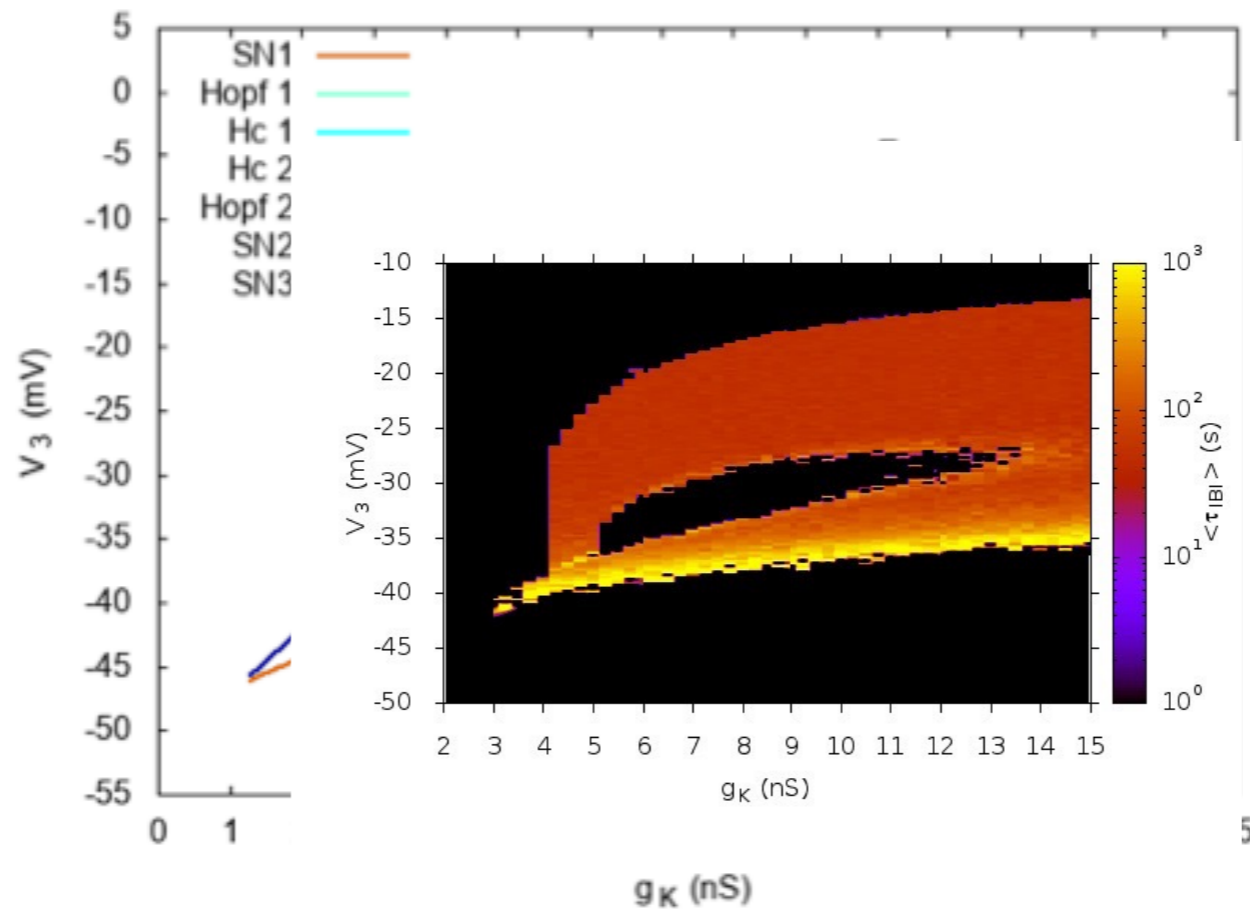
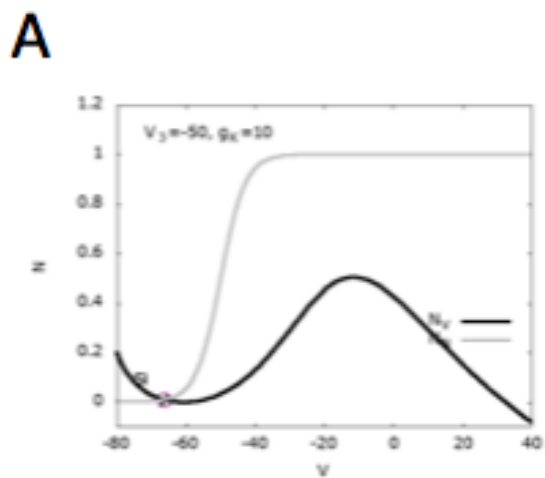
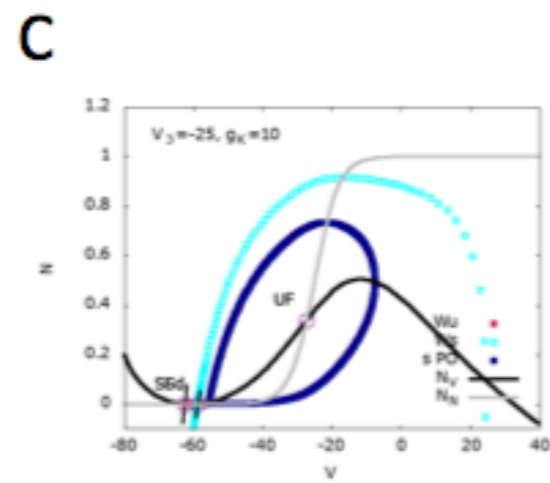
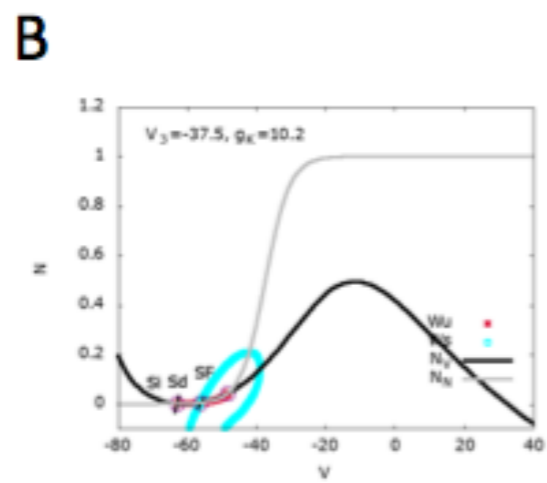
**A**



**Potassium channels  
(potentially Kv3)  
are modelled by 3  
parameters**  
**gK, V3, V4**

**\*TEA blocks Kv3 channels**

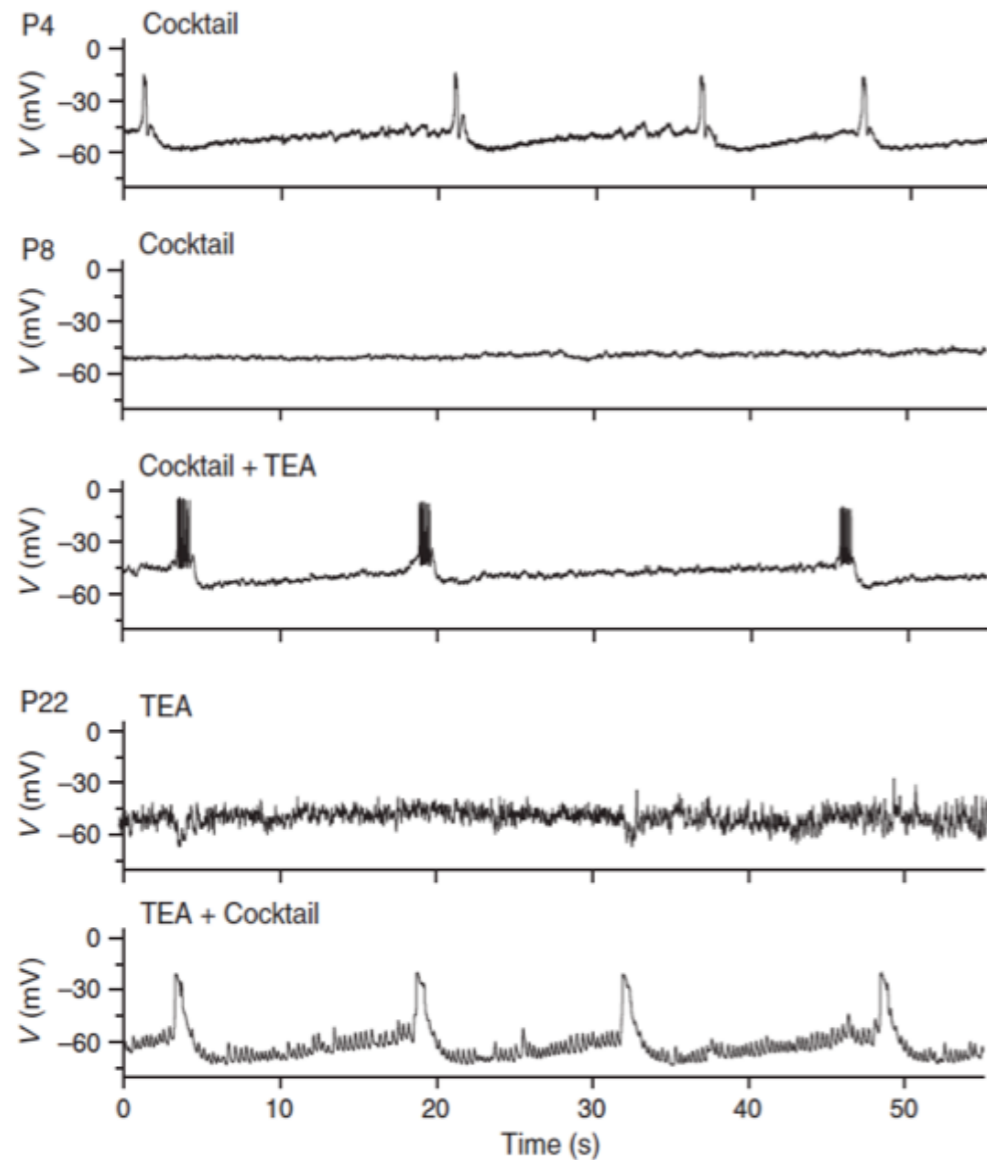
**B****C****A****E****H****G****F**



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

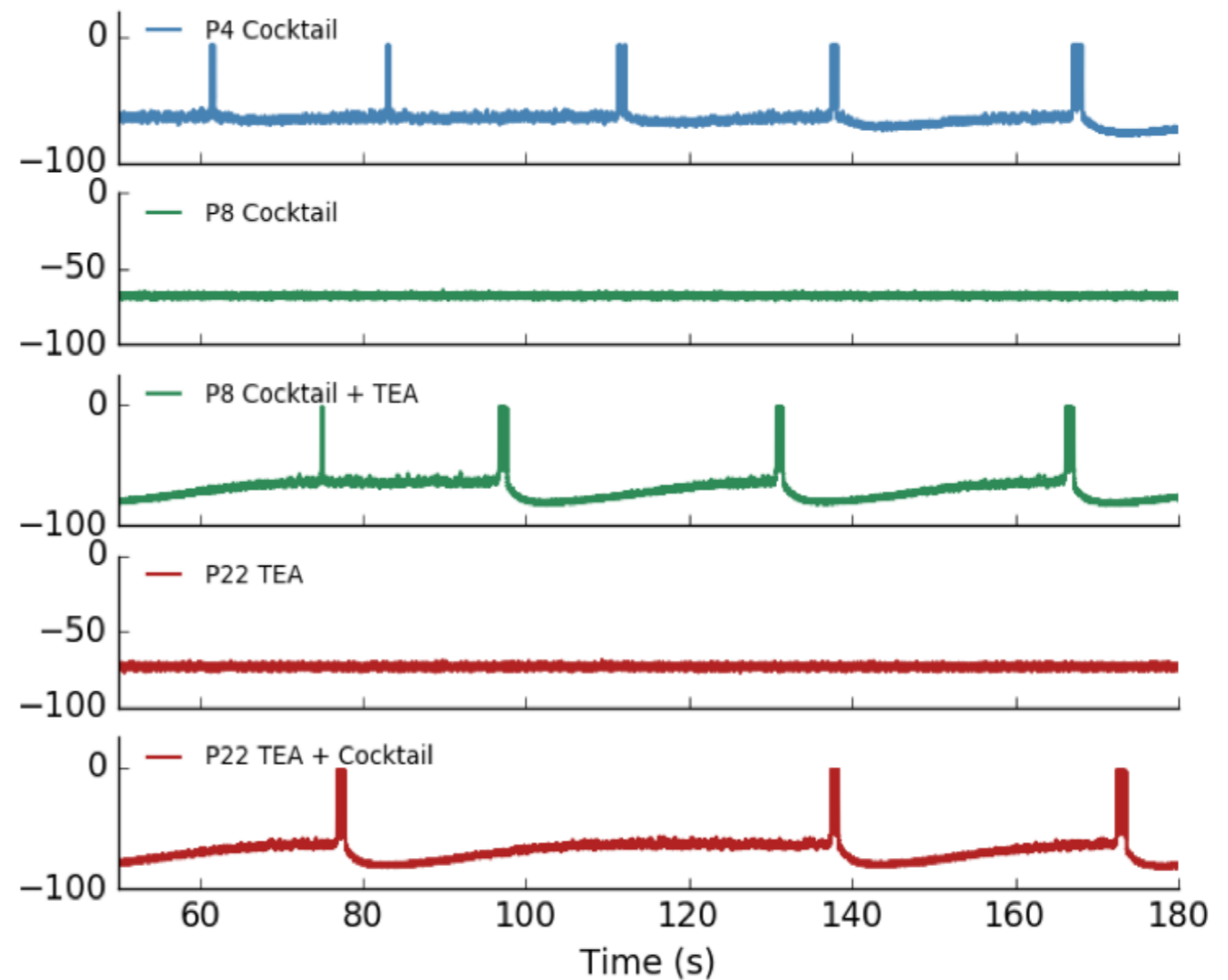
## A

### Experiment (Zheng et al. 2006)



## B

### Model

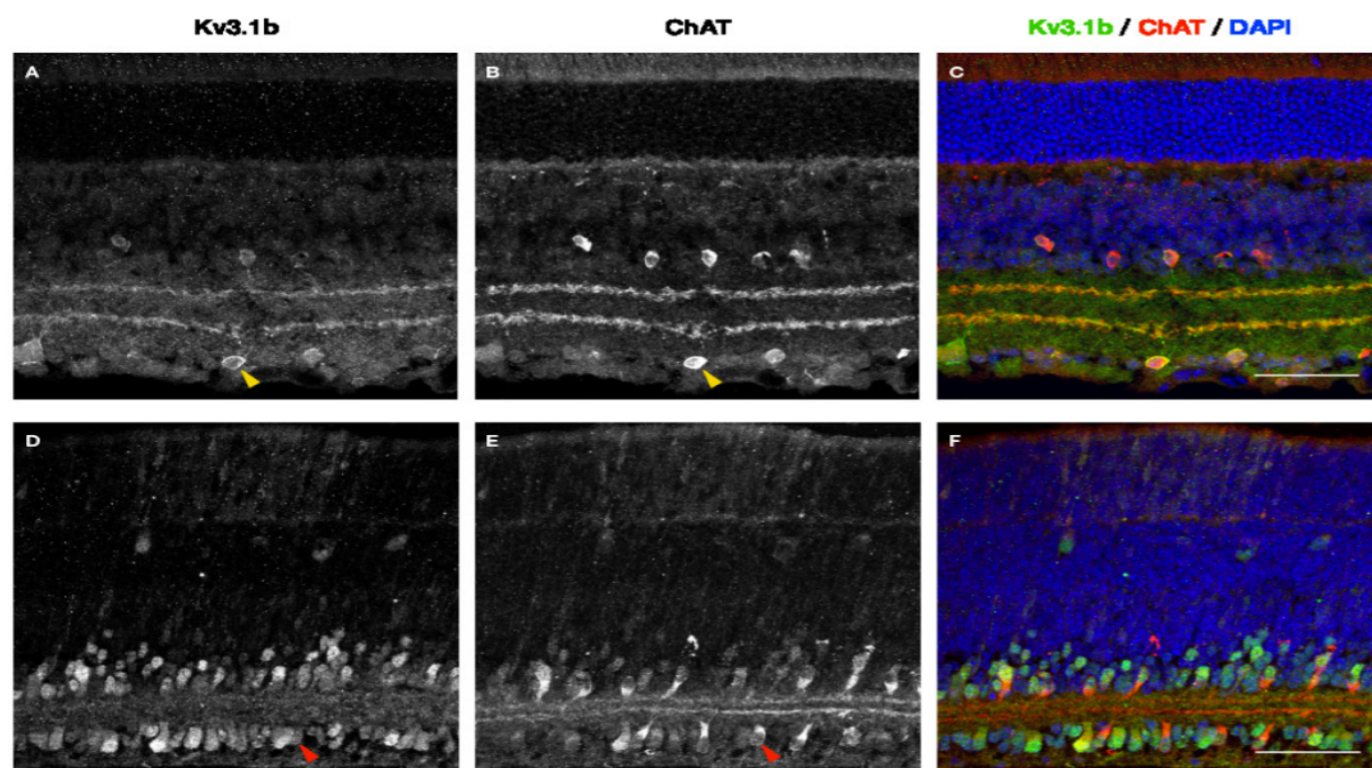




# How do SACs lose their excitability?

**Hypothesis: The expression of the potassium Kv3 channels increases upon maturation possibly leading to the loss of SACs excitability**

## Preliminary experimental exploration



(O.Marre-E. Orendorff)

### Localization of Kv3.1b in adult and P7 retinas.

(A-C) Adult retina section showing Kv3.1b (green) and choline acetyltransferase (ChAT, red) reactivity in starburst amacrine cells. Cell nuclei stain (DAPI, blue).

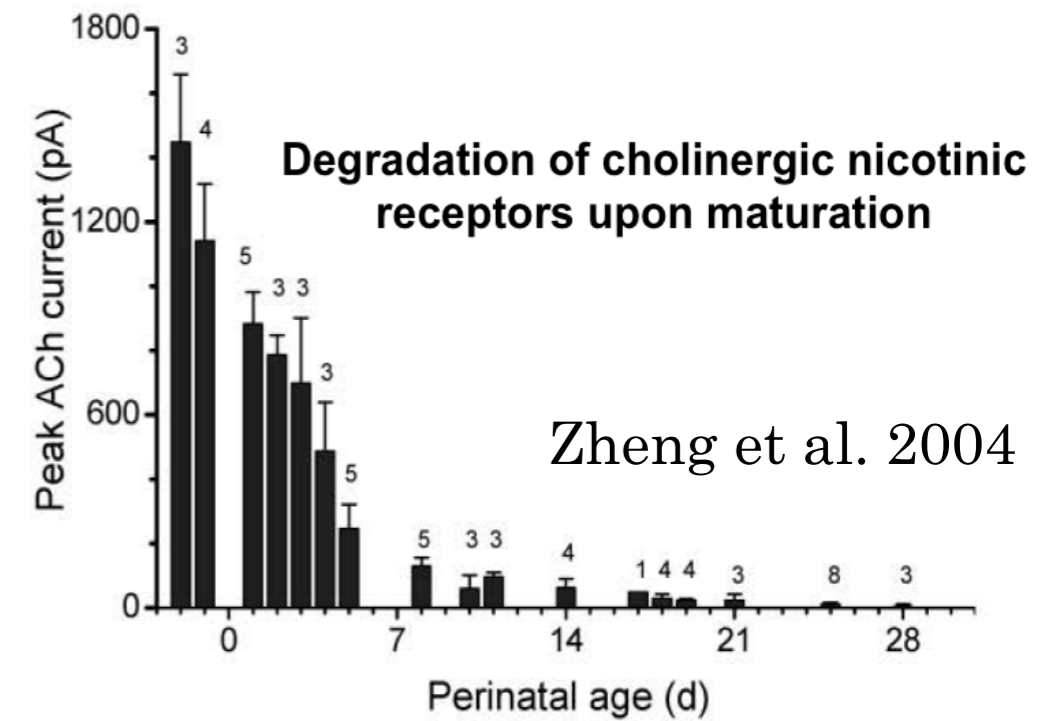
(D-F) P7 retina section showing little colocalization of Kv3.1b with ChAT in starburst amacrine cells.

**However, results are preliminary as experiment is not yet conclusive**

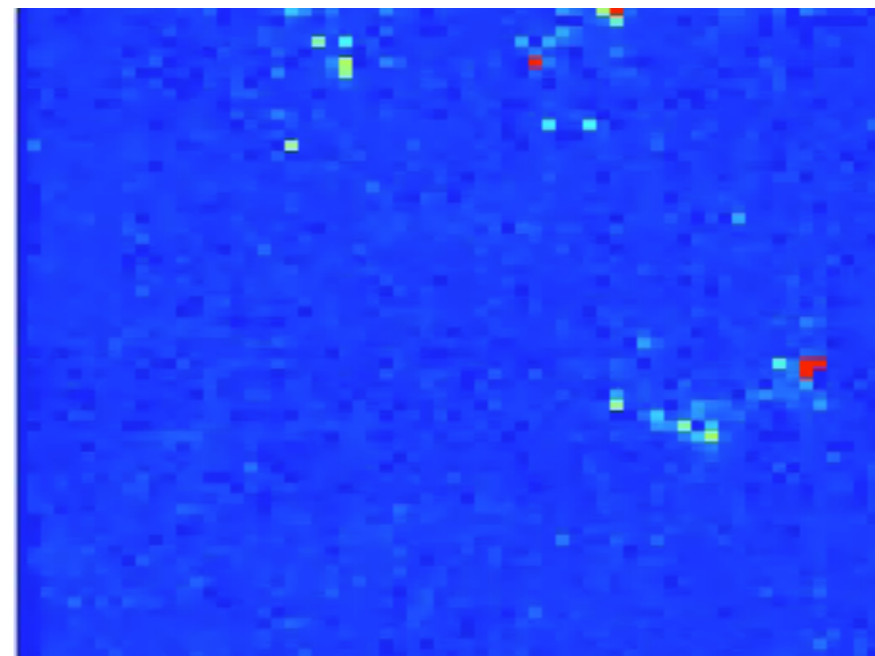


# Variability within retinal waves

## ii) Development

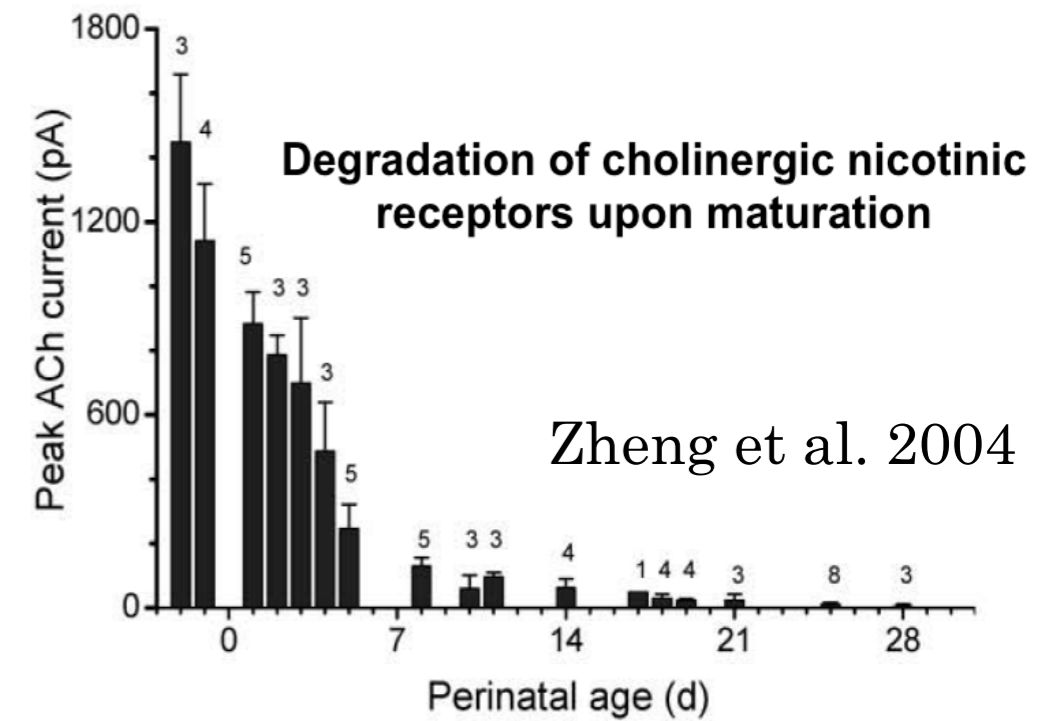


## iv) Spatial Variability

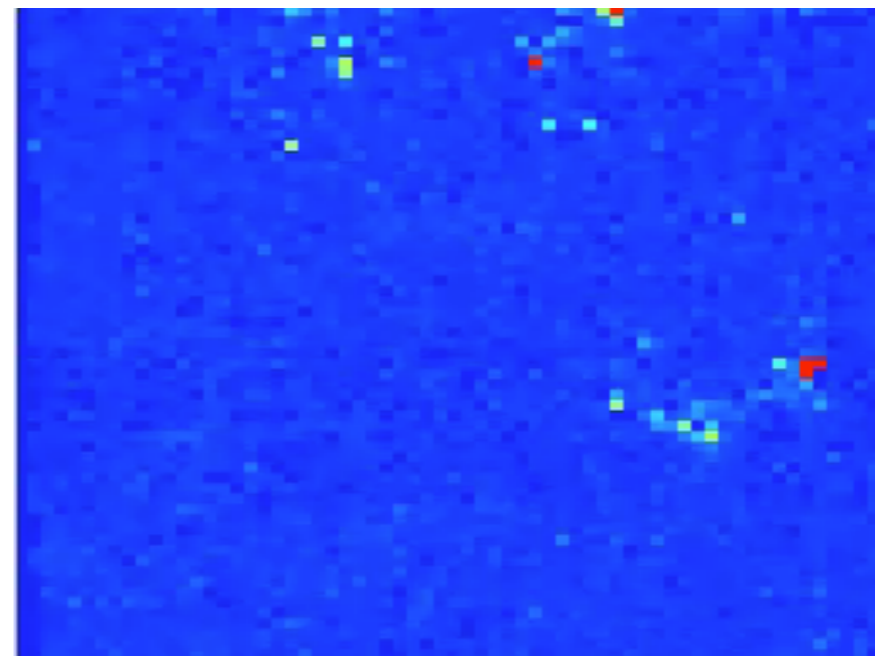


# Variability within retinal waves

## ii) Development



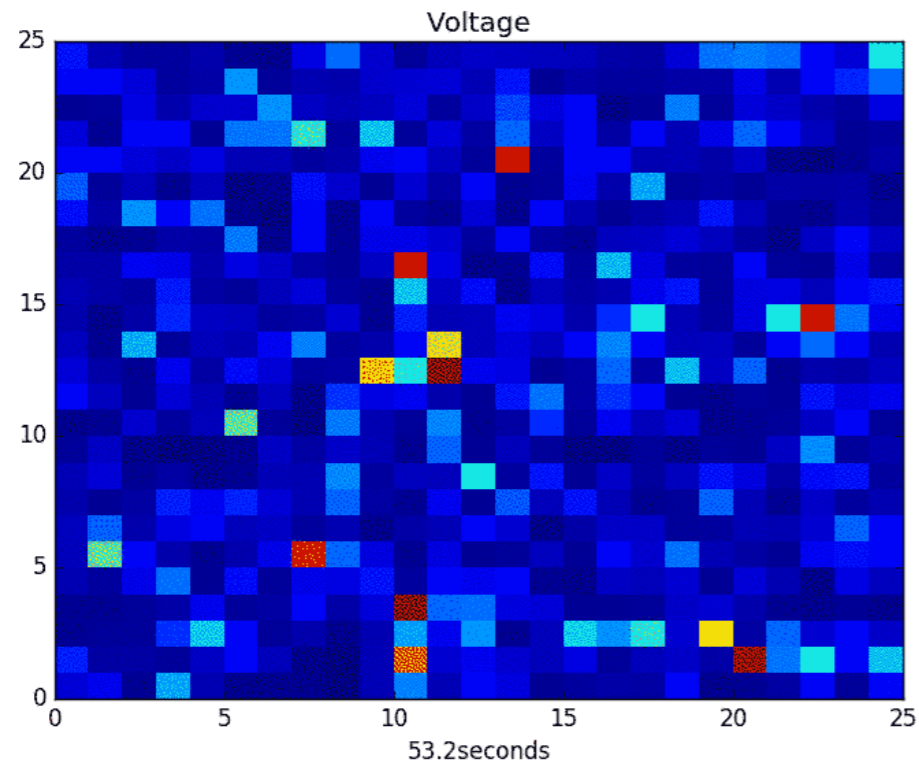
## iv) Spatial Variability



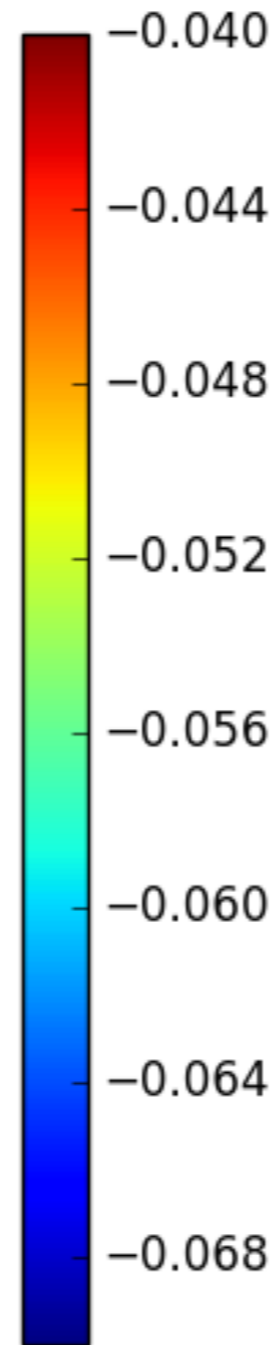
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

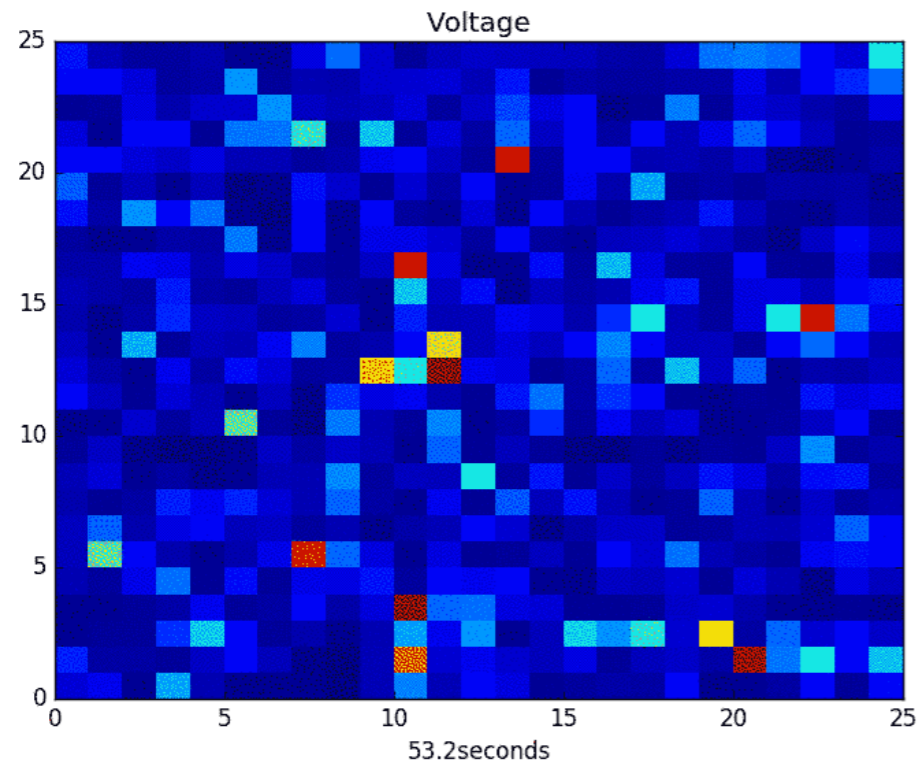


$g_{ach}=0.21$  nS

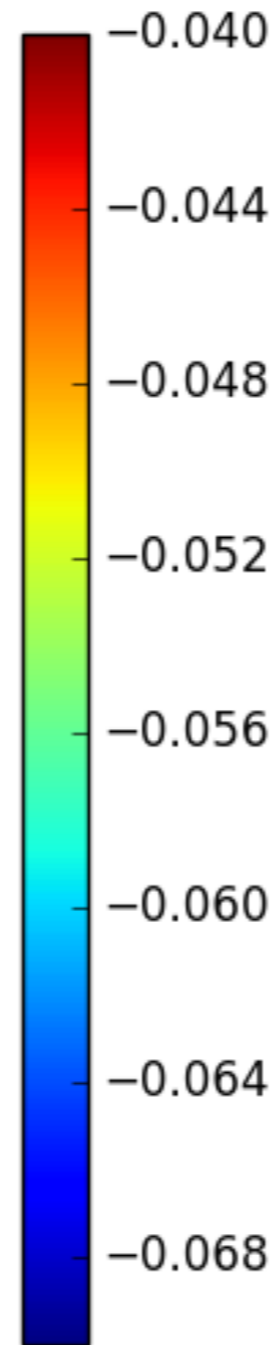
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

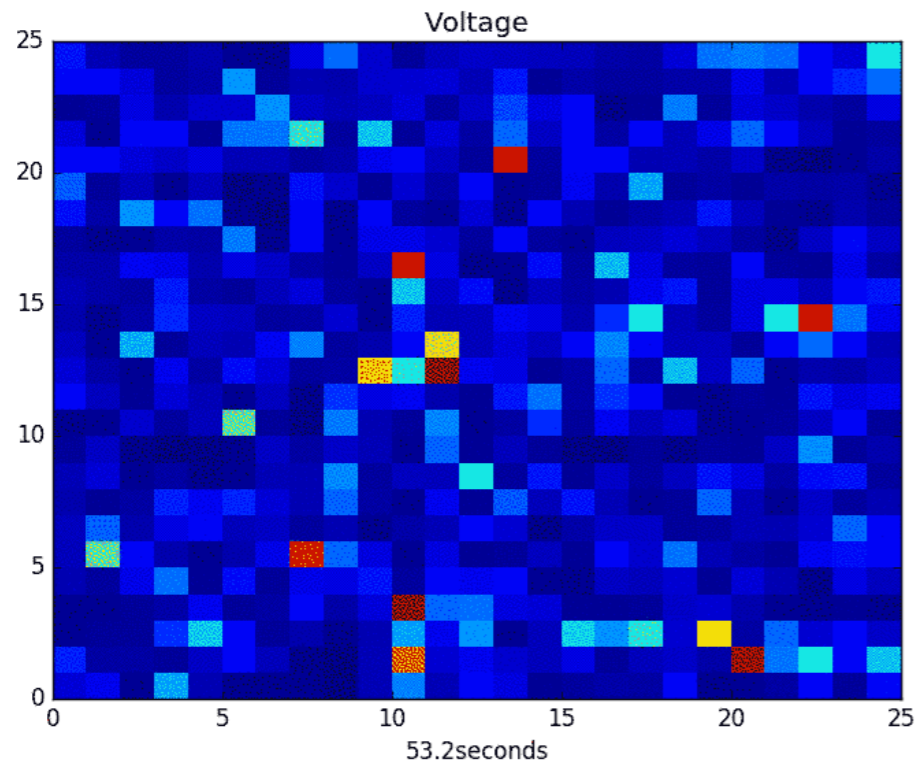


$g_{ach}=0.21$  nS

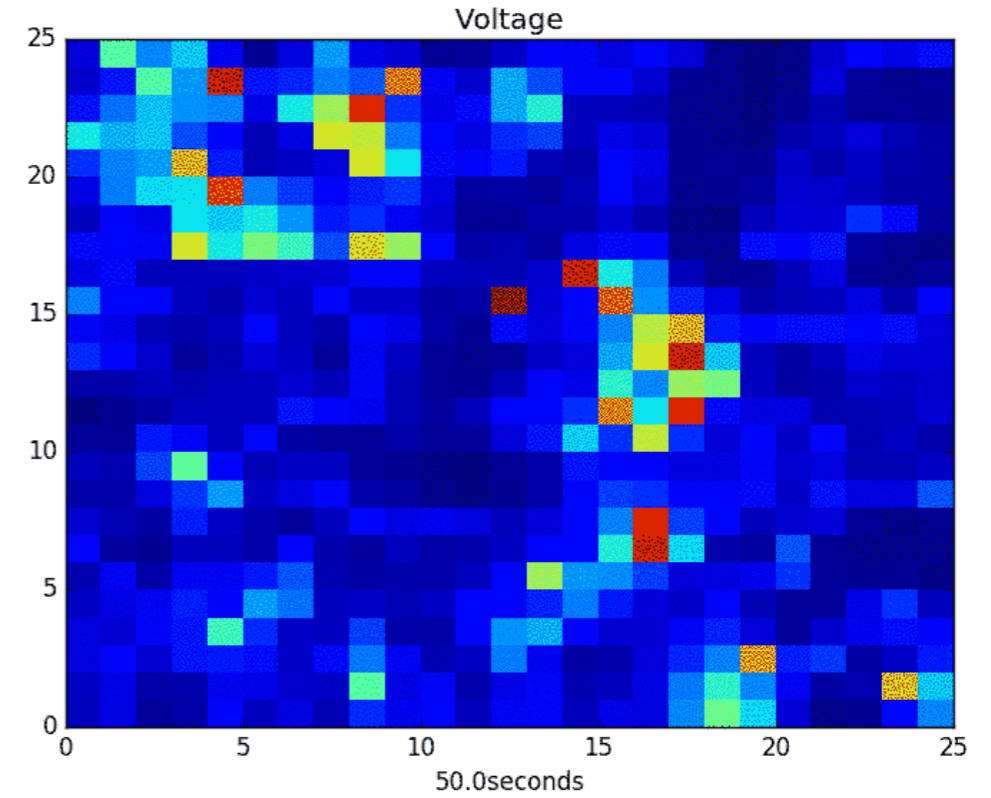
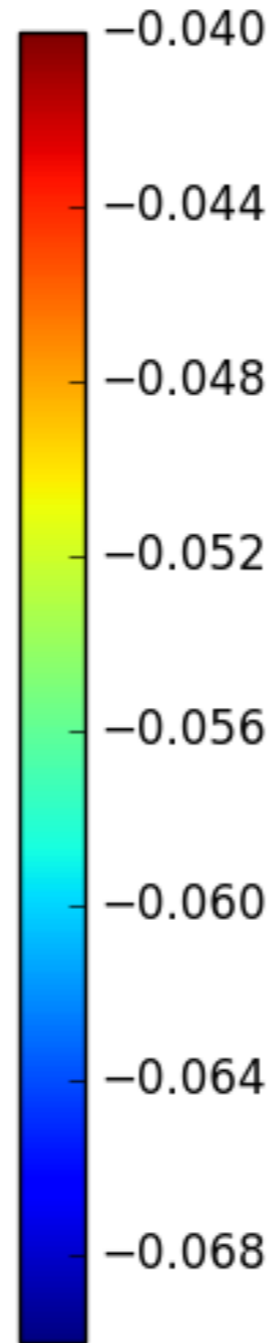
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



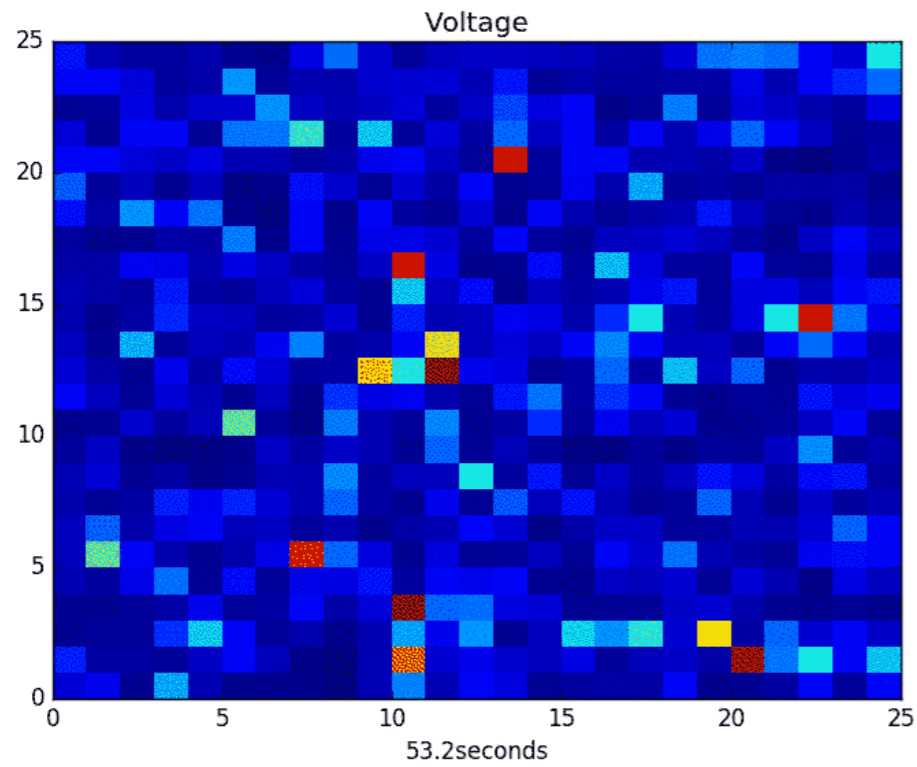
$g_{ach}=0.21$  nS



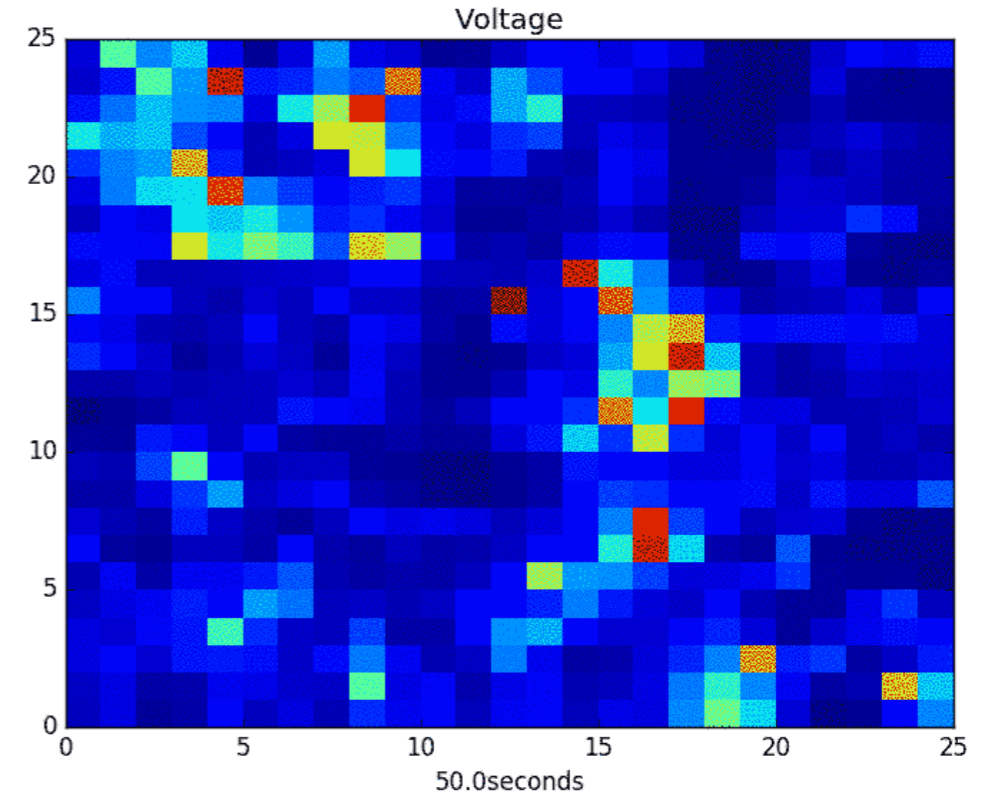
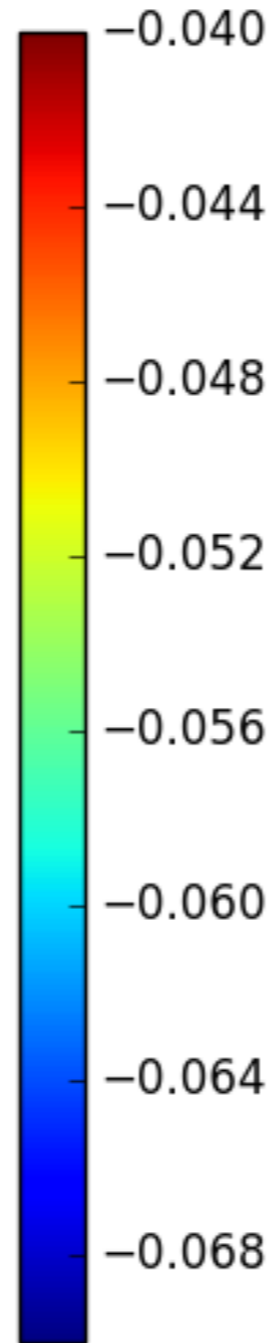
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

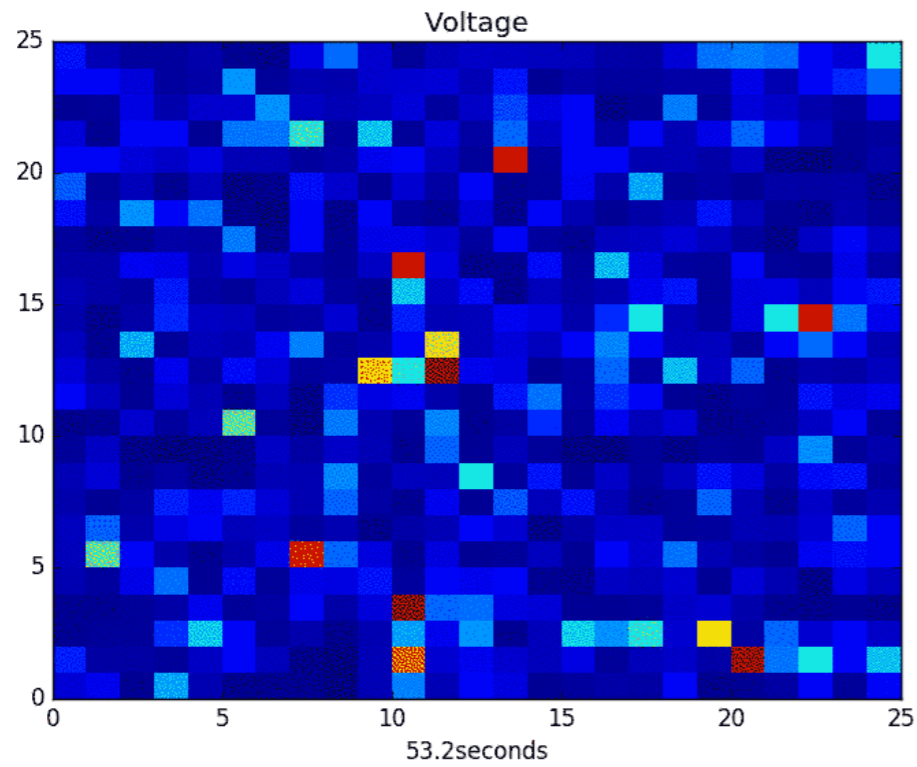


$g_{ach}=0.21$  nS

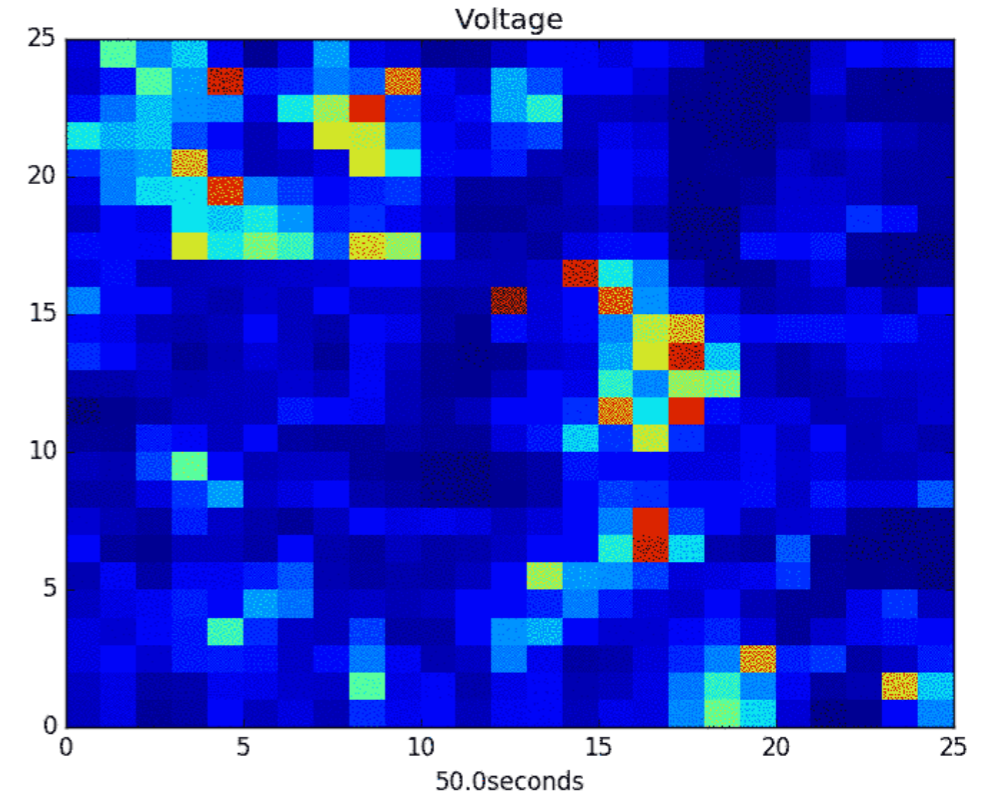
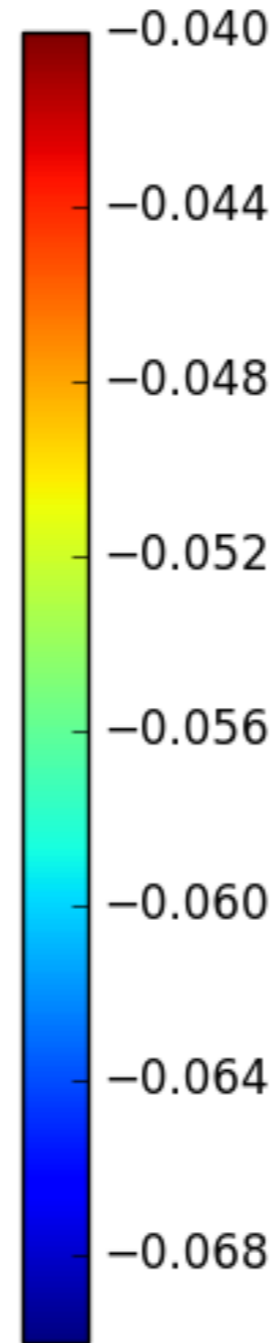
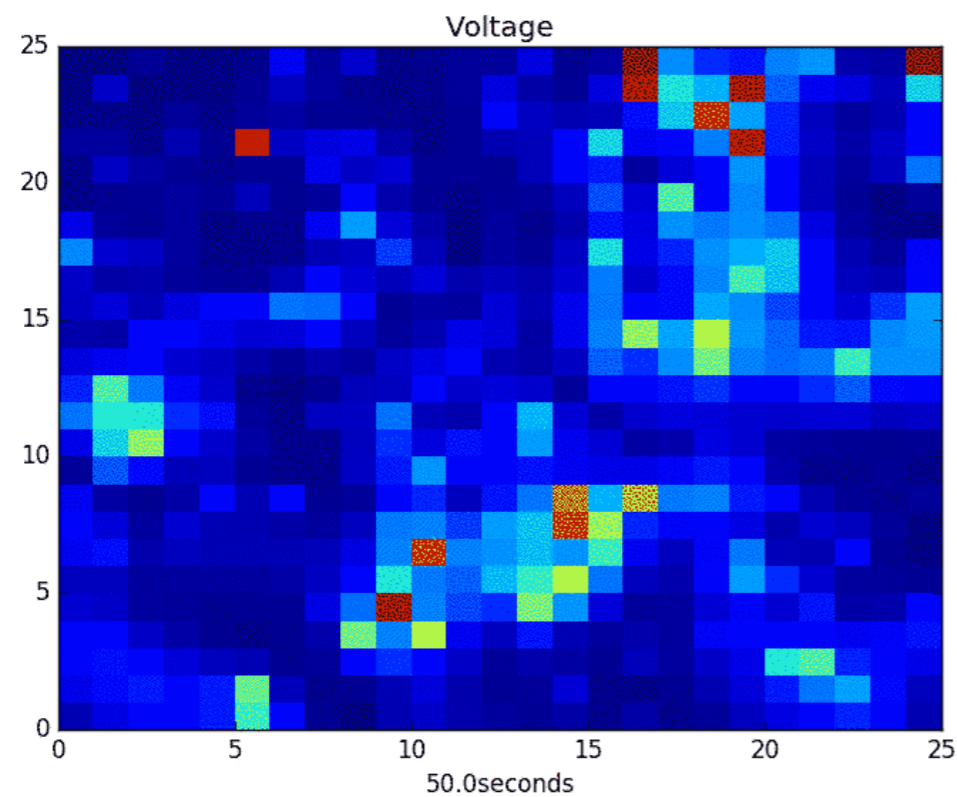
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



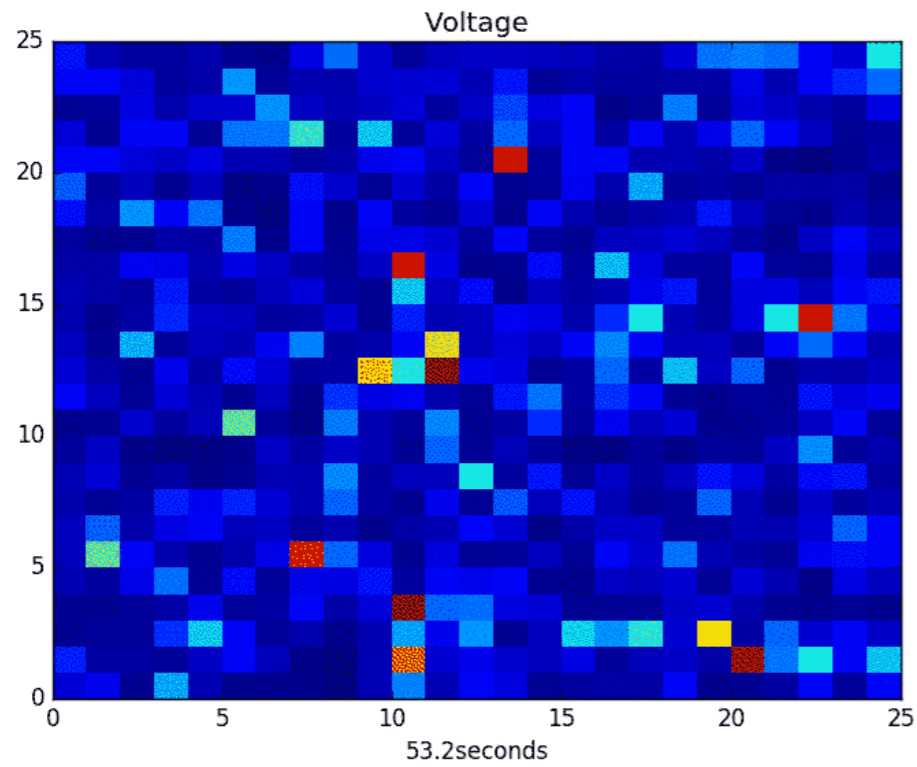
$g_{ach}=0.21$  nS



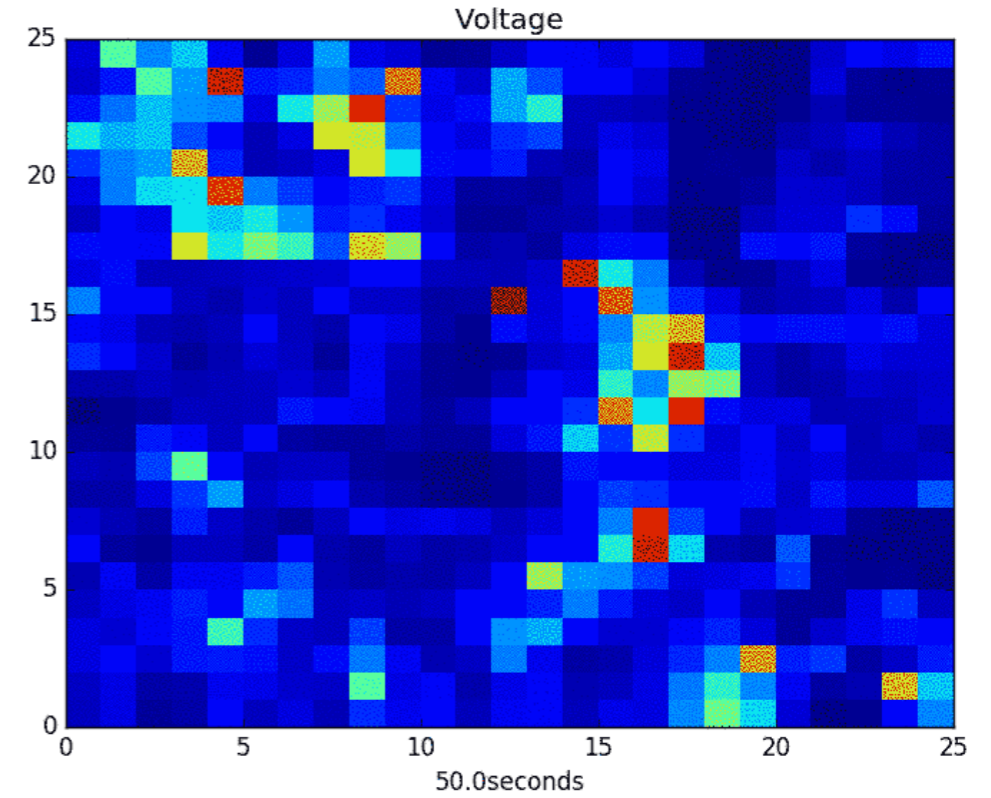
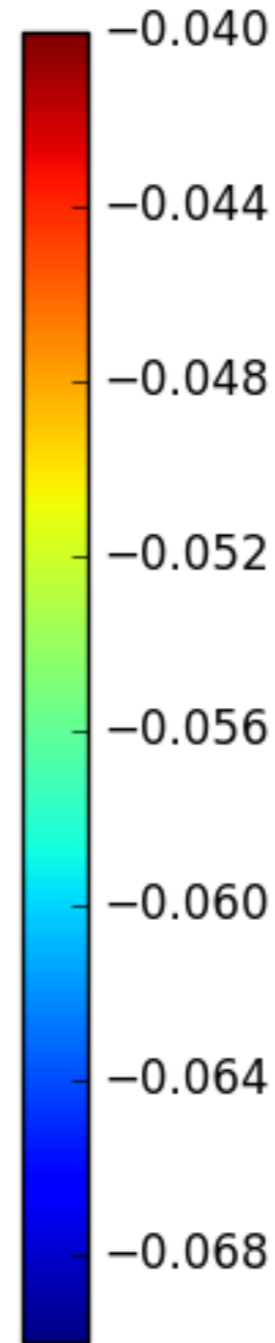
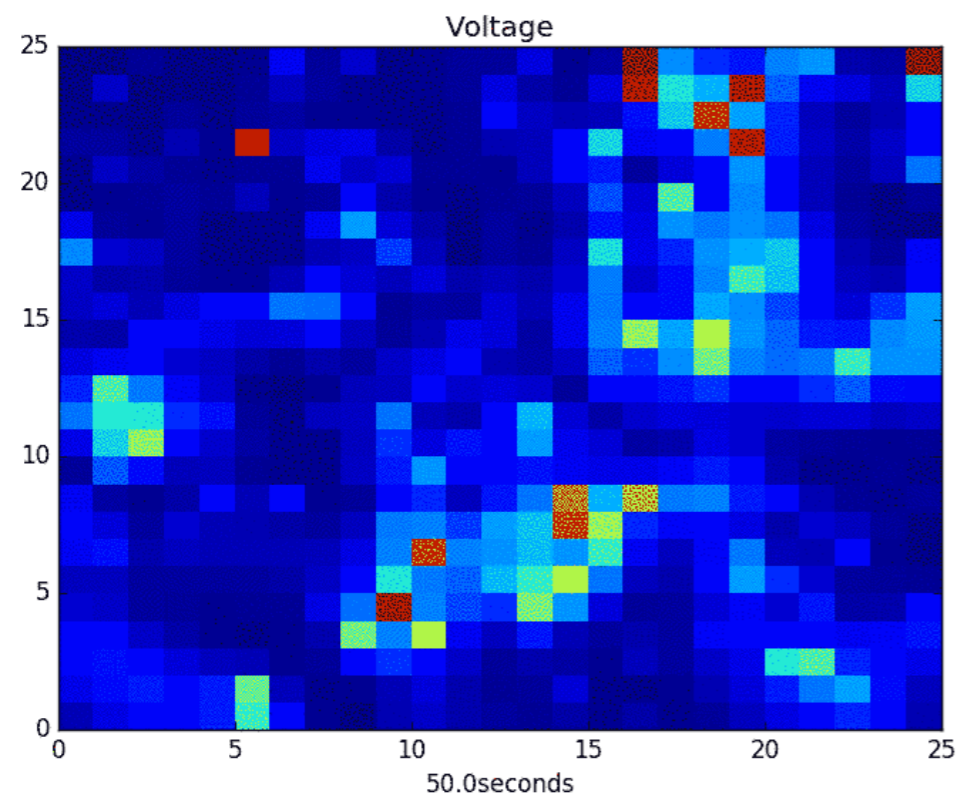
# Network of SACs : Simulated Voltage

Isolated Neurons

$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



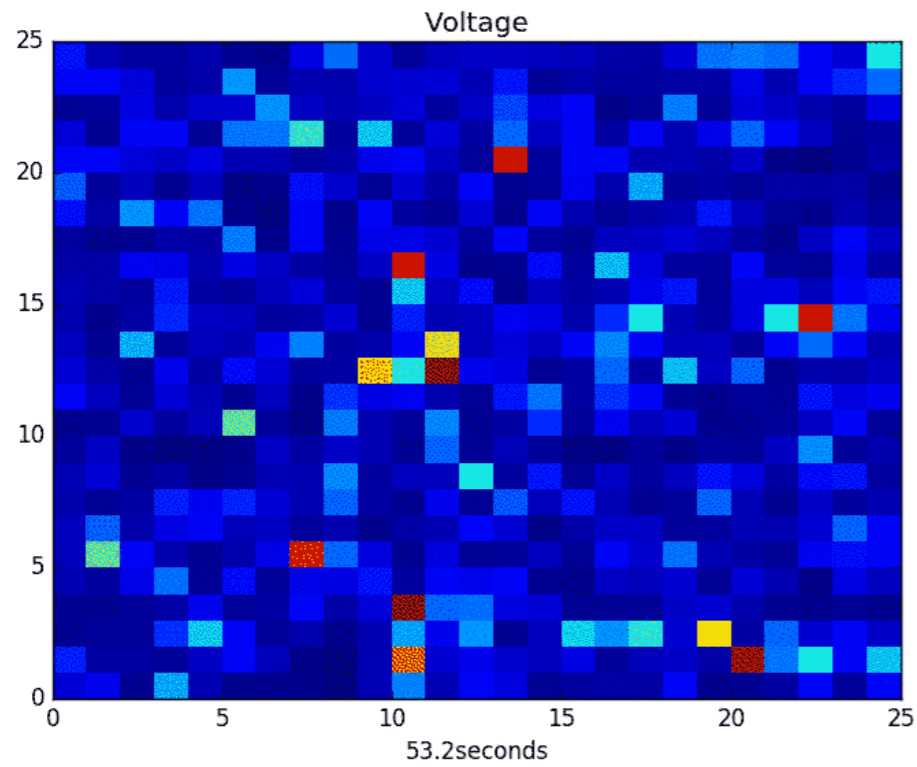
$g_{ach}=0.21$  nS



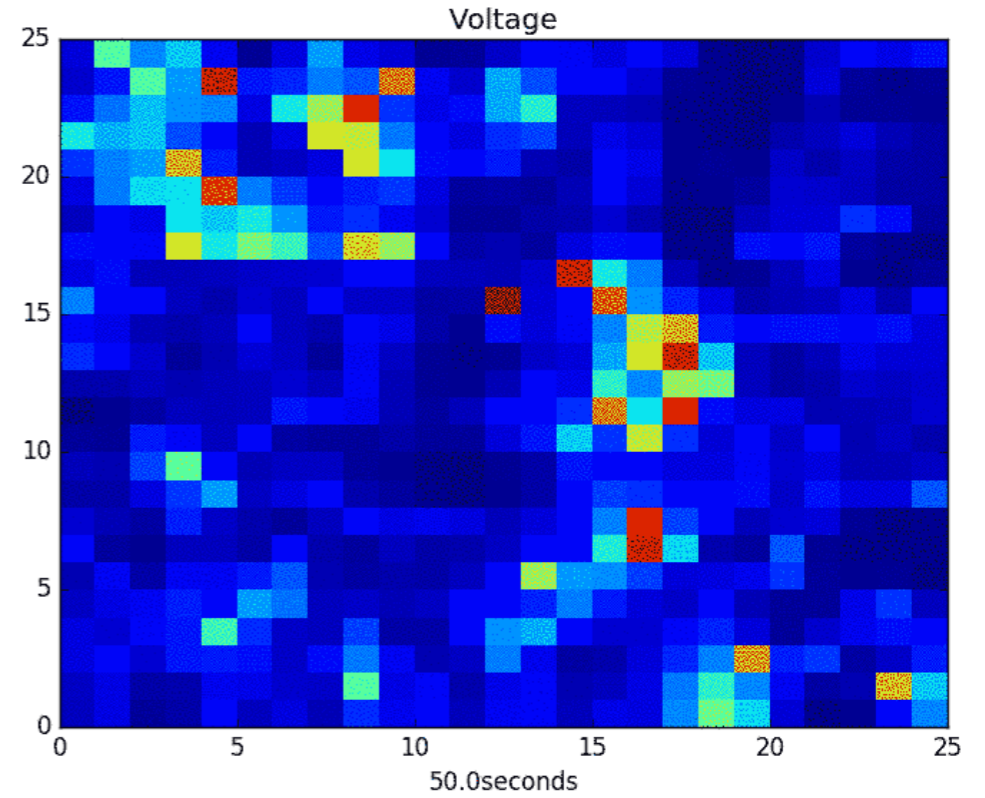
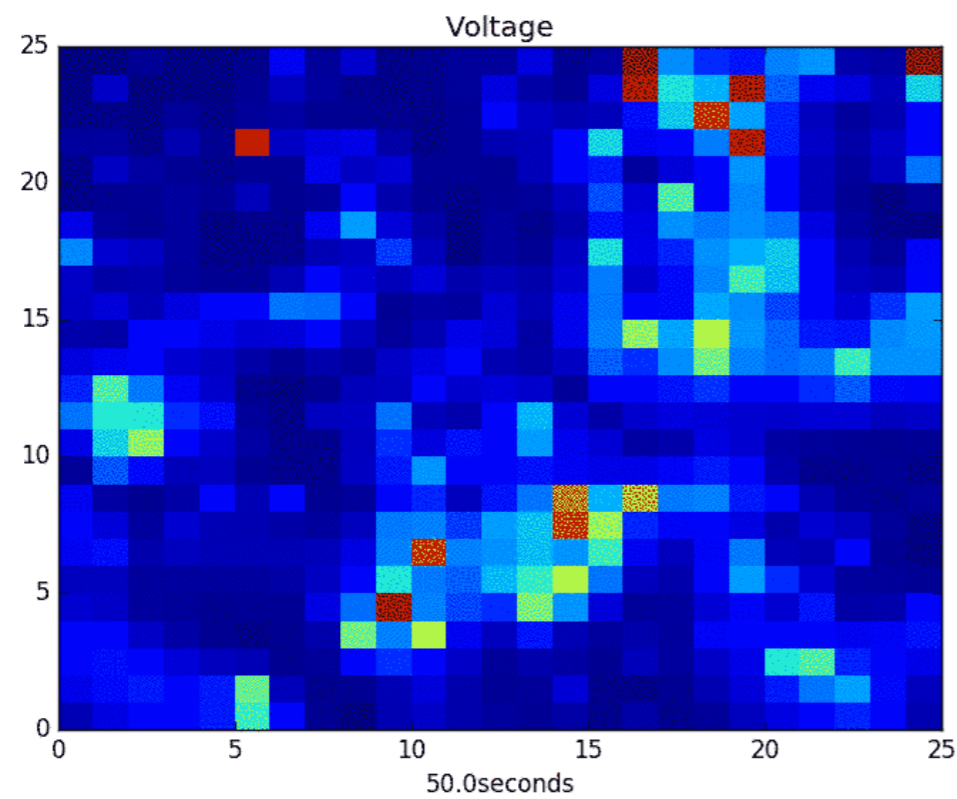
# Network of SACs : Simulated Voltage

Isolated Neurons

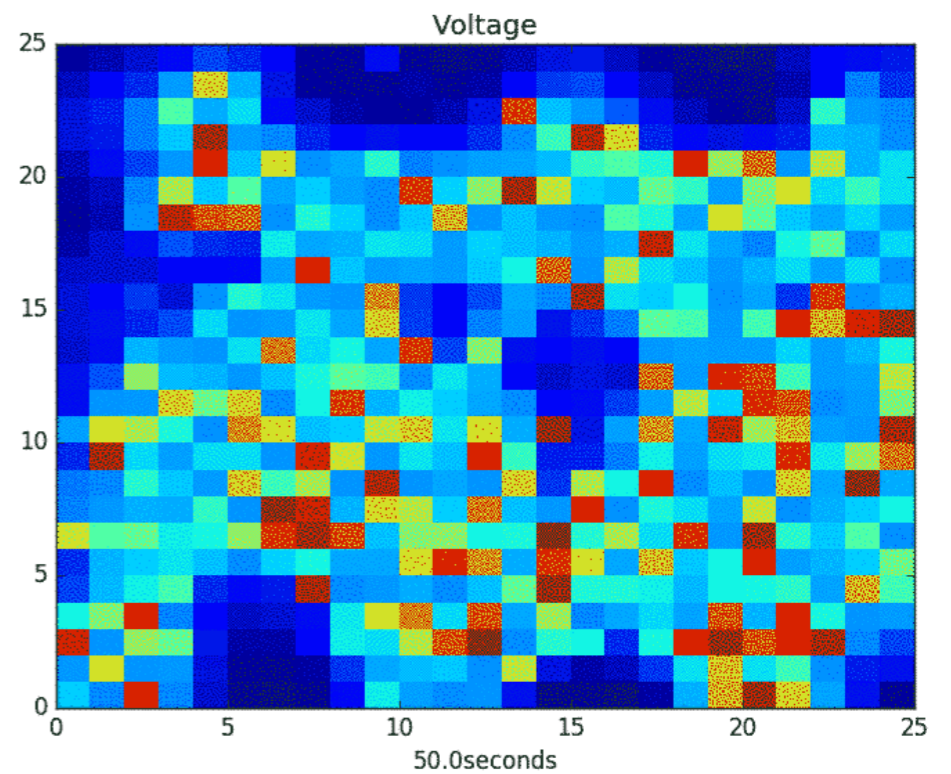
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS



$g_{ach}=0.21$  nS

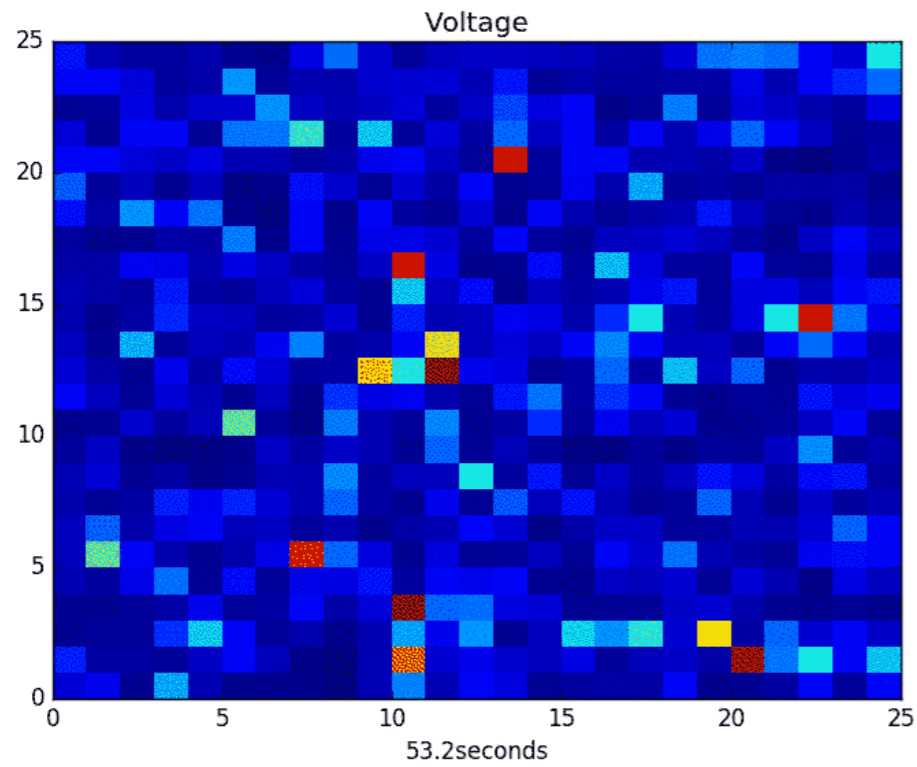




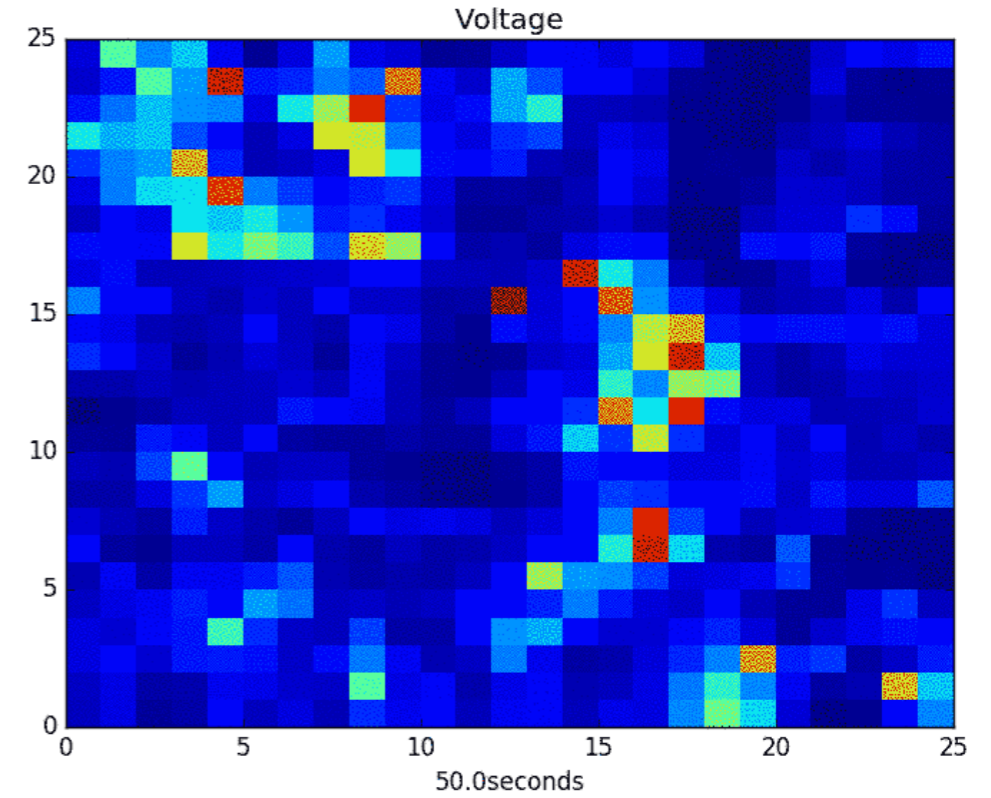
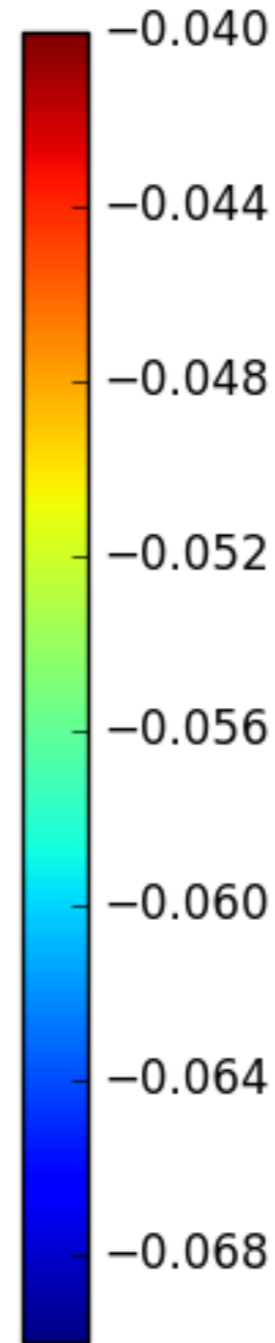
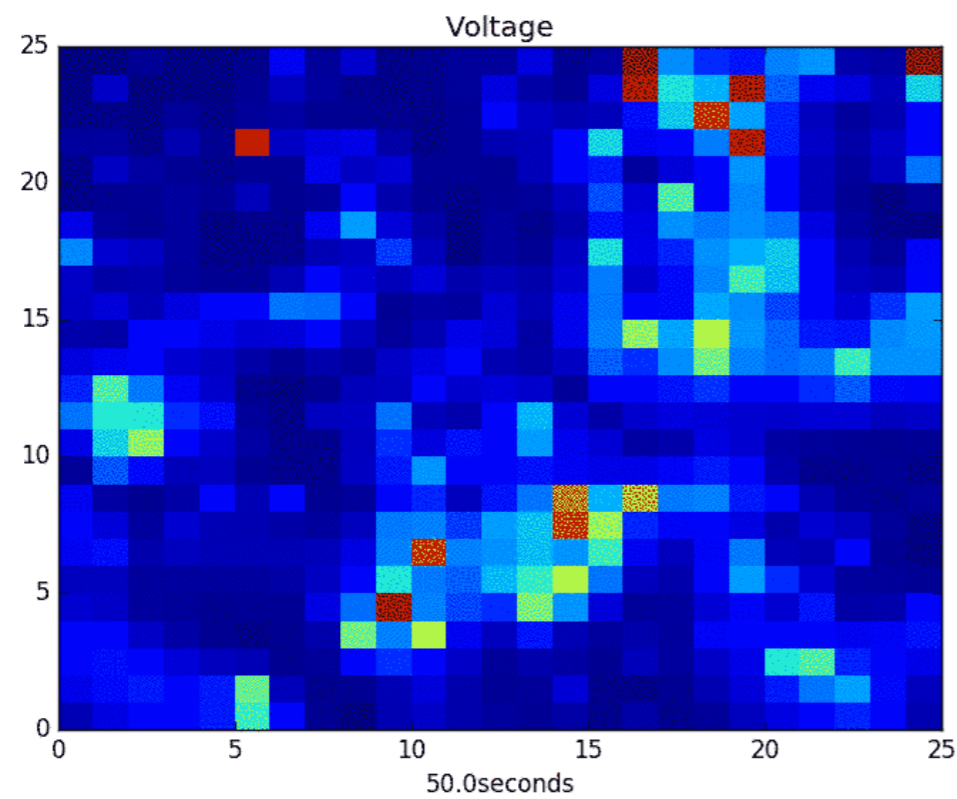
# Network of SACs : Simulated Voltage

Isolated Neurons

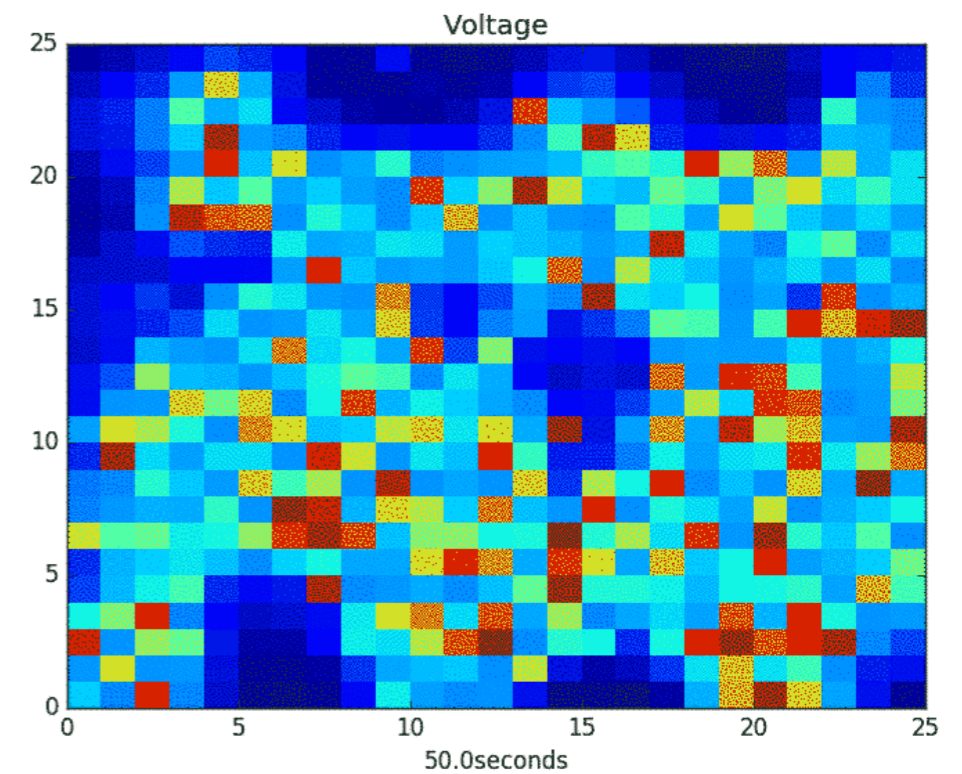
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

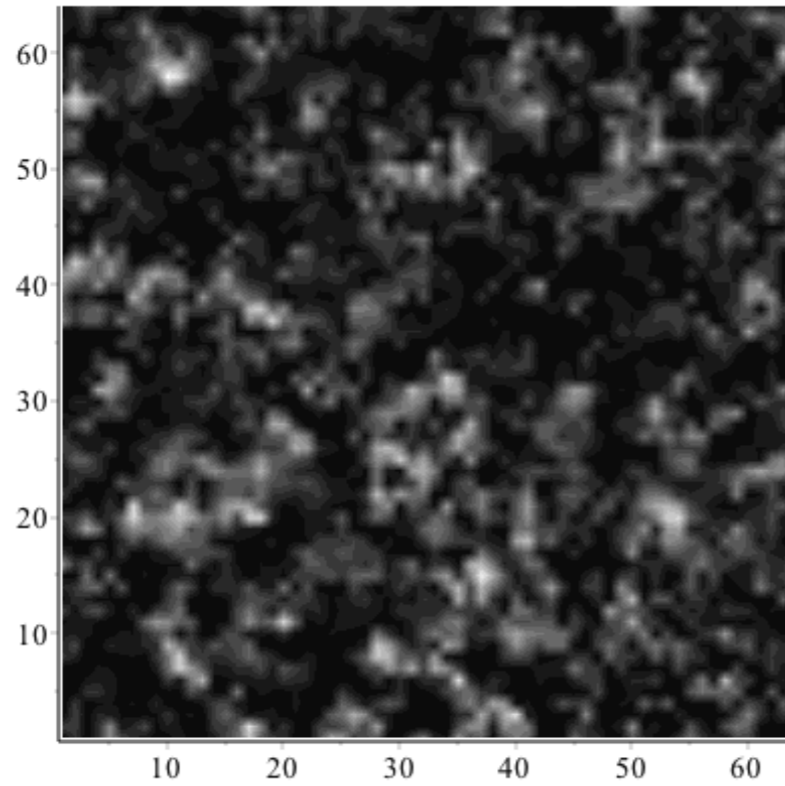


$g_{ach}=0.21$  nS

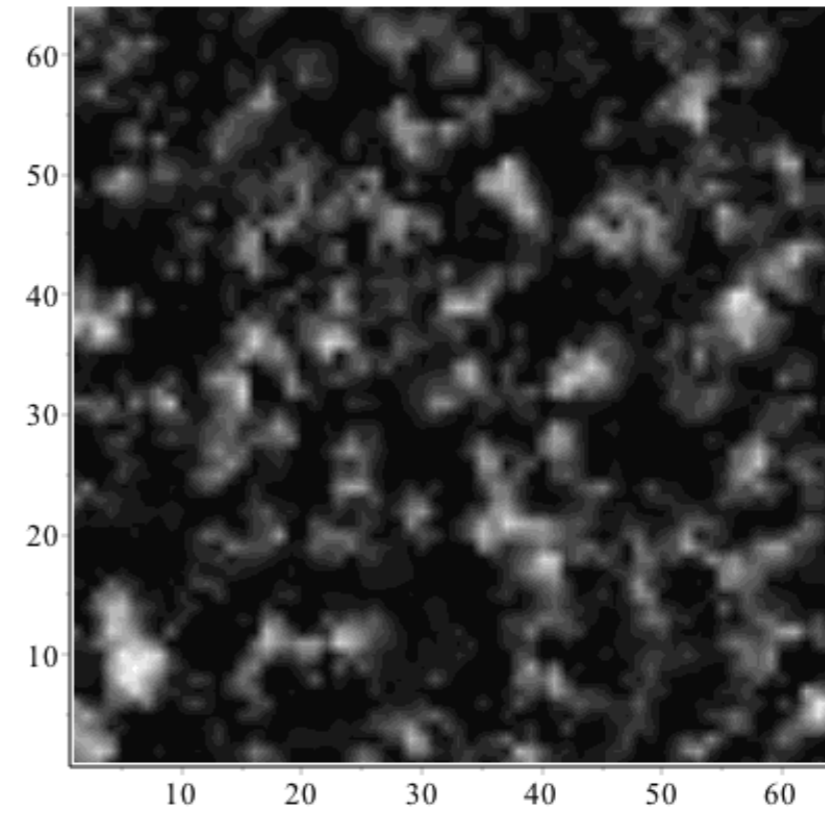


# Network of SACs : Simulated Calcium Concentration

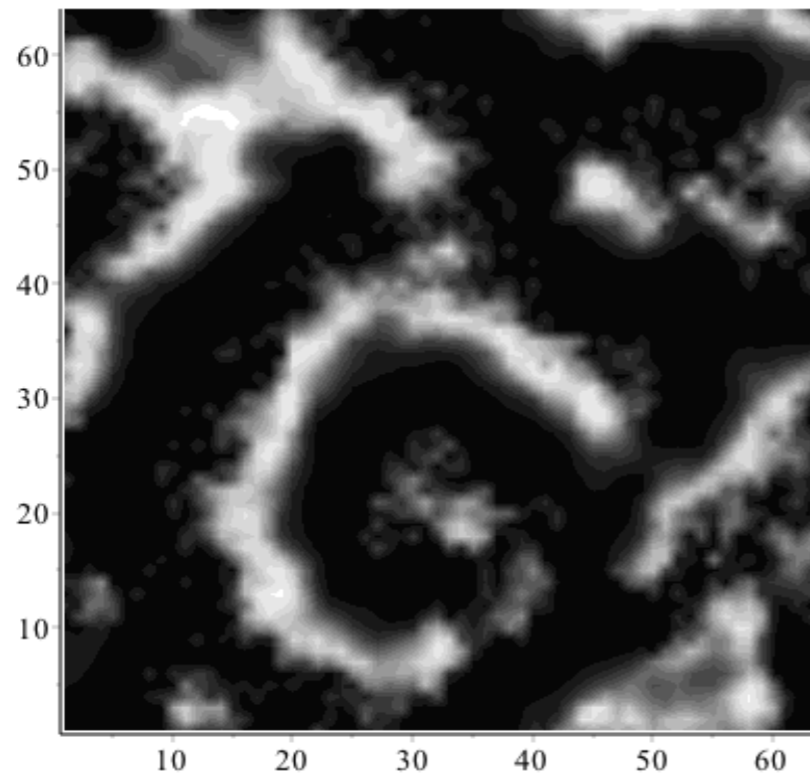
$g_{ach}=0.102$  nS



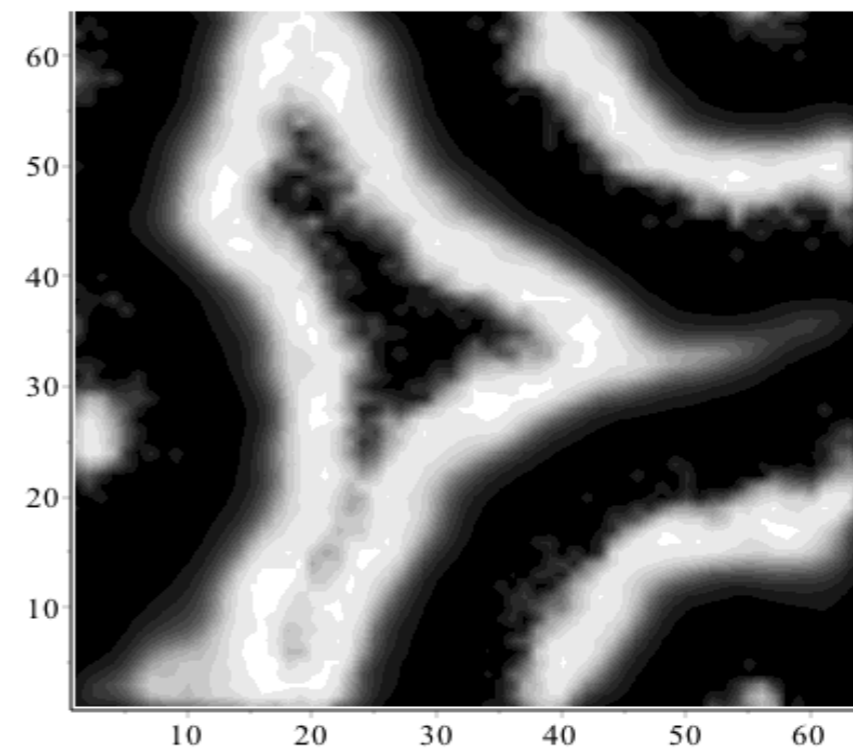
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

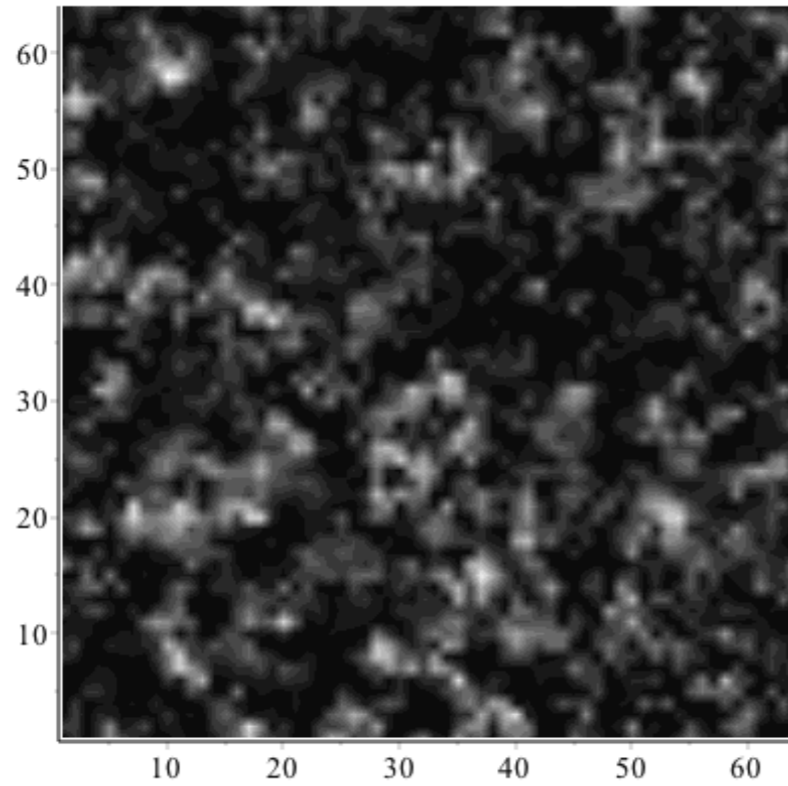


$g_{ach}=0.21$  nS

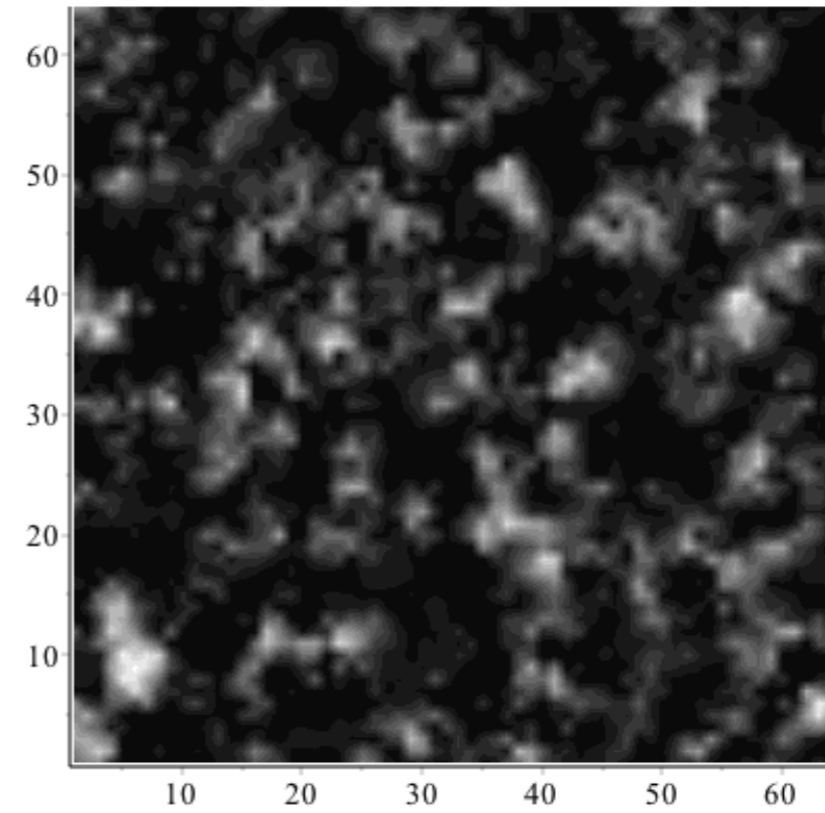


# Network of SACs : Simulated Calcium Concentration

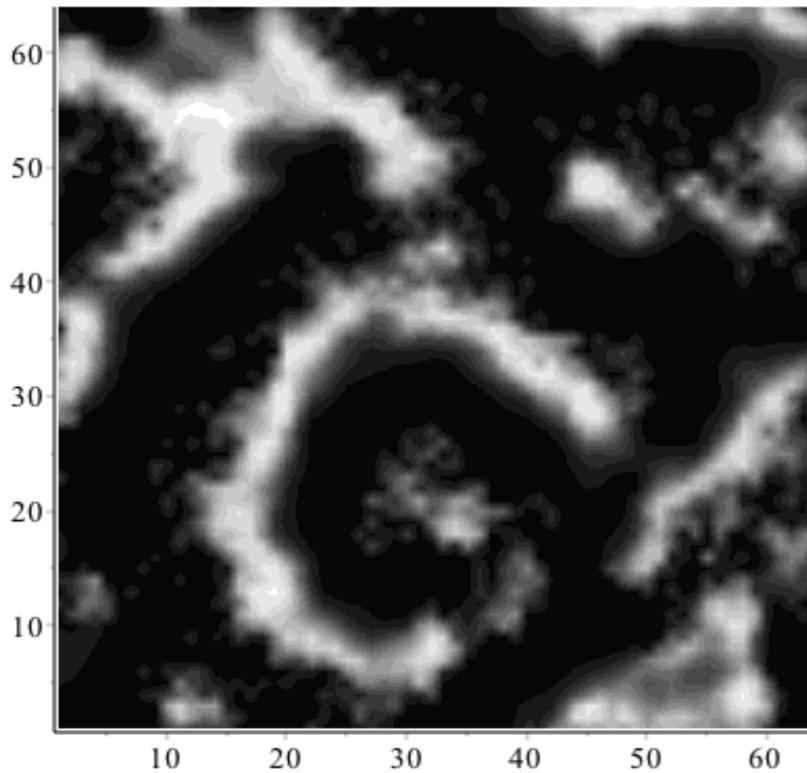
$g_{ach}=0.102$  nS



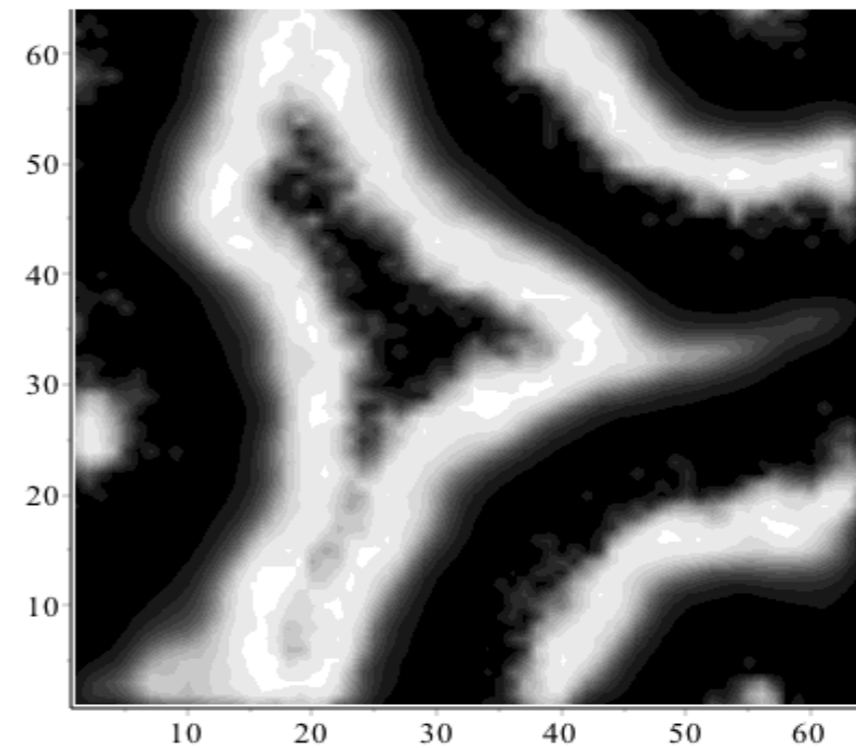
$g_{ach}=0.126$  nS



$g_{ach}=0.168$  nS

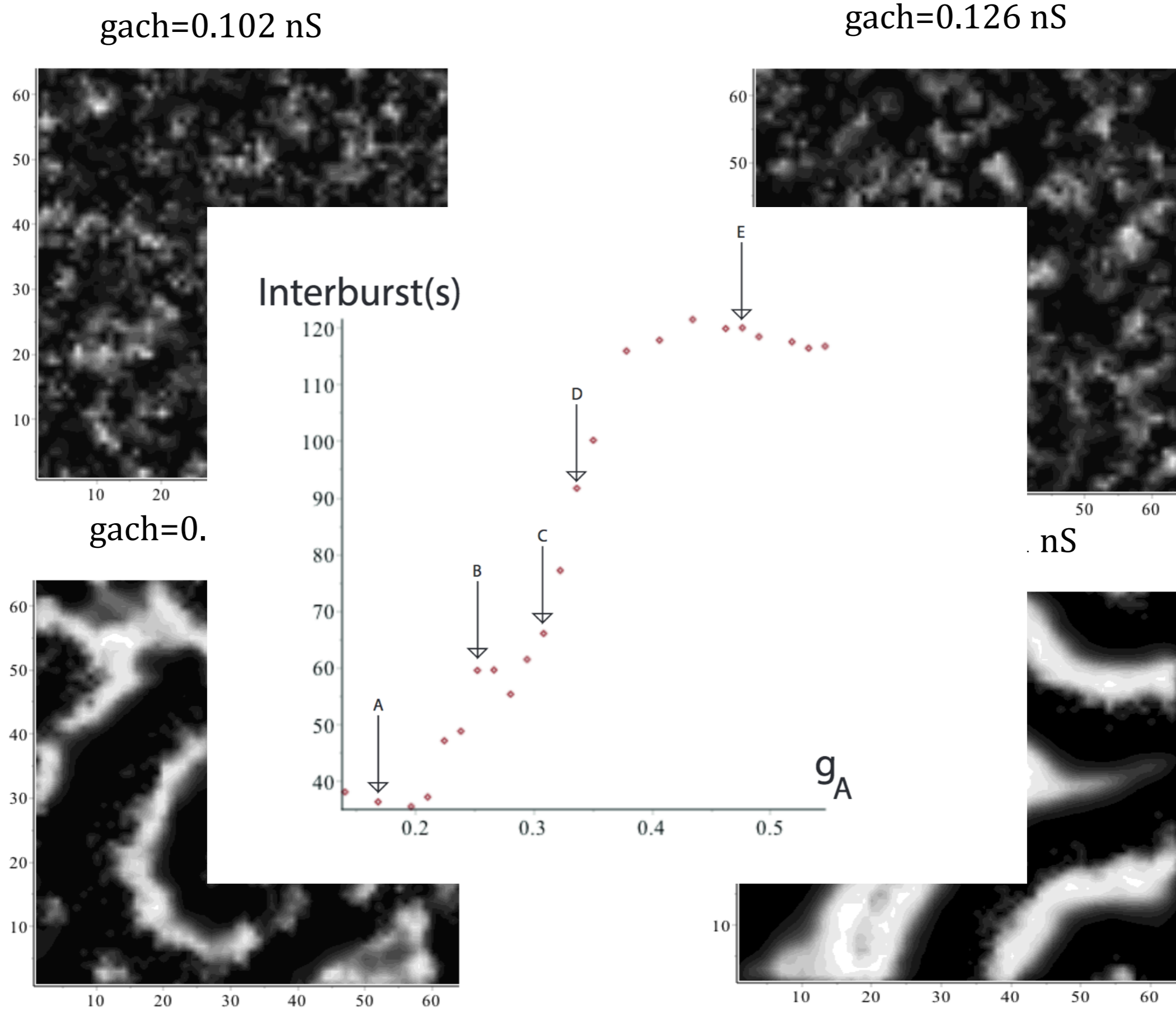


$g_{ach}=0.21$  nS

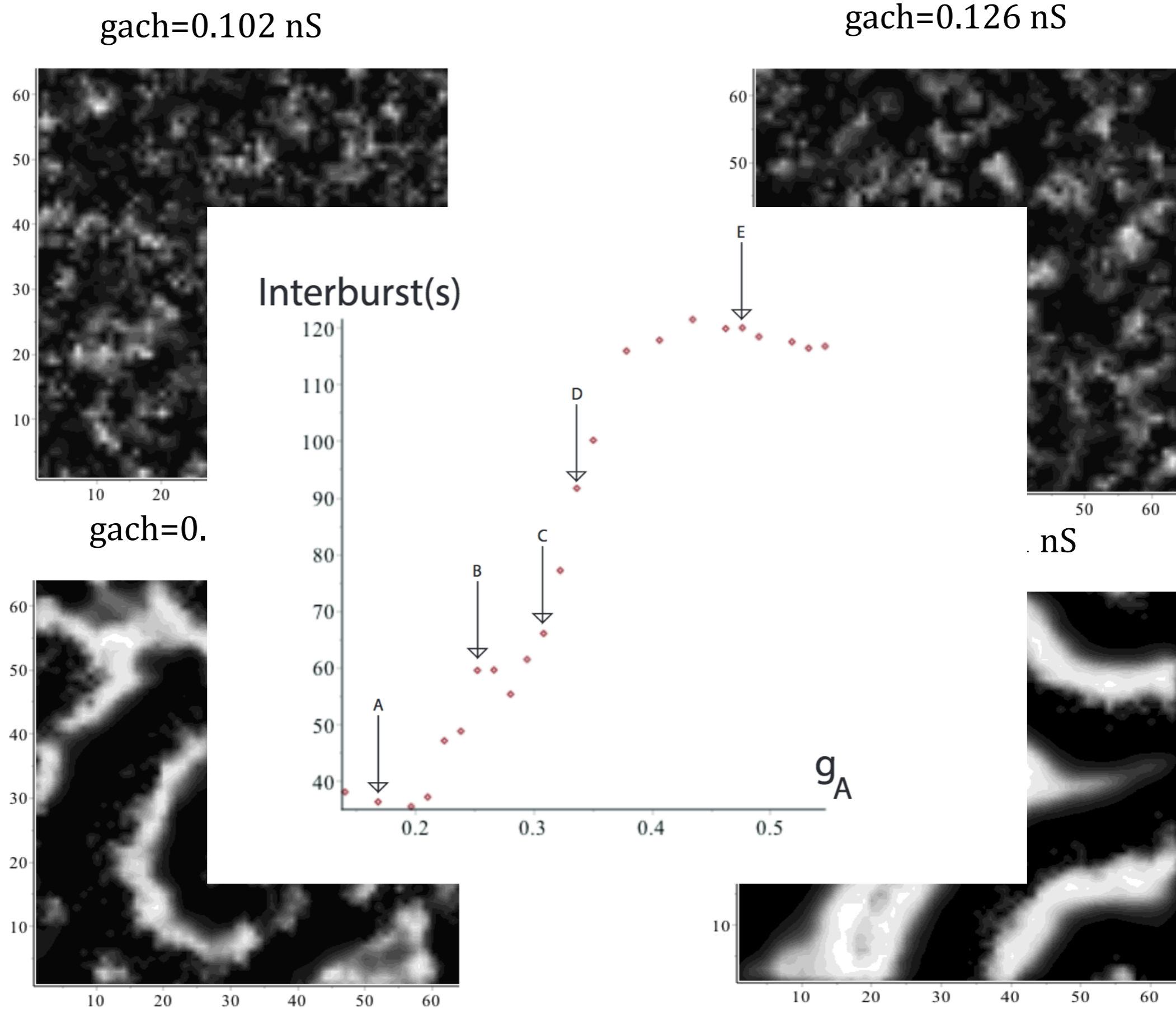




# Network of SACs : Simulated Calcium Concentration



# Network of SACs : Simulated Calcium Concentration

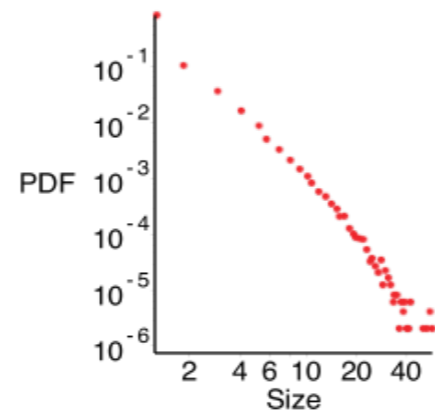
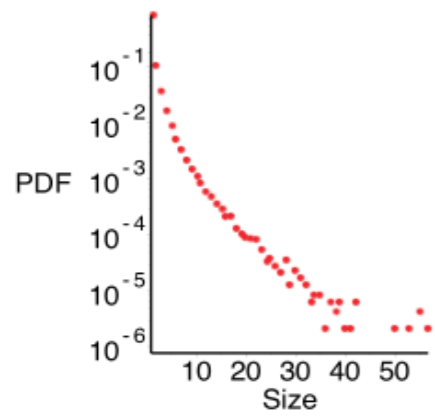


# Waves size distribution

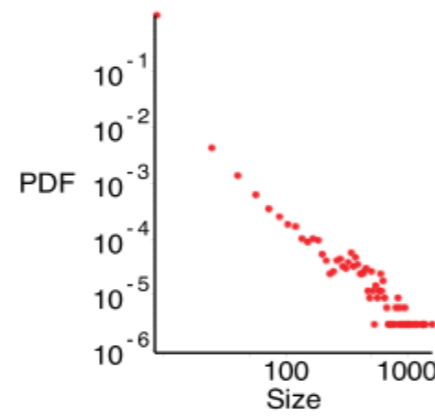
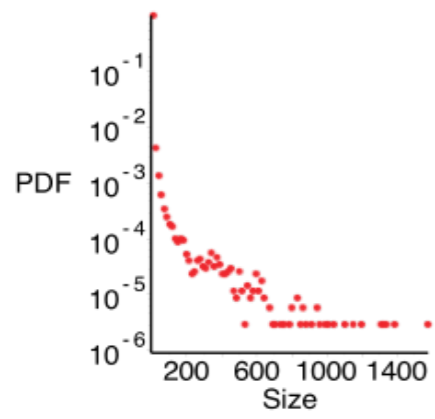
lin-log

log-log

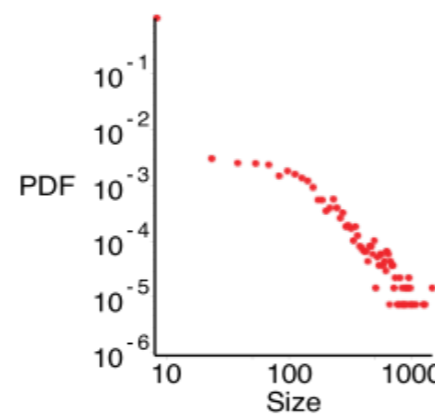
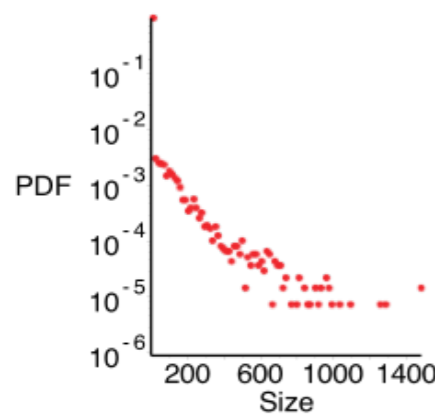
A



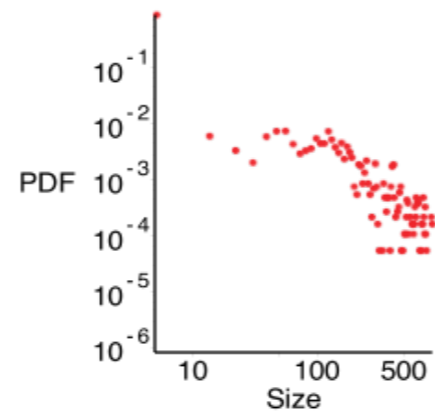
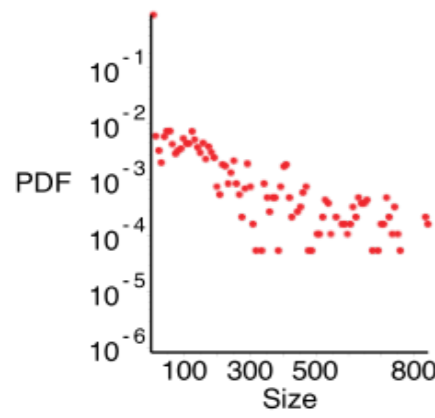
B



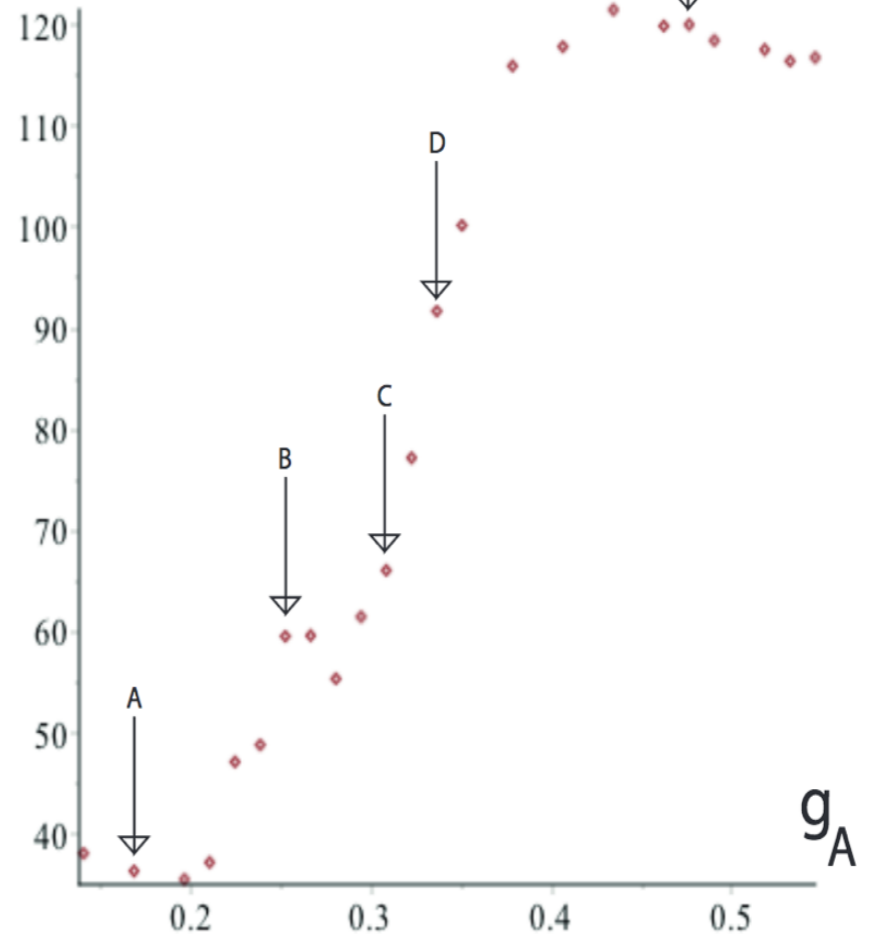
C



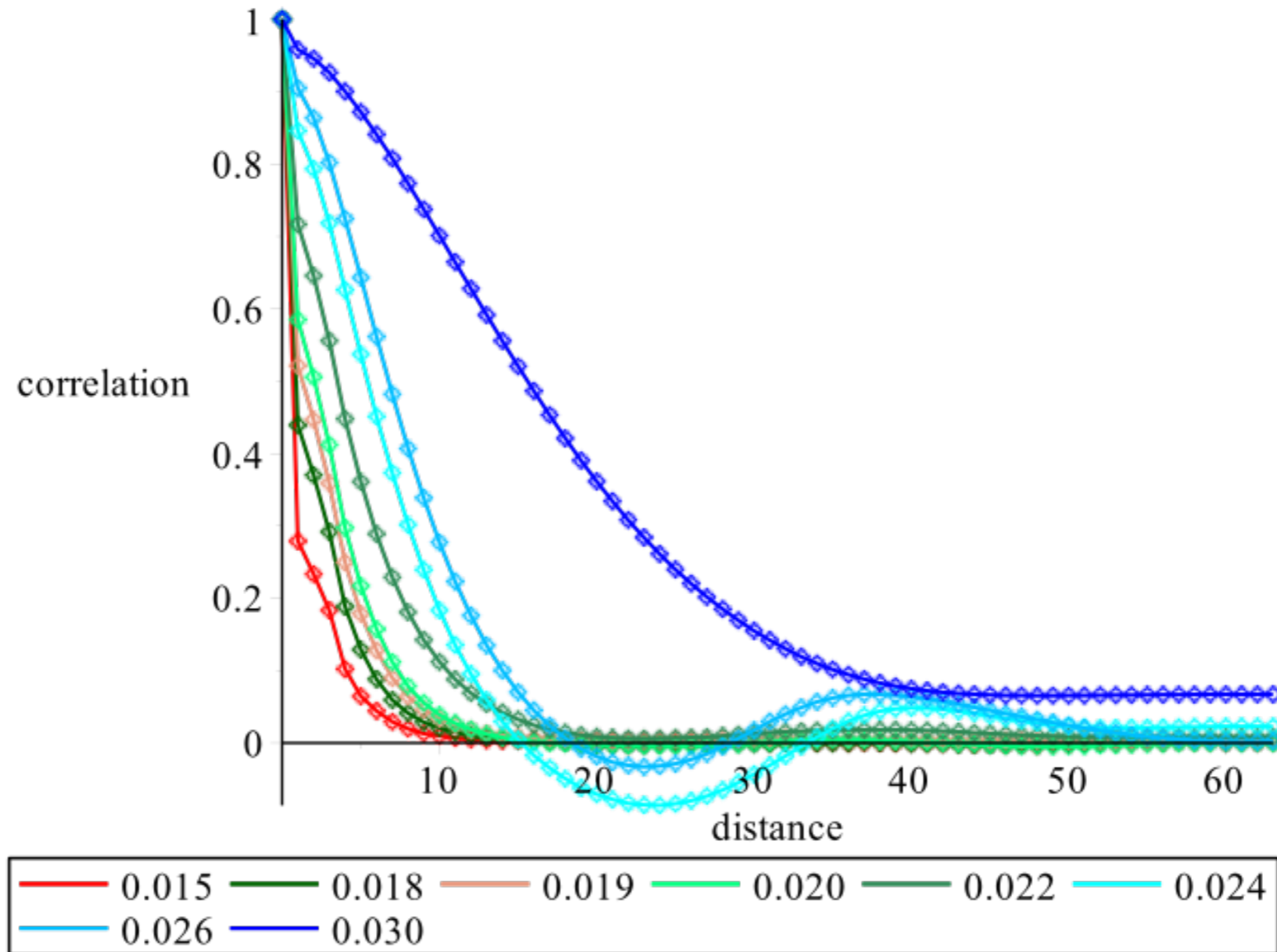
E



Interburst(s)



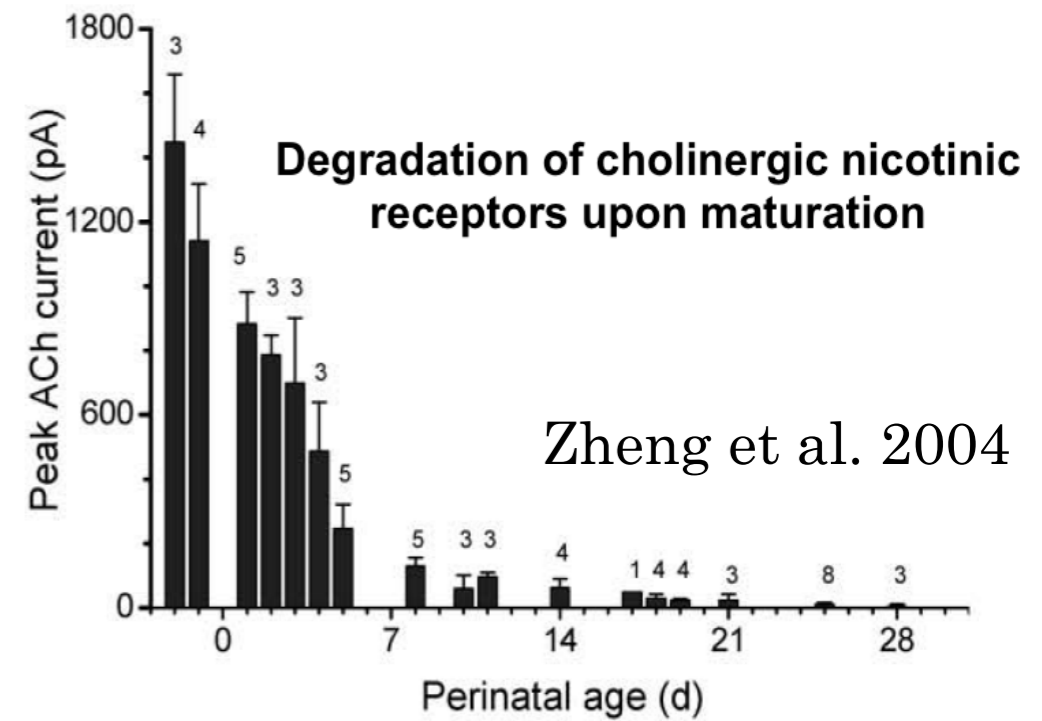
# Distance Pairwise Correlations



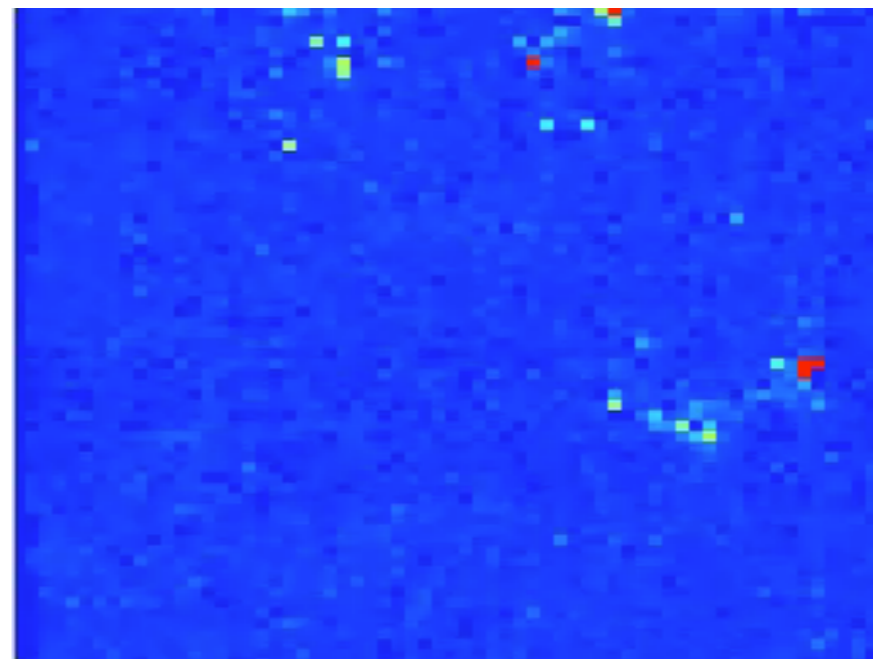


# Variability within retinal waves

## ii) Development

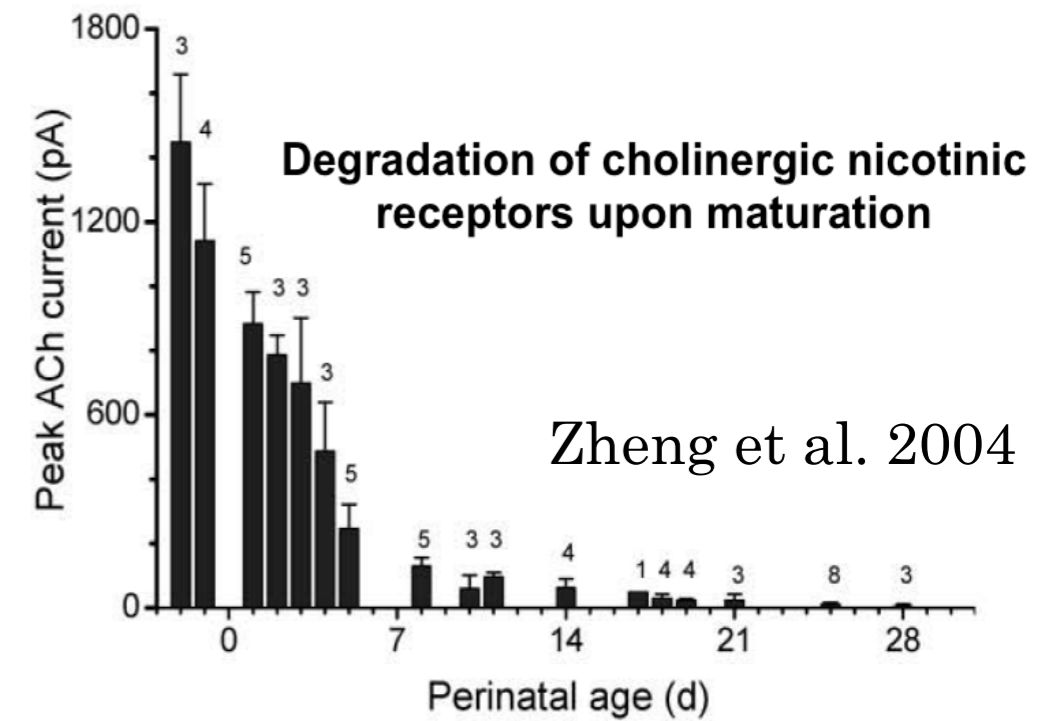


## iv) Spatial Variability

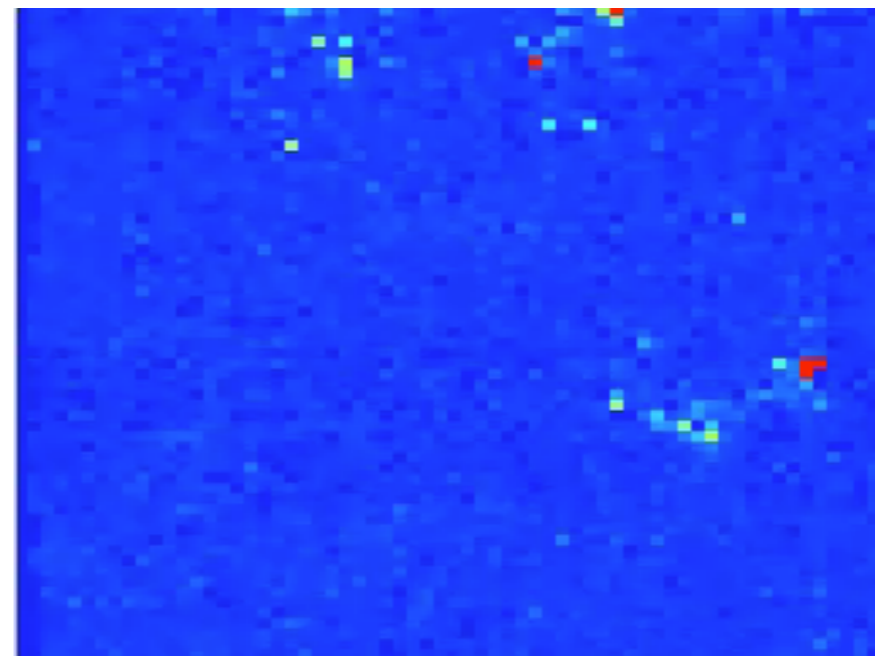


# Variability within retinal waves

## ii) Development



## iv) Spatial Variability

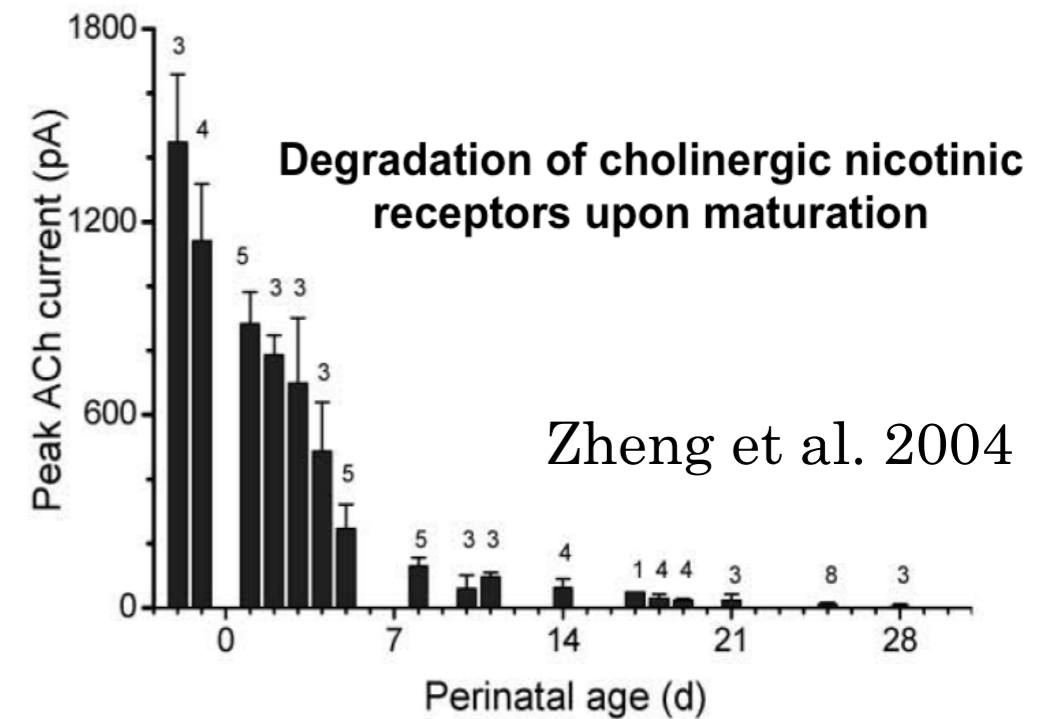


# Variability within retinal waves

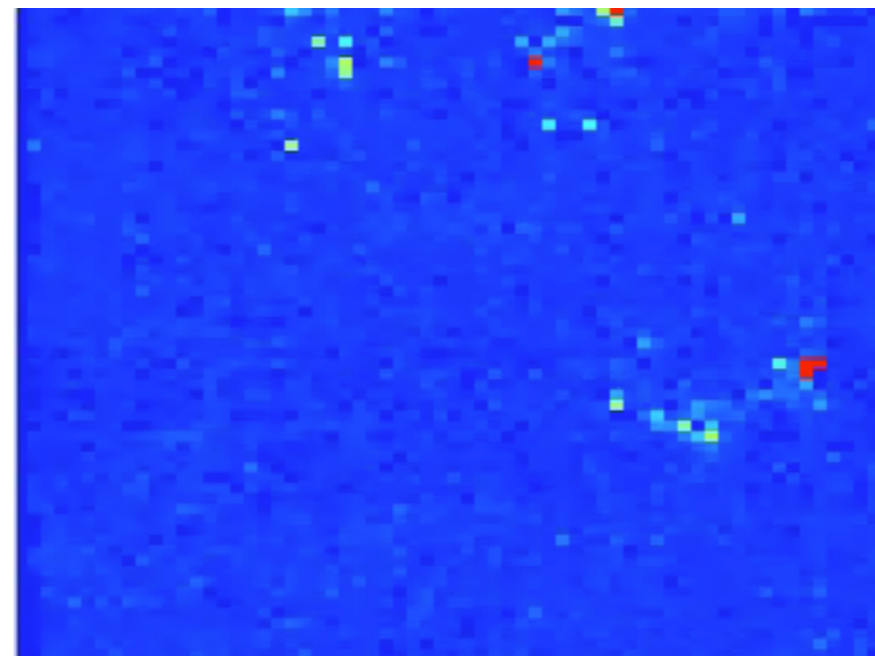
## Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.
2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)
3. Waves cannot cross each others => characteristic length, **exponential distribution**.
4. There is a critical point where waves are **power law** distributed.

## ii) Development



## iv) Spatial Variability





# Variability within retinal waves

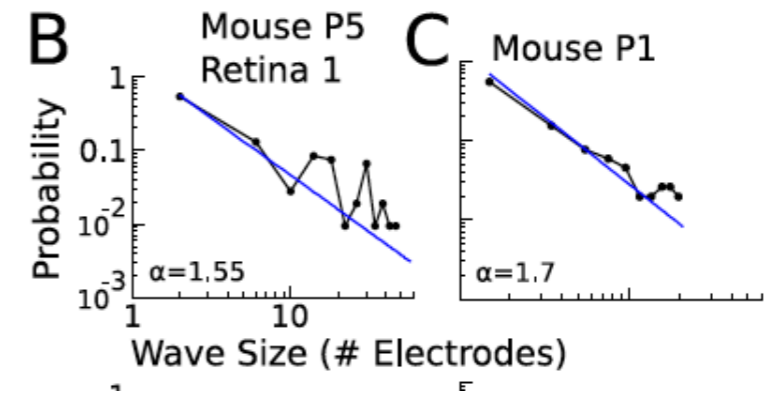
## Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.
2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)
3. Waves cannot cross each others => characteristic length, **exponential distribution**.
4. There is a critical point where waves are **power law** distributed.

# Variability within retinal waves

## Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.
2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)
3. Waves cannot cross each others => characteristic length, **exponential distribution**.
4. There is a critical point where waves are **power law** distributed.



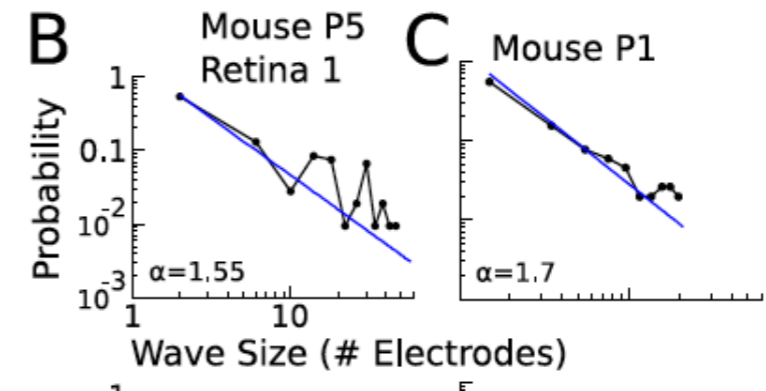
Hennig et al. 2009



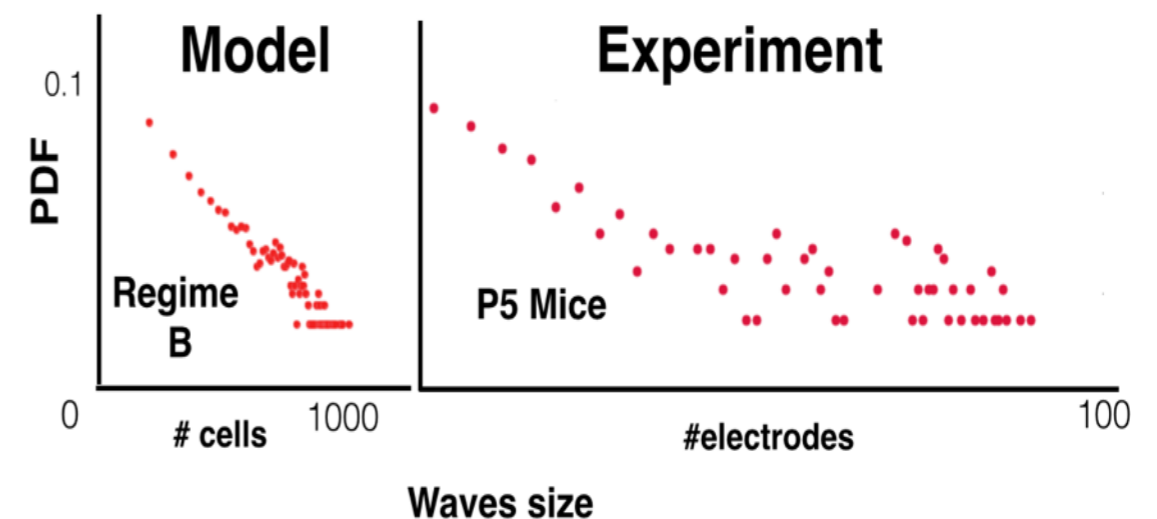
# Variability within retinal waves

## Analytical results

1. There is a **critical** transition for the Acetylcholine conductance, given by the bifurcation analysis, where **waves start to appear**.
2. A wave propagates in the sAHP profile left by previous waves (**random landscape**)
3. Waves cannot cross each others => characteristic length, **exponential distribution**.
4. There is a critical point where waves are **power law** distributed.



Hennig et al. 2009



**Experimentally varying Ach conductance  
(Data D. Karvouniari + Institut de la Vision)**

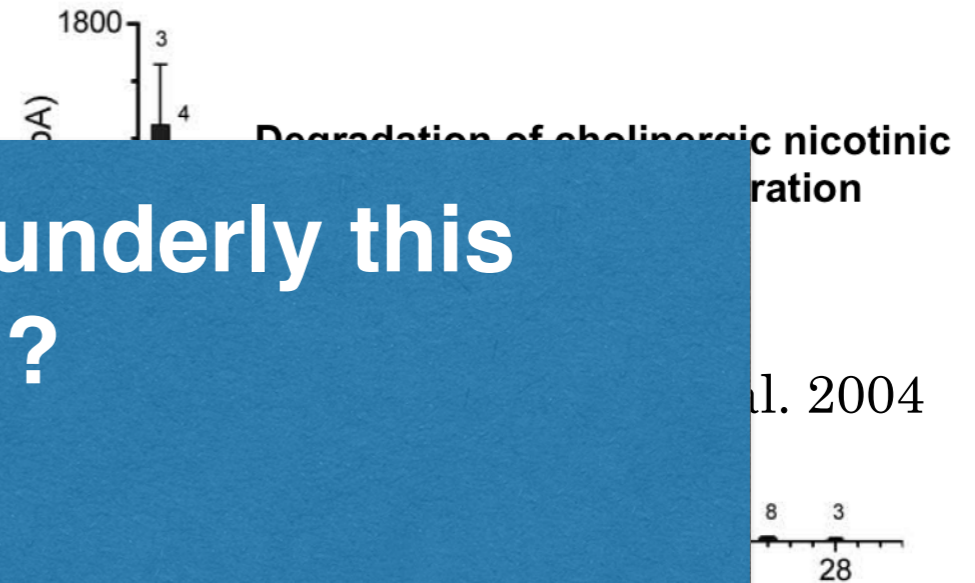


# Variability within retinal waves

## i) Across species



## ii) Development



Which mechanisms underly this variability ?

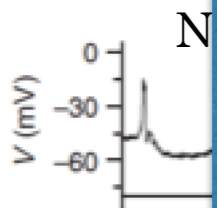
Randomness ?

Genetics ?

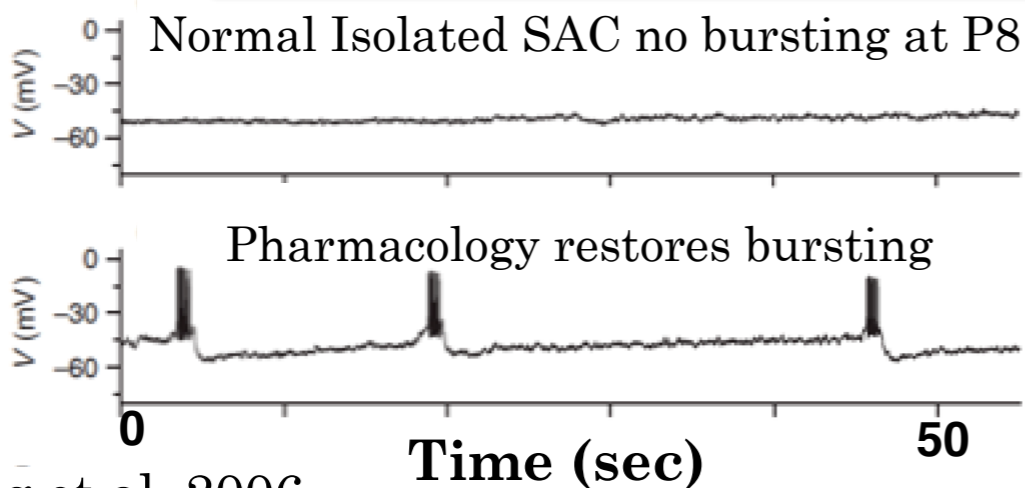
Non linear dynamics ?

## iii)

P4



P8



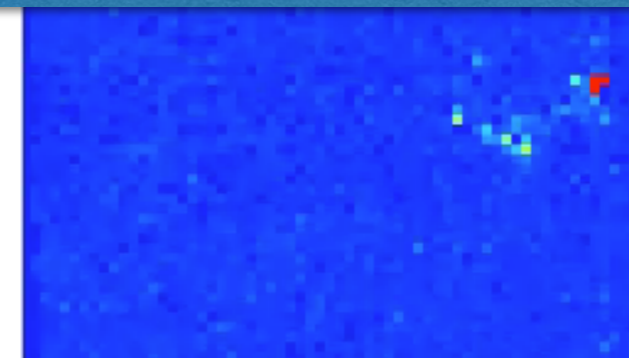
Zheng et al. 2006

Time (sec)

50

ability

have variable shapes due to a refractory mechanism which controls their borders.



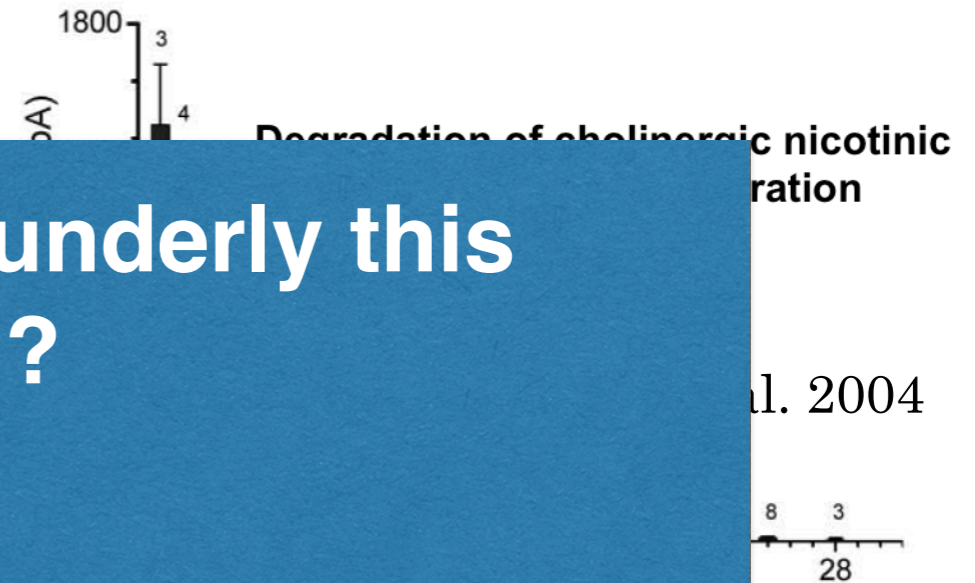
Maccione et al. 2014

# Variability within retinal waves

## i) Across species



## ii) Development



Which mechanisms underly this variability ?

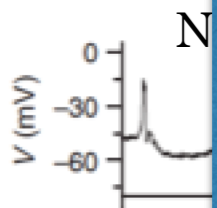
Randomness ?

Genetics ?

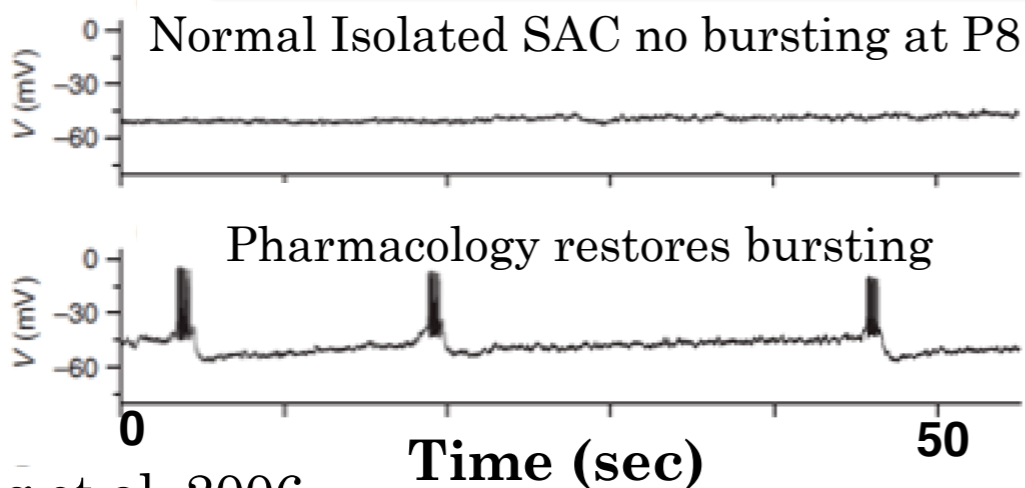
Non linear dynamics ?

## iii)

P4



P8



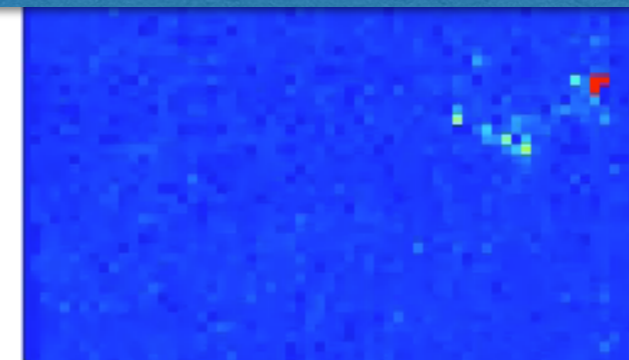
Zheng et al. 2006

Time (sec)

50

ability

have variable shapes due to a refractory mechanism which controls their borders.

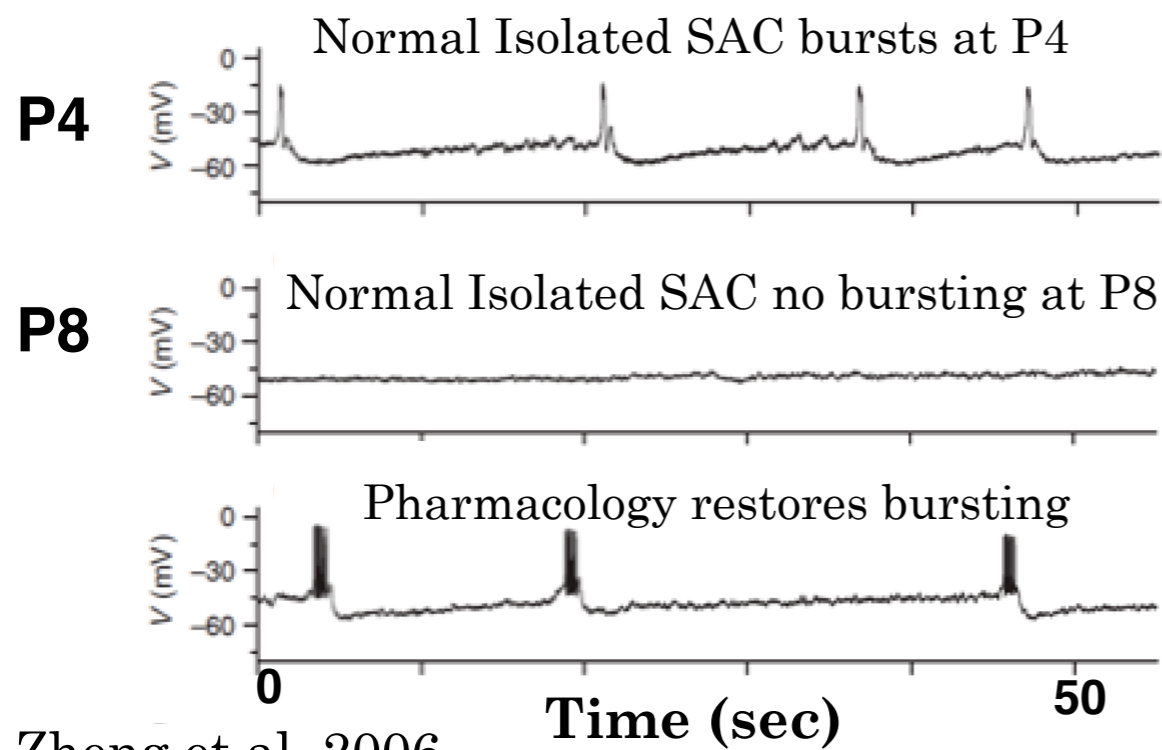


Maccione et al. 2014

# Variability within retinal waves

# Variability within retinal waves

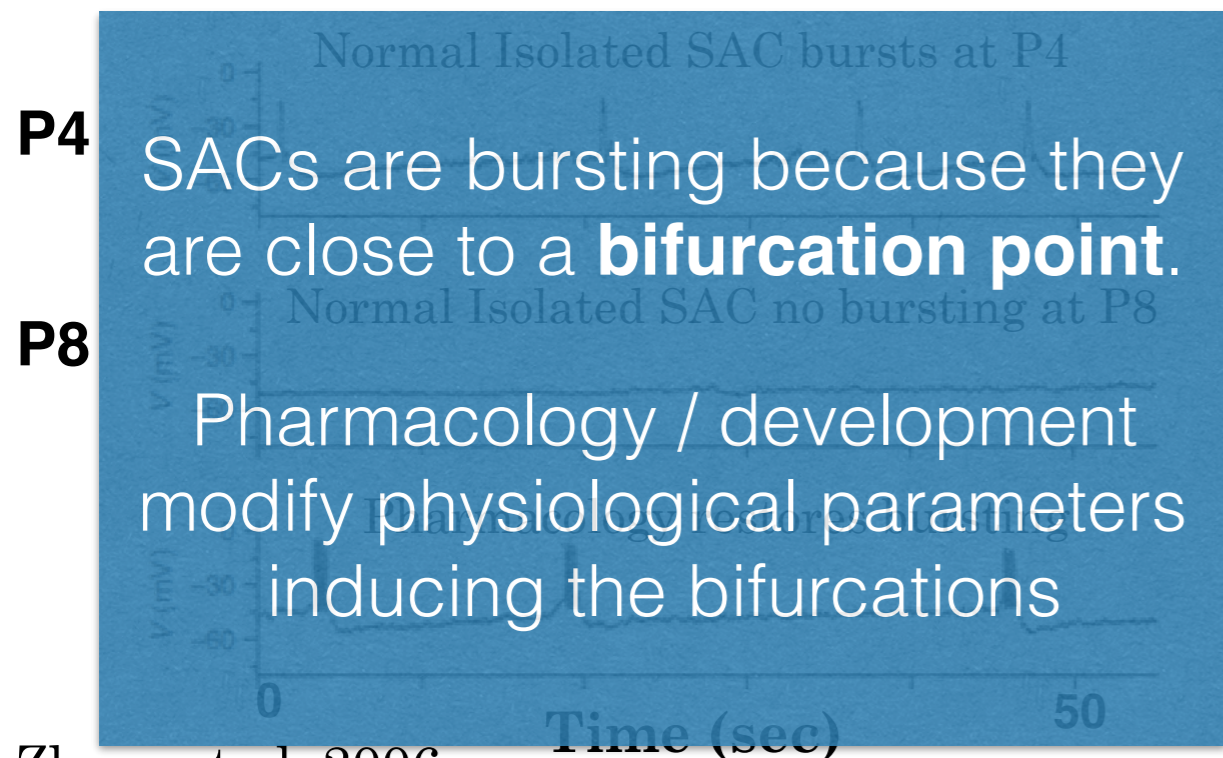
## iii) Pharmacology





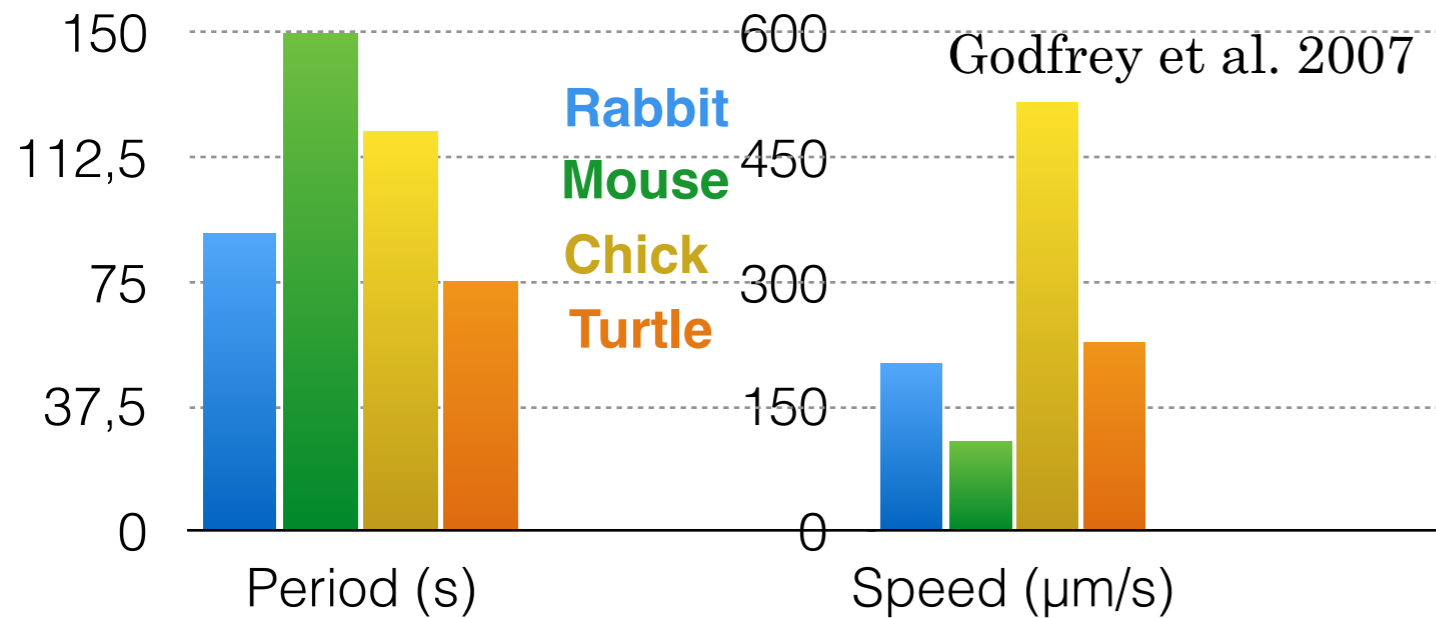
# Variability within retinal waves

## iii) Pharmacology

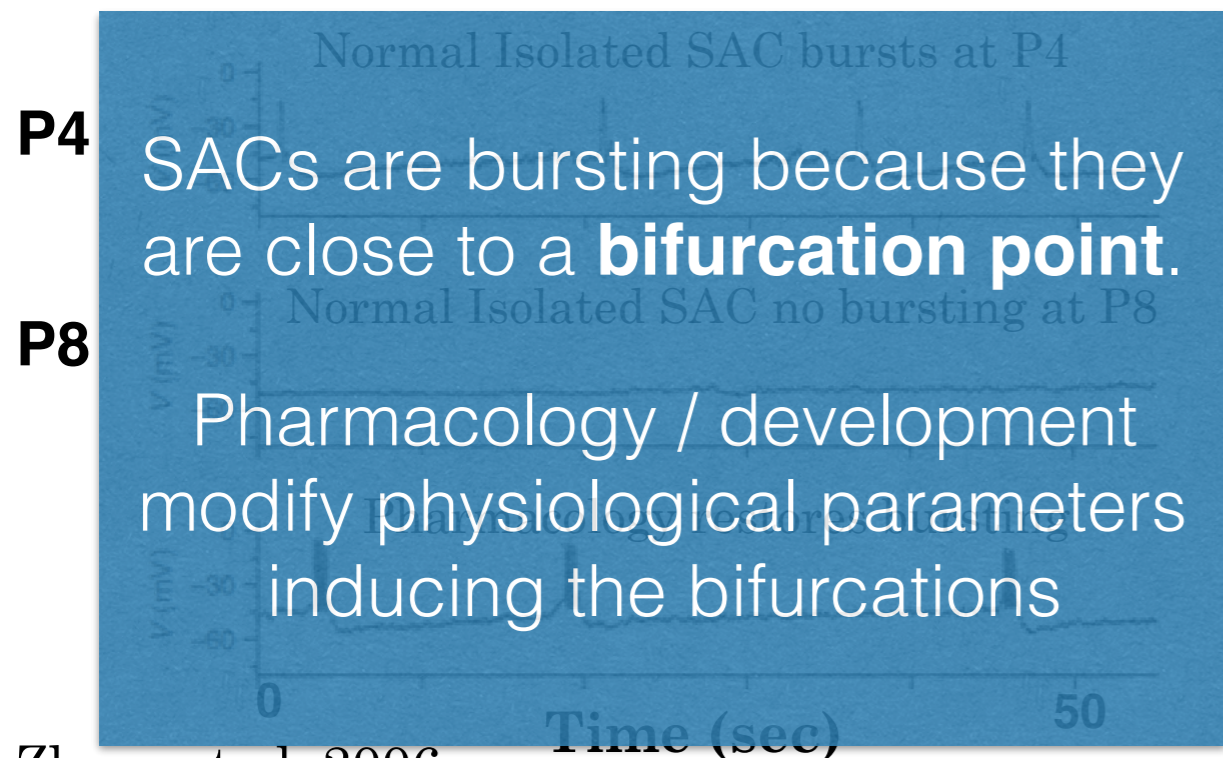


# Variability within retinal waves

## i) Across species



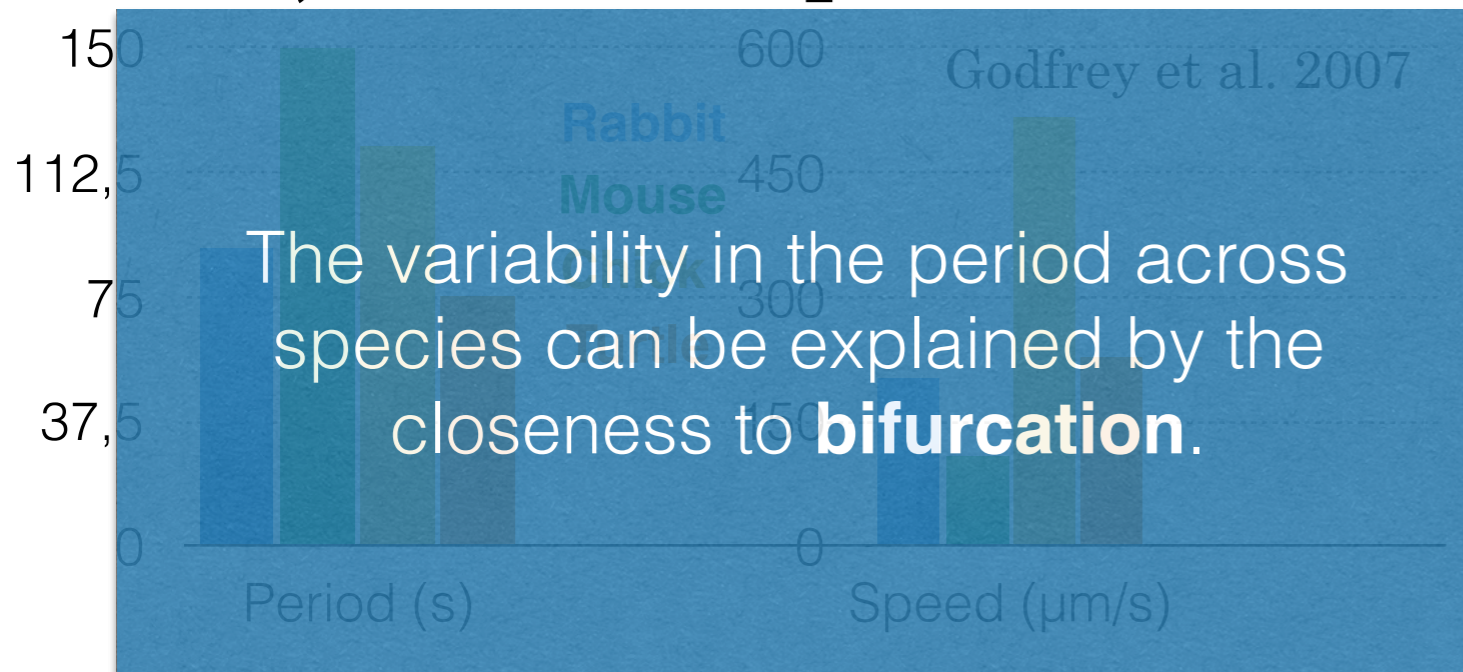
## iii) Pharmacology



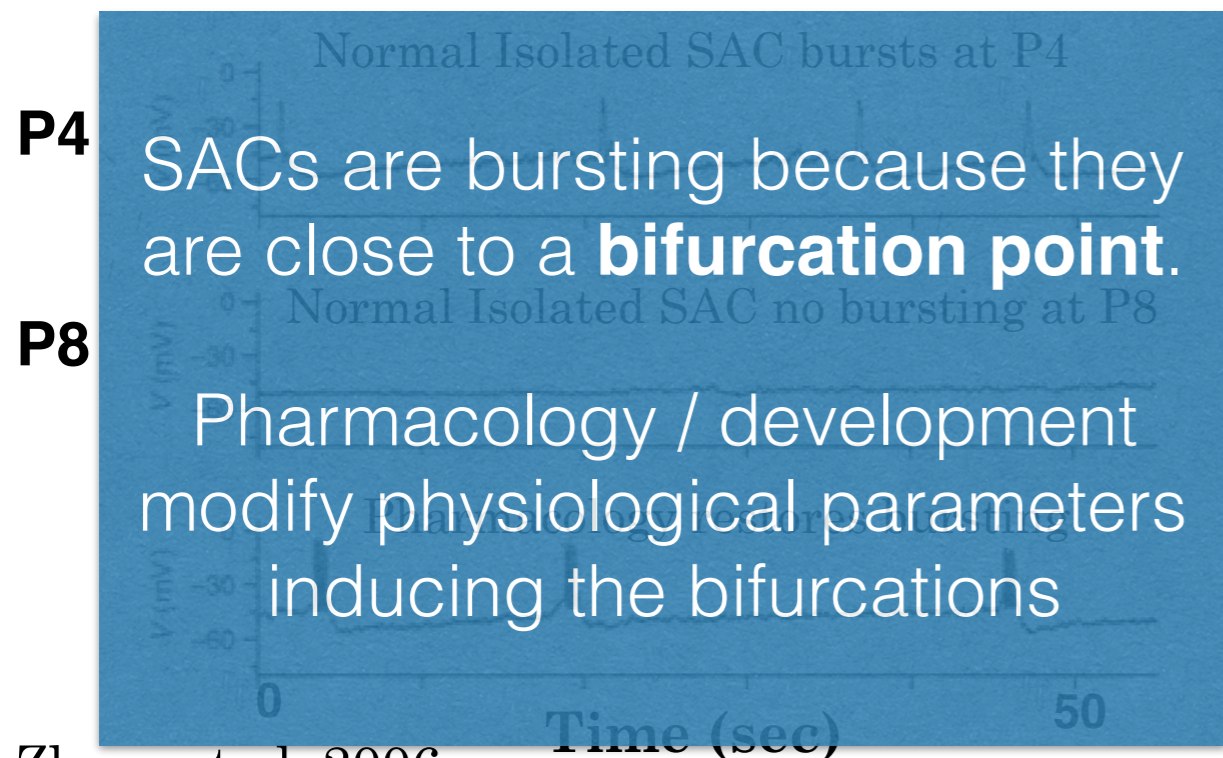


# Variability within retinal waves

## i) Across species

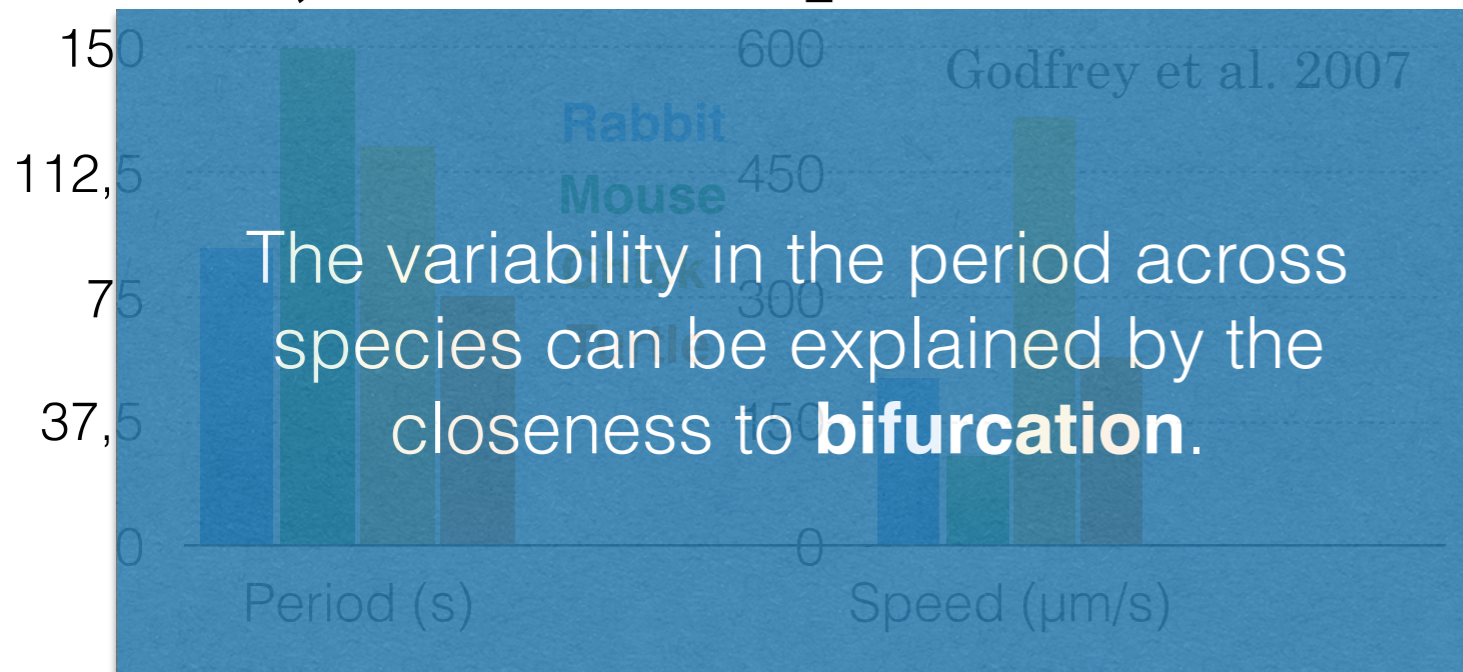


## iii) Pharmacology

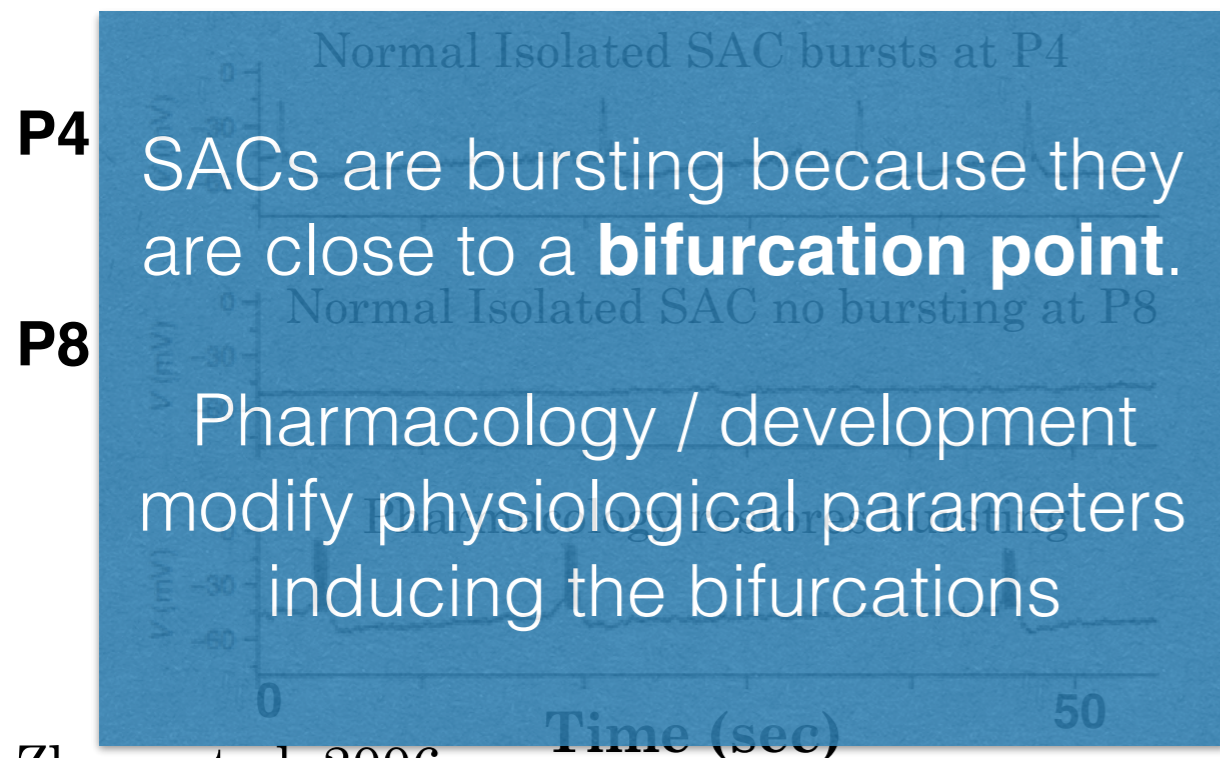


# Variability within retinal waves

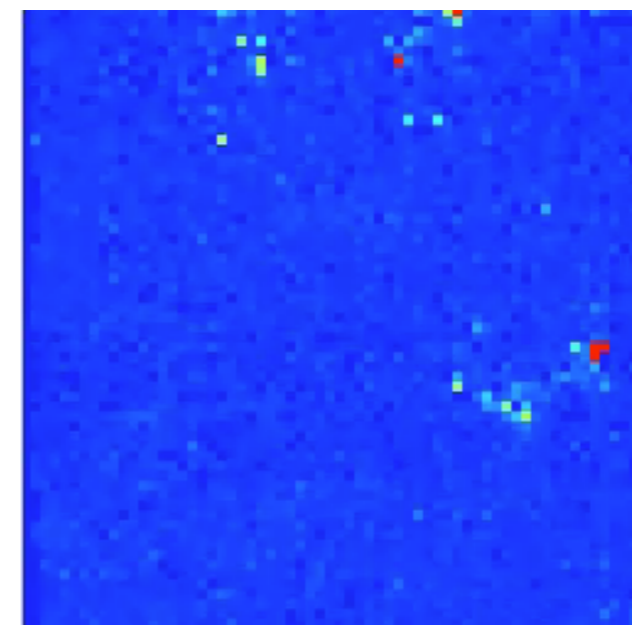
## i) Across species



## iii) Pharmacology



## iv) Spatial Variability



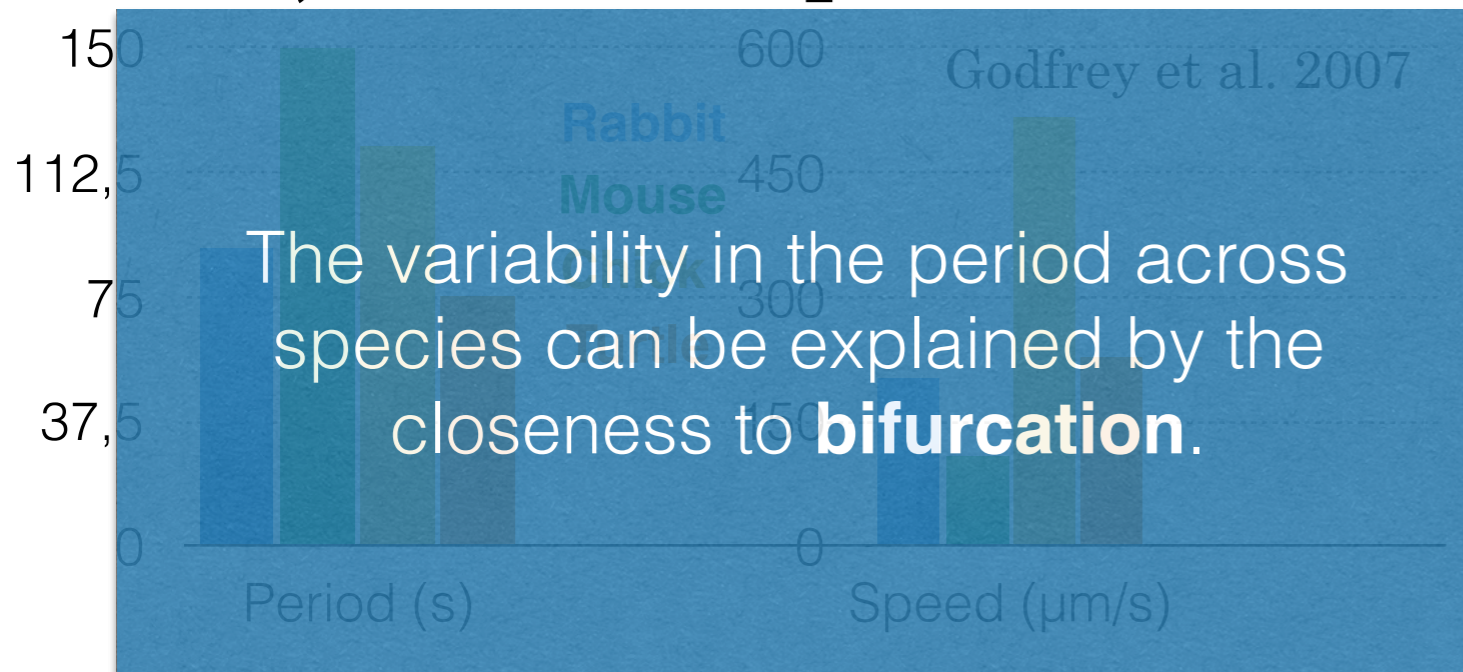
Waves have variable shapes due to a refractory mechanism which controls their borders. It is called **sAHP** (slow **A**fter**H**yper**P**olarization) for stage II.

Maccione et al. 2014

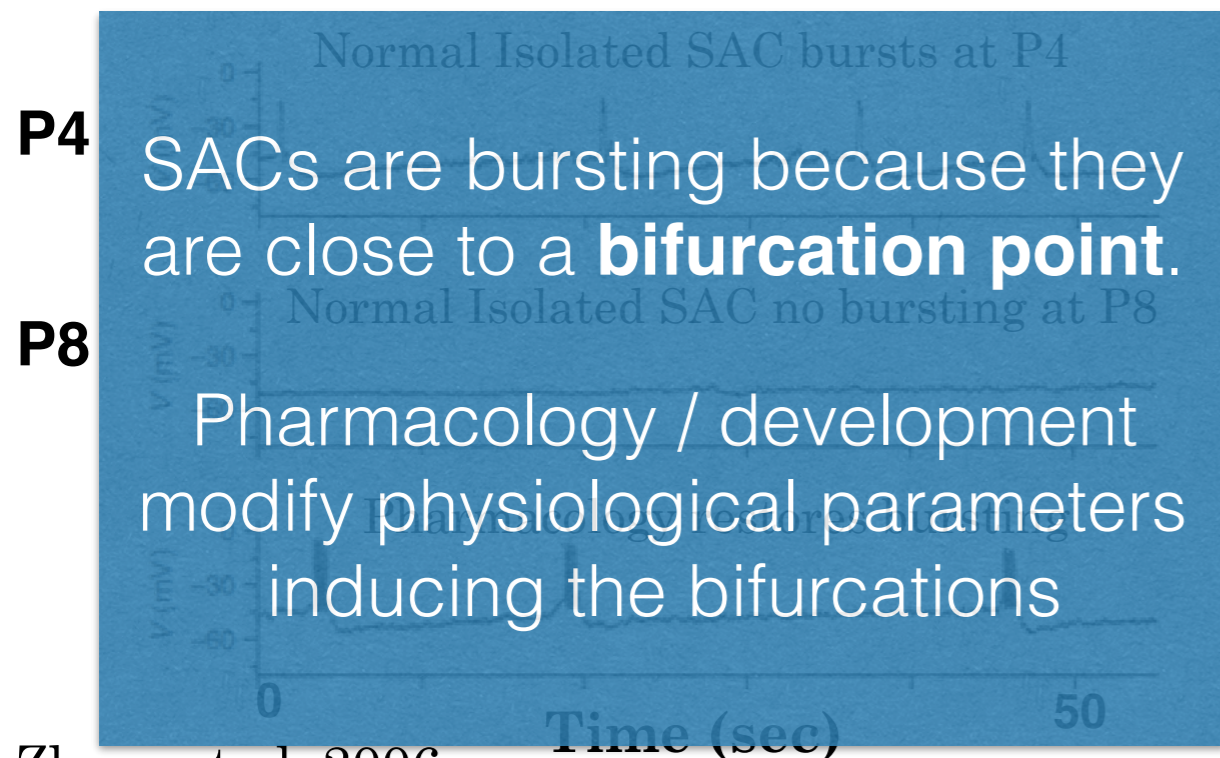


# Variability within retinal waves

## i) Across species



## iii) Pharmacology



## iv) Spatial Variability

Waves have variable shapes due to a refractory mechanism which controls their borders. It is called **Hyper Polarization**.

**Non linear dynamics** and **initial conditions** induce a wave propagation in a **random, history dependent landscape** inducing a strong variability in wave duration or size.

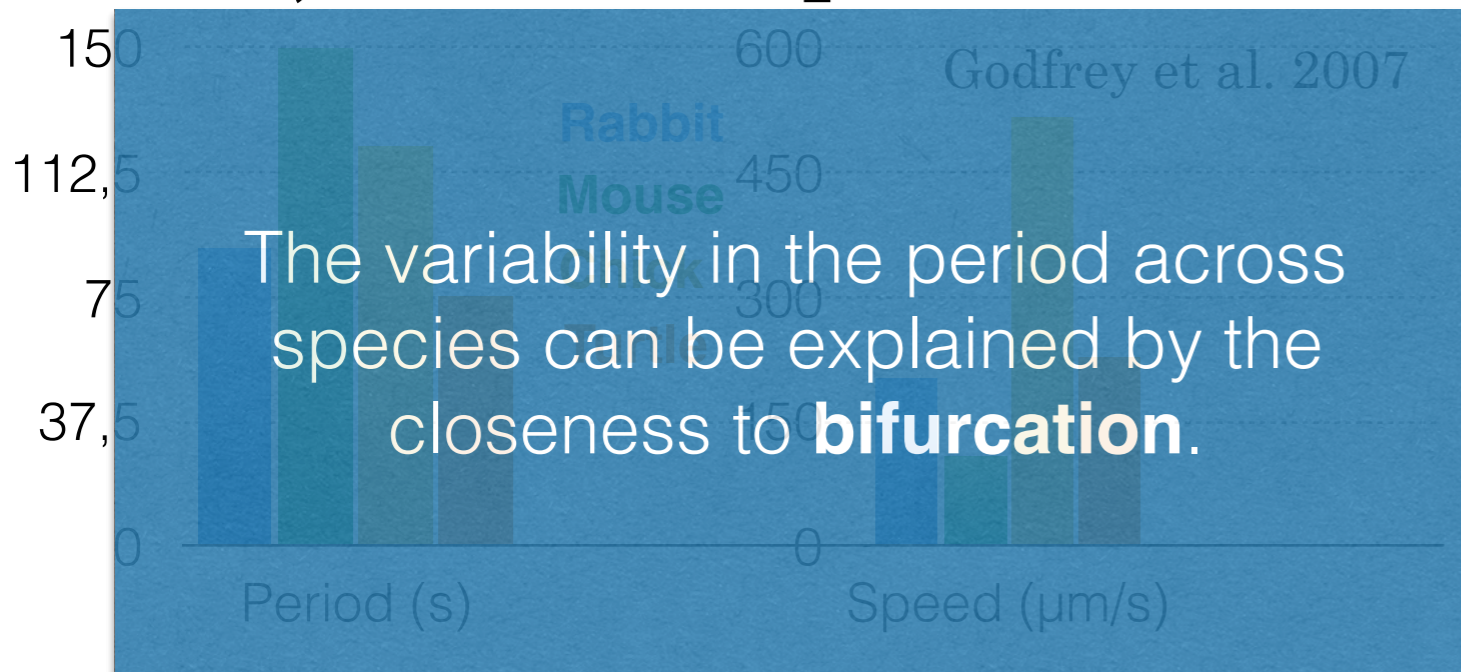
The distribution is, in general, exponential.

Maccione et al. 2014

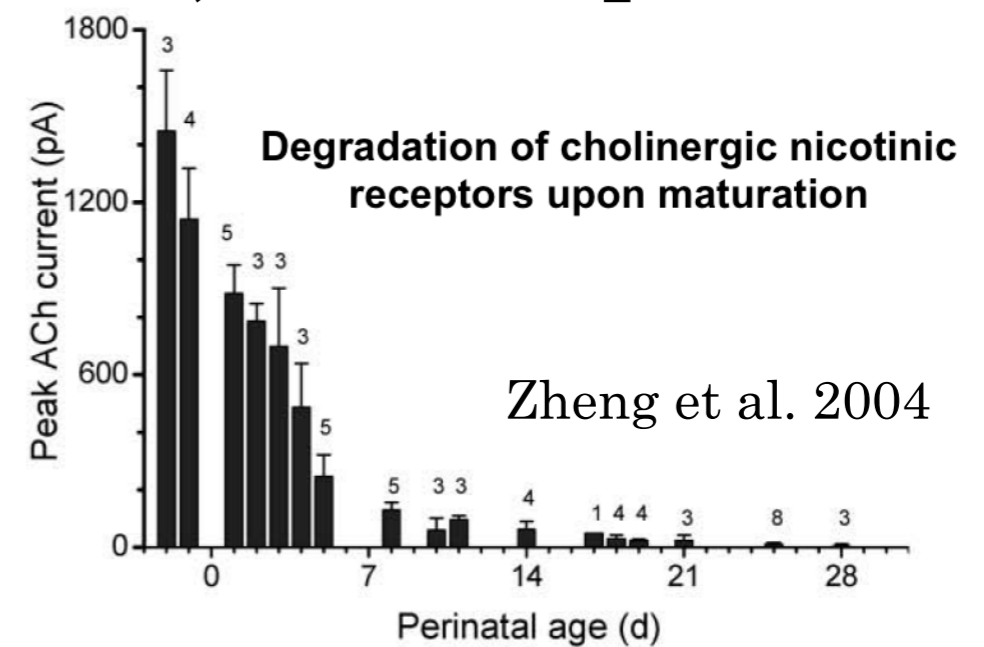


# Variability within retinal waves

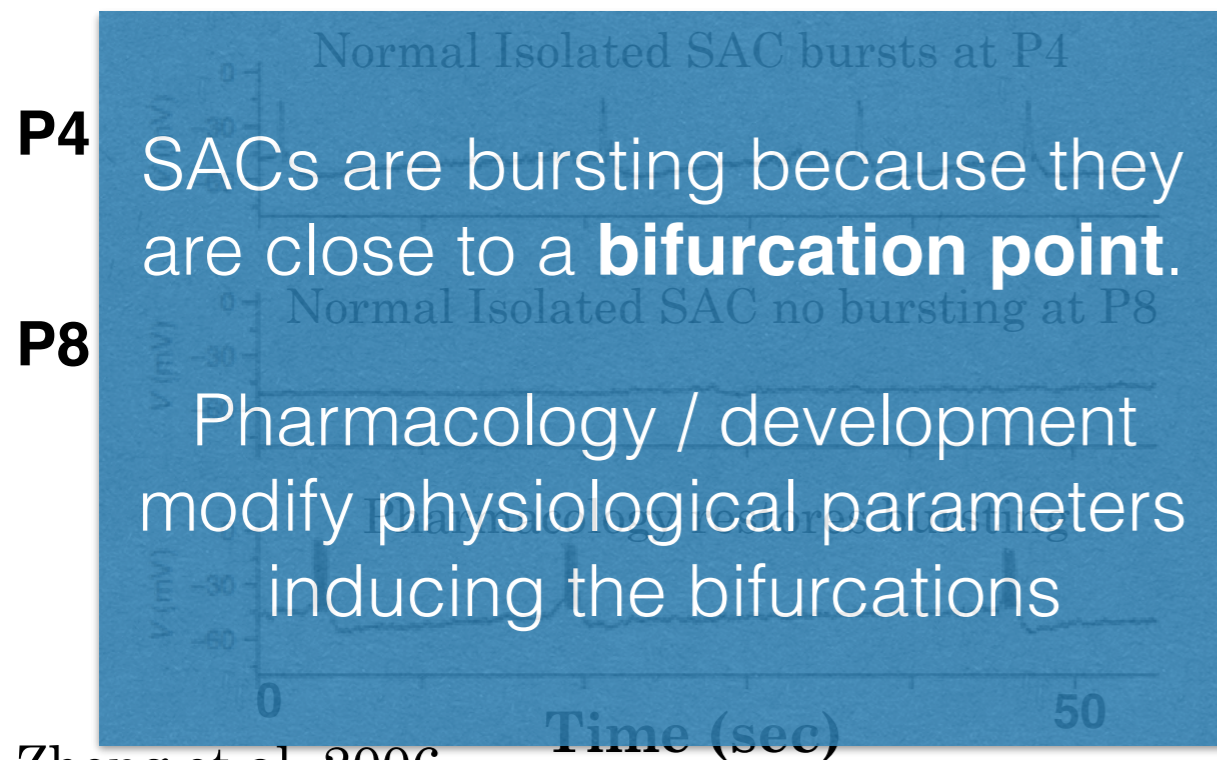
## i) Across species



## ii) Development



## iii) Pharmacology



## iv) Spatial Variability

Waves have variable shapes due to a refractory mechanism which controls their borders. It is called **slow Hyper Polarization**.

**Non linear dynamics** and **initial conditions** induce a wave propagation in a **random, history dependent landscape** inducing a strong variability in wave duration or size.

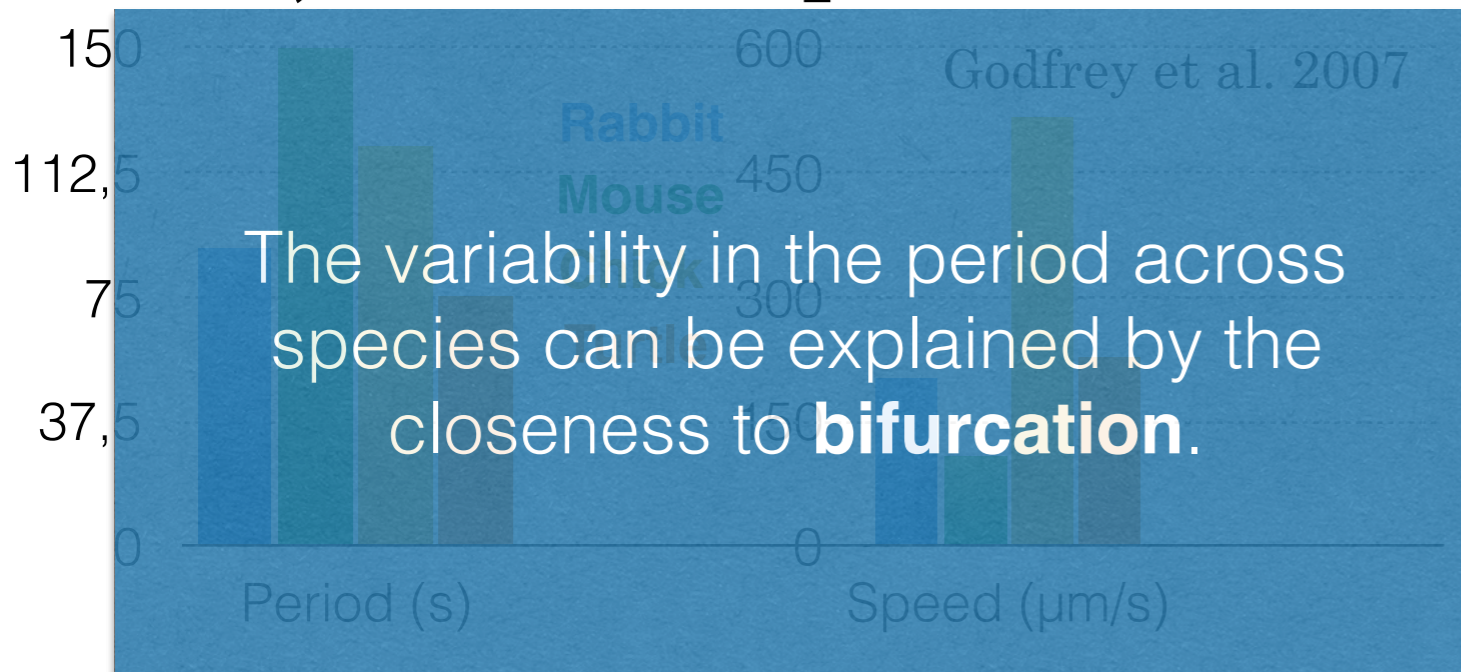
The distribution is, in general, exponential.

Maccione et al. 2014

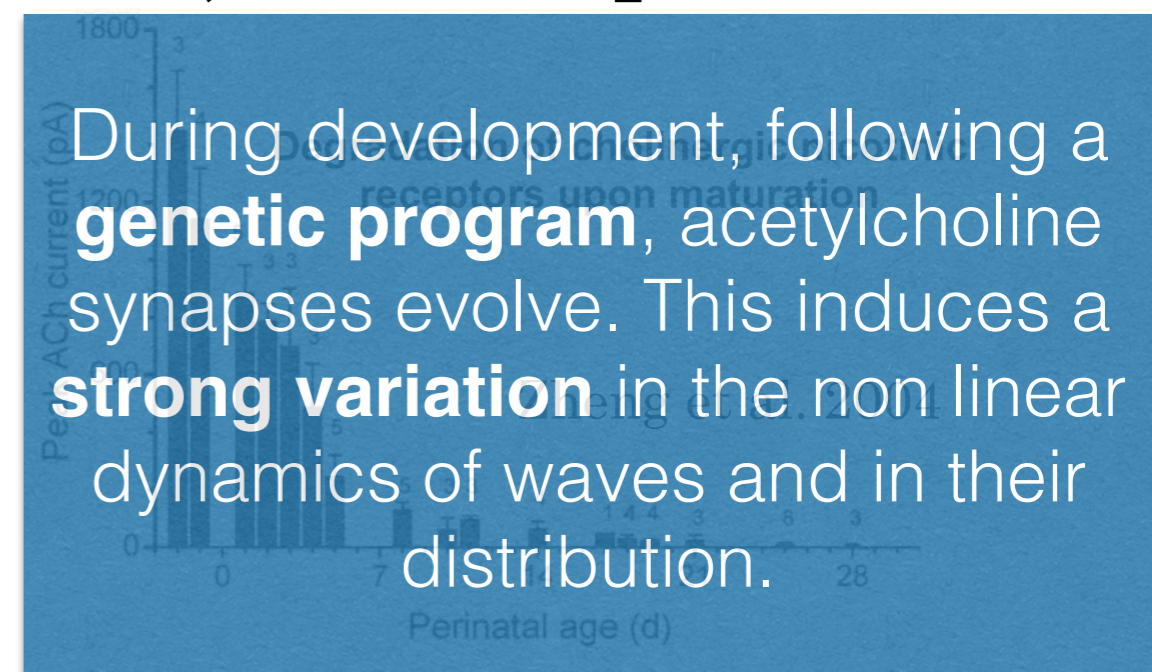


# Variability within retinal waves

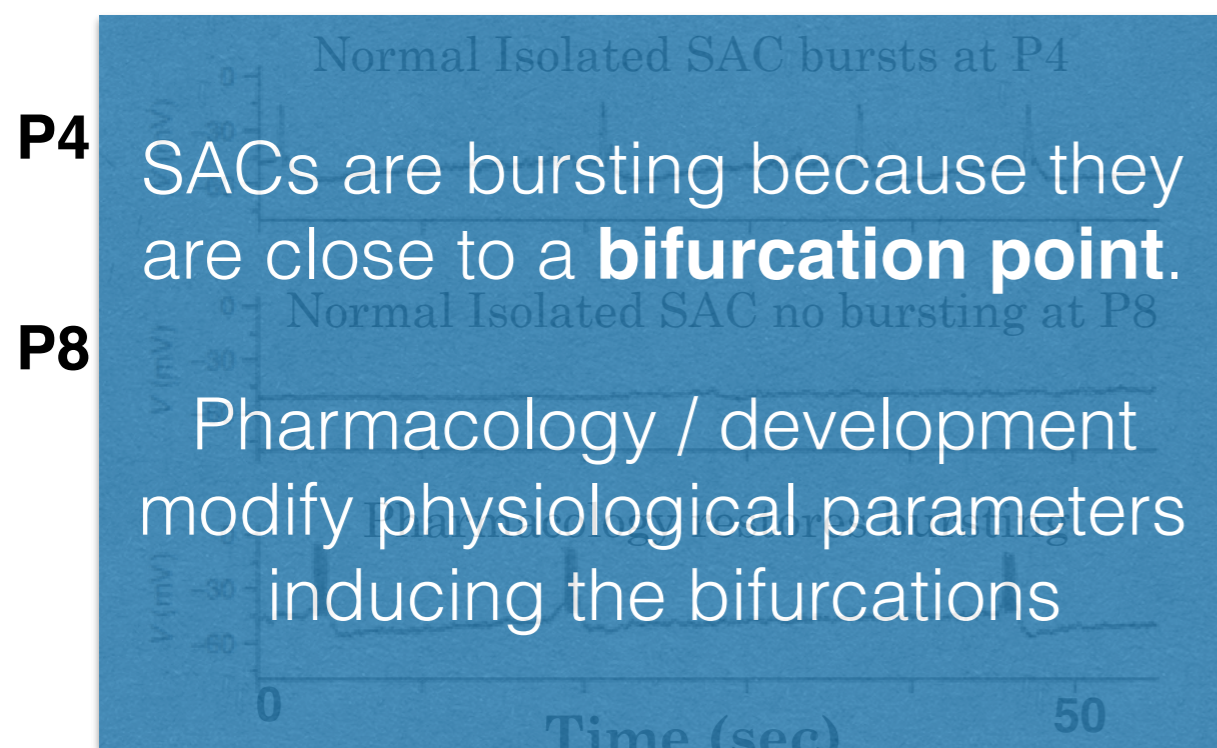
## i) Across species



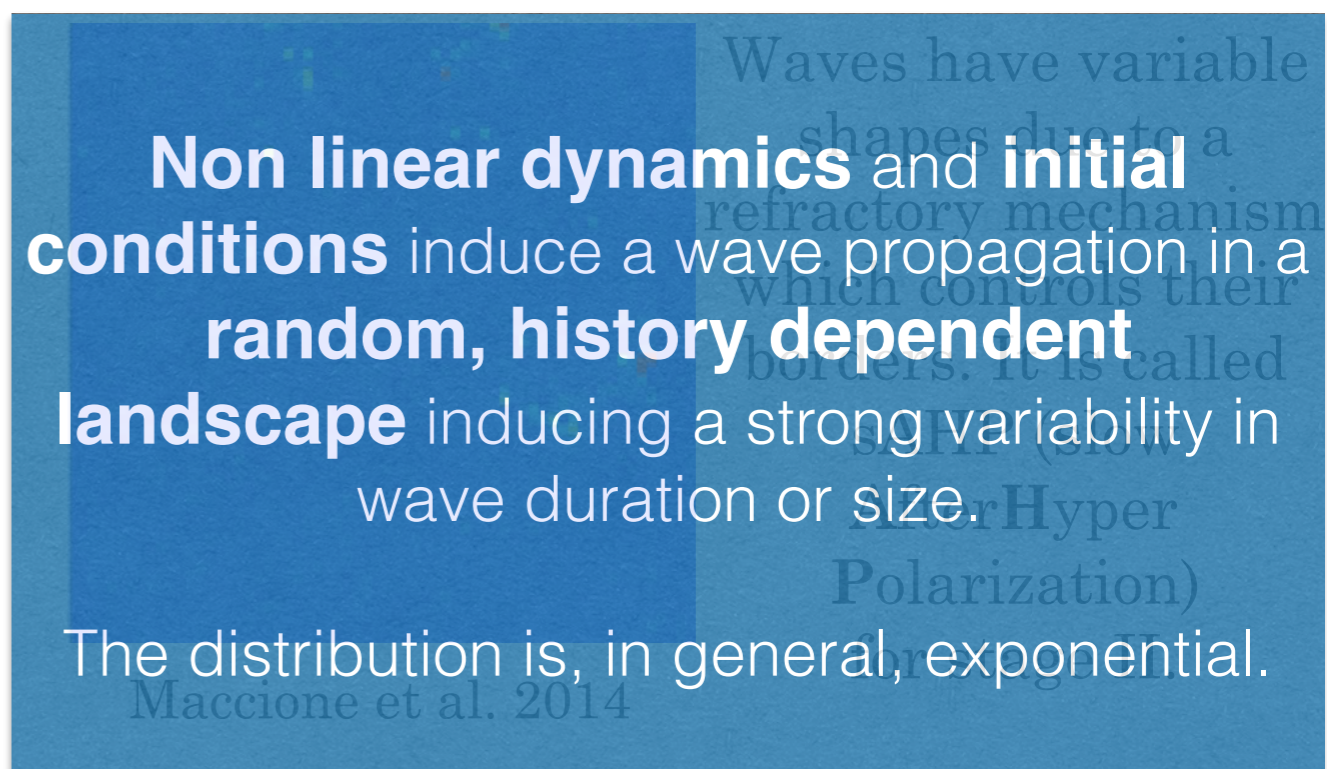
## ii) Development



## iii) Pharmacology



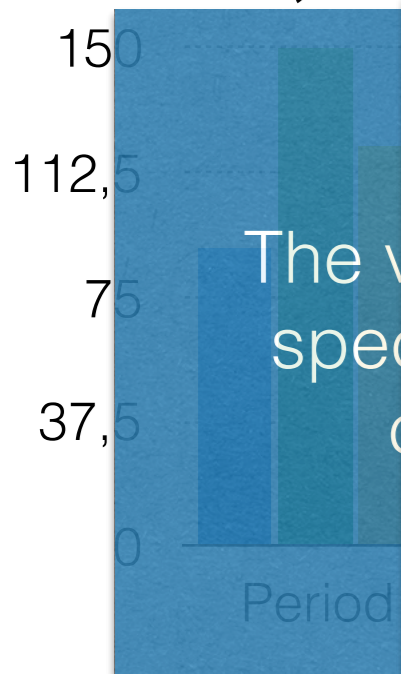
## iv) Spatial Variability





# Variability within retinal waves

## i) Across species



## ii) Development

Is there a benefit for the visual system, at this stage of development, to generate power law distributed waves ?

following a  
cetylcholine  
s induces a  
e non linear  
and in their  
n. 28

## iii)

Which mechanism could enable this fine tuning ?  
Homeostasis ?

## ability

P4

SACs are close

P8

Pharmacology / development modify physiological parameters inducing the bifurcations

have variable  
types due to a  
and **initial**  
ory mechanism  
opagation in a  
controls their  
**endent**  
rs. It is called

The distribution is, in general, exponential.

Maccione et al. 2014



*Thanks*