



# Modelling spontaneous propagating waves in the early retina

Bruno Cessac, Dora Matzakos-Karvouniari, Lionel Gil

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# Modelling spontaneous propagating waves in the early retina

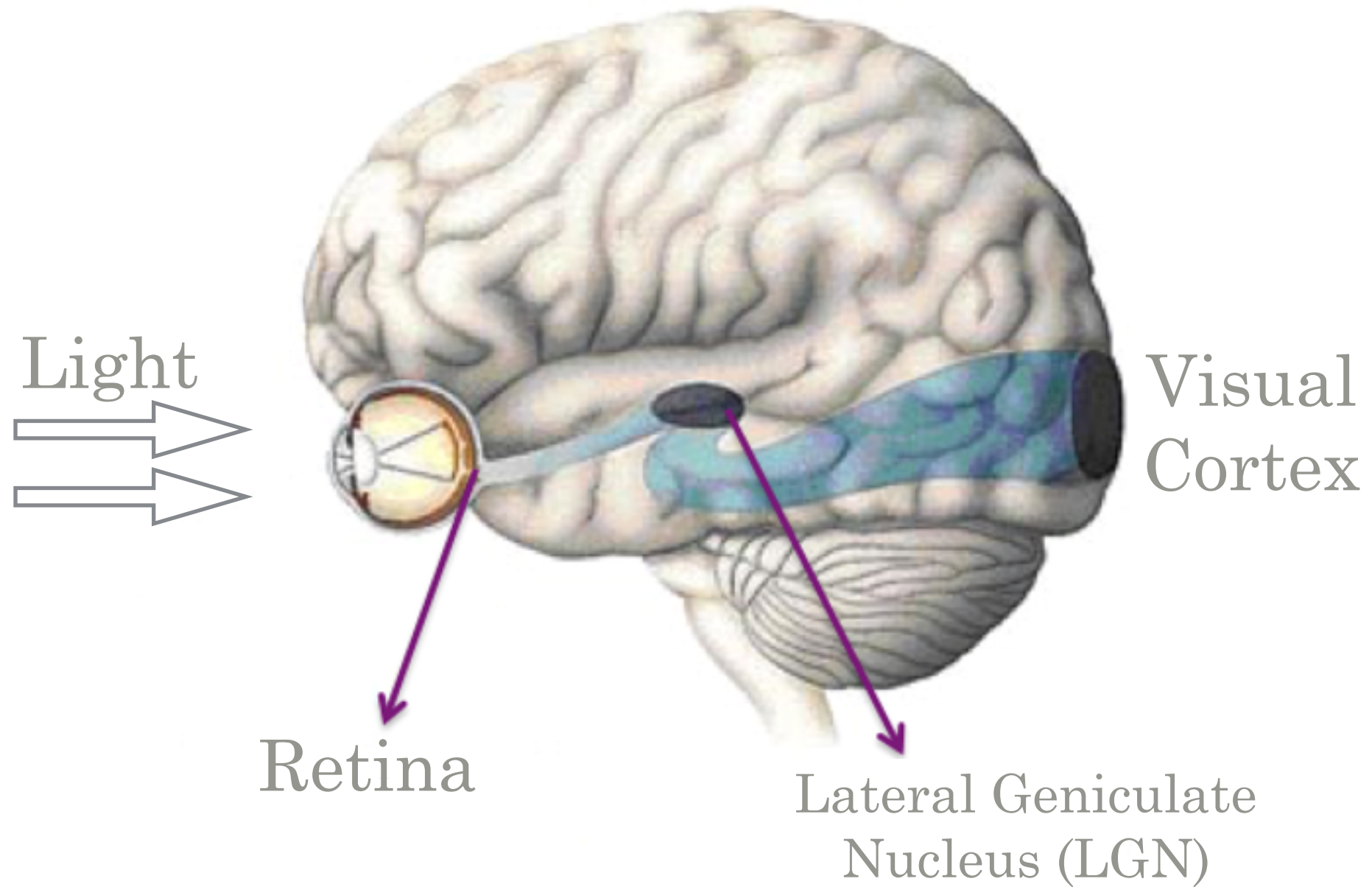
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*Dora Matzakos-Karvouniari, LJAD, UCA*

*Lionel Gil, INPHYNI, UCA*

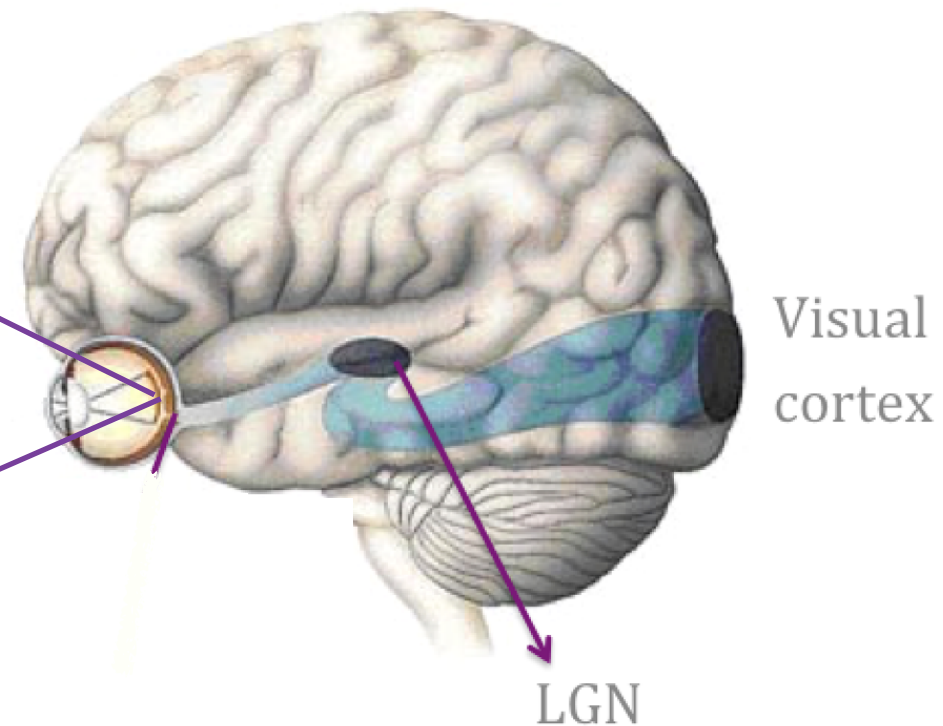
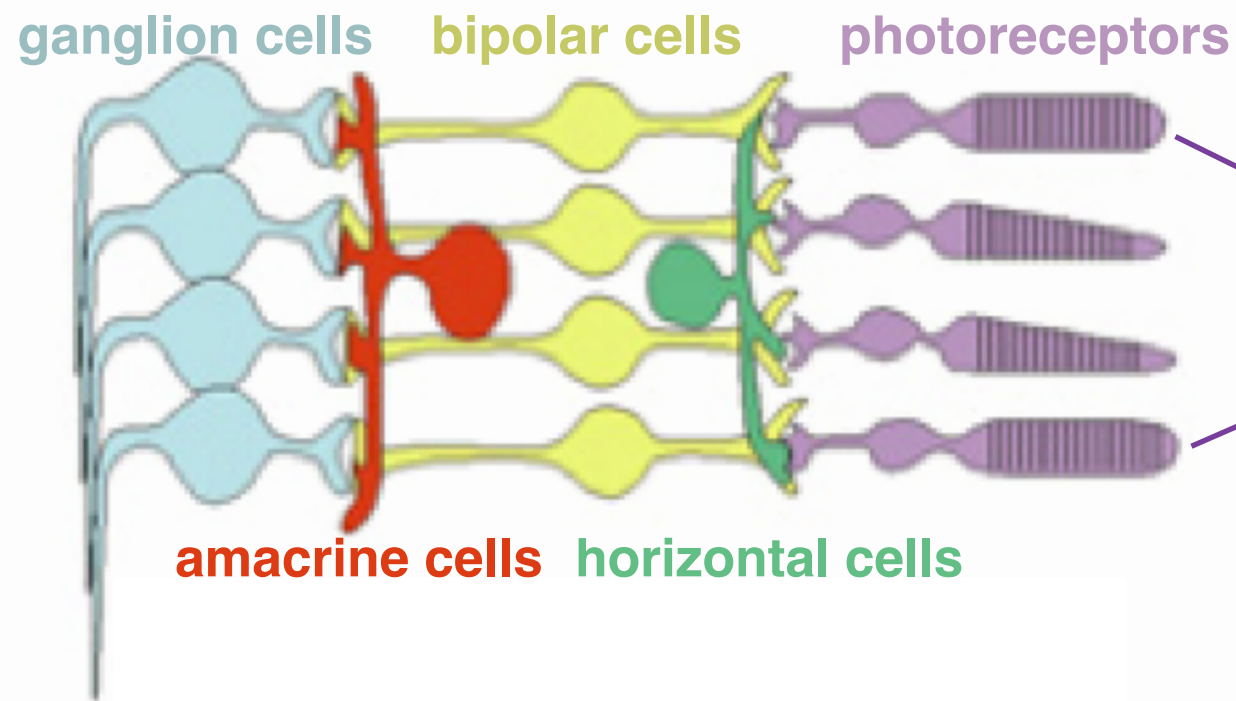
*Bruno Cessac, Biovision, Inria*

# Visual system



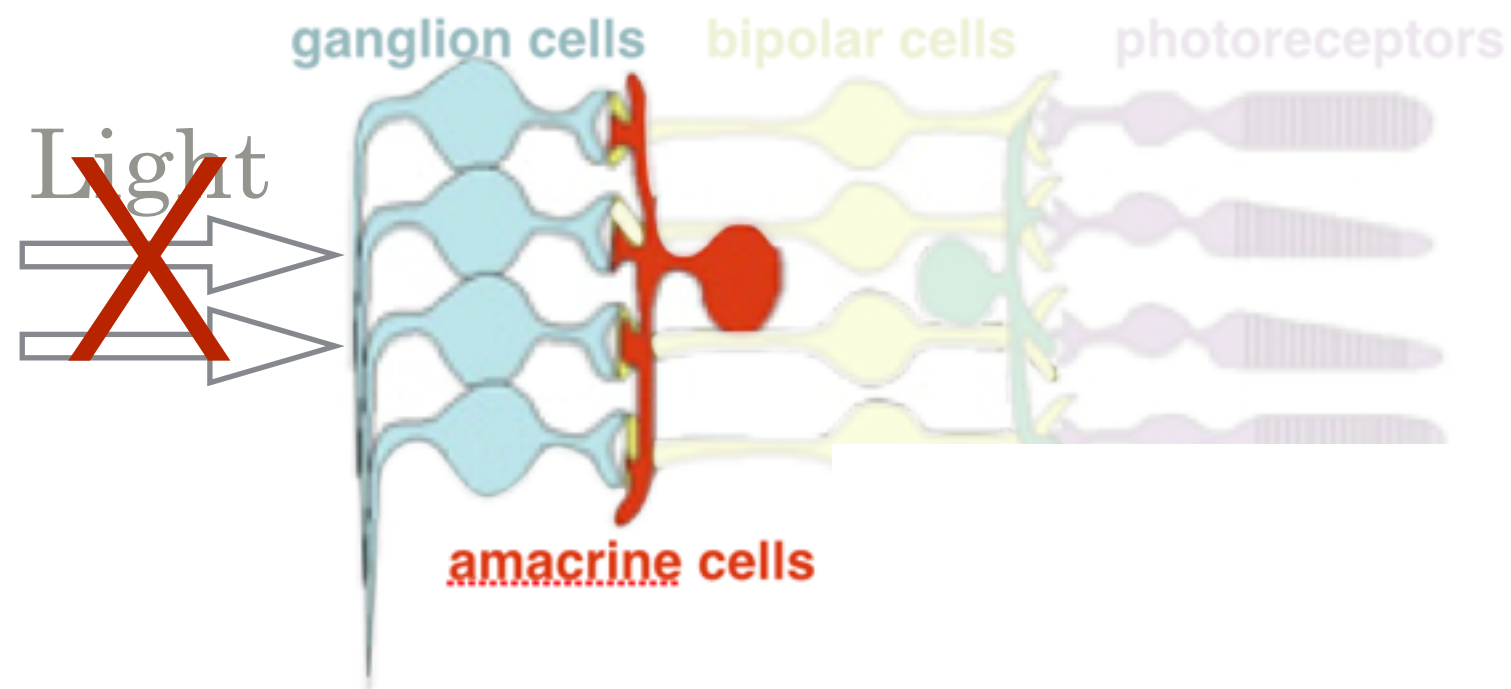
# The structure of the adult retina

## Retina's layered structure



# The structure of the retina during development

Retina's layered structure  
is shaped during development



But How?



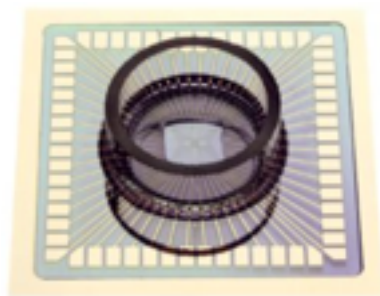
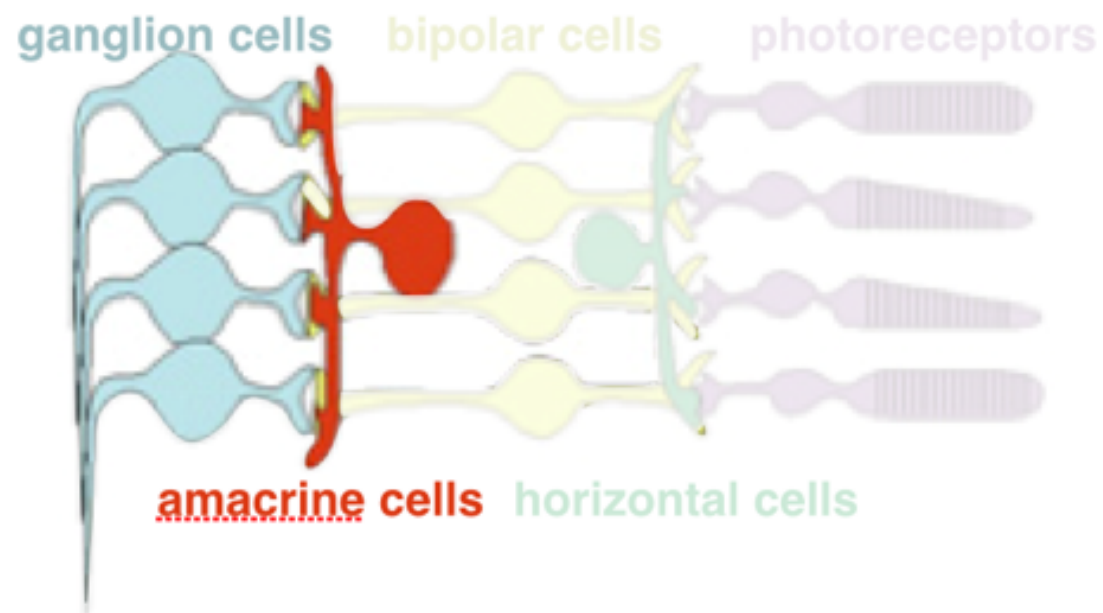
**Retinal waves!**



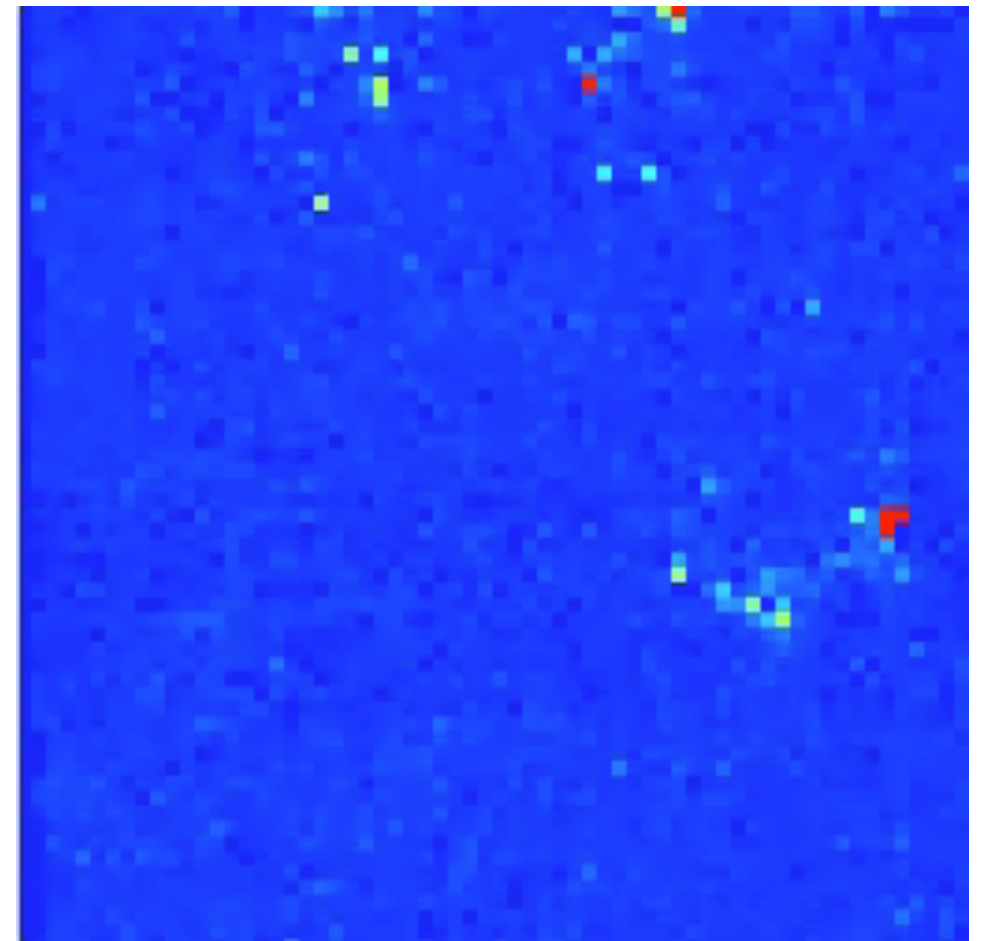
# What are Retinal waves?

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

## Recordings from the retina



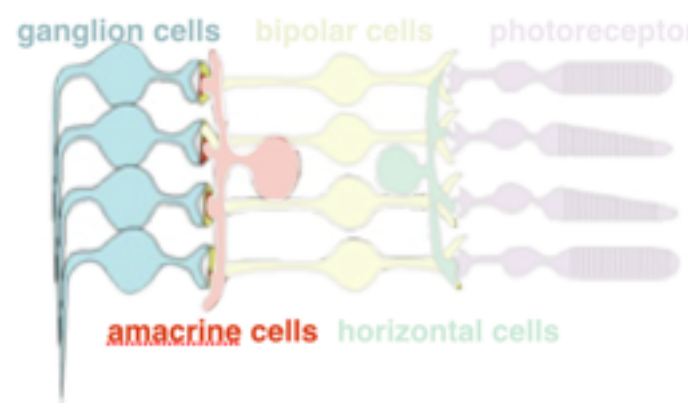
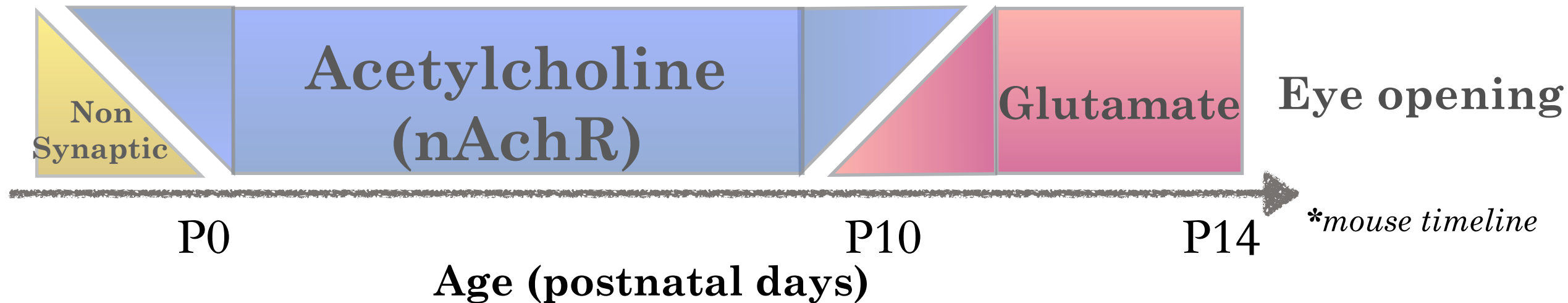
**Multi-electrode array  
(MEA)**



*(Maccione et al. 2014)*

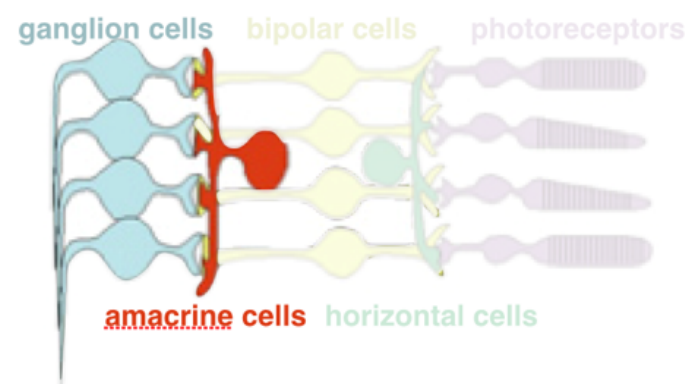
*MEA recording of the voltage from a P11 mouse retina in the presence of 10  $\mu$ M bicuculline.*

# The timeline of retinal waves



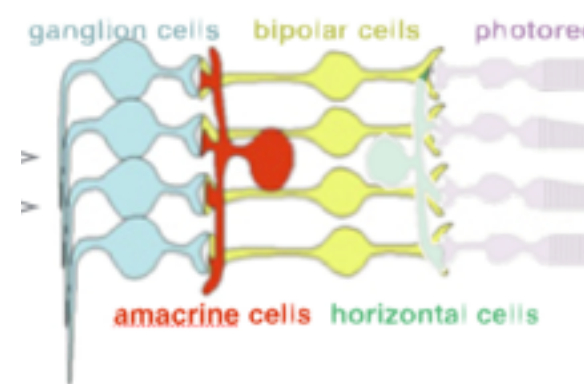
## Stage I

- Formation of early retinal circuitry
- Chemical synapses are not formed yet
- **Electrical synapses mediated**



## Stage II

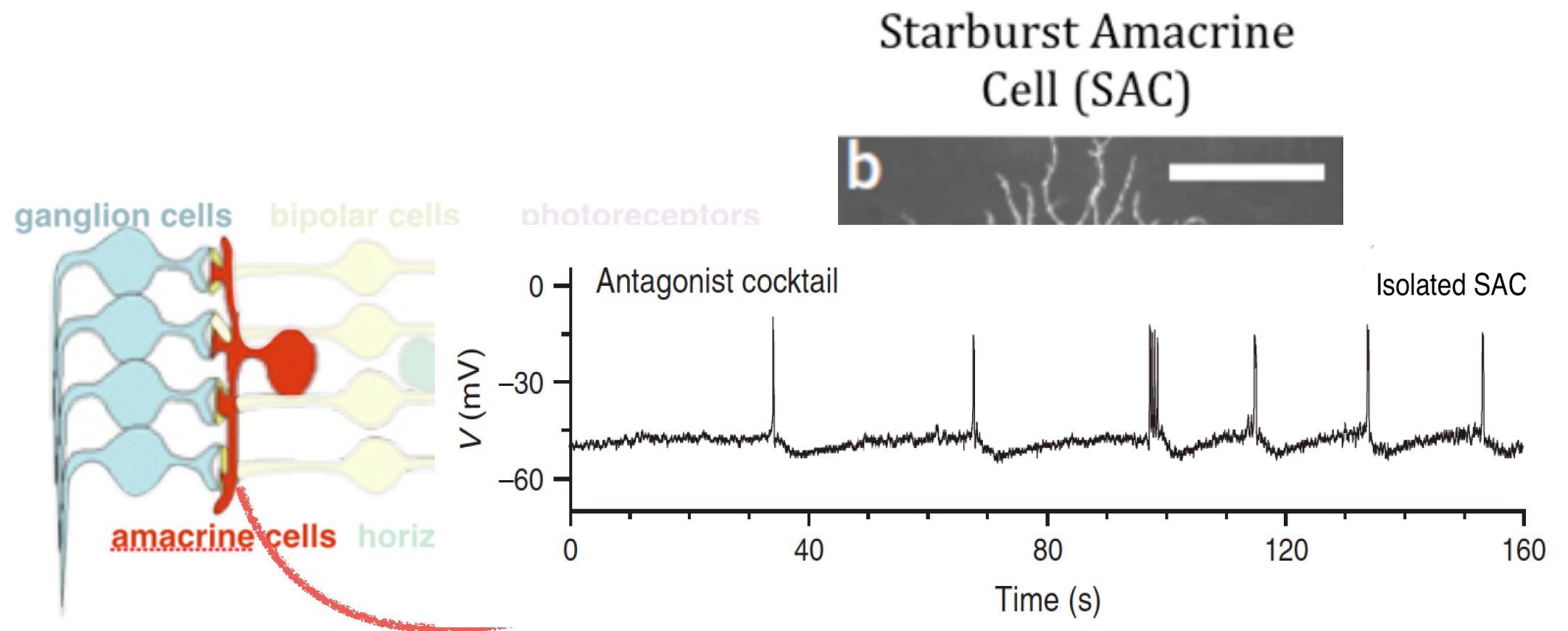
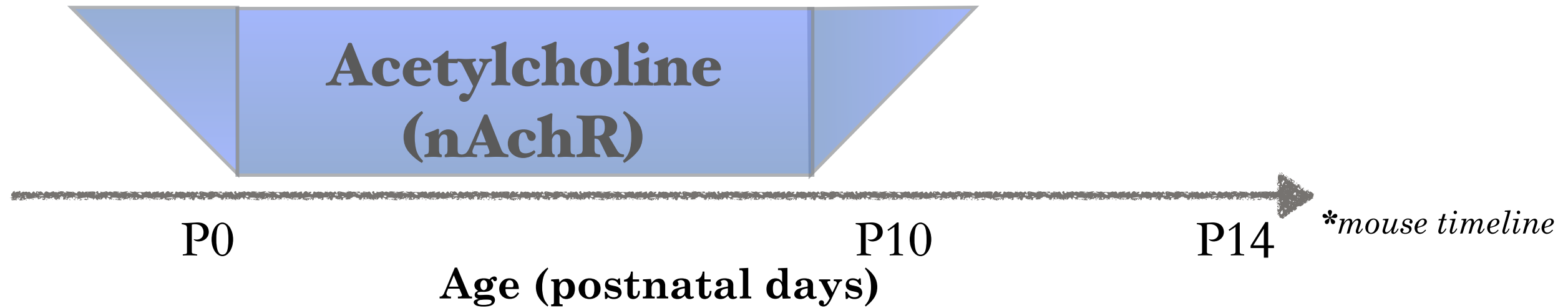
- Retinotopic mapping
- Eye specific segregation
- **Nicotinic Acetylcholine Receptors (nAchR)**



## Stage III

- Disappear when vision is functional
- **Glutamate/AMPA Receptors**

# Focusing on stage II retinal waves



Zheng et al. 2006

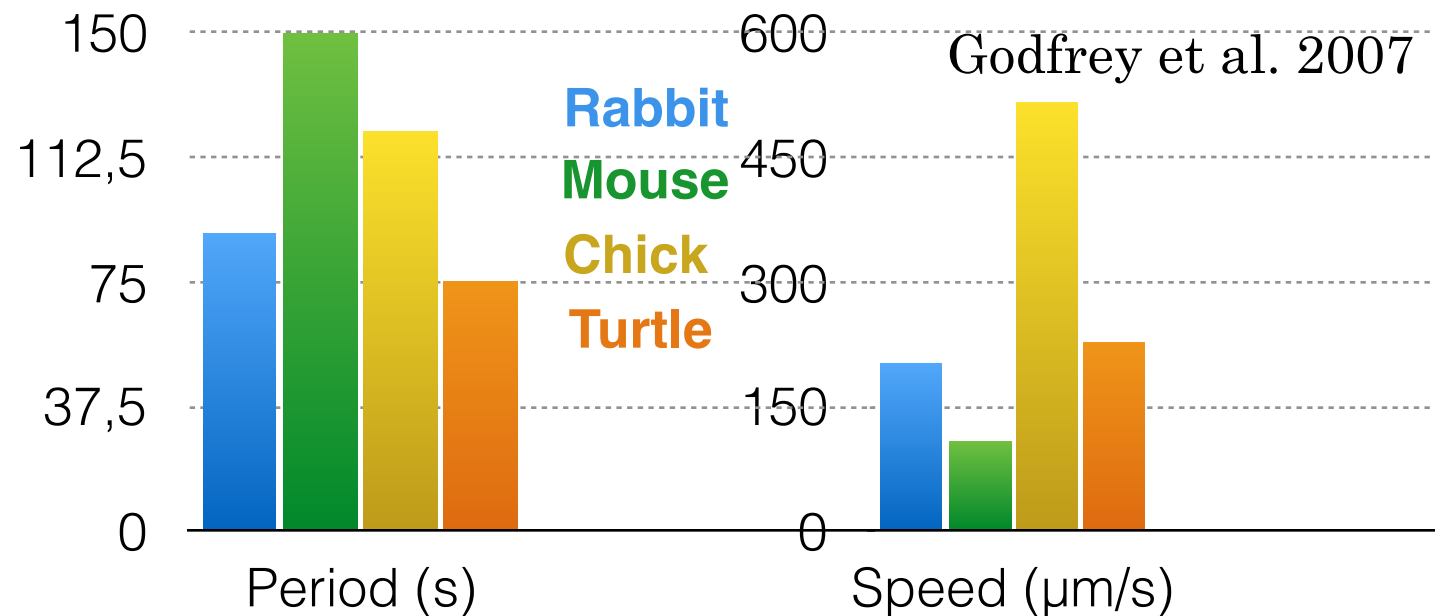


# Why modelling retinal waves is an interesting problem?

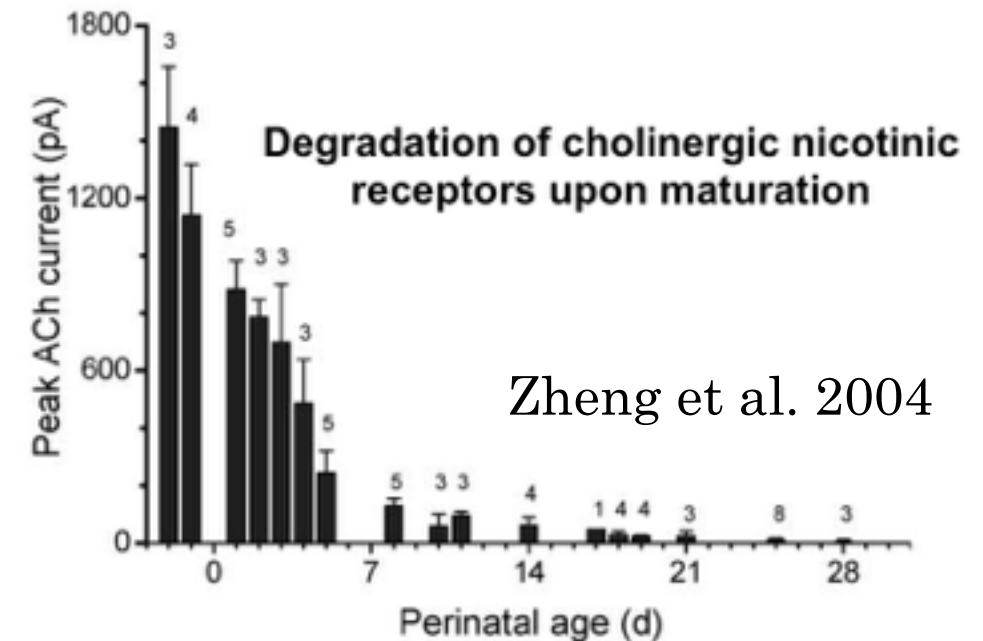
- Retinal waves **instruct the shaping** of the visual system
- Using biophysical modelling we could
  - i) find **generic principles**
  - ii) explain **experiments** and propose new onesleading to the better understanding of the underlying mechanisms of waves.
- The mathematical modelling of the dynamics of a complex biological process is a very interesting physical problem with real consequences in biology
- Understanding the mechanisms that generate them may help to **control them pharmacologically**.

# Variability within retinal waves

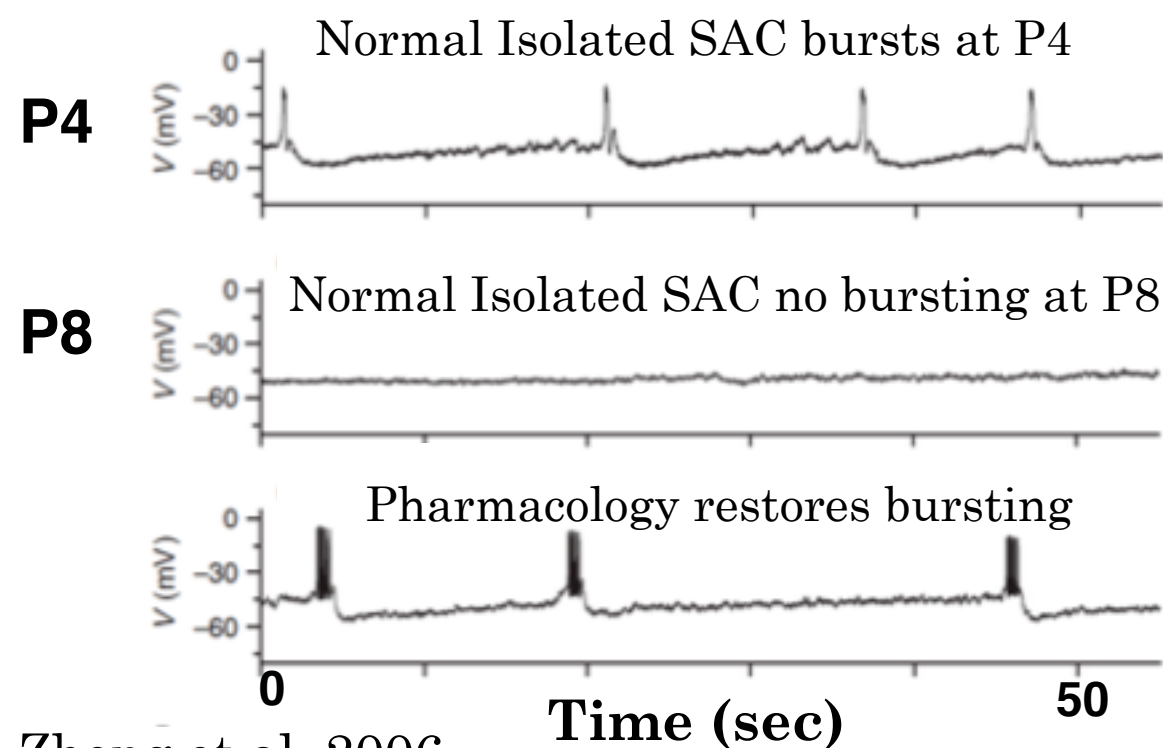
## i) Across species



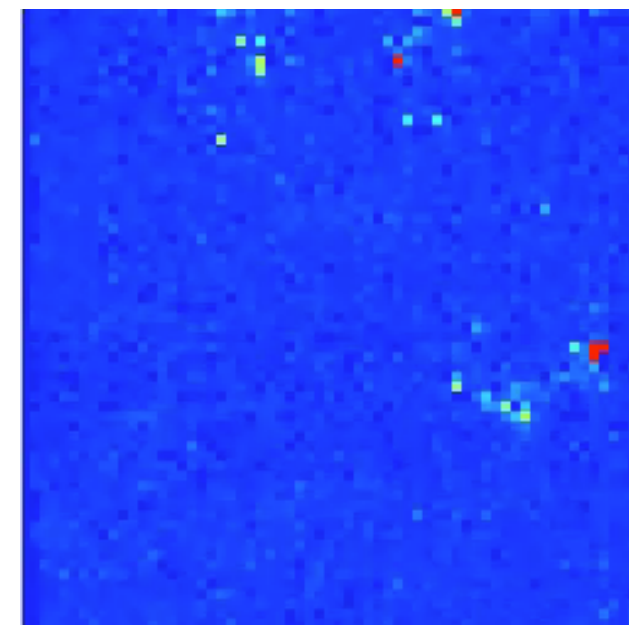
## ii) Development



## iii) Pharmacology



## iv) Spatial Variability



Maccione et al. 2014

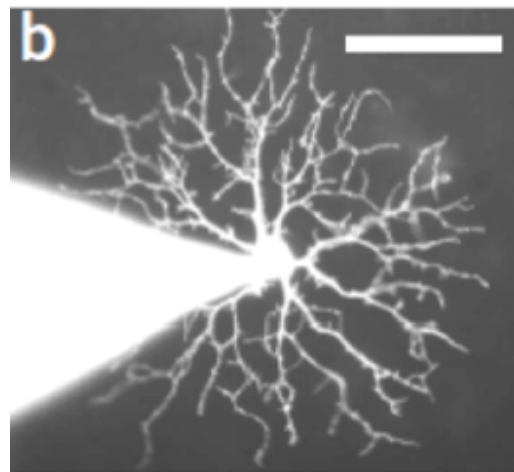
Waves have variable shapes due to a refractory mechanism which controls their borders. It is called sAHP (slow AfterHyperPolarization) for stage II.

# Modelling stage II retinal waves dynamics

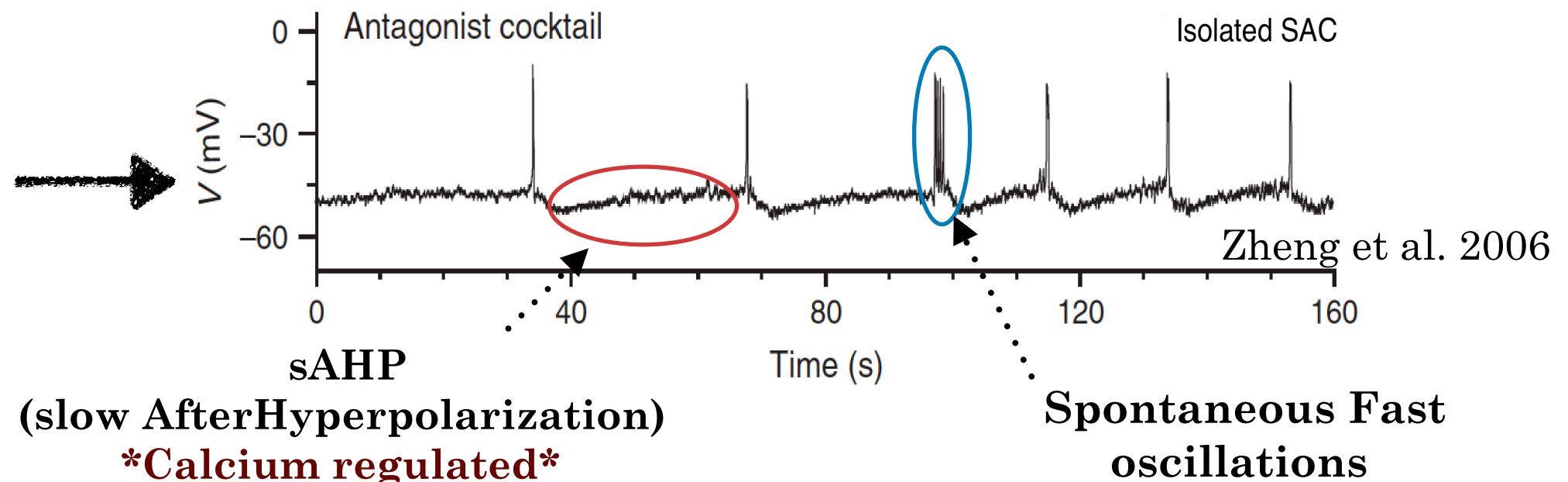
1. D. Matzakos-Karvouniari et al., *A biophysical model explains the bursting activity in the immature retina*, Nat Sci Rep, 2019

# The biophysics of stage II retinal waves

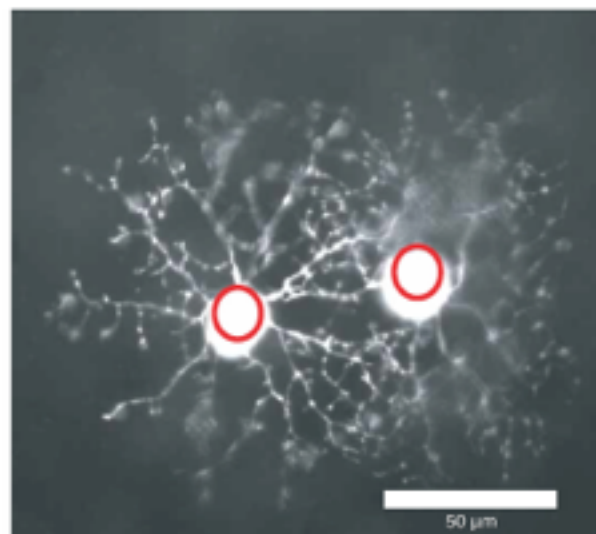
## Individual SACs burst spontaneously



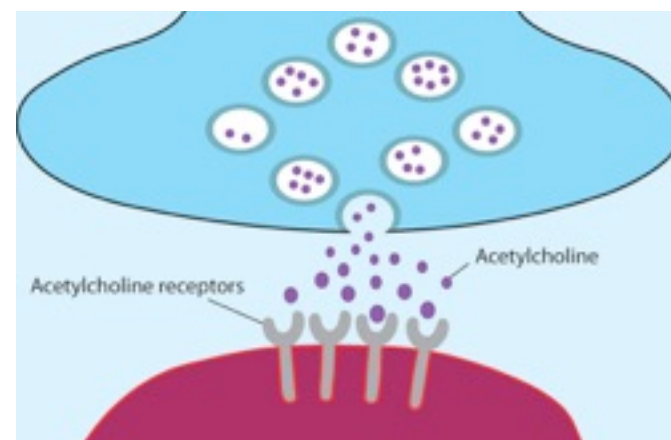
Zheng et al. 2006



## Immature SACs form a transient cholinergic network



## Nicotinic Acetylcholine Receptors



Mutual Excitatory  
synapses

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

# A model for stage II retinal waves

*Matzakos-Karvouniari et al.*  
*2019, Lansdell et al. 2014,*  
*Hennig et al. 2009, Morris-Lecar*  
*1981*

**6 variables: V, N, C, R, S, A**  
**3 time scales: Fast, Medium, Slow**  
**Nonlinear cholinergic coupling**  
**~30 parameters**

**Fast**

$$C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) - g_{sAHP} R_i^4(V_i - V_K) - g_A(V_i - V_A) \sum_{j \in \mathcal{B}_i} \frac{A_j^2}{\gamma_A + A_j^2}$$

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

**Medium**

$$\tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C(V_i)(V_i - V_C) \quad \frac{dA_i}{dt} = -\mu A_i + \beta_A T_A(V_i).$$

**Slow**

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

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

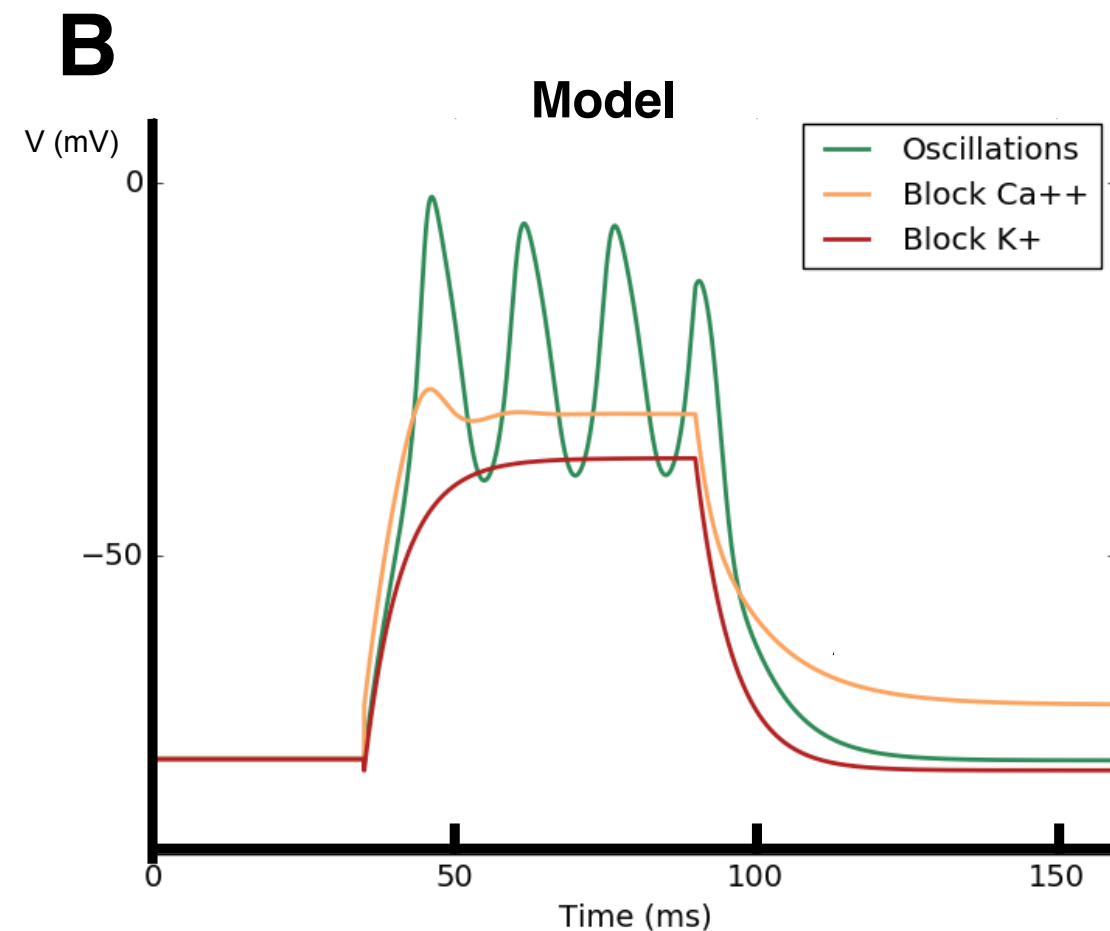
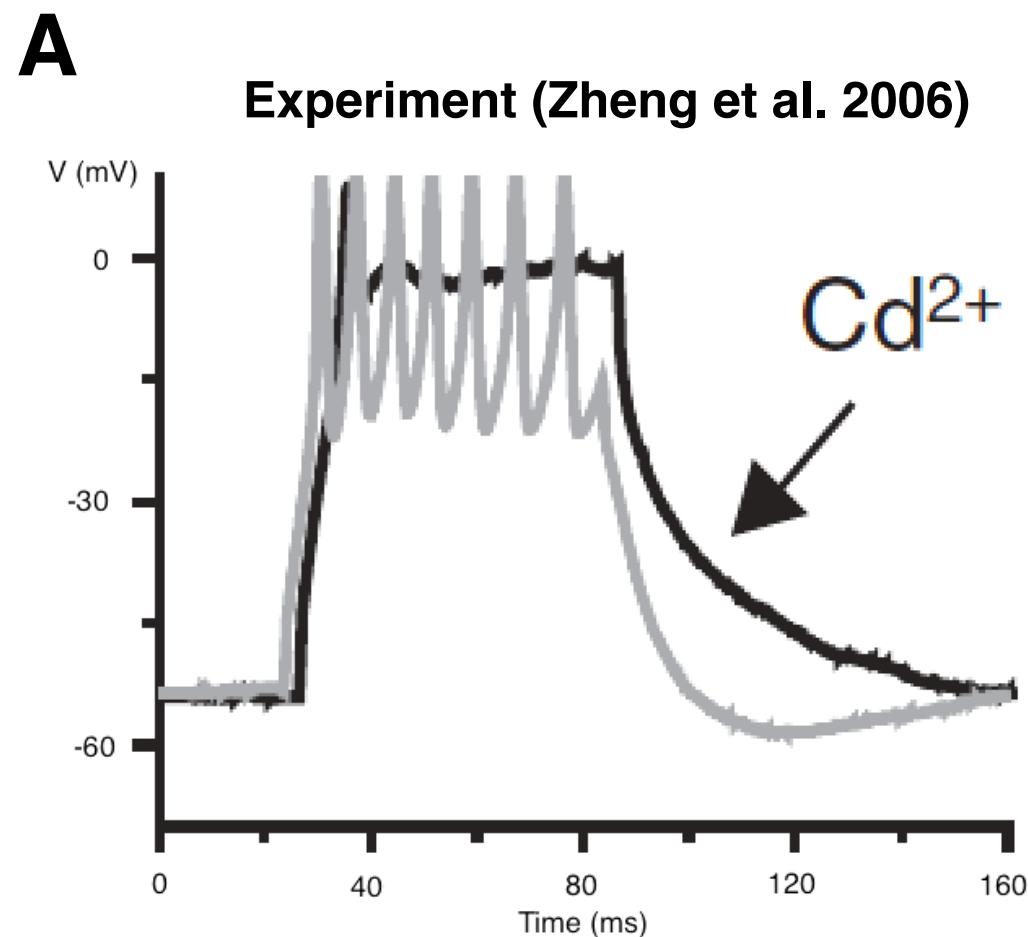
**Fast** V, N.  $\tau_L = 11$  ms,  $\tau_N = 5$  ms.

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

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



# Validating our equations by reproducing experiments



- I. Equations **reproduce** the role of **voltage-gated  $\text{Ca}^{++}$  channels** on fast oscillations
- II. We **predict** that a **fast potassium channel** is needed to produce fast oscillations

# Analysis through bifurcation theory

How do waves start?

1. D. Matzakos-Karvouniari et al., *A biophysical model explains the bursting activity in the immature retina*, Nat Sci Rep, 2019

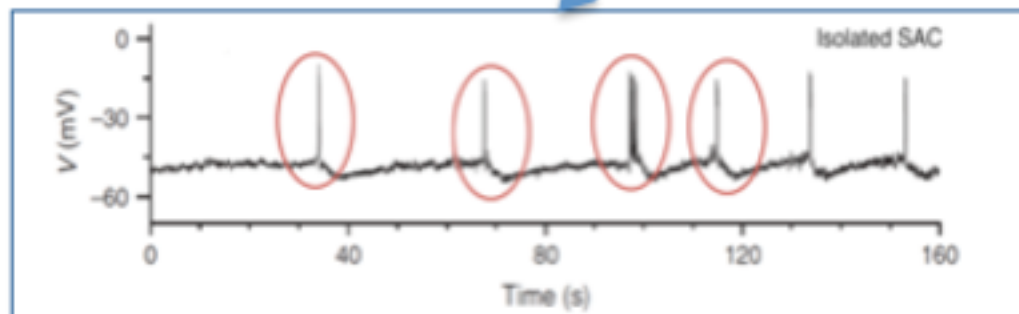
# The mechanism of bursting revealed through bifurcations

## Fast subsystem

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

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

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



# The mechanism of bursting revealed through bifurcations

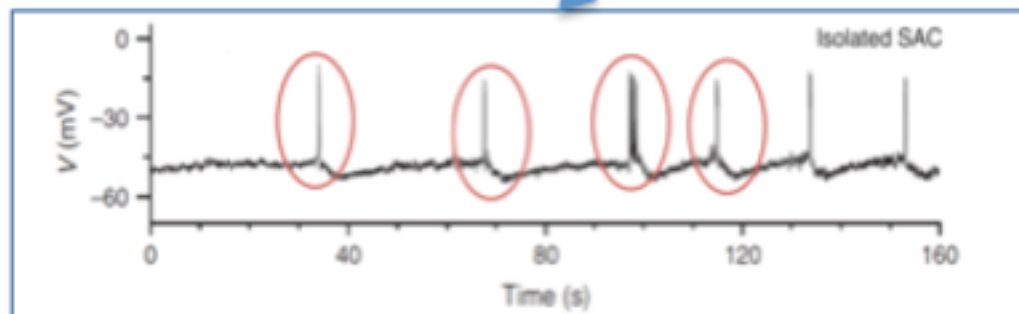
Fast subsystem

$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K) + I_{ext}$$

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

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

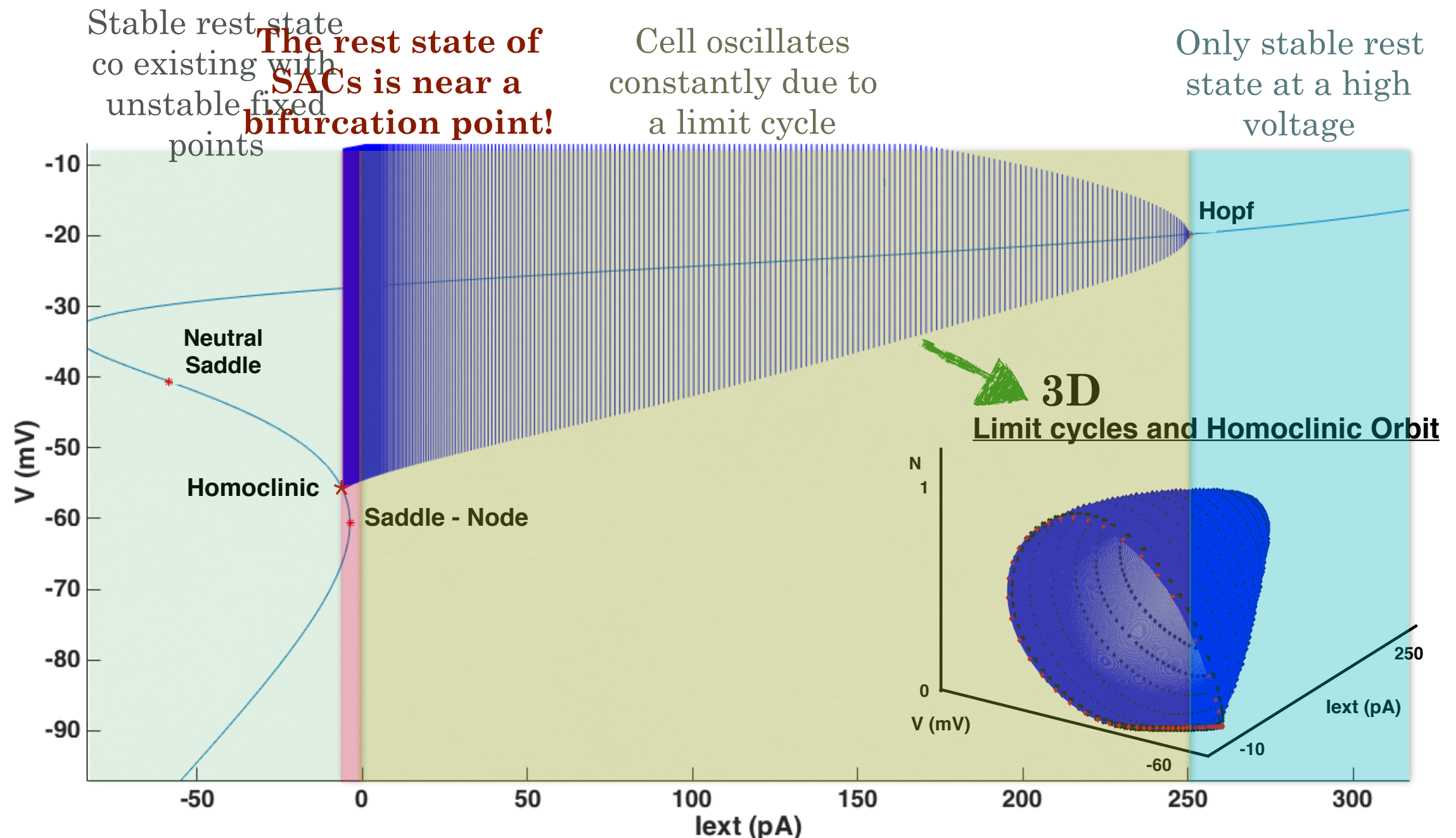
**Constant current  
(bifurcation  
parameter)**



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

What do we learn about SACs?

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



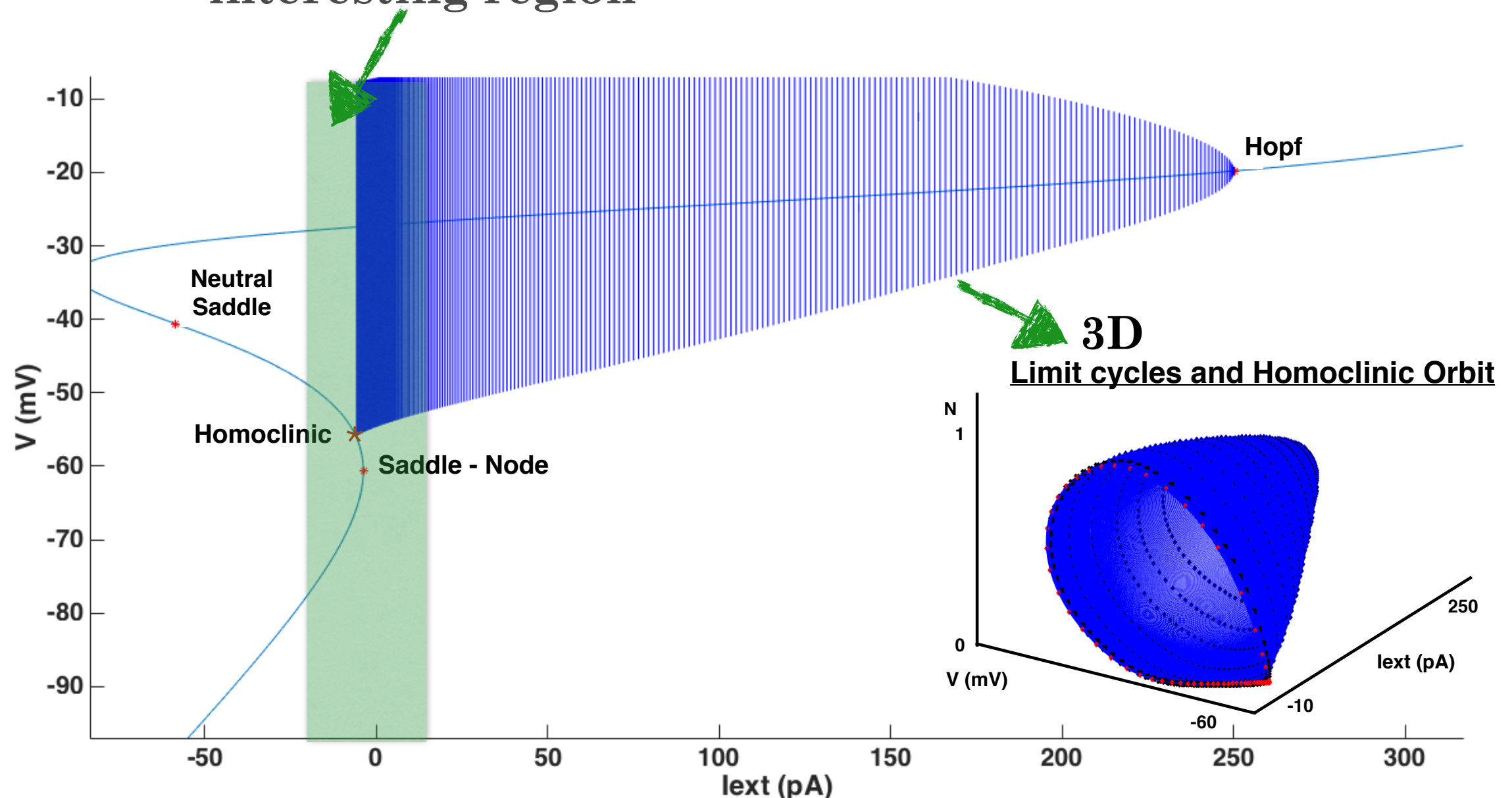


# Bifurcation diagram of the fast subsystem (V,N)

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Zoom in this  
interesting region

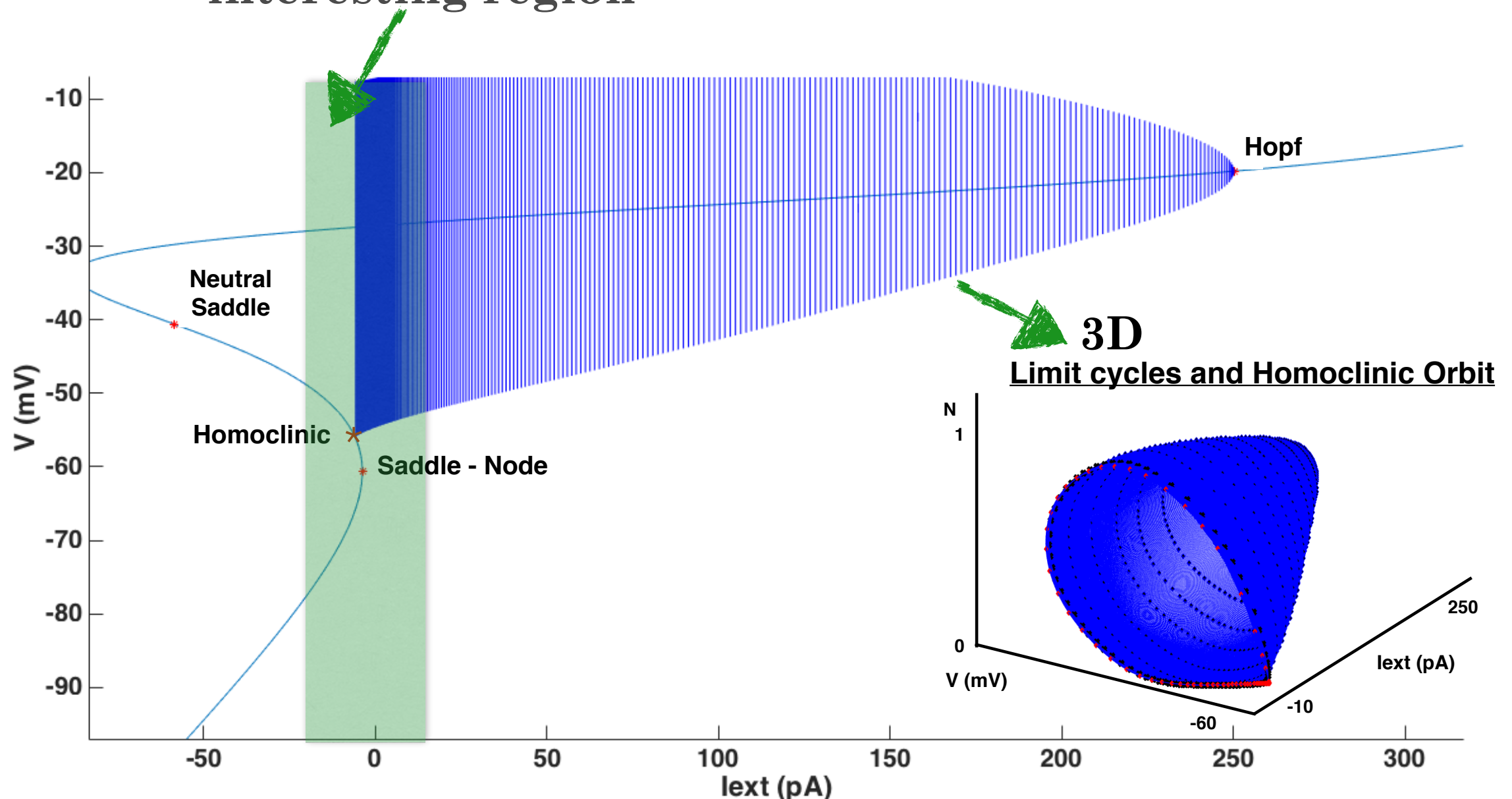


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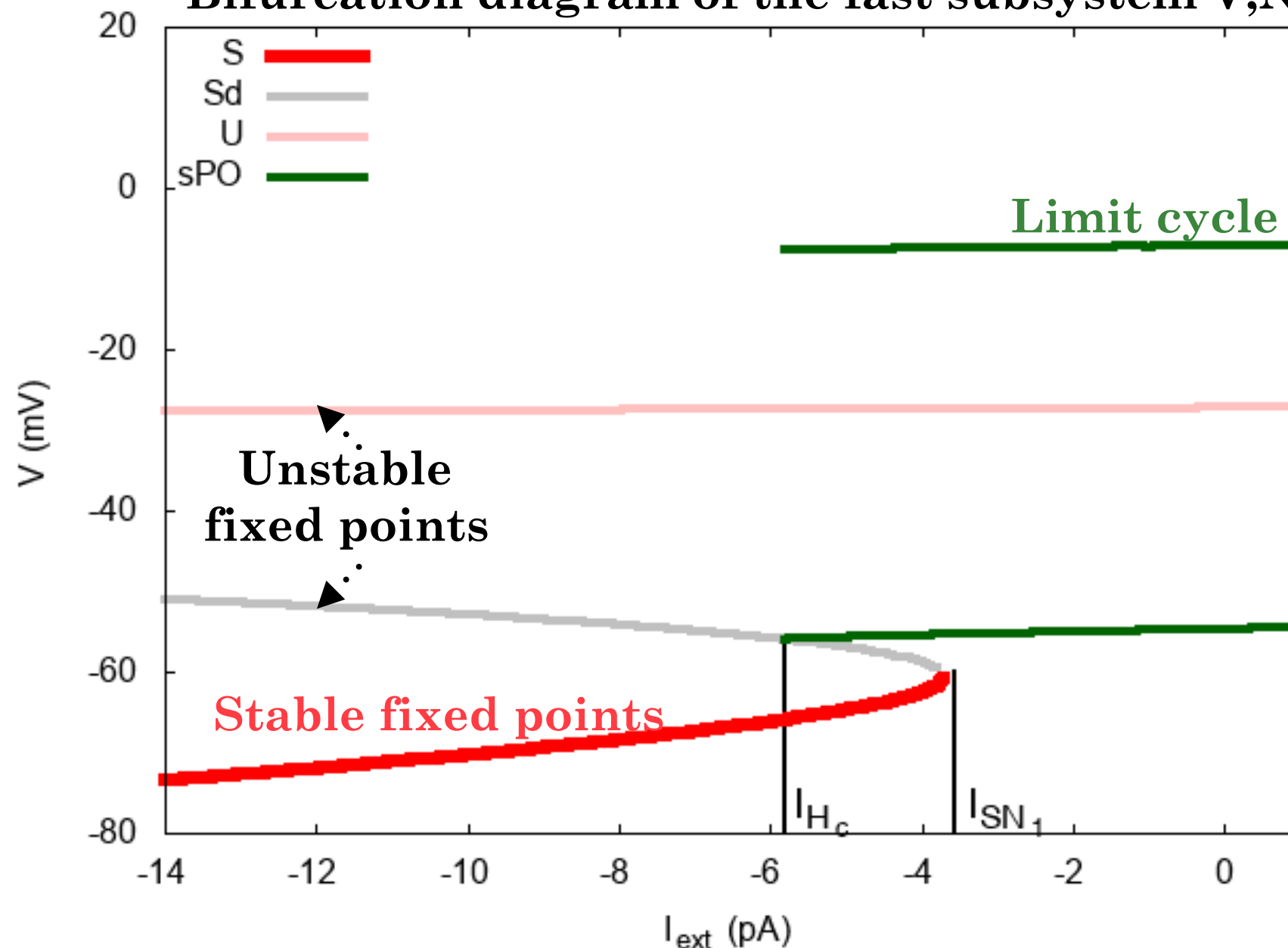


# The mechanism of bursting revealed through bifurcations

What do we learn about SACs?

## II. The role of sAHP for the bursting mechanism

Bifurcation diagram of the fast subsystem V,N

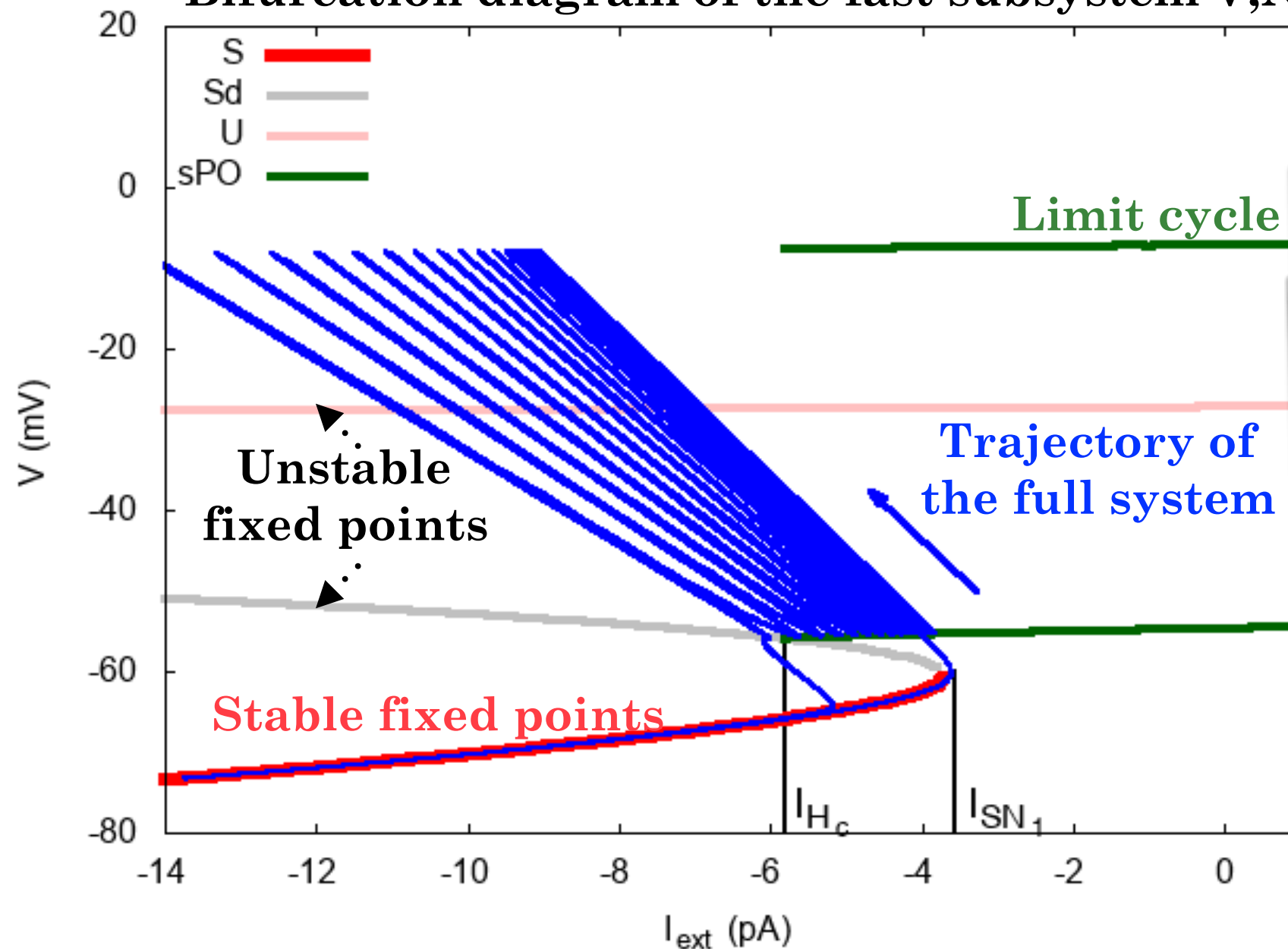


# The mechanism of bursting revealed through bifurcations

What do we learn about SACs?

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Bifurcation diagram of the fast subsystem V,N



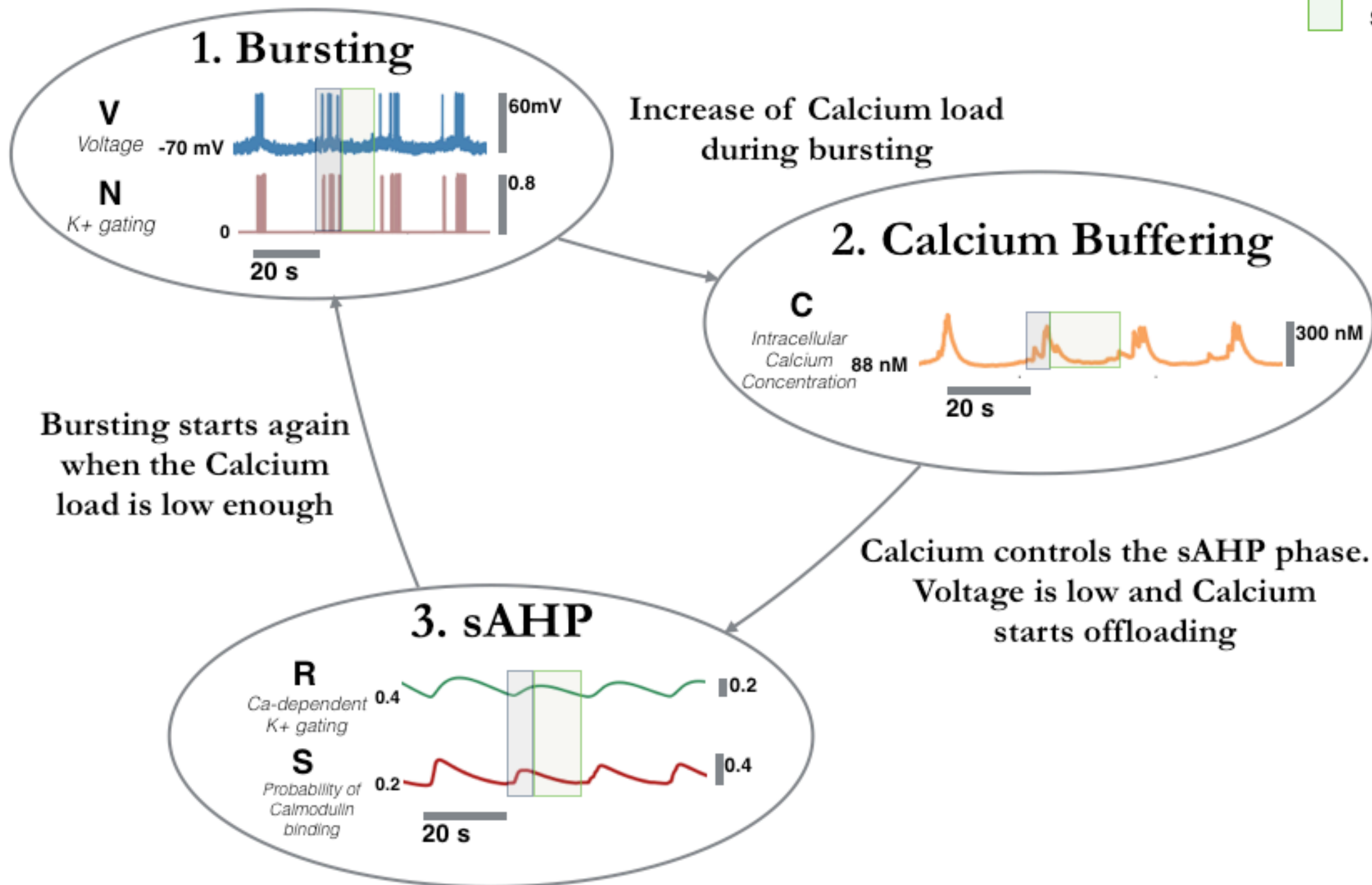
Due to time scale separation, we make the approximation and superimpose the trajectory of the full system on the bifurcation diagram

$$I_{sAHP} = g_{sAHP}^m R^4 (V - V_K)$$

# The mechanism of bursting revealed through bifurcations

## The biophysical interpretation

■ Bursting  
■ sAHP

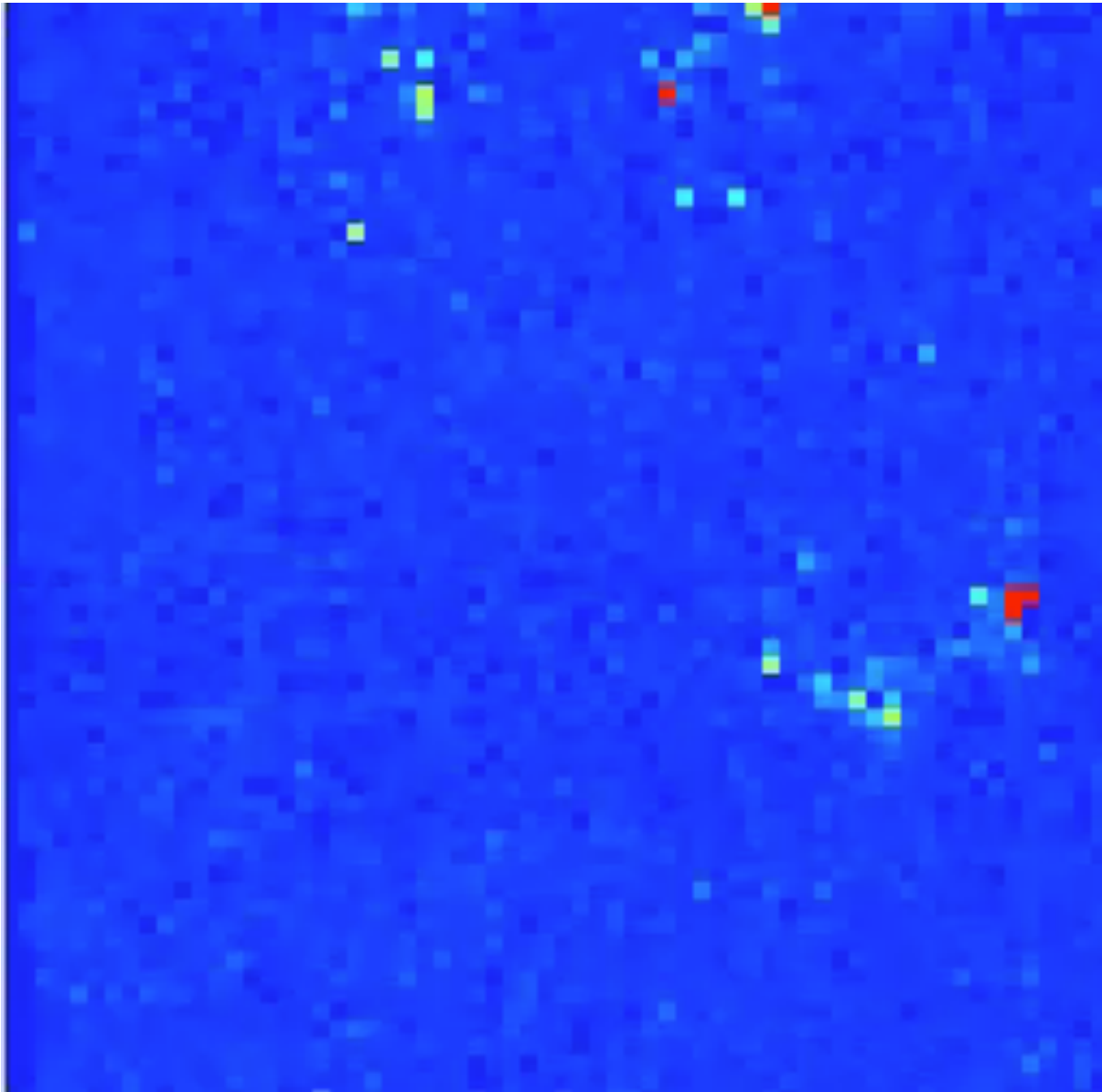




How do waves  
propagate and stop?

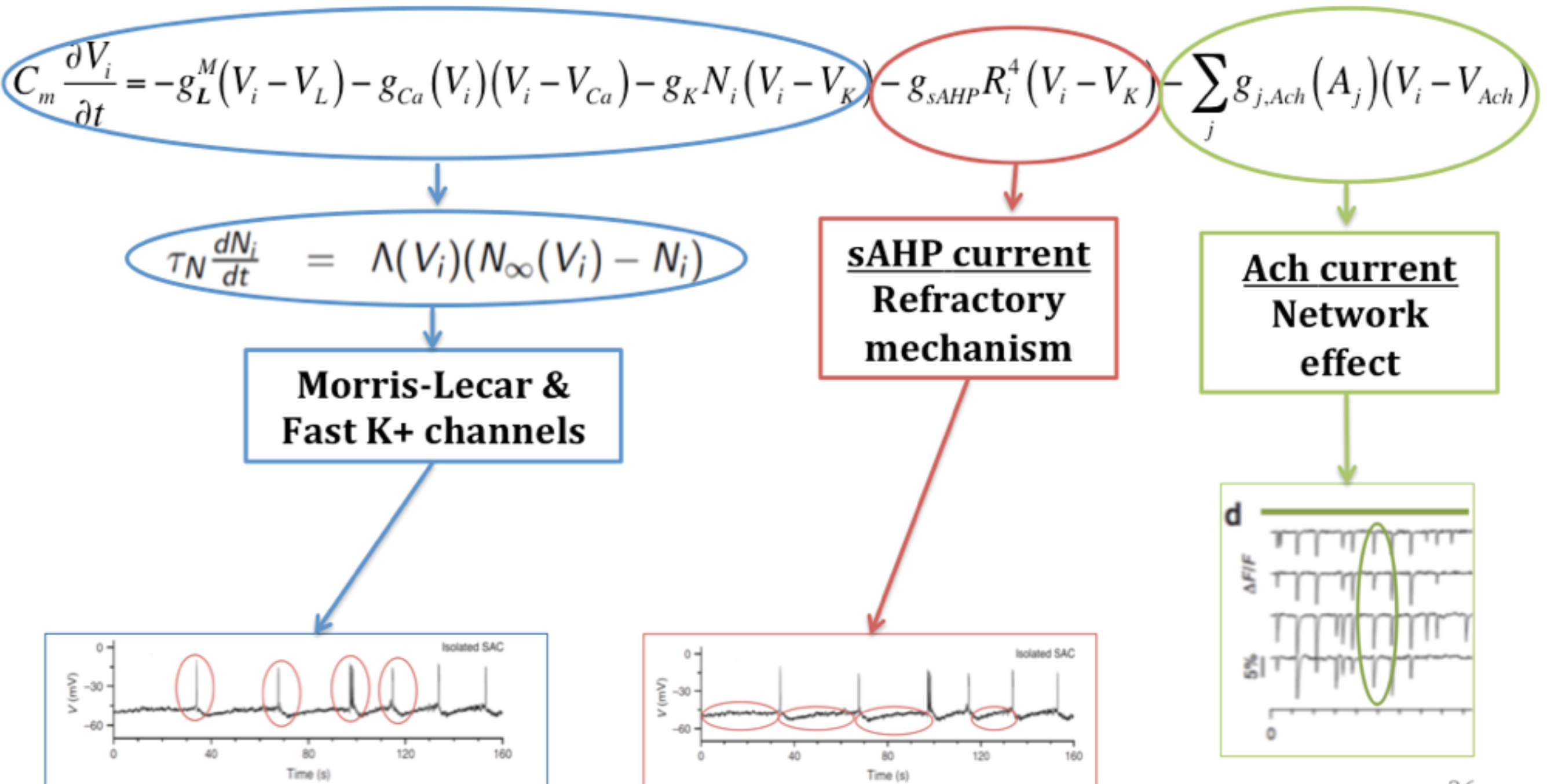
2. D. Karvouniari et al., *Spontaneous emergence of spatio-temporal structure in the early retina*, (under preparation for Phys. Review E)

# How do waves propagate?

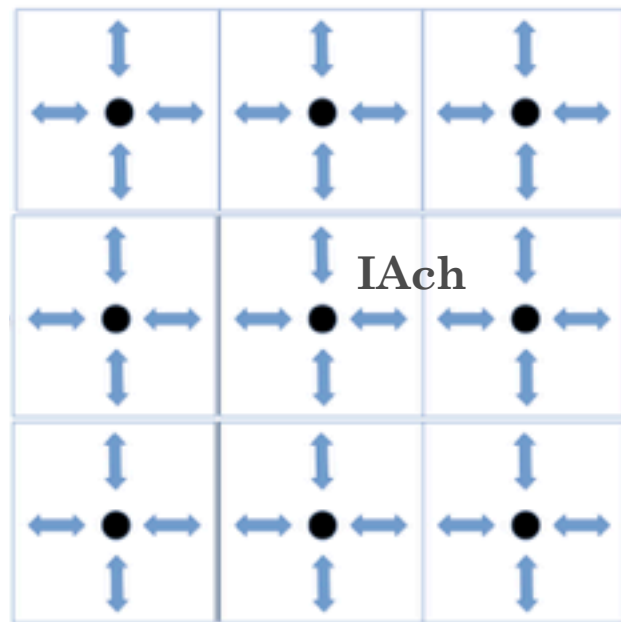


- **Full interacting waves are a complex paradigm**
- **Waves propagate in a landscape changing constantly**
- **It is hard to extract a mechanism of propagation**

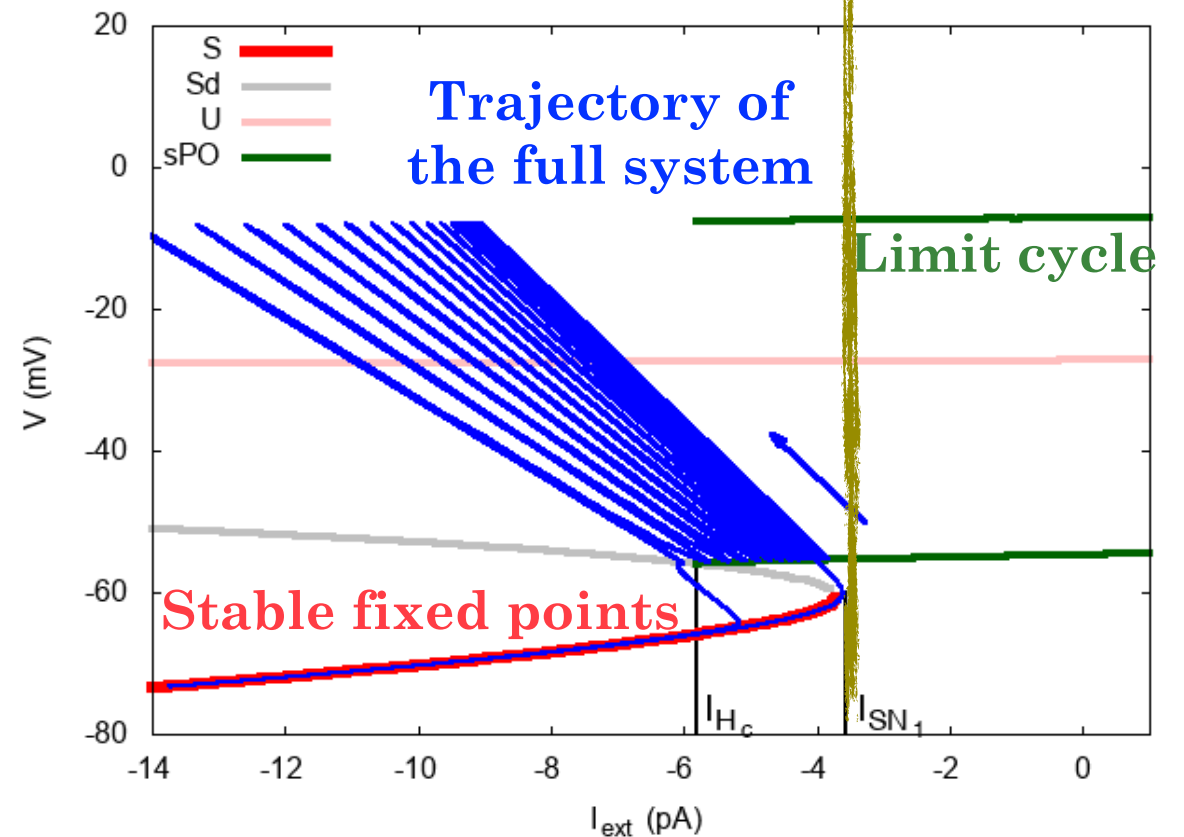
# A network model of stage II retinal waves



# Condition for wave propagation: $I_{Ach} + I_{sAHP} = I_{SN}$



SACs become points on  
a lattice

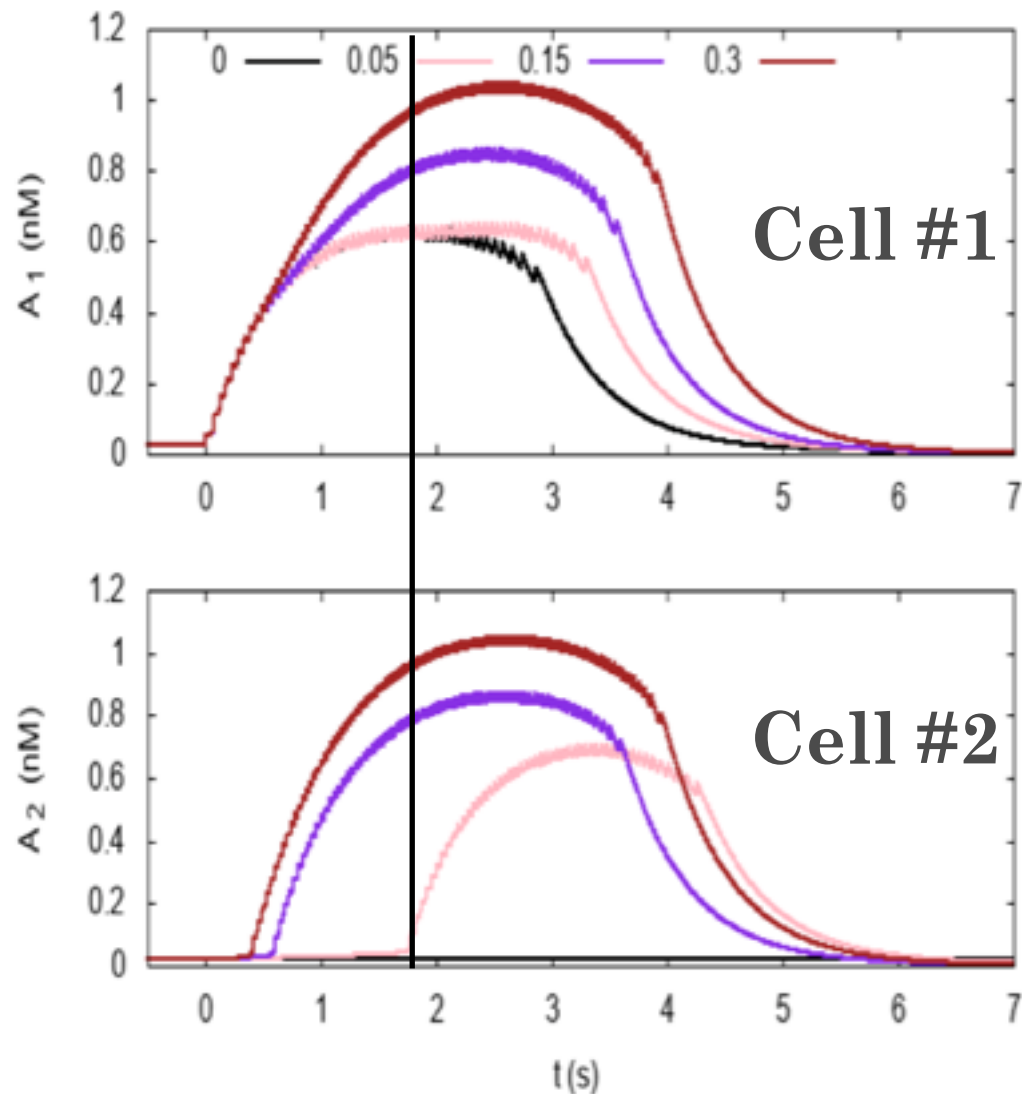


$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K) + I_{Ach} + I_{sAHP}$$

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

# The coupled dynamics of 2 SACs

Ach profile



Condition for bursting to start:

$$I_{Ach} + I_{sAHP} = I_{SN}$$



Response Time

$$t_i = -\frac{1}{\mu} \log \left( 1 + \frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \left( \frac{I_{SN} + g_{sAHP}R^4(V_- - V_K)}{g_A(V_- - V_A)} \right) \right)$$



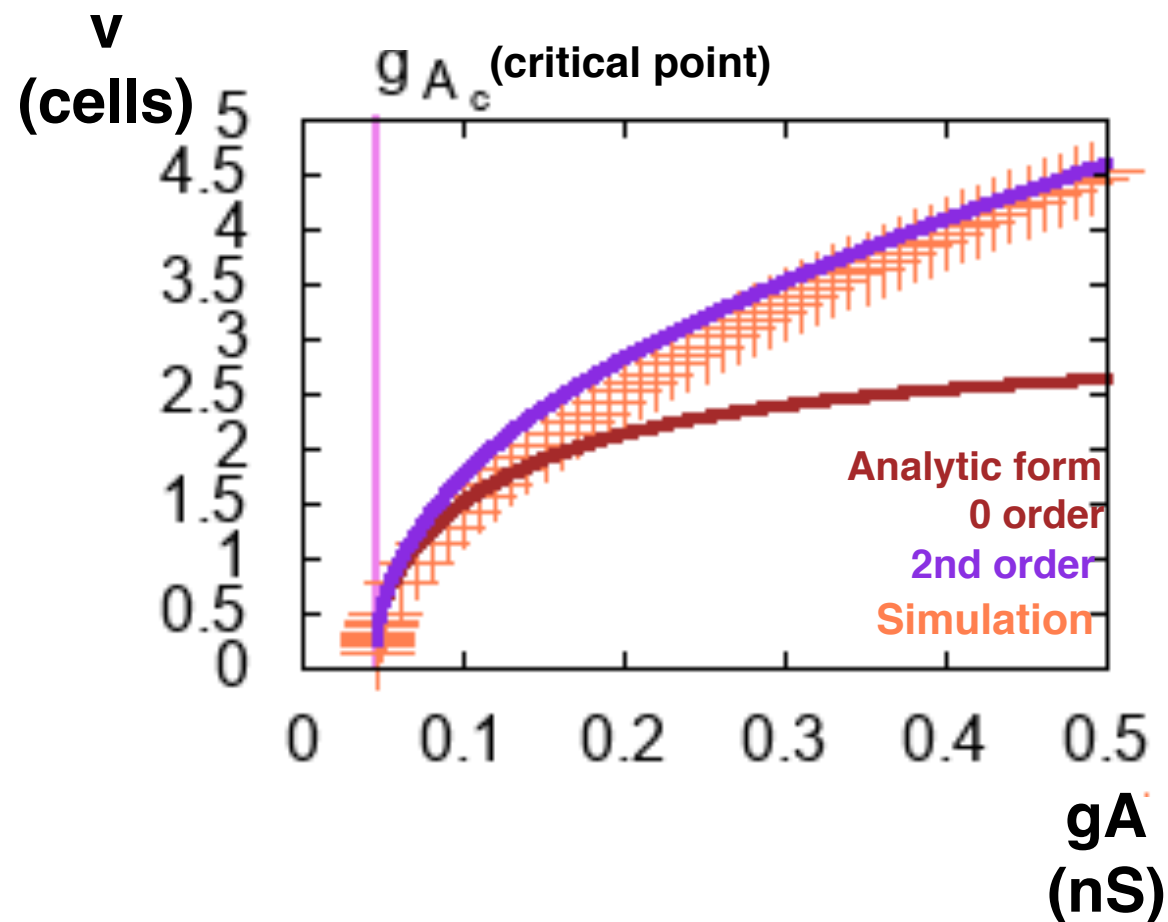
Waves speed

$$v_0 = \frac{1}{t_C - \frac{1}{\mu} \log \left( 1 + \frac{1}{g_A} \frac{2\mu\sqrt{\gamma_A}}{d\beta\Omega} \left( \frac{I_{SN} + g_{sAHP}R^4(V_- - V_K)}{(V_- - V_A)} \right) \right)}$$



# Analytic form of waves propagation coupling threshold

## Waves speed (1D)



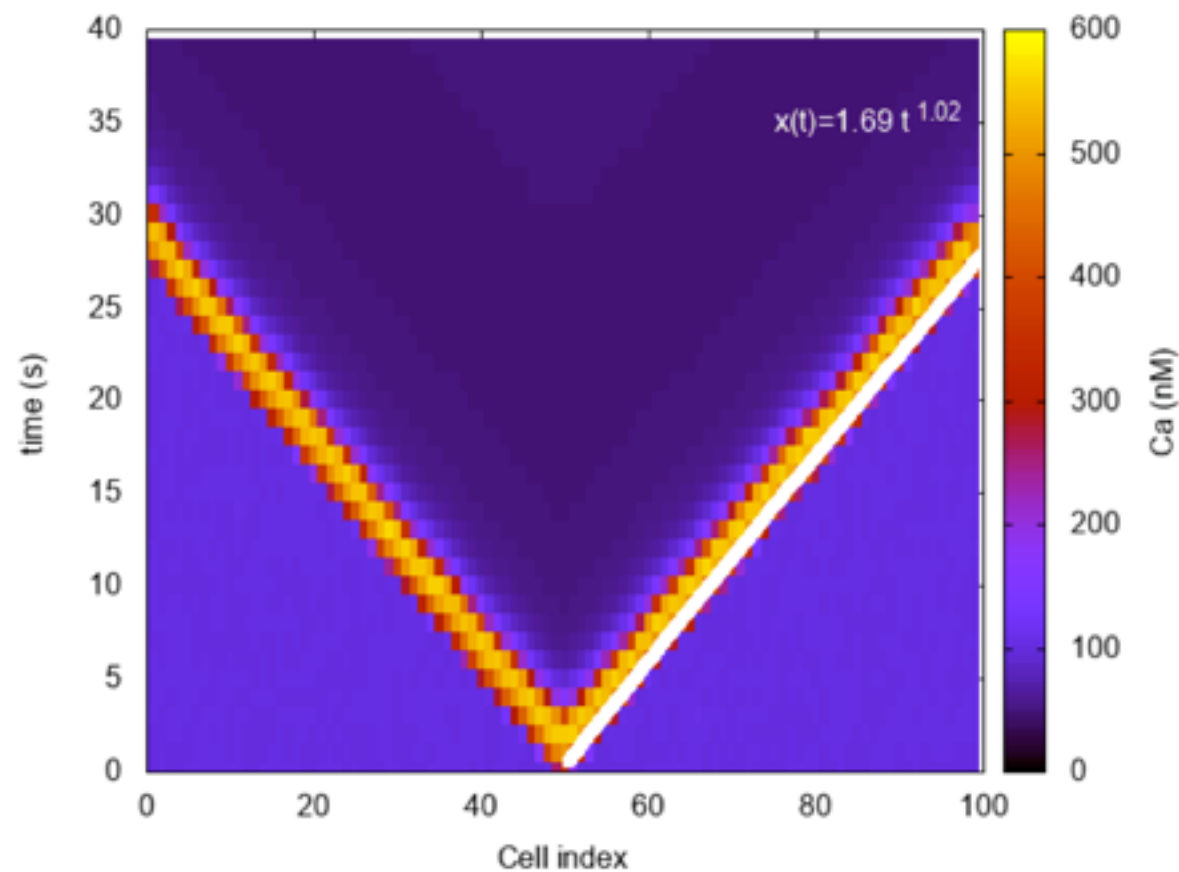
- For the zero order approximation we assumed that  $V_-$ ,  $R$  and  $\Omega$  do not depend on  $gA$ . **Fit holds for smaller  $gA$**

Based on our model, where wave propagation is only possible when the **total current received by a neighbouring cell exceeds the** (saddle-node) **bifurcation threshold**, we extract the analytic form for the waves propagation coupling threshold (1D case).

$$g_{A_c} = -\frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \frac{I_{SN} + g_S R^4 (V_- - V_K)}{V_- - V_A}$$

# Propagation in 1D without friction

$$g_A > g_{A_c}$$

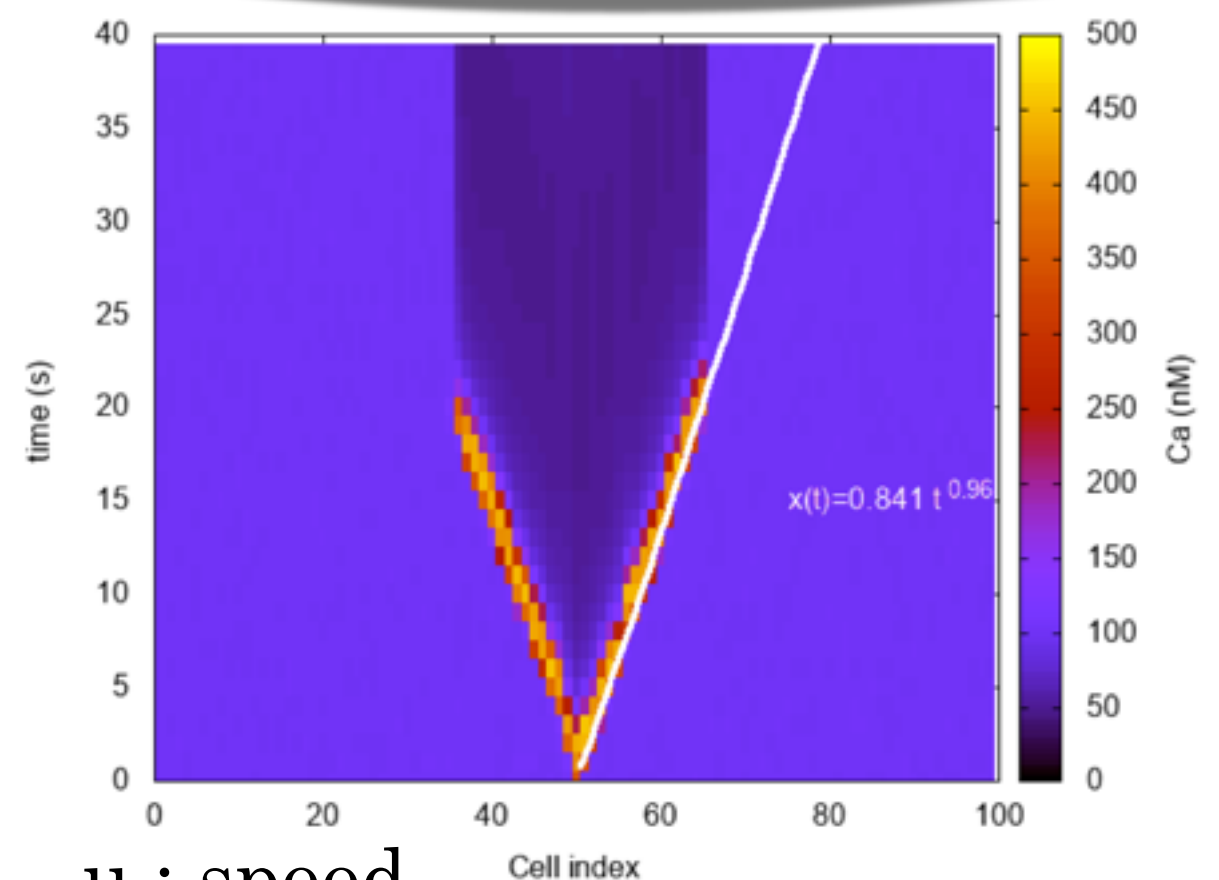


**Fitting trajectory:**

$$\langle \rho \rangle = \rho_0 + vt^z$$



$$g_{A_c} = -\frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \frac{I_{SN} + g_S R^4 (V_- - V_K)}{V_- - V_A}$$



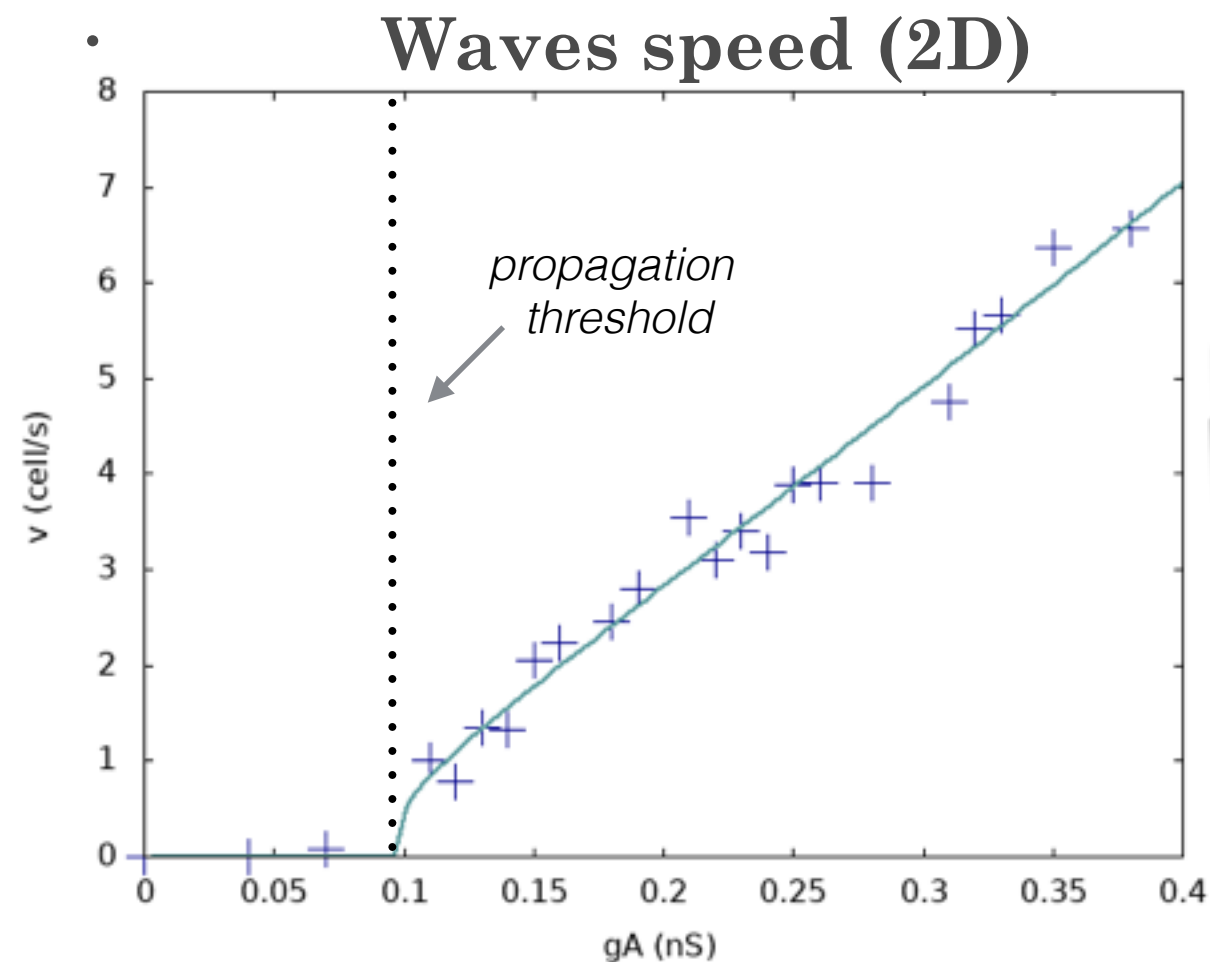
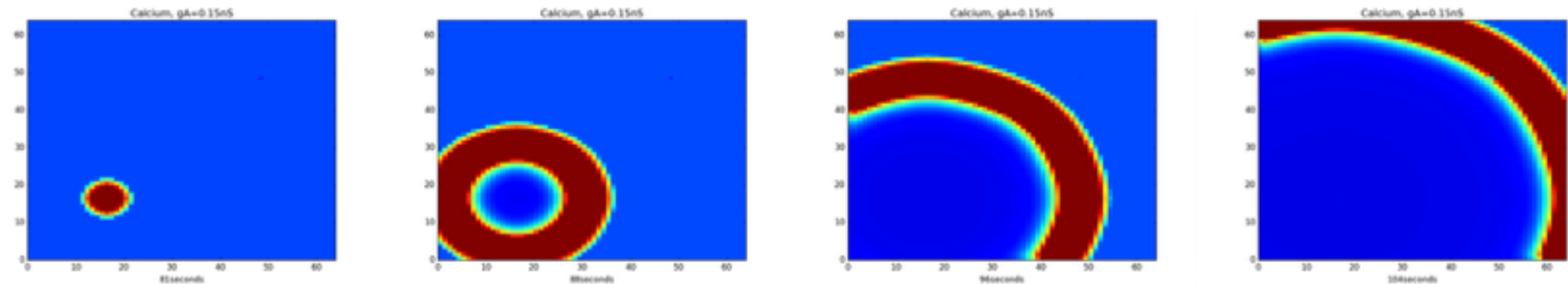
u : speed

z : propagation exponent  
(e.g. z=1 ballistic)

- Around the propagation threshold, waves could stop even without friction, due to noise and the fact that the Ach current is not sufficient to fulfil the propagation condition

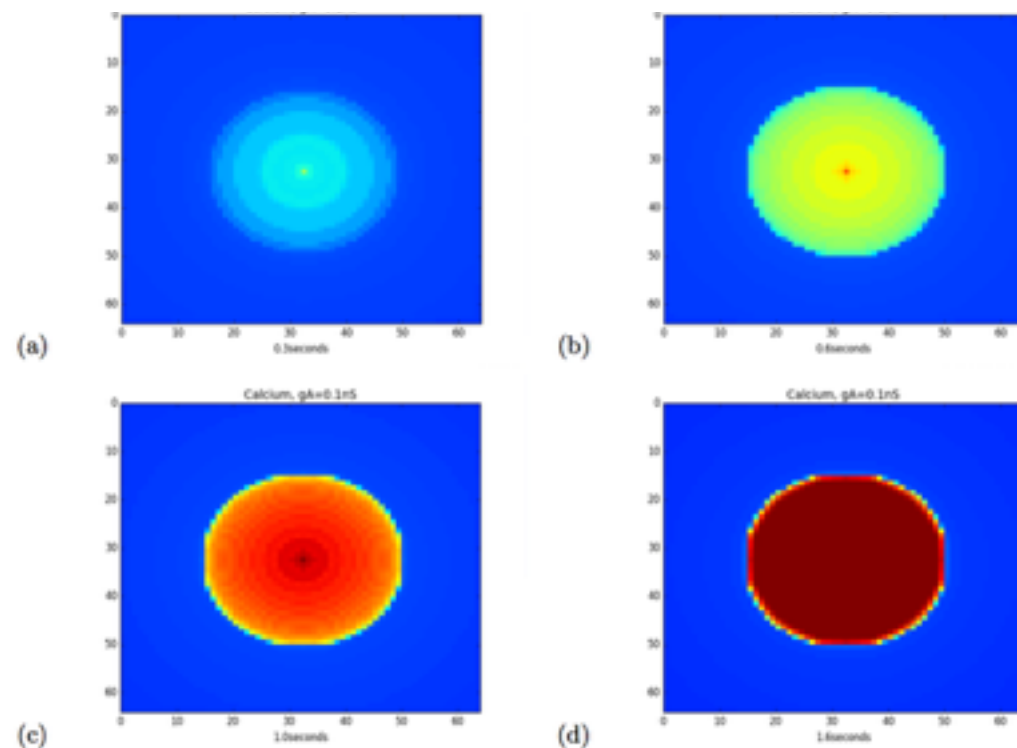
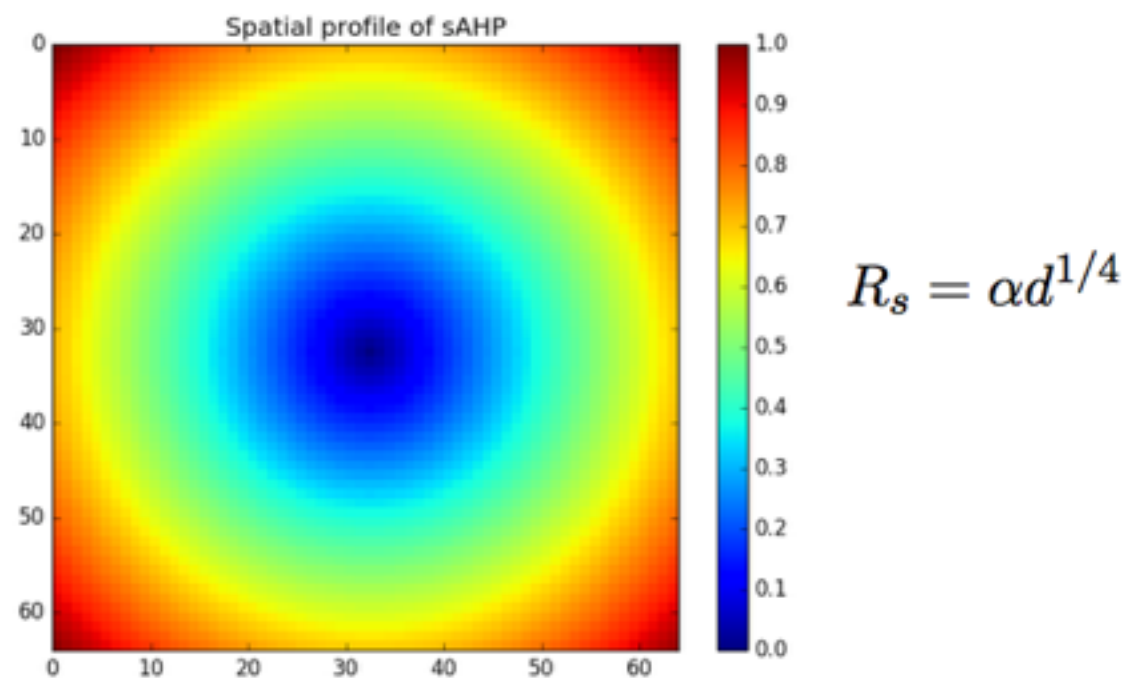
# Propagation in 2D without friction

Approximation, free propagation no friction, all cells are at rest



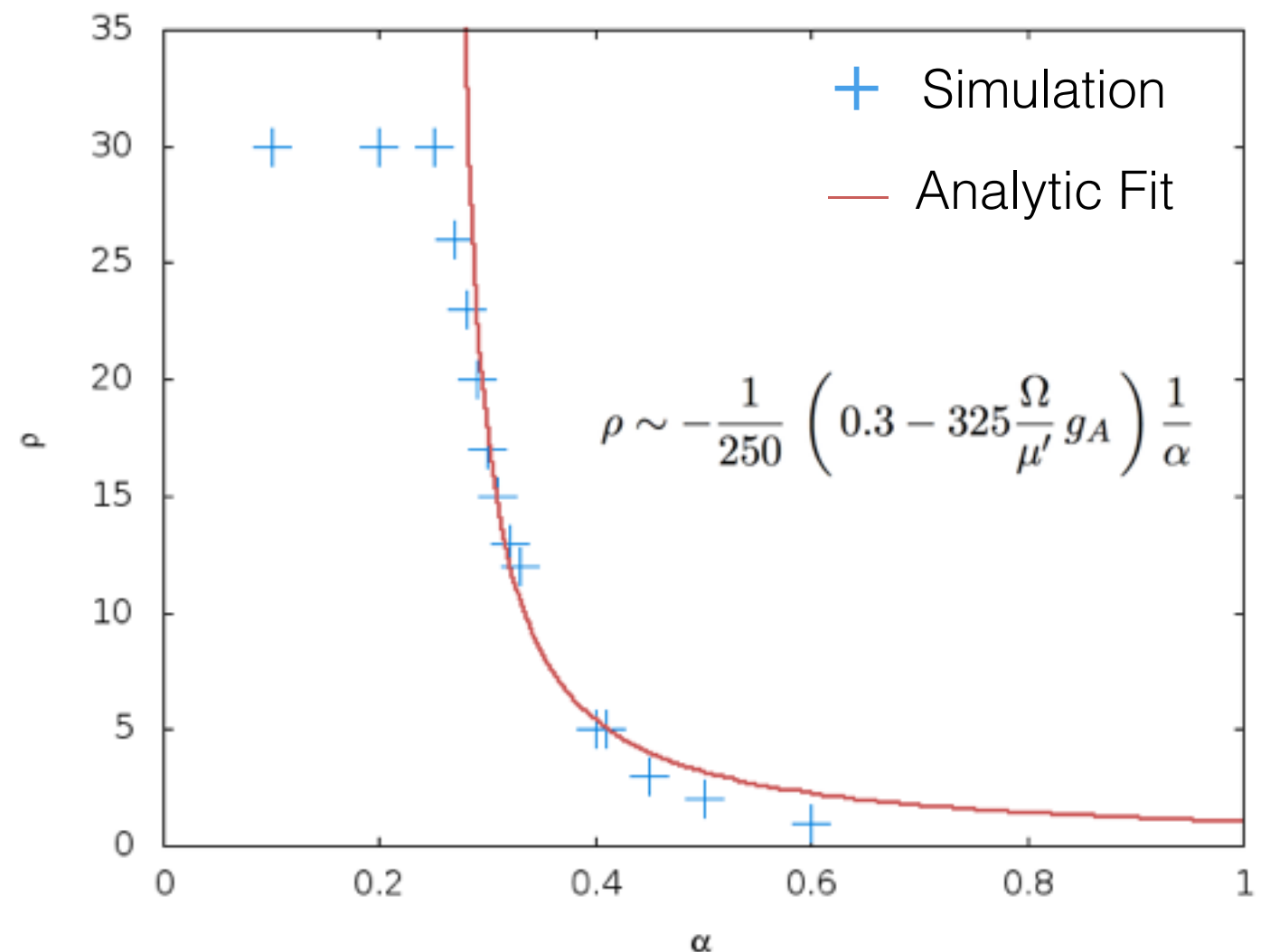
- **The speed increases with the coupling strength**

# How do waves stop? The sAHP saga



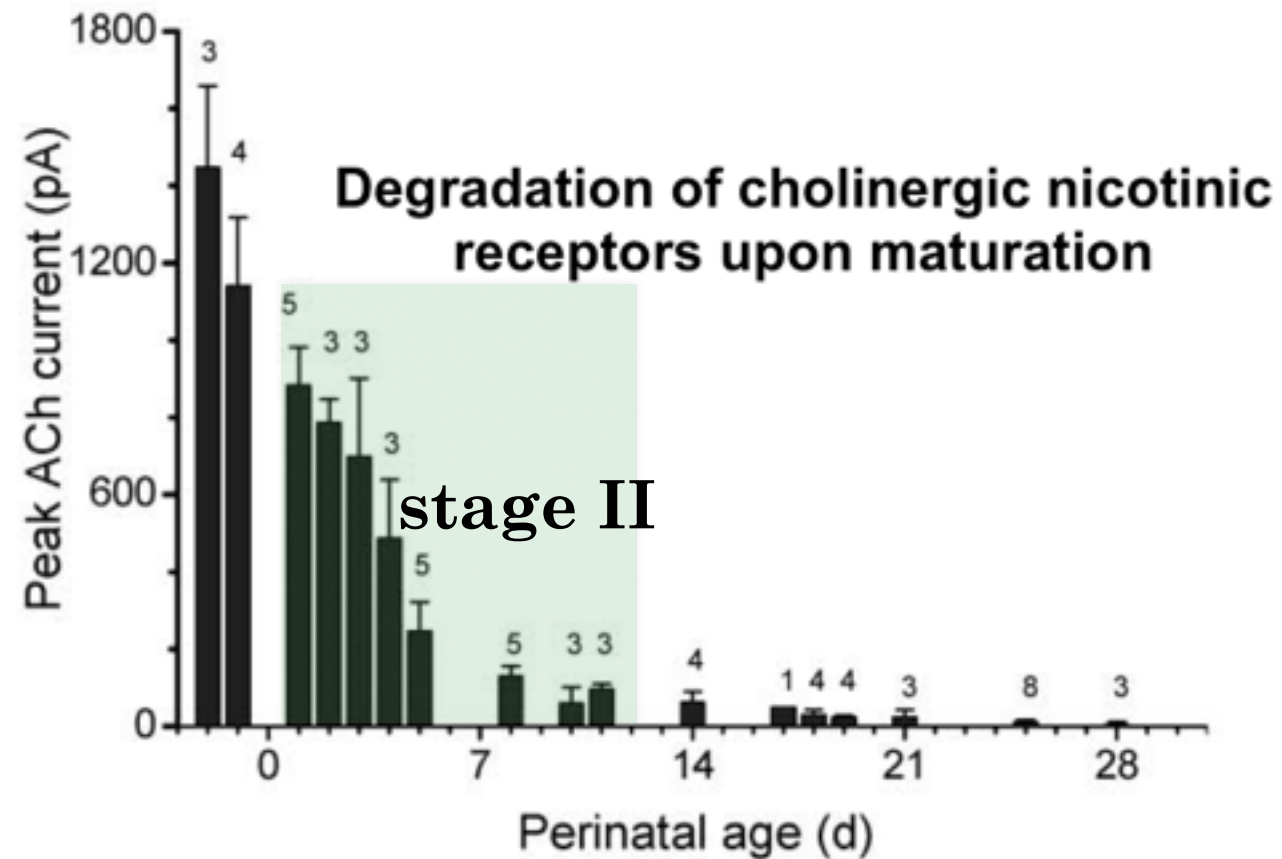
Example of a wave propagation  
in a radial landscape of R

Max Waves size as a  
function of the strength of sAHP

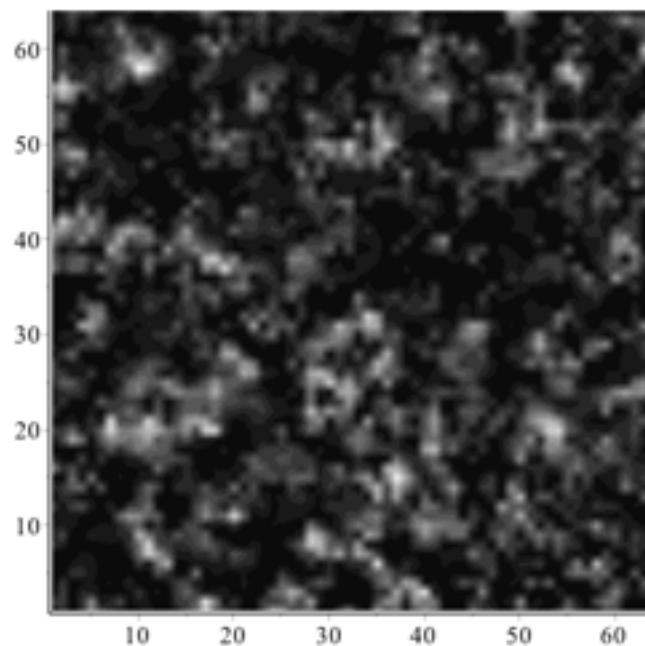


The waves size decreases  
hyperbolically  
with the strength of sAHP

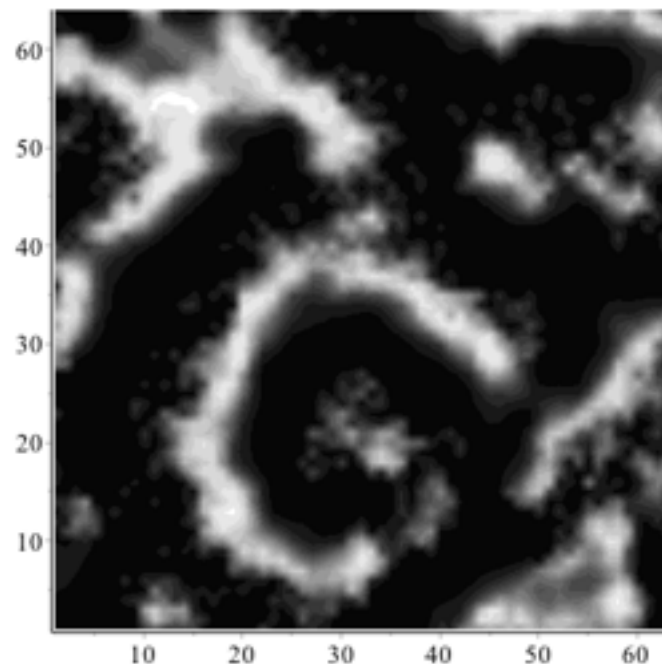
# Patterns evolve within stage II



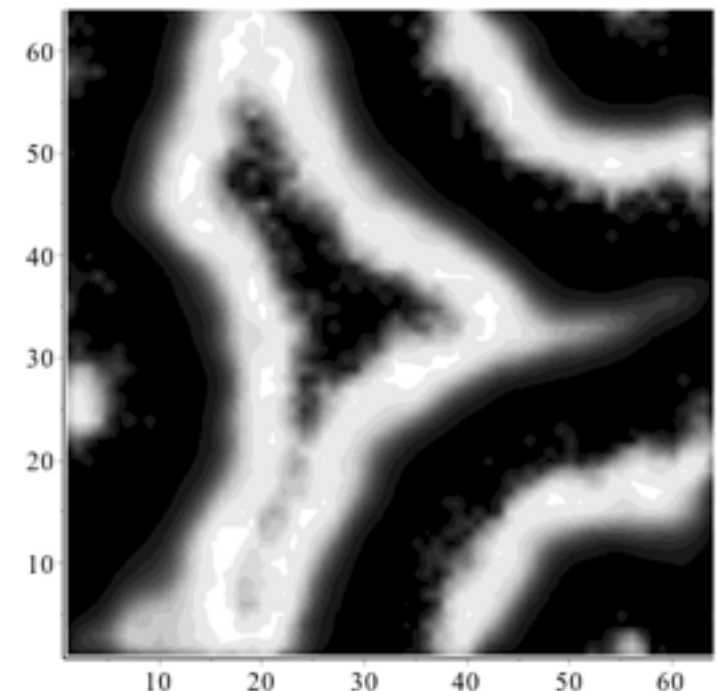
Weak



Moderate

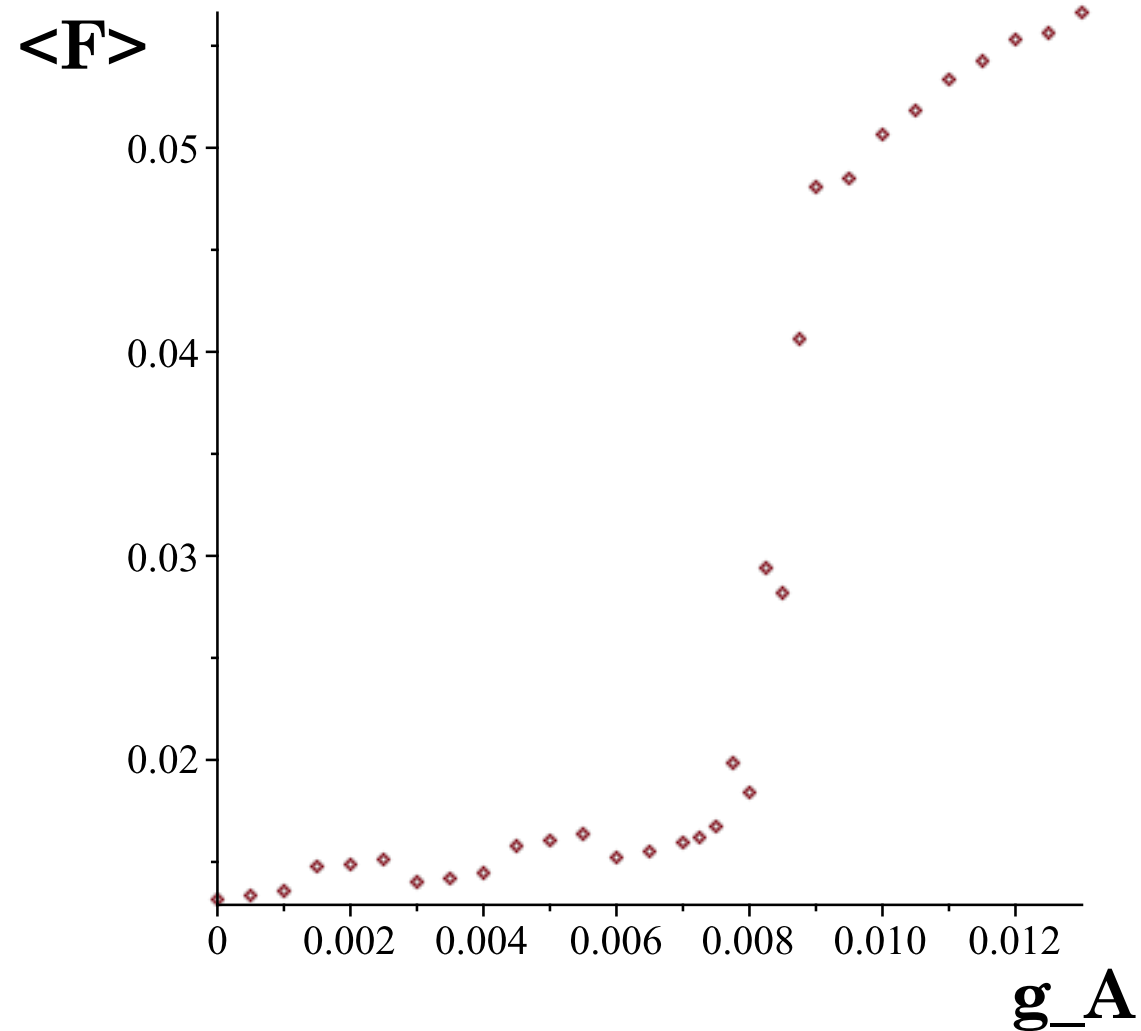


Strong

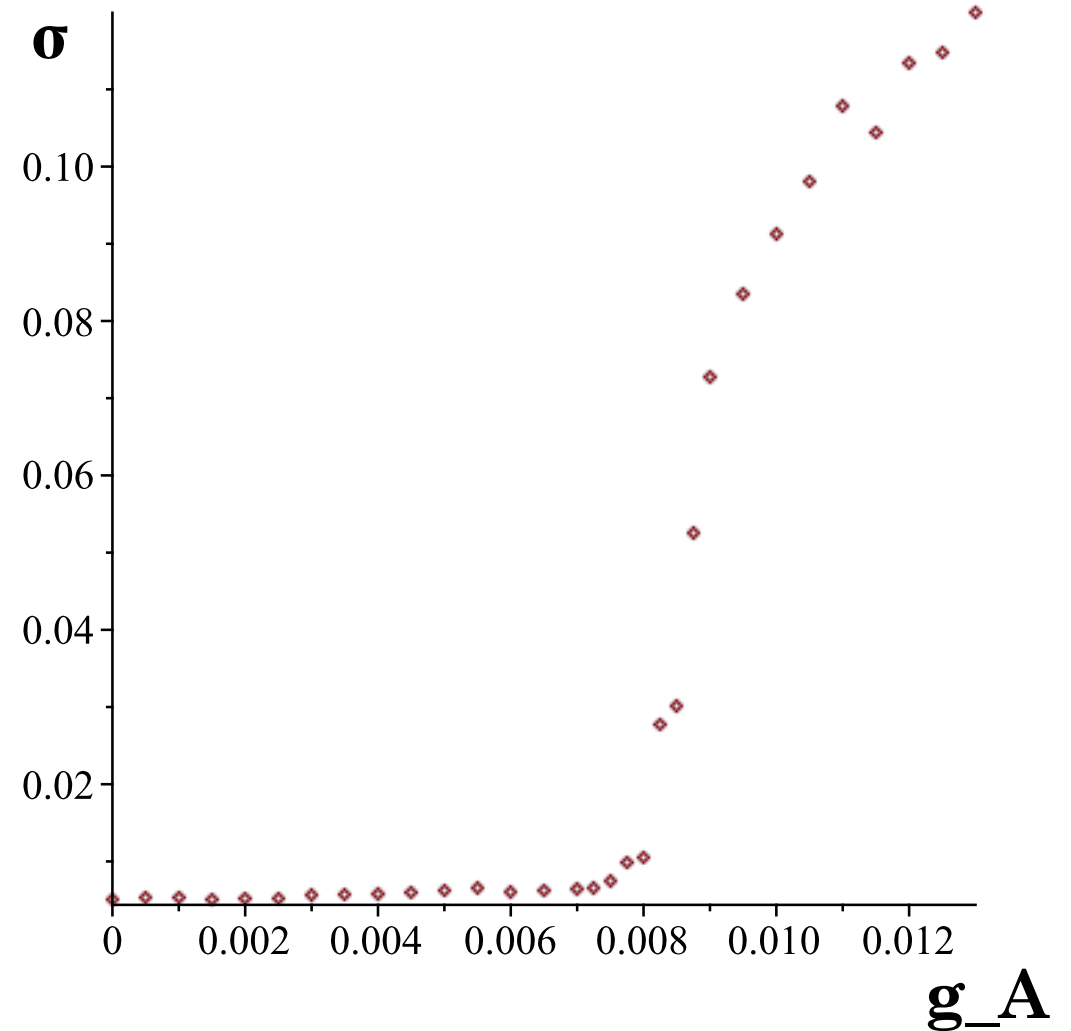


# Synchronisation Transition

Average population firing rate



Standard deviation firing rate

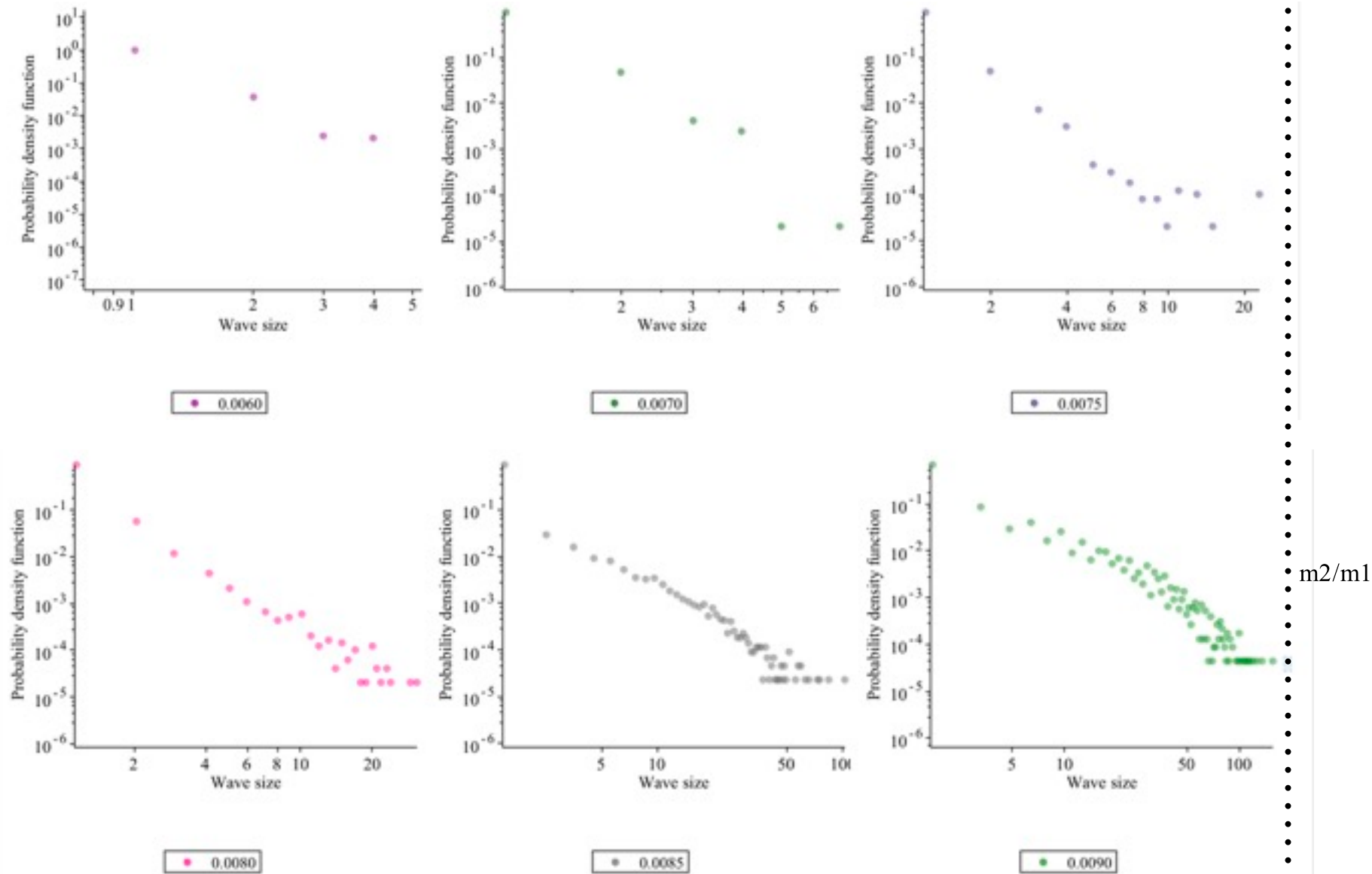


The average and the std of the population firing rate undergo a transition at a specific range of cholinergic coupling



# Synchronisation Transition

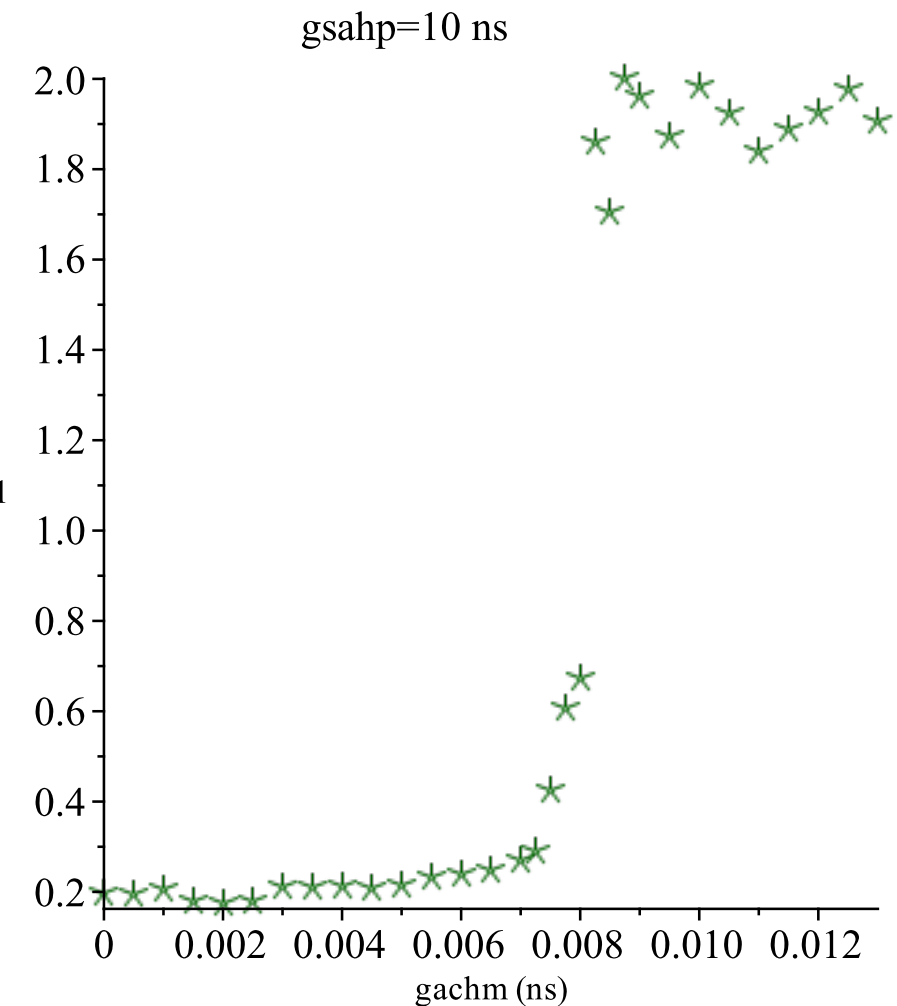
## Distribution of waves sizes



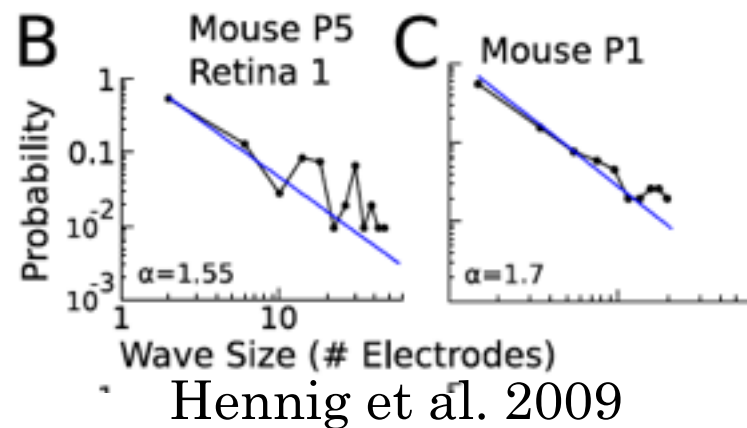
Our model indicates the existence of power law like distributions for waves sizes for a range of coupling strength

## Fano coefficient

Ratio of mean and standard deviation of a distribution



# Indications for criticality in experiments



- Hennig et. al 2009 also found **power law -like distributions** for the waves sizes
- Criticality is a precise concept in physics and **power law distributions are not enough** to characterise it
- Also, criticality is not a natural state and it is achieved by **bringing the system to a specific point**

## Two “critical” points:

- i) **Experimental data** need to be analysed in a **more elaborate way** to reveal the actual distributions of waves characteristics
- ii) If indeed there is criticality and power laws, then we miss a **mechanism that brings the system to the critical point**

# Conclusions & Perspectives

- **Analysing** the dynamics of our model using **dynamical systems theory** leading to a main hypothesis: **Immature SACs are near a bifurcation point!**
- **Consequences:**
  - individual SACs properties\*
  - how SACs lose their excitability upon maturation
  - explain variability of wave features across species
  - wave propagation conditions\*
  - criticality and power laws\*
  - spontaneous activity could be generated by a SACs network that is optimised for input processing=dynamic range
- **Future direction towards completing studying waves in a dynamically changing landscape**
- **Characterise criticality in our model and use the same tools to characterise experimental data**
- **Proposing new experiments** based on theoretical hypothesis

*Thank you all*  
:)