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Modelling spontaneous propagating waves in the early retina

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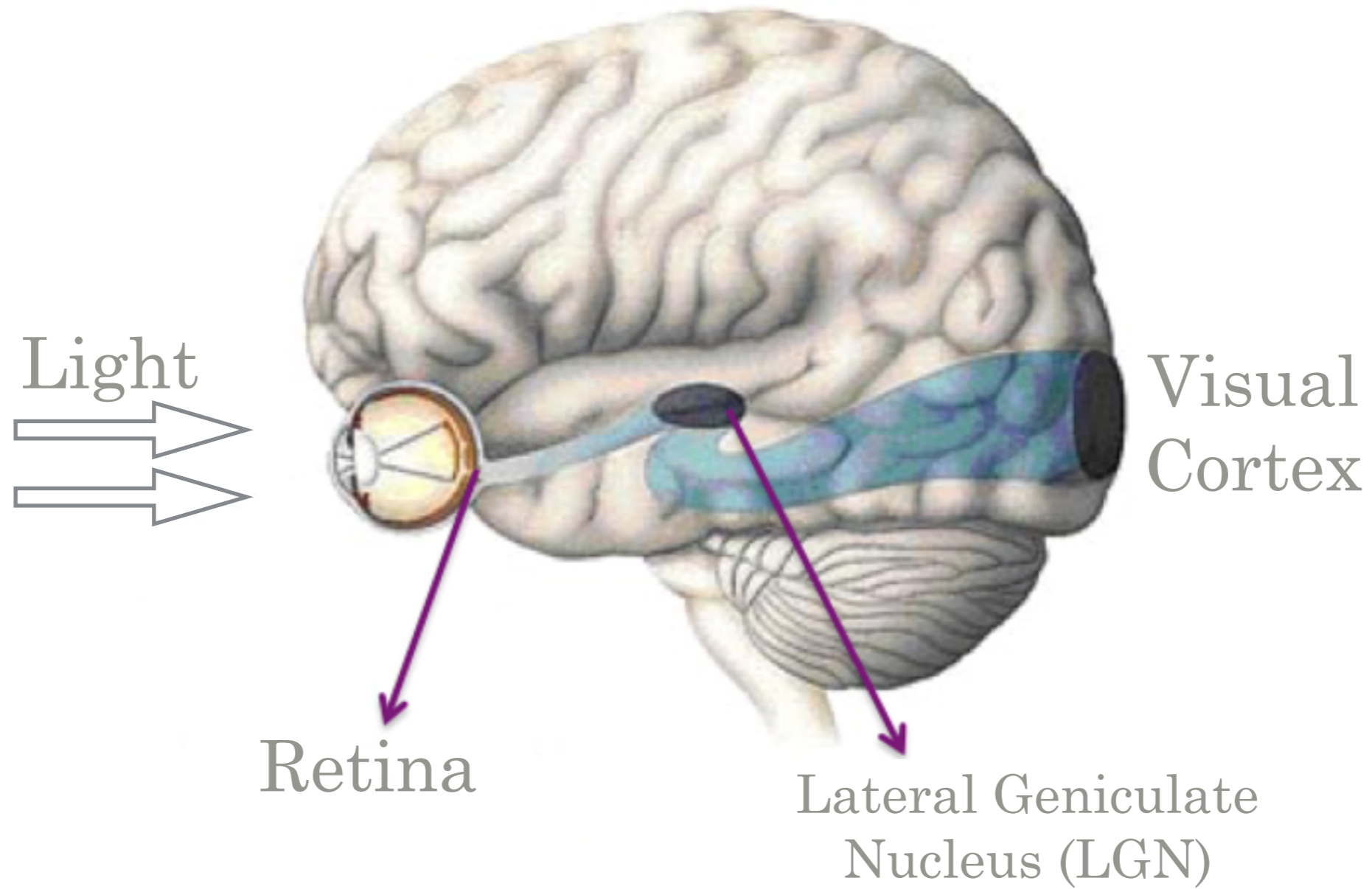
Modelling spontaneous propagating waves in the early retina

Dora Matzakos-Karvouniari, LJAD, UCA

Lionel Gil, INPHYNI, UCA

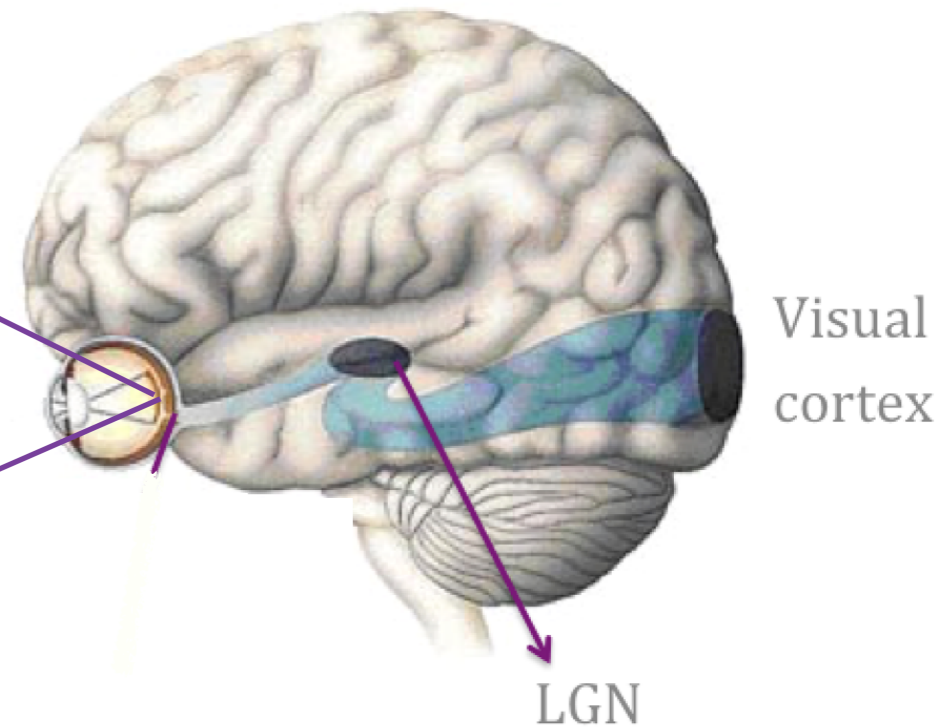
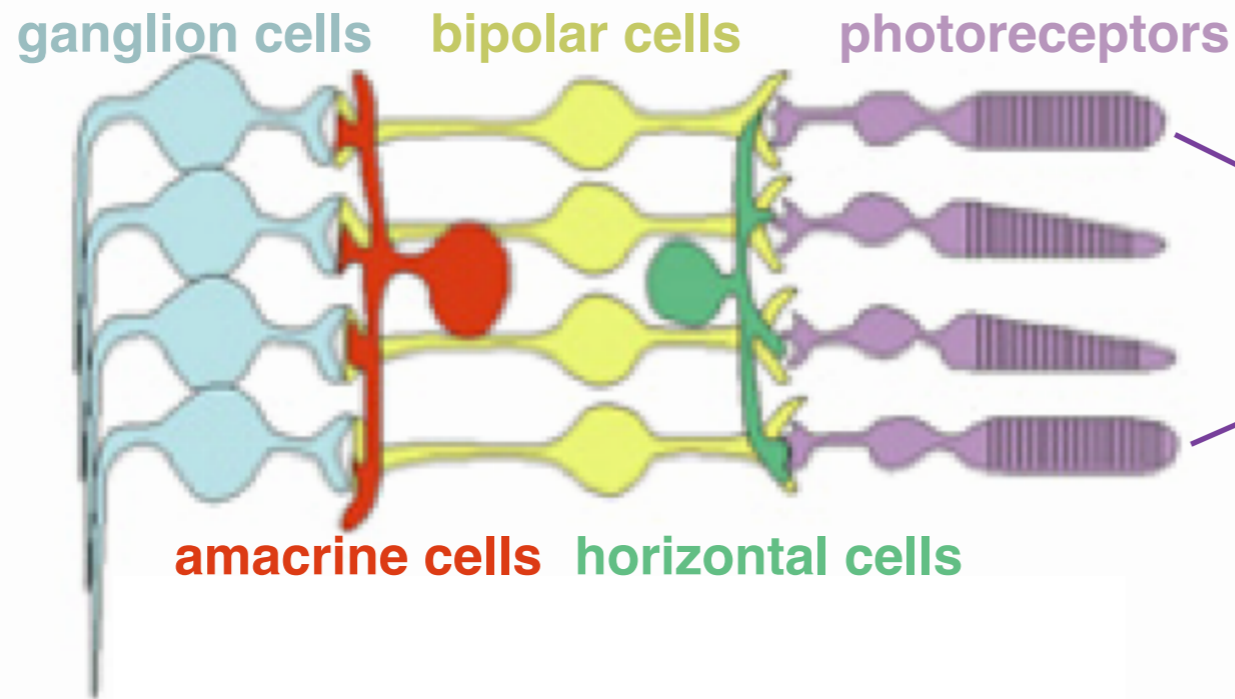
Bruno Cessac, Biovision, Inria

Visual system



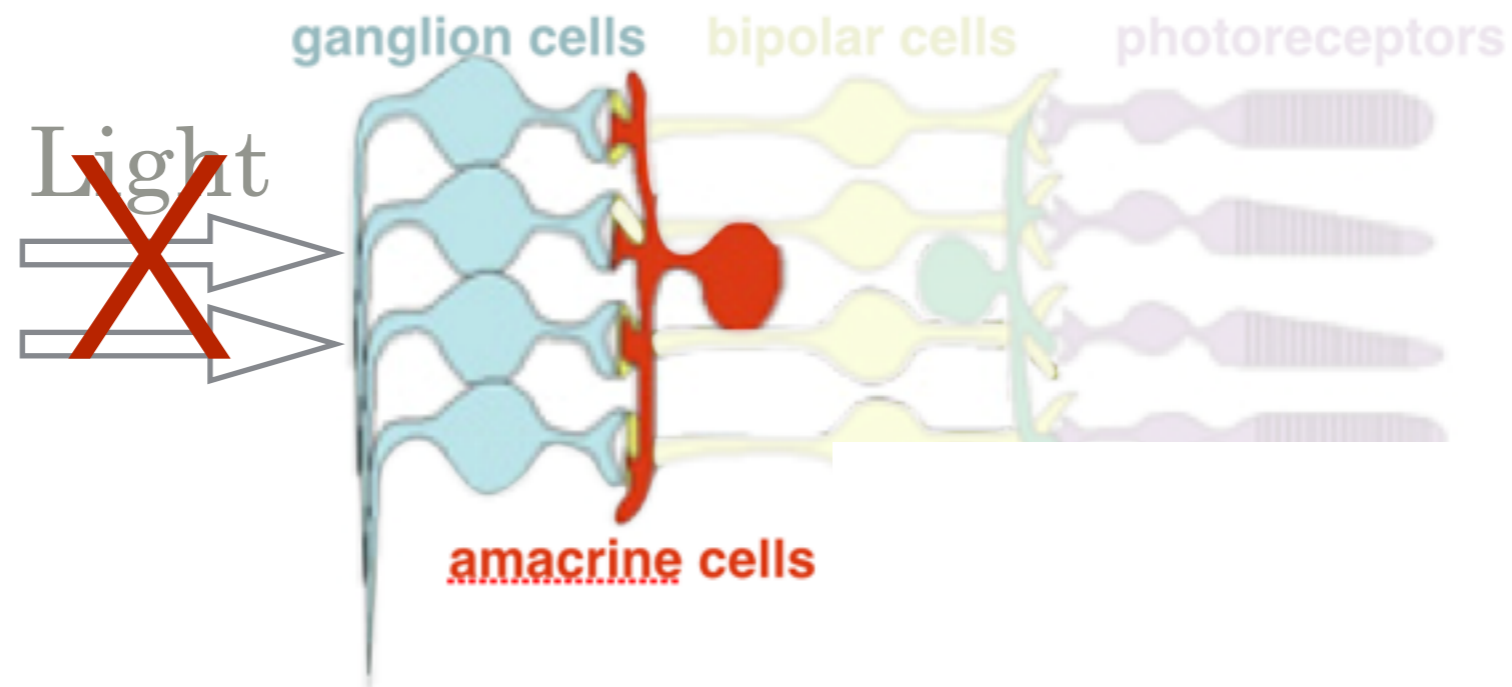
The structure of the adult retina

Retina's layered structure



The structure of the retina during development

Retina's layered structure is shaped during development



But How?

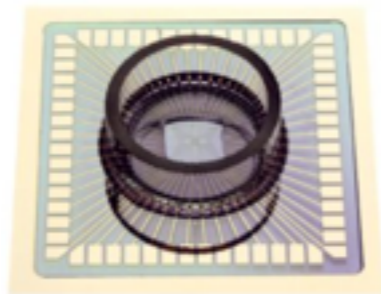
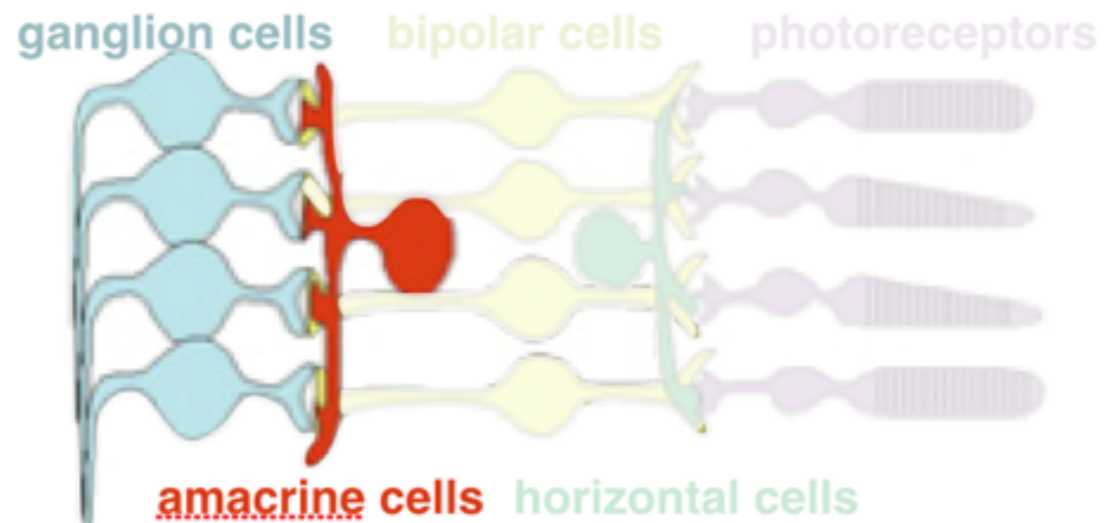


Retinal waves!

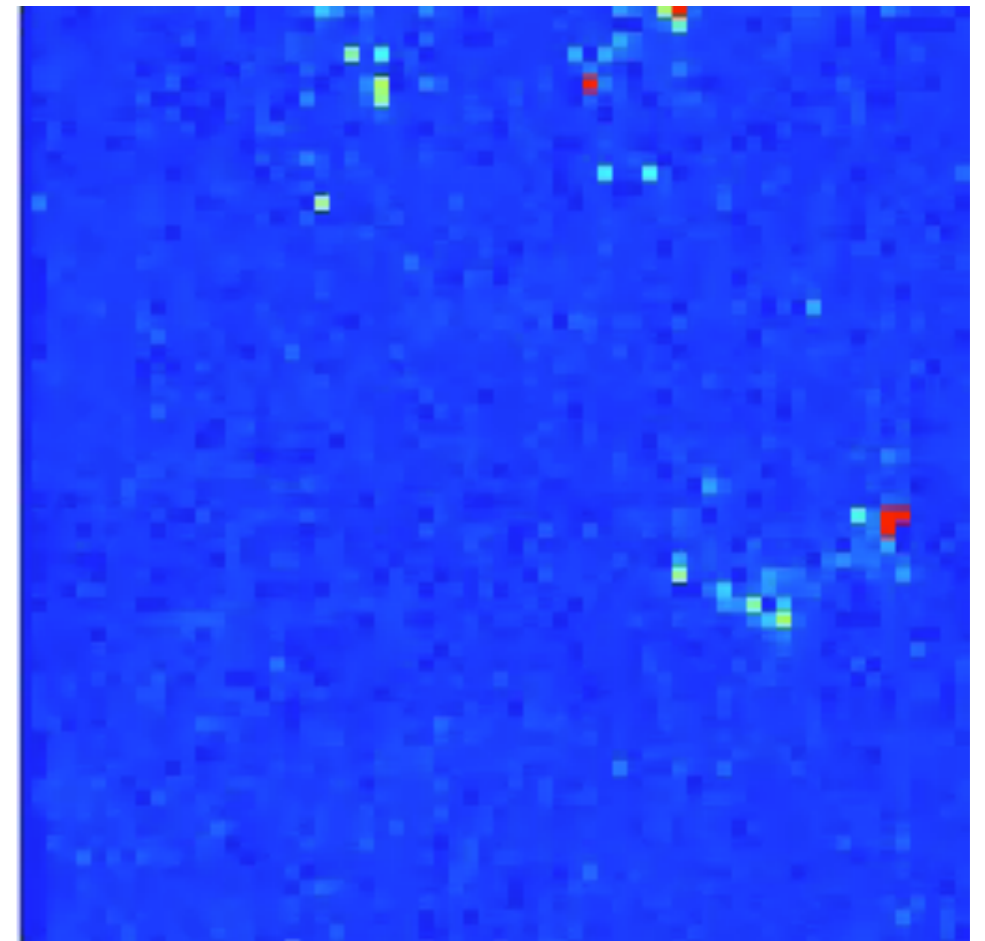
What are Retinal waves?

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

Recordings from the retina

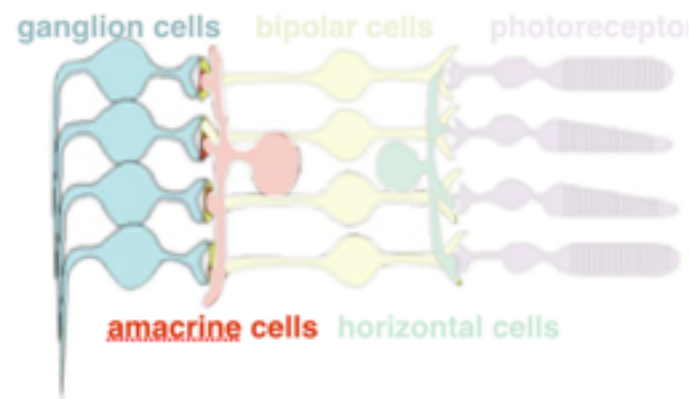
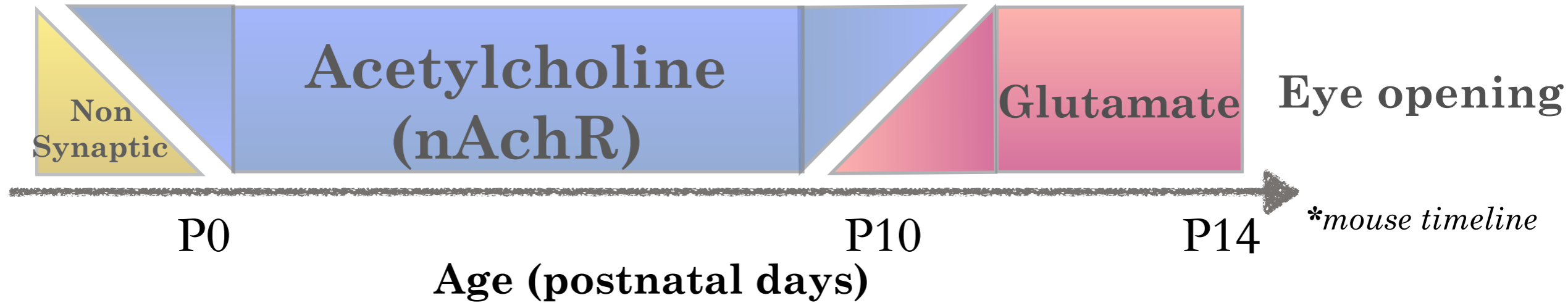


Multi-electrode array (MEA)



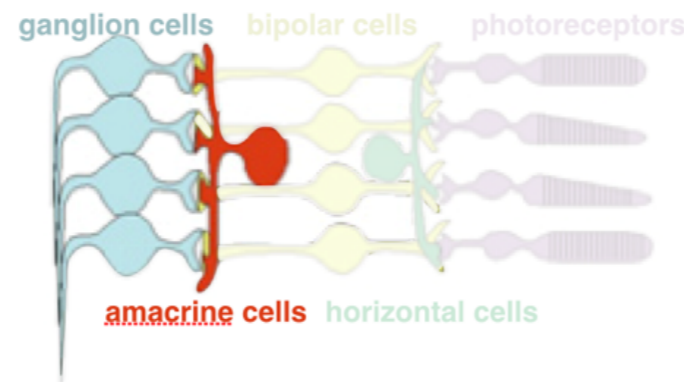
MEA recording of the voltage from a P11 mouse retina in the presence of 10 μ M bicuculline.

The timeline of retinal waves



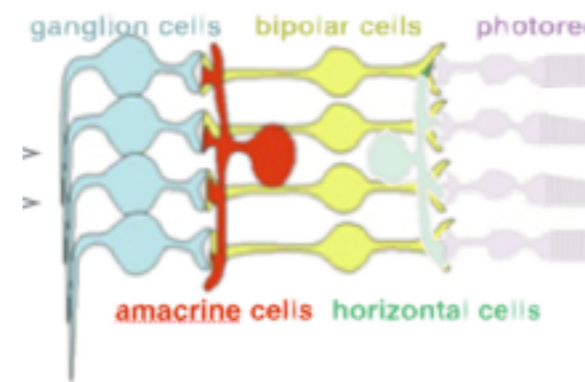
Stage I

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



Stage II

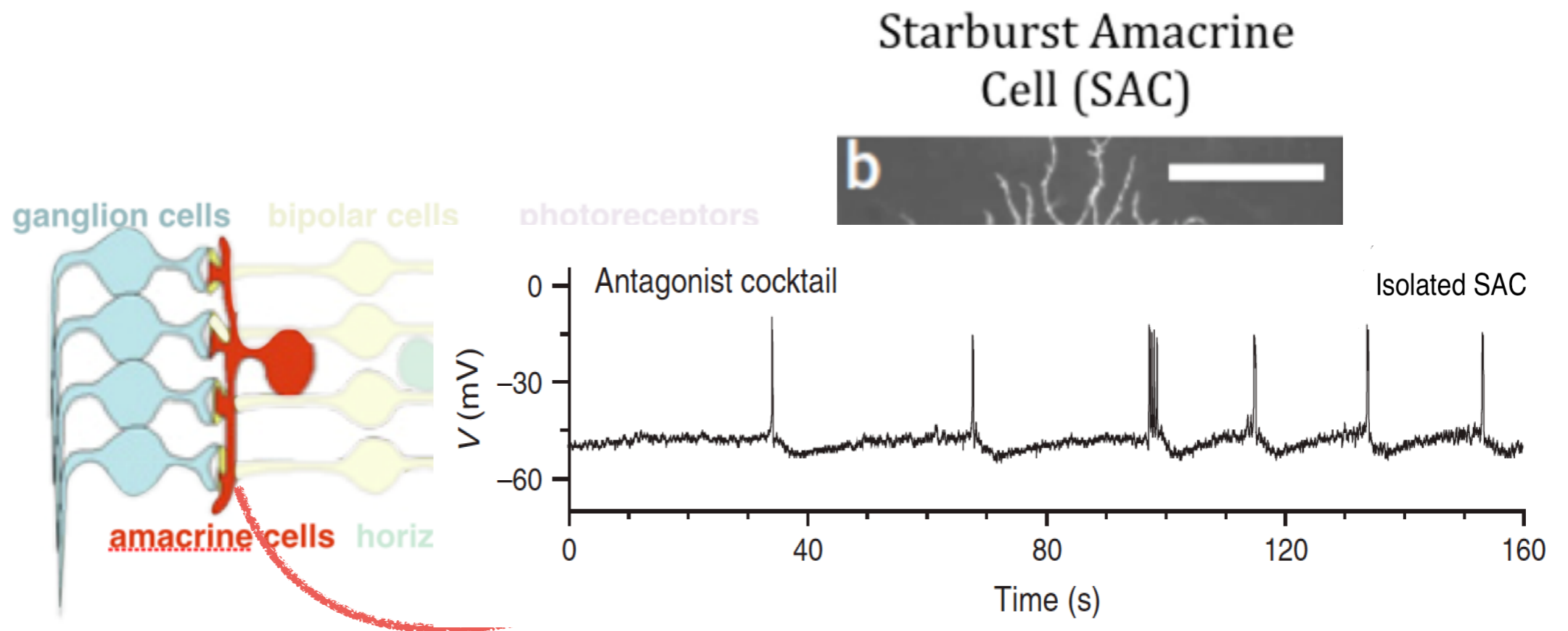
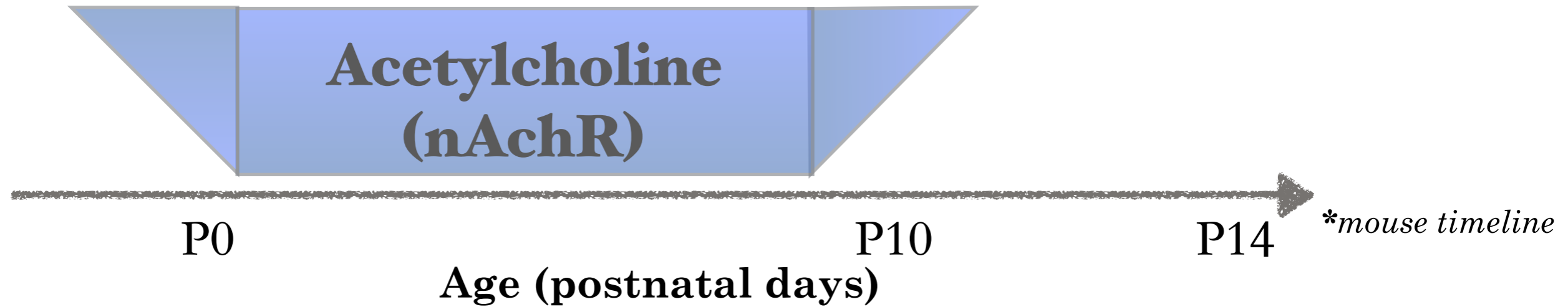
- Retinotopic mapping
- Eye specific segregation
- **Nicotinic Acetylcholine Receptors (nAchR)**



Stage III

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

Focusing on stage II retinal waves



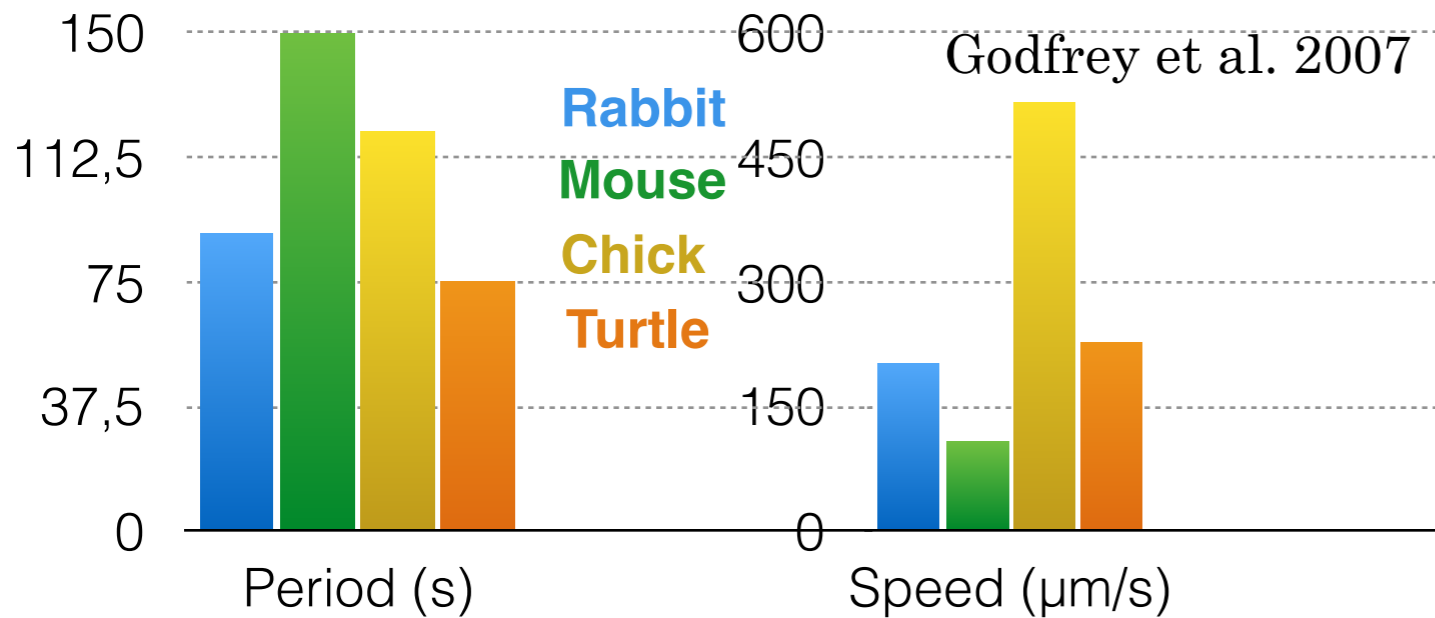
Zheng et al. 2006

Why modelling retinal waves is an interesting problem?

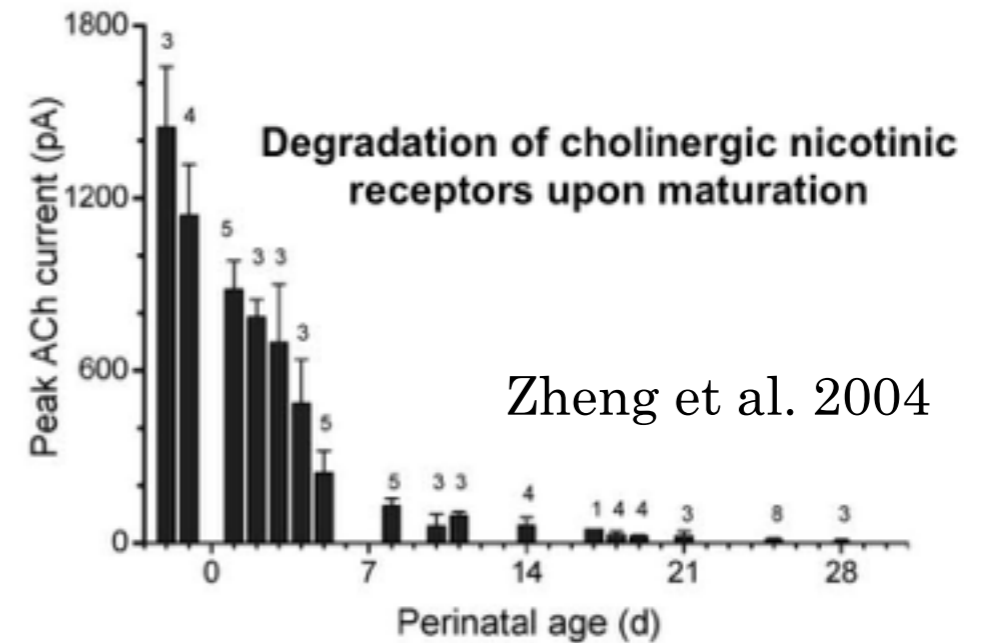
- Retinal waves **instruct the shaping** of the visual system
- Using biophysical modelling we could
 - i) find **generic principles**
 - ii) explain **experiments** and propose new onesleading to the better understanding of the underlying mechanisms of waves.
- The mathematical modelling of the dynamics 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

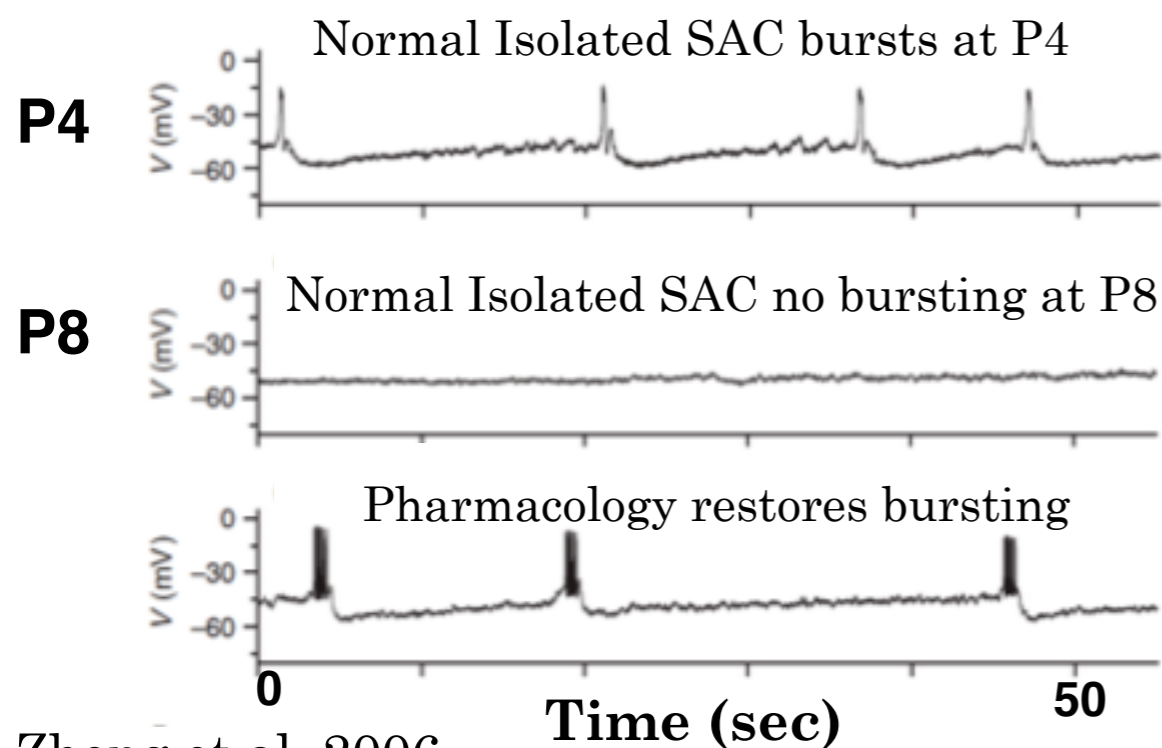
i) Across species



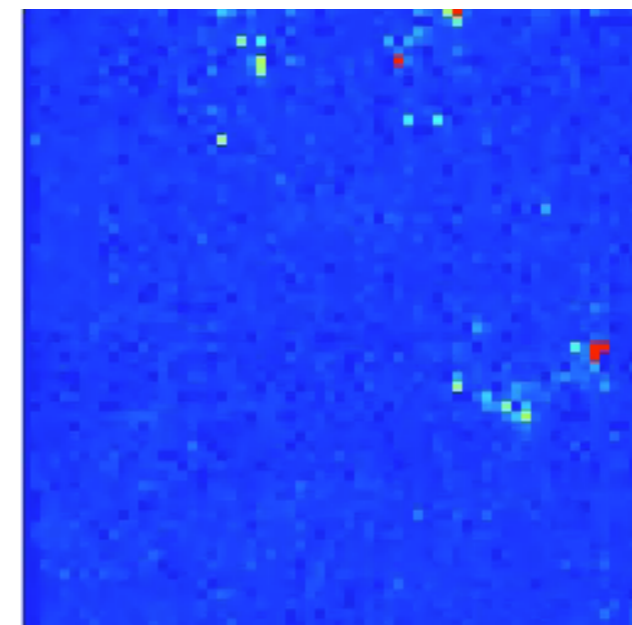
ii) Development



iii) Pharmacology



iv) Spatial Variability



Maccione et al. 2014

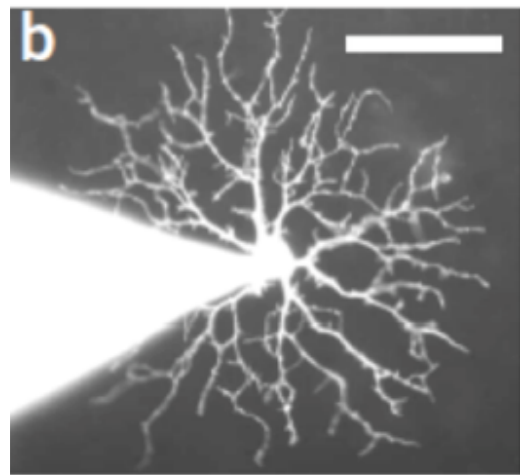
Waves have variable shapes due to a refractory mechanism which controls their borders. It is called sAHP (slow AfterHyperPolarization) for stage II.

Modelling stage II retinal waves dynamics

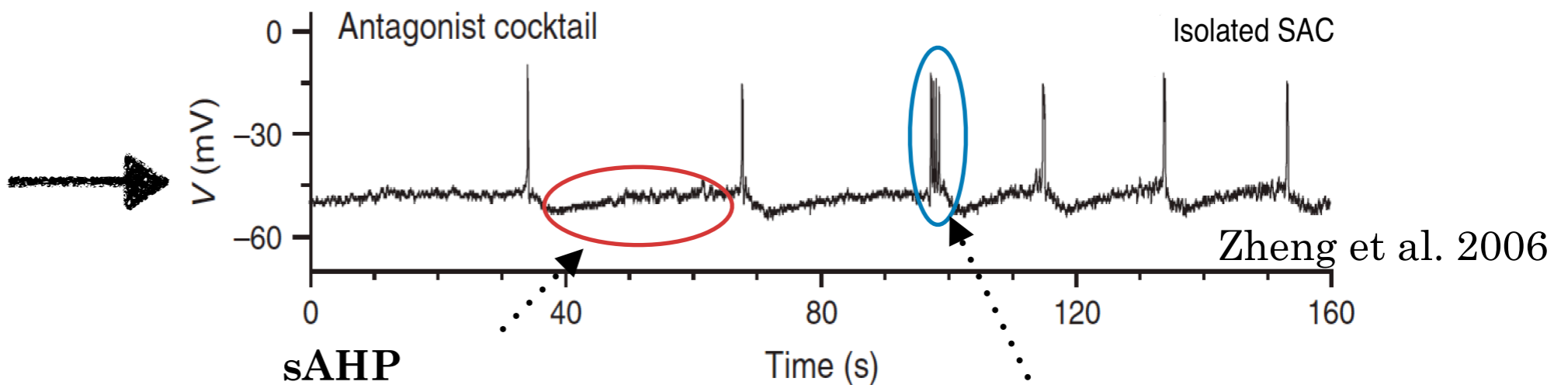
1. D. Matzakos-Karvouniari et al., *A biophysical model explains the bursting activity in the immature retina*, Nat Sci Rep, 2019

The biophysics of stage II retinal waves

Individual SACs burst spontaneously



Zheng et al. 2006

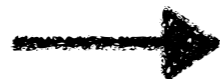
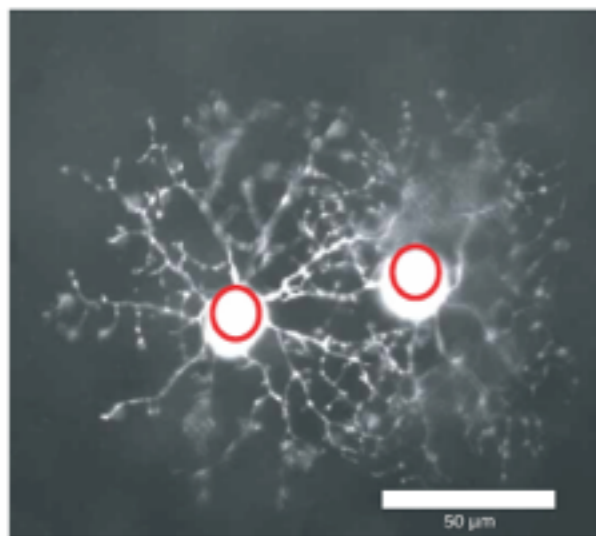


(slow AfterHyperpolarization)
Calcium regulated

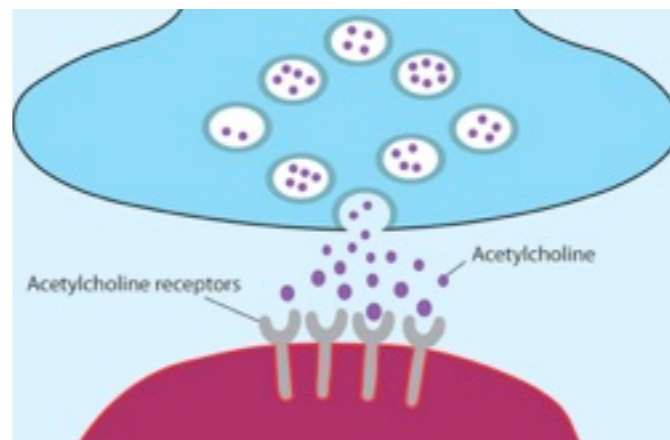
Spontaneous Fast oscillations

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

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

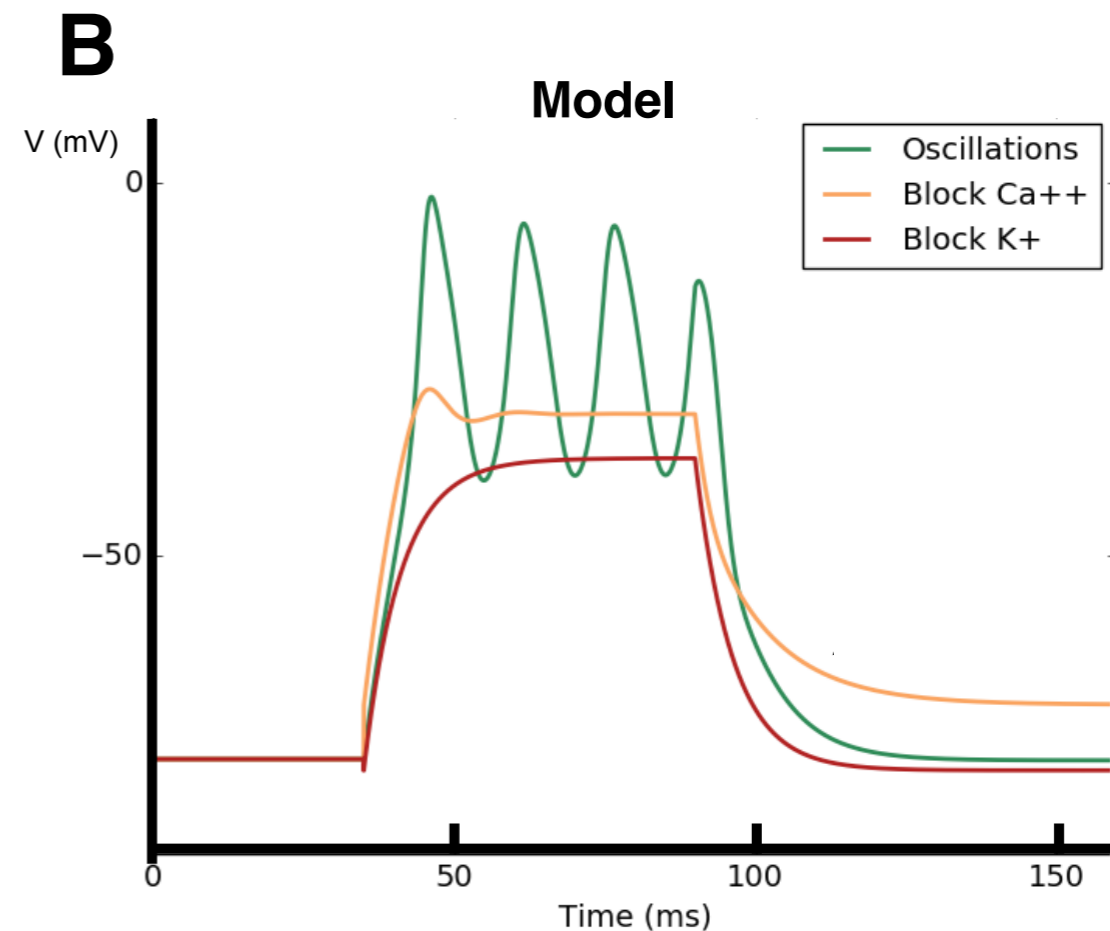
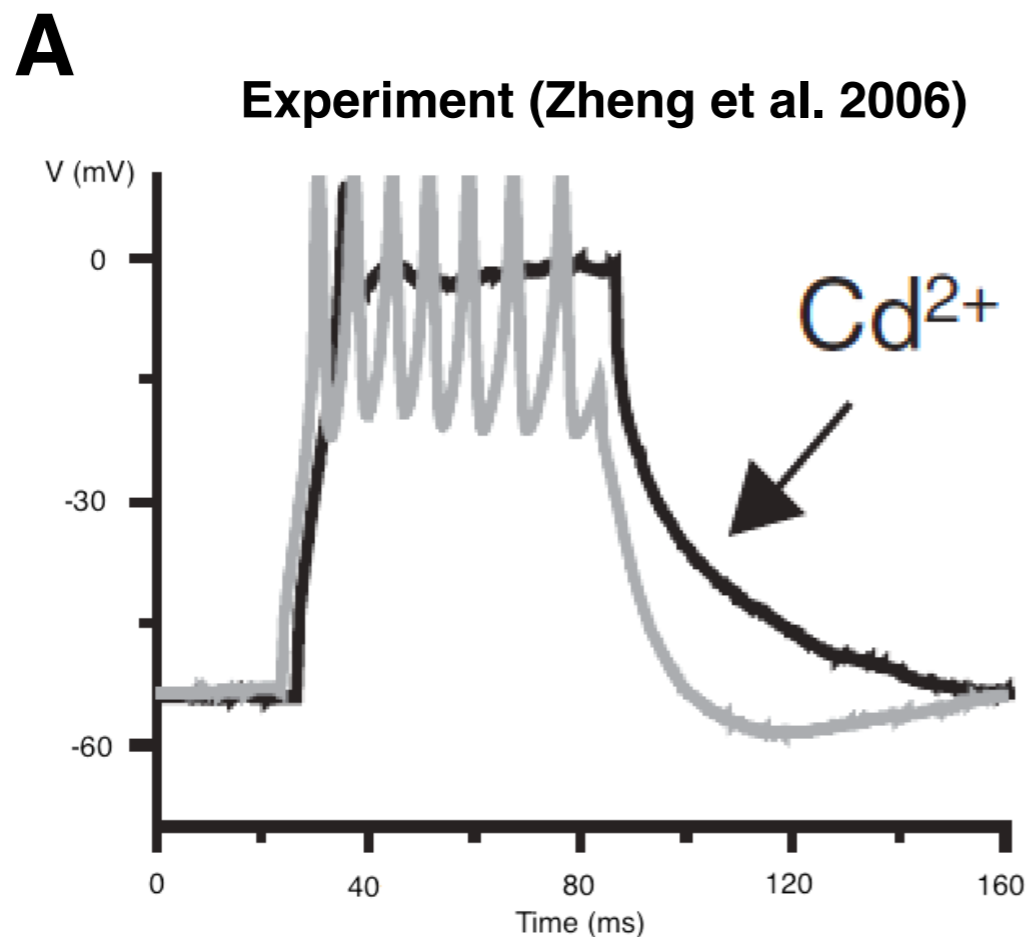
$$\tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i$$

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 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

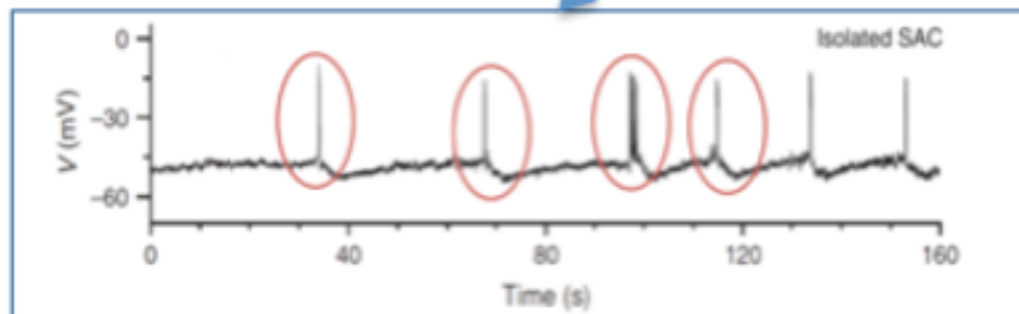
The mechanism of bursting revealed through bifurcations

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⁺ channels**



The mechanism of bursting revealed through bifurcations

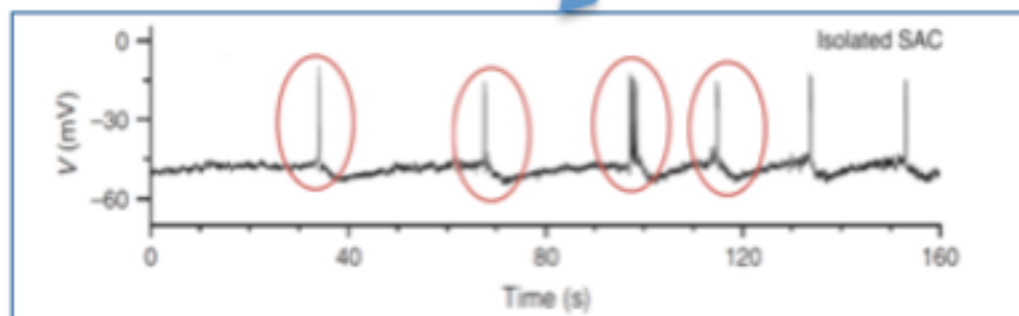
Fast subsystem

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

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

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

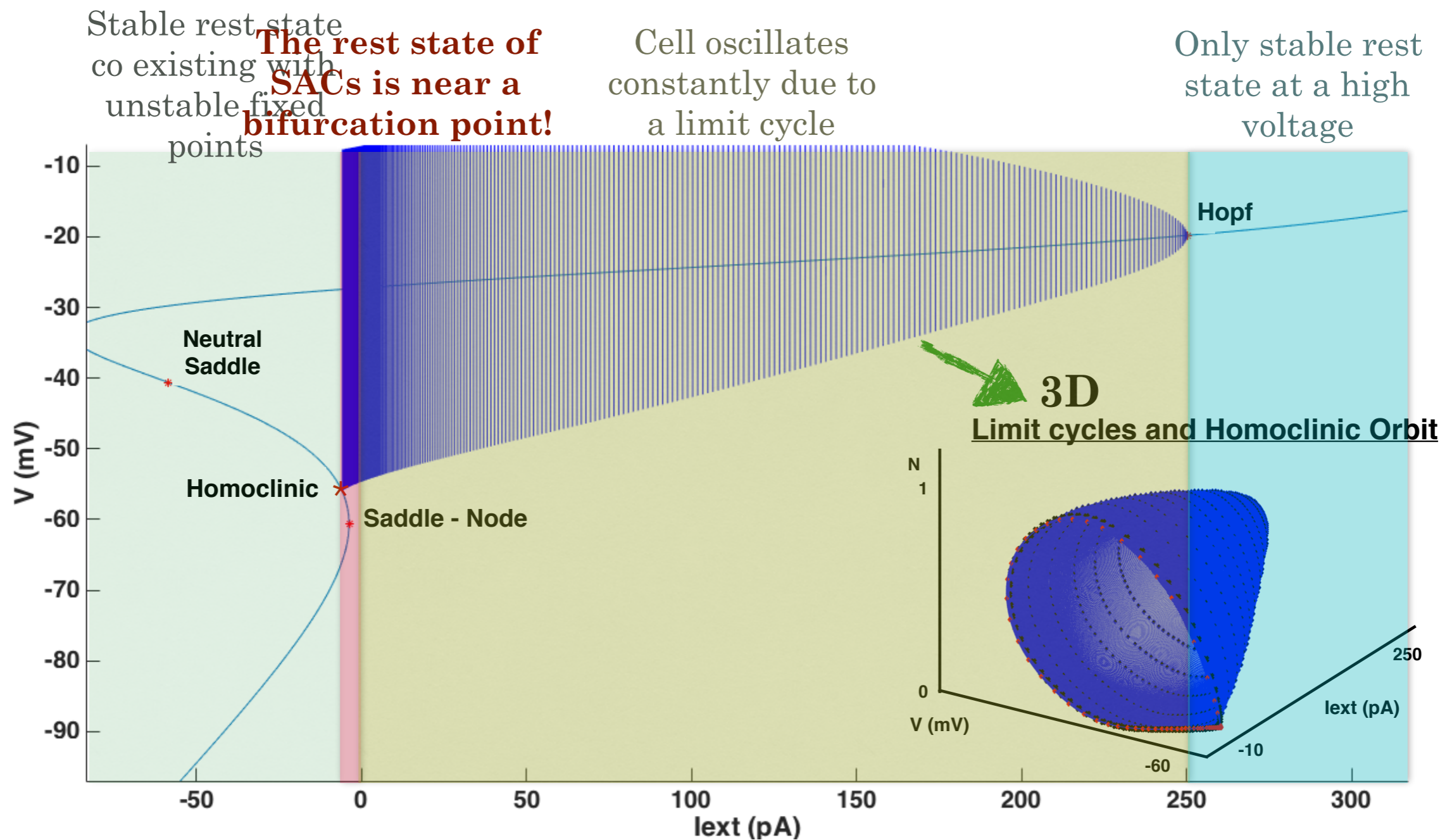
**Constant current
(bifurcation
parameter)**



Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

I. The SACs repertoire of dynamics upon a current application

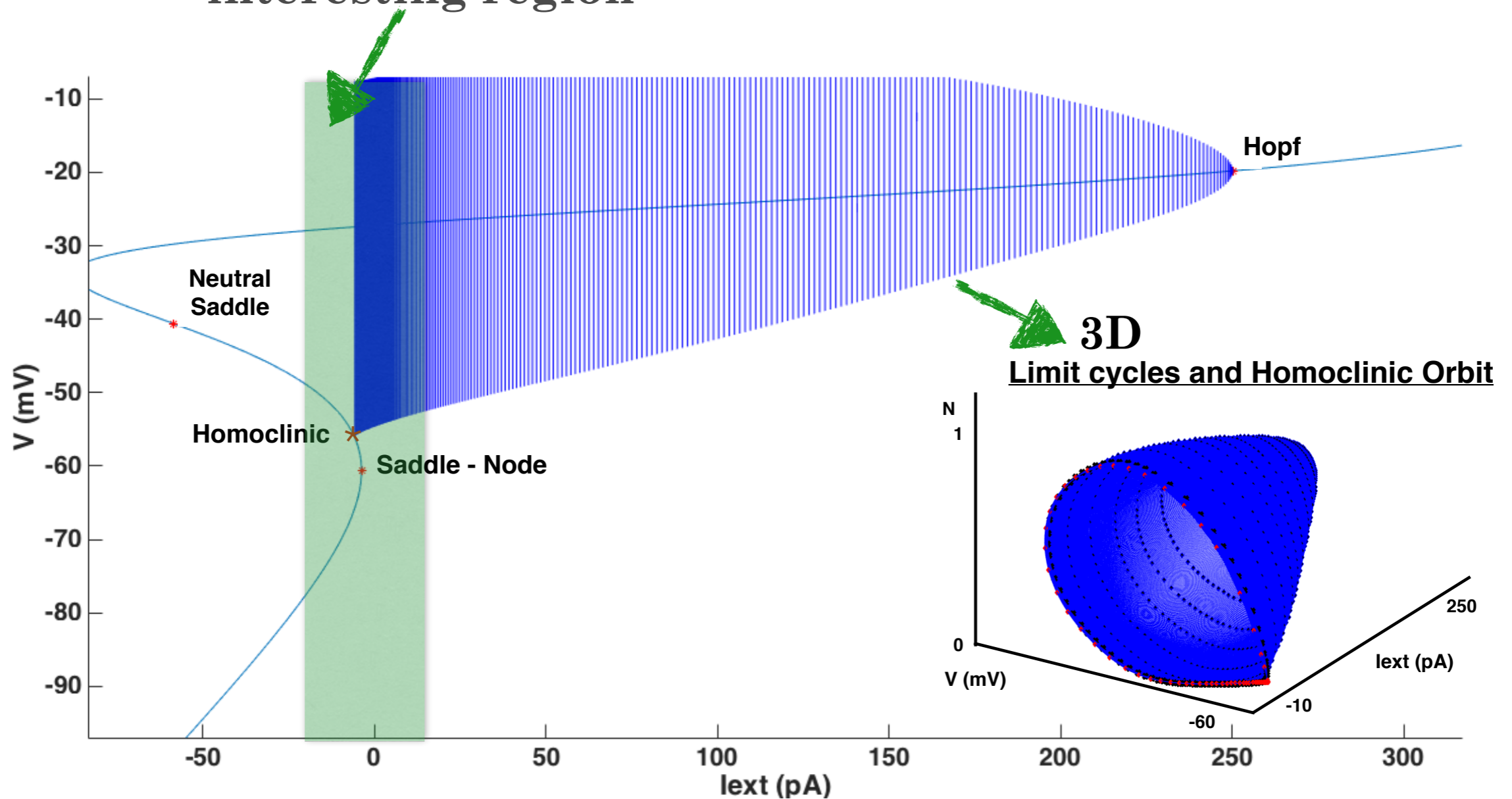


Bifurcation diagram of the fast subsystem (V,N)

What do we learn about SACs?

I. The SACs repertoire of dynamics upon a current application

Zoom in this interesting region

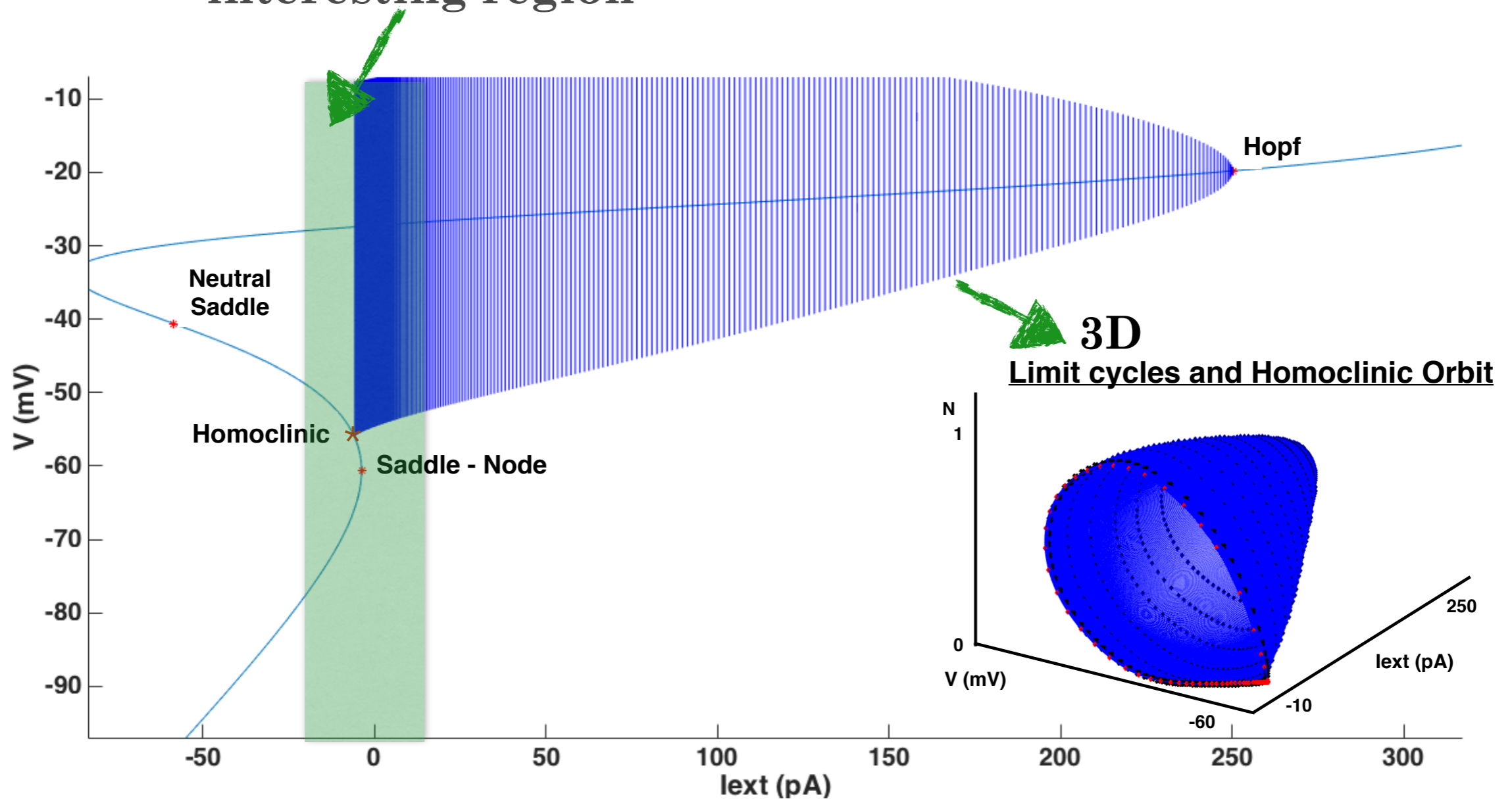


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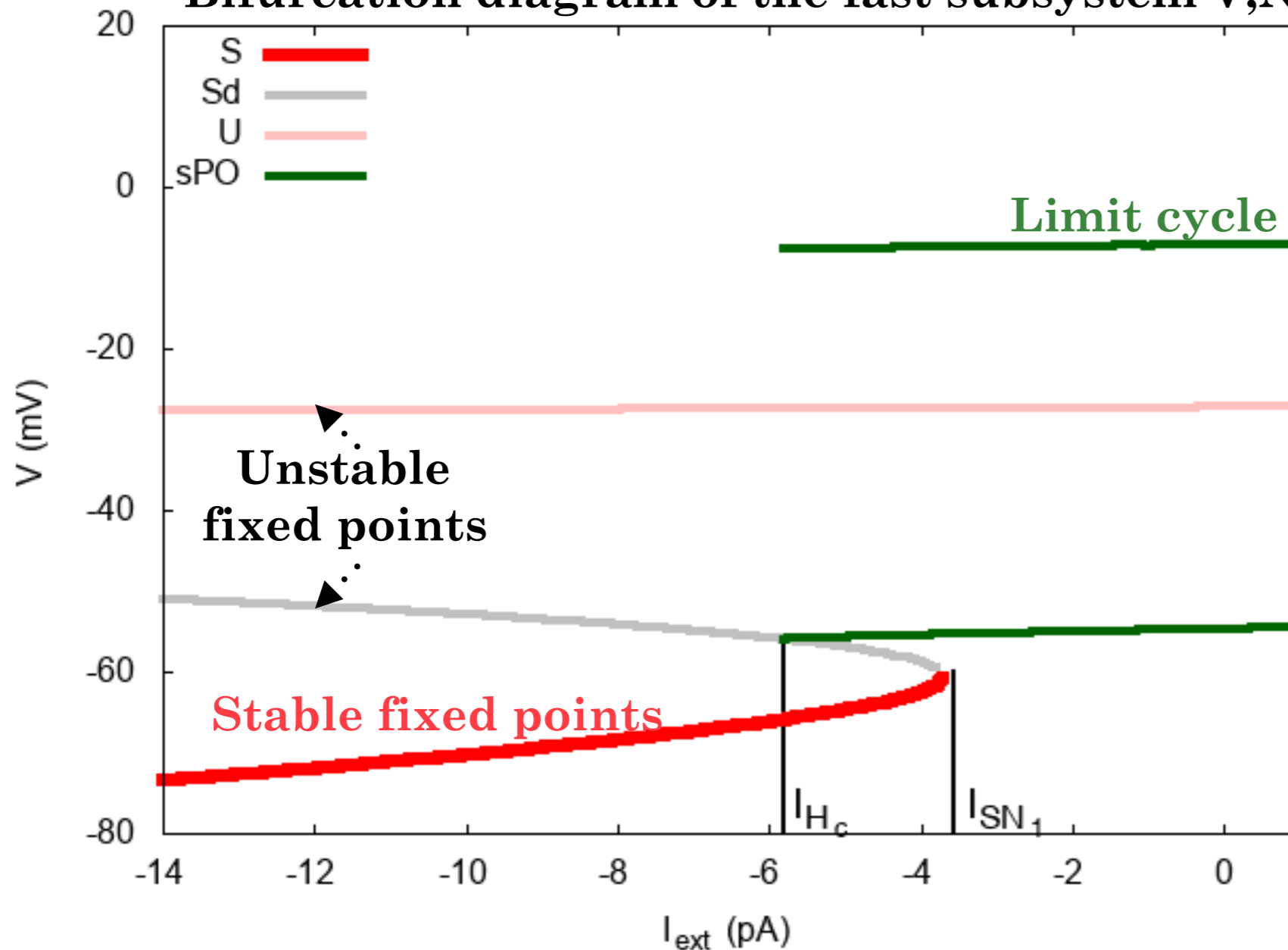


The mechanism of bursting revealed through bifurcations

What do we learn about SACs?

II. The role of sAHP for the bursting mechanism

Bifurcation diagram of the fast subsystem V,N

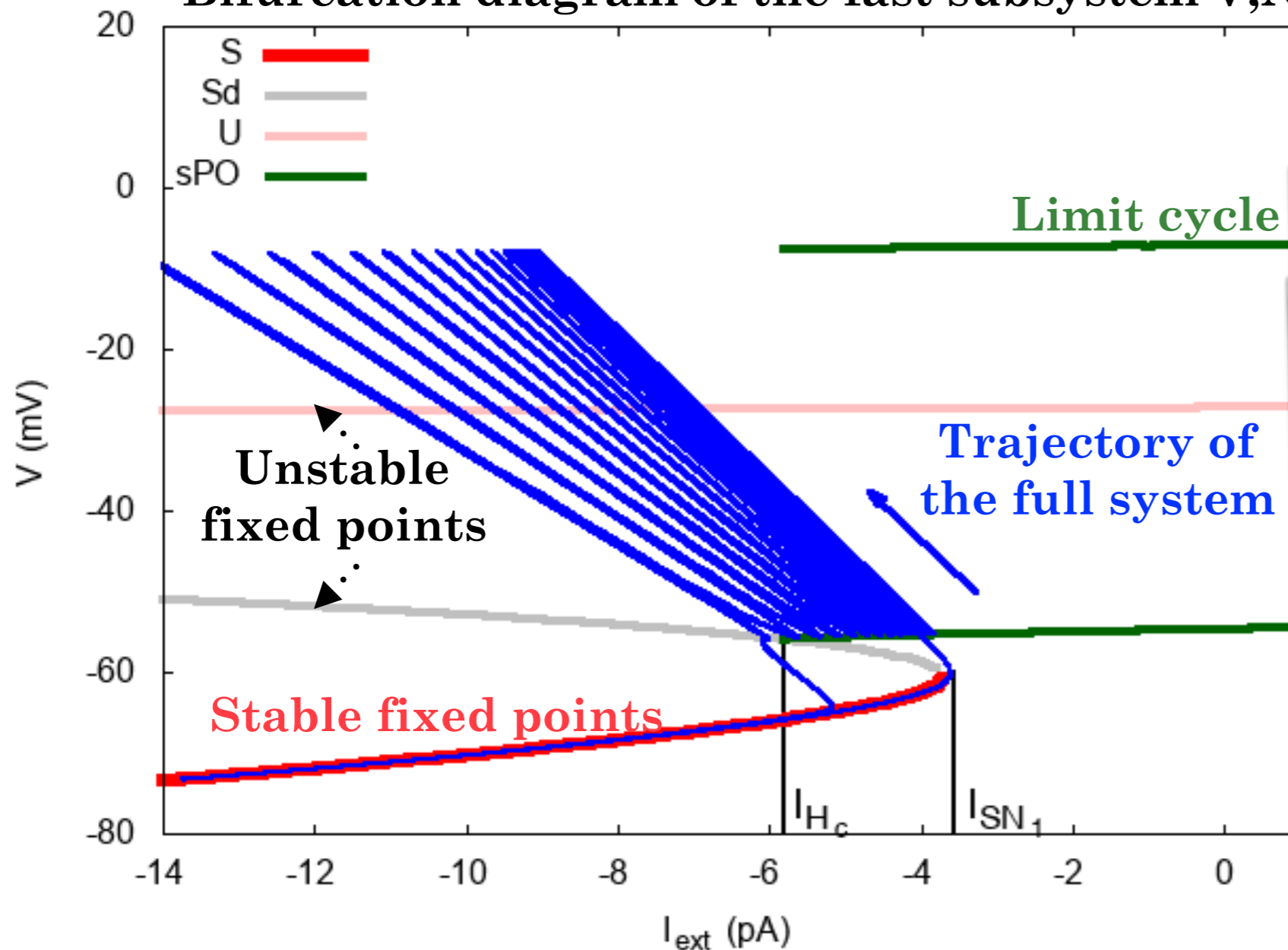


The mechanism of bursting revealed through bifurcations

What do we learn about SACs?

II. The role of sAHP for the bursting mechanism

Bifurcation diagram of the fast subsystem V,N



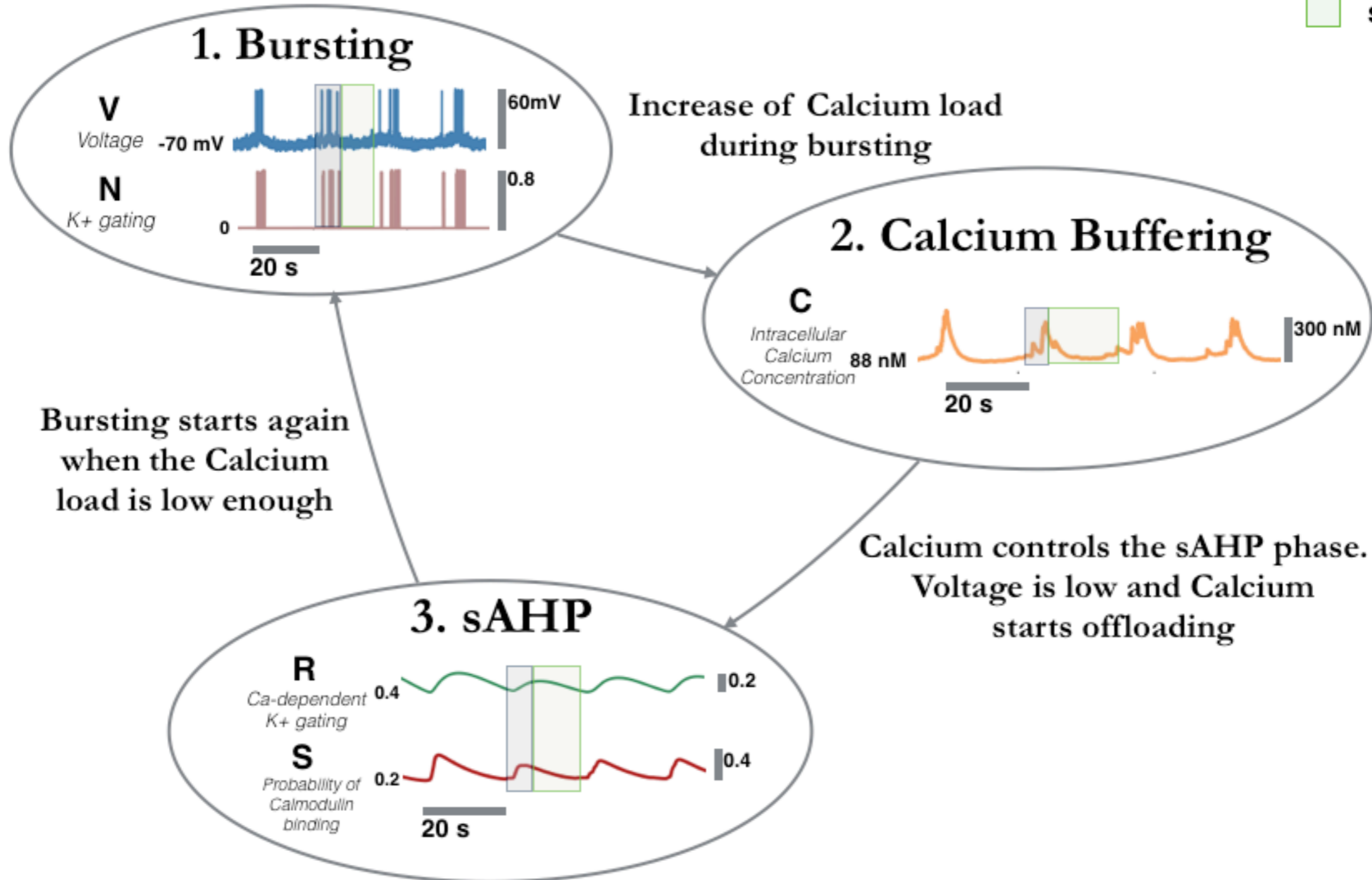
Due to time scale separation, we make the approximation and superimpose the trajectory of the full system on the bifurcation diagram

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

The mechanism of bursting revealed through bifurcations

The biophysical interpretation

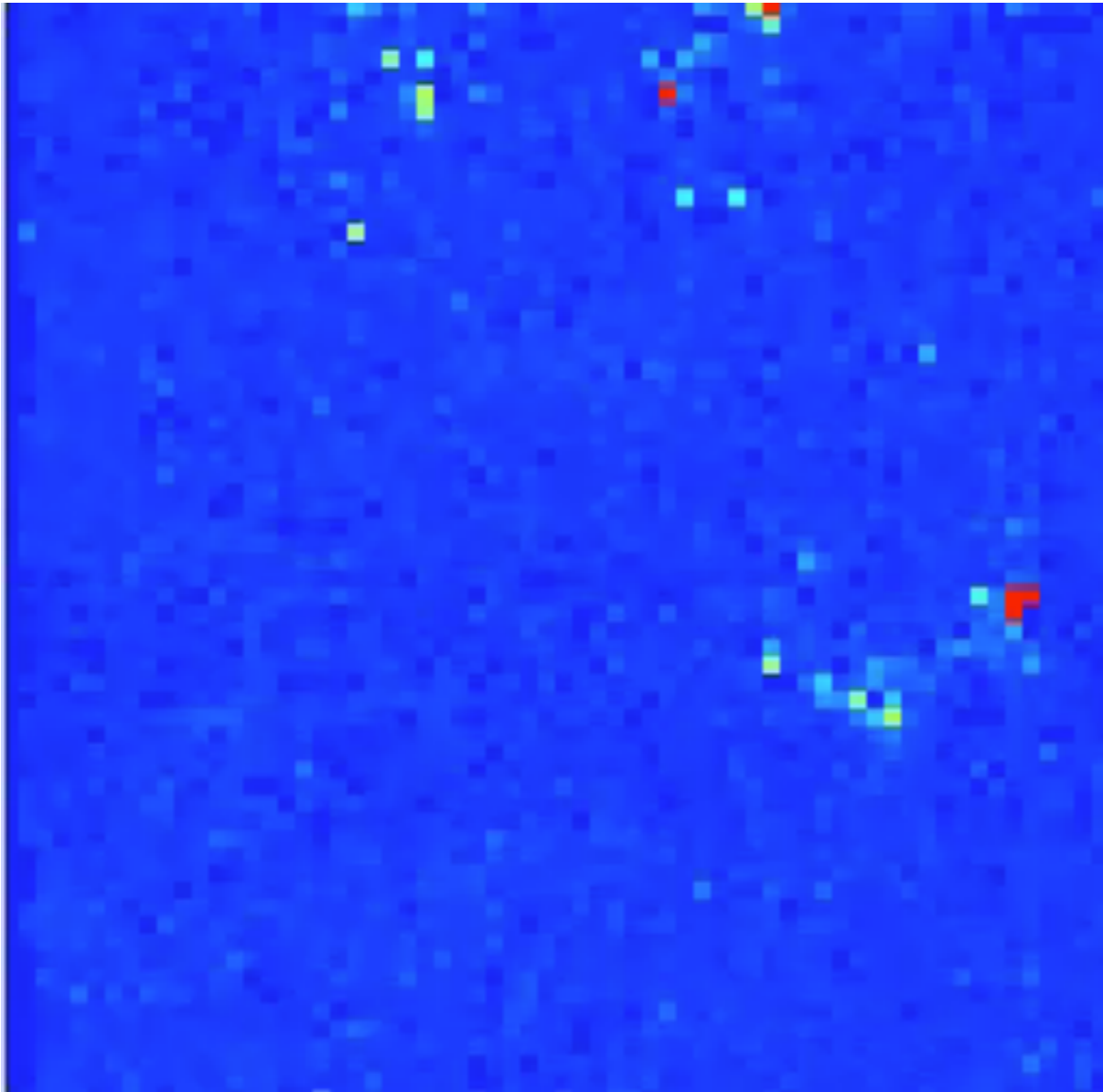
■ Bursting
■ sAHP



How do waves
propagate and stop?

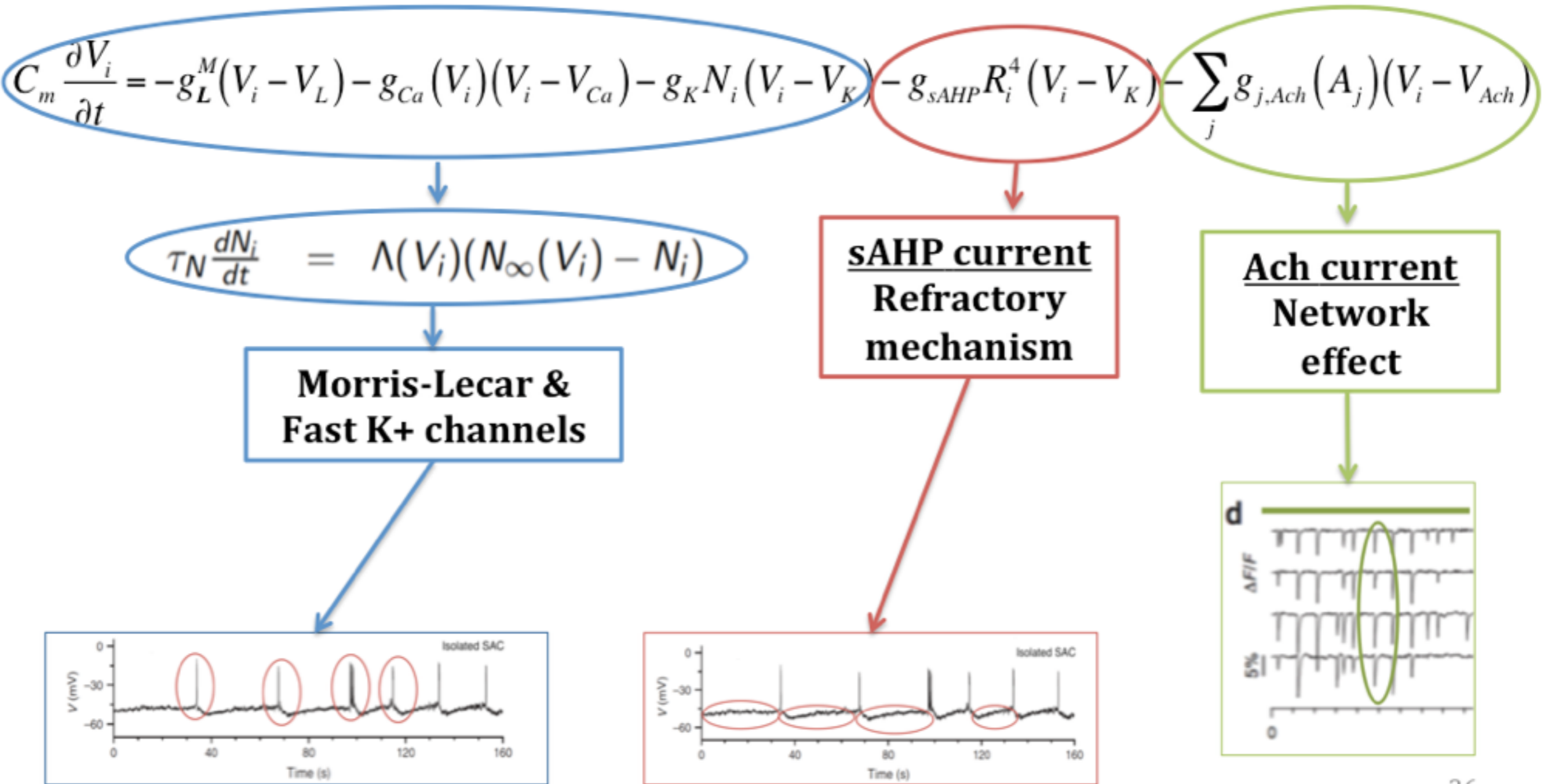
2. D. Karvouniari et al., *Spontaneous emergence of spatio-temporal structure in the early retina*, (under preparation for Phys. Review E)

How do waves propagate?

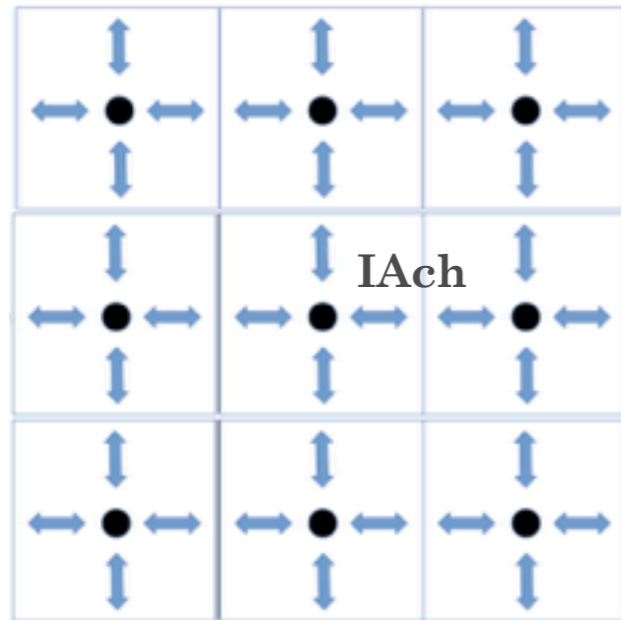


- **Full interacting waves are a complex paradigm**
- **Waves propagate in a landscape changing constantly**
- **It is hard to extract a mechanism of propagation**

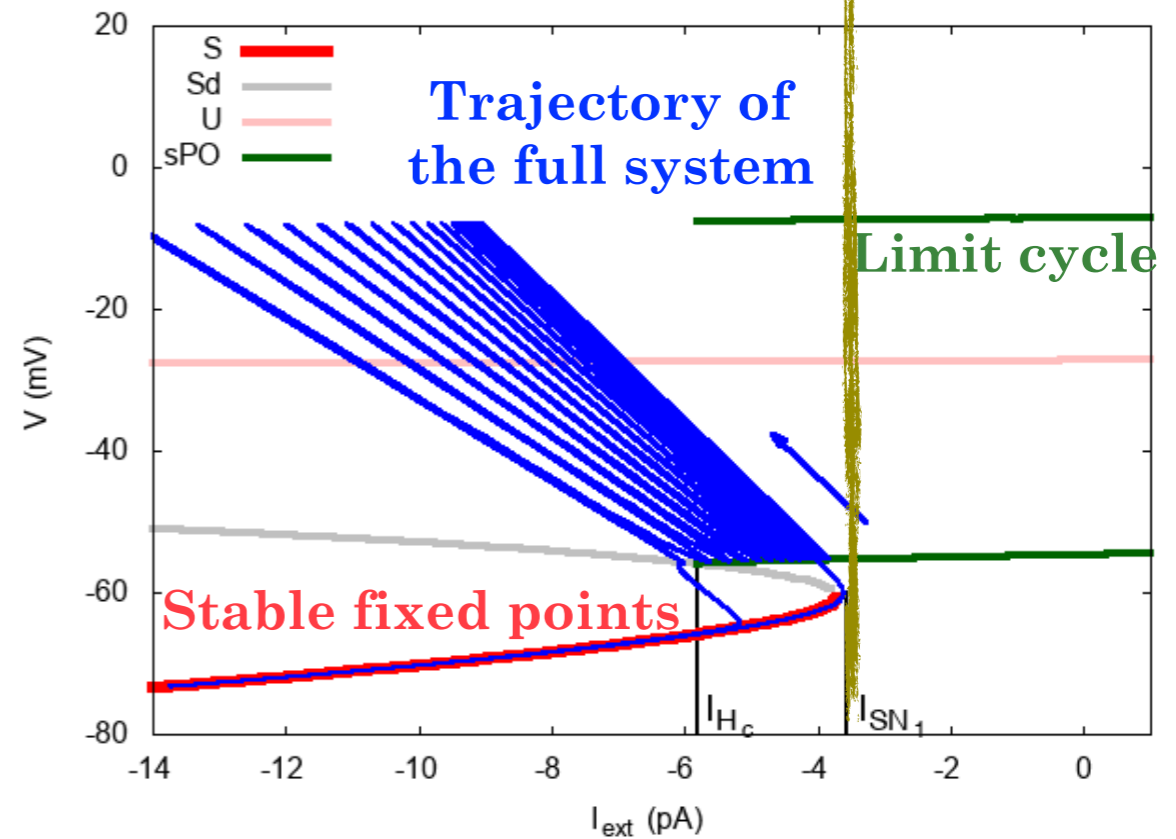
A network model of stage II retinal waves



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



SACs become points on a lattice

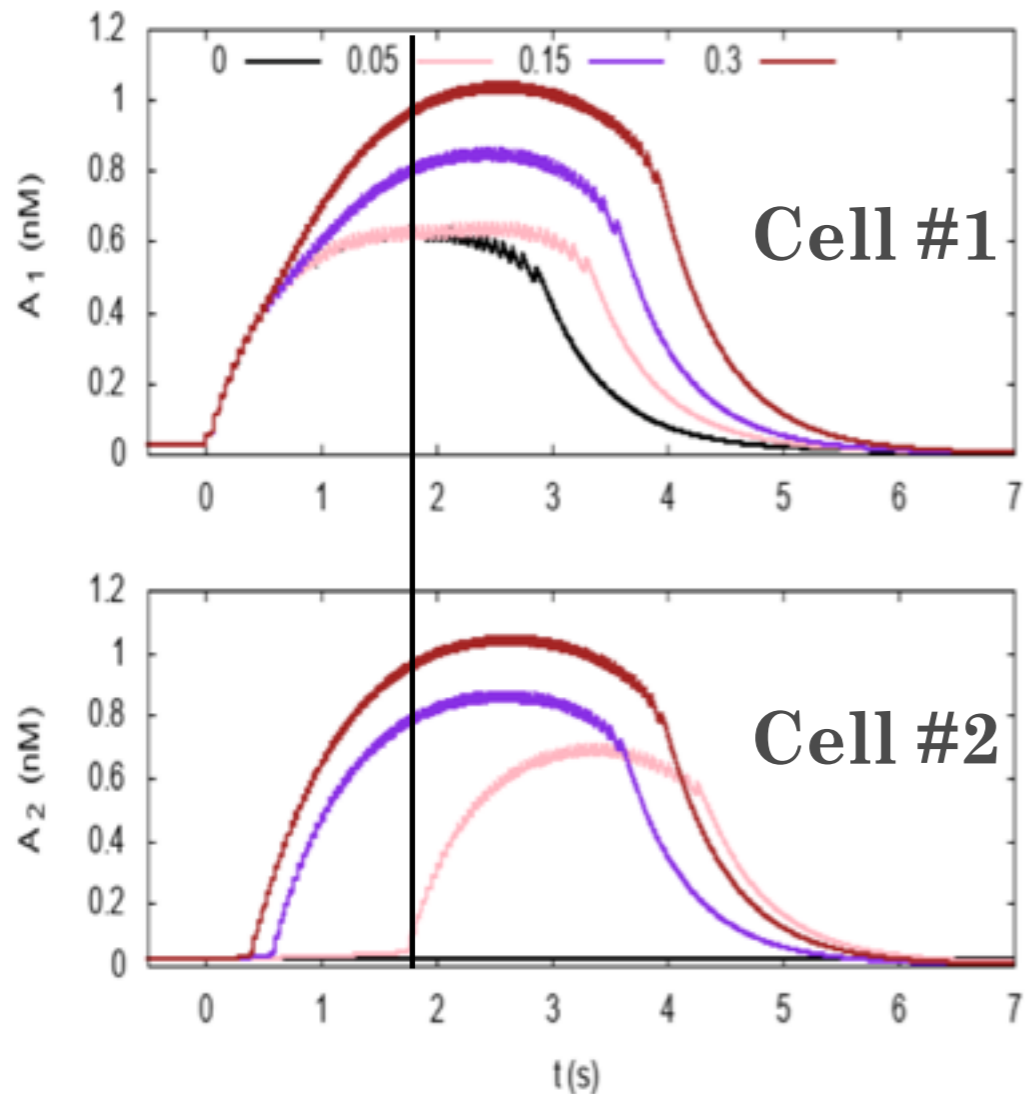


$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca} (V_i) (V_i - V_{Ca}) - g_K N_i (V_i - V_K) + I_{Ach} + I_{sAHP}$$

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

The coupled dynamics of 2 SACs

Ach profile



Condition for bursting to start:
 $I_{Ach} + I_{sAHP} = I_{SN}$

Response Time

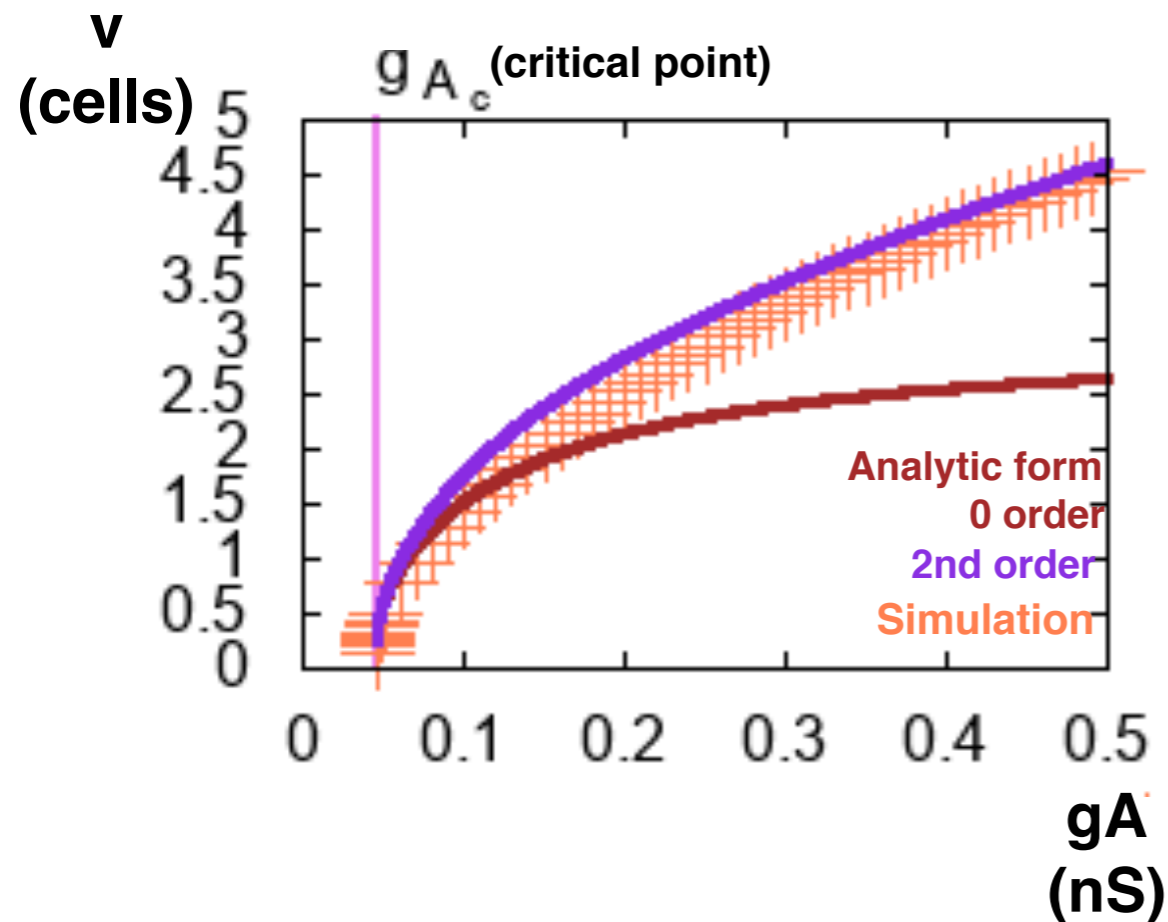
$$t_i = -\frac{1}{\mu} \log \left(1 + \frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \left(\frac{I_{SN} + g_{sAHP}R^4(V_- - V_K)}{g_A(V_- - V_A)} \right) \right)$$

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 Ω do not depend on gA . **Fit holds for smaller gA**

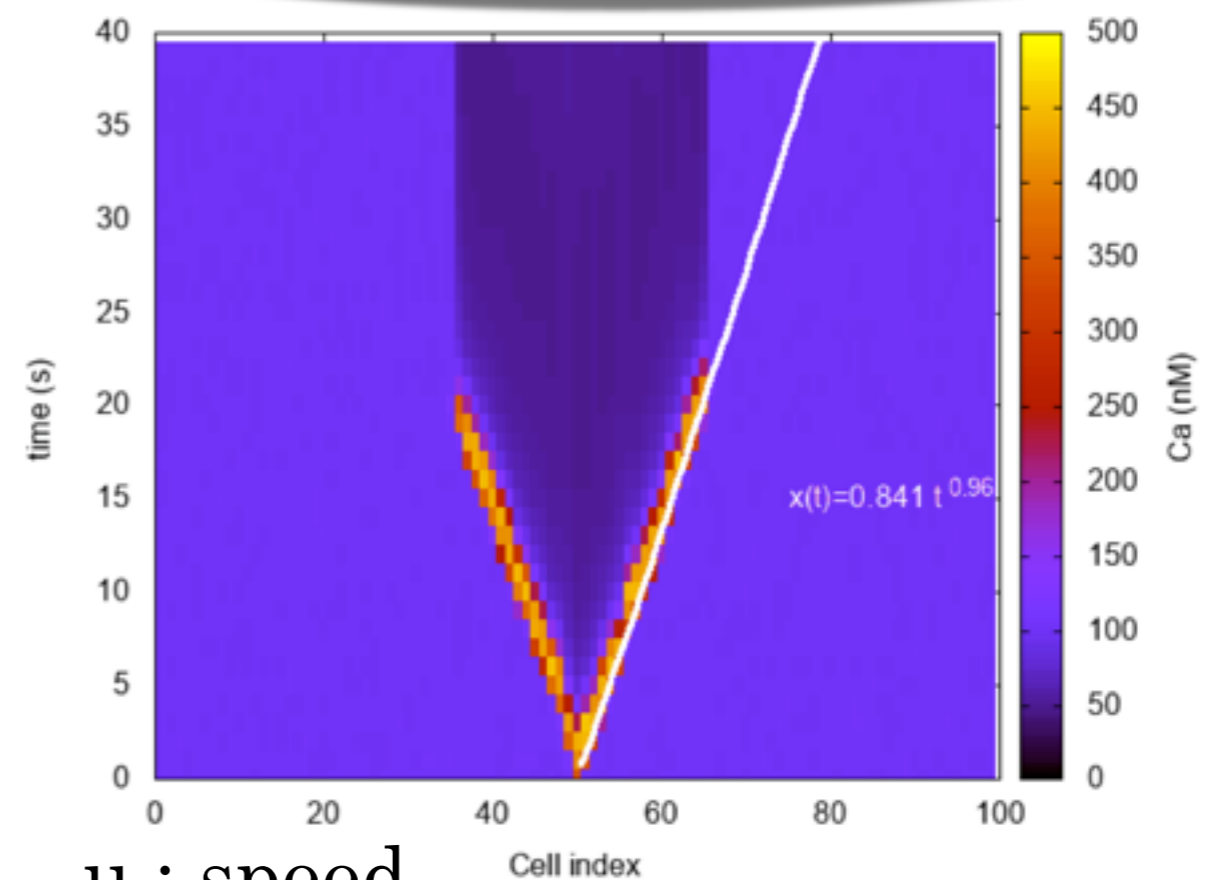
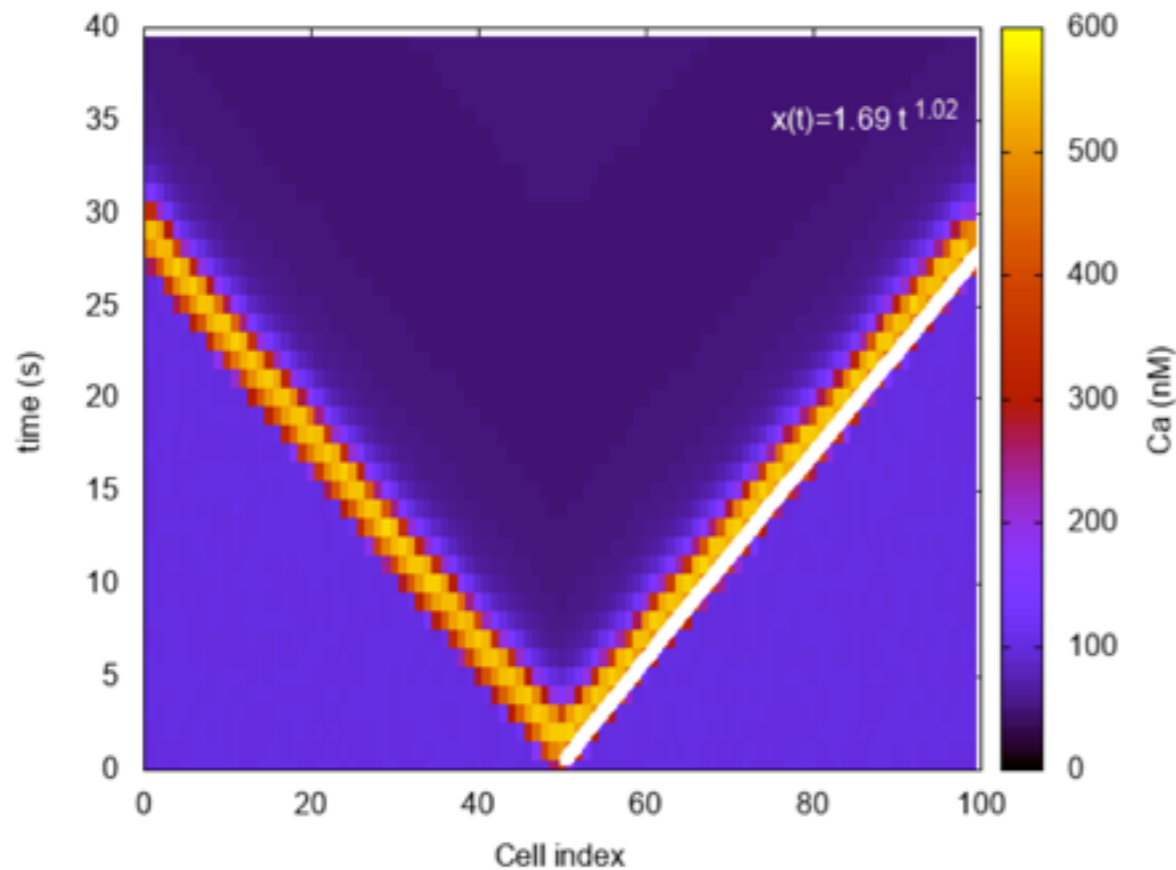
Based on our model, where wave propagation is only possible when the **total current received by a neighbouring cell exceeds the (saddle-node) bifurcation threshold**, we extract the analytic form for the waves propagation coupling threshold (1D case).

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

Propagation in 1D without friction

$$g_A > g_{Ac}$$

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



Fitting trajectory:

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



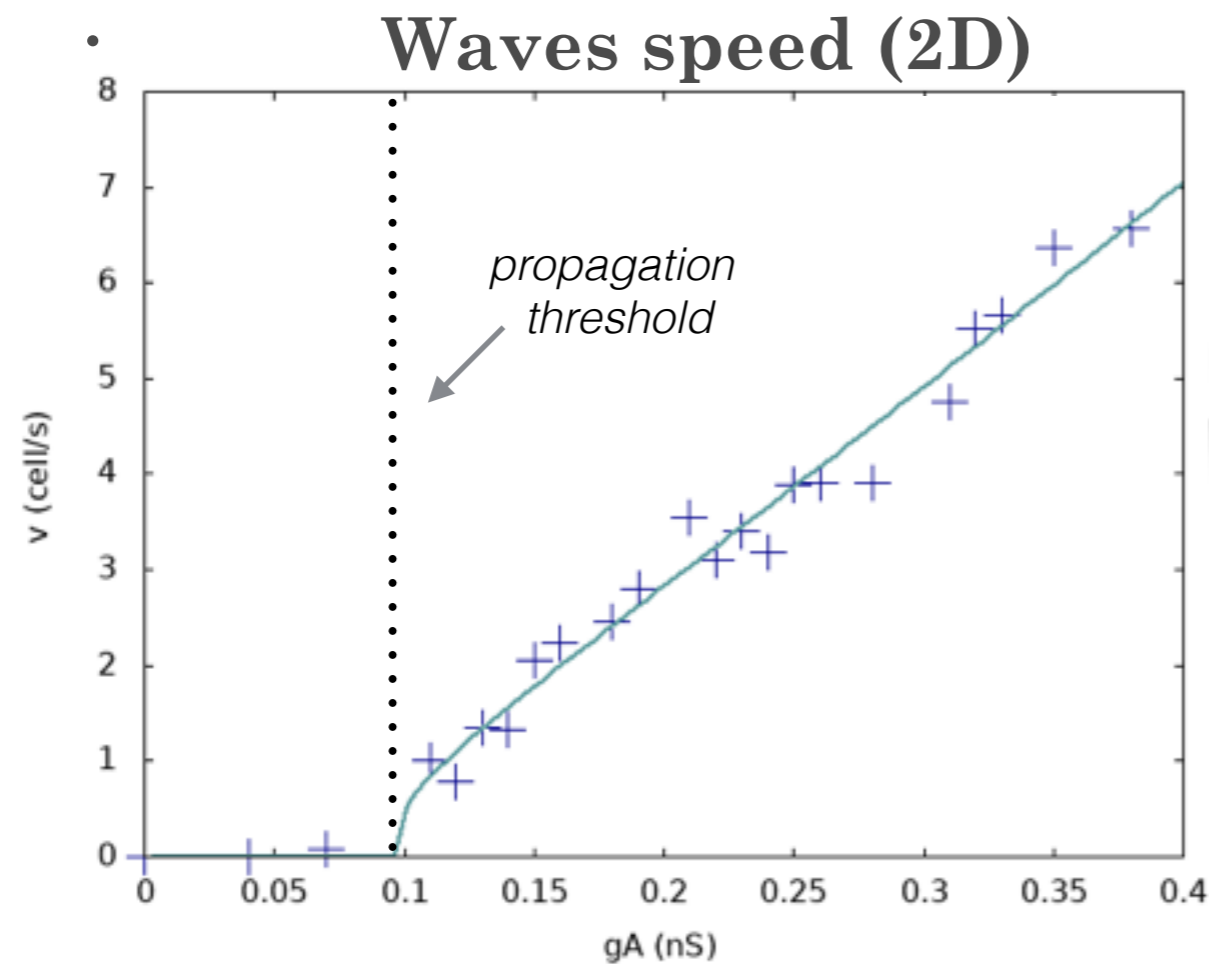
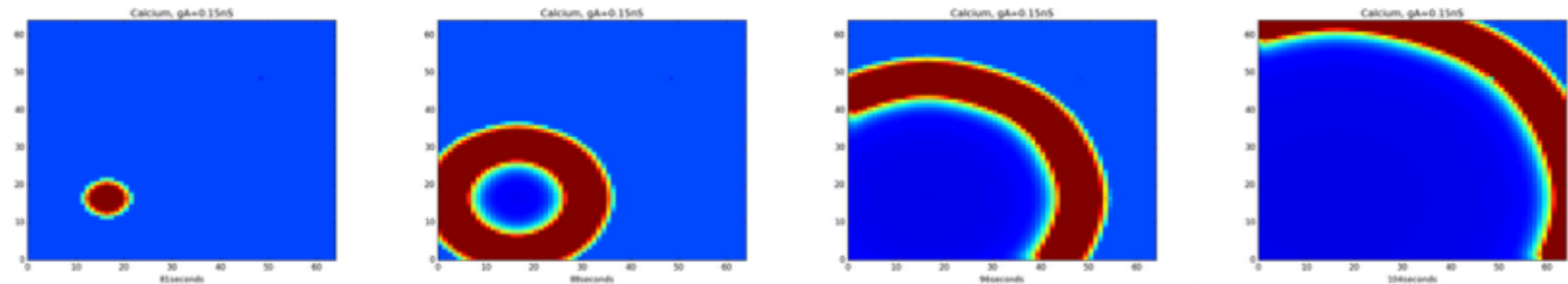
u : speed

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

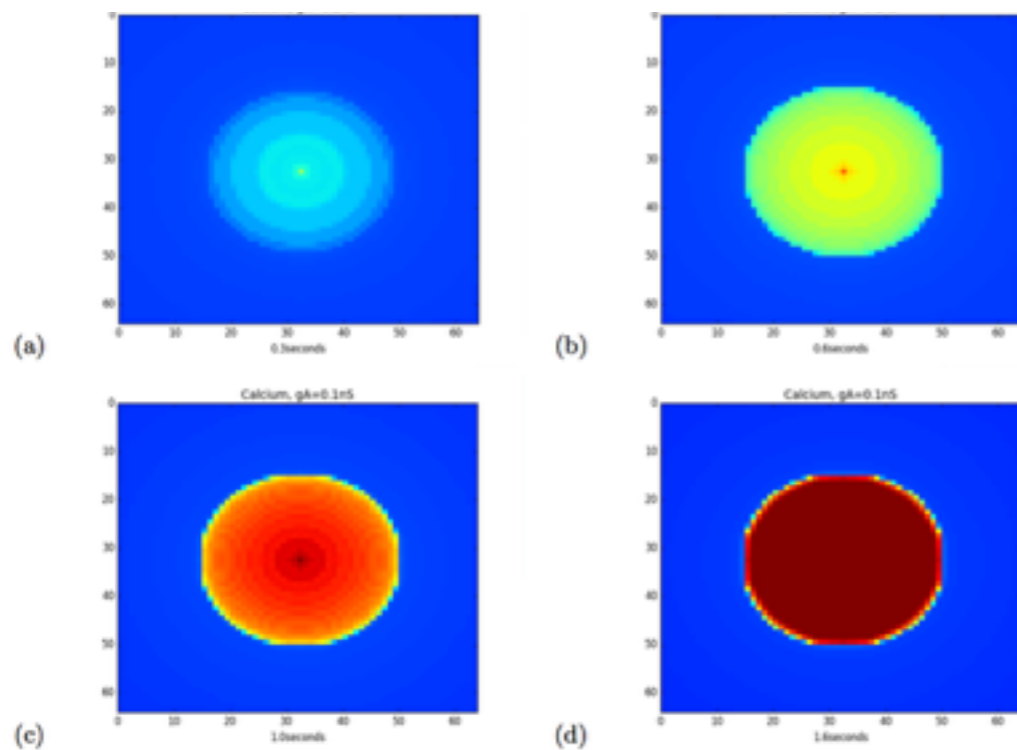
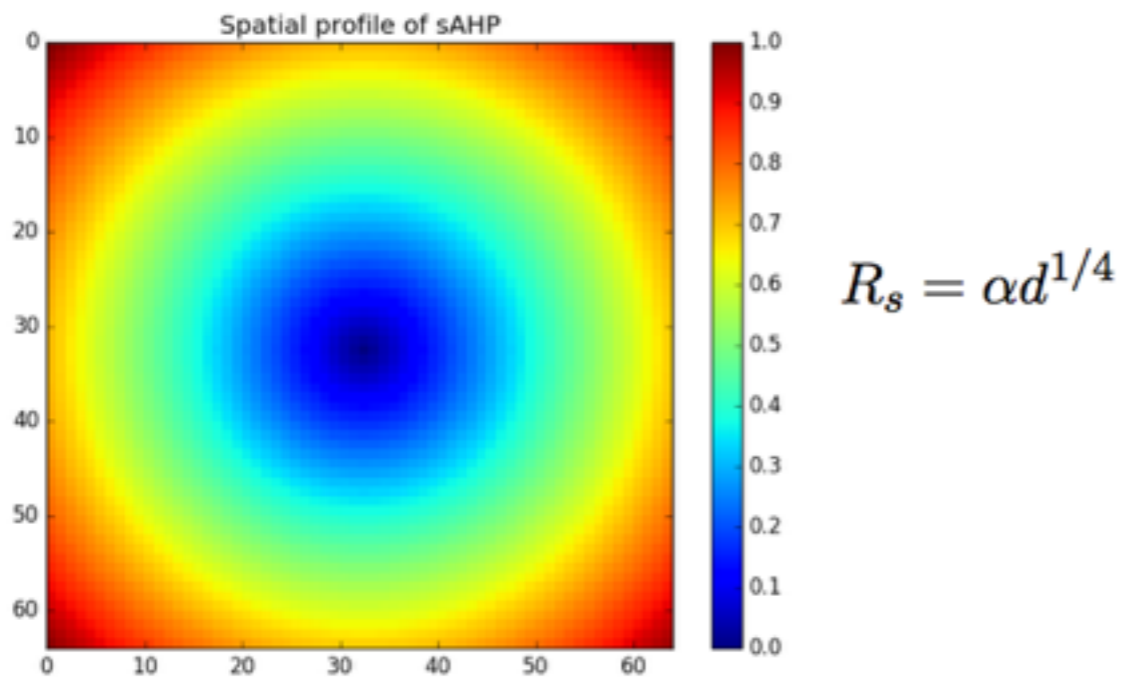
Propagation in 2D without friction

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



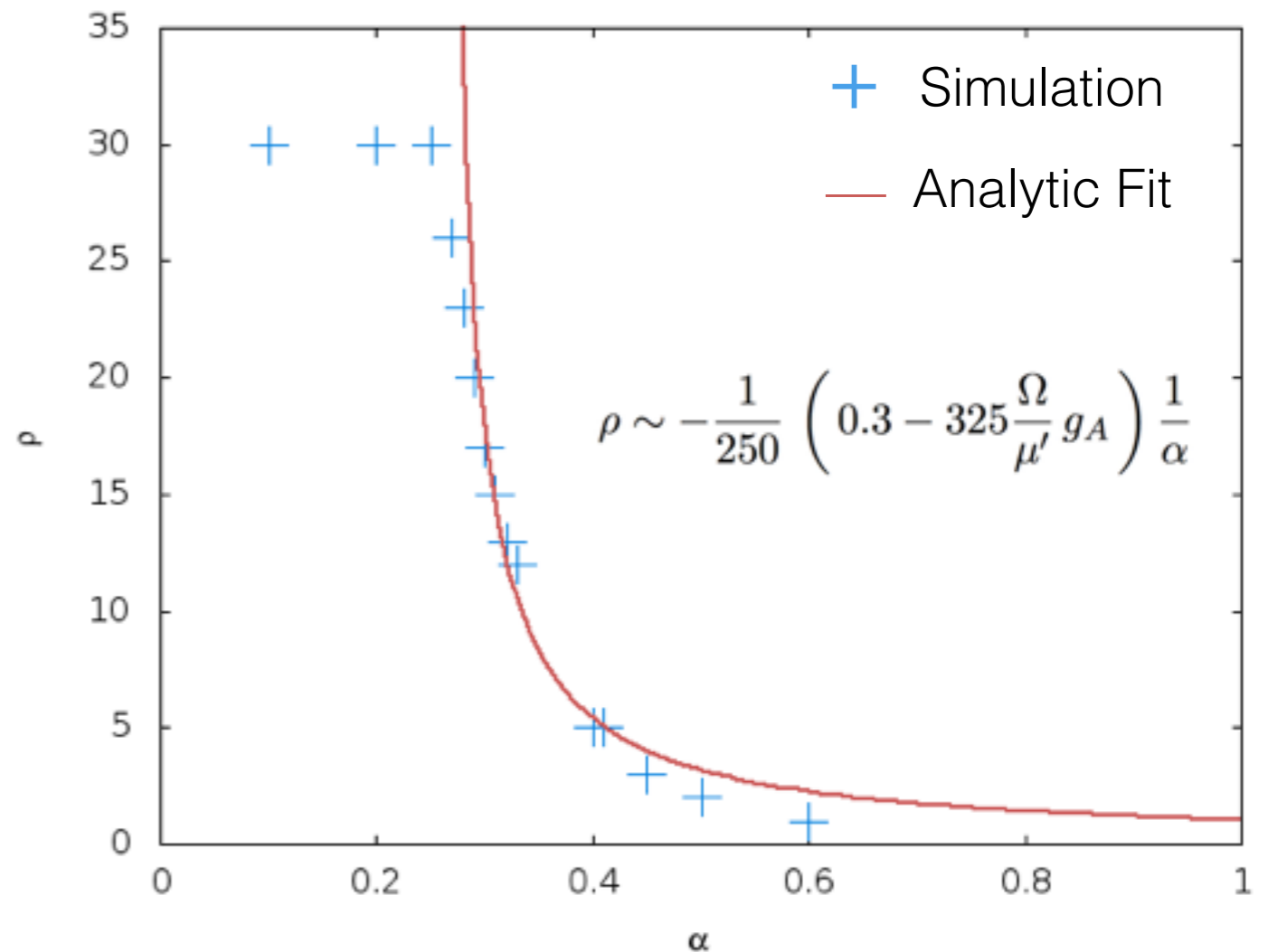
• The speed increases with the coupling strength

How do waves stop? The sAHP saga



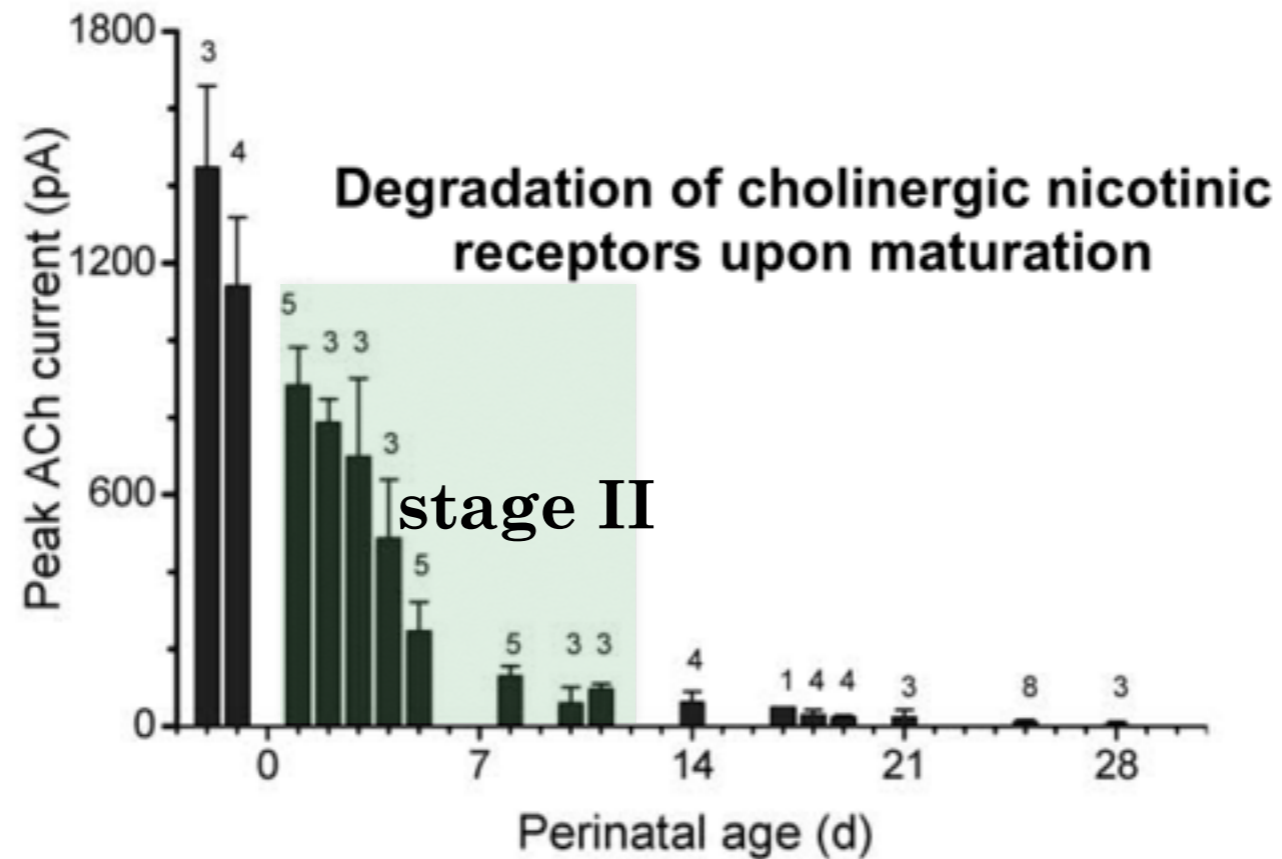
Example of a wave propagation in a radial landscape of R

Max Waves size as a function of the strength of sAHP

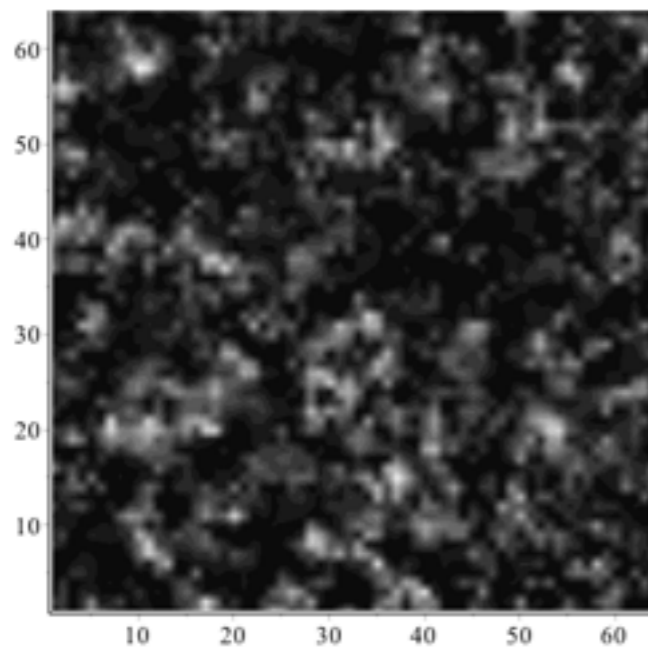


The waves size decreases hyperbolically with the strength of sAHP

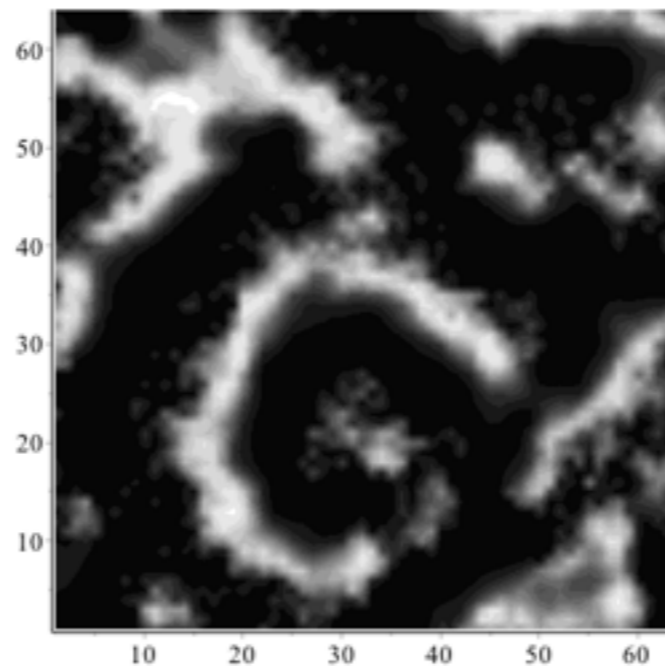
Patterns evolve within stage II



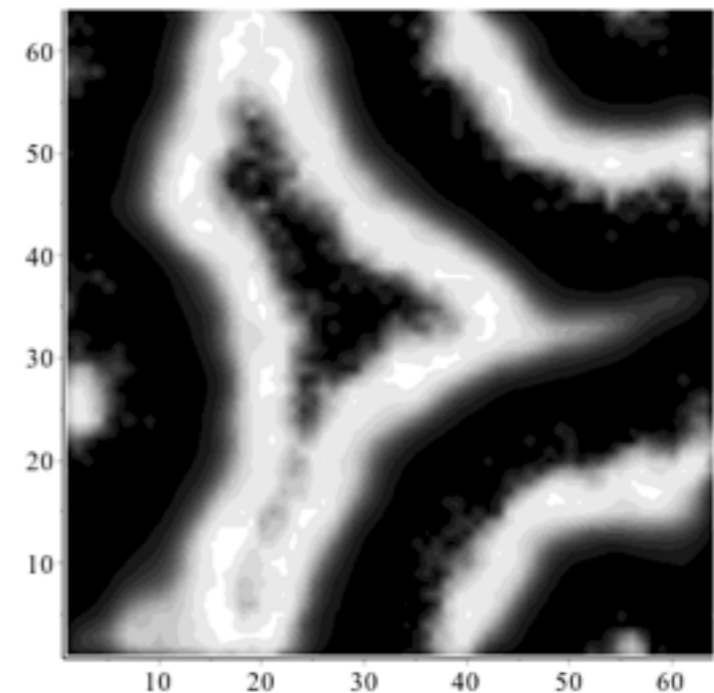
Weak



Moderate

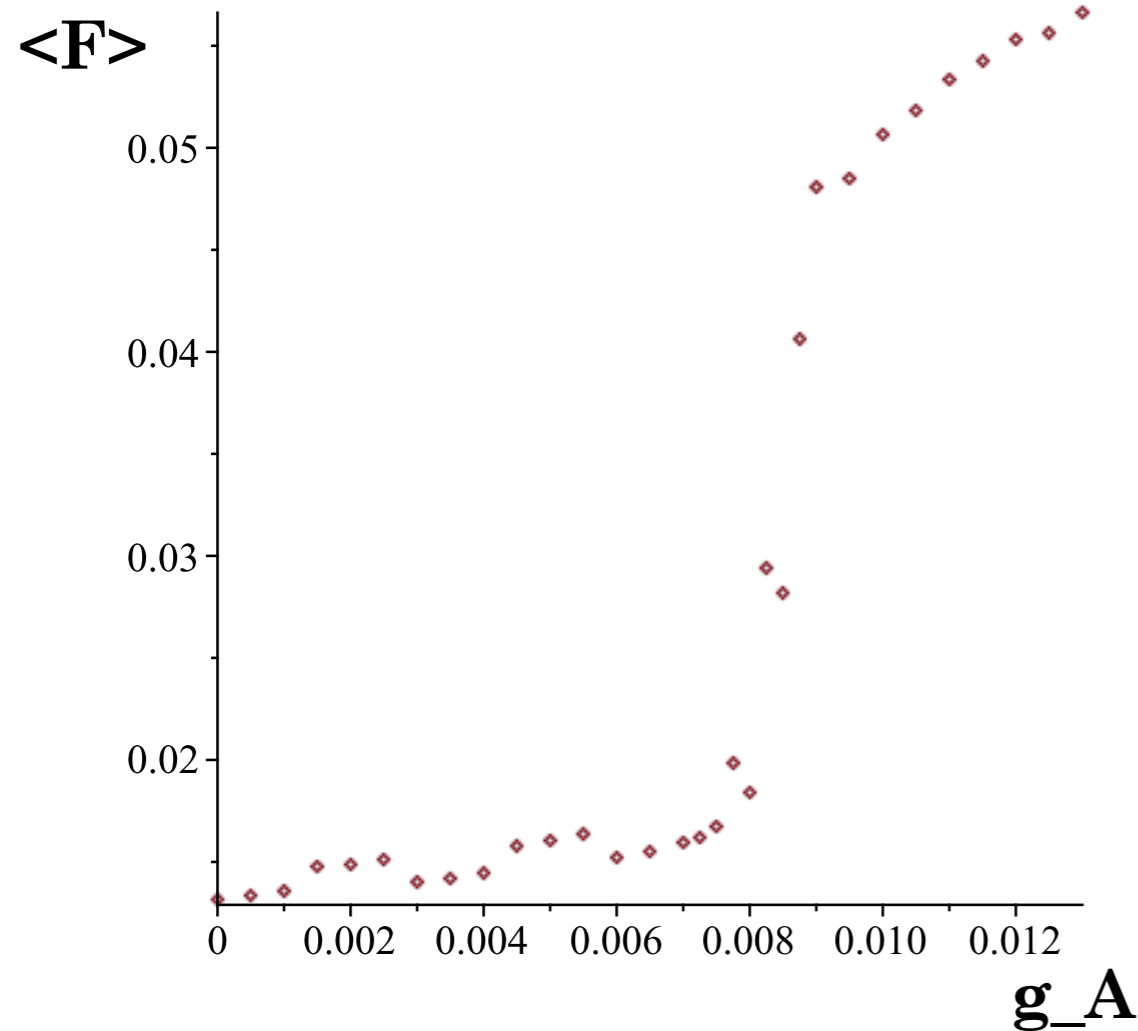


Strong

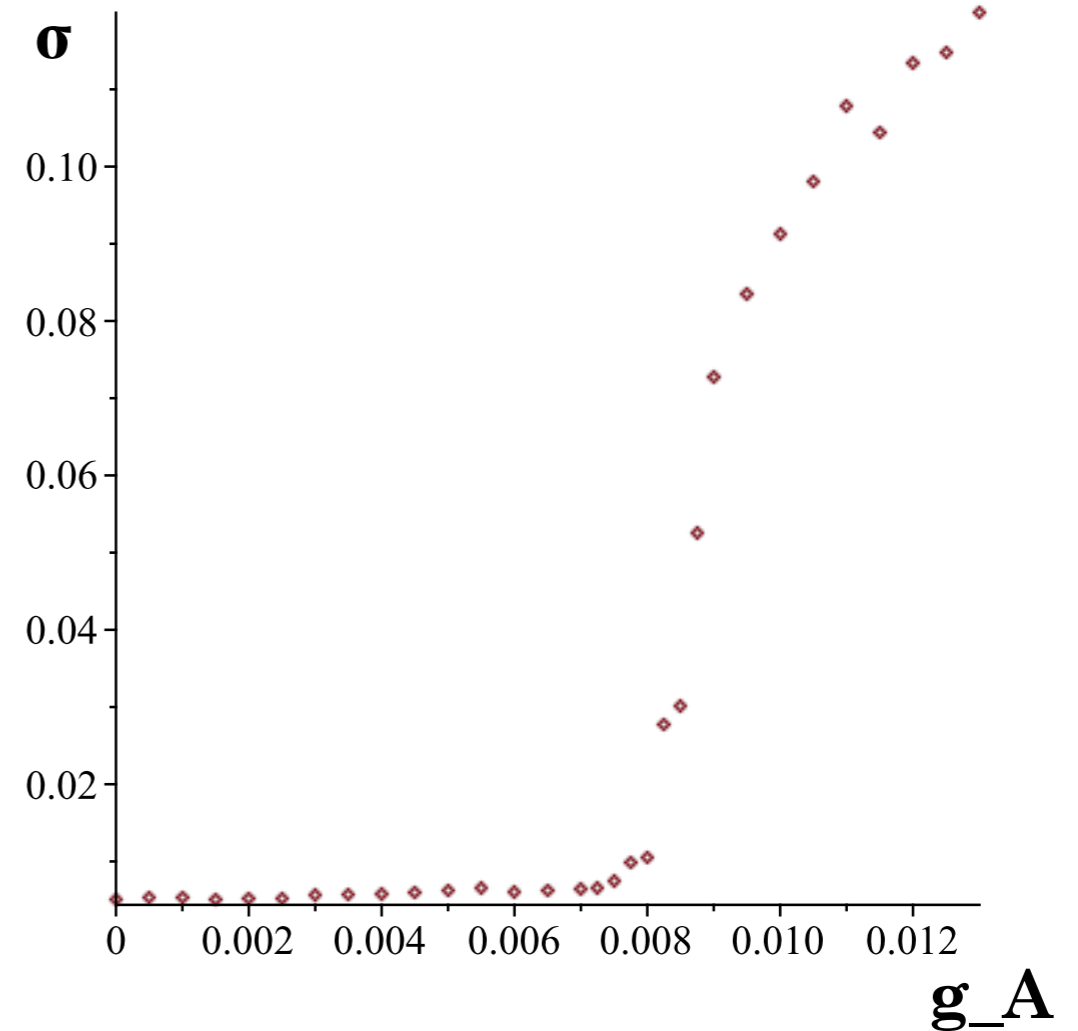


Synchronisation Transition

Average population firing rate



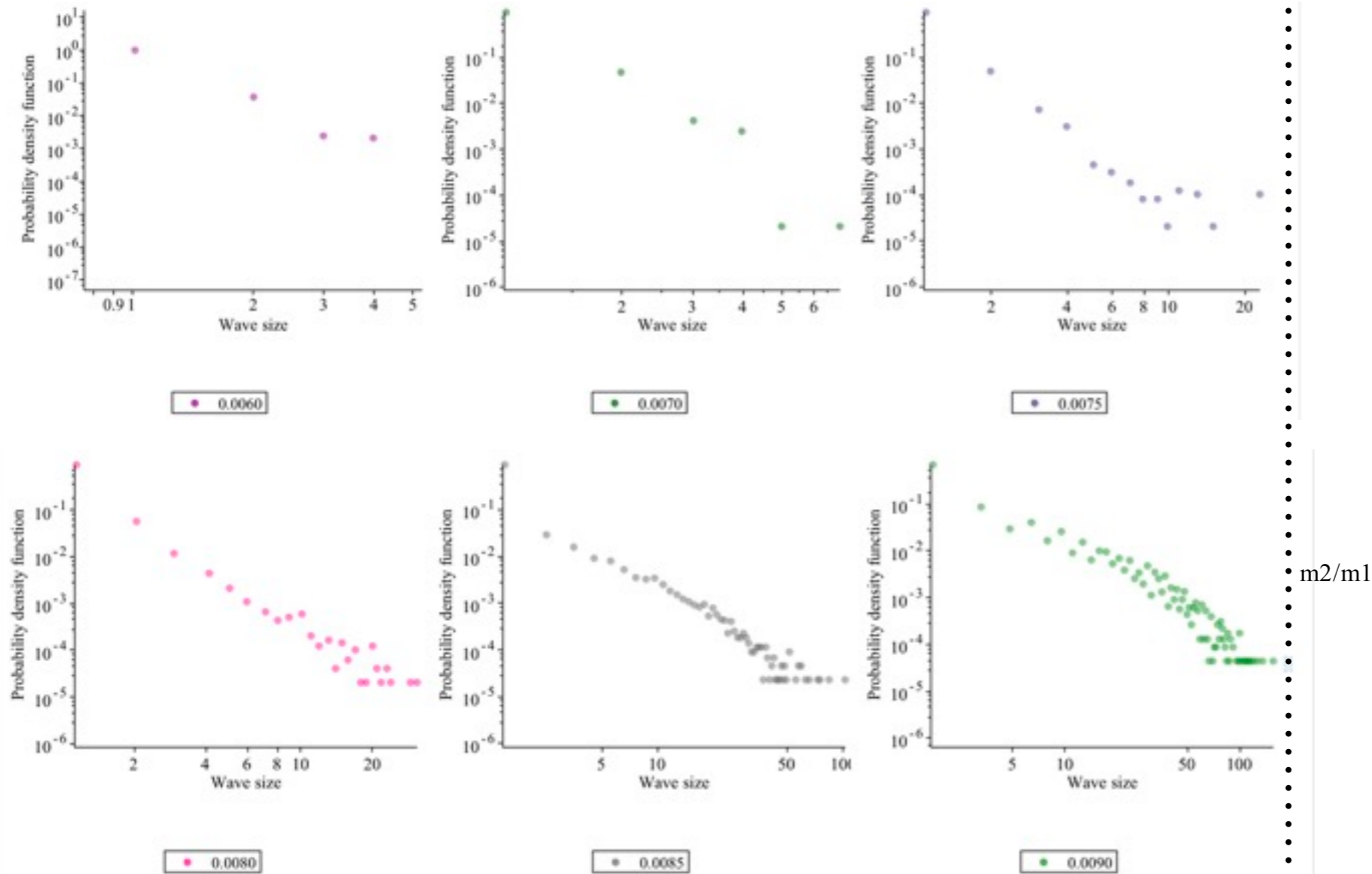
Standard deviation firing rate



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

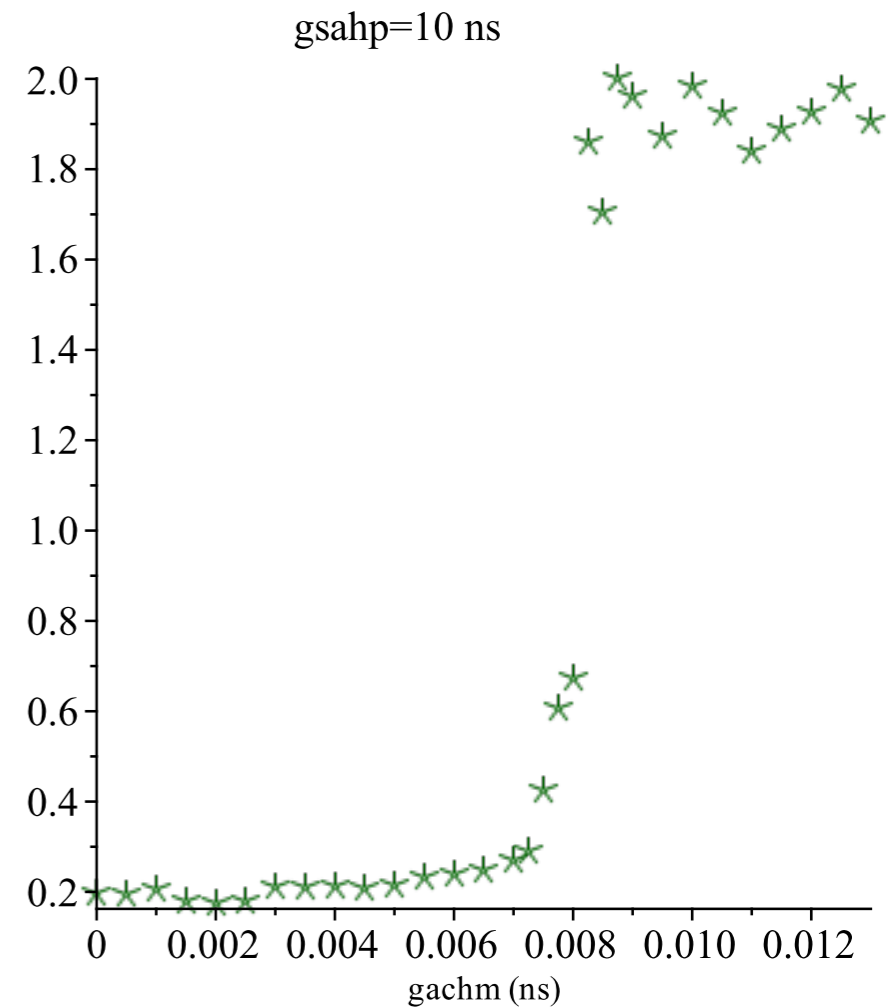
Synchronisation Transition

Distribution of waves sizes



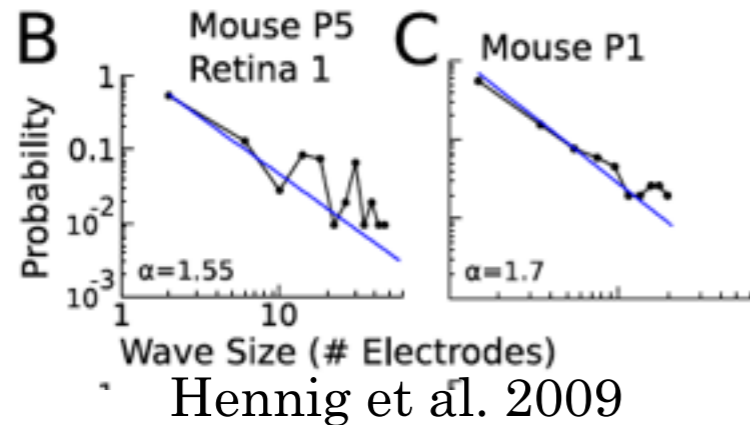
Fano coefficient

Ratio of mean and standard deviation of a distribution



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

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
:)