Biophysical reaction-diffusion model for stage II retinal waves and bifurcations analysis

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Université Nice Sophia Antipolis

Inria
INVENTEURS DU MONDE NUMÉRIQUE

Our goal

Idea:

Build a biophysical generic model to study mechanisms generating stage II retinal waves

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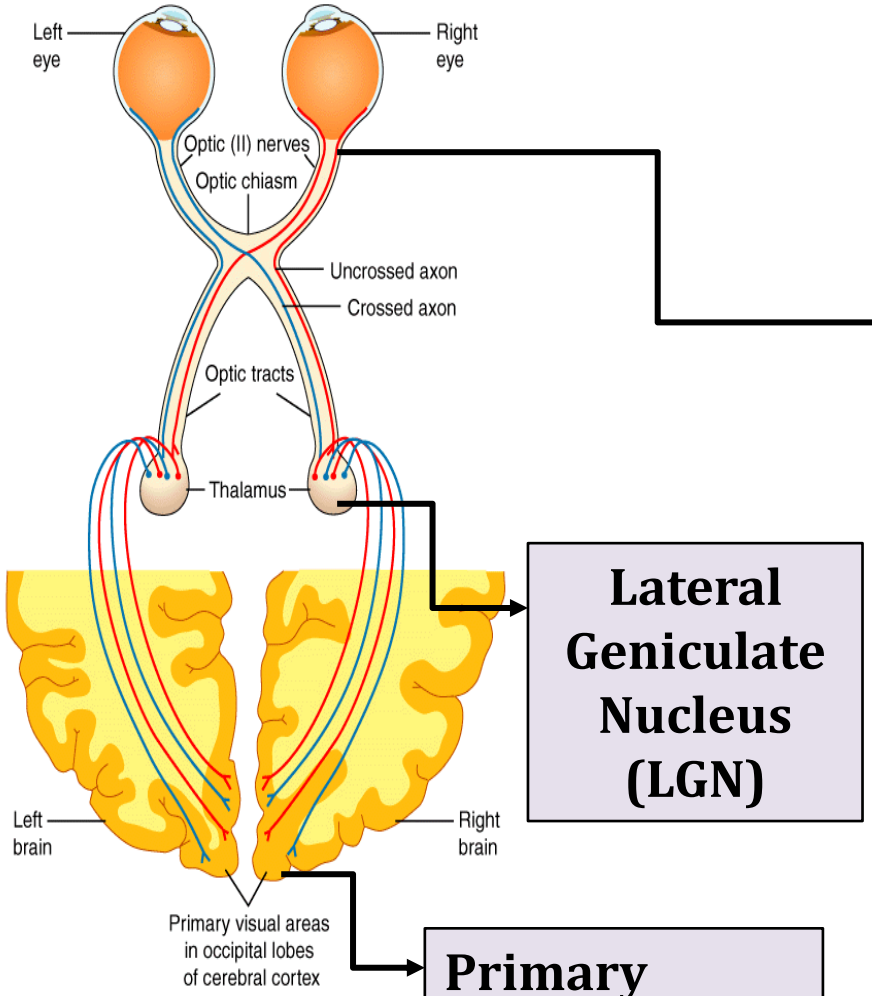
Motivation:

- Retinal waves instruct the shaping of the visual system
- Understanding the mechanisms that generate them may help to control them
- Use retinal waves to re-train the retina re-wire and possibly restore vision partially for certain pathologies

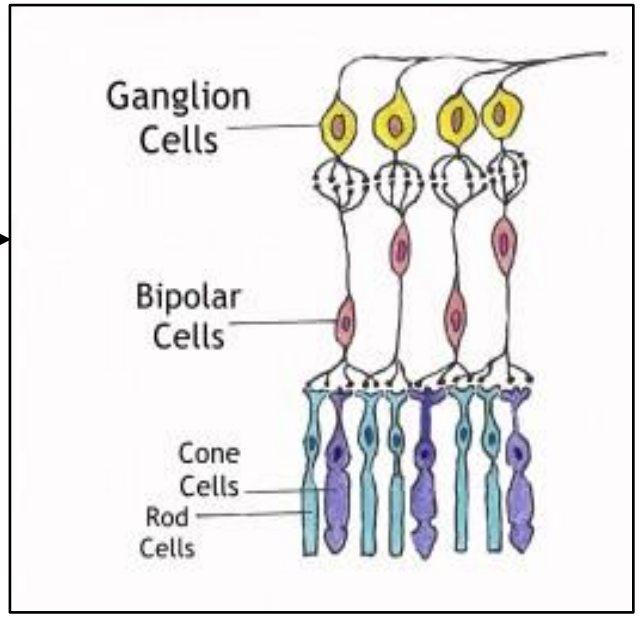
Visual System



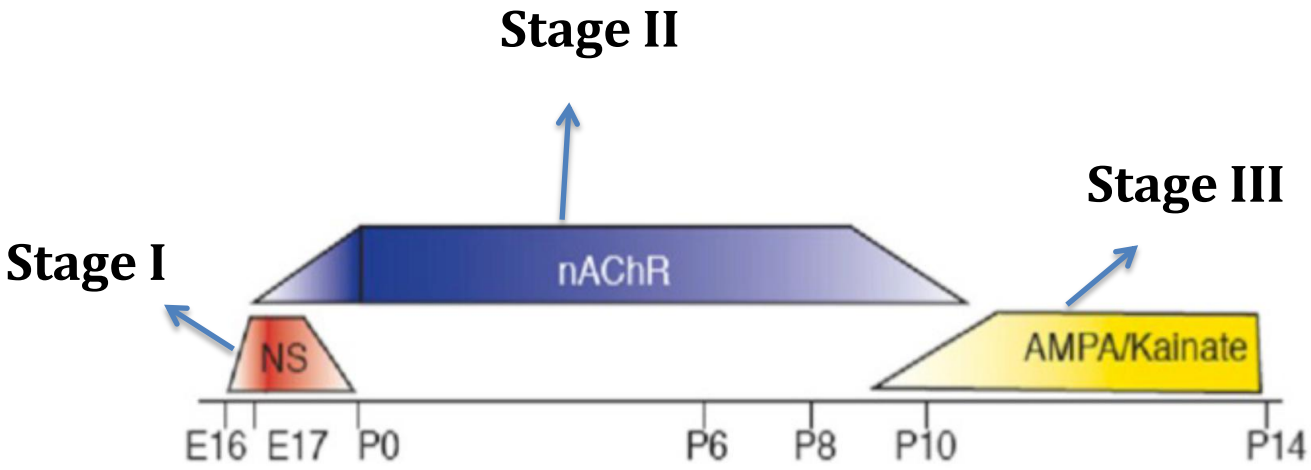
Lateral Geniculate Nucleus (LGN)

Primary Visual Cortex

Retina



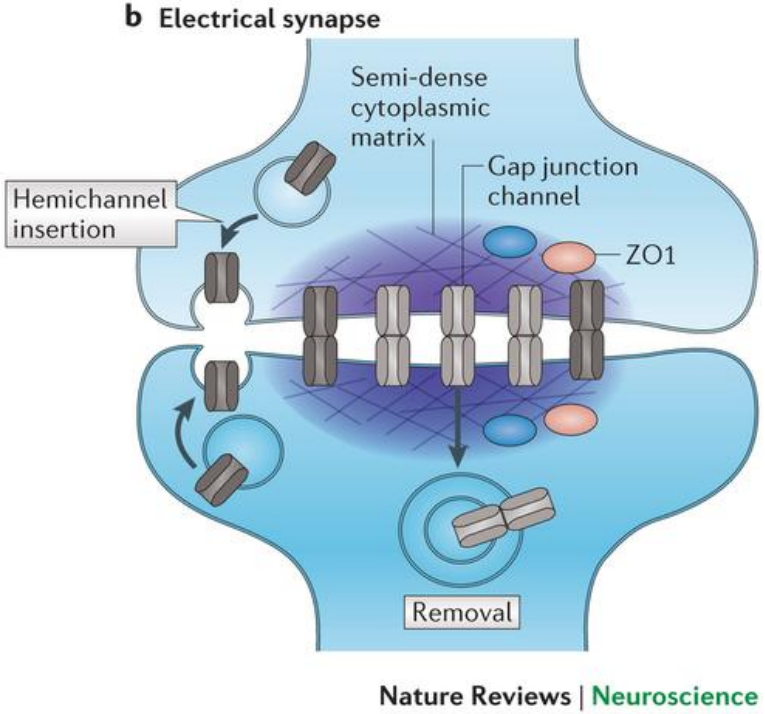
Stages of Retinal Waves During Development

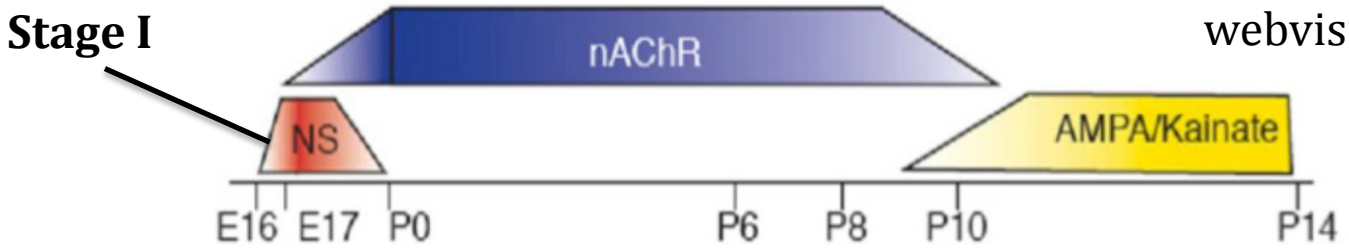


Stages of Retinal Waves During Development

Stage I

- Formation of retina circuitry
- Chemical synapses <u>not</u> formed yet
- Gap juction-mediated





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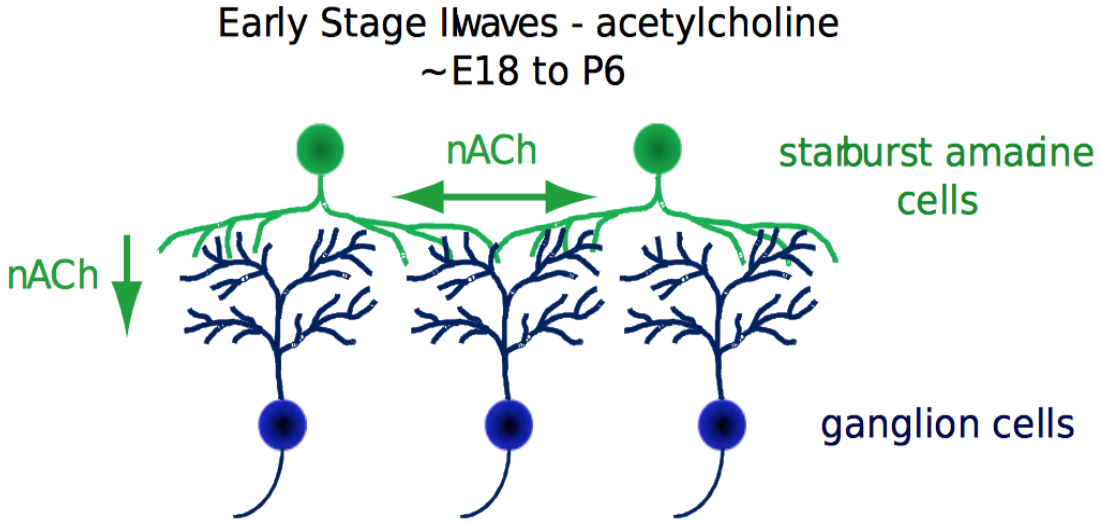
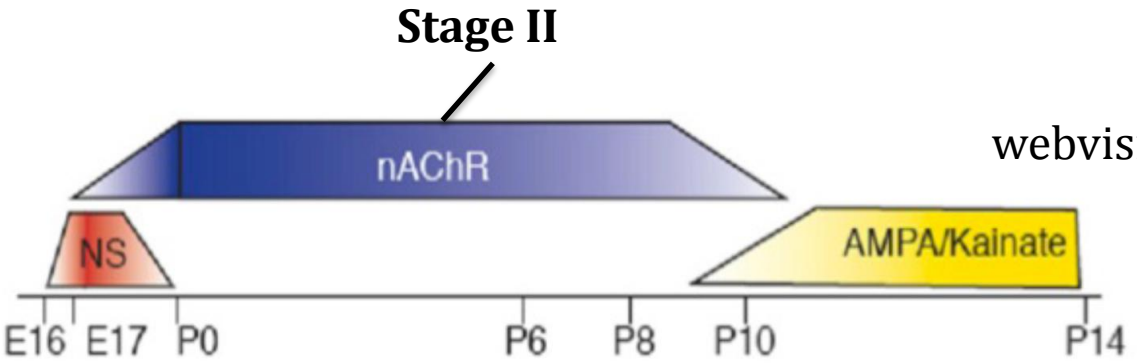
Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)
- Starbust Amacrine Cells (SACs)
- Refractory mechanism
- Random ignition and random boundaries
- No overlapping



E. Sernagor, M. Hennig,2012



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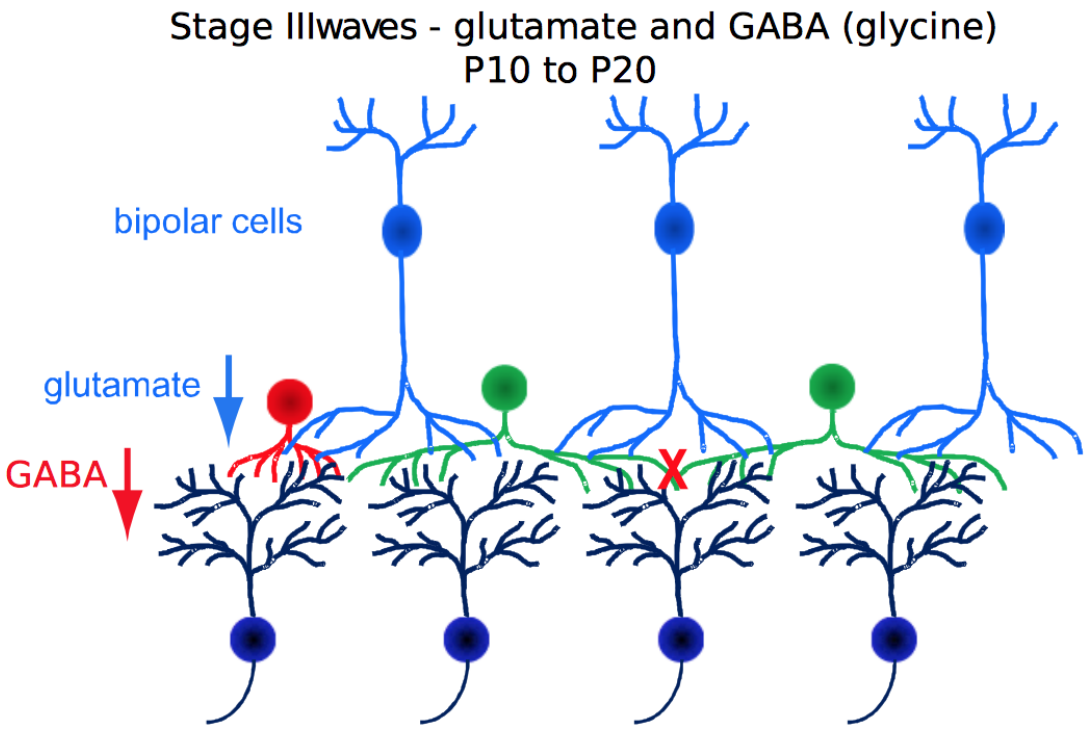
Stages of Retinal Waves During Development

Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors
- Bipolar cells – IPL
- GABA switches polarity
- Characteristics depend on species



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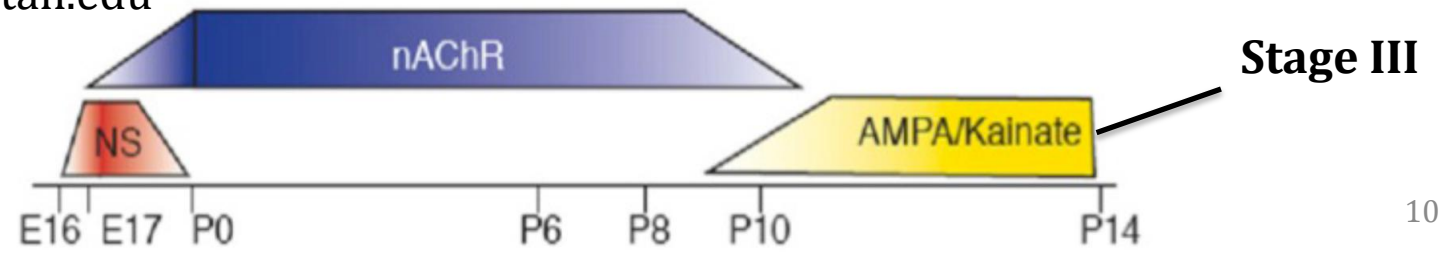

Retinal waves in adult retina

- Some wave activity can be restored pharmacologically in the adult retina

but

Retinal waves in adult retina

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but

- It is not yet known which type of « waves » is re-initiated in the adult retina

- Re-initiating waves in adult retina could help re-induce plasticity in pathological retina and possibly have a link to therapy

- In order to study adult retina wave activity we need to first study developmental waves

How to characterize developmental Retinal Waves?

Biophysical characterization

- Pharmacological manipulations allow to differentiate retinal waves in to 3 stages (I,II,III)

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Biophysical characterization

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Quantitative characterization

- *Distribution of the waves* :
  - Size
  - Duration
  - Power law distributions (maximal variance)
- *Compute the waves :*
  - Speed
  - Frequency

How to characterize developmental Retinal Waves?

Mathematical characterization

From the non linear physics perspective a retinal wave is a spatiotemporal activity which:

- is generated by the conjunction of local (cell level) nonlinear characteristics and network effects
- can have different forms (fronts, spiral, standing waves, spatio-temporal chaos)
- is induced by generic mechanisms that can be studied in the context of dynamical systems
- can be associated with bifurcations

Open Questions

- Which type of « wave » (spatio-temporal activity) is observed? (front, spiral, standing wave etc.)

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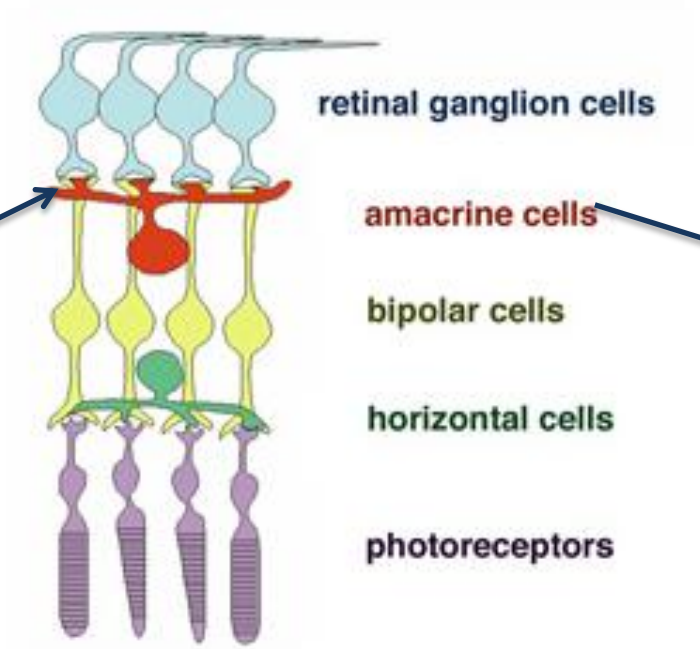
- What are the effects of local characteristics (neuron properties) versus the network effects?
- How waves depend on pharmacological manipulation?
- Which type of spatiotemporal correlations do retinal waves generate and what is the effect in the shaping of visual system?

Focus on stage II retinal waves

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

Stage II (cholinergic retinal waves)



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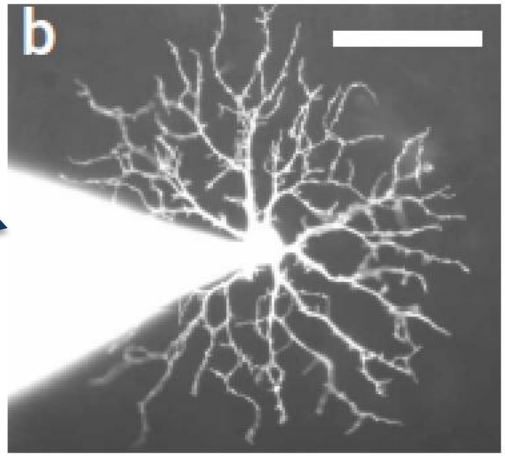
Starbust Amacrine Cell (SAC)



Zheng et al. 2006

Our goal

Idea:

Build a generic model to study the mechanisms generating stage II retinal waves

First step:

Generalization and adaptation of Hennig et al. 2009 and Lansdell et al. 2014 models

A reaction-diffusion neuron model for stage II retinal waves

Morris-Lecar

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

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

Morris-Lecar

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Morris-Lecar

sAHP current
Refractory mechanism

A reaction-diffusion neuron model for stage II retinal waves

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Network effect

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Morris-Lecar

sAHP current
Refractory mechanism

Ach current
Network effect

External current
Ignition of waves

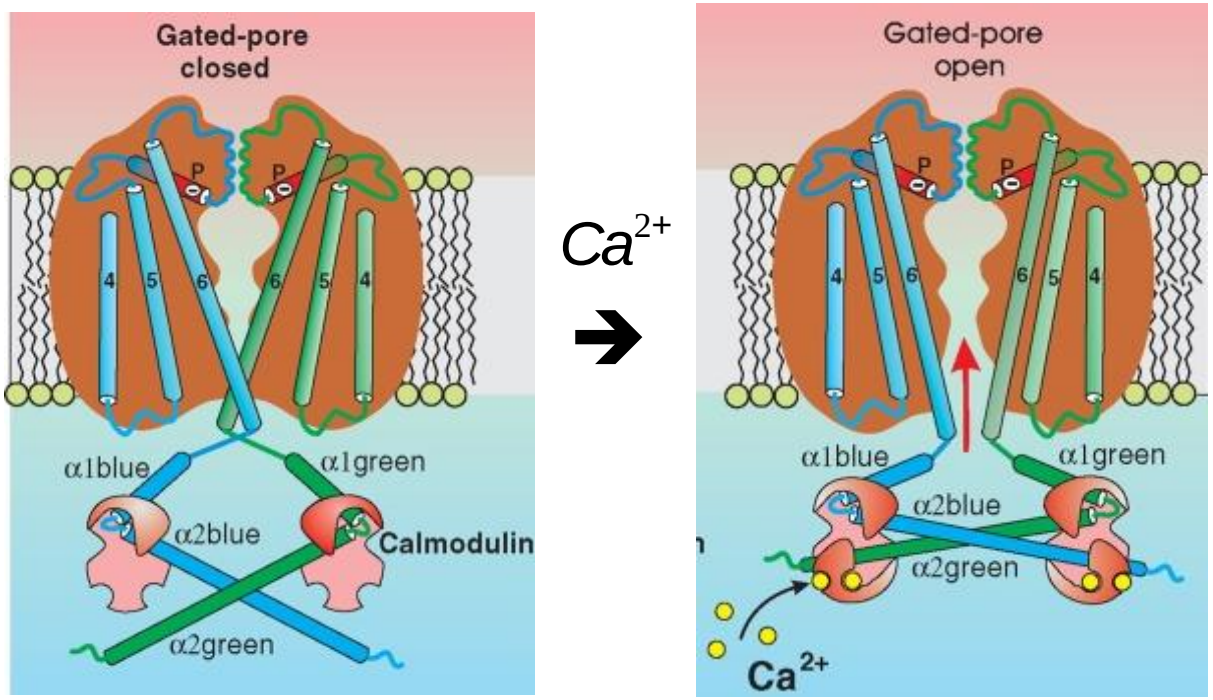
sAHP current

- ***Role and effect on retinal waves*** [Zheng 2006 , Ford 2012]
  - Alters the refractory period in between waves
    - ✧ Modulates wave frequency
    - ✧ Random boundaries of the waves
  - Network effect - sAHP dictates the interburst intervals

sAHP current

- ***Definition***
  - Slow After Hyperpolarization Current
  - Calcium-dependent slow potassium current

- **Mechanism**
  - Model SK-like channels [Abel 2004]
  - Gating Mechanism: Calmodulin(CaM) binds to four ions Ca^{2+}



Calcium gated potassium channel

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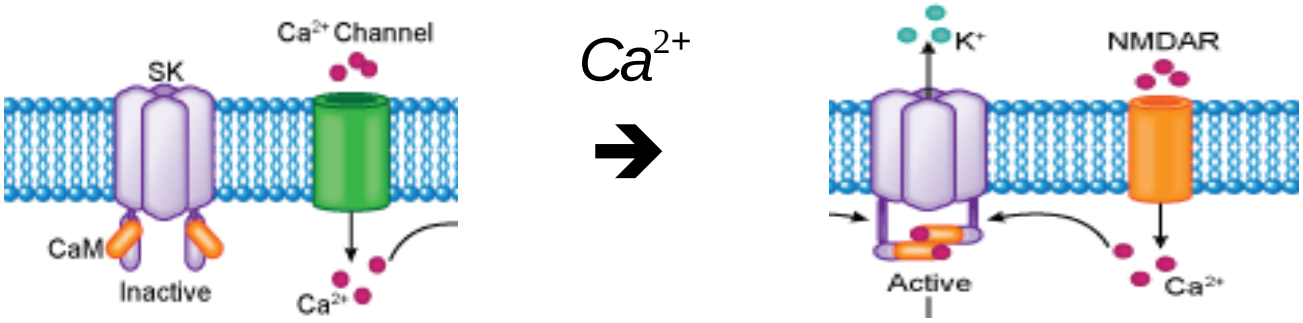
Set of equations for sAHP current

$$t_S \frac{dS}{dt} = -S + \frac{bC^4}{K_d^4 + C^4}(1 - S)$$

$$[CaM] = \frac{bC^4}{K_d^4 + C^4}$$

S : Fraction of saturated calmodulin concentration (CaM)

[CaM] : Steady state for saturated calmodulin concentration



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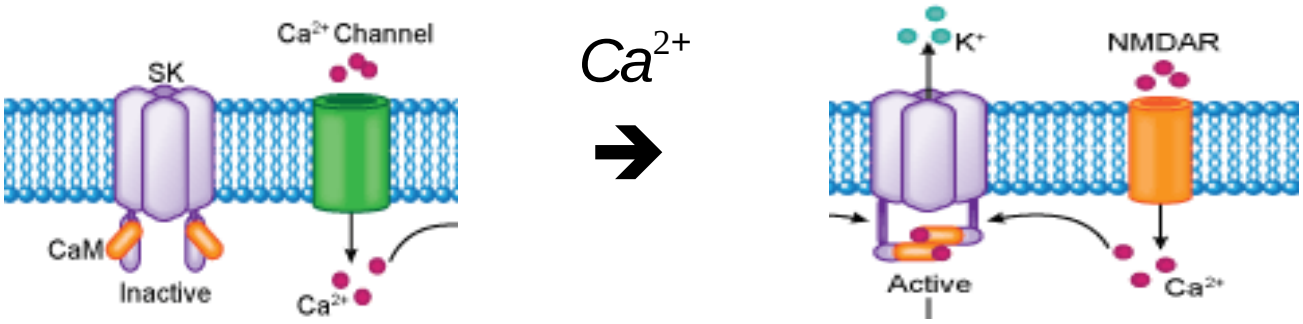
$$\tau_R \frac{\partial R}{\partial t} = (\alpha_R C + S)(1 - R) - R$$

R : Probability that one terminal of the channel is open



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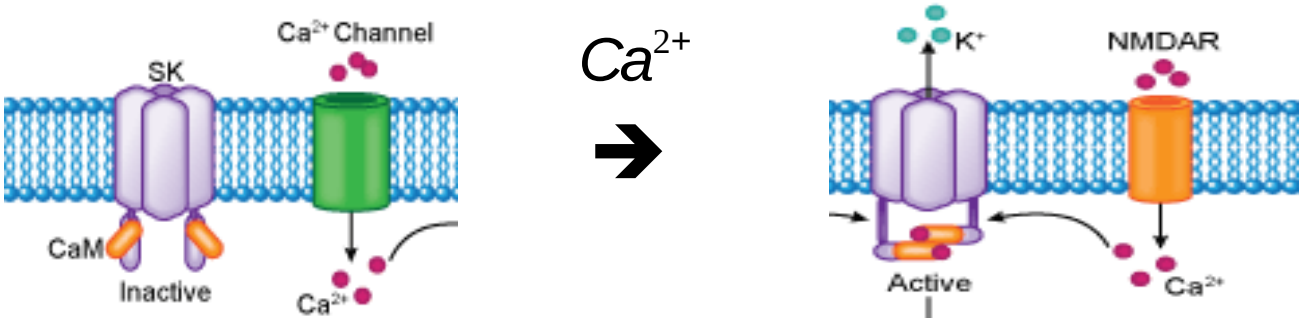
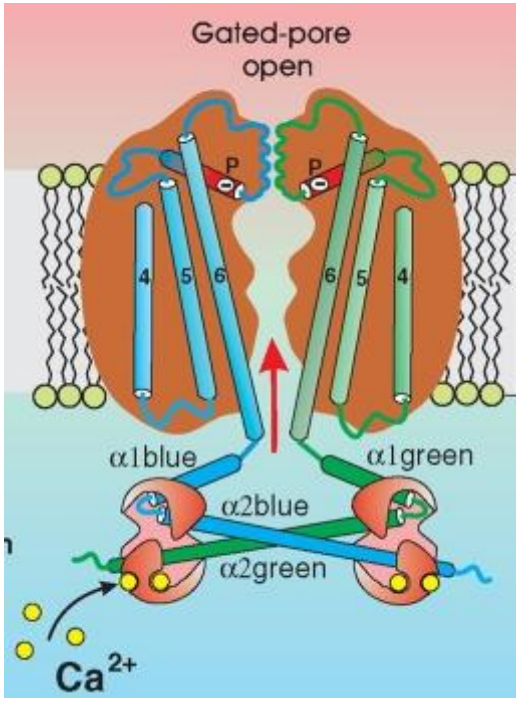
C : Intracellular Calcium concentration



Calcium gated potassium channel

sAHP current

- Equations for R,S mimic the binding of CaM subunits and their changes of conformation
- Four Ca^{2+} ions bind to calmodulin and open the channel
- I_{sAHP} current depends on gating variable R as follows:



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

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

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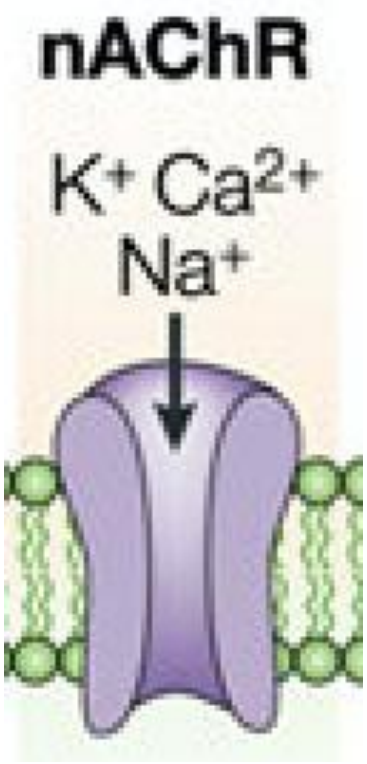
Parameter issues

The choice of the parameters values can change dramatically the behaviour of the system

- Issues with two parameters values , K_d, d_{Ca} given in the paper of Hennig et al.
  - In Hennig et al. model $K_d = 10^{-8}$ with no units
  - In Graupner et al. 2003 $K_d = 10^{6} - 10^{8}\, nM^{4}$
  - In Hennig et al. Model $d_{Ca} = 10^{8}$ with no units
  - After computation based on physics $d_{Ca} = 10^{5}\, nMnA^{-1}$

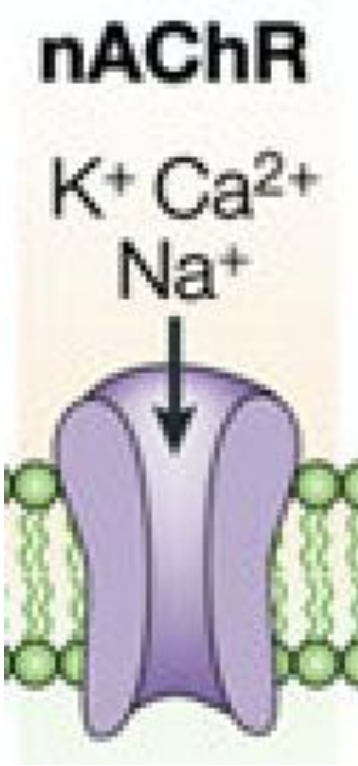
Acetylcholine current

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



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

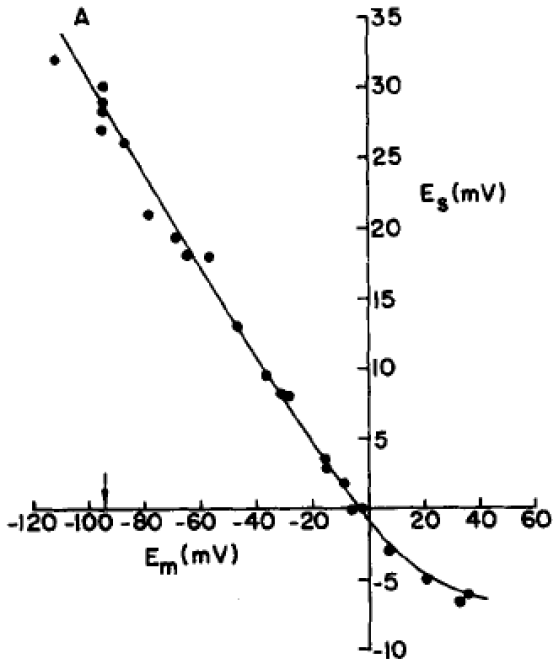
Acetylcholine current



- nAchR channel is permeable to three cations

$$K^+, Ca^{2+}, Na^+$$

- Reversal potential $V_{Ach} \sim 0$ [Lassignal 1977]



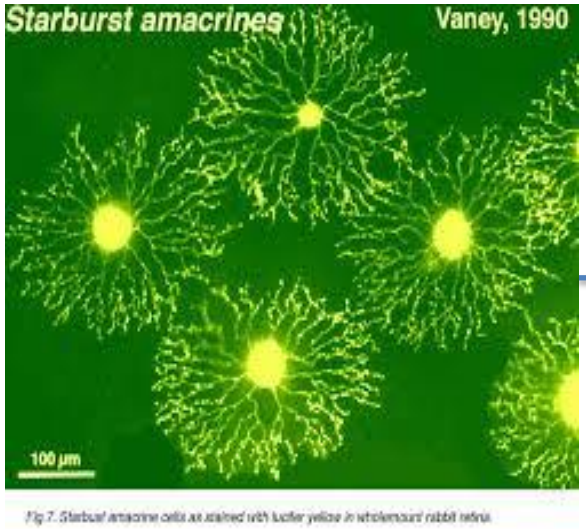
$$\neq V_{Ach} = 50mV$$

Which was chosen by Lansdell et al.

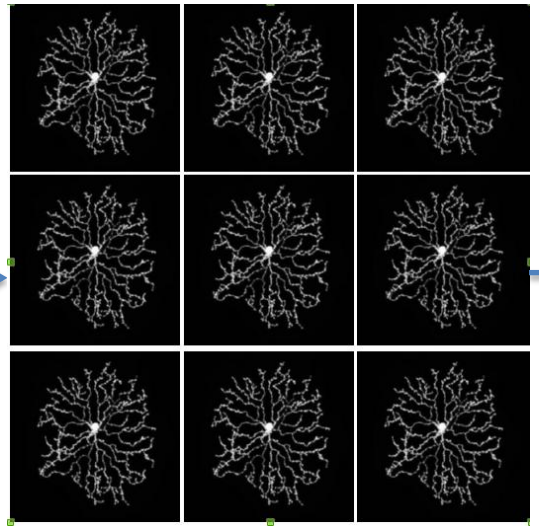
Reversal potential of Ach,Lassignal,1977

SACs & Diffusion

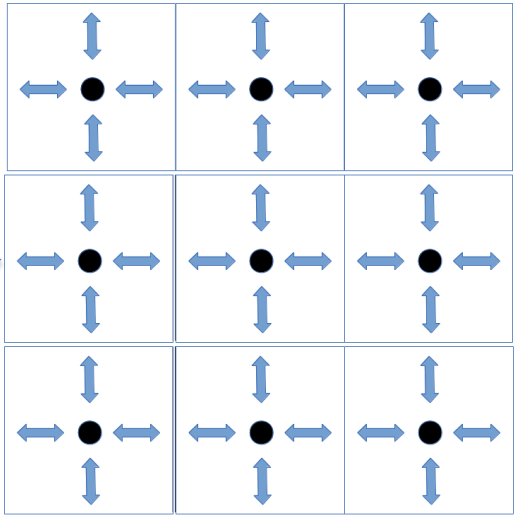
Model synaptic interactions



SACs realistic connections



SACs on a lattice



SACs become points on a lattice

Acetylcholine current

- Diffusion of acetylcholine neurotransmitter in nicotinic receptors [Lansdell 2014]
- Diffusion is the only spatial coupling in the model
    - Effective diffusion process – averaging

- Cholinergic waves modulated by Ach extracellular concentration A

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

External current

- Mimics the random opening of Ca channels generating an intrinsic extra current in SACs activity [Zheng, 2006]

- Add a voltage dependent external current to play the role of the trigger of a burst [Hennig, 2009]

Full set of equations

$$C_m \frac{\P V}{\P t} = - g_L^M (V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N (V - V_K) - g_{sAHP} R^4 (V - V_K) - g_{Ach}(A)(V - V_{Ach}) + I_n(V)$$

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Fixing the parameters of the model

- We have a nonlinear system with high sensitivity in the change of some parameters

- Some values of parameters are fixed by biophysics
    - E.g. Reversal potentials

- Then vary some free parameters to study the effect on the dynamics
    - Mainly varying the conductance of a channel due to pharmacological manipulations

Reducing the equations towards Lansdell et al. model

$$C_m \frac{\P V}{\P t} = - g_L^M (V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N (V - V_K) - g_{sAHP} R^4 (V - V_K) - g_{Ach}(A)(V - V_{Ach}) + I_n(V)$$

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

Lansdell et al. model

$$C_m \frac{\P V}{\P t} = - g_L^M (V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N (V - V_K) - g_{Ach}(A)(V - V_{Ach}) + I_n(V)$$

$$\frac{dS}{dt} = gG(V) - \frac{S}{t_S}$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N) + a_S S(1 - N)$$

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

Exploring the range of parameters in Lansdell et al. Model

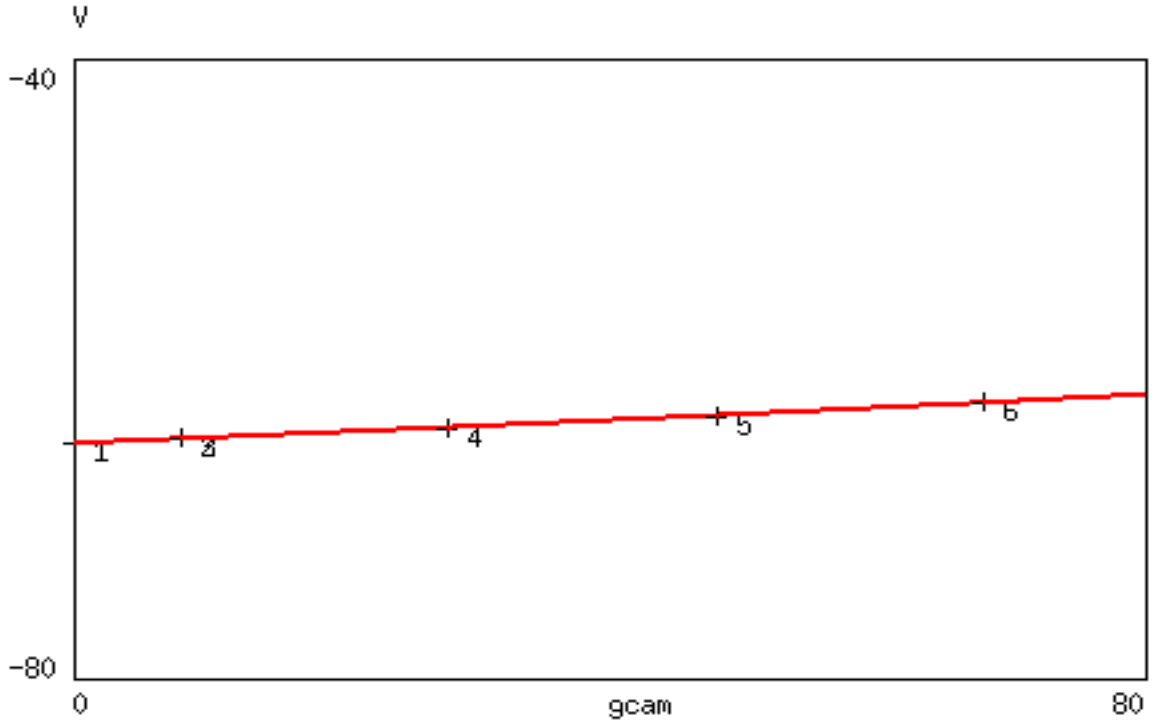
Calcium and potassium conductance

- Start from Lansdell et al. model which is a specific case of ours with their chosen values of parameters
- Varying the amplitude of the calcium conductance g_{Ca}
- Then keep the model but change the value of K_d of acetylcholine and test the effect on dynamics

Bifurcation analysis of Lansdell et al. Model

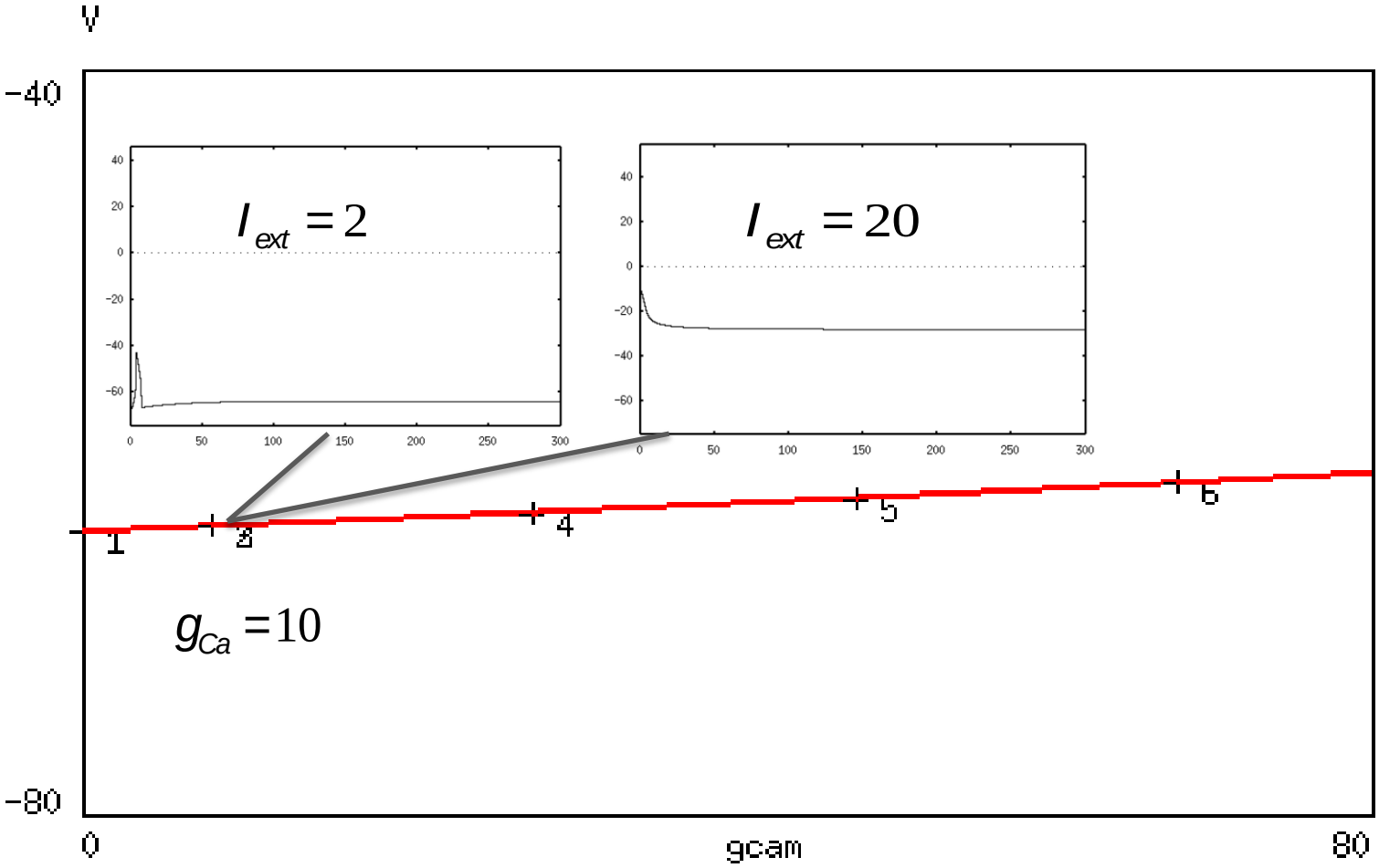
Calcium conductance

- We performed the bifurcation analysis for the given set of parameters in the paper of Lansdell varying the parameter g_{Ca}



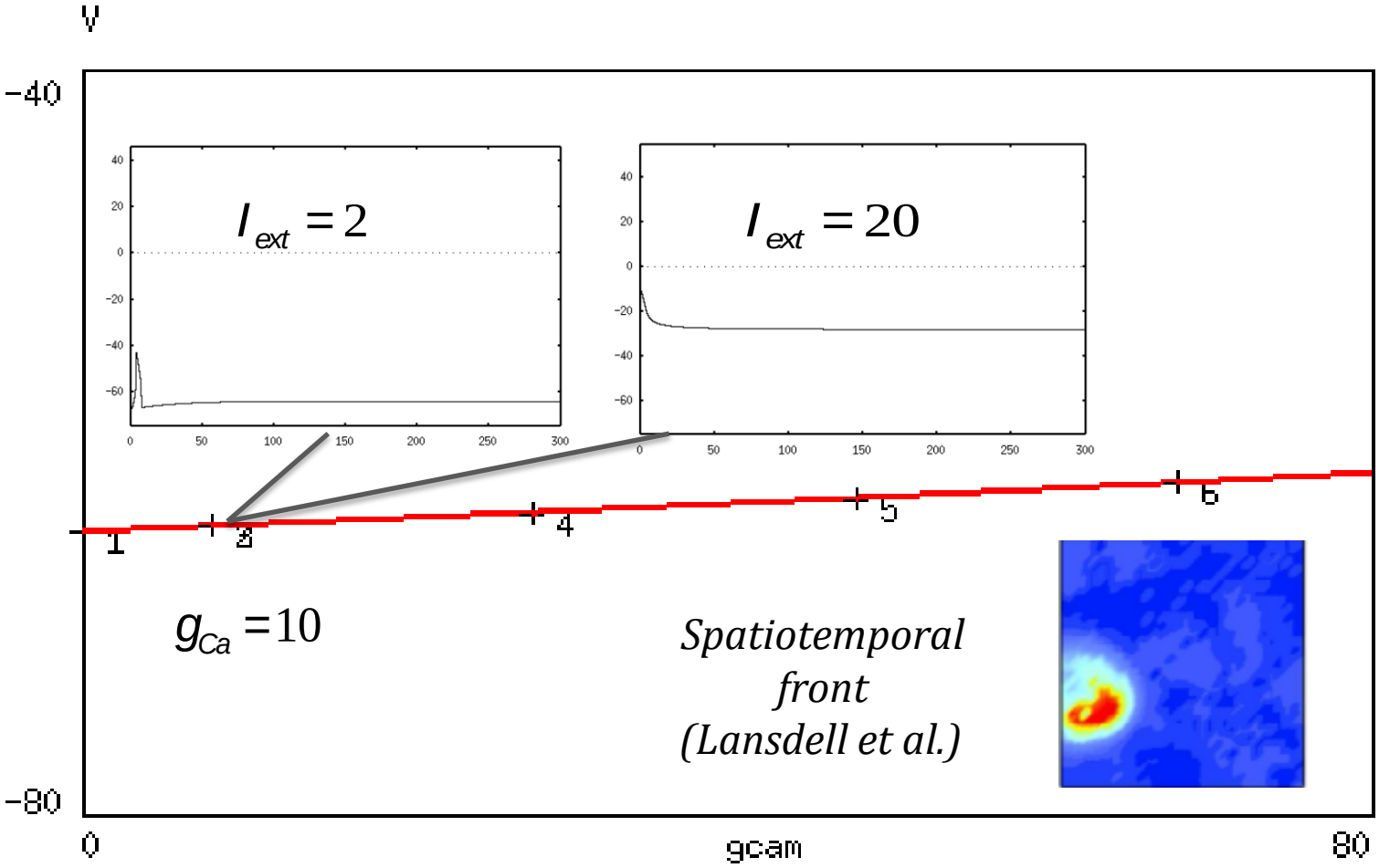
Bifurcation analysis of Lansdell et al. Model

Calcium conductance



Bifurcation analysis of Lansdell et al. Model

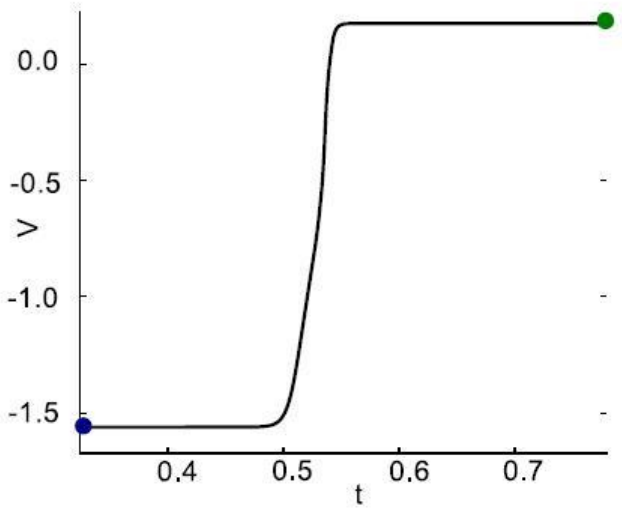
Calcium conductance



Conclusions on Lansdell et al. model

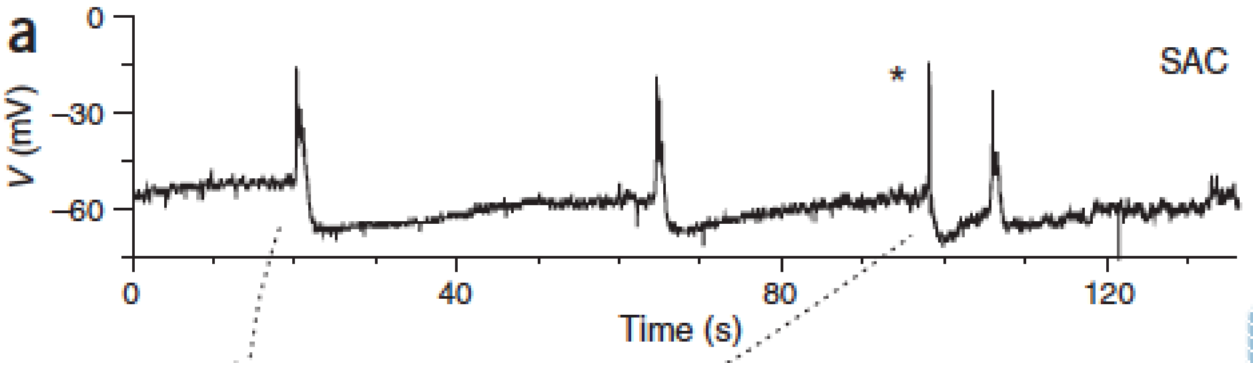
- Varying the amplitude of the external excitatory current In we have a transition from a low voltage state to a high one.
- In the paper they obtain fronts as a result of heteroclinic orbits connecting low and high states of activity

Heteroclinic orbit- Voltage profile of the wave front, Lansdell et al.



Conclusions on Lansdell et al. model

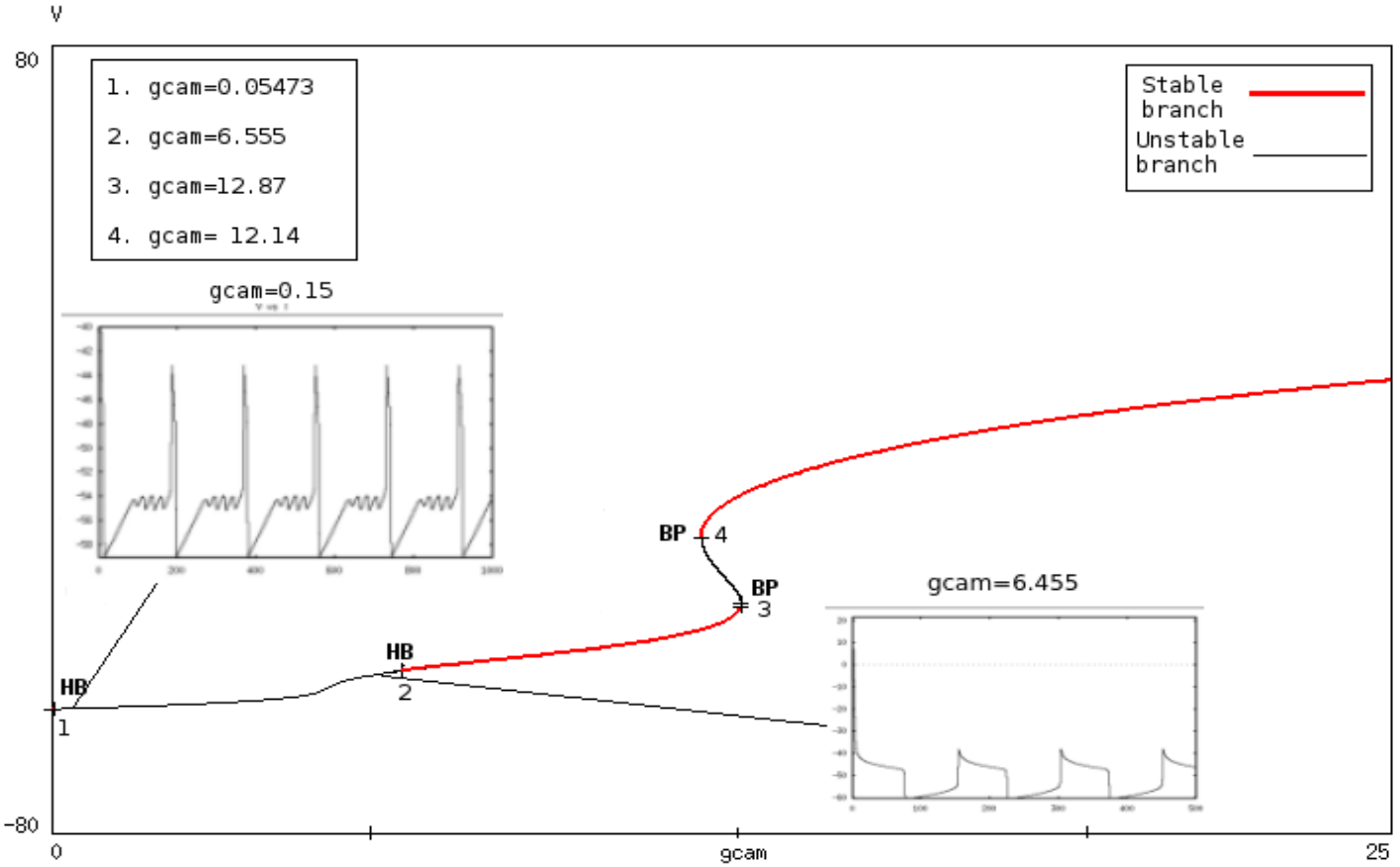
- Also there is no bursting activity for SACs as it is found in Zheng 2006.



Zheng 2006, Busting activity SACs

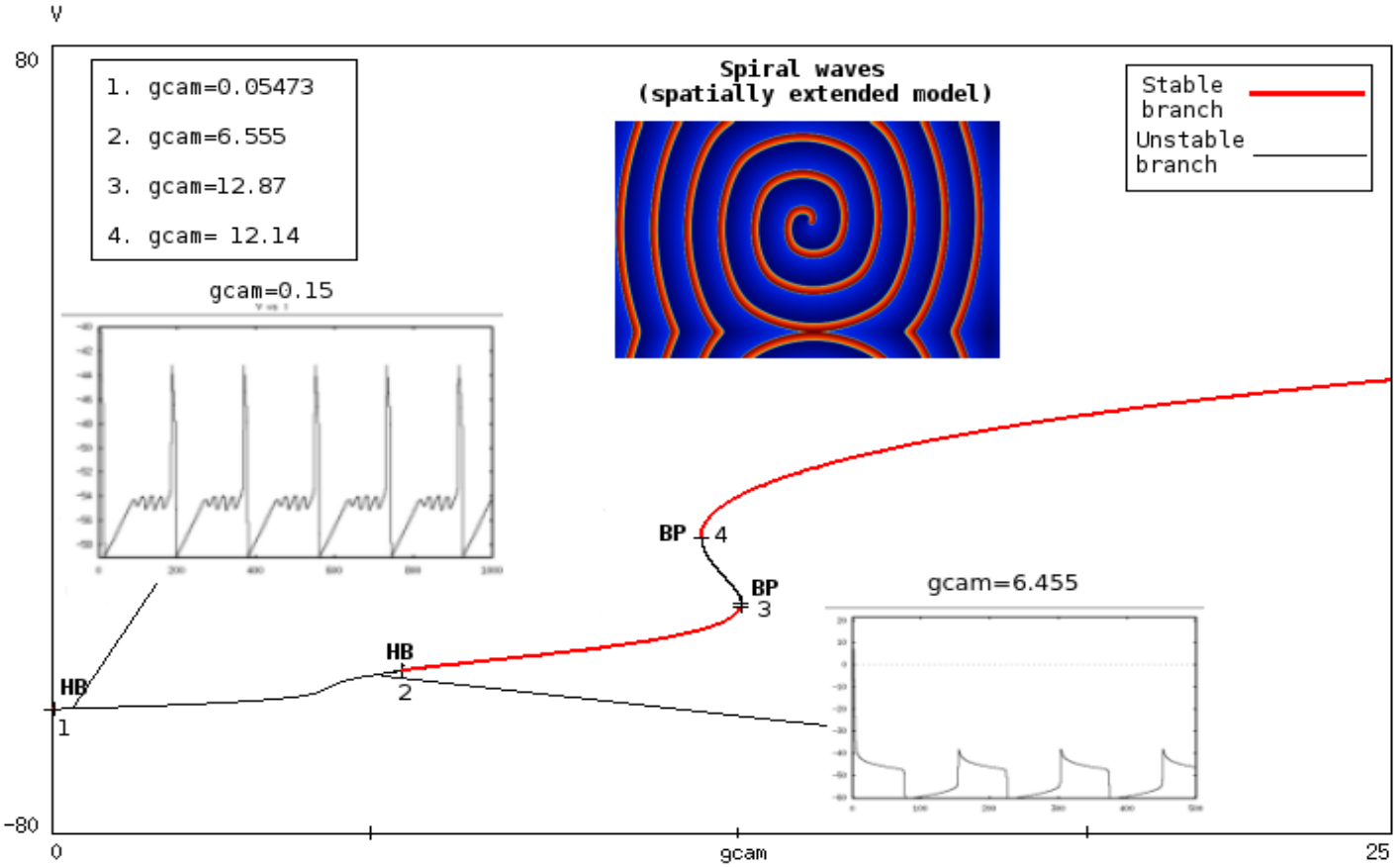
Bifurcation analysis of Lansdell et al. Model with a tuned set of parameters

- Now if we change the value of the binding constant K_d for acetylcholine to what was found in the literature we obtain the following:



Bifurcation analysis of Lansdell et al. Model with a tuned set of parameters

- The reward of using bifurcation analysis tools: when we couple neurons by diffusion, local spiking activity generically produces spiral waves in 2D (theorem by Schell et al.)



Comments

- Lansdell et al. model produces spiral waves after a biophysical tuning of parameters
- Spirals seem too perfect and not biophysically related
- Why?
  - sAHP is not realistically modeled
    - Symmetries in Lansdell model
    - Refractory mechanism due to sAHP should disrupt the waves

Ongoing and Future Work

- Vary parameters which are related to conductances of the ionic channels of the full model
- Which type of local dynamics can we observe varying parameters?
- Which type of dynamics (fronts, spirals,etc) can we produce by varying pharmacological terms?
- Investigate a higher order effect (non linear) for the acetylcholine diffusion.
- Do we predict some regimes of behaviour not observed before?

Aknowledgements

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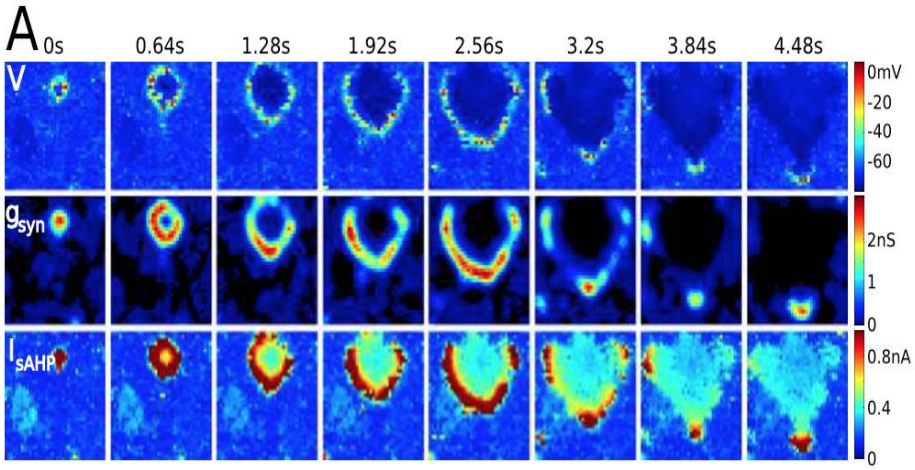
- Serge Picaud, *Vision Institute, Paris*

Thank you for your attention! ☺

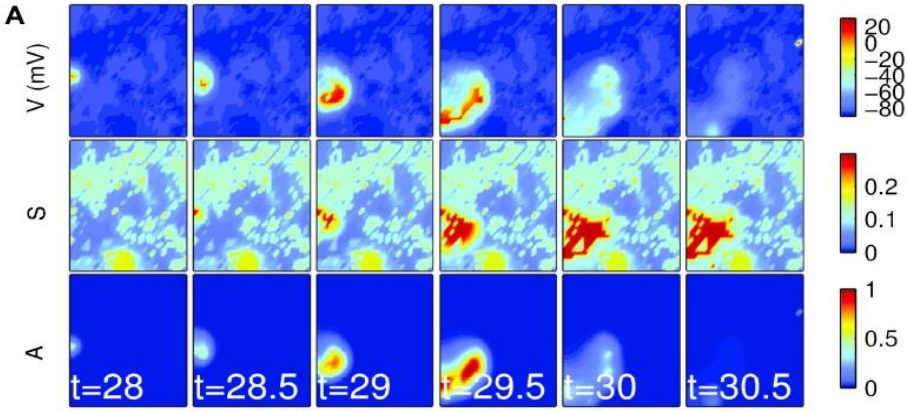
Existing Models for Stage II Retinal Waves

1.Hennig et. al (2009)



Evolution of the membrane potential v, synaptic conductance gsyn, Isahp

2. Lansdell et. al (2014)



Evolution of the membrane potential V, gating variable for sahp current S, acetylcholine concentration A