



Ion channels and properties of large neuronal networks: a computational study of re.nal waves during development

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Ion channels and properties of large neuronal networks: a computational study of retinal waves during development.

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O. Marre, Institut de la Vision, Paris

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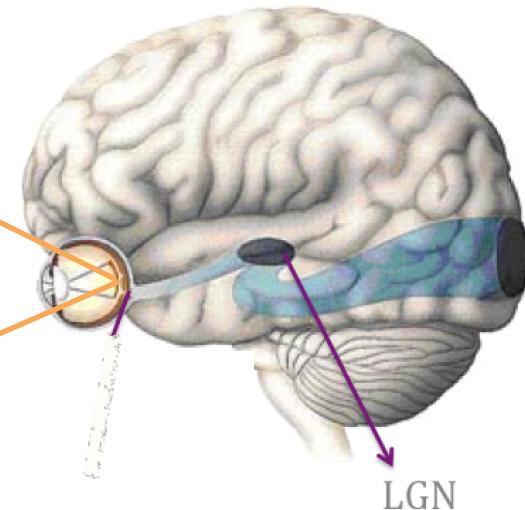
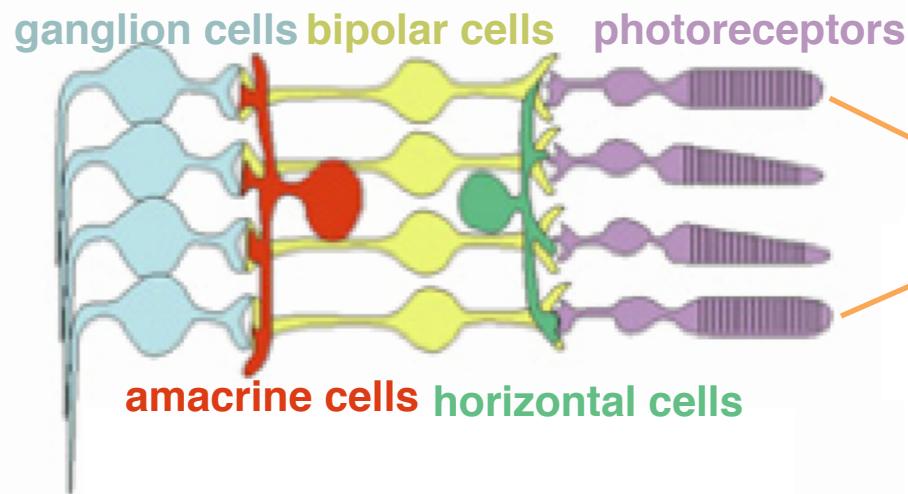
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The structure of the adult retina

Retina's layered structure

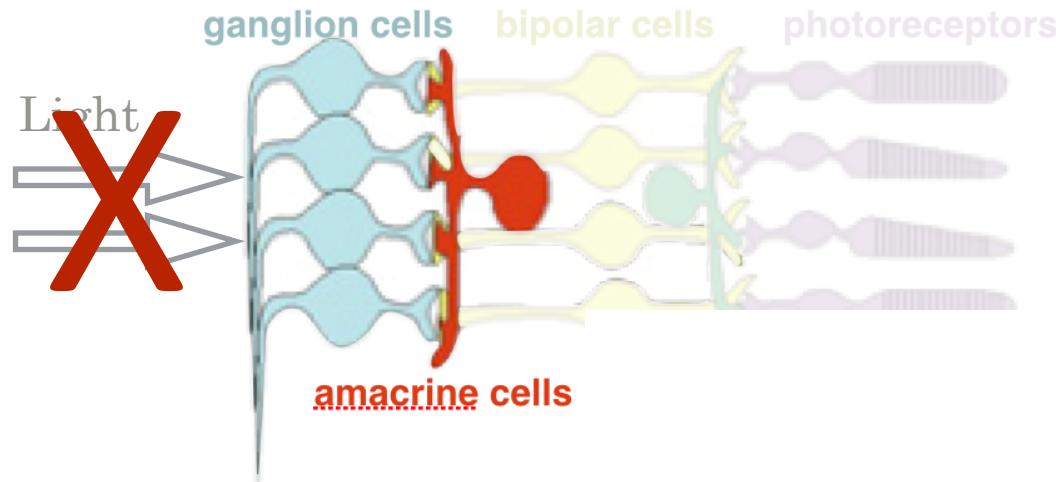


Visual cortex

LGN

The structure of the retina during development

Retina's layered structure
is shaped during development



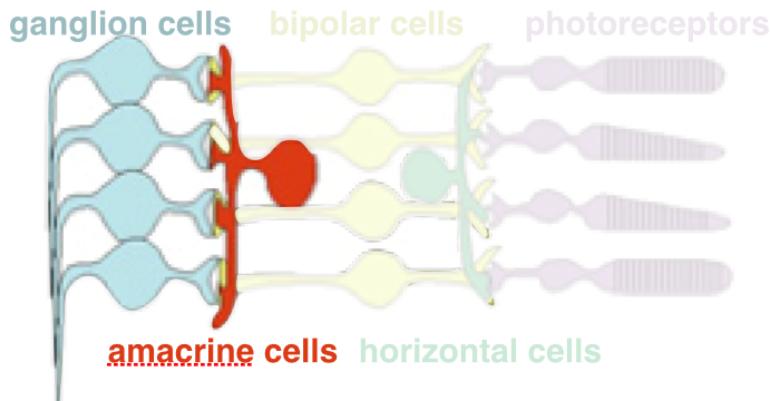
But How?



Retinal waves!

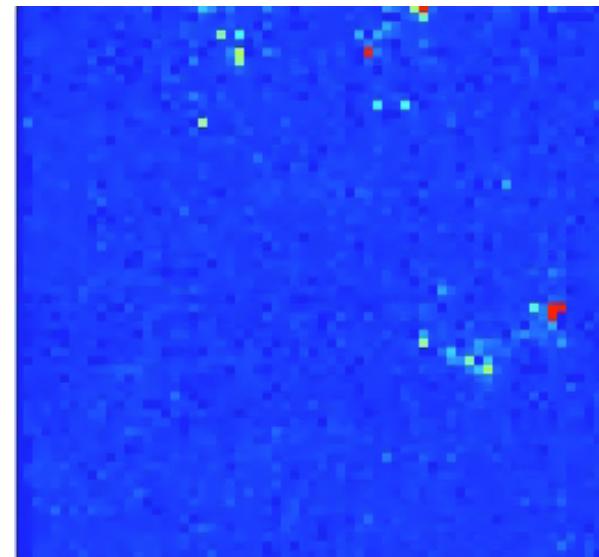
Retinal waves

Recordings from the retina



**Multi-electrode
array
(MEA)**

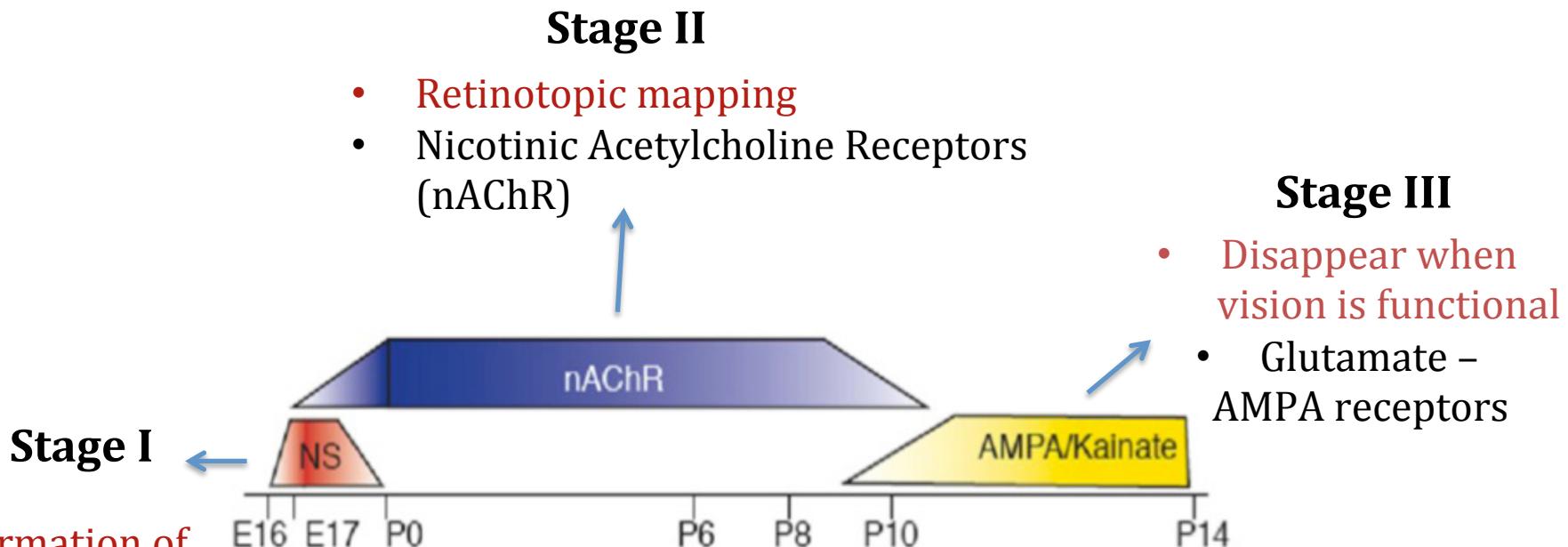
Spontaneous spatio-temporal
waves during development
Disappear short after birth
when vision is
functional



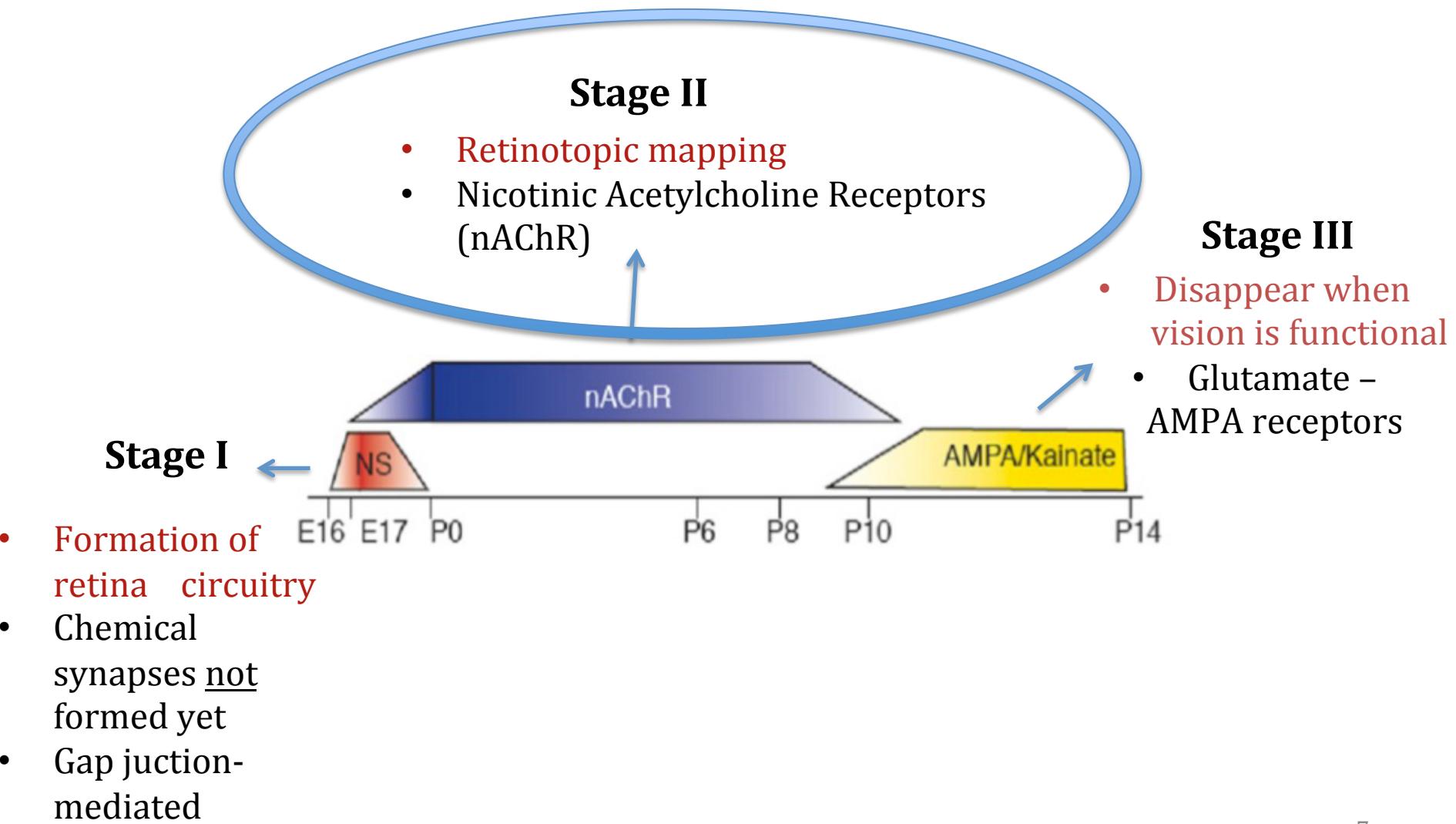
(Maccione et al. 2014)

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

Stages of Retinal Waves During Development



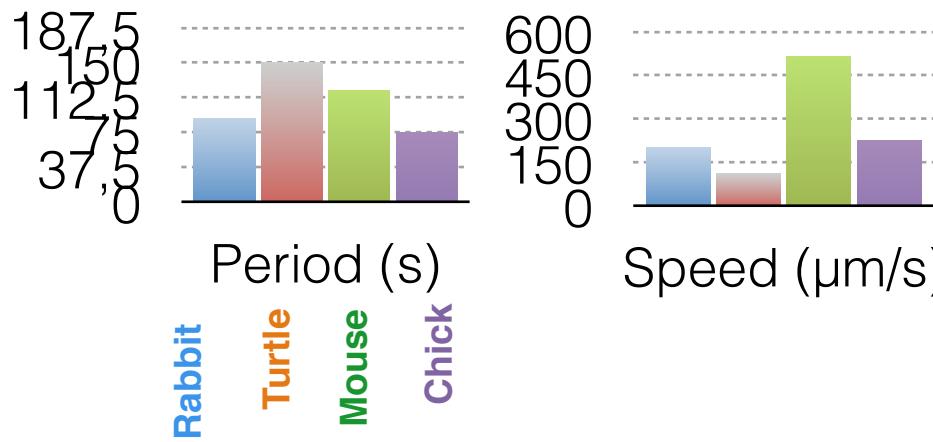
Stages of Retinal Waves During Development



Variability within retinal waves

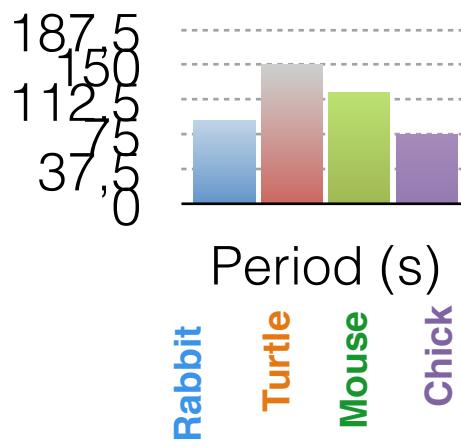
i) Across species

Godfrey et al. 2007

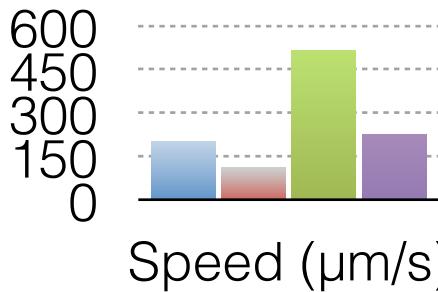


Variability within retinal waves

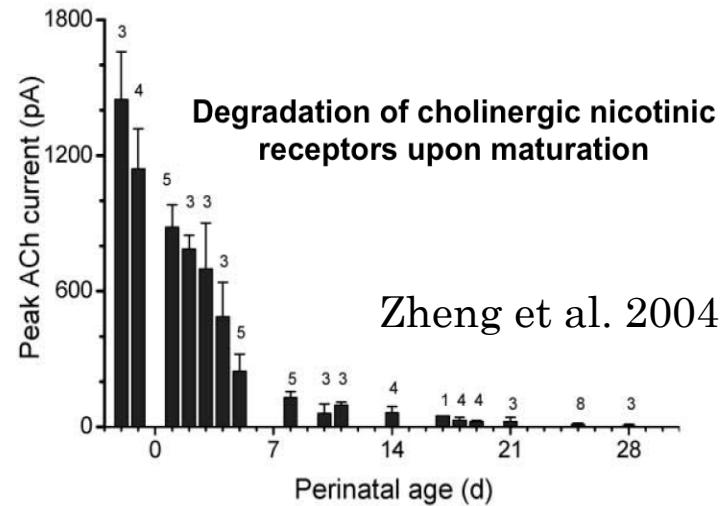
i) Across species



Godfrey et al. 2007

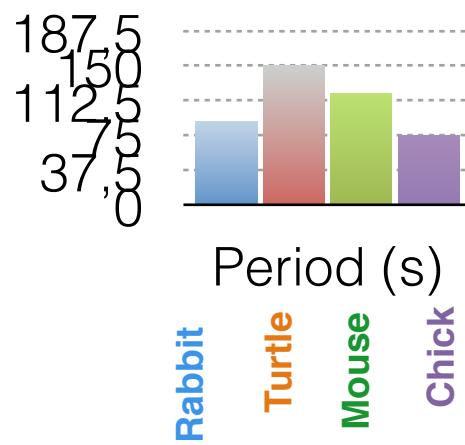


ii) Development

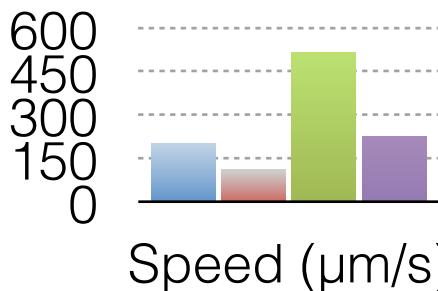


Variability within retinal waves

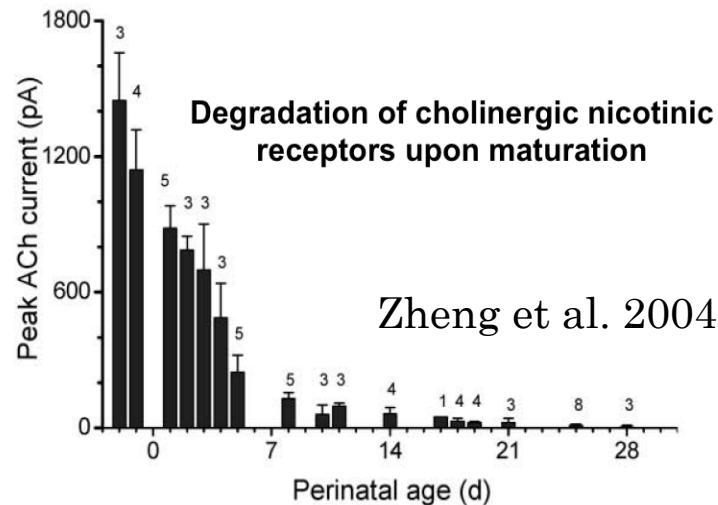
i) Across species



Godfrey et al. 2007

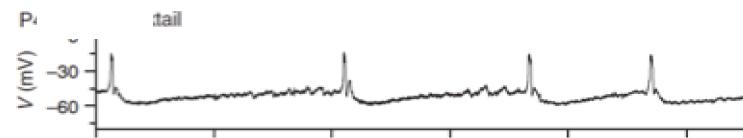


ii) Development

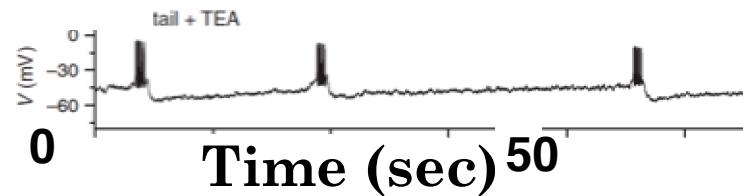
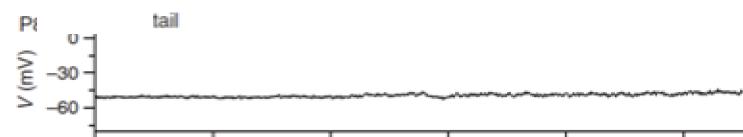


iii) Pharmacology

P4

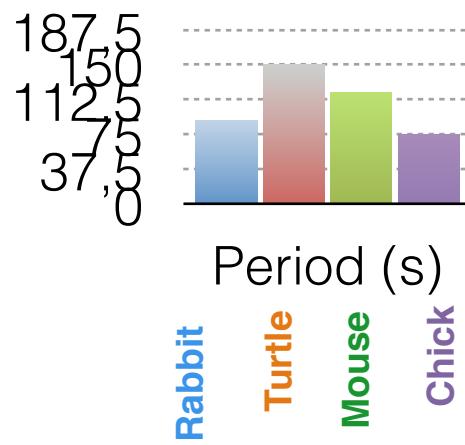


P8

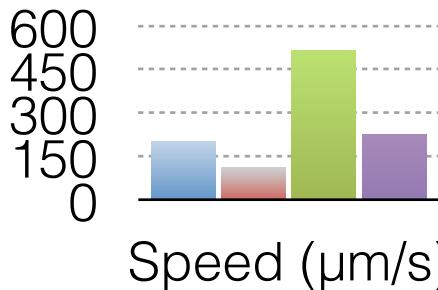


Variability within retinal waves

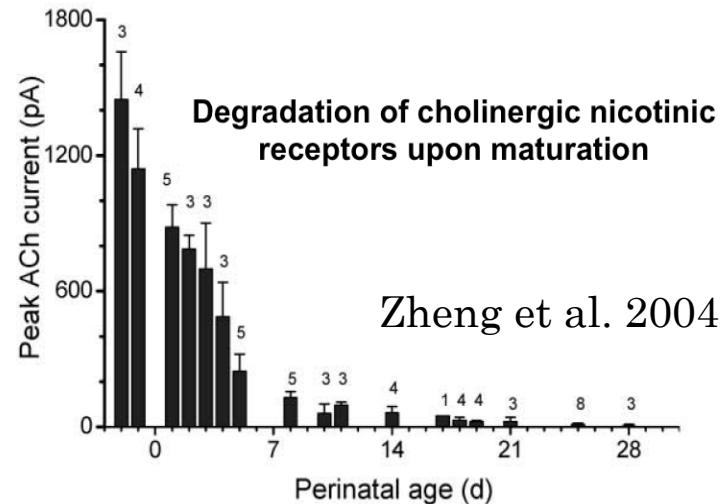
i) Across species



Godfrey et al. 2007

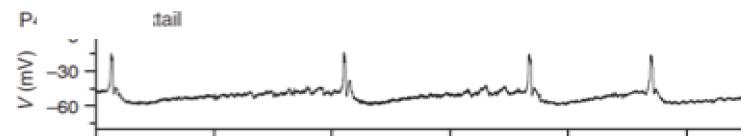


ii) Development

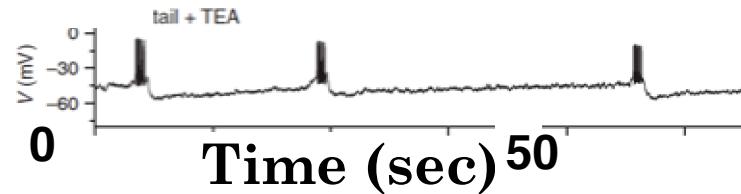
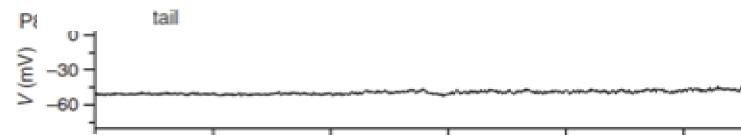


iii) Pharmacology

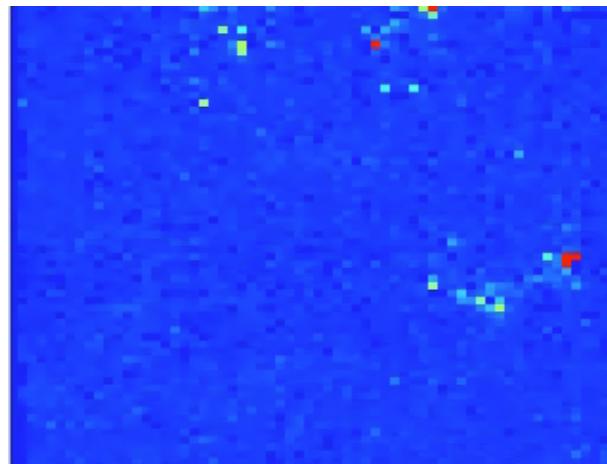
P4



P8



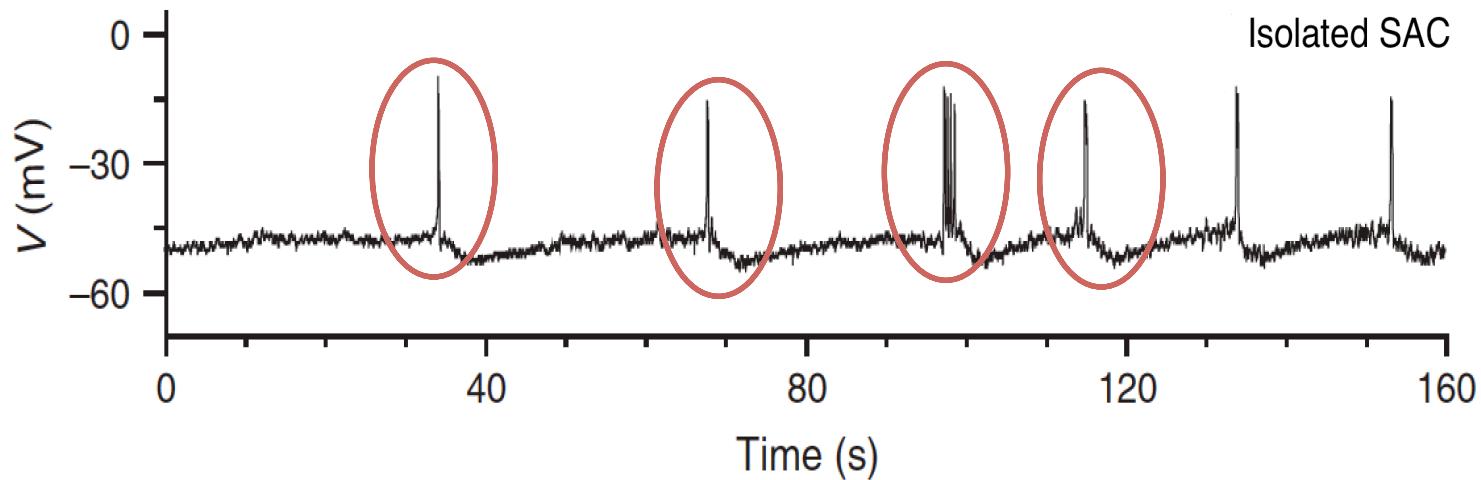
iv) Spatial Variability



Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity

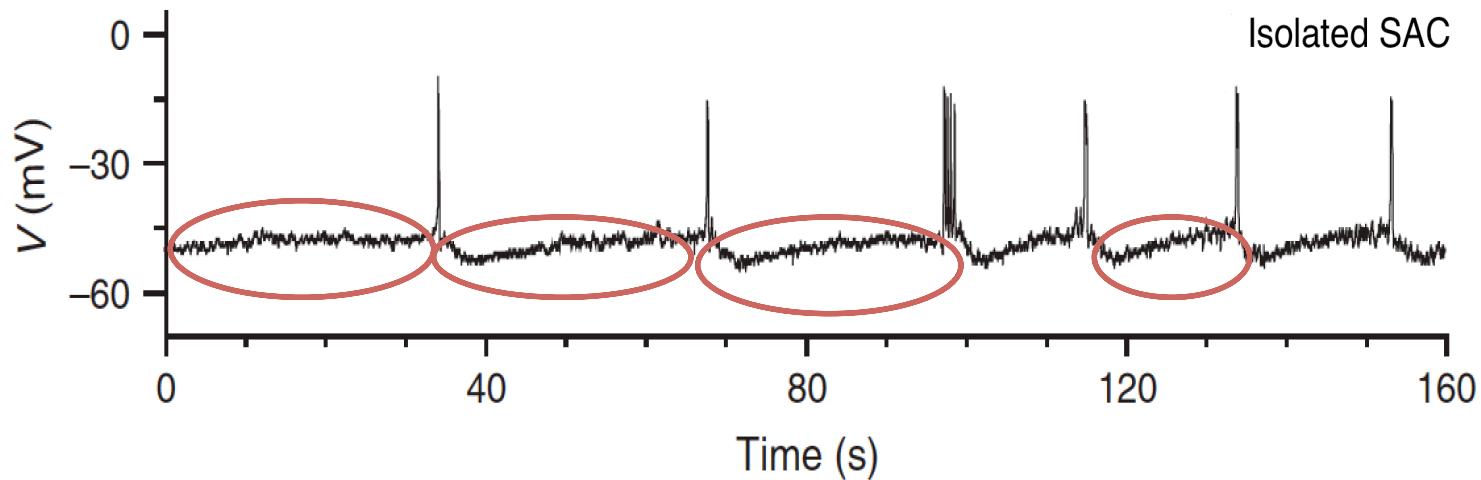


Experiment for isolated neurons,
Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

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

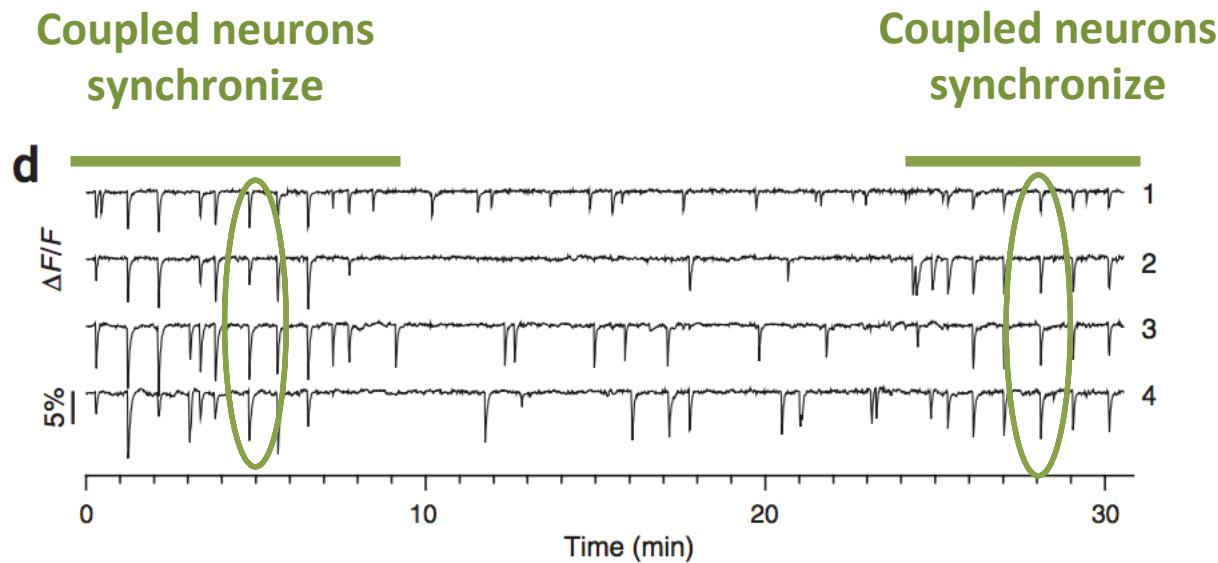


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Experiments for the emergence of retinal waves

Retinal waves require three components:

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

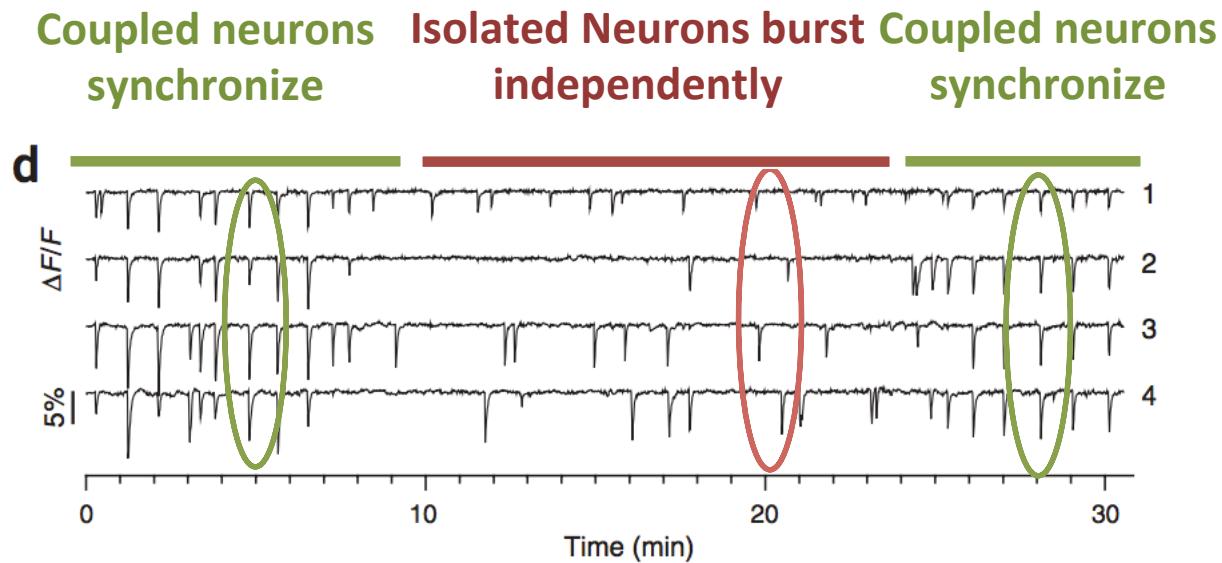


Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

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



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

Why study retinal waves?

Strategy:

To propose a model (i) sufficiently close from biophysics to explain and propose experiments and (ii) sufficiently well posed mathematically to analyse its dynamics upon varying biophysical parameters (development - pharmacology).

- Modelling one cell bursting
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

Why study retinal waves?

Strategy:

To propose
its

Multiscale modelling

and
analyse
t -

From ionic channel to neuron to retina scale

Non linear dynamics, dynamical systems theory,
statistical physics.

- Modelling ionic channels
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

Main assumption

There are a few physiological parameters controlling retinal waves dynamics, evolution and variability.

Find these parameters from a mathematical analysis

Bifurcation theory

A network model for stage II retinal waves

A network model for stage II retinal waves

Membrane potential dynamics

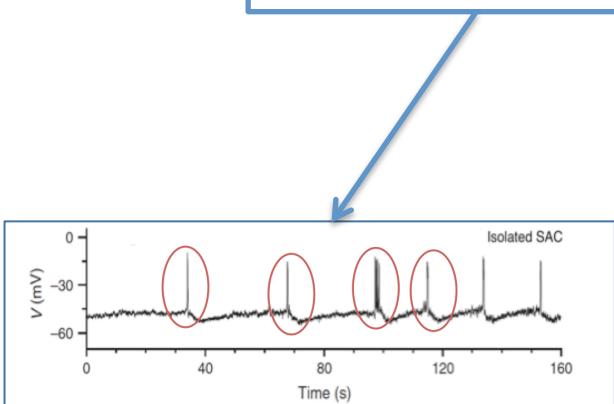
$$C_m \frac{\partial V}{\partial t} = -g_L^M(V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N(V - V_K)$$



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



**Morris-Lecar &
Fast K⁺ channels**



A network model for stage II retinal waves

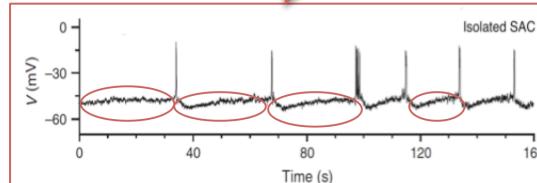
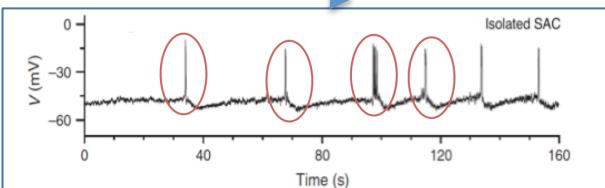
Membrane potential dynamics

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

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

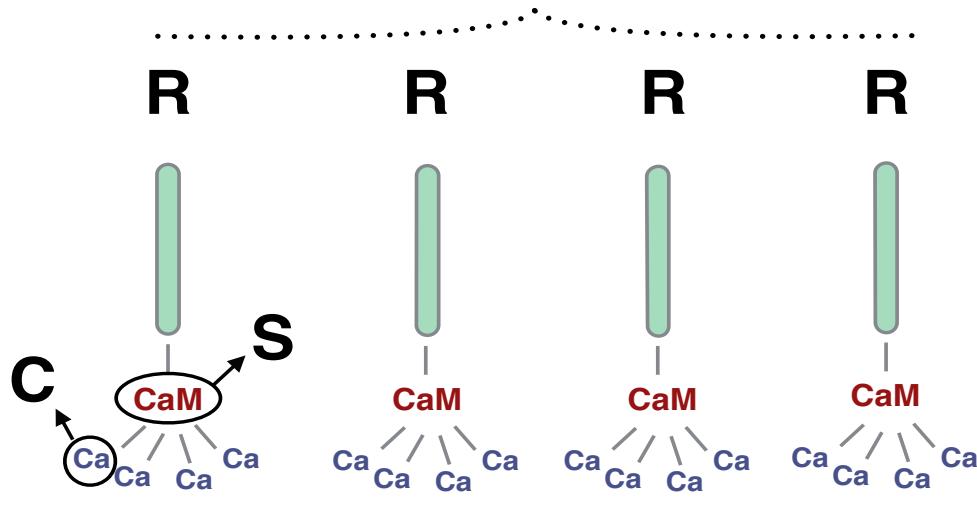
Morris-Lecar &
Fast K⁺ channels

sAHP current
Refractory
mechanism



Set of equations for sAHP current

Activated Ca-gated K⁺ channel



Gating mechanism

All 4 subunits R of the channel are bound to activate the channel



Saturated Calmodulin molecule (CaM) bind to each channel subunit



4 Calcium ions bound to each saturated Calmodulin complex S

SACs Network

Model synaptic interactions

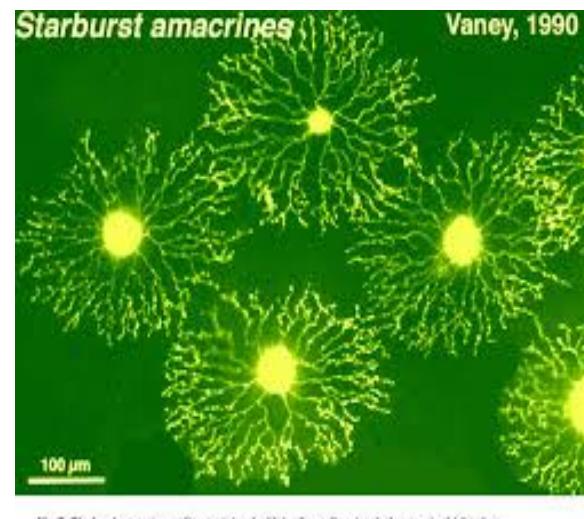
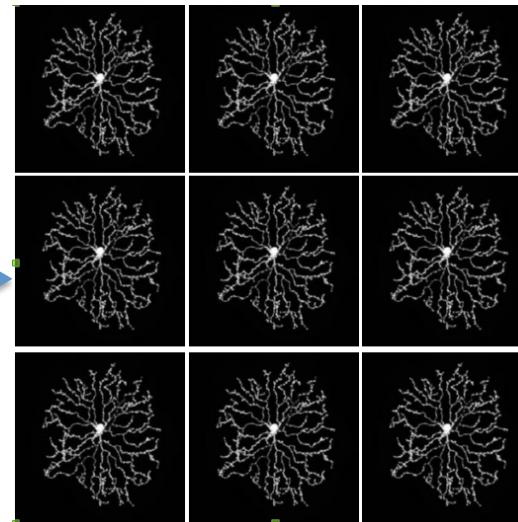
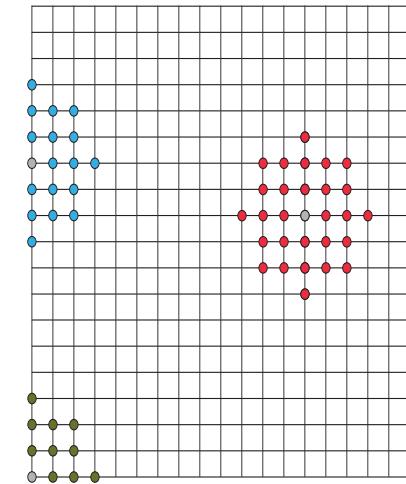


Fig. 7. Starburst amacrine cells stained with Lucifer yellow in wholemount rabbit retina.

SACs realistic connections



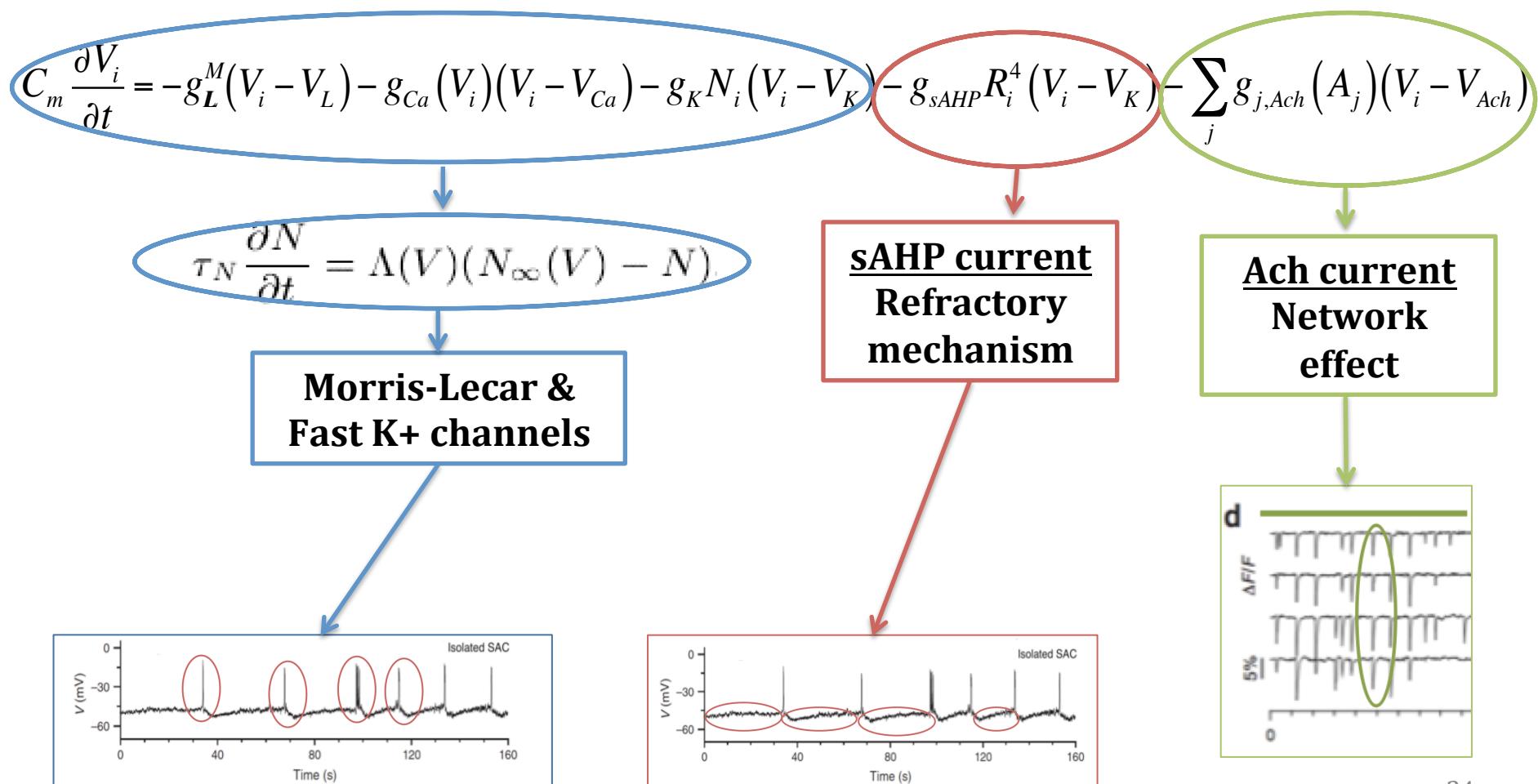
SACs on a lattice



SACs become points on a lattice

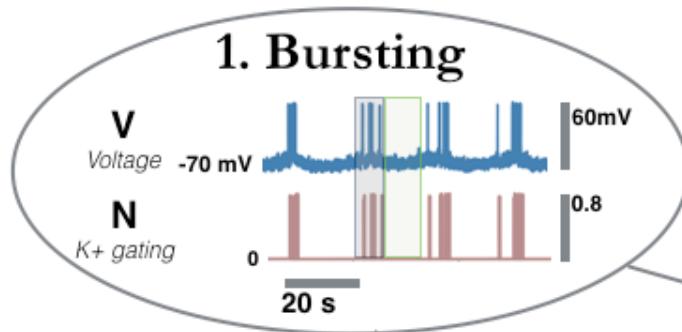
A network model for stage II retinal waves

Membrane potential dynamics

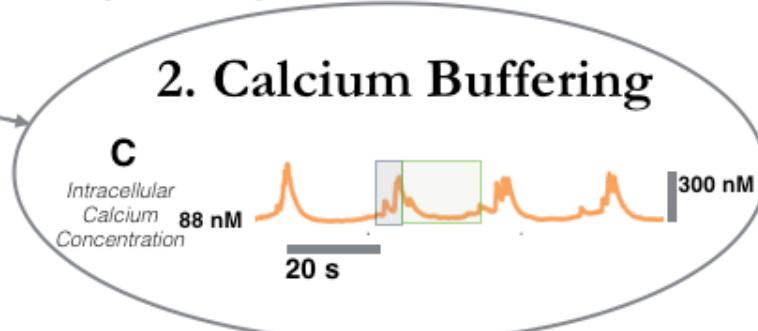


Spontaneous Bursting Mechanism of SACs

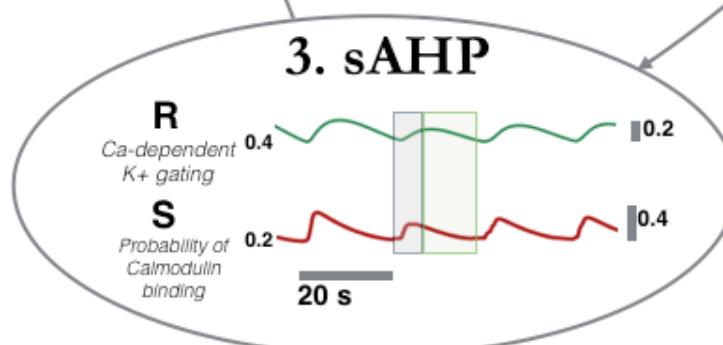
Bursting
sAHP



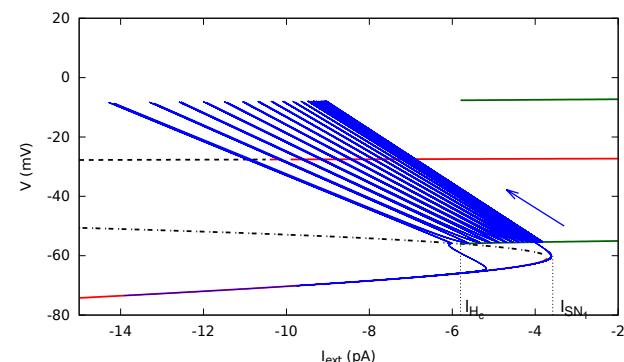
Increase of Calcium load
during bursting



Bursting starts again
when the Calcium
load is low enough



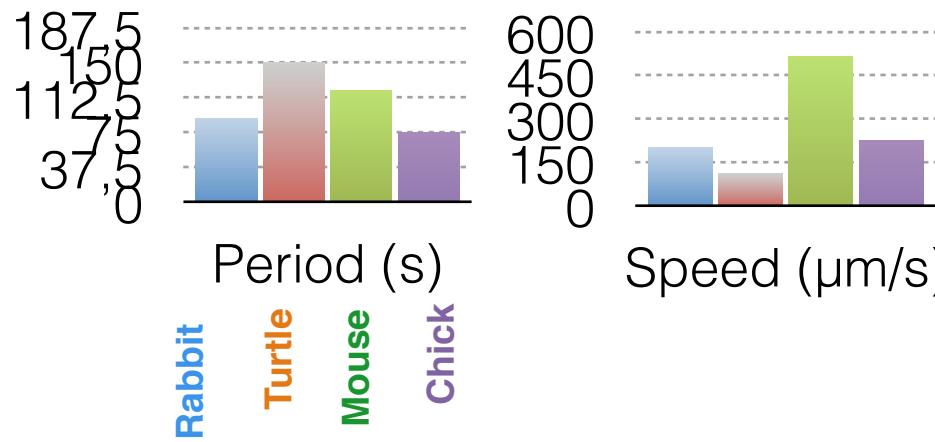
Calcium controls the sAHP phase.
Voltage is low and Calcium
starts offloading



Variability within retinal waves

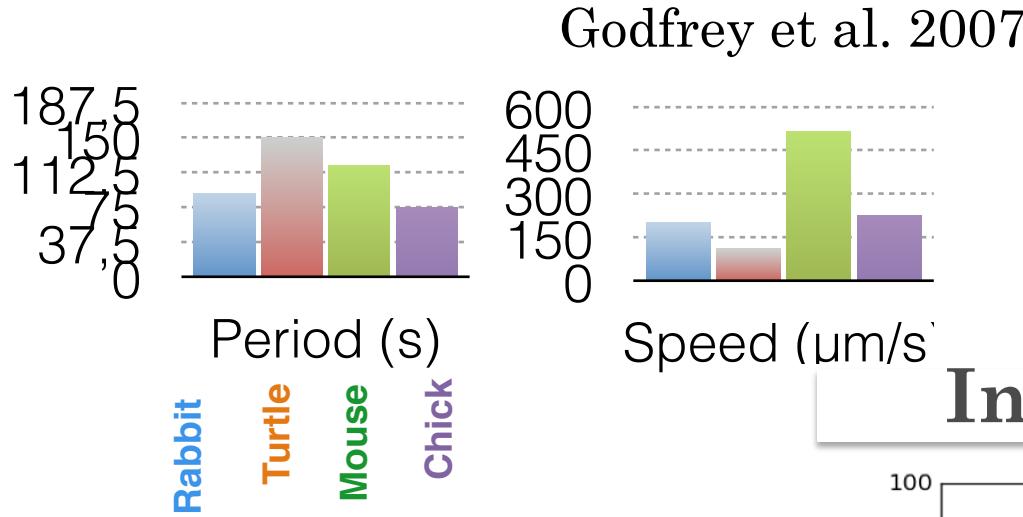
i) Across species

Godfrey et al. 2007

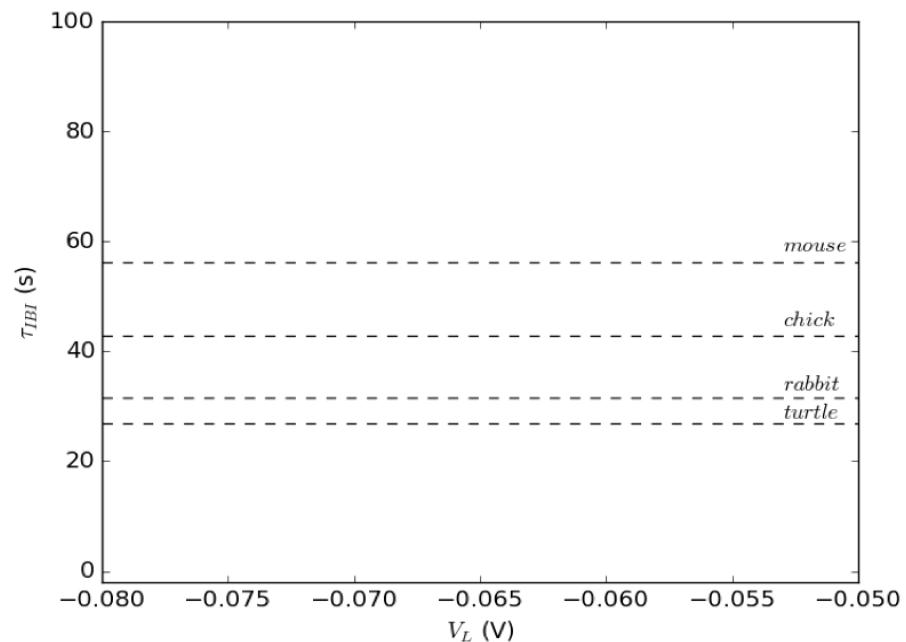


Variability within retinal waves

i) Across species

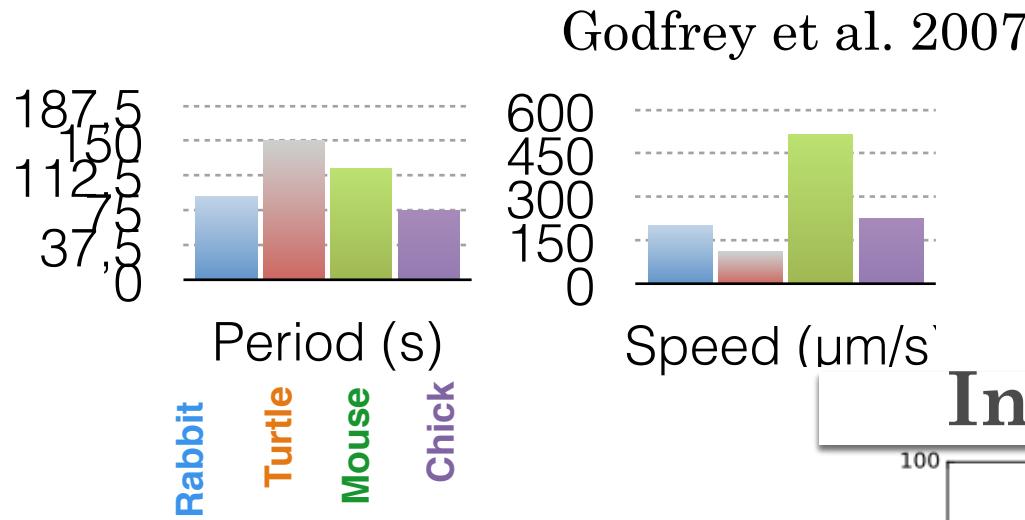


Interburst intervals

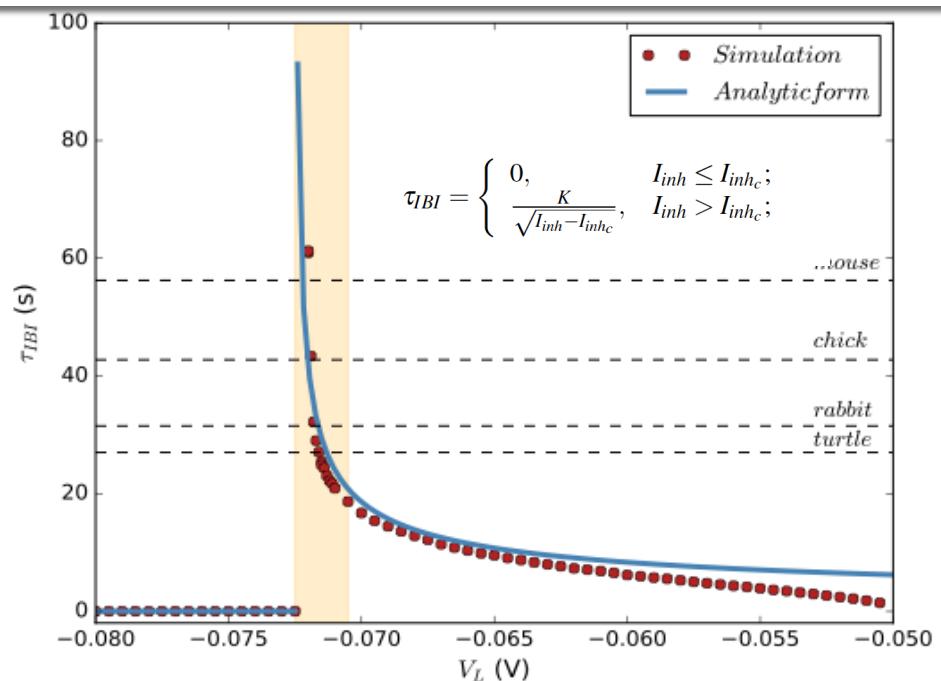


Variability within retinal waves

i) Across species



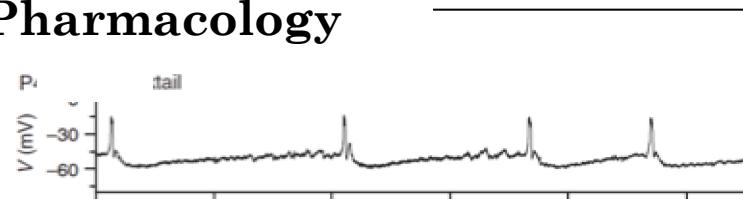
Interburst intervals



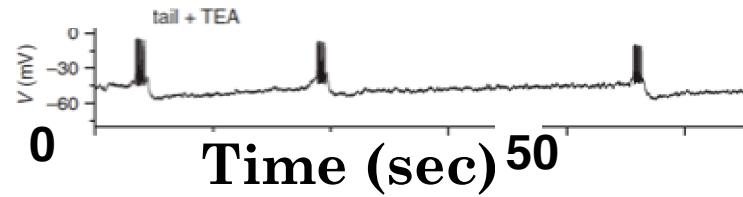
Variability within retinal waves

iii) Pharmacology

P4

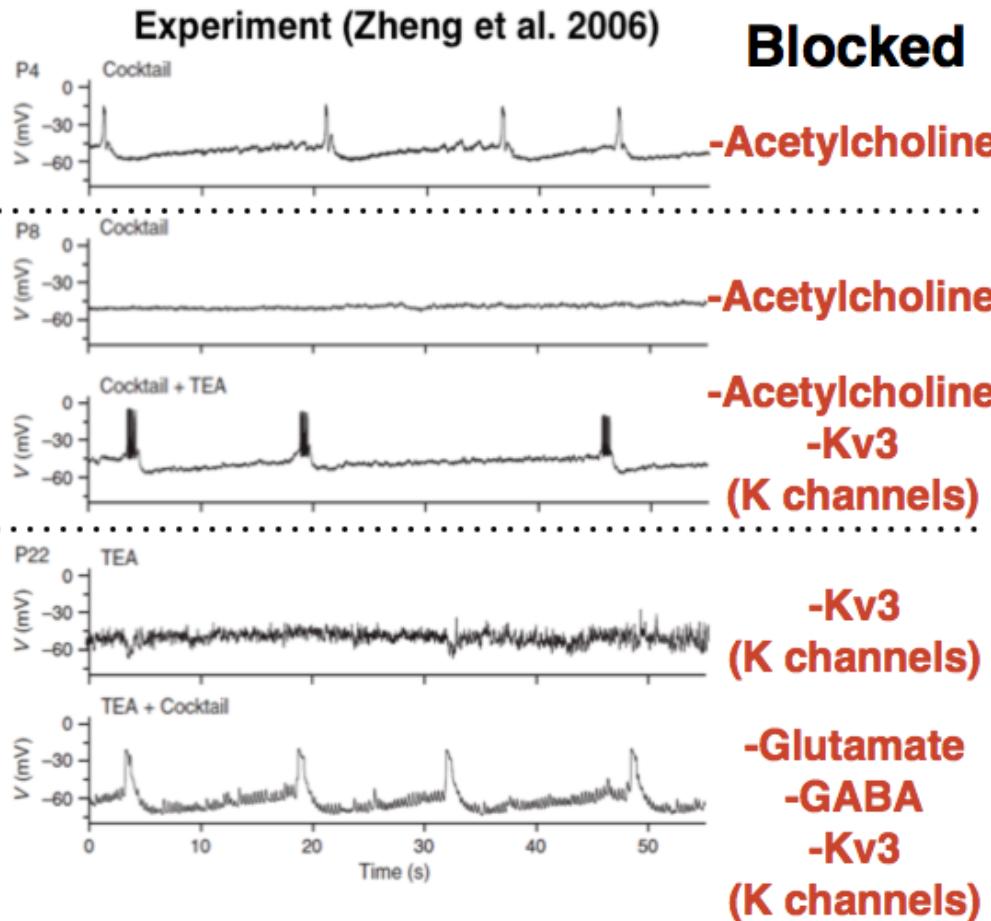


P8



How do SACs lose their excitability?

A

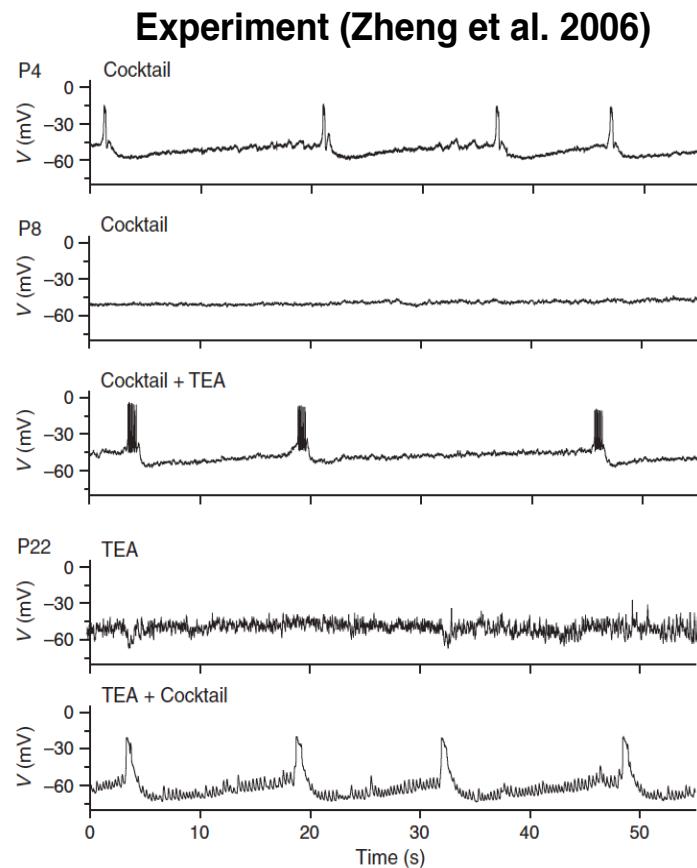


Potassium channels
(potentially Kv3)
are modelled by 3
parameters
 gK , $V3$, $V4$

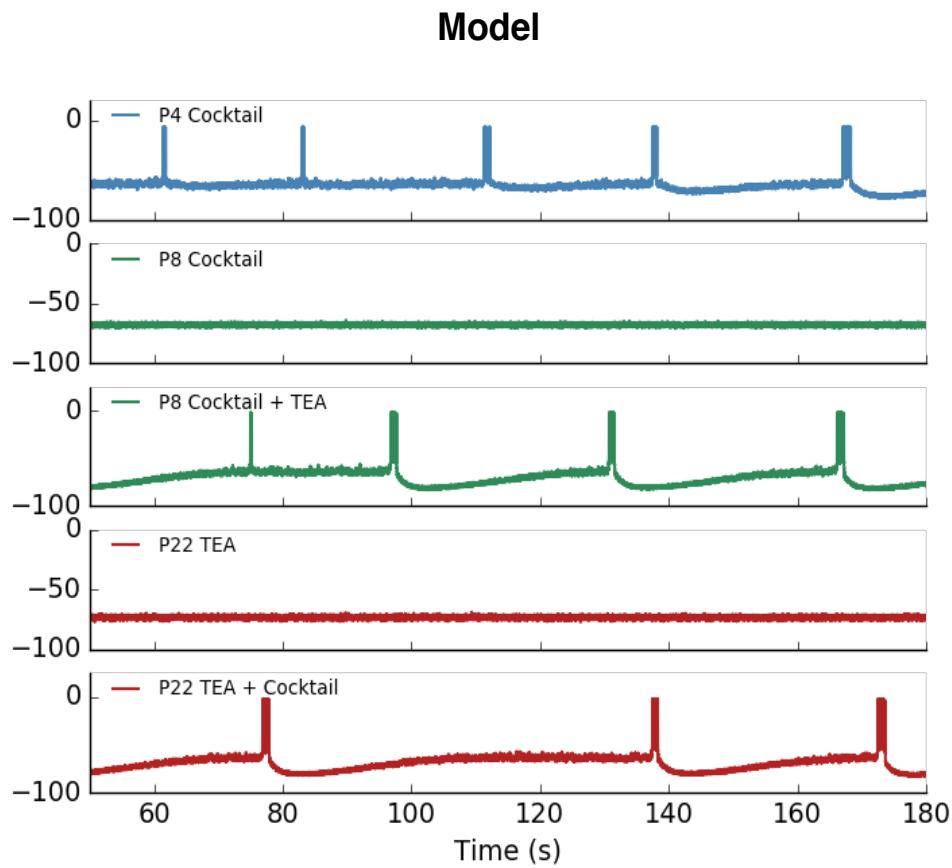
*TEA blocks Kv3 channels

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

A



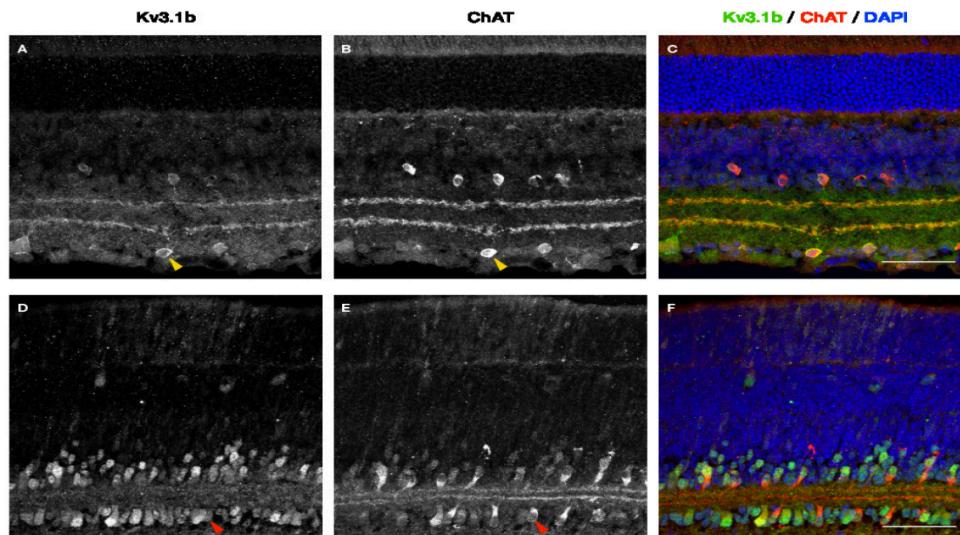
B



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.

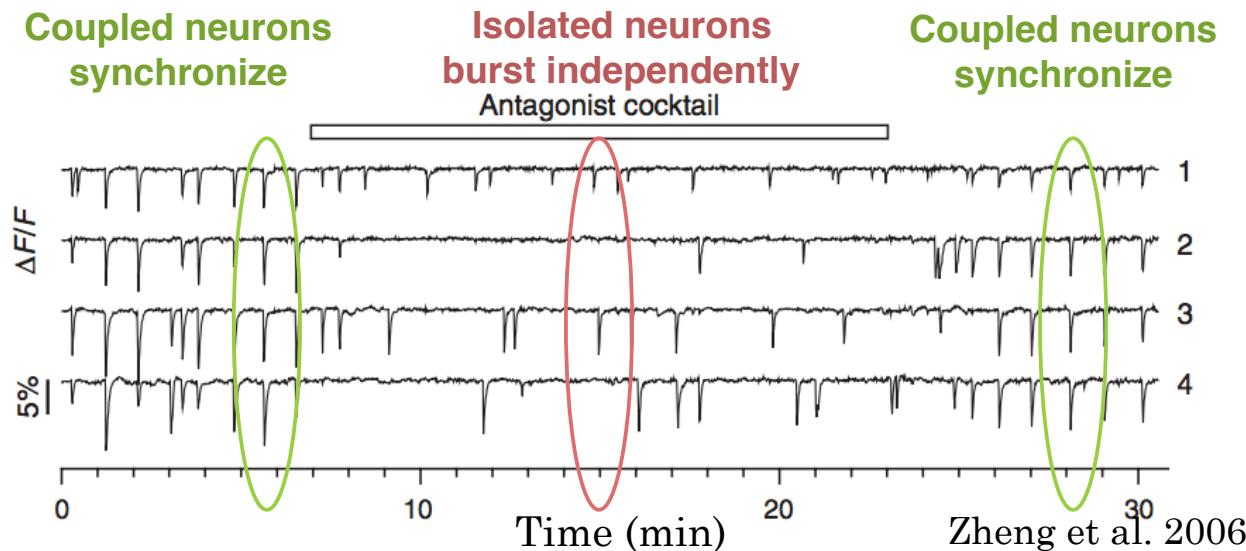
(A-C) Adult retina section showing Kv3.1b (green) and choline acetyltransferase (ChAT, red) reactivity in starburst amacrine cells. Cell nuclei stain (DAPI, blue).

(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

Cellular mechanisms of stage II retinal waves

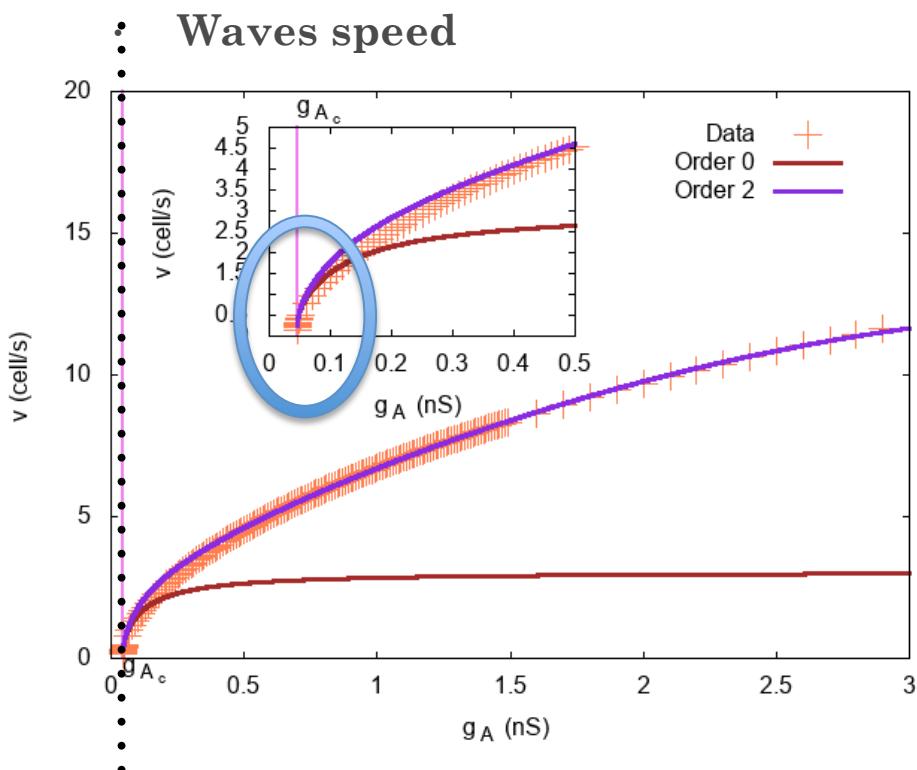
C. Synchrony through Acetylcholine



Mutual excitatory
connections between SACs through
Acetylcholine

Waves speed

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

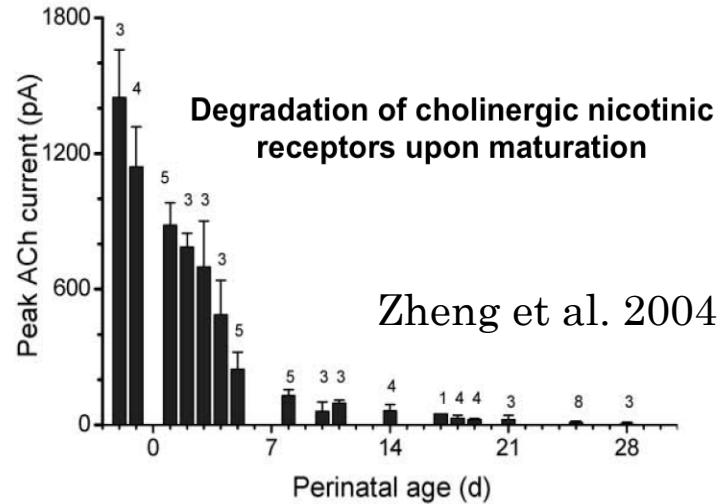


Propagation threshold

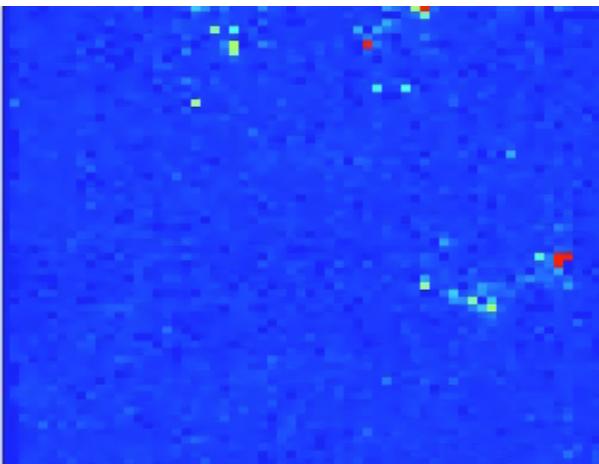
$$g_{A_c} = -\frac{2\mu\sqrt{\gamma_A}}{n_i\beta\Omega} \frac{I_{SN} + g_S R^4 (V_- - V_K)}{V_- - V_A}$$

Variability within retinal waves

ii) Development



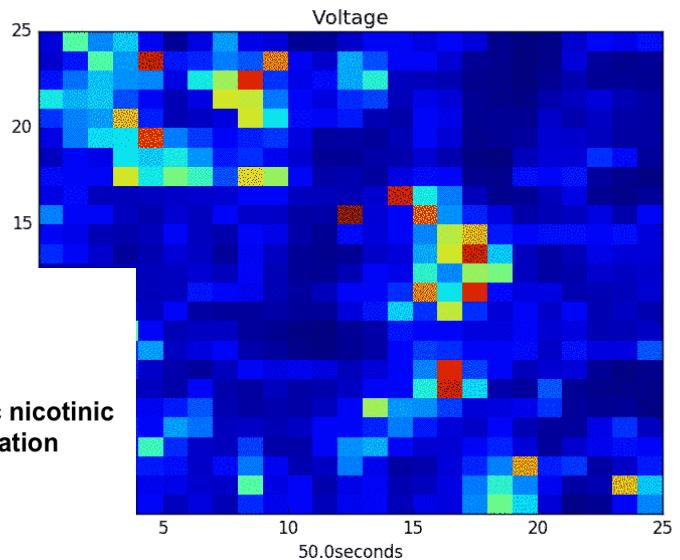
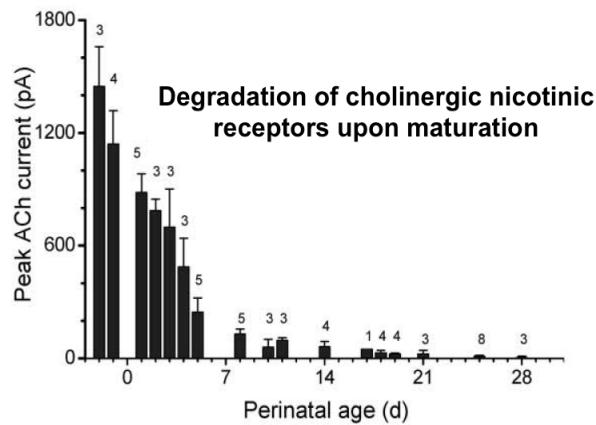
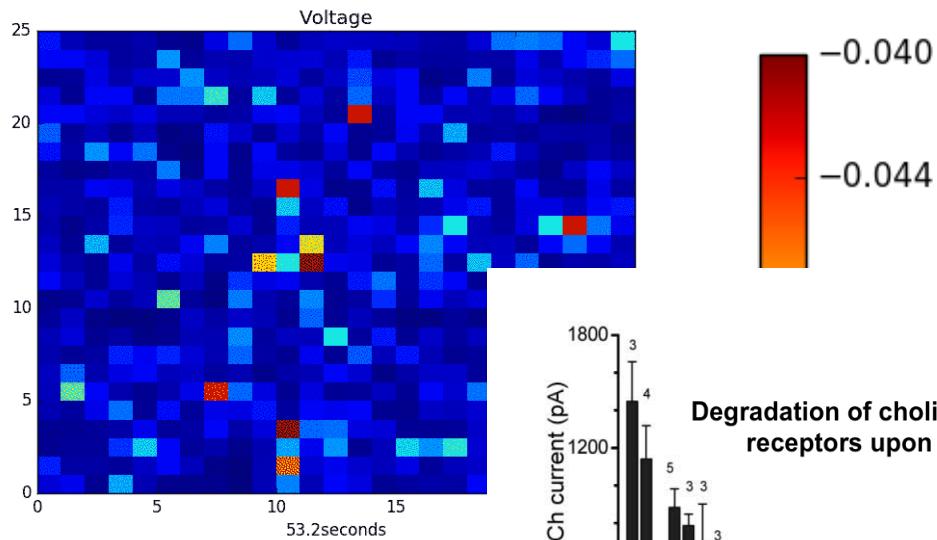
iv) Spatial Variability



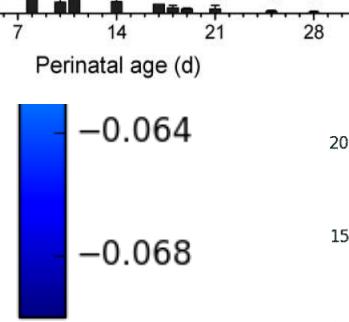
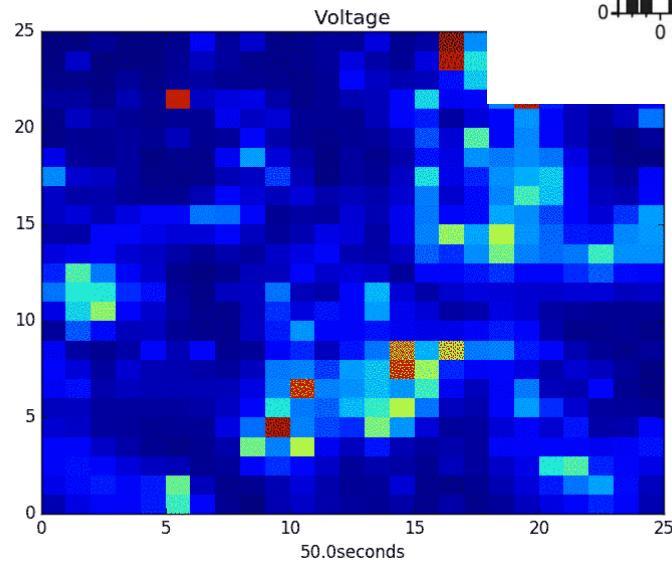
Network of SACs : Simulated Voltage

Isolated Neurons

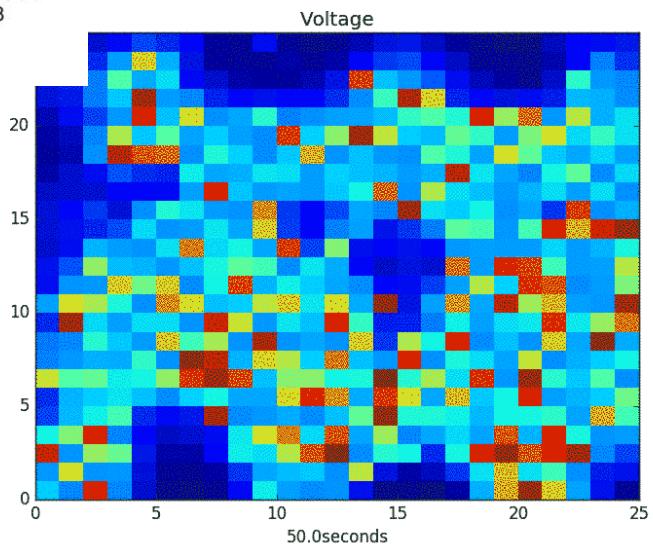
$g_{ACH} = 0.126 \text{ nS}$



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

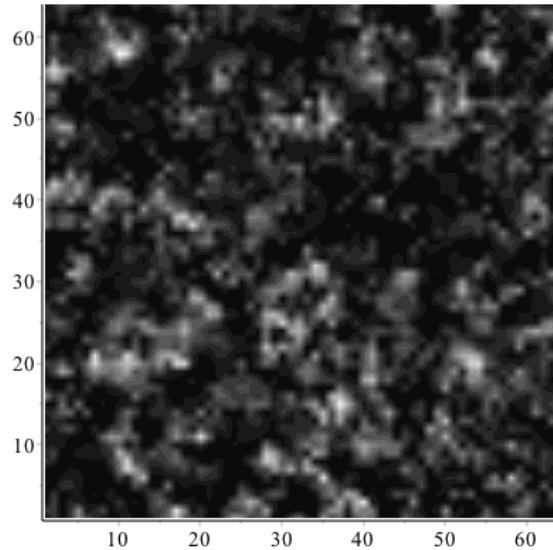


$g_{ACH} = 0.21 \text{ nS}$

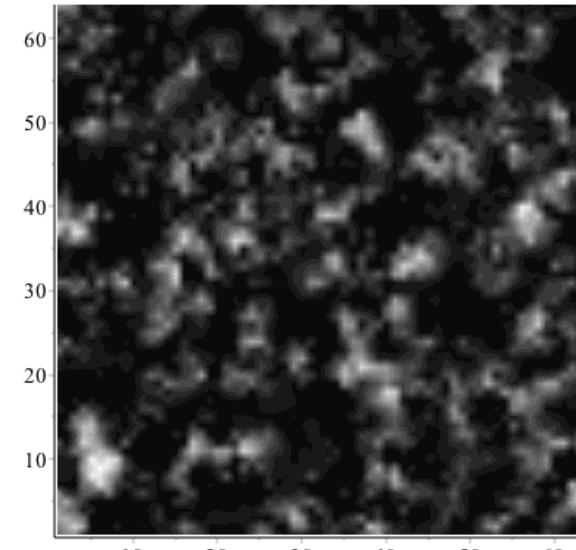


Network of SACs : Simulated Calcium Concentration

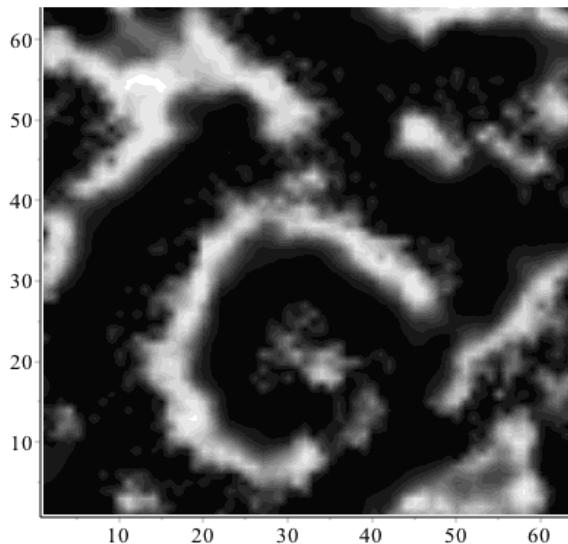
gach=0.102 nS



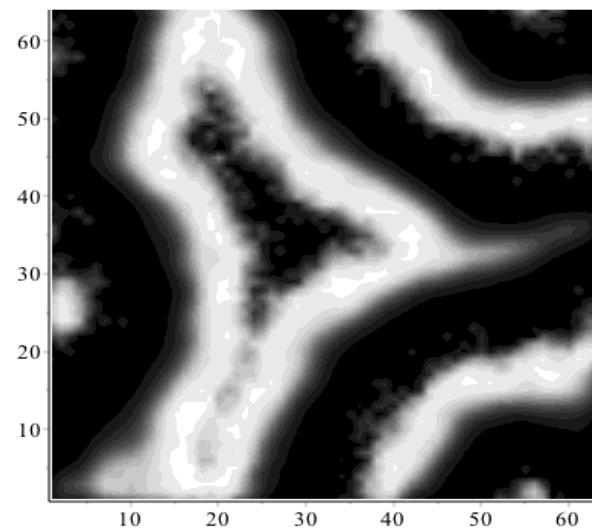
gach=0.126 nS



gach=0.168 nS

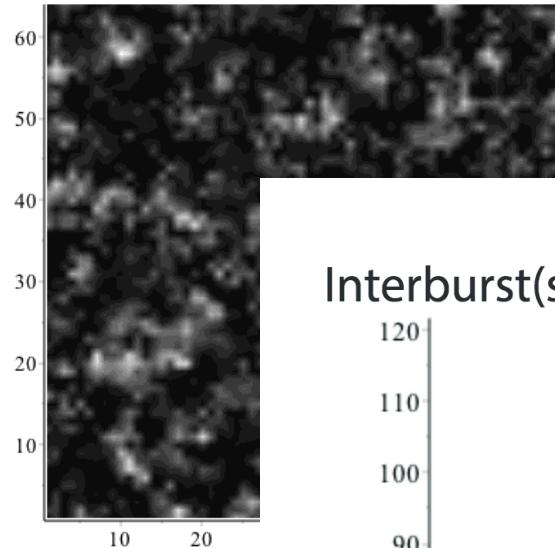


gach=0.21 nS

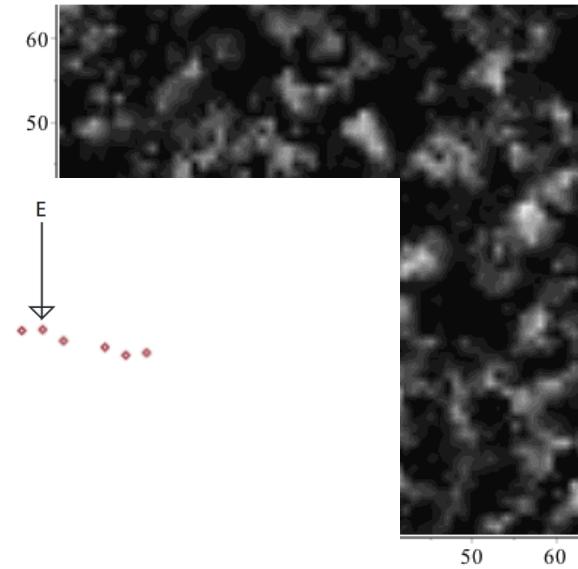


Network of SACs : Simulated Calcium Concentration

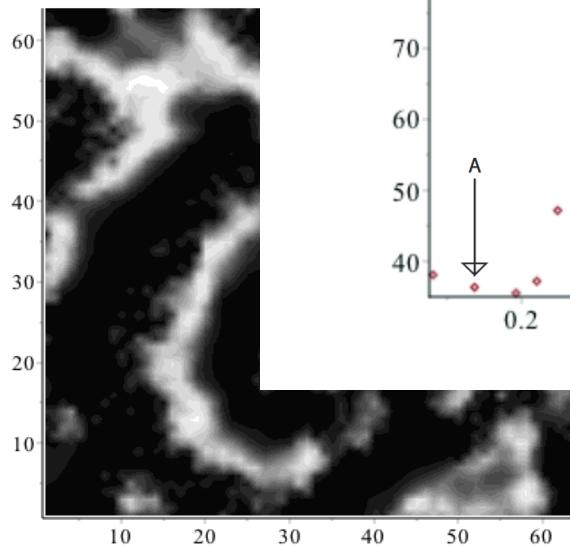
$g_{ach}=0.102 \text{ nS}$



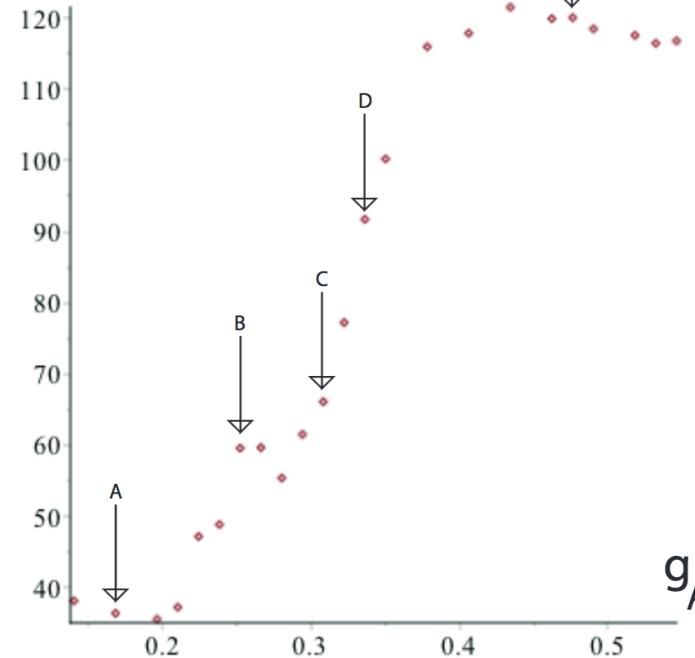
$g_{ach}=0.126 \text{ nS}$



$g_{ach}=0$

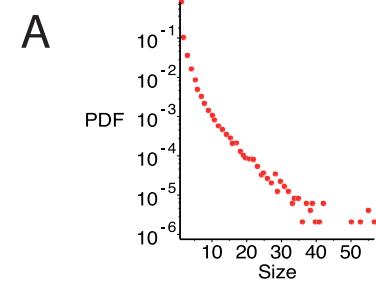


Interburst(s)

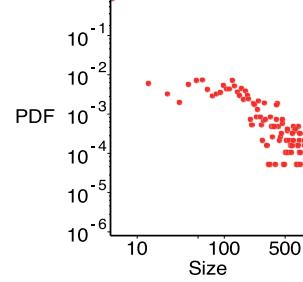
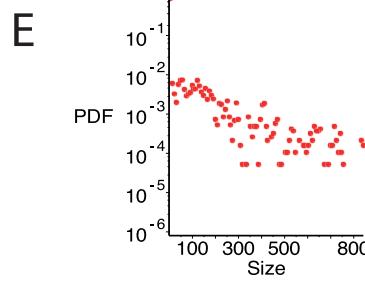
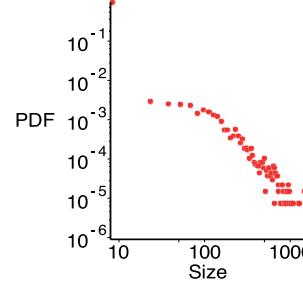
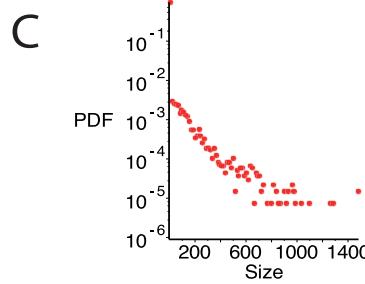
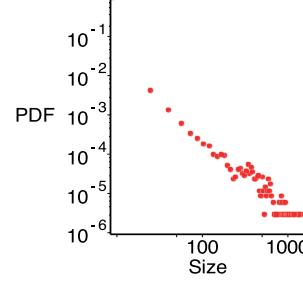
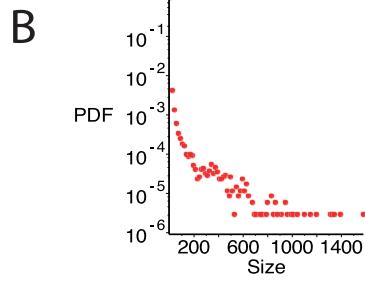
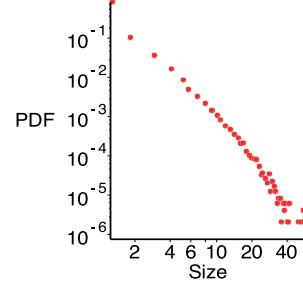


Waves size distribution

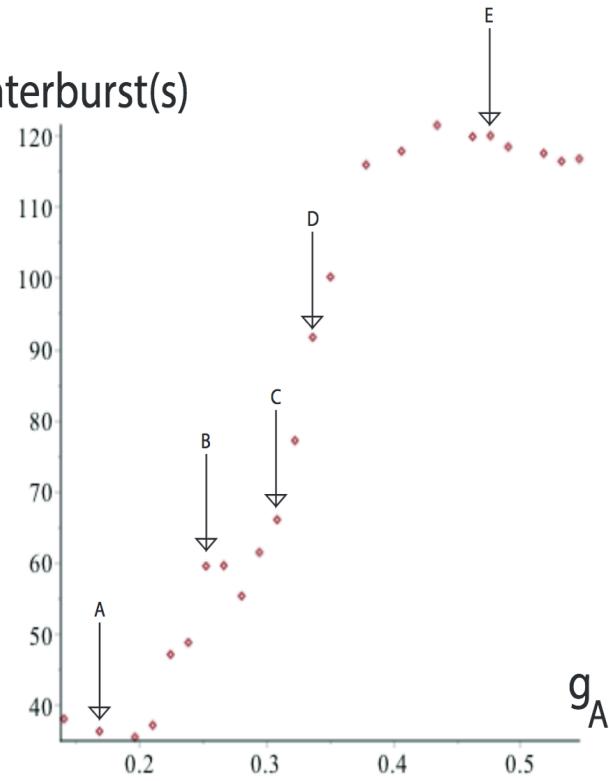
lin-log



log-log



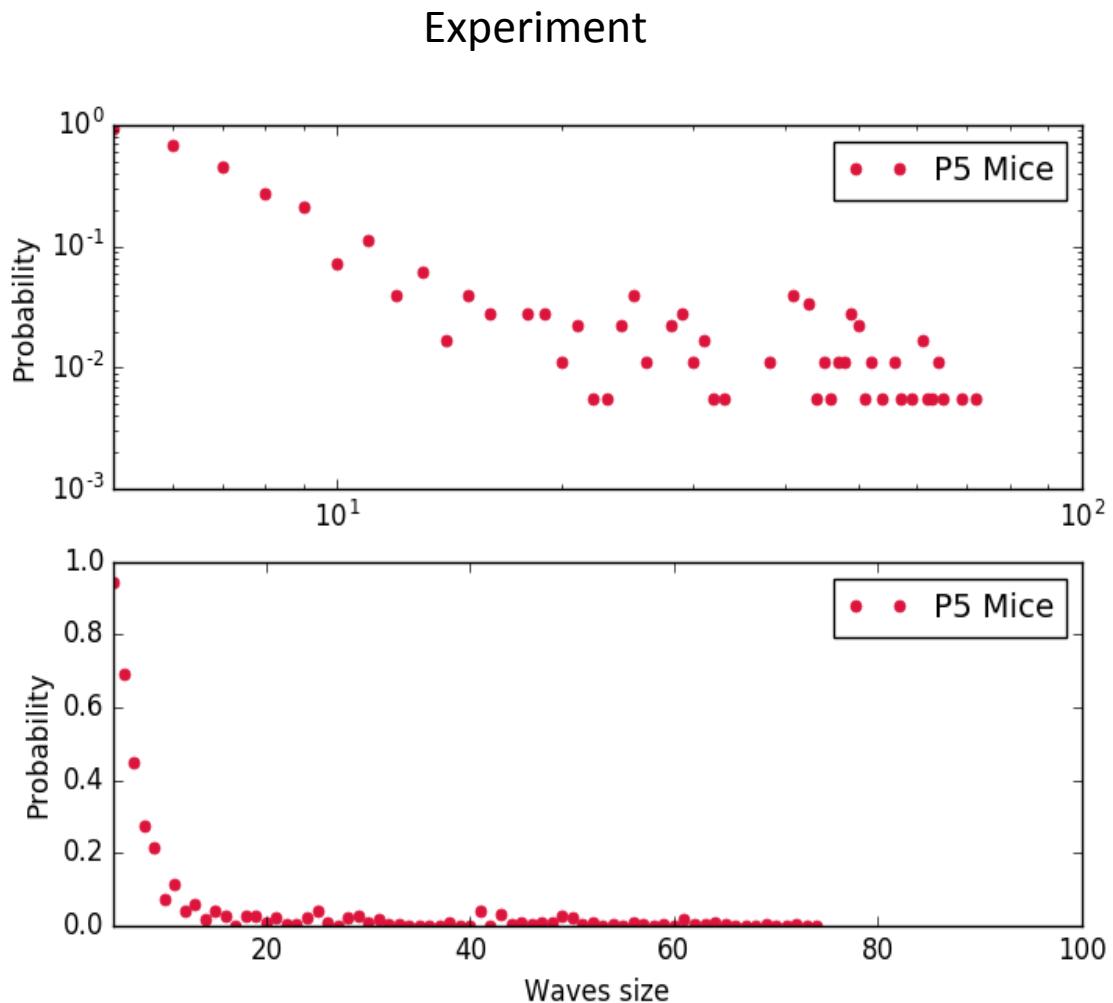
Interburst(s)



N-neuron model

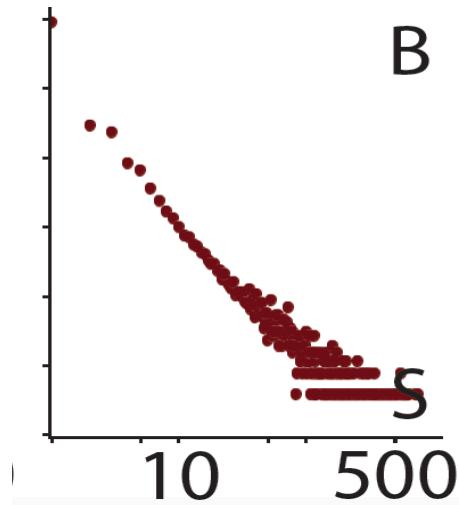
- There is a **competition** between 2 mechanisms:
 - Period variability which tends **to desynchronise**
 - Acetylcholine which tends **to synchronise**
- There is an intermediate regime of coupling, where **variability** is maximum
- Therefore there is a wide repertoire of patterns
 - **Weak coupling**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

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



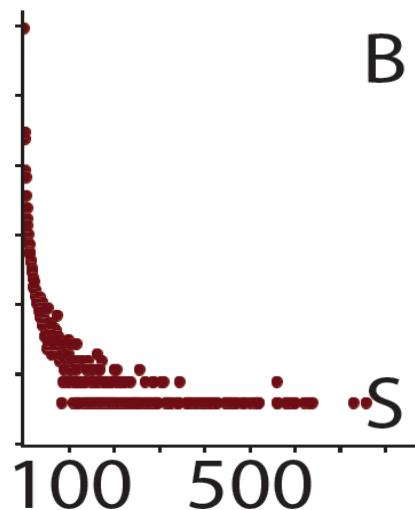
Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

Model



10 500

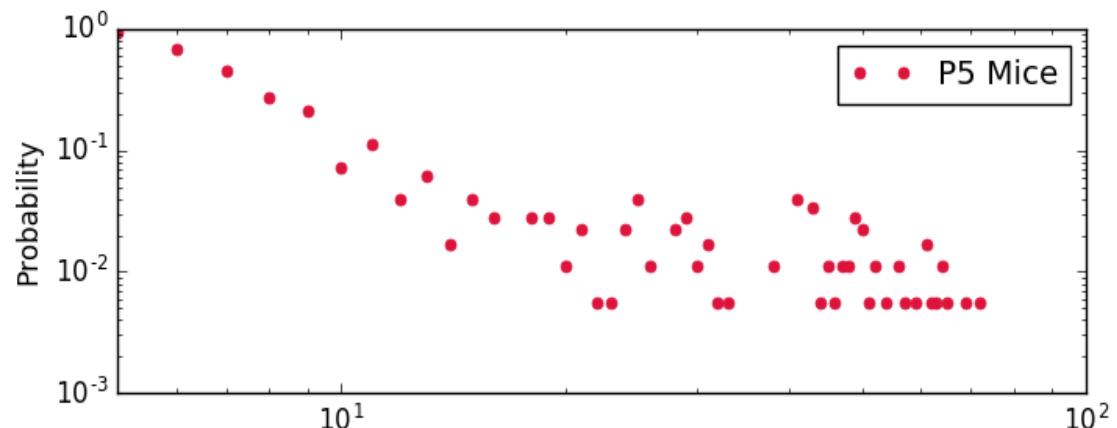
B



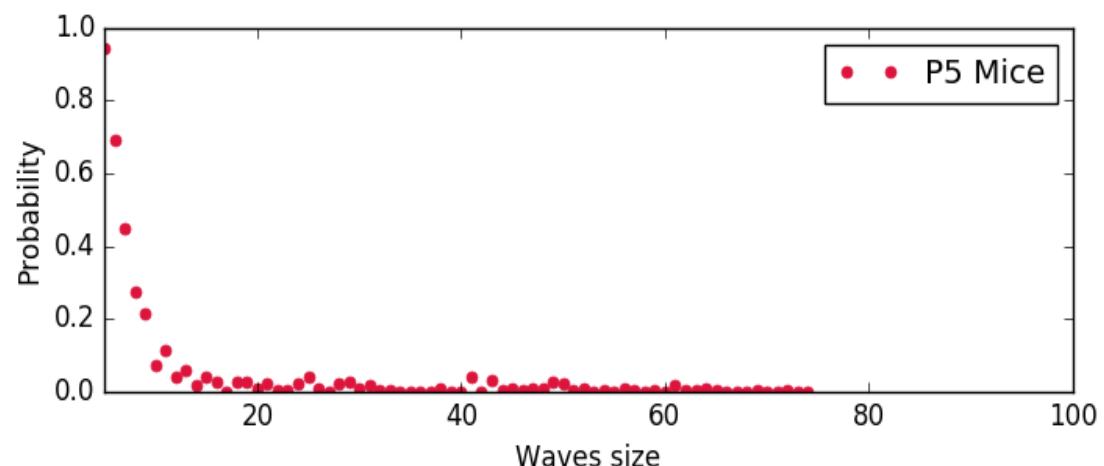
100 500

S

Experiment



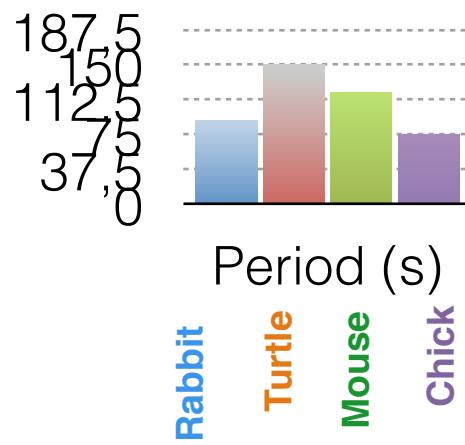
P5 Mice



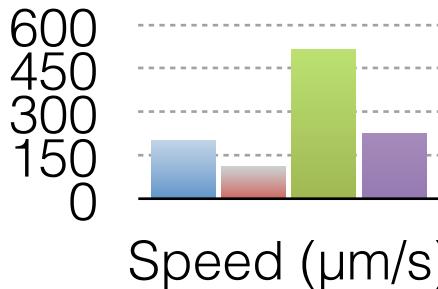
P5 Mice

Variability within retinal waves

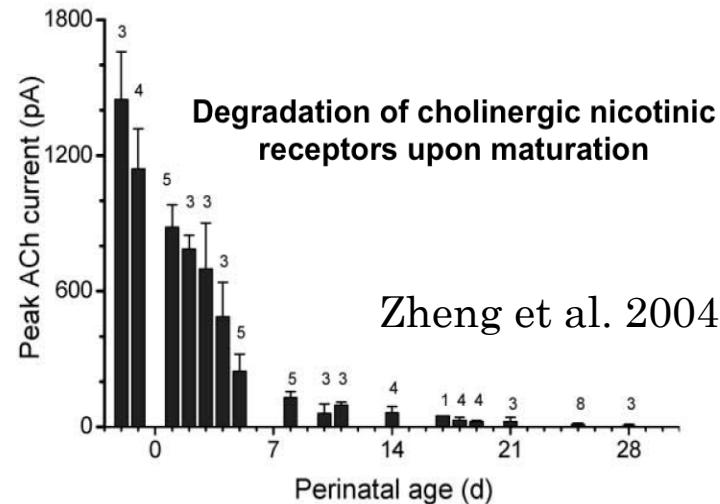
i) Across species



Godfrey et al. 2007

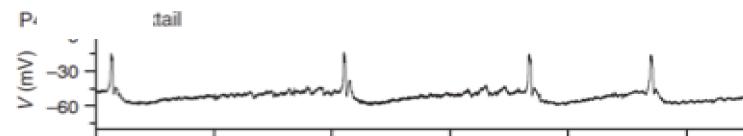


ii) Development

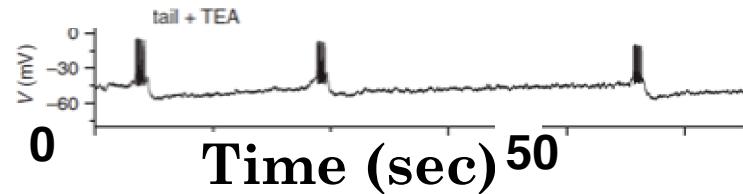
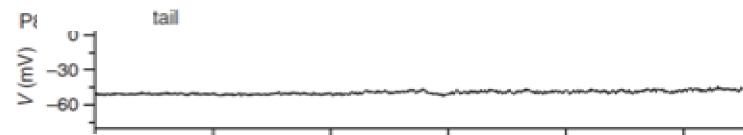


iii) Pharmacology

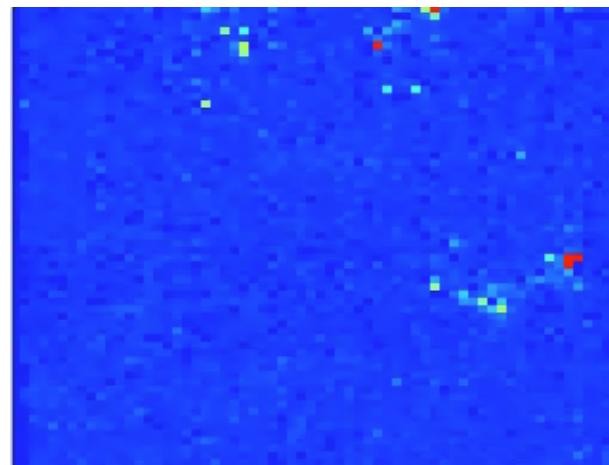
P4



P8



iv) Spatial Variability



Conclusion

- **Biophysical model of stage II retinal waves relevant at:**
 - The cells scale (bursting, experimental match and predictions)
 - The network scale (waves propagation)
 - The developmental level (evolution of ionic channels and synapses).
- **Theoretical description via bifurcation theory**
 - Bursting
 - Interburst variability
 - Waves patterns
- **Next step: reactivating waves in adults.**