Multi scale dynamics in retinal waves

D. Karvouniari, Biovision team, INRIA, Sophia Antipolis
L. Gil, INLN, Sophia Antipolis
O. Marre, Institut de la Vision, Paris
S. Picaud, Institut de la Vision, Paris
B. Cessac, Biovision team, INRIA, Sophia Antipolis

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The structure of the <u>adult retina</u>



The structure of the retina <u>during</u> <u>development</u>

Retina's layered structure is shaped during development



Retinal waves

Recordings from the retina



<u>Spontaneous</u> 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 µM bicuculline.

Stages of Retinal Waves During Development



- Chemical synapses <u>not</u> formed yet
- Gap juctionmediated

Stages of Retinal Waves During Development

Stage II



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Variability <u>within</u> retinal waves



Variability within retinal waves



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Focus on stage II retinal waves

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



Starburst Amacrine

Retinal waves require three components: i) Spontaneous bursting activity



Zheng et al., 2006, Nature

Retinal waves require three components:

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



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iii) Coupling (through Acetylcholine neurotransmitter)



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

Retinal waves require three components:

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Retinal waves require three components:

Several models of stage II retinal waves have been proposed already:

ii) **Refractory mechanism (**slow After HyperPolarisation- sAHP)

- Feller et all Neuron, 1997. et vicholine neurotransmitter).
- Eglen et al, J. Neuroscience 2000.
- Godfrey & Swindale. PLoS Comput Biol, 2007.
- Hennig et al, J. Neuroscience, 2009
- Lansdell et al, PLoS Computational Biology, 2014.

But none of them as studied simultaneously these 3 aspects:

(i) realistic model of spontaneous bursting
 (ii) sAHP biophysical modelling
 (iii) realistic Ach interaction.

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

Why study retinal waves?

Motivations:

- Retinal waves instruct **the shaping of the visual system**
 - Retina structuration
 - Retinotopy
 - Binocularity
- Understanding the mechanisms that generate them may help to **control them pharmacologically.**
- Using modelling to find **generic organizing principles**, explain **experiments** and propose new ones.
- Interesting **physical/mathematical** problem.

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 (conductances).

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

Membrane potential dynamics



sAHP current

• Definition

- Slow After Hyperpolarisation Current
- Calcium-dependent slow potassium channels

Mechanism

- Model SK-like channels (Abel et al. 2004)
- Gating Mechanism: Four ions Ca²⁺ bind to Calmodulin (CaM)



Calcium gated potassium channel

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sAHP current

- Four *Ca*²⁺ions bound to calmodulin open the channel
- I_{sAHP} current depends on gating variable R as follows:

$$I_{sAHP} = g_{sAHP}^{m} R^{4} \left(V - V_{K} \right)$$
 (Hennig et al. 2009)



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

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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

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Saturated Calmodulin molecule (CaM) bind to each channel subunit

4 Calcium ions bound to each saturated Calmodulin complex S

Set of equations for sAHP current

Activated

$$\tau_R \frac{dR}{dt} = a_R S (1 - R) - R$$

$$\tau_{S} \frac{dS}{dt} = -S + a_{S}C^{4} \left(1 - S\right)$$

S : Fraction of saturated calmodulin concentration (CaM)

$$\tau_{Ca}\frac{dC}{dt} = -a_R\frac{C}{H_x} + C_o + \delta_{Ca}I_{Ca}(V)$$

C : Intracellular Calcium concentration



SACs Network

Model synaptic interactions



Fig 7. Starbuar annacrime cells as stained with funder yellow in wholemount rabbit refina

SACs on a lattice

SACs become points on a lattice

SACs realistic connections

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



A: Extracellular Acetylcholine concentration



Experimental fits from Zhou et al. 2004, Neuron



$$C_{m} \frac{dV_{i}}{dt} = -g_{L}(V_{i} - V_{L}) - g_{C}M_{\infty}(V_{i})(V_{i} - V_{C}) - g_{K}N_{i}(V_{i} - V_{K}) -G_{sAHP}(R_{i})(V_{i} - V_{K}) - G_{A}(\{A_{k}\}_{k\in\mathcal{B}_{i}})(V_{i} - V_{A})$$

$$\tau_{N} \frac{dN_{i}}{dt} = \Lambda(V_{i})(N_{\infty}(V_{i}) - N_{i})$$

$$\tau_{C} \frac{dC_{i}}{dt} = -\frac{\alpha_{C}}{H_{X}}C_{i} + C_{0} - \delta_{C}g_{C}M_{\infty}(V_{i})(V_{i} - V_{C})$$

$$\tau_{S} \frac{dS_{i}}{dt} = \alpha_{S}(1 - S_{i})C_{i}^{4} - S_{i}$$

$$\tau_{R} \frac{dR_{i}}{dt} = -\mu A_{i} + \beta_{A}T_{A}(V_{i}),$$

$$T_{R} \frac{dV_{i}}{dt} = -g_{L}(V_{i} - V_{L}) - g_{C}M_{\infty}(V_{i})(V_{i} - V_{C}) - g_{K}N_{i}(V_{i} - V_{K}) - G_{s} + 20^{P} parameters per neuron (V_{i} - V_{A})$$

$$\tau_{N} \frac{dN_{i}}{dt} = (\text{But neurons are assumed identical}) \tau_{C} \frac{dC_{i}}{dt} = -\frac{\alpha_{C}}{H_{X}}C_{i} + C_{0} - \delta_{C}g_{C}M_{\infty}(V_{i})(V_{i} - V_{C}) \tau_{S} \frac{dS_{i}}{dt} = \alpha_{S}(1 - S_{i})C_{i}^{4} - S_{i} \tau_{R} \frac{dR_{i}}{dt} = -\mu A_{i} + \beta_{A}T_{A}(V_{i}),$$

N neurons, 6 N equations

$$C_{m} \frac{dV_{i}}{dt} = -g_{L}(V_{i} - V_{L}) - g_{C}M_{\infty}(V_{i})(V_{i} - V_{C}) - g_{K}N_{i}(V_{i} - V_{K}) - G_{s}N_{1}20^{\circ} parameters per neuron (V_{i} - V_{A})$$

$$\tau_{N} \frac{dN_{i}}{dt} = (But neurons are assumed identical)$$

$$\tau_{C} \frac{dC_{i}}{dt} = -\frac{\alpha_{C}}{H_{X}}C_{i} + C_{0} - \delta_{C}g_{C}M_{\infty}(V_{i})(V_{i} - V_{C}) - Time scale separation$$

$$\tau_{S} \frac{dS_{i}}{dt} = -\alpha_{C}(1 - S_{i})C^{4} - S_{i}$$
Fast $V, N. \tau_{L} = 11 \text{ ms}, \tau_{N} = 5 \text{ ms}.$

$$\tau_{R} \frac{dR_{i}}{dt} = Medium C, A. \tau_{C} = 2 \text{ s}, \tau_{A} = 1.86 \text{ s}.$$

$$\frac{dA_{i}}{dt} = Slow S, R. \tau_{R} = \tau_{S} = 44 \text{ s}.$$

Fast time scale

Fast time scale

Morris-Lecar model with fast dynamics, in the presence of a slow external current

$$\begin{cases} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) + I_{ext} \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \end{cases}$$
Fast time scale

Morris-Lecar model with fast dynamics, in the presence of a slow external current

$$\left(\begin{array}{ll} \frac{dV}{dt_f} &= -\tilde{g}_L(V - V_L) - \tilde{g}_C M_{\infty}(V)(V - V_C) - \tilde{g}_K N(V - V_K) + I_{ext} \\ \frac{dN}{dt_f} &= \frac{\tau_L}{\tau_N} \Lambda(V)(N_{\infty}(V) - N) \end{array}\right)$$



Experiment by Zheng et al. 2006, Nature











The mechanism of bursting



The mechanism of bursting



Spontaneous Bursting Mechanism of SACs



The mechanism of bursting (spontaneous)



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The mechanism of bursting (noise induced)



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Variability <u>within</u> retinal waves

Variability <u>within</u> retinal waves



Variability within retinal waves



Variability within retinal waves







Variable bursting period across species



Variable bursting period across species



Variability within retinal waves



Variability <u>within</u> retinal waves



How do SACs lose their excitability?



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



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

Cellular mechanisms of stage II retinal waves

C. Synchrony through Acetylcholine



Mutual excitatory connections between SACs through Acetylcholine

A network model for stage II retinal waves



The coupled dynamics of 2 SACs

V,R,A profiles of a single SAC



The coupled dynamics of 2 SACs



Synchrony: Arnold tongues



Synchrony: Arnold tongues



Synchrony: Arnold tongues



t (s)

The coupled dynamics of 2 SACs



The coupled dynamics of 2 SACs


Waves speed in one dimensional chain

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



Waves speed in one dimensional chain





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

Waves propagation



Waves propagation



Waves propagation





С

Variability <u>within</u> retinal waves



iv) Spatial Variability



SACs Network

Model synaptic interactions



Fig 7. Starbust anacome cells as stained with tucher yellow in wholemount rabbit tetra.

SACs on a lattice

SACs become points on a lattice

SACs realistic connections





gach=0.168 nS



-0.064

-0.068



gach=0.168 nS





-0.060

-0.064

-0.068



gach=0.168 nS







Network of SACs : Simulated Calcium Concentration

gach=0.102 nS



gach=0.168 nS



gach=0.126 nS





Network of SACs : Simulated Calcium Concentration

gach=0.102 nS

gach=0.126 nS

Interburst(s) D ÷ gach=(l nS R g_A 0.2 0.3 0.4 0.5 20-



Distance Pairwise Correlations



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)

Experiment



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

Model

Experiment





Fig.7. Starbust amounte cells as stained with tucher yellow in wholemount rabbit retruit

- Nearest neighbours interaction;
- State variable are continuous in space ;



Assume:

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Oh ! Yes !!! This a reaction diffusion model !!

Lansdell et al, Plos Com Bio, 2014



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Assume free diffusion of Ach

- Nearest neighbours interaction;
- State variable are continuous in space ;
- Ach production vanishes in the rest state
- Ach production is maximum in the bursting state.



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Assume:

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Transport of Ach conductance.

$$\frac{\partial \Gamma}{\partial t} = -\Gamma + 2d\Omega H \left[\Gamma - \Gamma_c(R) \right] + a^2 \Omega \Delta H \left[\Gamma - \Gamma_c(R) \right]$$



Assume:

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Transport of Ach conductance.





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Transport of Ach conductance.





Singular diffusion with R dependent threshold

- How do wave propagate (ballistic, normal diffusion, anomalous ?)
- How do wave stop ?
- What determines the wave scale ? The wave distribution ?
- When do we have power laws in the wave distribution ?



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$$\frac{\partial G_A}{\partial t} = g_A D_M \left[\left(\nabla G_S, \nabla G_A \right) D_H^2 \left(\begin{array}{c} \nabla G_S \\ \nabla G_A \end{array} \right) + \frac{\partial H}{\partial G_S} \Delta G_S + \frac{\partial H}{\partial G_A} \Delta G_A \right] + S(G_S, G_A).$$

Variability <u>within</u> retinal waves



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.
