



A mathematical approach to retinal waves

Bruno Cessac, Dora Karvouniari

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A mathematical approach to retinal waves

B. Cessac, D. Karvouniari
Biovision team, INRIA, Sophia
Antipolis

Inria



Acknowledgement

L. Gil, INLN, Sophia Antipolis

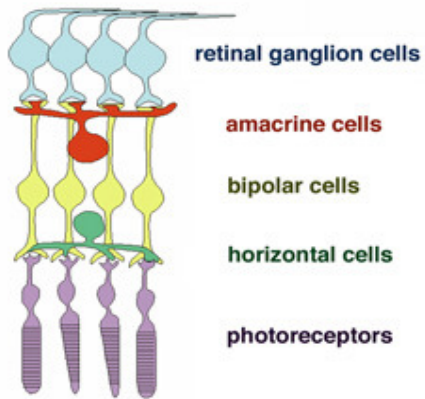
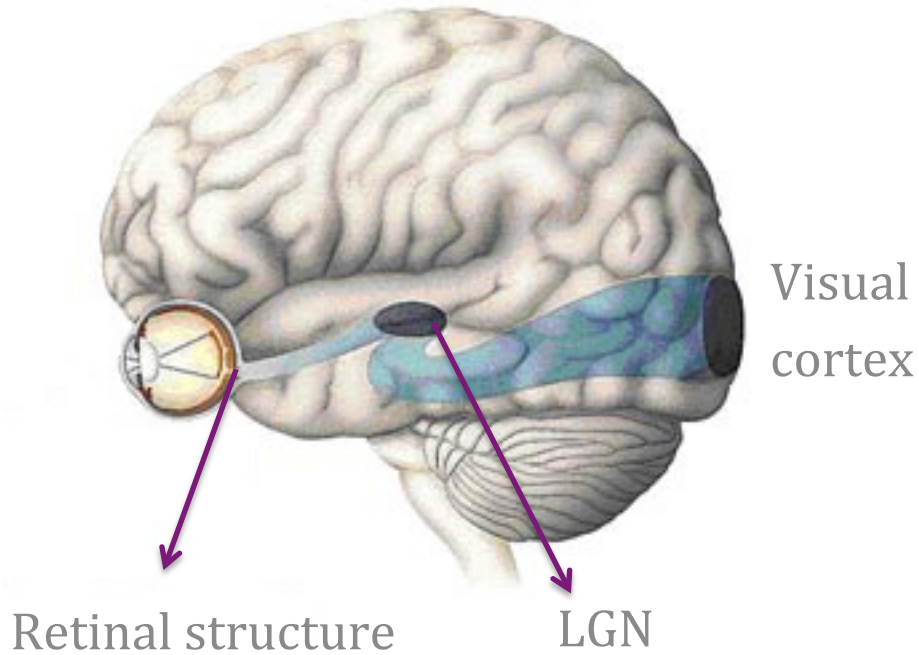
O. Marre, Institut de la Vision, Paris

S. Picaud, Institut de la Vision, Paris

Matthias Hennig, *University of Edinburgh*

Evelyne Sernagor, *Newcastle University*

Visual system and retinal waves

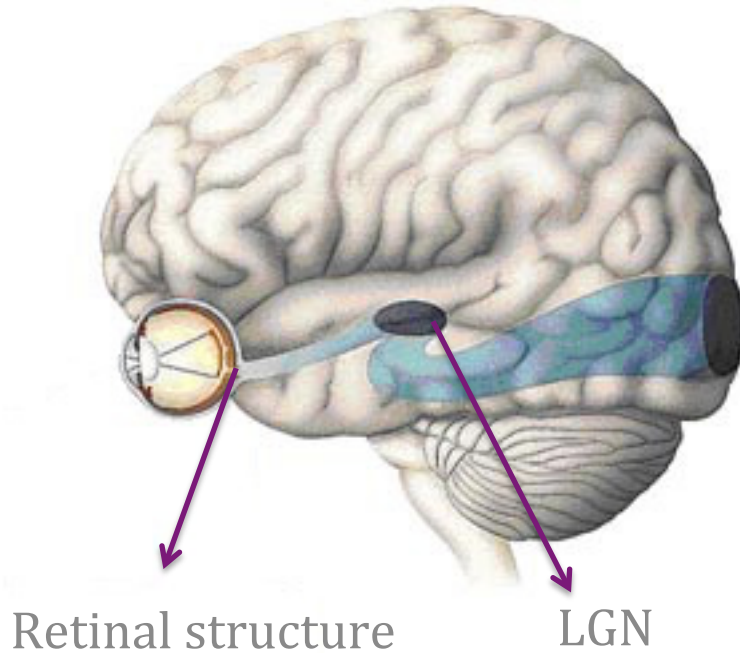


Visual system and retinal waves

Spontaneous spatio-temporal “waves”
during development

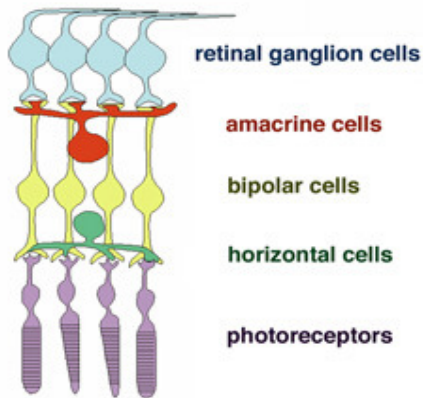
- Disappear short after birth

Visual
cortex



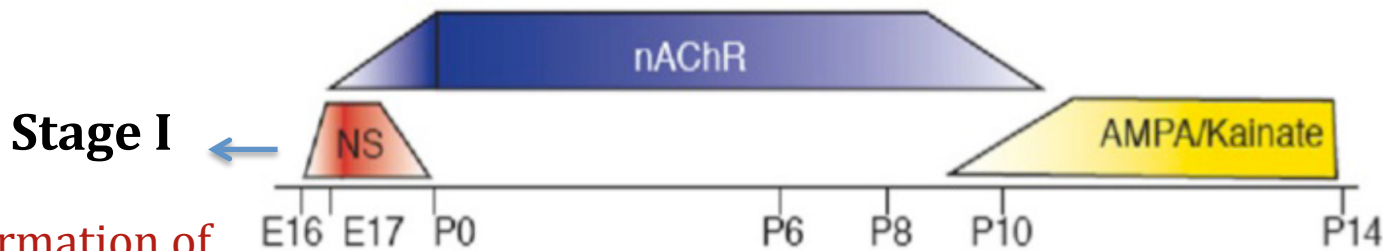
Retinal structure

LGN



*Spatio-Temporal evolution of a
retinal wave in mice during
development, Maccione et al. 2014*

Stages of Retinal Waves During Development



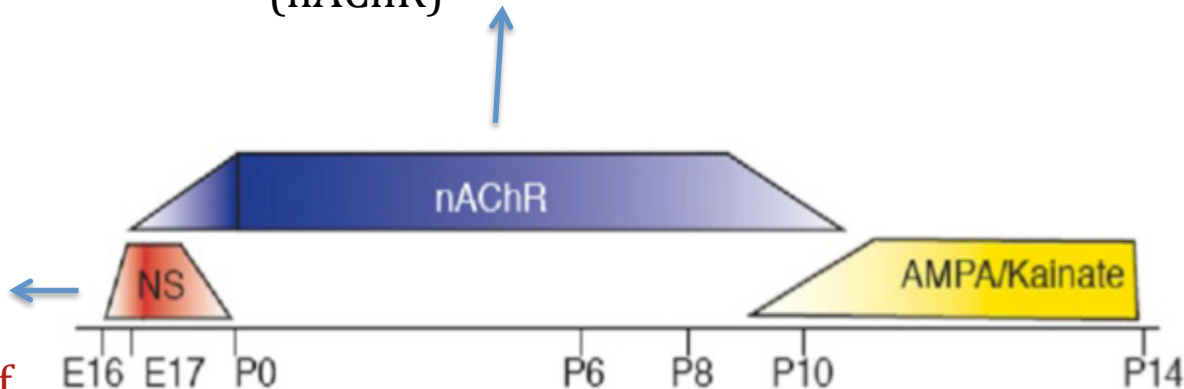
- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

Stage I



- Formation of retina circuitry
- Chemical synapses not formed yet
- Gap junction-mediated

Stages of Retinal Waves During Development

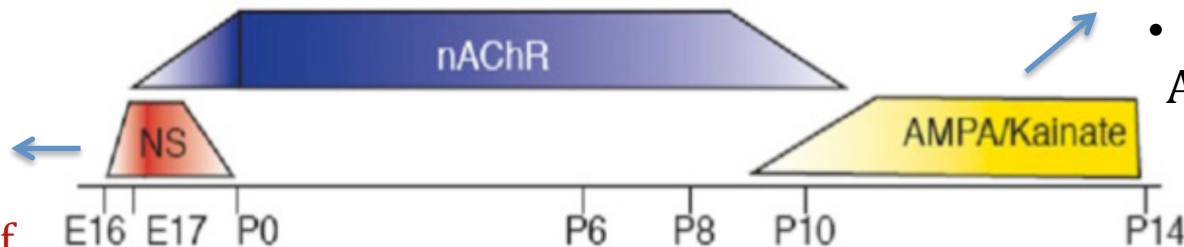
Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors

Stage I

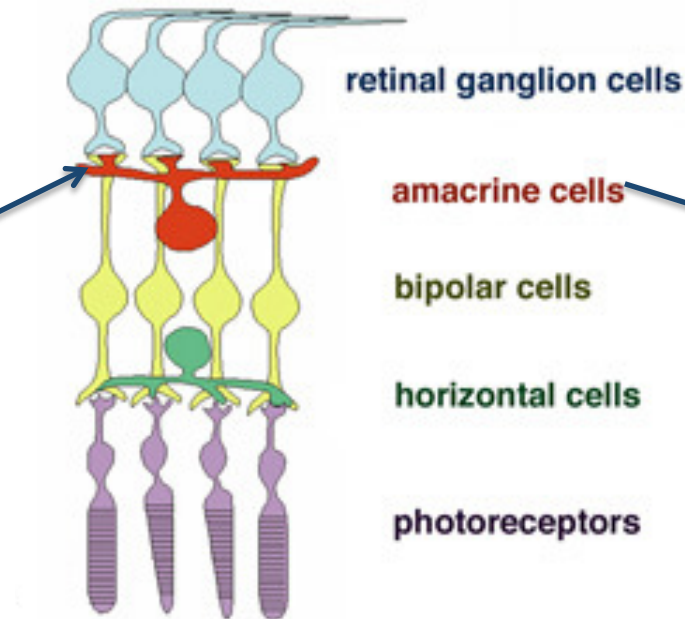


- Formation of retina circuitry
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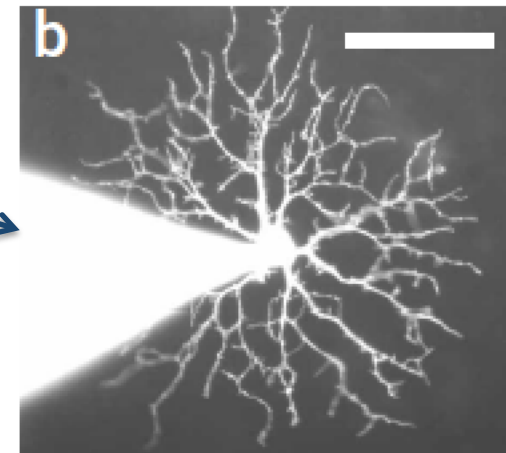
Focus on stage II retinal waves

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

**Stage II
(cholinergic
retinal waves)**



Starburst Amacrine Cell (SAC)



Zheng et al. 2006

groups.oist.jp/dnu/

Goal of this lecture

Idea:

Identify generic mechanisms generating stage II retinal waves and analyze them mathematically.

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Motivation:

- Retinal waves instruct the shaping of the visual system

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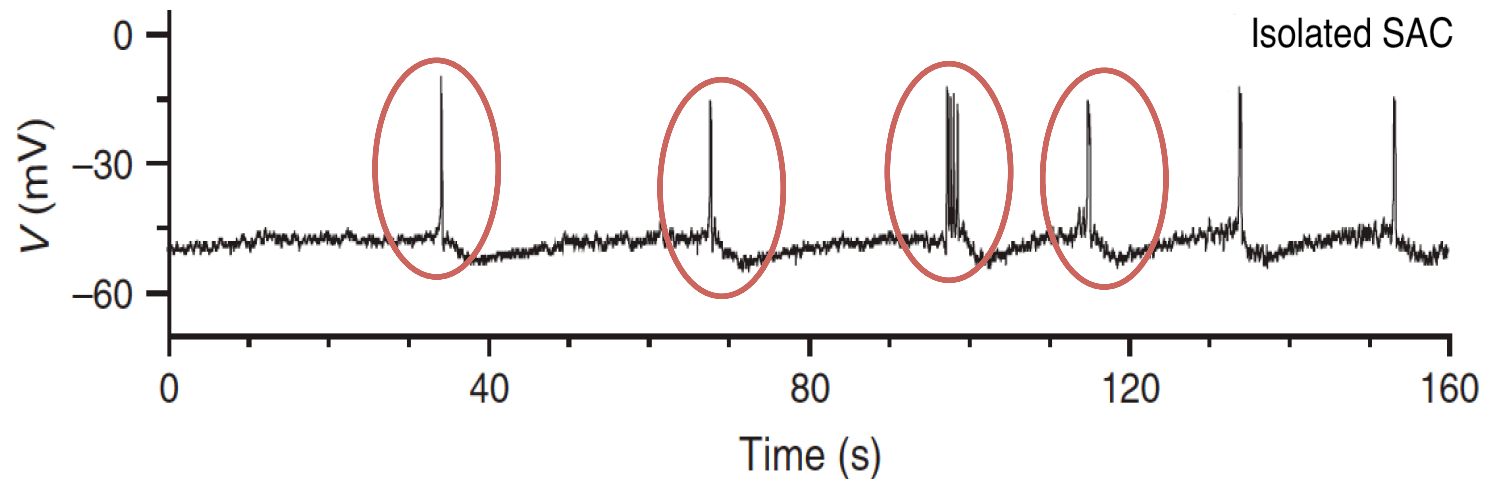
Motivation:

- Retinal waves instruct the shaping of the visual system
- Understanding the mechanisms that generate them may help to control them
- New mathematical problems and new techniques.

Experiments for the emergence of retinal waves

Retinal waves require three components:

- i) Spontaneous bursting activity

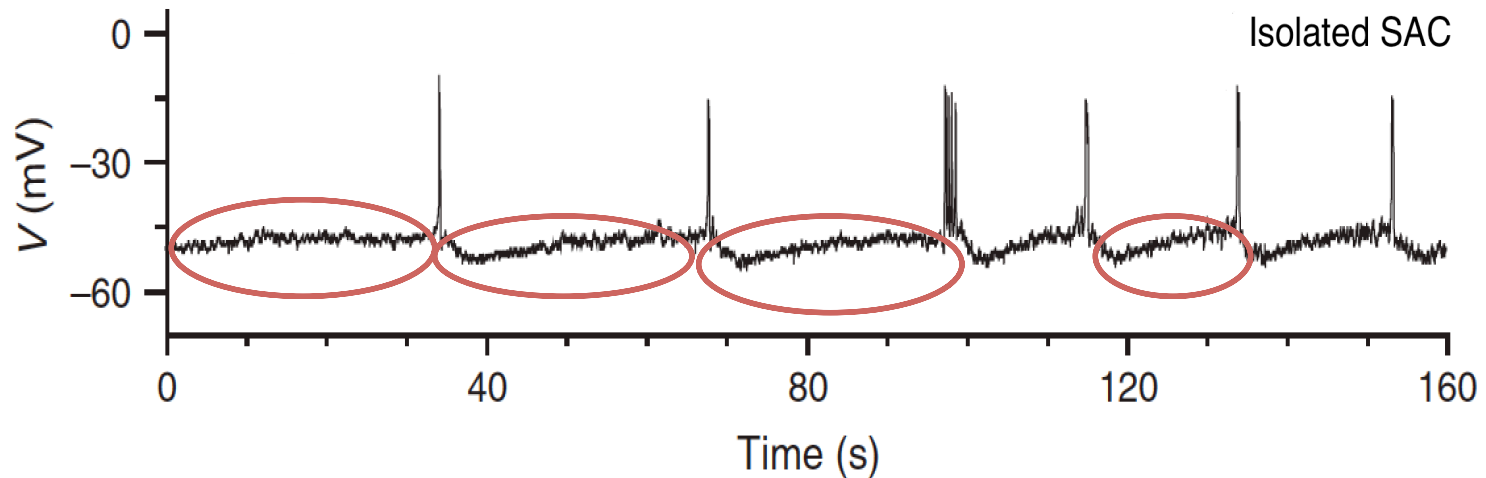


Experiment for isolated neurons,
Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

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

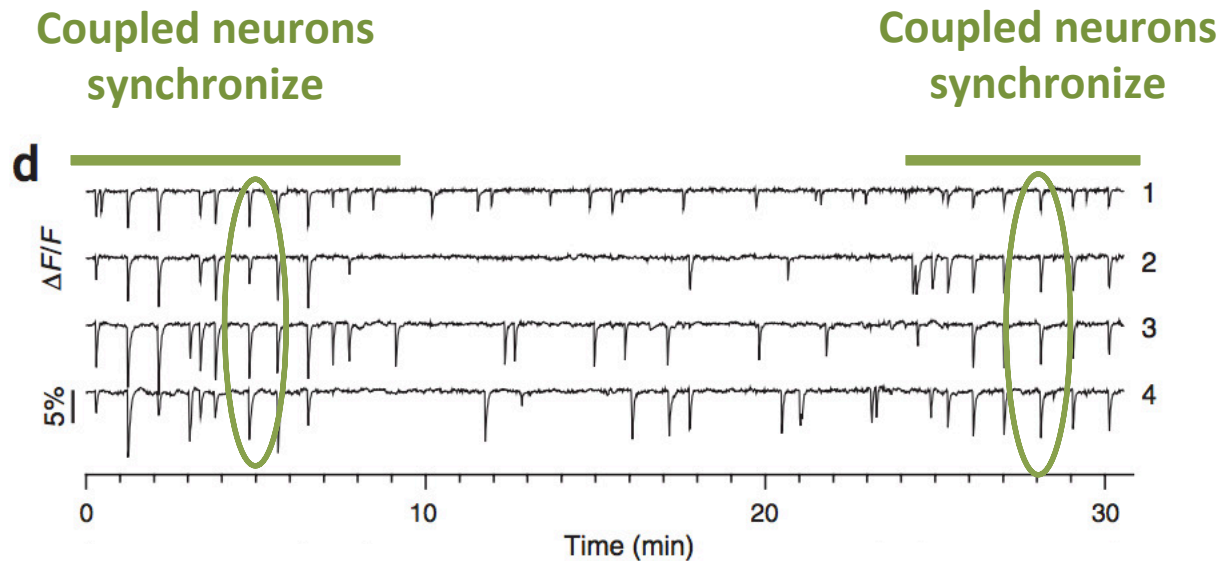


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Retinal waves require three components:

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- iii) Coupling (through Acetylcholine neurotransmitter)

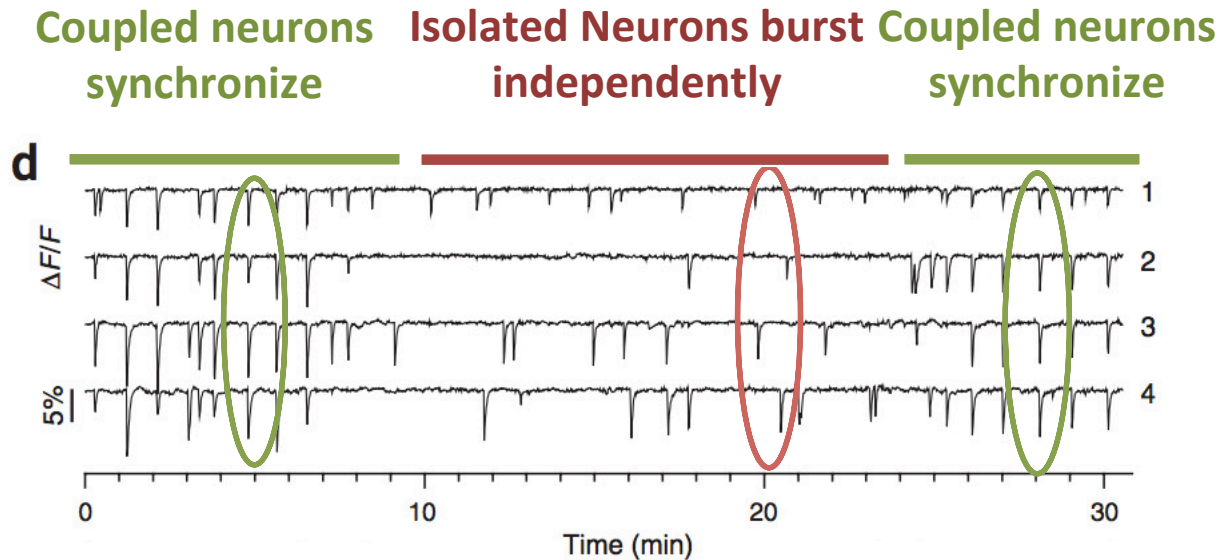


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Mathematical characterization of Retinal Waves

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

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- is **induced by generic mechanisms** that can be studied in the context of dynamical systems theory
- can be associated with **bifurcations**

Our strategy

- Model **biophysically** the dynamics of **isolated neurons** (SACs)
 - Carefully model all currents involved
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Our strategy

- Model **biophysically** the dynamics of **isolated neurons** (SACs)
 - Carefully model all currents involved
 - Fix parameters from experiments
- **Bifurcation analysis** of the non-linear dynamical system for isolated neurons
- Extract a **generic biophysical mechanism** of spontaneous bursting activity for SACs
- Model the network interactions:
 - Study the effects of synaptic coupling to **synchrony and wave initiation**
 - Search for biophysical parameters which control **spatiotemporal patterns**

Modelling the bursting of individual Starburst Amacrine Cells

Bruno Cessac and Dora Karvouniari

Biovision Team, INRIA Sophia Antipolis, France.

15-01-2017

- 1 From biophysics to modelling
- 2 Model analysis
- 3 Conclusions

From biophysics to modelling

Biophysics of bursting SAC

Retinal waves require three components:

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Biophysics of bursting SAC

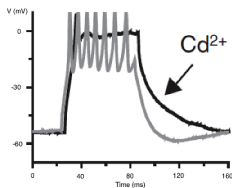


Figure: Zheng et al., Nature, 2006. Grey curve: Fast oscillations due to voltage-gated Ca^{+2} channels and Ca^{+2} dependent K^{+} channels. Black curve: Application of Cd^{+} blocking Ca^{+2} related channels.

Biophysics of bursting SAC

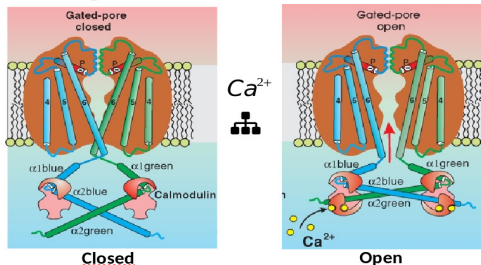
Morris-Lecar model with fast Potassium.

$$\left\{ \begin{array}{l} C_m \frac{dV}{dt} = -g_L(V - V_L) - g_C M_\infty(V)(V - V_C) - g_K N(V - V_K) \\ \quad + I_{ex}(\bullet) \\ \tau_N \frac{dN}{dt} = \Lambda(V)(N_\infty(V) - N) \end{array} \right. \quad (1)$$

Biophysics of sAHP

Biophysics of sAHP

- **Definition**
 - Slow After Hyperpolarisation Current
 - Calcium-dependent slow potassium channels
- **Mechanism**
 - Model SK-like channels (Abel et al. 2004)
 - Gating Mechanism: Four ions Ca^{2+} bind to Calmodulin (CaM)



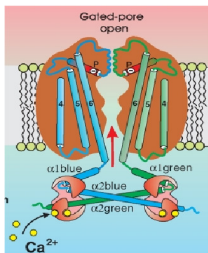
*Calcium gated
potassium
channel*

*superhimik.livejournal.c
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Biophysics of sAHP

- Four Ca^{2+} ions bound to calmodulin bind to a terminal
- I_{sAHP} current depends on gating variable R as follows:

$$I_{sAHP} = g_{sAHP}^m R^4 (V - V_K) \quad (\text{Hennig et al. 2009})$$



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

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Biophysics of sAHP

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

R : Probability that one terminal of the channel is open

$$\tau_S \frac{dS}{dt} = -S + a_S C^4(1-S)$$

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



Calcium gated potassium channel

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Model analysis

Dynamics

$$\left\{ \begin{array}{l}
 C_m \frac{dV}{dt} = -g_L(V - V_L) - g_C M_\infty(V)(V - V_C) - g_K N(V - V_K) \\
 \quad \quad \quad - g_{sAHP} R^4 (V - V_K) \\
 \tau_N \frac{dN}{dt} = \Lambda(V)(N_\infty(V) - N) \\
 \tau_C \frac{dC}{dt} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\
 \tau_S \frac{dS}{dt} = \alpha_S(1 - S)C^4 - S \\
 \tau_R \frac{dR}{dt} = \alpha_R S(1 - R) - R
 \end{array} \right. \quad (2)$$

Dynamics

$$\left\{ \begin{array}{l}
 C_m \frac{dV}{dt} = -g_L(V - V_L) - g_C M_\infty(V)(V - V_C) - g_K N(V - V_K) \\
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 \tau_S \frac{dS}{dt} = \alpha_S(1 - S)C^4 - S \\
 \tau_R \frac{dR}{dt} = \alpha_R S(1 - R) - R
 \end{array} \right. \quad (3)$$

Dynamics

Leak time scale: $\tau_L = \frac{C}{g_L}$.

Conductances rescaling: $\tilde{g}_X = \frac{g_X}{g_L}$.

$$\left\{ \begin{array}{l} \tau_L \frac{dV}{dt} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \tau_N \frac{dN}{dt} = \Lambda(V)(N_\infty(V) - N) \\ \tau_C \frac{dC}{dt} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \tau_S \frac{dS}{dt} = \alpha_S(1 - S)C^4 - S \\ \tau_R \frac{dR}{dt} = \alpha_R S(1 - R) - R \end{array} \right.$$

Multi-scale dynamics

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

Medium C . $\tau_C = 2$ s.

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

Fast-scale

$$t_f = \frac{t}{\tau_L} \Rightarrow dt = \tau_L dt_f$$

$$\left\{ \begin{array}{l} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{SAHP}(R)(V - V_K) \\ \frac{\tau_N}{\tau_L} \frac{dN}{dt_f} = \Lambda(V)(N_\infty(V) - N) \\ \frac{\tau_C}{\tau_L} \frac{dC}{dt_f} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \frac{\tau_S}{\tau_L} \frac{dS}{dt_f} = \alpha_S(1 - S)C^4 - S \\ \frac{\tau_R}{\tau_L} \frac{dR}{dt_f} = \alpha_R S(1 - R) - R \end{array} \right.$$

Fast-scale

Set $\epsilon_X = \frac{\tau_L}{\tau_X}$, $X = C, R, S$.

$$\epsilon_C = \frac{11}{2} \times 10^{-3} \sim 5.5 \times 10^{-3}, \quad \epsilon_S = \epsilon_R = \frac{11}{44} \times 10^{-3} \sim 2.5 \times 10^{-4}$$

$$\left\{ \begin{array}{l} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \\ \frac{dC}{dt_f} = \epsilon_C \left[-\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \right] \\ \frac{dS}{dt_f} = \epsilon_S [\alpha_S(1 - S)C^4 - S] \\ \frac{dR}{dt_f} = \epsilon_R [\alpha_R S(1 - R) - R] \end{array} \right.$$

Fast-scale: approximation

$$\left\{ \begin{array}{l} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \\ \frac{dC}{dt_f} = 0 \\ \frac{dS}{dt_f} = 0 \\ \frac{dR}{dt_f} = 0 \end{array} \right.$$

C, R, S are constant at this time scale.

Morris-Lecar model analysis

$$\left\{ \begin{array}{l} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \end{array} \right. \quad (4)$$

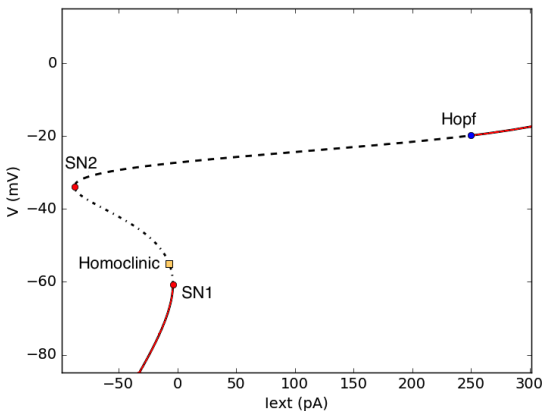
Morris-Lecar model analysis

$$\begin{cases} \frac{dV}{dt_f} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) + I_{ext} \\ \frac{dN}{dt_f} = \frac{\tau_L}{\tau_N} \Lambda(V)(N_\infty(V) - N) \end{cases} \quad (5)$$

Bifurcation analysis when varying the parameter I_{ext} .

Morris-Lecar model analysis

Karvouniari et al, submitted to Plos Comp. Bio.



The saddle-node bifurcation

saddle-node bifurcation

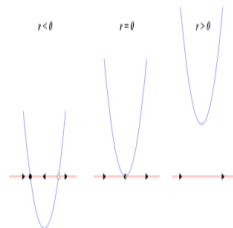
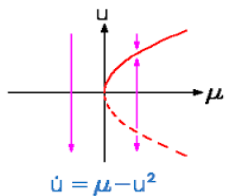


Figure: From <https://elmer.unibas.ch/pendulum/bif.htm> and https://it.wikipedia.org/wiki/Biforcazione_a_nodo_sella.

The Hopf bifurcation

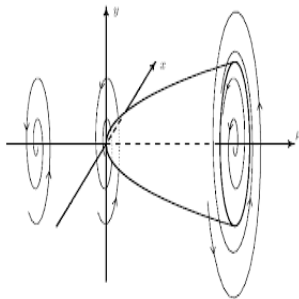
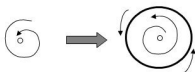


Figure: From Navarro et al, "Control of the Hopf bifurcation in the Takens-Bogdanov bifurcation", CDC2008

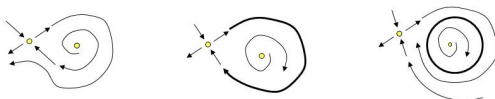
The homoclinic bifurcation

Hopf Bifurcation



Small amplitude, frequency = $\text{Im}(\lambda)$, finite period

Homoclinic Bifurcation

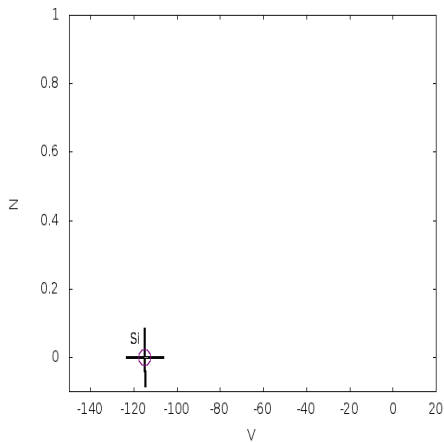
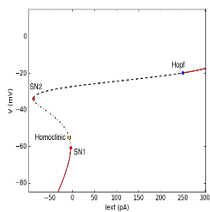


Finite amplitude, small frequency, infinite period

Figure: From J. Tyson, <http://slideplayer.com/slide/8870556/>

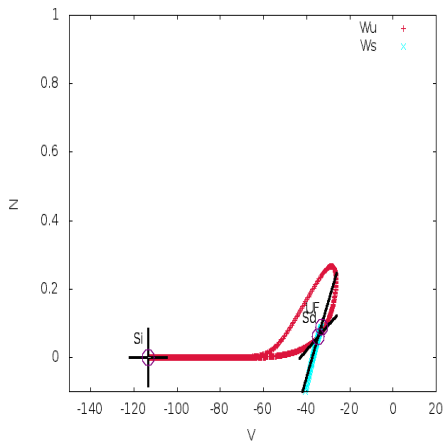
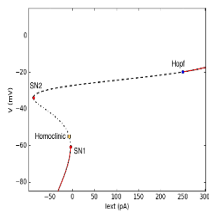
The complete movie

Karvouniari et al, ICMNS, 2016



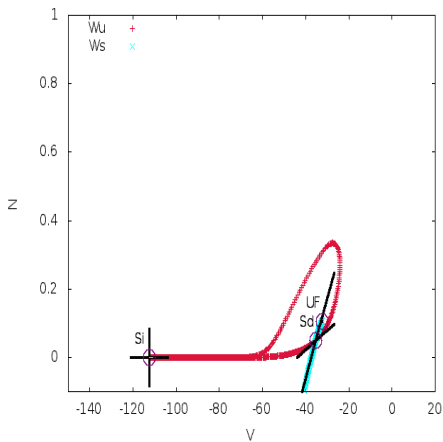
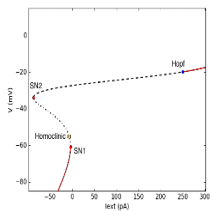
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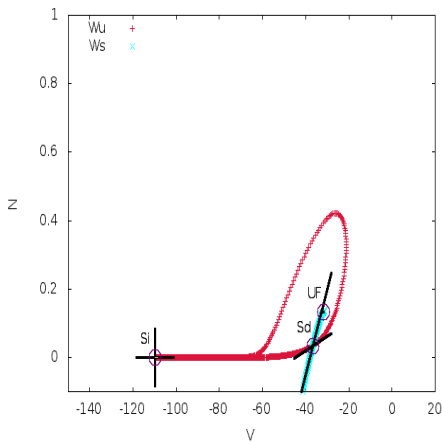
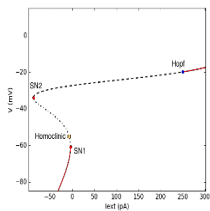
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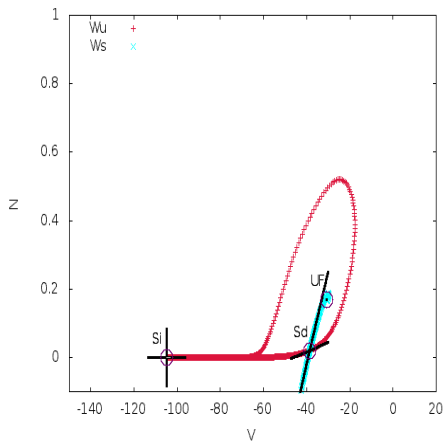
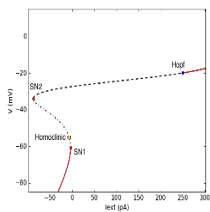
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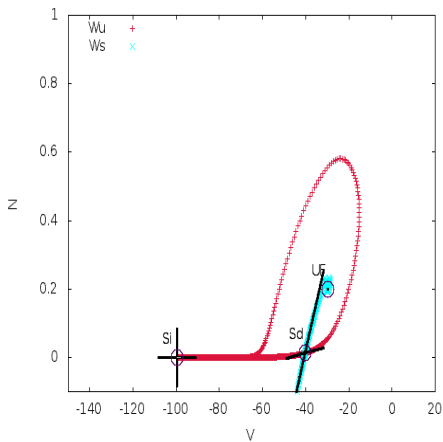
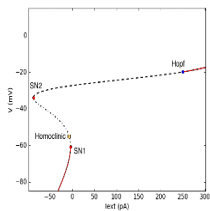
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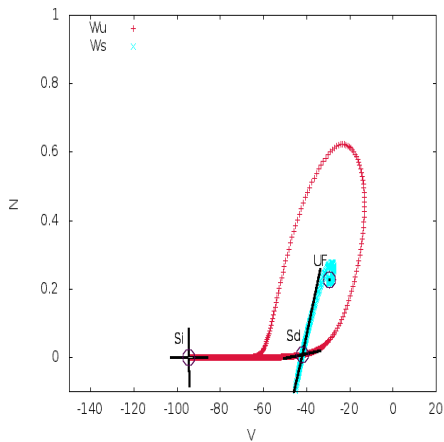
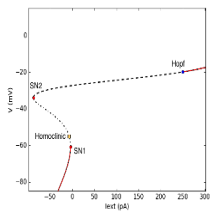
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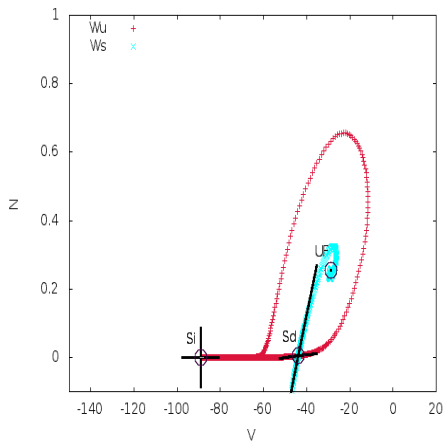
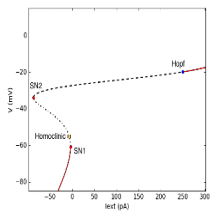
The complete movie

Karvouniari et al, submitted



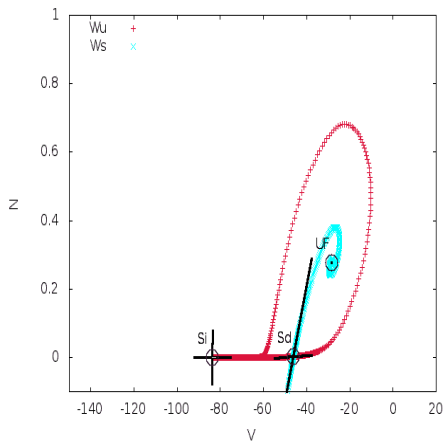
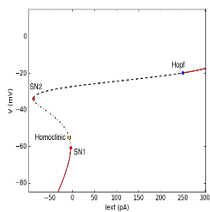
The complete movie

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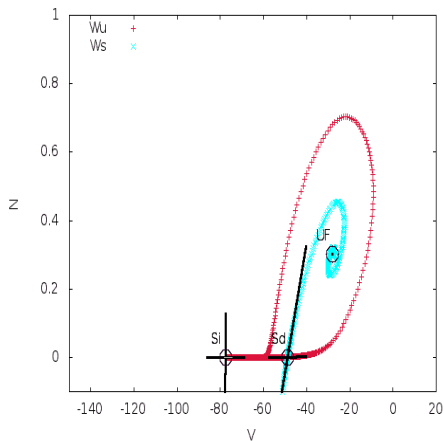
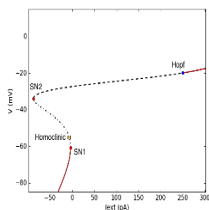
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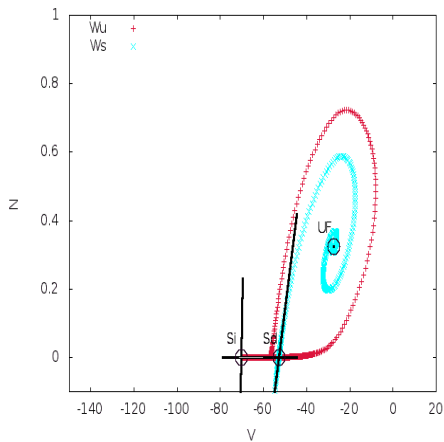
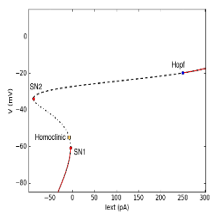
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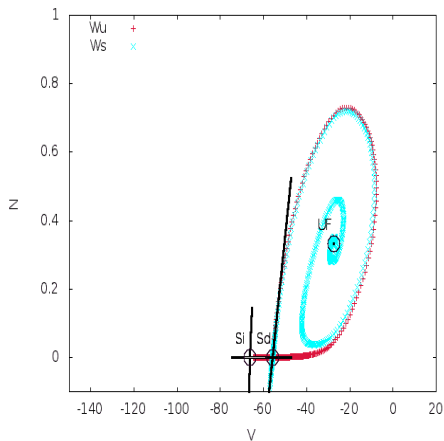
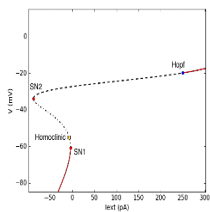
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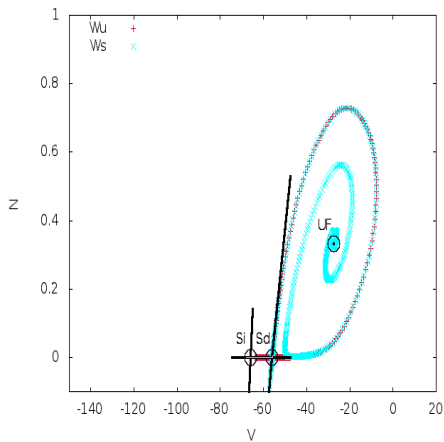
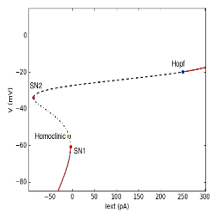
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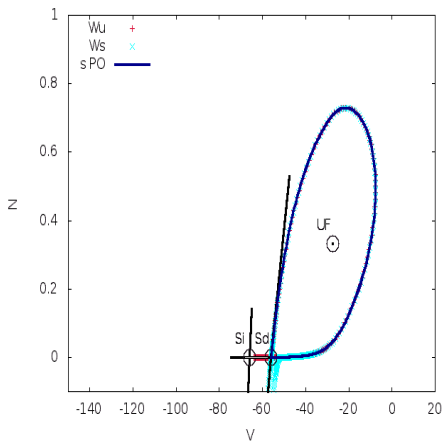
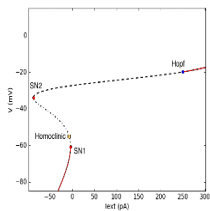
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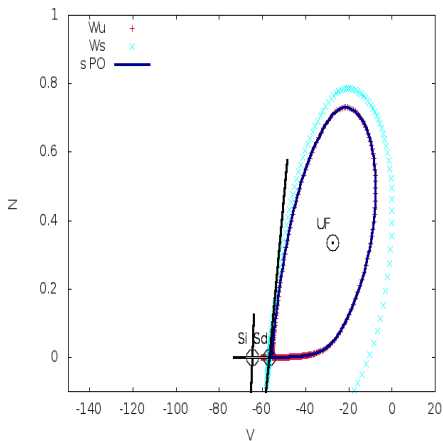
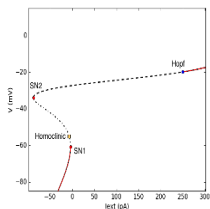
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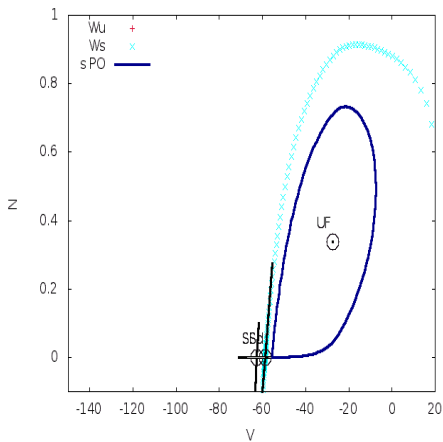
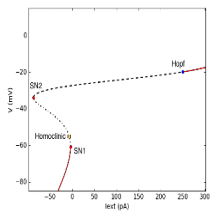
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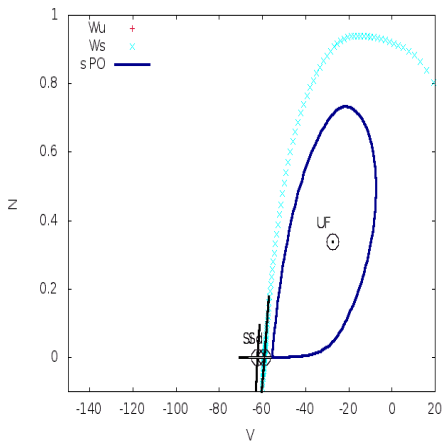
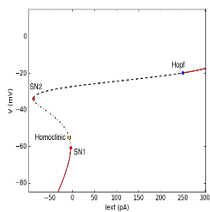
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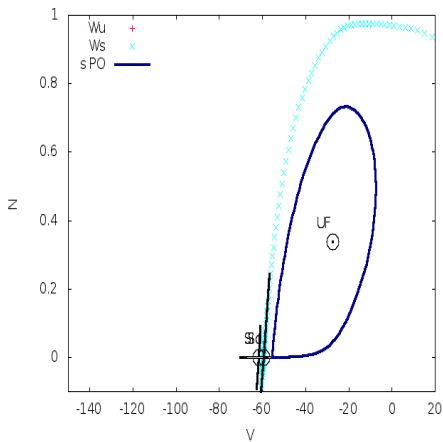
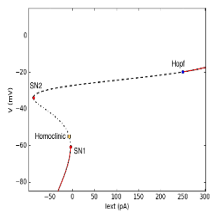
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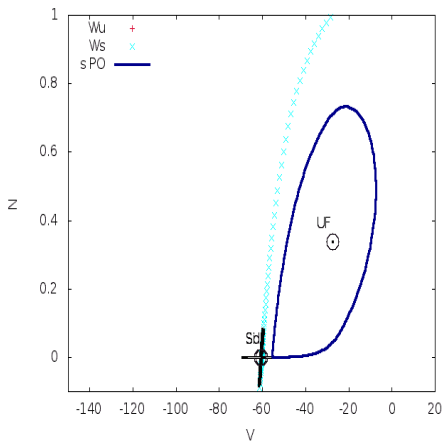
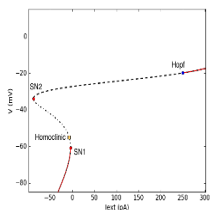
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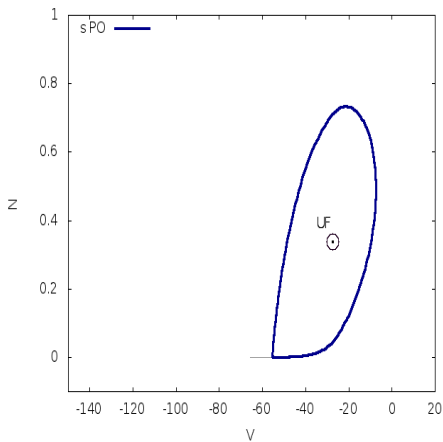
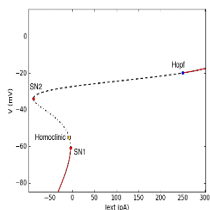
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Karvouniari et al, ICMNS, 2016



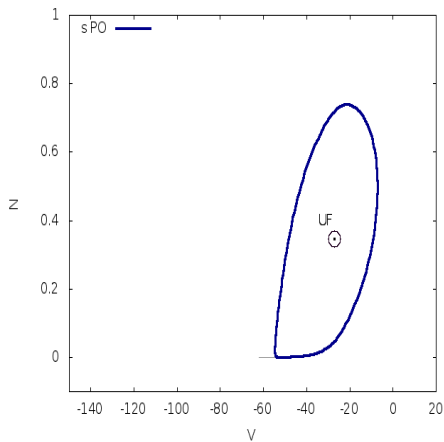
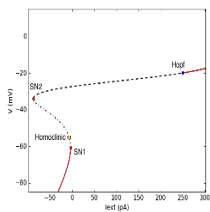
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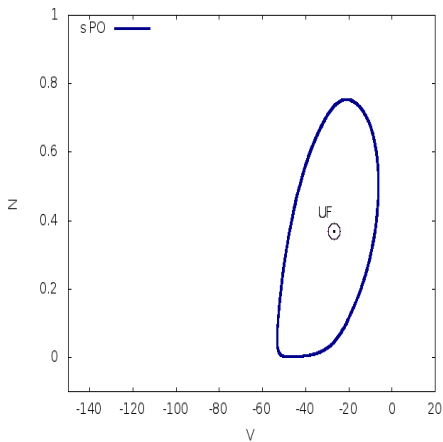
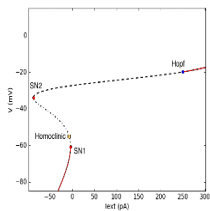
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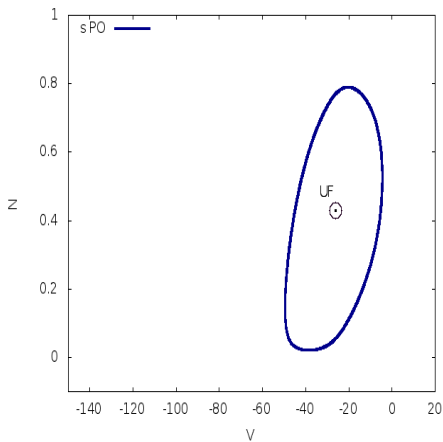
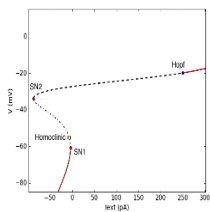
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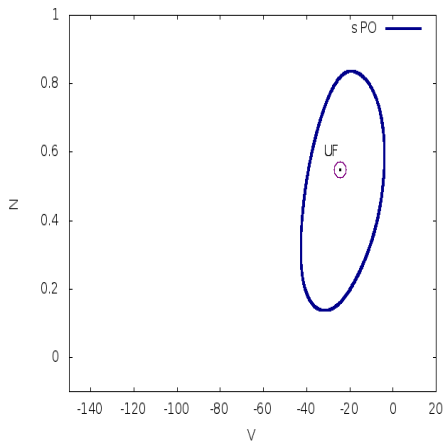
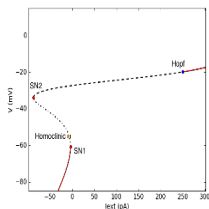
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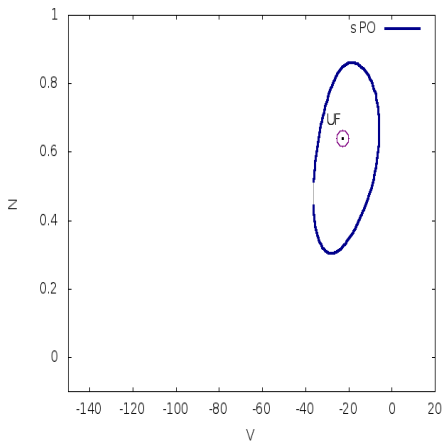
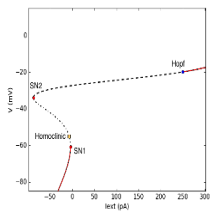
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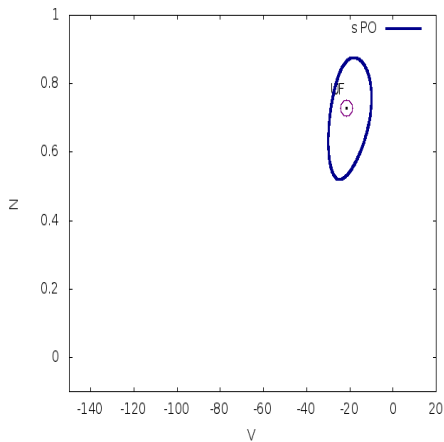
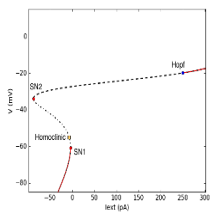
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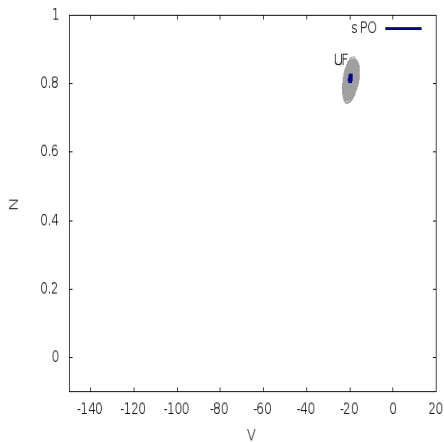
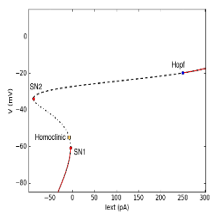
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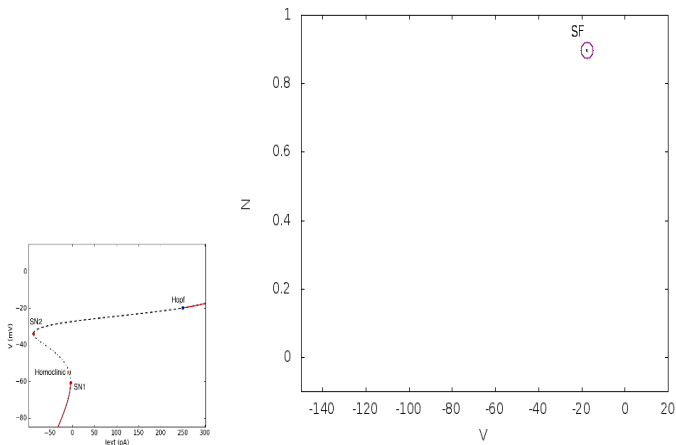
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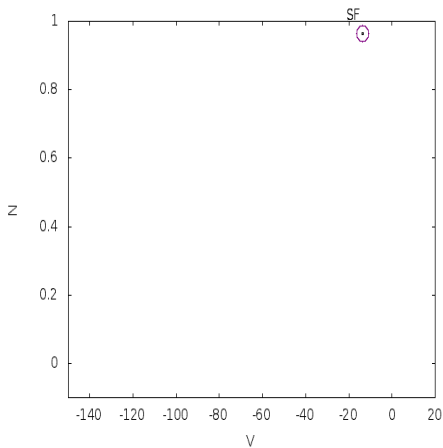
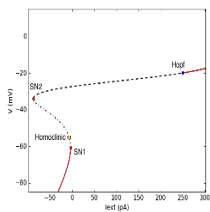
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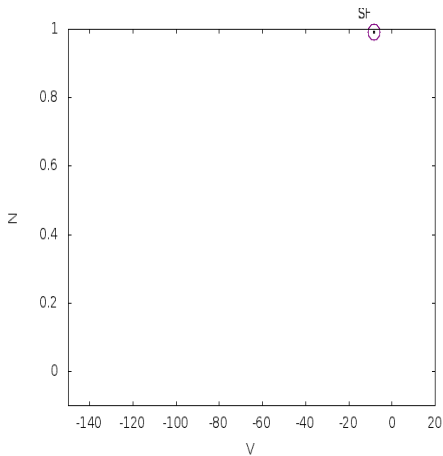
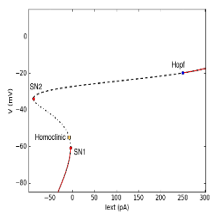
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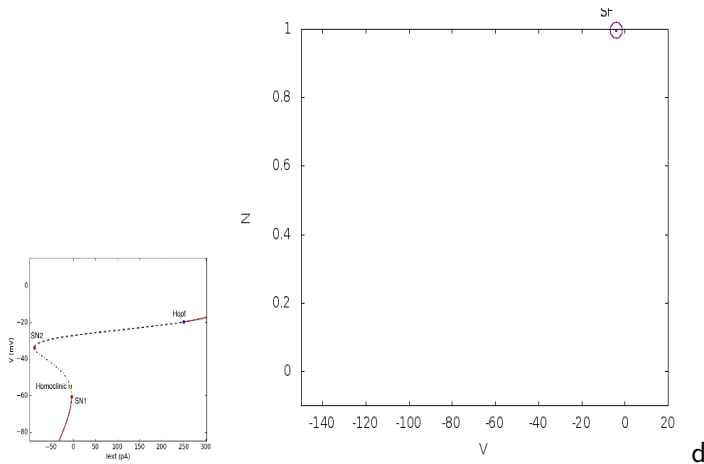
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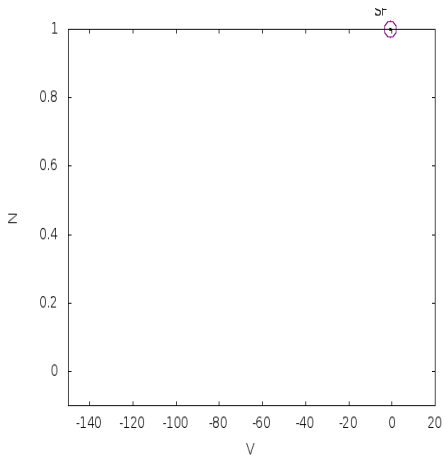
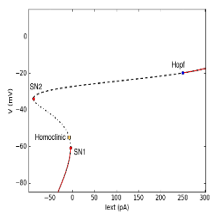
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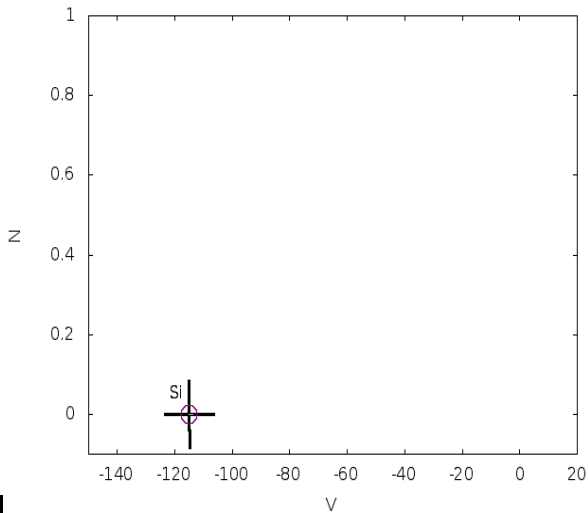
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The complete movie

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Back to Zhou experiment

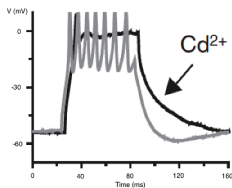
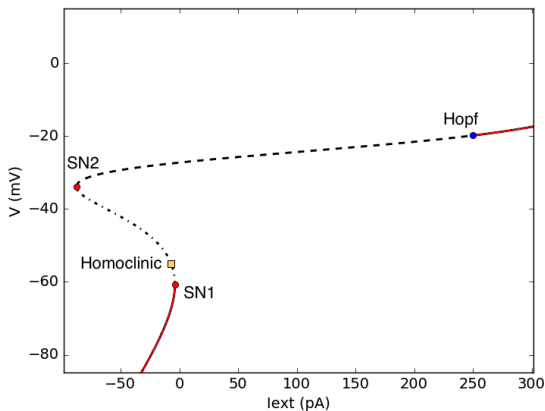


Figure: Zheng et al., Nature, 2006. Grey curve: Fast oscillations due to voltage-gated Ca^{+2} channels and Ca^{+2} dependent K^{+} channels. Black curve: Application of Cd^{+} blocking Ca^{+2} related channels.

Back to Zhou experiment

Karvouniari et al, submitted to Plos Comp. Bio.



Back to Zhou experiment

Karvouniari et al, submitted to Plos Comp. Bio.

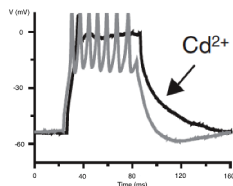
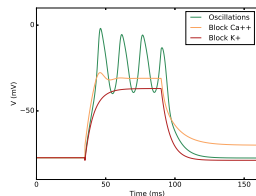


Figure: *Left.* *Green.* Application of a current step pulse of 150 pA for 60ms. *Orange:* Oscillations disappear when Ca^{+2} related conductances are set to zero. *Red.* Blocking the oscillations upon setting the voltage-gated K^+ conductance to zero. *Right:* Zheng et al. 2006 experimental figure. Grey curve: Fast oscillations due to voltage-gated Ca^{+2} channels and Ca^{+2} dependent K^+ channels. Black curve: Application of Cd^+ blocking Ca^{+2} related channels.

Dynamics of bursting

Dynamics of bursting

$$\left\{ \begin{array}{l} \tau_L \frac{dV}{dt} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \tau_N \frac{dN}{dt} = \Lambda(V)(N_\infty(V) - N) \\ \tau_C \frac{dC}{dt} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \tau_S \frac{dS}{dt} = \alpha_S(1 - S)C^4 - S \\ \tau_R \frac{dR}{dt} = \alpha_R S(1 - R) - R \end{array} \right.$$

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

Medium C . $\tau_C = 2$ s.

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

Slow time-scale

$$t_s = \frac{t}{\tau_S} \Rightarrow dt = \tau_S dt_s$$

$$\left\{ \begin{array}{l} \frac{\tau_L}{\tau_S} \frac{dV}{dt_s} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \frac{\tau_N}{\tau_S} \frac{dN}{dt_s} = \Lambda(V)(N_\infty(V) - N) \\ \frac{\tau_C}{\tau_S} \frac{dC}{dt_s} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \frac{dS}{dt_s} = \alpha_S(1 - S)C^4 - S \\ \frac{dR}{dt_s} = \alpha_R S(1 - R) - R \end{array} \right.$$

Slow time-scale

$$\epsilon_V = \frac{\tau_L}{\tau_S} \sim 2.5 \times 10^{-4}, \quad \epsilon_N = \frac{\tau_N}{\tau_S} \sim 1 \times 10^{-3}$$

$$\epsilon_C = \frac{\tau_C}{\tau_S} \sim 4.5 \times 10^{-2}$$

$$\left\{ \begin{array}{l} \epsilon_V \frac{dV}{dt_s} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \epsilon_N \frac{dN}{dt_s} = \Lambda(V)(N_\infty(V) - N) \\ \epsilon_C \frac{dC}{dt_s} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \frac{dS}{dt_s} = \alpha_S(1 - S)C^4 - S \\ \frac{dR}{dt_s} = \alpha_R S(1 - R) - R \end{array} \right.$$

Slow time-scale approximation

$$\left\{ \begin{array}{l}
 0 = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\
 \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\
 0 = \Lambda(V)(N_\infty(V) - N) \\
 0 = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\
 \frac{dS}{dt_s} = \alpha_S(1 - S)C^4 - S \\
 \frac{dR}{dt_s} = \alpha_R S(1 - R) - R
 \end{array} \right.$$

Steady state

$$V = \frac{V_{ML}(V) + \tilde{G}_{sAHP}(R)V_K}{\tilde{g}_{ML}(V) + \tilde{G}_{sAHP}(R)}$$

where:

$$\begin{aligned} V_{ML}(V) &= V_L + \tilde{g}_C M_\infty(V)V_C + \tilde{g}_K N_\infty(V)V_K; \\ \tilde{g}_{ML}(V) &= 1 + \tilde{g}_C M_\infty(V) + \tilde{g}_K N_\infty(V), \end{aligned}$$

Steady state

V follows "adiabatically" R .

$$V \equiv f(V, R) = \frac{V_{ML}(V) + \tilde{G}_{sAHP}(R)V_K}{\tilde{g}_{ML}(V) + \tilde{G}_{sAHP}(R)} \quad (6)$$

Steady state

V follows "adiabatically" R .

$$V \equiv f(V, R) = \frac{V_{ML}(V) + \tilde{G}_{sAHP}(R)V_K}{\tilde{g}_{ML}(V) + \tilde{G}_{sAHP}(R)} \quad (6)$$

Implicit function theorem.

Whenever $\frac{\partial f}{\partial V} \neq 1$ V follows a unique and differentiable branch $V \equiv V(R)$. At points R where $\frac{\partial f}{\partial V} = 1$ this branch may disappear or several branch may appear simultaneously (bifurcation).

Hint

$$V \equiv f(V, R) = \frac{V_{ML}(V) + \tilde{G}_{sAHP}(R)V_K}{\tilde{g}_{ML}(V) + \tilde{G}_{sAHP}(R)} \quad (7)$$

Taking the differential gives:

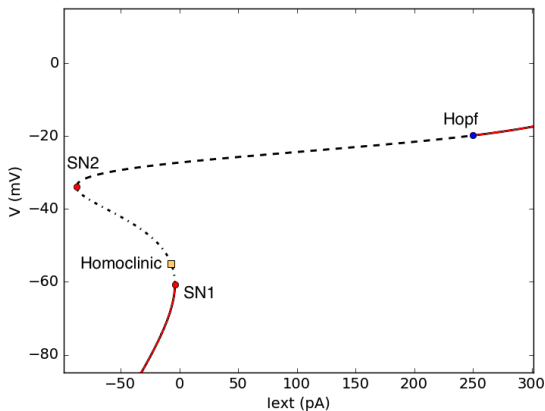
$$dV \left(1 - \frac{\partial f}{\partial V} \right) = \frac{\partial f}{\partial R} dR$$

\Rightarrow

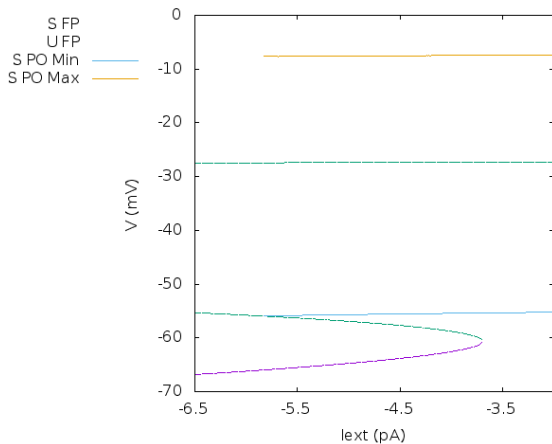
$$\frac{dV}{dR} = \frac{\frac{\partial f}{\partial R}}{1 - \frac{\partial f}{\partial V}}$$

Morris-Lecar model analysis

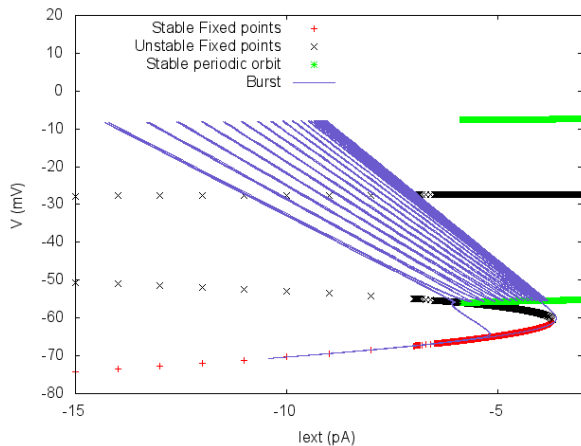
V follows adiabatically $\tilde{G}_{sAHP}(R)$.



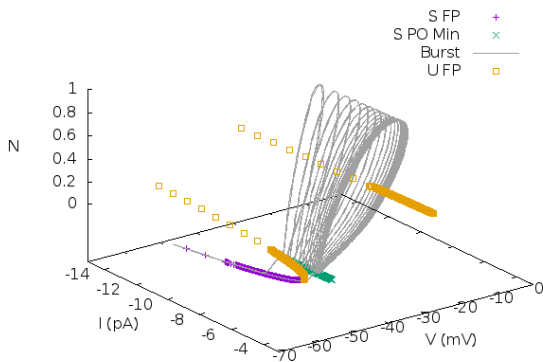
Morris-Lecar model analysis



Morris-Lecar model analysis

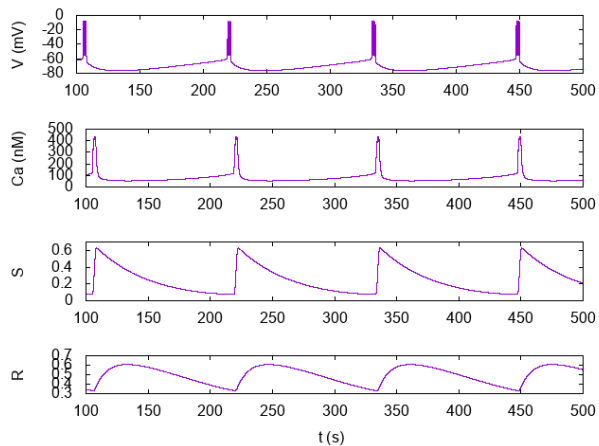


Morris-Lecar model analysis

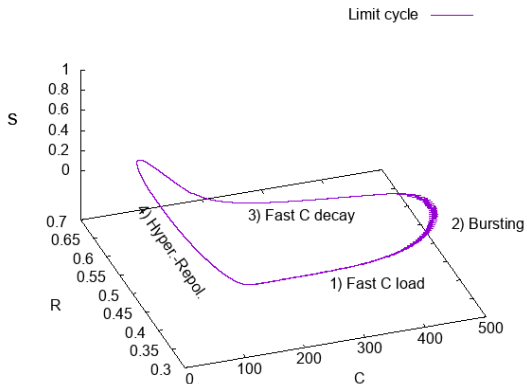


Complete dynamics

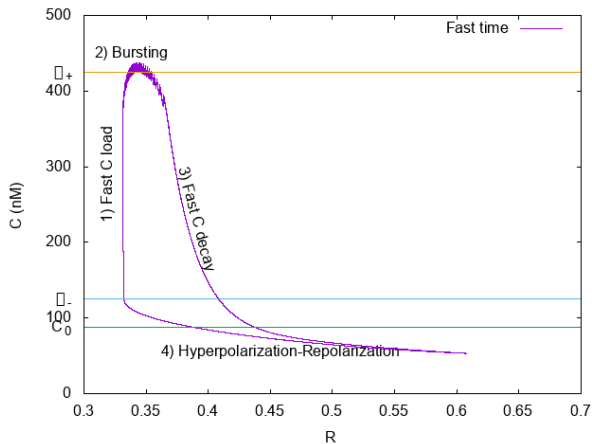
Complete dynamics



Medium and fast dynamics



Medium and fast dynamics



Medium-scale

$$t_m = \frac{t}{\tau_C} \Rightarrow dt = \tau_C dt_m$$

$$\left\{ \begin{array}{l} \frac{\tau_L}{\tau_C} \frac{dV}{dt_m} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \frac{\tau_N}{\tau_C} \frac{dN}{dt_m} = \Lambda(V)(N_\infty(V) - N) \\ \frac{dC}{dt_m} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \frac{\tau_S}{\tau_C} \frac{dS}{dt_m} = \alpha_S(1 - S)C^4 - S \\ \frac{\tau_R}{\tau_C} \frac{dR}{dt_m} = \alpha_R S(1 - R) - R \end{array} \right.$$

Medium-scale

$$\epsilon_V = \frac{\tau_L}{\tau_C} \sim 5 \times 10^{-3}, \quad \epsilon_N = \frac{\tau_N}{\tau_C} \sim 2.5 \times 10^{-3}$$

$$\epsilon_S = \epsilon_R = \frac{\tau_C}{\tau_S} \sim 4.5 \times 10^{-2}$$

$$\left\{ \begin{array}{l} \epsilon_V \frac{dV}{dt_m} = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\ \epsilon_N \frac{dN}{dt_m} = \Lambda(V)(N_\infty(V) - N) \\ \frac{dC}{dt} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\ \frac{dS}{dt_m} = \epsilon_S [\alpha_S(1 - S)C^4 - S] \\ \frac{dR}{dt_m} = \epsilon_R [\alpha_R S(1 - R) - R] \end{array} \right.$$

Medium-scale approximation

$$\left\{ \begin{array}{l}
 0 = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\
 \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\
 0 = \Lambda(V)(N_\infty(V) - N) \\
 \frac{dC}{dt_m} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\
 \frac{dS}{dt} = 0 \\
 \frac{dR}{dt} = 0
 \end{array} \right.$$

Medium-scale approximation

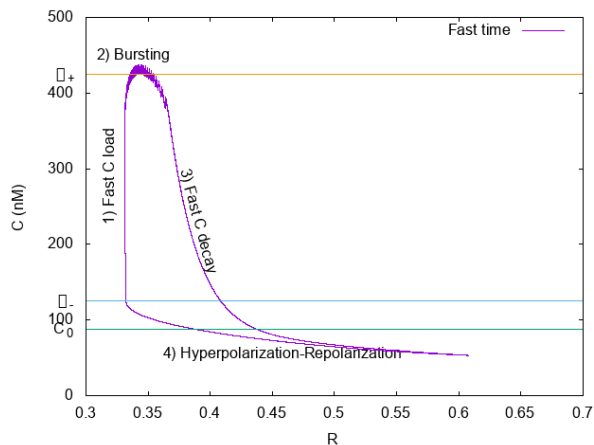
At this time scale:

- R, S are constant;
- V follows the variations of R ;
- $\frac{dC}{dt_m} = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C)$

\Rightarrow

Medium-scale approximation

Rapid (medium time scale between upper/lower branch) "Outer dynamics".



Slow time-scale approximation

$$\left\{ \begin{array}{l}
 0 = -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\
 \quad - \tilde{G}_{sAHP}(R)(V - V_K) \\
 0 = \Lambda(V)(N_\infty(V) - N) \\
 0 = -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\
 \frac{dS}{dt_s} = \alpha_S(1 - S)C^4 - S \\
 \frac{dR}{dt_s} = \alpha_R S(1 - R) - R
 \end{array} \right.$$

"Inner dynamics"

- V follows R ;
- C follows V ;
- Note $P(R) \equiv C^4$, the average value of C^4 for a given value of R .

\Rightarrow

Dynamics on the slow branches.

$$\begin{cases} \frac{dR}{dt_s} = \alpha_R S(1 - R) - R \\ \frac{dS}{dt_s} = \alpha_S(1 - S)P(R) - S \end{cases}$$

"Inner dynamics"

Nullclines.

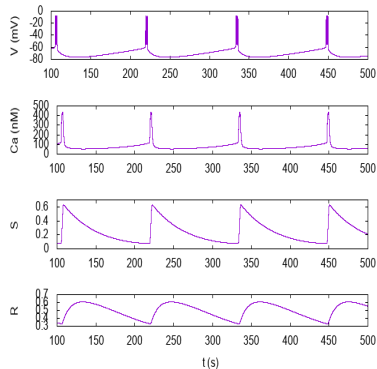
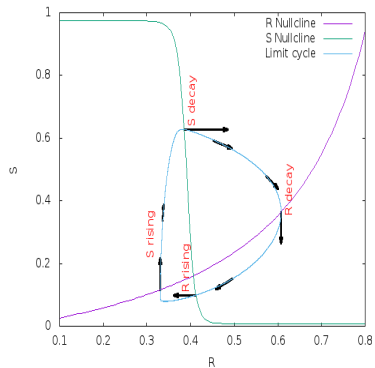
$$R \text{ Nullcline: } \frac{dR}{dt_s} = 0 \Rightarrow$$

The vector field is vertical on the line $S = \frac{R}{\alpha_R(1-R)}$

$$S \text{ Nullcline: } \frac{dS}{dt_s} = 0 \Rightarrow$$

The vector field is horizontal on the line $S = \frac{\alpha_S P(R)}{1 + \alpha_S P(R)}$

Inner dynamics



Conclusions

- We have now a model reproducing individual SACs bursting.

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Conclusions

- We have now a model reproducing individual SACs bursting.
- Here SACs burst periodically with a frequency determined by the parameters of the model (mainly τ_R).
- A small change of parameters make them into a rest state where they burst only upon an external excitation (noise).
- **What happens when they cells are coupled with Acetylcholine ?**

Modelling stage II retinal waves

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Biovision Team, INRIA Sophia Antipolis, France.

15-01-2017

- 1 Coupling SACs with Acetylcholine
- 2 Dynamical systems analysis
- 3 A simplified setting to mathematically study retinal waves
- 4 Generalisations
- 5 Conclusions

Coupling SACs with Acetylcholine

Coupling SACs with Acetylcholine

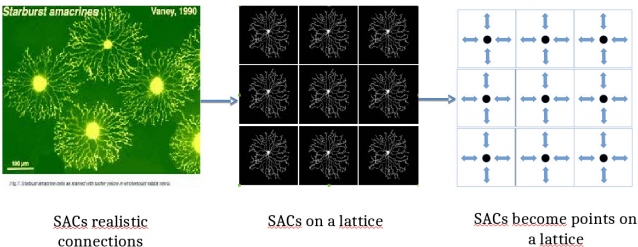


Figure: SACs network.

Coupling SACs with Acetylcholine

- 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

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

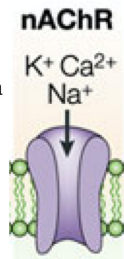
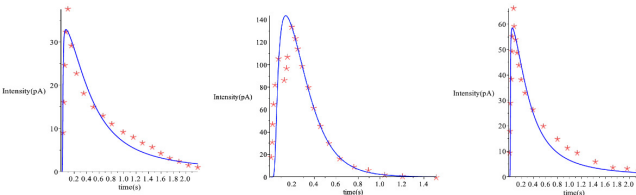


Figure: Nicotinic receptors and conductance.

Coupling SACs with Acetylcholine

$$\frac{\partial A}{\partial t} = \beta_{ACh} T_{ACh}(V) - \frac{A}{\tau_{ACh}}$$

A: Extracellular Acetylcholine concentration



Intensity of Acetylcholine current for three Voltage clamp levels
Experimental fits from Zhou et al. 2004, Neuron

Figure: Ach production.

Coupling SACs with Acetylcholine

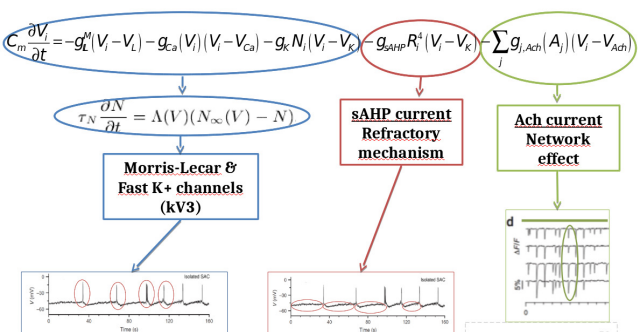


Figure: Equation of membrane potential.

Dynamical systems analysis

Main currents

$$G_{sAHP}(R_i) = g_{sAHP} R_i^4, \quad (1)$$

sAHP conductance,

$$G_A(\{A_k\}_{k \in \mathcal{B}_i}) = g_A \sum_{k \in \mathcal{B}_i} U(A_k), \quad (2)$$

Ach synaptic conductance with:

$$U(A) = \frac{A^2}{\gamma_A + A^2}, \quad (3)$$

\mathcal{B}_i is the set of index of neurons connected to i .

Dynamics

$$\left\{ \begin{array}{l}
 C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\
 \quad - G_{sAHP}(R_i)(V_i - V_K) - G_A(\{A_k\}_{k \in \mathcal{B}_i})(V_i - V_A) \\
 \tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i) \\
 \tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C) \\
 \tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i)C_i^4 - S_i \\
 \tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i \\
 \frac{dA_i}{dt} = -\mu A_i + \beta_A T_A(V_i),
 \end{array} \right. \quad (4)$$

Dynamics

Leak time scale: $\tau_L = \frac{C}{g_L}$. Ach time scale: $\tau_A = \frac{1}{\mu}$.

Conductances rescaling: $\tilde{g}_X = \frac{g_X}{g_L}$.

$$\left\{ \begin{array}{l} \tau_L \frac{dV_i}{dt} = -(V_i - V_L) - \tilde{g}_C M_\infty(V_i)(V_i - V_C) - \tilde{g}_K N_i(V_i - V_K) \\ \quad - \tilde{G}_{sAHP}(R_i)(V_i - V_K) - \tilde{G}_A(\{A_k\}_{k \in \mathcal{B}_i})(V_i - V_A); \\ \tau_N \frac{dN_i}{dt} = \Lambda(V_i)(N_\infty(V_i) - N_i); \\ \tau_C \frac{dC_i}{dt} = -\frac{\alpha_C}{H_X} C_i + C_0 - \delta_C g_C M_\infty(V_i)(V_i - V_C); \\ \tau_S \frac{dS_i}{dt} = \alpha_S(1 - S_i)C_i^4 - S_i; \\ \tau_R \frac{dR_i}{dt} = \alpha_R S_i(1 - R_i) - R_i; \\ \tau_A \frac{dA_i}{dt} = -A_i + \frac{\beta_A}{\mu} T_A(V_i); \end{array} \right.$$

Multi-scale dynamics

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.

A simplified setting to mathematically study retinal waves

Inspired from Lansdell et al, Plos. Comp. Bio, 2014

A simplified setting to mathematically study retinal waves

Main hypotheses:

- 1) We neglect the fast Potassium current. V_i has only two stable states: low and high. In the high state SAC does not burst.

A simplified setting to mathematically study retinal waves

Main hypotheses:

2) To switch from low to high state, neuron i needs an external excitatory current. This can be:

- The Ach current coming from neighbours;
- A "shot noise" current of the form:

$$g_N B_i (V_i - V_C)$$

where $B \in \{0, 1\}$ is a Bernoulli variable with probability
 $Prob [B_i(s) = 1, s \in [t, t + dt]] = p dt$, with $p \sim \frac{1}{\tau_R}$.

A simplified setting to mathematically study retinal waves

Main hypotheses:

- 3) sAHP has a simplified form (does not depend on Calcium). We only keep the variables S, R where S depends directly on V :

$$\tau_S \frac{dS_i}{dt} = -S_i + \gamma G(V_i)$$

with:

$$G(V_i) = \frac{1}{1 + e^{-\kappa(V - V_0)}}.$$

A simplified setting to mathematically study retinal waves

Main hypotheses:

4) Acetylcholine synapses are **assumed** not to be yet functional (Ford-Feller, 2011). The main source of Ach coupling is Ach *diffusion*.

$$\tau_A \frac{dA_i}{dt} = -A_i + \frac{\beta_A}{\mu} T_A(V_i) + D\Delta A_i;$$

where Δ is the Laplacian on a square lattice.
Boundary conditions are ignored.

The Ach current depends only on the local Ach: $I_A = -g_A U(A)(V - V_A)$.

A simplified setting to mathematically study retinal waves

Main hypotheses:

- 1 Two state voltage.
- 2 Shot noise.
- 3 Simplified form for sAHP.
- 4 Ach diffusion.

Dynamics

From now we consider that variables depend continuously on space

$$\Rightarrow \frac{d}{dt} \rightarrow \frac{\partial}{\partial t}$$

$$\left\{ \begin{array}{l} \tau_L \frac{\partial V}{\partial t} = -(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) + \tilde{g}_N B(V - V_C) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) - \tilde{g}_A U(A)(V - V_A); \\ \tau_S \frac{\partial S}{\partial t} = -S + \gamma G(V); \\ \tau_R \frac{\partial R}{\partial t} = \alpha_R S(1 - R) - R; \\ \tau_A \frac{\partial A}{\partial t} = -A + \frac{\beta_A}{\mu} T_A(V) + D\Delta A(V); \end{array} \right.$$

Medium-scale

$$t_m = \frac{t}{\tau_A} \Rightarrow dt = \tau_A dt_m$$

$$\epsilon_V = \frac{\tau_L}{\tau_A} \sim 5 \times 10^{-3}; \quad \epsilon_S = \epsilon_R = \frac{\tau_A}{\tau_S} \sim 4.5 \times 10^{-2}$$

$$\left\{ \begin{array}{l} \epsilon_V \frac{\partial V}{\partial t_m} = -(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - g_N B(V - V_C) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) - \tilde{g}_A U(A)(V - V_A); \\ \frac{\partial S}{\partial t_m} = \epsilon_S [-S + \gamma G(V)]; \\ \frac{\partial R}{\partial t_m} = \epsilon_R [\alpha_R S(1 - R) - R]; \\ \frac{\partial A}{\partial t_m} = -A + \frac{\beta_A}{\mu} T_A(V) + D\Delta A; \end{array} \right.$$

Medium-scale approximation

$$\left\{ \begin{array}{l} 0 = -(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) + g_N B(V - V_C) \\ \quad - \tilde{G}_{sAHP}(R)(V - V_K) - \tilde{g}_A U(A)(V - V_A); \\ \frac{\partial S}{\partial t_m} = 0; \\ \frac{\partial R}{\partial t_m} = 0; \\ \frac{\partial A}{\partial t_m} = -A + \frac{\beta_A}{\mu} T_A(V) + D\Delta A; \end{array} \right.$$

Medium-scale approximation

At this time scale:

- R, S are constant;
- V follows the variations of R, A ;

$$V = \frac{V_L + \tilde{g}_C M_\infty(V) V_C + \tilde{g}_N B V_C + \tilde{G}_{sAHP}(R) V_K + \tilde{g}_A U(A) V_A}{1 + \tilde{g}_C M_\infty(V) + \tilde{g}_N B + \tilde{G}_{sAHP}(R) + \tilde{g}_A U(A)}$$

From the implicit functions theorem: $V = f(R, A, B)$.

Acetylcholine front propagation

We consider here a propagation in 1 dimension.

$$\frac{\partial A}{\partial t_m} = -A + \frac{\beta_A}{\mu} T_A(V) + D\Delta A \Rightarrow$$

$$\frac{\partial A}{\partial t_m} = -A + \frac{\beta_A}{\mu} T_A(V) + D\frac{\partial^2 A}{\partial x^2}$$

Spatially homogeneous state

Low voltage state. If all neurons are in the low voltage state, V_- , $\Delta A = 0 \Rightarrow A$ reaches a stationary homogeneous state on the medium time scale.

$$A_- = \frac{\beta_A}{\mu} T_A(f(R, A_-, 0)),$$

where 0 means that $B = 0$ everywhere (no shot noise current).

In this state, the S production $G(V_-) \sim 0$ so there is no sAHP on the slow time scale.

Spatially homogeneous state

High voltage state. If all neurons are in the high voltage state, V_+ , $\Delta A = 0 \Rightarrow A$ reaches a stationary homogeneous state on the medium time scale.

$$A_+ = \frac{\beta_A}{\mu} T_A(f(R, A_+, B)).$$

Here, the state can be reached either due to shot noise or to Ach current.

In this state, the S production $G(V_+) \gg 0$ so there is an sAHP on the slow time scale.

Acetylcholine front propagation

Local perturbation of the low state. At some point x_0 we induce a shot noise current at time 0 ($B(x_0, 0) = 1$).

- This raises the voltage to its upper value V_+ .
- This increases the Ach production at x_0 .
- Ach diffuses to neighbours and induces an excitatory current.
- If g_A conductance is large enough this current raises the neighbours voltage to V_+ .
- This can lead to a propagating wave.

Under which conditions?

Acetylcholine front propagation

Moving frame:

$\xi = x - ct_m$ where c is a constant $\Rightarrow d\xi = dx - cdt_m$.

For a function $A(x, t_m) \equiv A(\xi)$ we have:

$$dA = \frac{\partial A}{\partial \xi} d\xi = \frac{\partial A}{\partial \xi} (dx - cdt_m) \Rightarrow$$

$$\frac{\partial A}{\partial x} = \frac{\partial A}{\partial \xi}; \quad ; \quad \frac{\partial^2 A}{\partial x^2} = \frac{\partial^2 A}{\partial \xi^2}; \quad \frac{\partial A}{\partial t_m} = -c \frac{\partial A}{\partial \xi}$$

$$-c \frac{\partial A}{\partial \xi} = -A + \frac{\beta_A}{\mu} T_A(f(R, A, B)) + D \frac{\partial^2 A}{\partial \xi^2}$$

Acetylcholine front propagation

Potential well: $\frac{\partial \mathcal{V}}{\partial A} = A - \frac{\beta_A}{\mu} T_A(f(R, A, B))$

$$\mathcal{V}(A) = \frac{A^2}{2} - \frac{\beta_A}{\mu} \int T_A(f(R, a, B)) da + K$$

Rest states: $\frac{\partial \mathcal{V}}{\partial A} = 0$.

Newton equation

$$D \frac{\partial^2 A}{\partial \xi^2} = -c \frac{\partial A}{\partial \xi} - \frac{\partial \mathcal{V}}{\partial A}.$$

We note $\frac{\partial A}{\partial \xi} \equiv \dot{A}$; $\frac{\partial A^2}{\partial \xi^2} \equiv \ddot{A}$

$$D \ddot{A} = -c \dot{A} - \frac{\partial \mathcal{V}}{\partial A}. \quad (5)$$

Acetylcholine front propagation

$$D\ddot{A} = -c\dot{A} - \frac{\partial \mathcal{V}}{\partial A}.$$

Formally, this is the equation of motion of a particle, with mass D , in a potential well \mathcal{V} , with a friction coefficient c .

\mathcal{V} has 3 extrema, given by $\frac{\partial \mathcal{V}}{\partial A} = A - \frac{\beta_A}{\mu} T_A(f(R, A, B)) = 0 \Rightarrow$:

$$A = \frac{\beta_A}{\mu} T_A(f(R, A, B))$$

These are the fixed points of the medium scale local dynamics ($\Delta A = 0$).

Maxima of \mathcal{V} correspond to stable fixed points.

Heteroclinic connection

Effect of sAHP

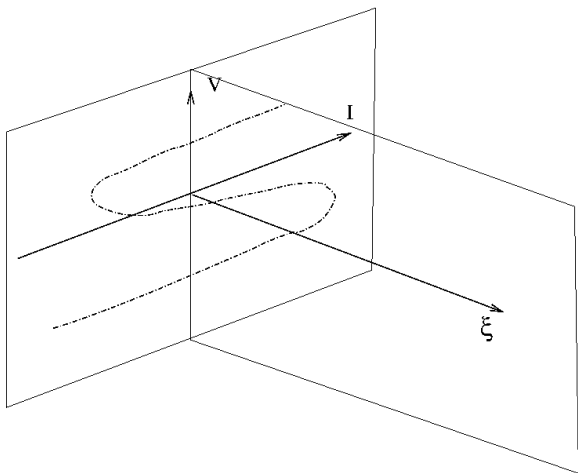


Figure: Bifurcation diagram in the space $I - V$.

Effect of sAHP

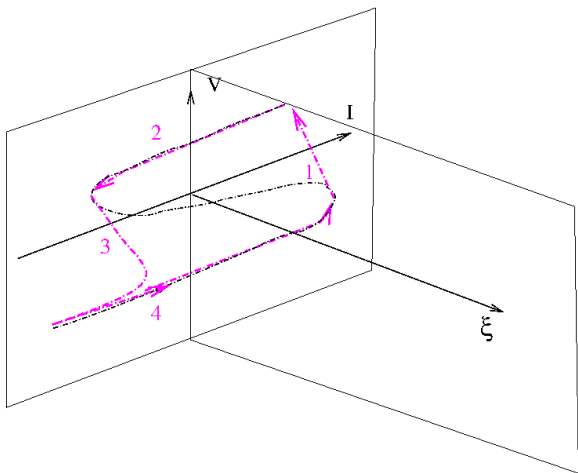


Figure: Trajectory in the space $I - V$.

Effect of sAHP

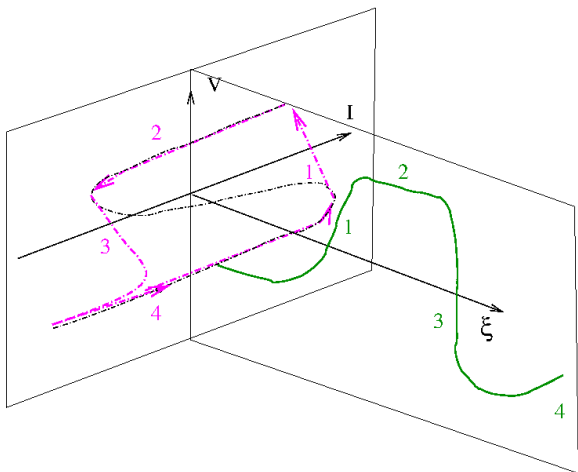


Figure: Pulse propagation.

Effect of sAHP

Time and space scales

- Ach raising and propagation, controlled by g_{ACh} and D (**Diffusion**);
- sAHP controlled by g_{sAHP} (**Local**);
- Time of excitation controlled by characteristic times and conductances;
- Time of propagation controlled by c depending on the other parameters.

⇒ Characteristic wave length depending on parameters.

Generalisations

Relaxing hypotheses

Main hypotheses:

- 1 Two state voltage.
- 2 Shot noise.
- 3 Simplified form for sAHP.
- 4 Ach diffusion.

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- 2 ~~Shot noise.~~ \Rightarrow Spontaneous bursting.
- 3 ~~Simplified form for sAHP.~~ Role of Ca ?
- 4 ~~Ach diffusion.~~ \Rightarrow Ach nicotinic coupling.

Ach nicotinic coupling

$$C_m \frac{dV_i}{dt} = -g_L(V_i - V_L) - g_C M_\infty(V_i)(V_i - V_C) - g_K N_i(V_i - V_K) \\ - G_{sAHP}(R_i)(V_i - V_K) - g_A(V_i - V_A) \sum_{k \in \mathcal{B}_i} U(A_k)$$

Coupling two bursting cells

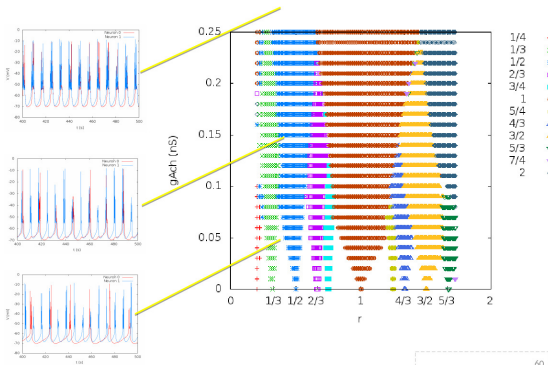
Karvouniari et al, ICMNS 2016

Figure: Synchronisation of two bursting cells.

Coupling N bursting cells

Karvouniari et al, ICMNS 2016

- There is a competition between 2 mechanisms:
 - Interburst variability which tends to desynchronise
 - Acetylcholine which tends to synchronise

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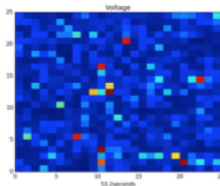
Karvouniari et al, ICMNS 2016

- There is a competition between 2 mechanisms:
 - Interburst 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

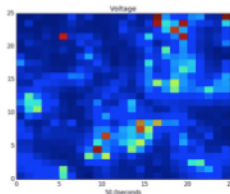
Spatio temporal patterns

Karvouniari et al, ICMNS 2016

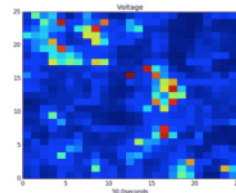
Isolated Neurons



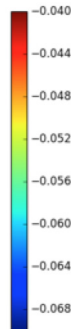
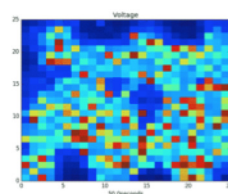
$g_{ach}=0.168$ nS



$g_{ach}=0.126$ nS

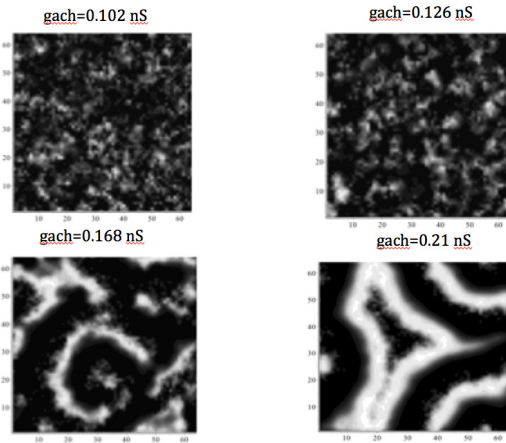


$g_{ach}=0.21$ nS



Spatio temporal patterns

Karvouniari et al, ICMNS 2016



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Figure:



Nearest neighbours interactions

- Neurons are located on a lattice with step a .
- A depends smoothly on coordinates.

$$\sum_{k \in \mathcal{B}_i} U(A_k) \sim 4U(A(x_i, y_i)) + a^2 \Delta U(A)$$

Non linear diffusion !

Conclusions

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- **More ??**

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- **More ??**
⇒ invite Dora as a speaker to the next LACONEU conference
.