A mathematical approach to retinal waves

Bruno Cessac, Dora Karvouniari

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Acknowledgement

L. Gil, INLN, Sophia Antipolis

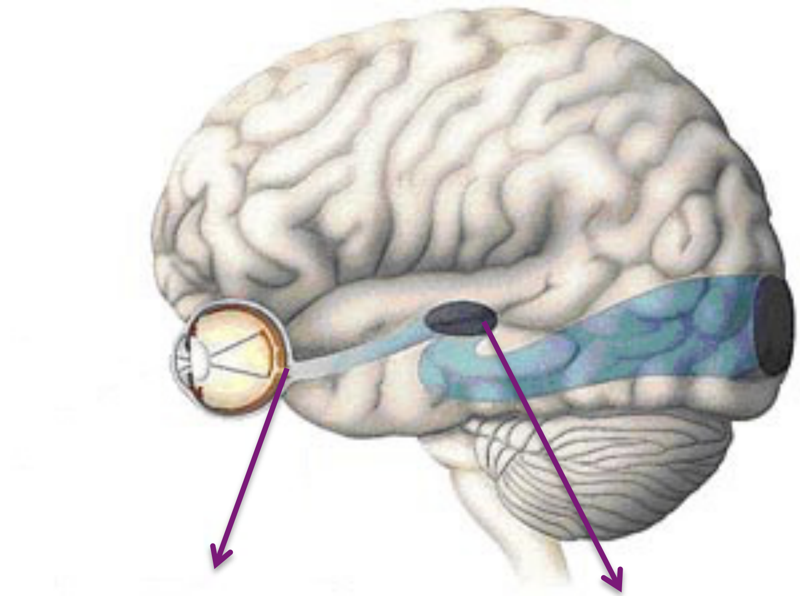
O. Marre, Institut de la Vision, Paris

S. Picaud, Institut de la Vision, Paris

Matthias Hennig, *University of Edinburgh*

Evelyne Sernagor, *Newcastle University*

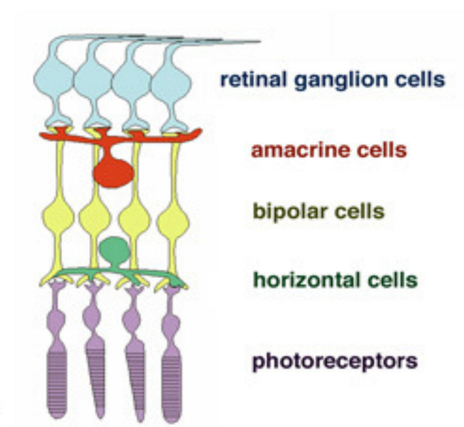
Visual system and retinal waves



Visual cortex

Retinal structure

LGN



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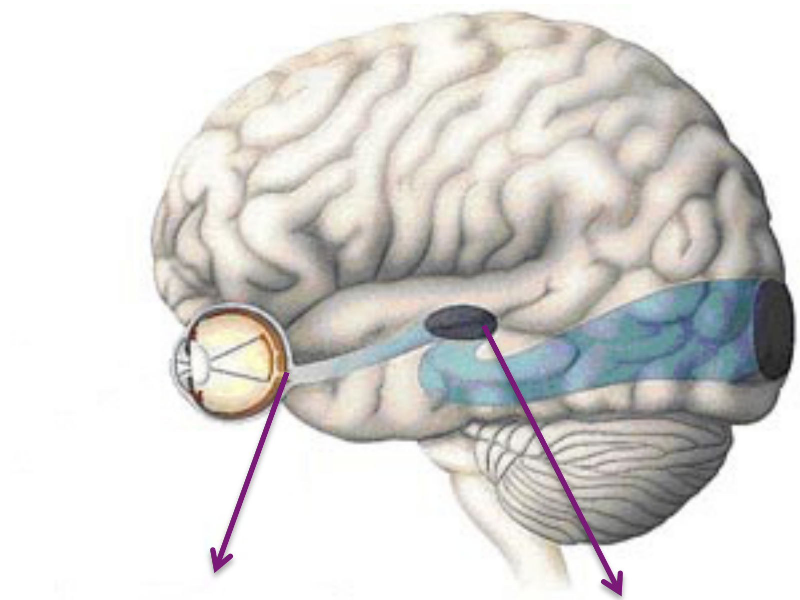
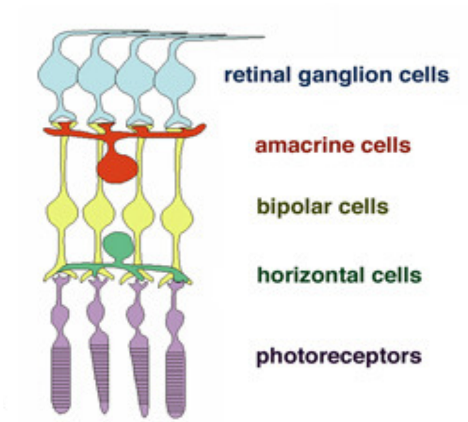




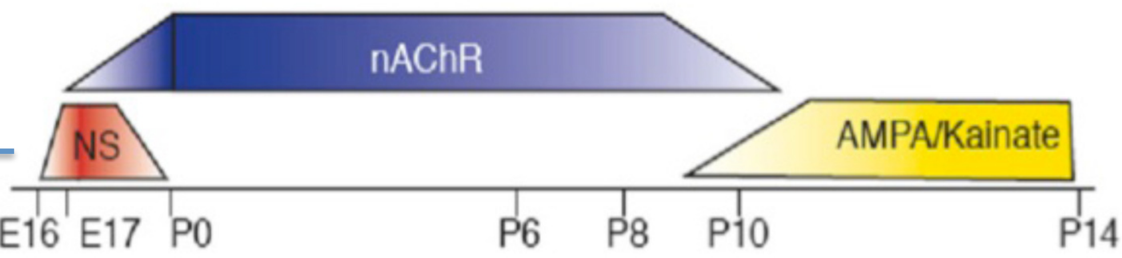
<u>Spontaneous</u> spatio-temporal ''waves'' during development

- Disappear short after birth

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

Stages of Retinal Waves During Development

Stage I

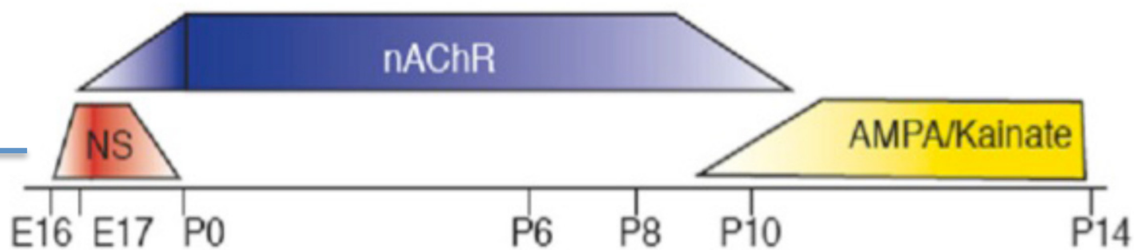


- Formation of retina circuitry
- Chemical synapses <u>not</u> formed yet
- Gap juction-mediated

Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)



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Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
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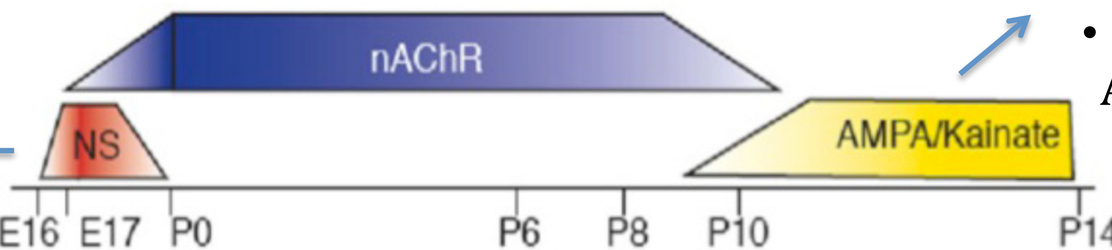
Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors



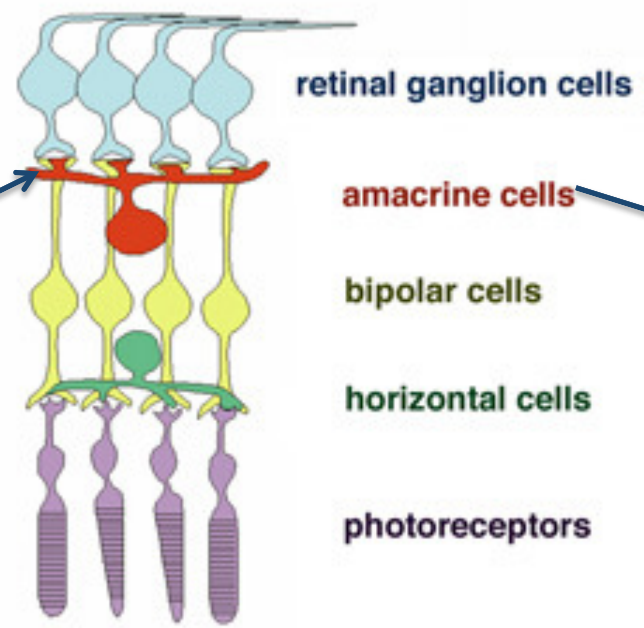
Stage I

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

Focus on stage II retinal waves

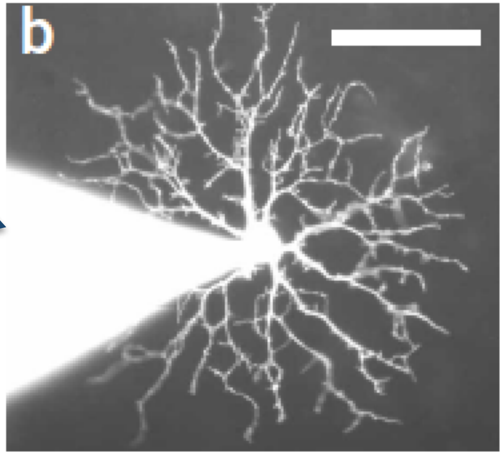
Stage II retinal waves are well studied experimentally and there is already existing work on their modelling

Stage II (cholinergic retinal waves)



groups.oist.jp/dnu/

Starburst Amacrine Cell (SAC)



Zheng et al. 2006

Goal of this lecture

Idea:

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

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

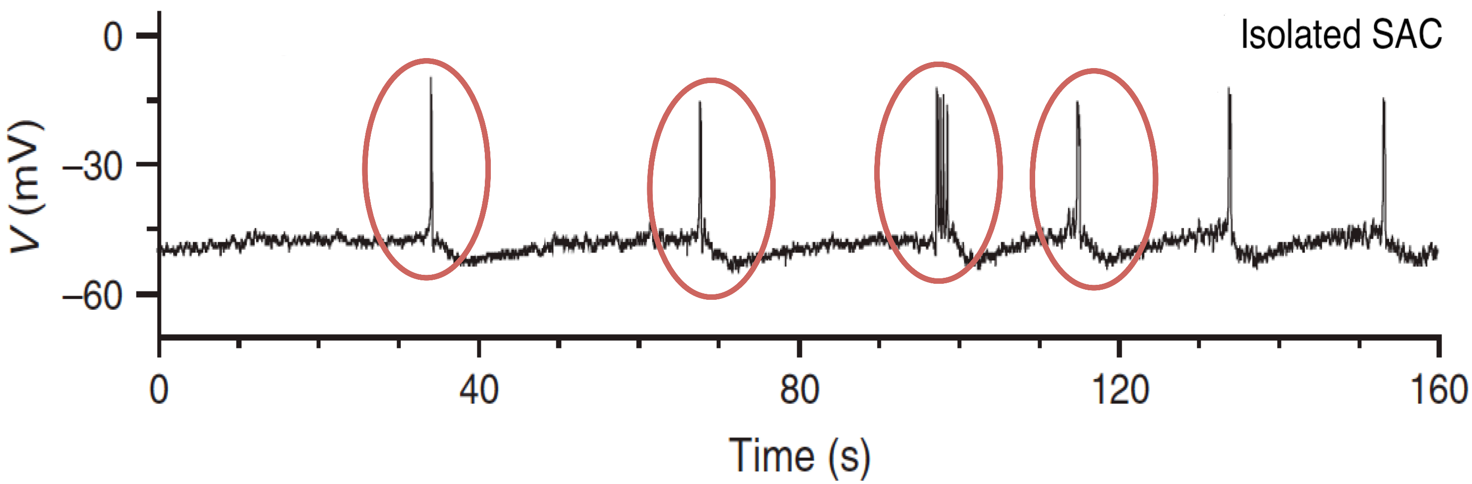
Motivation:

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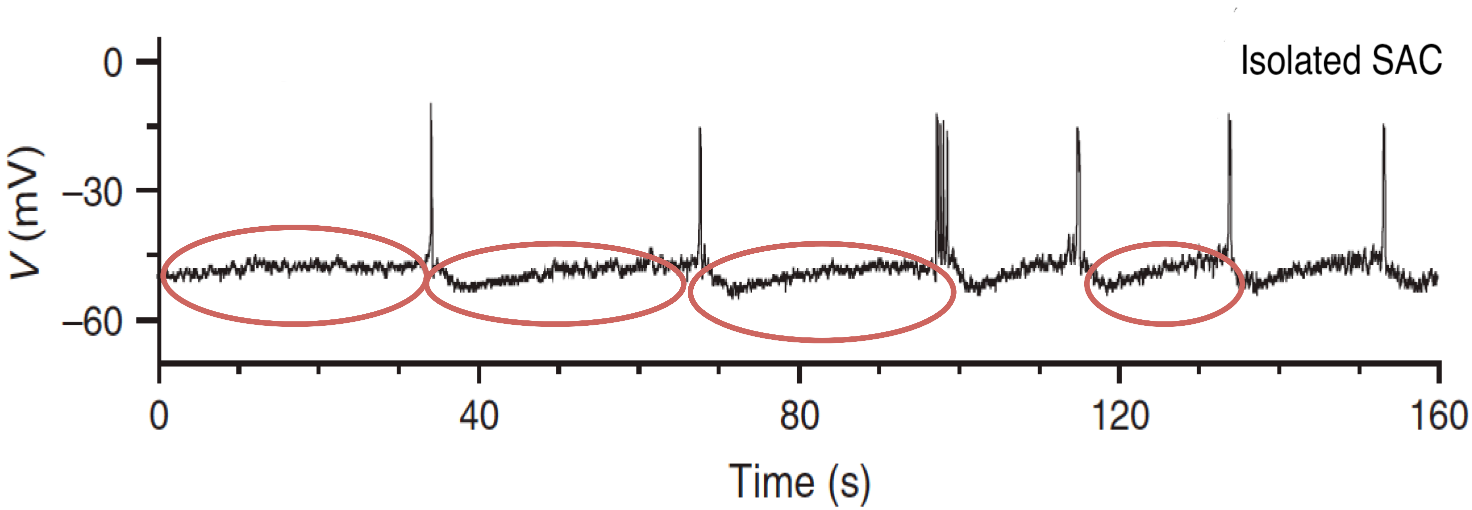
ii) Refractory mechanism (slow After HyperPolarisation- sAHP)



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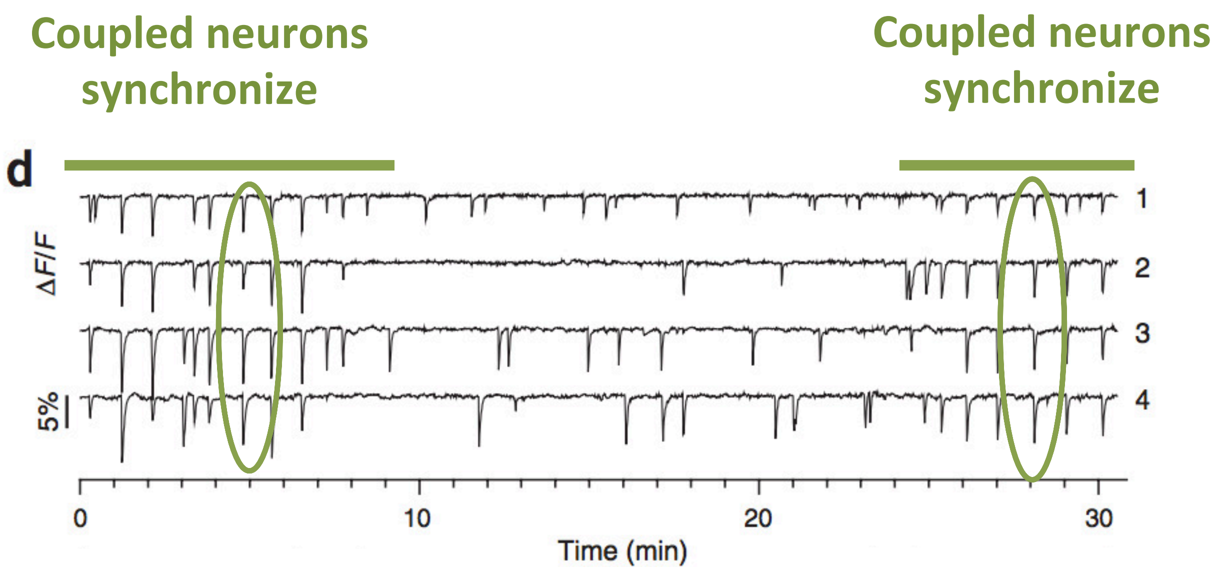

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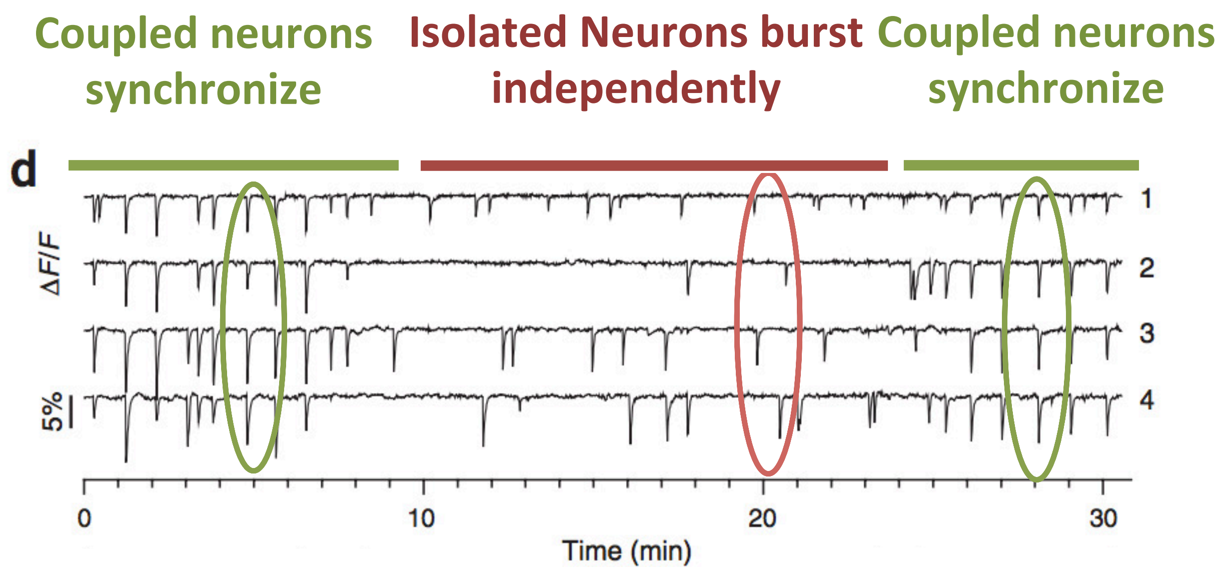

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Mathematical characterization of Retinal Waves

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

From biophysics to modelling

Biophysics of bursting SAC

Retinal waves require three components:

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

Biophysics of bursting SAC

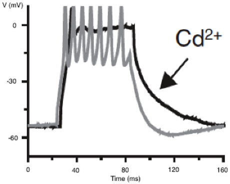


Figure: Zheng et al., Nature, 2006. Grey curve: Fast oscillations due to voltage-gated Ca^{+2} channels and Ca^{+2} dependent K^{+} channels. Black curve: Application of Cd^{+} blocking Ca^{+2} related channels.

Biophysics of bursting SAC

Morris-Lecar model with fast Potassium.

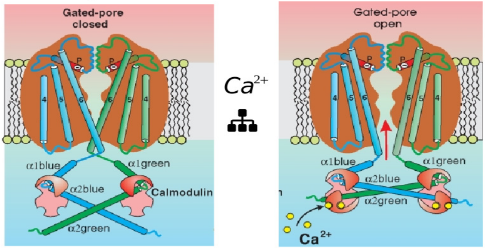
$$\begin{cases} C_m \frac{dV}{dt} & = & -g_L(V - V_L) - g_C M_\infty(V)(V - V_C) - g_K N(V - V_K) \\ & & +I_{ex}(\bullet) \\ & & \\ \tau_N \frac{dN}{dt} & = & \Lambda(V)(N_\infty(V) - N) \end{cases} \tag{1}$$

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)



Closed Open

Calcium gated potassium channel

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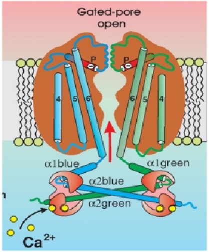
Biophysics of sAHP

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

$$I_{sAHP} = g^{m}_{sAHP} R^4 (V - V_K)$$ (Hennig et al. 2009)



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

Biophysics of sAHP

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

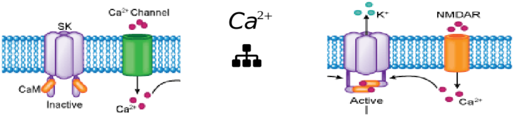
R : Probability that one terminal of the channel is open

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

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

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

Dynamics

$$
\left\{
\begin{array}{rcl}
C_m \frac{dV}{dt} & = & -g_L(V - V_L) - g_C M_\infty(V)(V - V_C) - g_K N(V - V_K) \\
 & & -\cancel{g_{sAHP} R^4}\, G_{sAHP}(R)(V - V_K) \\
\tau_N \frac{dN}{dt} & = & \Lambda(V)(N_\infty(V) - N) \\
\tau_C \frac{dC}{dt} & = & -\frac{H_X}{\alpha_C} C + C_0 - \delta_C g_C M_\infty(V)(V - V_C) \\
\tau_S \frac{dS}{dt} & = & \alpha_S (1 - S) C^4 - S \\
\tau_R \frac{dR}{dt} & = & \alpha_R S(1 - R) - R
\end{array}
\right.
\tag{3}
$$

Dynamics

Leak time scale: $\tau_L = \frac{C}{g_L}$.
Conductances rescaling: $\tilde{g}_X = \frac{g_X}{g_L}$.

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

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

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

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

Fast-scale

Set $\epsilon_X = \frac{\tau_L}{\tau_X}$, $X = C, R, S$.
$\epsilon_C = \frac{11}{2} \times 10^{-3} \sim 5.5 \times 10^{-3}, \quad \epsilon_S = \epsilon_R = \frac{11}{44} \times 10^{-3} \sim 2.5 \times 10^{-4}$

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

Fast-scale: approximation

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

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

Morris-Lecar model analysis

$$\begin{cases} \frac{dV}{dt_f} & = & -\tilde{g}_L(V - V_L) - \tilde{g}_C M_\infty(V)(V - V_C) - \tilde{g}_K N(V - V_K) \\ & & -\tilde{G}_{sAHP}(R)(V - V_K) \\ \\ \frac{dN}{dt_f} & = & \frac{\tau_L}{\tau_N}\Lambda(V)(N_\infty(V) - N) \end{cases} \tag{4}$$

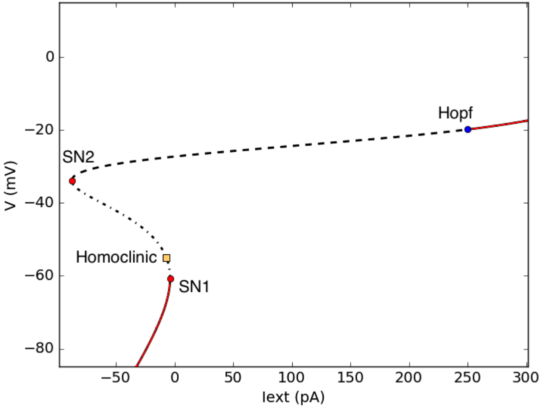
Morris-Lecar model analysis

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

Bifurcation analysis when varying the parameter I_{ext}.

Morris-Lecar model analysis

Karvouniari et al, submitted to Plos Comp. Bio.



The saddle-node bifurcation

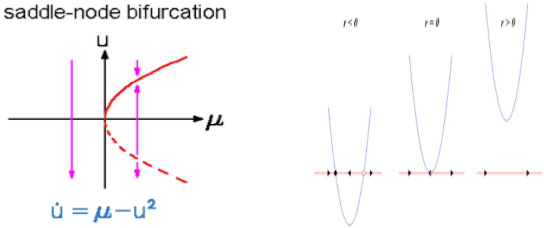


Figure: From https://elmer.unibas.ch/pendulum/bif.htm and https://it.wikipedia.org/wiki/Biforcazione_a_nodo_sella.

The Hopf bifurcation

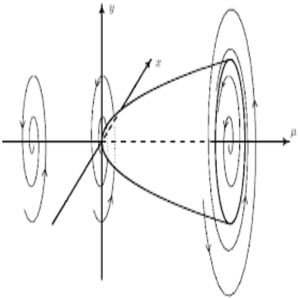


Figure: From Navarro et al, "Control of the Hopf bifurcation in the Takens-Bogdanov bifurcation", CDC2008

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The homoclinic bifurcation

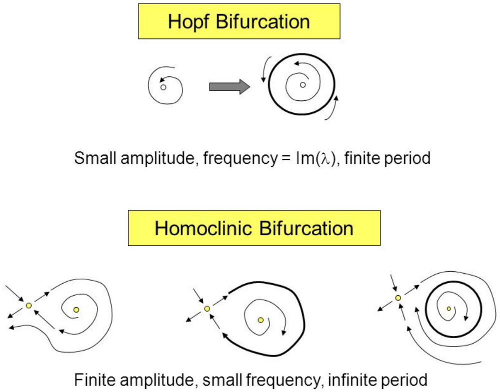
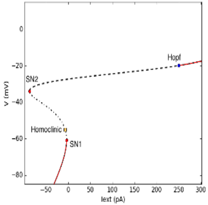
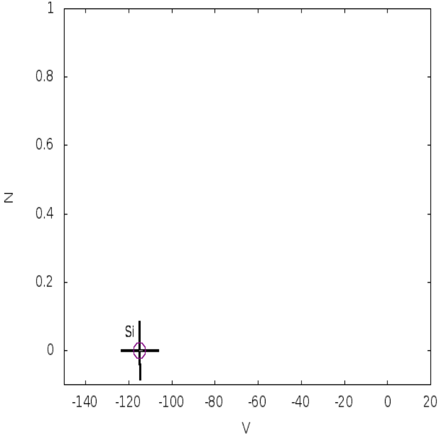


Figure: From J.Tyson,http://slideplayer.com/slide/8870556/

The complete movie

Karvouniari et al, ICMNS, 2016





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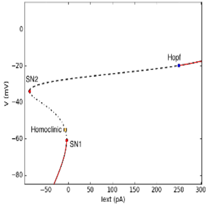

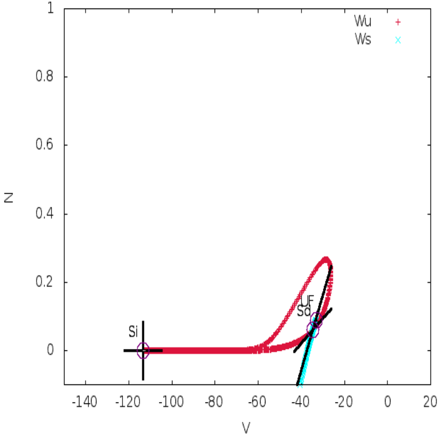

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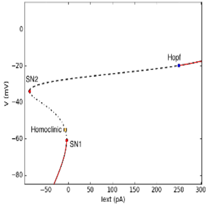

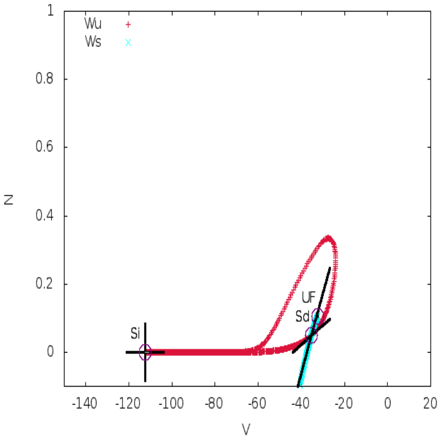

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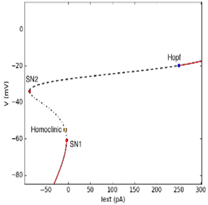

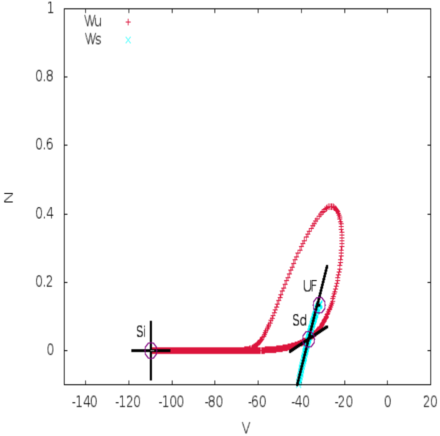

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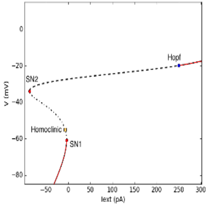

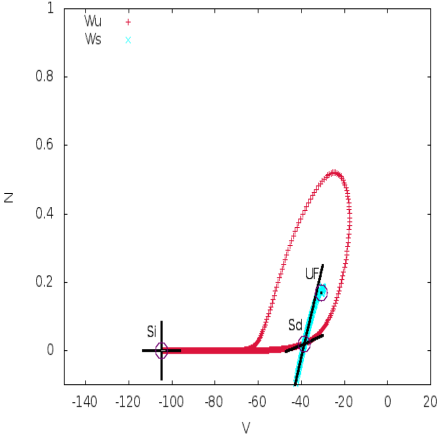

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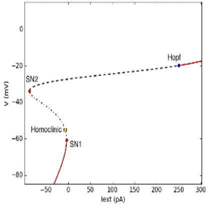

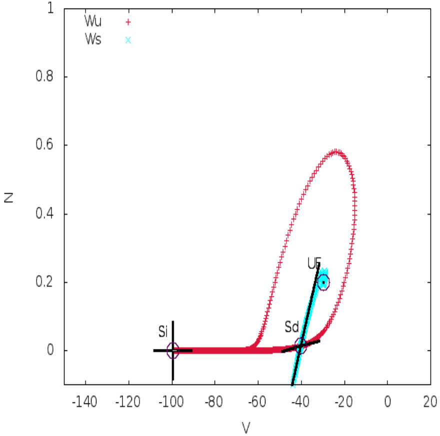

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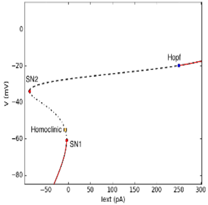
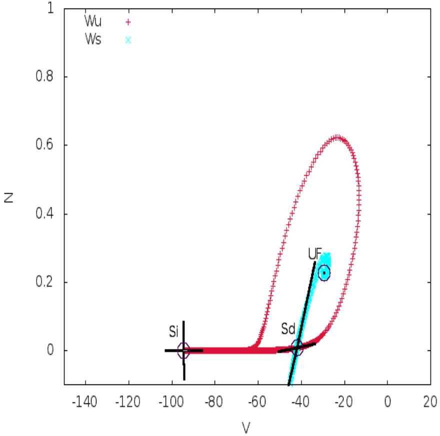
Karvouniari et al, submitted





The complete movie

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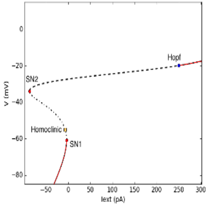

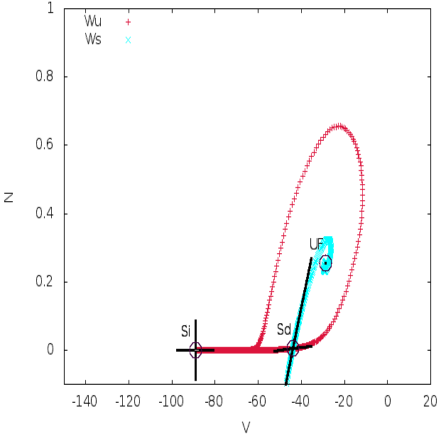

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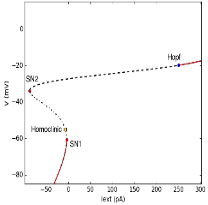

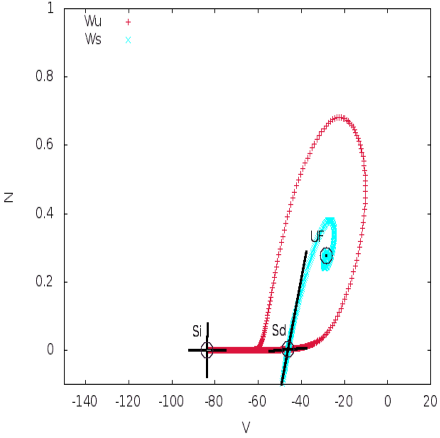

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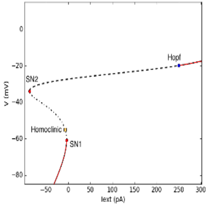

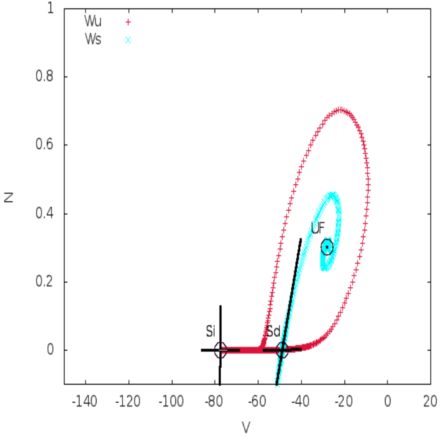

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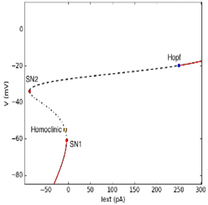

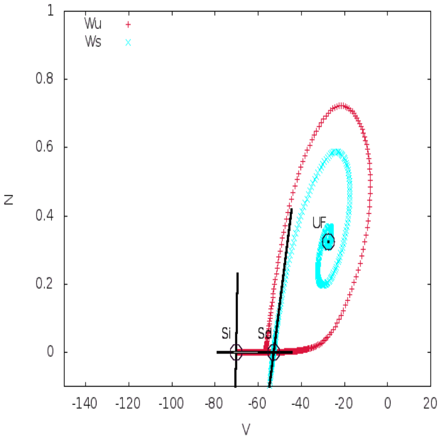

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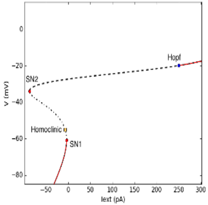

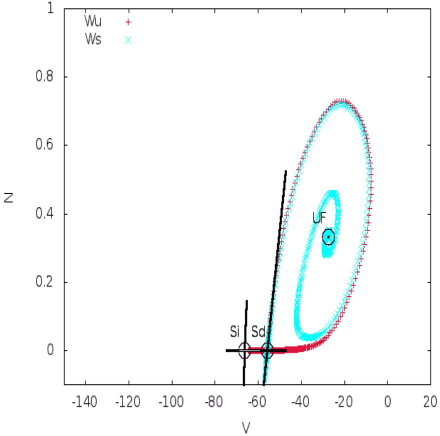

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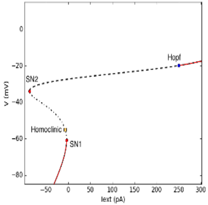

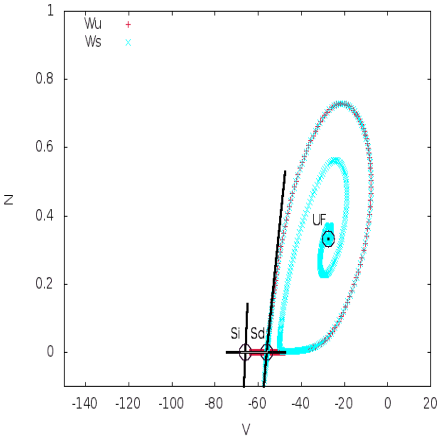

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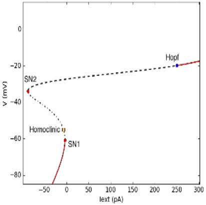

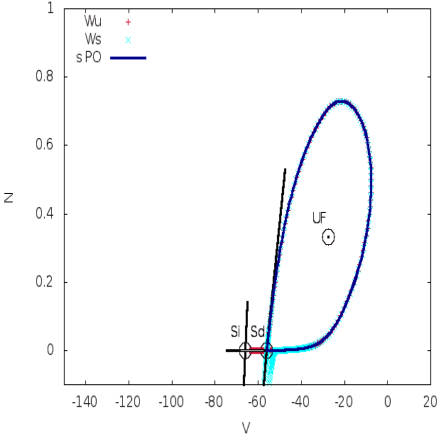

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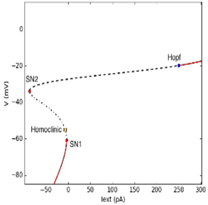

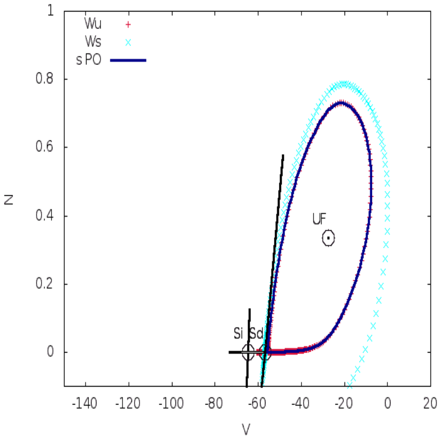

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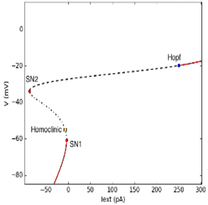

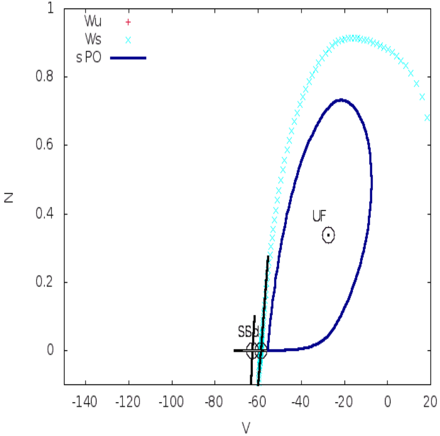

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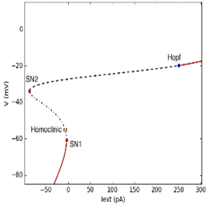

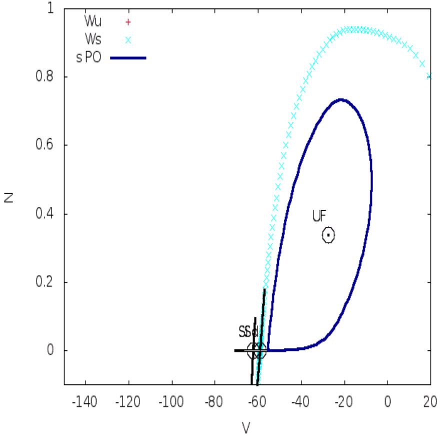

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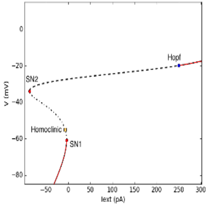

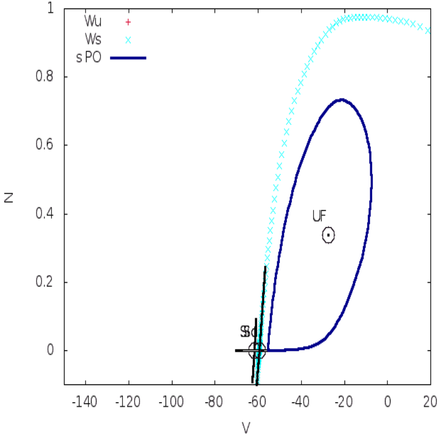

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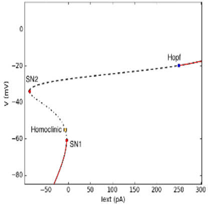

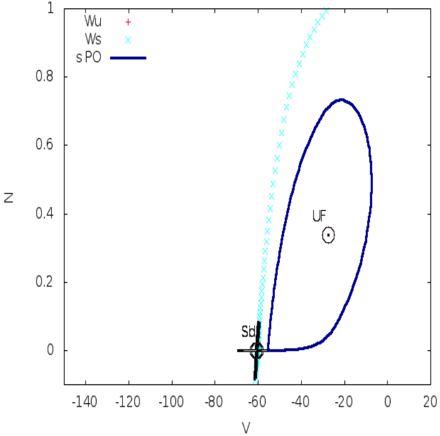

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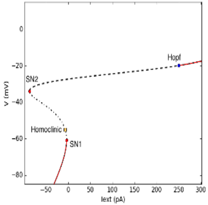

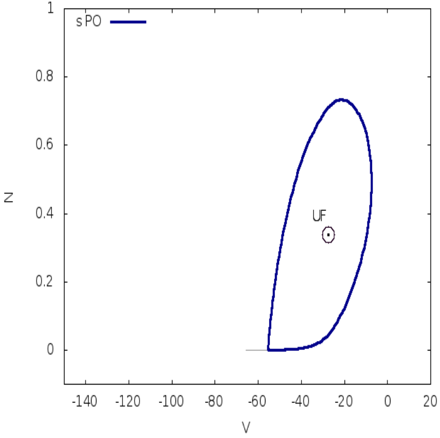

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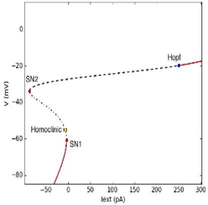

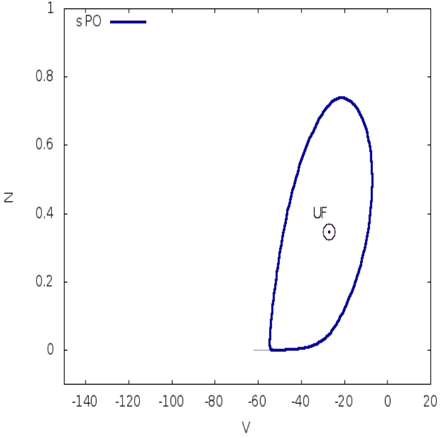

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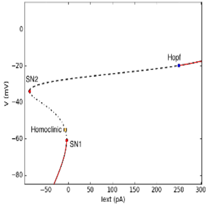

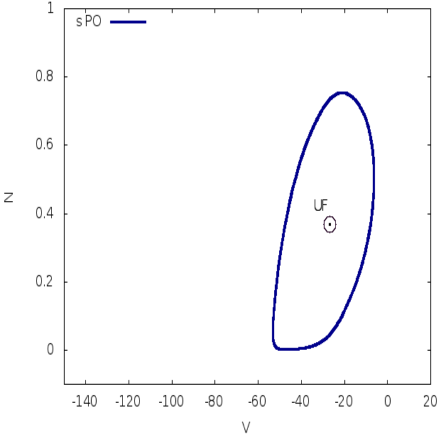

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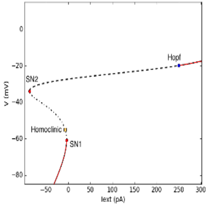

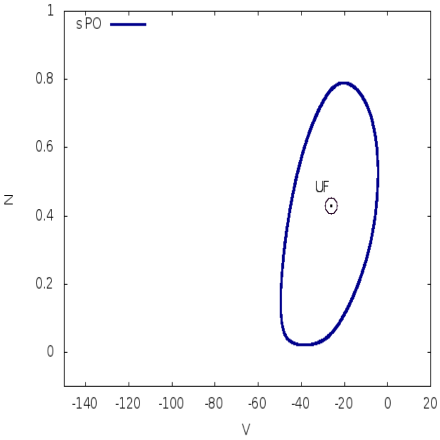

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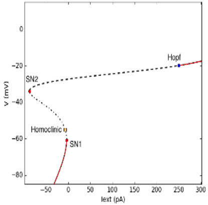

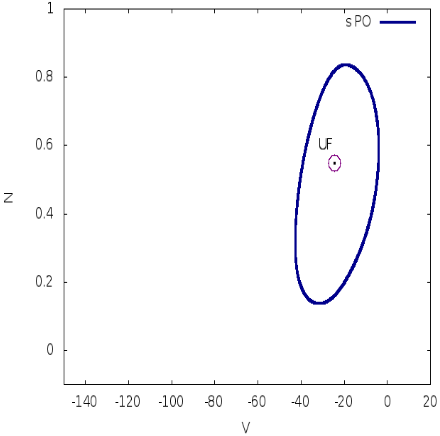

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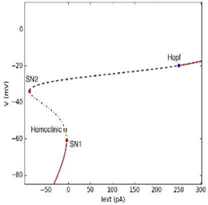

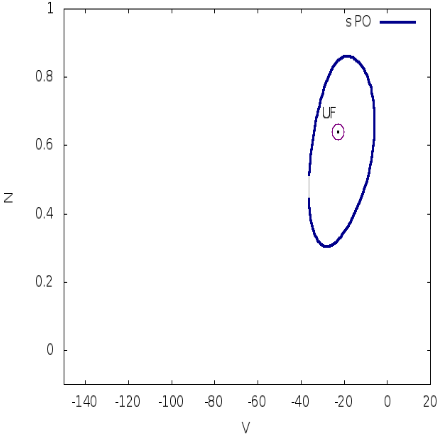

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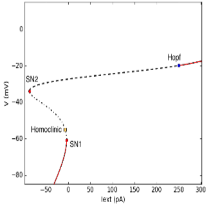

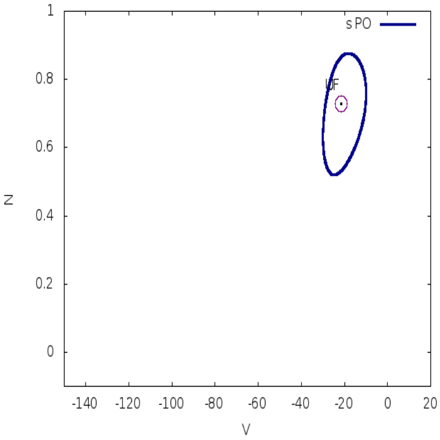

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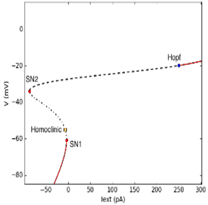

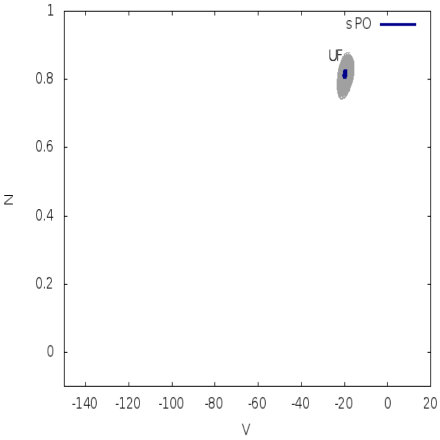

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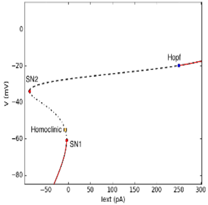

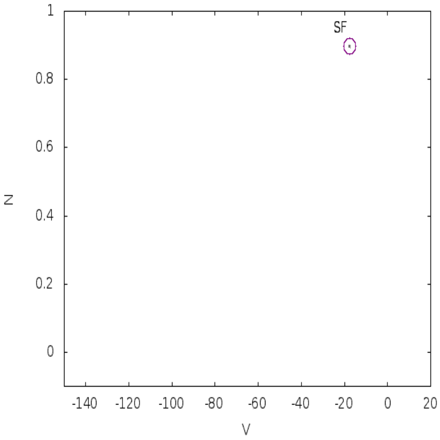

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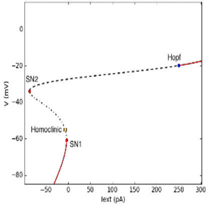

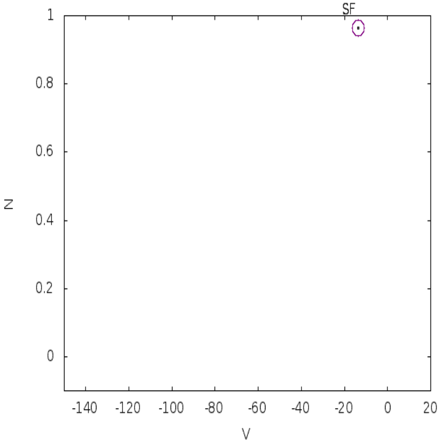

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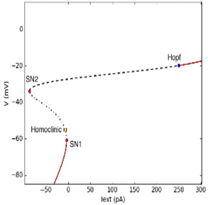

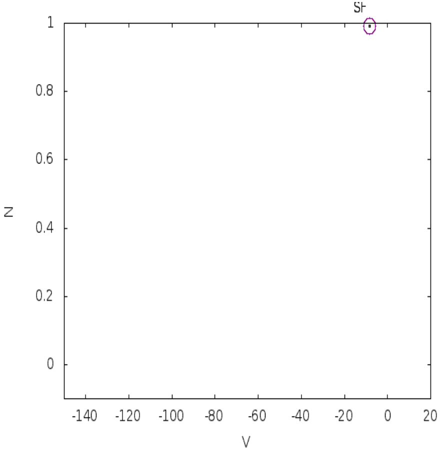

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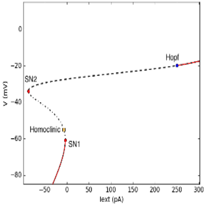

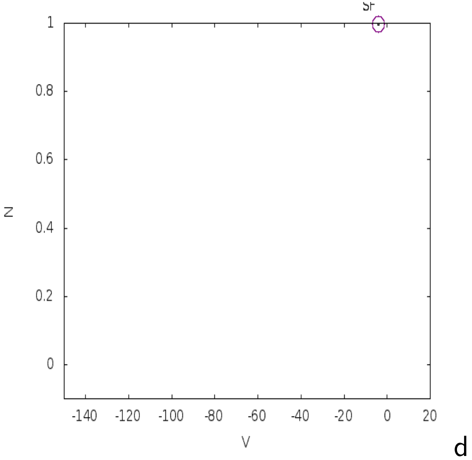

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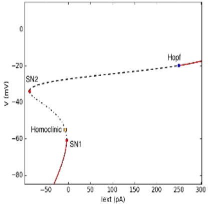

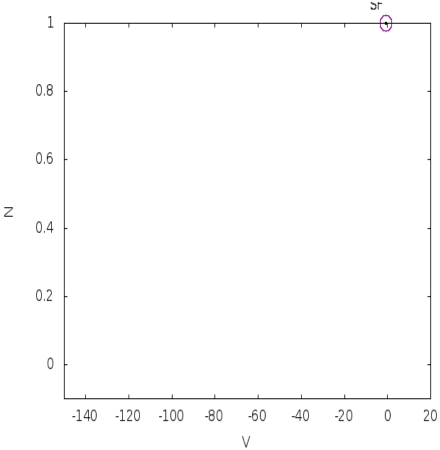

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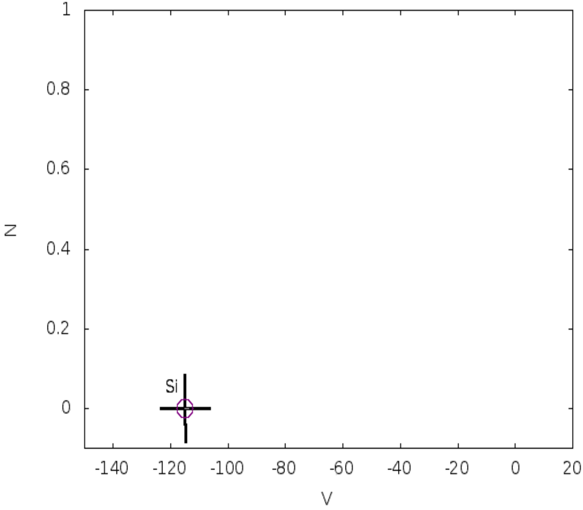


Back to Zhou experiment

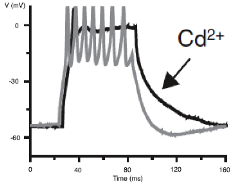
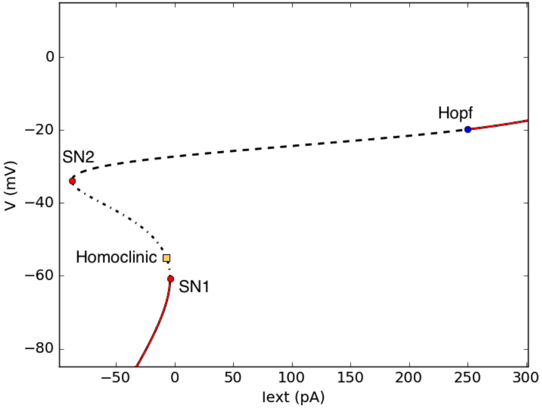


Figure: Zheng et al., Nature, 2006. Grey curve: Fast oscillations due to voltage-gated Ca^{+2} channels and Ca^{+2} dependent K^{+} channels. Black curve: Application of Cd^{+} blocking Ca^{+2} related channels.

Back to Zhou experiment

Karvouniari et al, submitted to Plos Comp. Bio.



Back to Zhou experiment

Karvouniari et al, submitted to Plos Comp. Bio.

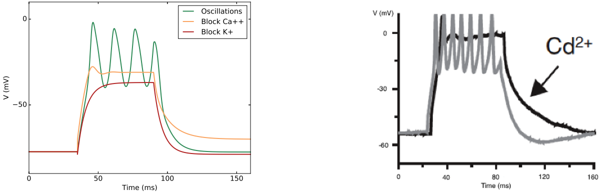


Figure: *Left. Green.* Application of a current step pulse of 150 pA for 60ms. *Orange*: Oscillations disappear when Ca^{+2} related conductances are set to zero. *Red.* Blocking the oscillations upon setting the voltage-gated $K+$ conductance to zero. *Right*: Zheng et al. 2006 experimental figure.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

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

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

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

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

Slow time-scale

$$\epsilon_V = \frac{\tau_L}{\tau_S} \sim 2.5 \times 10^{-4}, \quad \epsilon_N = \frac{\tau_N}{\tau_S} \sim 1 \times 10^{-3}$$
$$\epsilon_C = \frac{\tau_C}{\tau_S} \sim 4.5 \times 10^{-2}$$

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

Slow time-scale approximation

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

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.

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

Steady state

V follows "adiabatically" R.

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

Implicit function theorem.
Wherever $\frac{\partial f}{\partial V} \neq 1$ 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

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

Taking the differential gives:

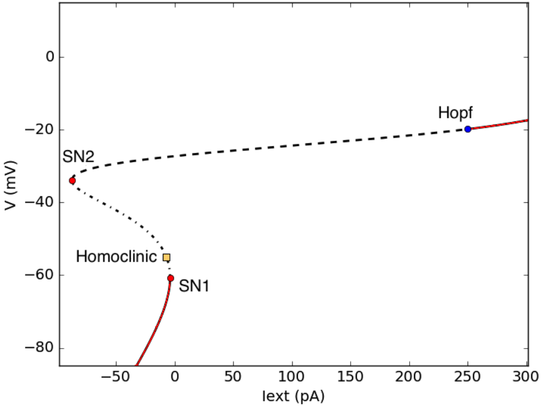
$$dV\left(1 - \frac{\partial f}{\partial V}\right) = \frac{\partial f}{\partial R}dR$$

$$\Rightarrow$$

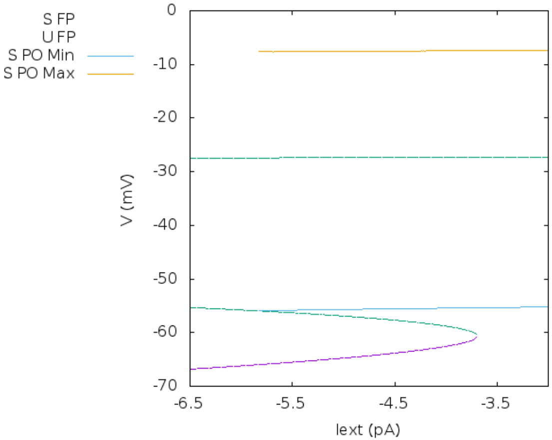
$$\frac{dV}{dR} = \frac{\frac{\partial f}{\partial R}}{1 - \frac{\partial f}{\partial V}}$$

Morris-Lecar model analysis

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



Morris-Lecar model analysis



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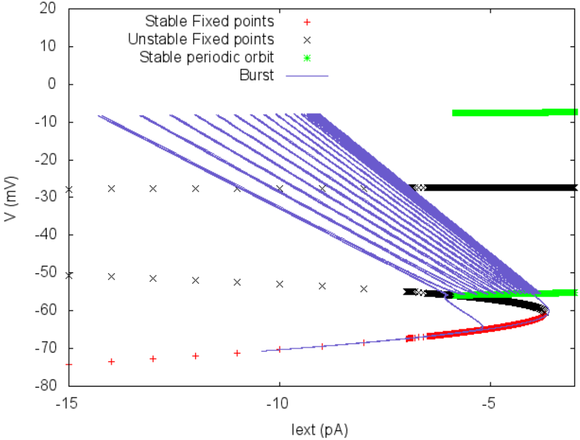

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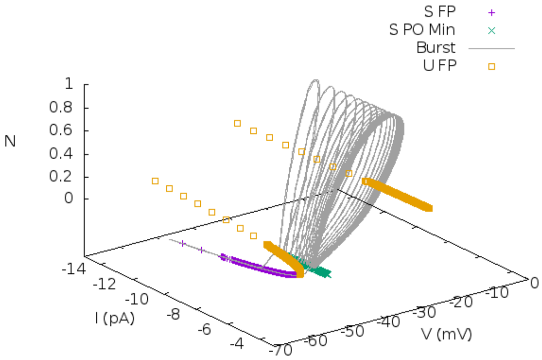
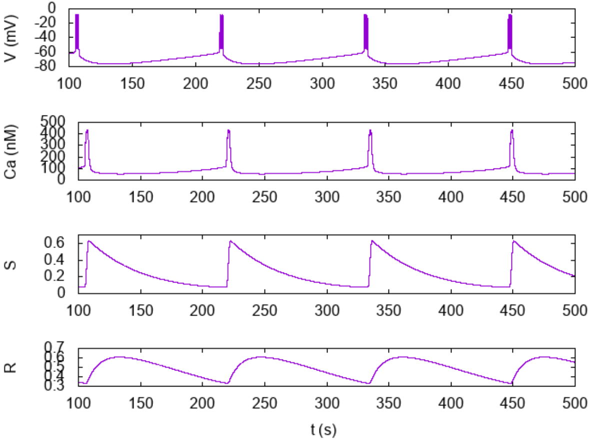
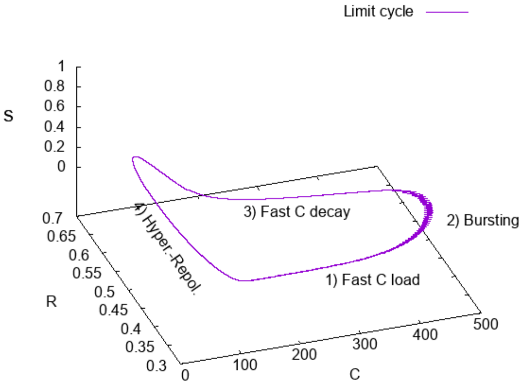


Complete dynamics

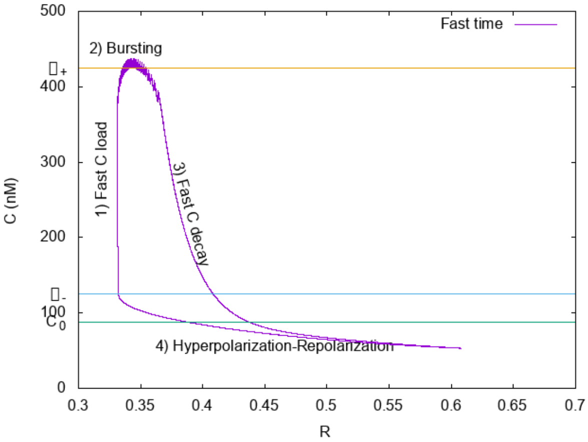
Complete dynamics



Medium and fast dynamics



Medium and fast dynamics



Medium-scale

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

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

Medium-scale

$$\epsilon_V = \frac{\tau_L}{\tau_C} \sim 5 \times 10^{-3}, \quad \epsilon_N = \frac{\tau_N}{\tau_C} \sim 2.5 \times 10^{-3}$$
$$\epsilon_S = \epsilon_R = \frac{\tau_C}{\tau_S} \sim 4.5 \times 10^{-2}$$

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

Medium-scale approximation

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

Medium-scale approximation

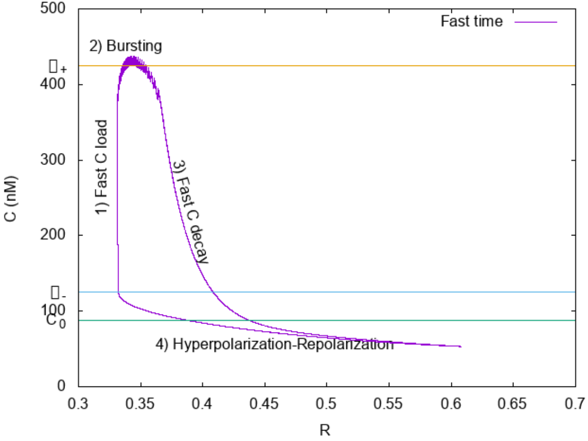
At this time scale:

- 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

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

"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.

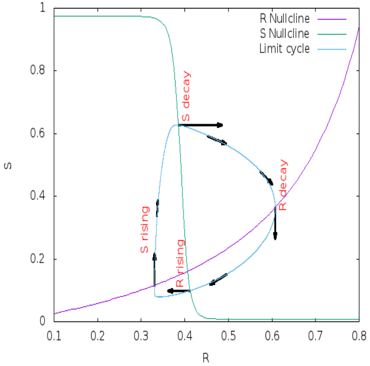
R Nullcline: $\frac{dR}{dt_s} = 0 \Rightarrow$

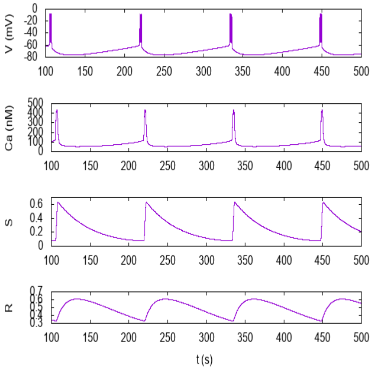
The vector field is vertical on the line $S = \frac{R}{\alpha_R(1-R)}$

S 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

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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

Bruno Cessac and Dora Karvouniari

Biovision Team, INRIA Sophia Antipolis,France.

15-01-2017

Coupling SACs with Acetylcholine

Coupling SACs with Acetylcholine

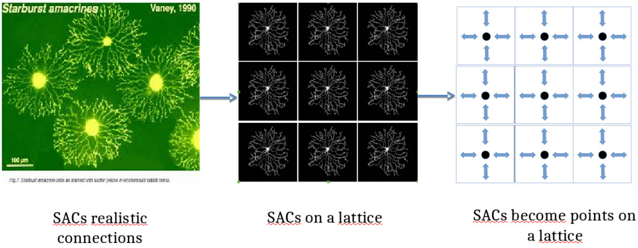


Figure: SACs network.

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

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

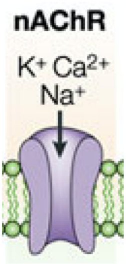
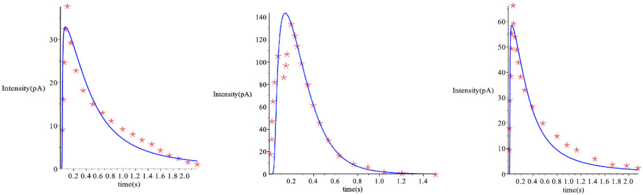


Figure: Nicotinic receptors and conductance.

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

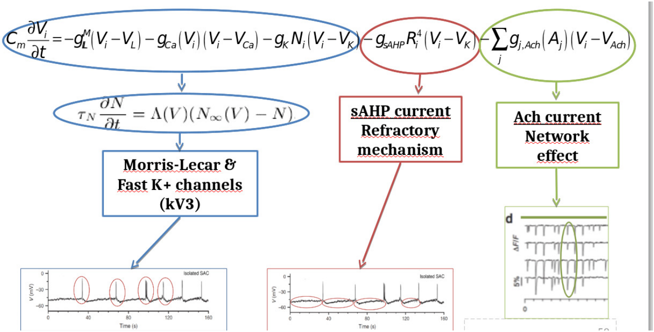


Figure: Equation of membrane potential.

Dynamical systems analysis

Main currents

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

sAHP conductance,

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

Ach synaptic conductance with:

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

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

Dynamics

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

Dynamics

Leak time scale: $\tau_L = \frac{C}{g_L}$. Ach time scale: $\tau_A = \frac{1}{\mu}$.
Conductances rescaling: $\tilde{g}_X = \frac{g_X}{g_L}$.

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

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 $Prob\,[\,B_i(s) = 1, s \in [t, t + dt\,] = pdt$, 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 $\Rightarrow \frac{d}{dt} \rightarrow \frac{\partial}{\partial t}$

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

Medium-scale

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

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

Medium-scale approximation

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

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 $G(V_+) >> 0$ 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:

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

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

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

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

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

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

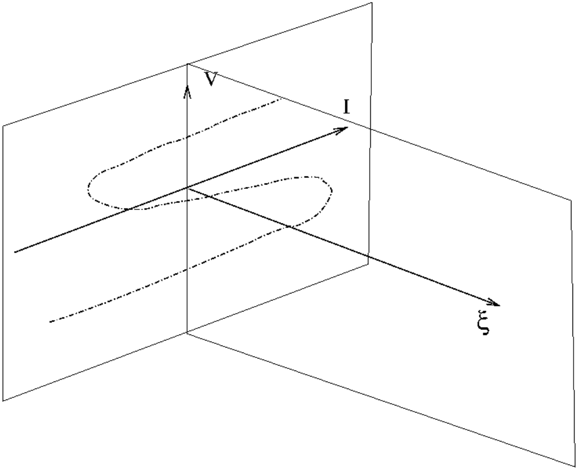


Figure: Bifurcation diagram in the space $I - V$.

Effect of sAHP

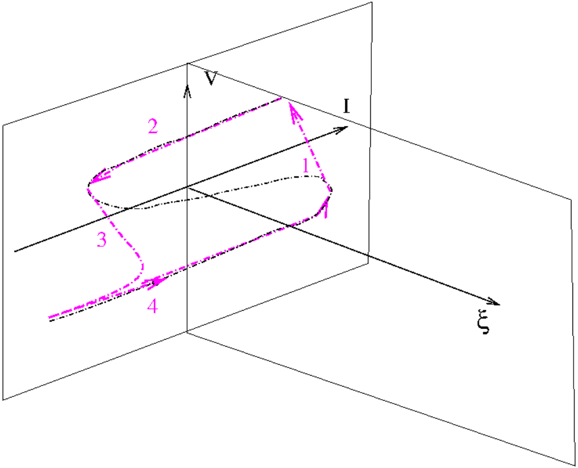


Figure: Trajectory in the space $I - V$.

Effect of sAHP

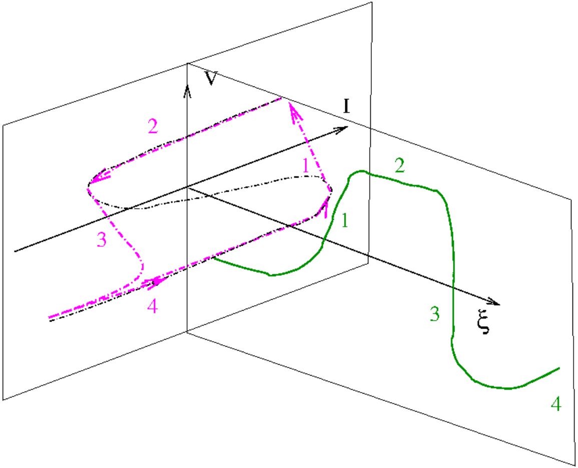


Figure: Pulse propagation.

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.

$\Rightarrow$ 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.

Relaxing hypotheses

Main hypotheses:

1. ~~Two state voltage.~~ $\Rightarrow$ Fast bursting in the high voltage state.
2. Shot noise.
3. Simplified form for sAHP.
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Relaxing hypotheses

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2. ~~Shot noise.~~ $\Rightarrow$ Spontaneous bursting.
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1. ~~Two state voltage.~~ $\Rightarrow$ Fast bursting in the high voltage state.
2. ~~Shot noise.~~ $\Rightarrow$ Spontaneous bursting.
3. ~~Simplified form for sAHP.~~ Role of Ca ?
4. Ach diffusion.

Relaxing hypotheses

Main hypotheses:

1. ~~Two state voltage.~~ $\Rightarrow$ Fast bursting in the high voltage state.
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

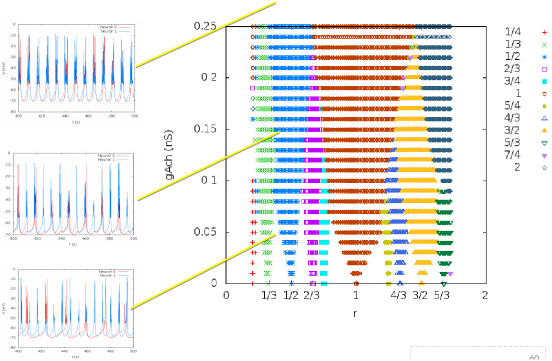

Figure: Synchronisation of two bursting cells.

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

Coupling N bursting cells

Karvouniari et al, ICMNS 2016

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- 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

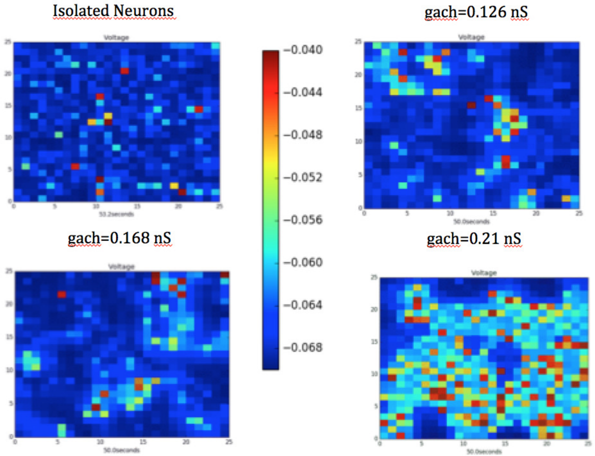

Figure:

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Karvouniari et al, ICMNS 2016

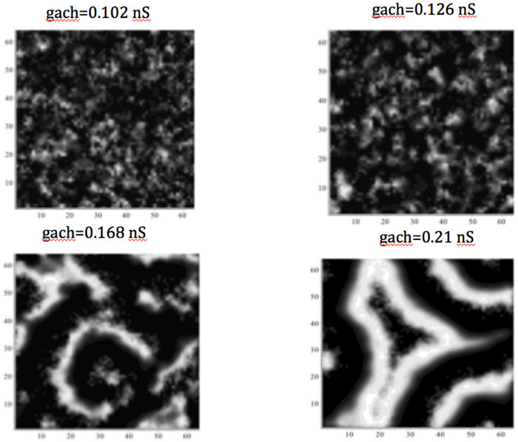

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Figure:

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 !

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$\Rightarrow$ invite Dora as a speaker to the next LACONEU conference

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