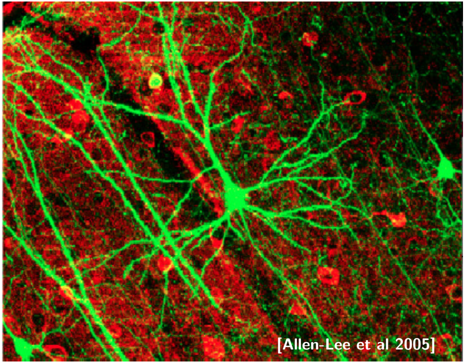
Inverse methods to estimate synaptic conductances with emphasis on non-smooth dynamical systems

Catalina Vich

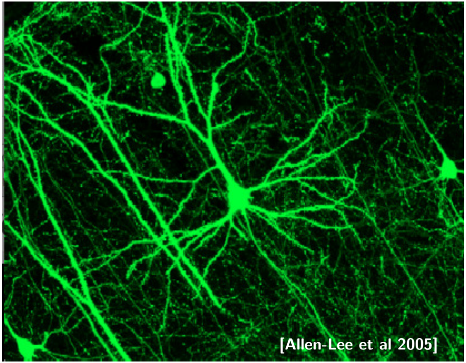
advisors: A. Guillamon (UPC), R. Prohens (UIB)

Ddays 2016

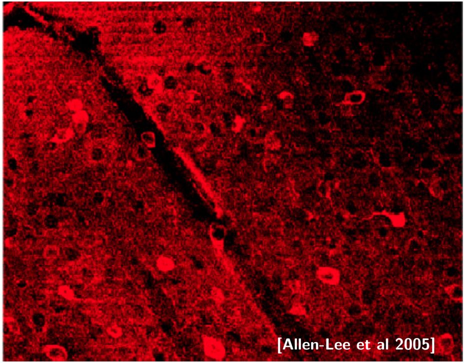
Brain's connectivity



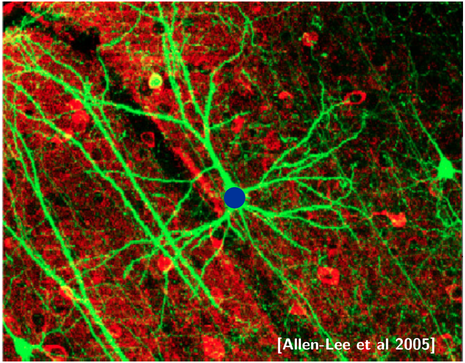
Excitatory neurons



Inhibitory neurons

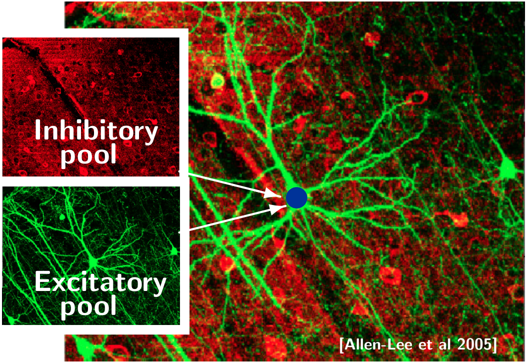


Target Neuron



Target Neuron

1. Synaptic currents

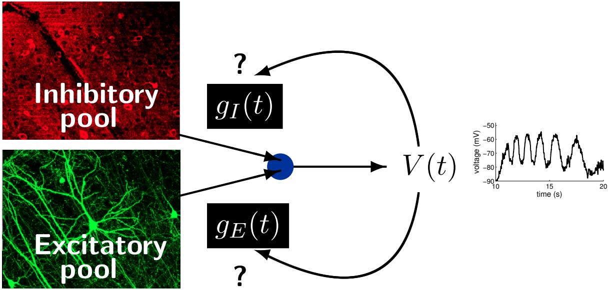


2. Ionic current

3. External current

Inverse problem

Given some observable, we aim at inferring the temporal contribution of the synaptic current and discerning global excitation from global inhibition arriving at a single cell.



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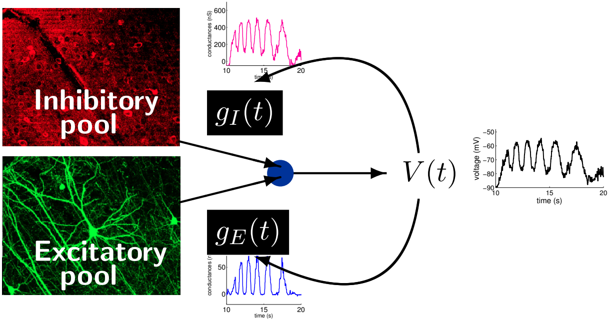


From the mathematical point of view

$$\begin{cases} C\dot{V} = f(V, \mathbf{w}) - I_{syn} + I_{app} \\ \dot{\mathbf{w}} = \mathbf{g}(V, \mathbf{w}), \quad \mathbf{w} \in \mathbb{R}^s \end{cases}$$

where

$I_{syn}(t) = g_E(t)(V(t) - V_E) + g_I(t)(V(t) - V_I)$: Synaptic input
$f(V, \mathbf{w})$: Ionic currents
I_{app}: Applied current

Main Question

How to estimate $g_E(t)$ and $g_I(t)$ given $V(t)$?

Drawbacks of the inverse methods

Nonlinearity: How to cope with the ionic currents $f(V, \mathbf{w})$ in this inverse problem?

Variability: Can we avoid repetitive trials? ($g_E(t)$ and $g_I(t)$ traces may vary across trials)

Model dependency: Can we perform model-free estimations?

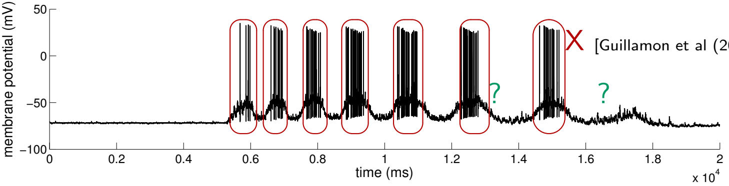
Noise: Experimental data is obtained with noise. Should it be considered?

Review of current strategies

- Model-independent strategies
  - Median Filtering + Linear estimation [Borg-Graham et al. (1998)], [Anderson et al. (2000)], [Wehr and Zador (2003)], ... **Multiple trials**
  - Oversampling method [Bédard et al. (2011)] **1 trial**
- Model-dependent strategies
  - Fokker-Planck equation approach [Rudolph and Destexhe (2003)] **2 trials**
  - Statistical inference methods [Paninsky et al. (2012)], [Lankarani et al. (2013)], [Berg and Ditlevsen (2013)],... **1 trial**

Ionic channel inactivity hypothesis

$$\begin{cases} C\dot{V} = \cancel{f(V,\mathbf{w})} - I_{syn} + I_{app} \\ \dot{\mathbf{w}} = \mathbf{g}(V,\mathbf{w}), \quad \mathbf{w} \in \mathbb{R}^n \end{cases}$$



[Guillamon et al (2006)]

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2. If misestimations in the subthreshold regime are relevant, can we provide new strategies to overcome such problem having also into account, as much as possible, the rest of obstacles of the inverse methods?

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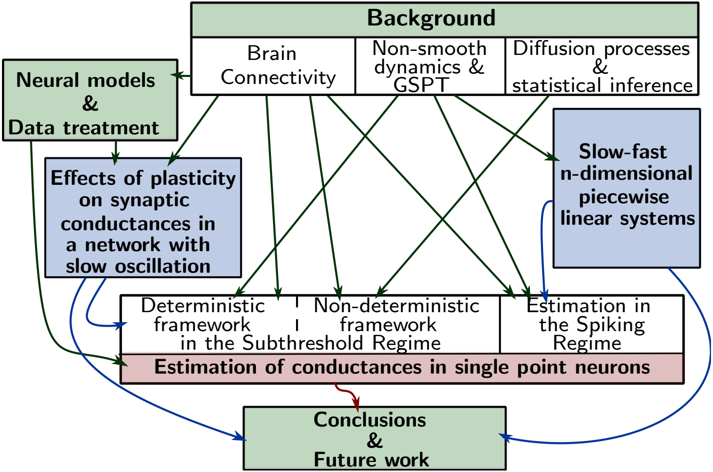
2. If misestimations in the subthreshold regime are relevant, can we provide new strategies to overcome such problem having also into account, as much as possible, the rest of obstacles of the inverse methods?
3. Can we also provide a first strategy to estimate conductances in those regimes where the target neuron presents an oscillatory behaviour?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Estimation of conductances in single point neurons
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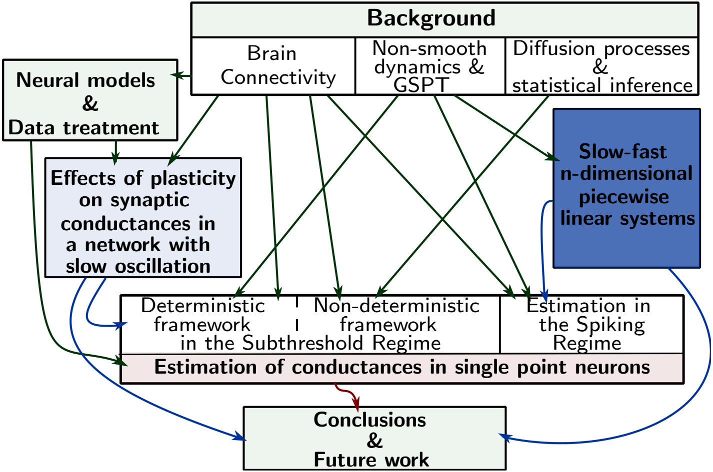
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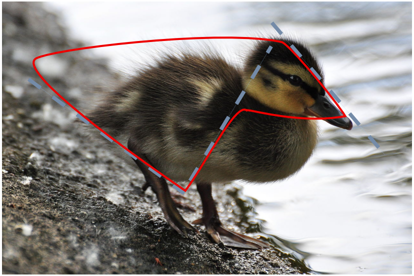
Understand slow-fast PWL systems. The Canard phenomena



[Prohens R., Teruel A. and Vich C. (2016), Journal of Differential Equations]

Model

$$\dot{\mathbf{u}} = \frac{d\mathbf{u}}{dt} = \varepsilon \mathbf{g}(\mathbf{u}, v), \qquad \dot{v} = \frac{dv}{dt} = f(\mathbf{u}, v).$$

$\mathbf{u} \in \mathbb{R}^s$ slow variable
$v \in \mathbb{R}$ fast variable

$0 < \varepsilon \ll 1$ ratio of time scales
$n = s + 1$ system dimension

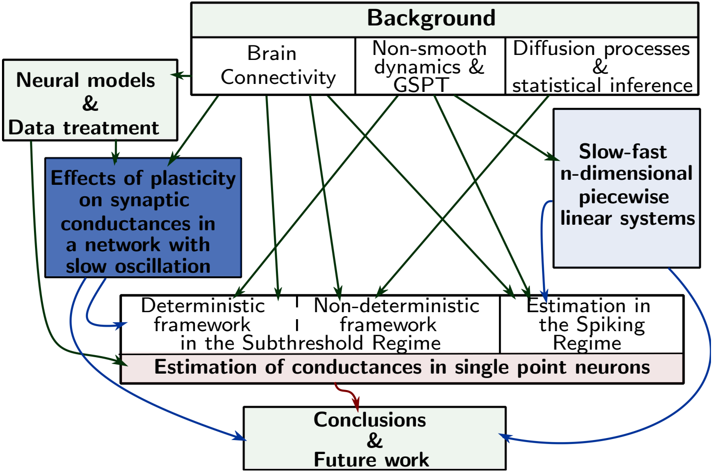
$$\begin{cases} \mathbf{g}(\mathbf{u}, v) = A\mathbf{u} + \mathbf{a}v + \mathbf{b} \\ f(\mathbf{u}, v) = u_1 + |v| \end{cases}$$

where
$A = (a_{ij})_{1 \le i,j \le s}$ $s \times s$ real matrix
$\mathbf{a} = (a_1, a_2, \ldots, a_s)^T$ vector in $\mathbb{R}^s$
$\mathbf{b} = (b_1, b_2, \ldots, b_s)^T$ vector in $\mathbb{R}^s$

Main results of this Chapter:

Theorem

- *Unperturbed and Perturbed Dynamics* $\rightarrow$ *Fenichel's like theorem*
- *Necessary and Sufficient conditions for the existence of Maximal Canard Orbits (Uniqueness)*
- *Source of Maximal Canard Orbits (from the unperturbed system to the perturbed one)*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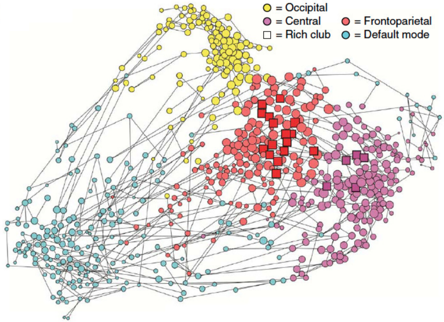
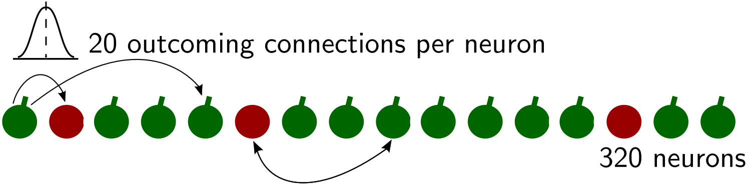
Understand brain connectivity



[C. Vich, P. Massobrio, A. Guillamon, work in progress]

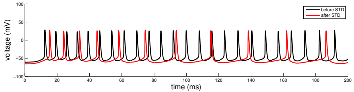


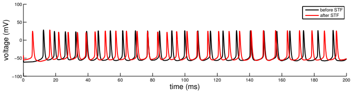
20% inhibitory neurons: 1 compartment

80% excitatory neurons: 2 compartments

Short term depression (STD) effects: $P_{rel} \leftarrow f_D \, P_{rel}$

Short term facilitation (STF) effects: $P_{rel} \leftarrow f_F(1 - P_{rel})$



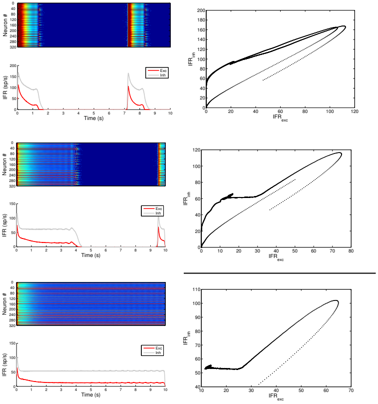


[Compte et al 2003] and [Benita et al 2012]

On the dynamics of the network

Effects of the STD

$f_D > f_D^*$

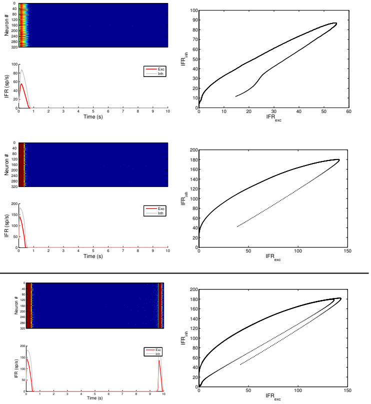


f_D^* —

$f_D < f_D^*$

Effects of the STF

$f_F < f_F^*$

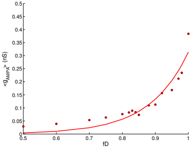


f_F^*

$f_F > f_F^*$

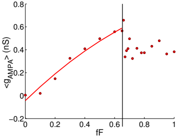
On the synaptic conductances

Effects of the STD

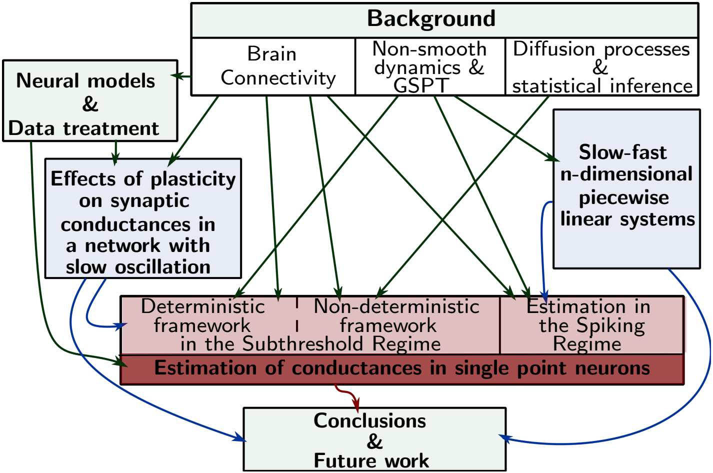


Conductances follow an **exponential** curve

Effects of the STF



Conductances follow a **parabolic** curve below f_F^*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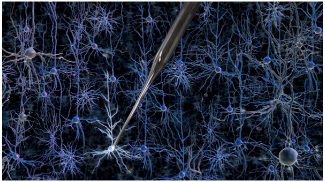
Problem of the Synaptic Conductances Estimation



Estimation of conductances in the subthreshold regime

- Are the subthreshold-activated ionic currents causing misestimations in this regime?
- In this case, can we provide new strategies to overcome the problem?

[Vich C. and Guillamon A. (2015), Journal of Computational Neuroscience]

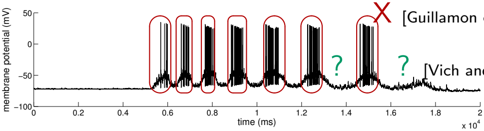
[Vich C., Berg R., Ditlevsen S., and Guillamon A. (2016), submitted]

Ionic channel inactivity hypothesis

$$\begin{cases} C\dot{v} = \cancel{f(v,\mathbf{w})} - I_{syn} + I_{app} \\ \dot{\mathbf{w}} = h(v,\mathbf{w}), \quad \mathbf{w} \in \mathbb{R}^n \end{cases}$$

Quadratic Ionic channel activity hypothesis

$$\begin{cases} C\dot{v} = av^2 - w - I_{syn} + I_{app} \\ \dot{w} = h(v,w). \end{cases}$$



[Guillamon et al (2006)]

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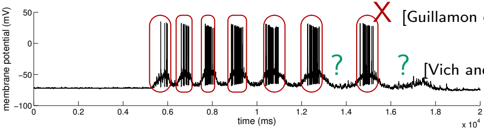
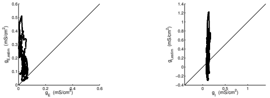


[Guillamon et al (2006)]

[Vich and Guillamon (2015)]

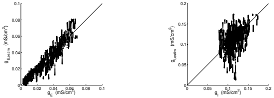
With subthreshold ionic currents

- inactive: They Do
- active: They Do Not



With subthreshold ionic currents

- active: It Does



Avoiding Multiple Trials + Considering noise

[Vich C., Berg R., Ditlevsen S., and Guillamon A. (2016), Preprint submitted]

We consider the stochastic version of the **Quadratic Integrate and Fire (QIF) model**

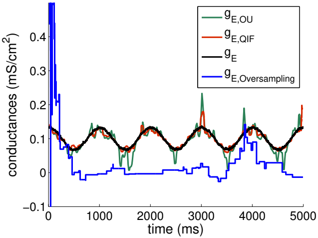
$$
\begin{aligned}
C\frac{dV}{dt} &= \alpha\,(V(t)-V_T)^2 - I_E(t) - I_I(t) - I_T + I_{app} + \eta(t) \\
I_E(t) &= g_E(t)\,(V(t)-V_E)\,, \\
I_I(t) &= g_I(t)\,(V(t)-V_I)
\end{aligned}
$$

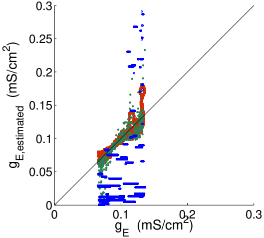
Procedure

Using a recursive process based on the Maximum Likelihood Estimator inside a time window W, we compute $\hat{\alpha}$, $\hat{g}_E(t)$ and $\hat{g}_I(t)$

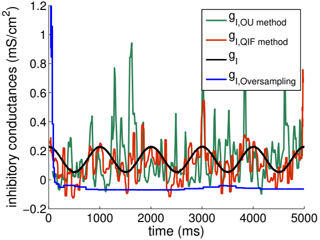
Results of the comparison

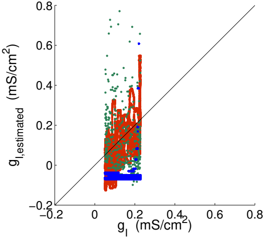
Excitatory conductance





Inhibitory conductance

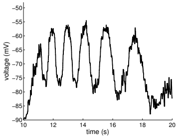




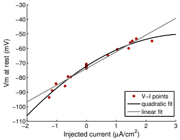
Experimental data results

Intracellular recordings in current-clamp mode of spinal motoneurons of red-eared turtles [Prof. R. Berg].

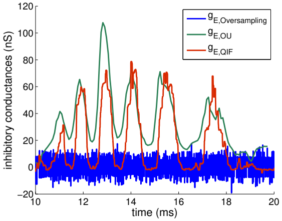
membrane potential



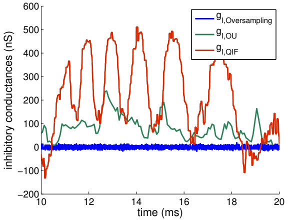
V-I curve



$g_E(t)$



$g_I(t)$



Estimation of conductances in the spiking regime

- Can we also provide a first strategy to estimate conductances in those regimes where the target neuron presents an oscillatory behaviour?

[Guillamon A., Prohens R., Teruel A.E. and Vich C. (2016), preprint submitted]

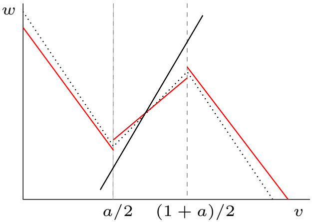
We consider a version of the McKean model given by

$$\begin{cases} C\dot{v} = f(v) - w - w_0 + I_{syn} - I_{syn}(v), \\ \dot{w} = v - \gamma w - v_0, \end{cases}$$

where

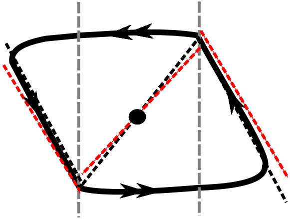
$$I_{syn}(v) = g_{syn}(v - V_{syn})$$

$$f(v) = \begin{cases} -v & v < a/2, \\ v - a & a/2 \leq v \leq (1+a)/2, \\ 1 - v & v > (1+a)/2. \end{cases}$$



Aim

We want to find an expression of the period T of the periodic orbit as a function of g_{syn} and I, i.e. $T(I, g_{syn})$.



Some approximations have been done by [Coombes (2001)], [Fernández-García et al (2015)]

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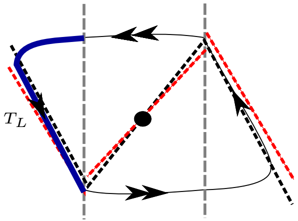

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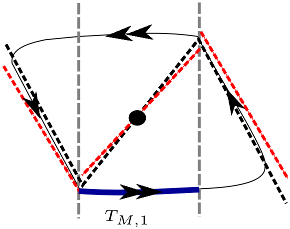

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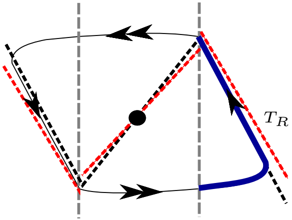

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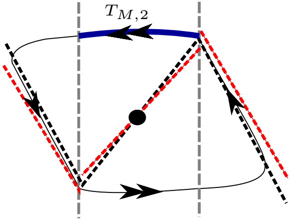
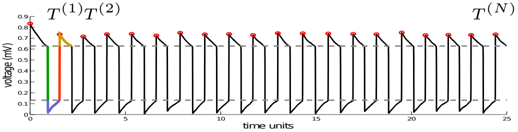


Procedure

Solving $\hat{T}(I^*, g_{syn}) = T^*$, we estimate g_{syn}

Estimation procedure for $g_{syn}(t)$:

1. Given $v(t)$ for an specific I^* such that the neuron oscillates, extract a sequence of times $\{T_i^{(k)}\}_{k=1}^N$ such that

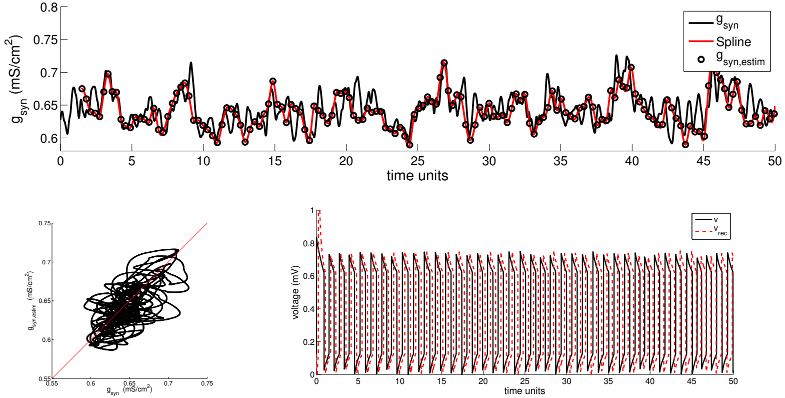


$$\underbrace{\{T_R^{(1)},\ T_{M,1}^{(1)},\ T_L^{(1)},\ T_{M,2}^{(1)},}_{T^{(1)}}\ \ldots\ \underbrace{T_R^{(N)},\ T_{M,1}^{(N)},\ T_L^{(N)},\ T_{M,2}^{(N)}\}}_{T^{(N)}}$$

2. Solve $\hat{T}(I^*, g_{syn}^{(k)}) = T^{(k)}$, for each $T^{(k)}$, to find $g_{syn}^{(k)}$.

3. Interpolate $(t^{(k)}, g_{syn}^{(k)})$ and obtain $\hat{g}_{syn}(t)$.

Results using prescribed conductances from a V1 computational network [Tao et al (2004)]



Conclusions

In the preliminar chapters...

- We have studied Slow-fast n-dimensional systems by using geometric singular perturbation theory.
- We gave necessary and sufficient conditions to ensure the existence of Maximal Canard Orbits
- The effects caused by the Short Term Plasticity (both depression and facilitation)

In the subthreshold regime...

- Subthreshold ionic currents can cause misestimations on the estimation of conductances.
- Solutions, in both deterministic and stochastic frameworks, have been obtained by considering second order approximations.

In the spiking regime...

- A proof-of concept to estimate synaptic conductances in the deterministic case has been obtained.

Acknowledgements



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your attention