Revisiting the hypoelliptic stochastic FitzHugh-Nagumo model

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Joint work with

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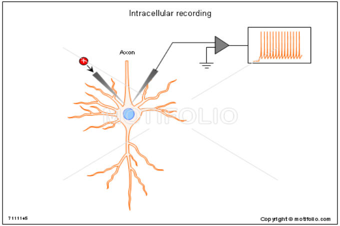
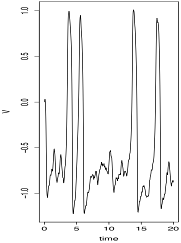
The hypoelliptic Fitzhugh-Nagumo model

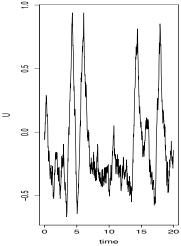
[Lindner et al 1999, Gerstner and Kistler, 2002, Lindner et al 2004, Berglund and Gentz, 2006]

$$
\begin{aligned}
dV_t &= \frac{1}{\varepsilon}(V_t - V_t^3 - C_t - s)dt, \\
dC_t &= (\gamma V_t - C_t + \beta)\, dt + \tilde{\sigma} dB_t,
\end{aligned}
$$

- V_t membrane potential of a single neuron
- C_t recovery variable / channel kinetics
- ε time scale separation
- s stimulus input, β position of the fixed point, γ duration of excitation
- B_t Brownian motion, $\tilde{\sigma}$ diffusion coefficient







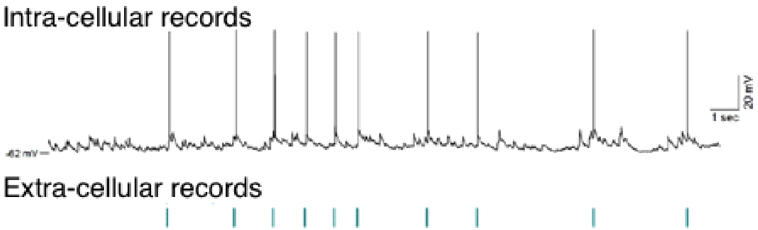
Where do hypoelliptic models come from ?

They appear as limit of

- Extra-cellular records modeling
- Intra-cellular records modeling

Objectives of the models

- Prediction of spike emission
- Estimation/identification



Extracellular stochastic models

Hawkes intensity [Ditlevsen, Locherbach, 2016]

- Population of n neurons
- $N_i(t)$ number of spikes emitted by neuron i during $[0, t]$, for $i = 1, \ldots, n$
- $N_i(t)$ follows a nonlinear Hawkes process with intensity

$$\lambda_i(t) = f\left(\sum_{j=1}^{n} \int_{]0,t]} h_{ij}(t-s)dN_j(s)\right)$$

  - $\lambda_i(t)$ is a stochastic process, depending on the whole history before time t
  - f is the spiking rate function
  - h_{ij} is a synaptic weight function describing the influence of neuron j on neuron i

- $V_i(t) = \int_{]0,t]} h(t-s)dN_i(s)$ membrane potential

Systems of interacting neurons

- All neurons behave in the same way: $h_{ij} = \frac{1}{n} h$
  - Intensity of neuron i

$$\lambda_i(t) = f\left(\frac{1}{n}\sum_{j=1}^{n}\int_{]0,t]} h(t-s)dN_j(s)\right)$$

  - All neurons have an influence on neuron i

- Mean field limit
  - Total number of neurons $n \to \infty$

$$\frac{1}{n}\sum_{j=1}^{n} dN_j(s) \to d\mathbb{E}(\bar{N}(s))$$

where $\bar{N}$ is the counting process of a typical neuron

Memory of the system [Ditlevsen, Locherbach, 2016]

- Hawkes processes are truly infinite memory processes
- Developing the memory
  - Erlang kernel with short memory

$$h(t) = c\, t\, e^{-\nu\, t}$$

$$h'(t) = -\nu h(t) + c\, e^{-\nu\, t} =: -\nu h(t) + h_1(t)$$

with

$$h_1'(t) = -\nu h_1(t)$$

- In terms of the intensity process: $\lambda(t) = f(V_t)$ with (V_t) the membrane potential:

$$V(t) := \int_{]0,t]} h(t-s)d\bar{N}(s)$$

and

$$U(t) = \int_{]0,t]} h_1(t-s)d\bar{N}(s)$$

- **Associated Piecewise Deterministic Markov Process (PDMP)**:

$$\begin{aligned} dV_t &= -\nu V_t dt + dC_t \\ dC_t &= -\nu C_t dt + cd\bar{N}(t) \end{aligned}$$

Diffusion approximation

- Diffusion approximation of the jump process $\bar{N}(t) = \frac{1}{n}\sum_{i=1}^{n} N_i(t)$ gives

$$
\begin{aligned}
dV_t &= (-\nu V_t + C_t)\, dt \\
dC_t &= (-\nu C_t + c\, f(V_t))\, dt + \frac{c}{\sqrt{n}}\sqrt{f(V_t)} dB_t
\end{aligned}
$$

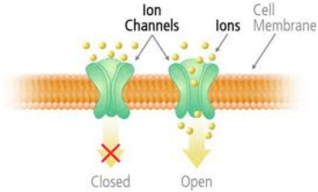
- Diffusion of dimension 2 driven by only one Brownian motion

Hypoellitic diffusion

Another hypoelliptic model for intracellular neuronal data

Deterministic Morris-Lecar neuronal model

- Calcium, potassium, leakage ionic currents
- g_{Ca}, g_K, g_L maximal conductances
- V_{Ca}, V_K, V_L reversal potential
- I input current
- C_t proportion of opened potassium channels
- Functions α and β: opening and closing rates



$$\frac{dV_t}{dt} = -g_{Ca} m_\infty(V_t)(V_t - V_{C_a}) - g_K C_t (V_t - V_K) - g_L(V_t - V_L) + I$$

$$\frac{dC_t}{dt} = \alpha(V_t)(1 - C_t) - \beta(V_t) C_t$$

Stochastic Morris-Lecar model

- N potassium gates
- $C_N(t)$ proportion of open gates among N gates at time t
- stochastic opening and closing at random times

$$C_{closed} \underset{\beta(V)}{\overset{\alpha(V)}{\rightleftharpoons}} C_{open}$$

Between jumps of C_N, the trajectory of the continuous component V_t follows

$$\frac{dV_t}{dt} = -g_{Ca} m_\infty(V_t)(V_t - V_{C_a}) - g_K\, C_N(t)\,(V_t - V_K) - g_L(V_t - V_L) + I$$

$\Rightarrow$ **Piecewise Deterministic Markov Process**

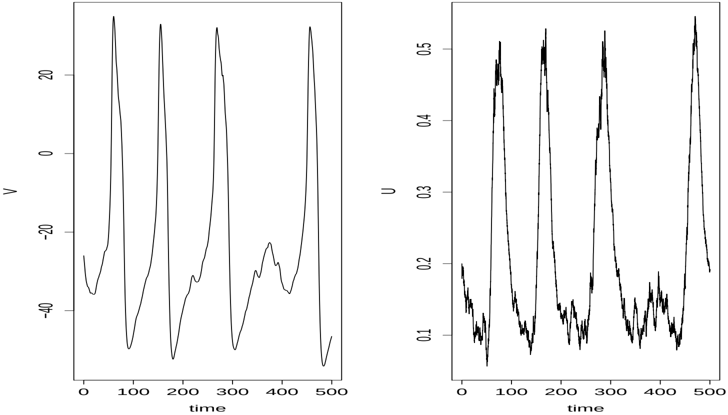
- **Diffusion approximation** [Wainrib, Thieullen, Pakdaman, EJP 2012]
  - $(V_t, C_N(t))$ is approximated by

$$\begin{aligned} dV_t &= (-g_{Ca} m_\infty(V_t)(V_t - V_{C_a}) - g_K C_t(V_t - V_K) - g_L(V_t - V_L) + I)\, dt \\ dC_t &= (\alpha(V_t)(1 - C_t) - \beta(V_t) C_t)\, dt + \sigma(V_t, C_t) dB_t \end{aligned}$$

- Diffusion of dimension 2 driven by only one Brownian motion

Hypoellitic diffusion

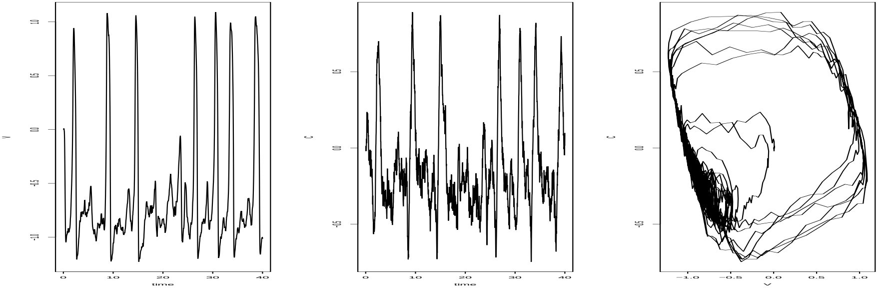
Hypoelliptic Morris-Lecar model



Morris-Lecar is highly non-linear $\Rightarrow$ Difficult to study

Fitzhugh-Nagumo model: a simplest model !

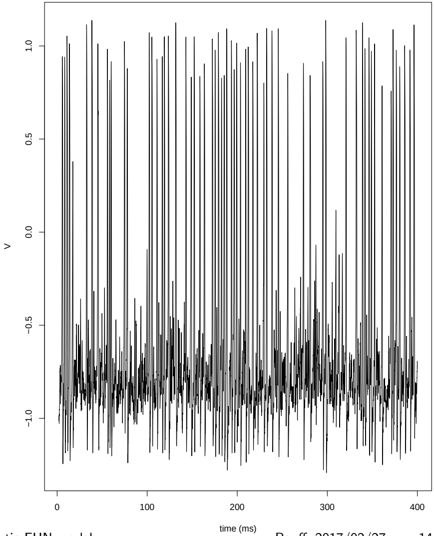
$$
\begin{aligned}
dV_t &= \frac{1}{\varepsilon}(V_t - V_t^3 - C_t - s)dt, \\
dC_t &= (\gamma V_t - C_t + \beta)\, dt + \tilde{\sigma}\, dB_t,
\end{aligned}
$$



Objectives of the talk

[Leòn and Samson, work in progress]

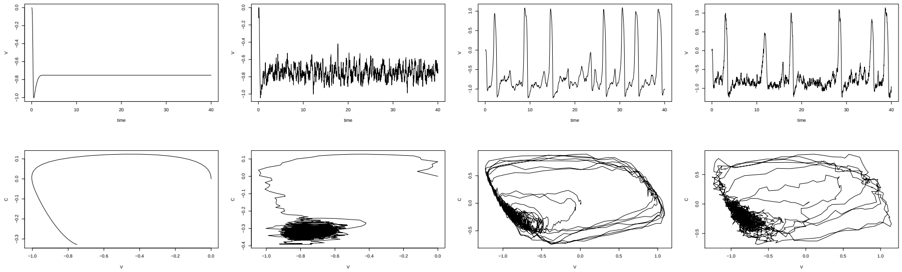
1. Probabilist properties of the system
   - hypoellipticity
   - stationary distribution
   - β-mixing
2. Neuronal properties
   - spiking rate
   - distribution of the length of inter-spike interval (ISI)
3. Estimation
   - stationary distribution
   - spiking rate
   - parameters



1. Probabilist properties

Hypoellipticity of the system

- Condition: drift of the first coordinate depends on C
- Noise of the second coordinate propagates to the first one



No noise | Noise on V | Noise on C | Noise on V, C

$\Rightarrow$ Hypoellipticity has consequences on the generation of spikes

Other probabilist properties

A difficult task

- Main results assume a non null noise
- A class of well studied hypoelliptic systems is

$$\begin{aligned} dV_t &= U_t dt, \\ dU_t &= -(c(V_t)\, U_t + \partial_v P(V_t))dt + \sigma dB_t, \end{aligned}$$

with $P(v)$ a potential, $c(v)$ a damping force.

  - Stochastic Damping Hamiltonian system [Wu 2001]
  - Langevin Equation [Wu 2001]
  - Hypocoercif model [Villani, 2009]

Good news !

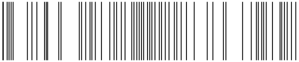
- We enter the previous class by setting $U_t = \frac{1}{\varepsilon}(V_t - V_t^3 - C_t - s)$:

$$\begin{aligned} dV_t &= U_t dt, \\ dU_t &= \frac{1}{\varepsilon}\left(U_t(1-\varepsilon-3V_t^2) - V_t(\gamma-1) - V_t^3 - (s+\beta)\right) dt - \frac{\tilde{\sigma}}{\varepsilon} dB_t, \end{aligned}$$

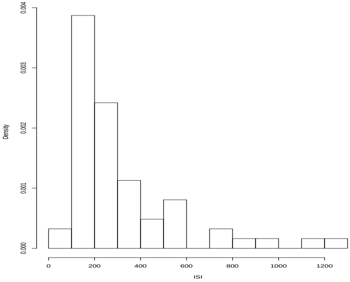
Stationary distribution

- Existence of Lyapounov function $\Psi(v,u) = e^{F(v,u) - \inf_{\mathbb{R}^2} F}$ with explicit F
- Existence and uniqueness of the stationary density [Wu, 2001]

- What does that mean?
  - FHN process generates spikes for ever

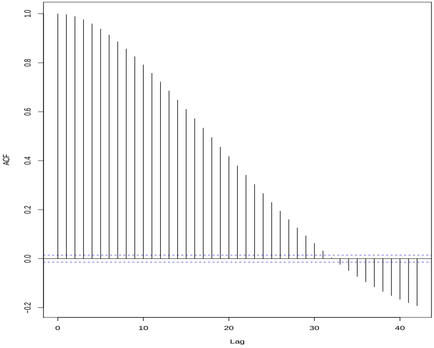


  - Inter-Spikes Intervals (ISI) have a random length
  - Distribution of ISI does not depend on time when s is constant



β-mixing

- Process $Z_t = (V_t, U_t)$ is β-mixing [Wu, 2001]
- What does that mean ?
  - Memory of the process decreases exponentially with time



2. Neuronal properties

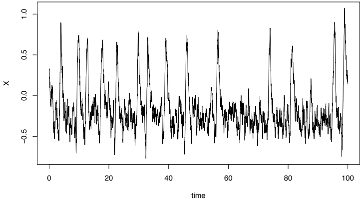
Spiking regime

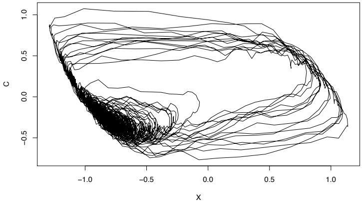
[Lindner, Schimansky-Geier, 1999]

(Back to the original system)

Spike = long excursion in the phase space

- Fixed point on the left bottom
- Excited state: V increases, C remains constant
- V stays at the top, C increases
- Refractory phase: V decreases, C stays high





Spiking rate

- N_t number of spikes during time interval $[0, t]$: random process
- Spike rate

$$\rho := \lim_{t \to \infty} \frac{N_t}{t} \quad a.s.$$

Mean length of Inter-Spikes Intervals (ISI)

- T_i time between spikes i and $i + 1$
- Mean length of ISI

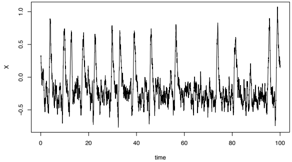
$$< T > := \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} T_i \quad a.s.$$

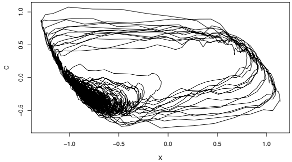
Spiking rate = inverse of the mean length of ISI

$$\rho = \lim_{t\to\infty} \frac{N_t}{t} = \lim_{N\to\infty} \frac{1}{N}\sum_{i=1}^{N} T_i = \frac{1}{< T >}$$

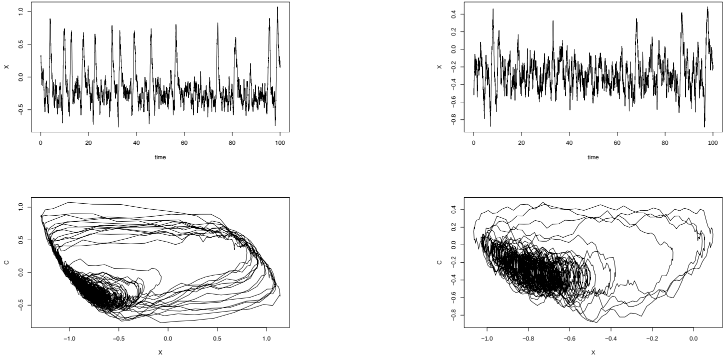
- But "limit in t = limit in N " is not easy to prove mathematically
- True for a Poisson process $(N_t, t \geq 0)$
- Difficulty with FHN
  - How to define $(N_t, t \geq 0)$ from the stochastic process (V_t, C_t) ?

Back to the definition of spikes

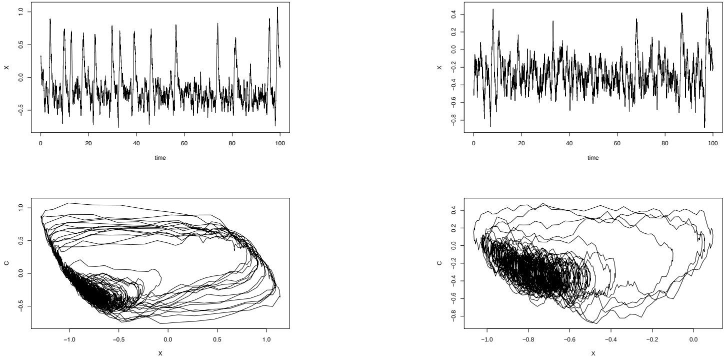




Back to the definition of spikes



Back to the definition of spikes

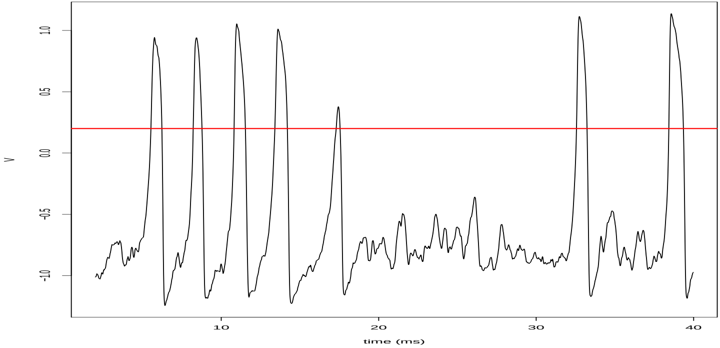


How decide what is an excursion ?

How define precisely (T_i) ?

Alternative definition: up-crossing process

- For a level v, $M_t(v)$: number of up-crossings of V during interval $[0, t]$

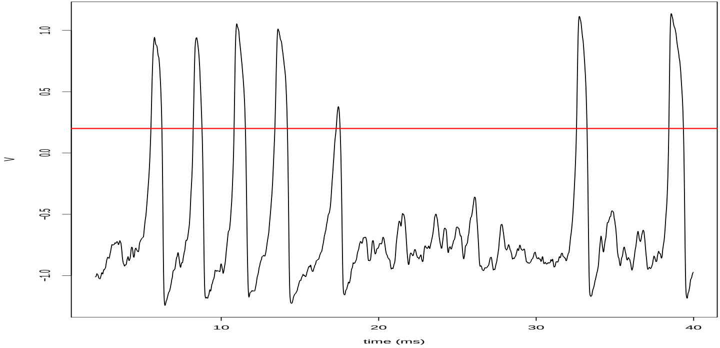


$v = 0.2$

Alternative definition: up-crossing process

- For a level v, $M_t(v)$: number of up-crossings of V during interval $[0, t]$
- To ease the definition, work with the transform system ($dV_t = U_t dt$):

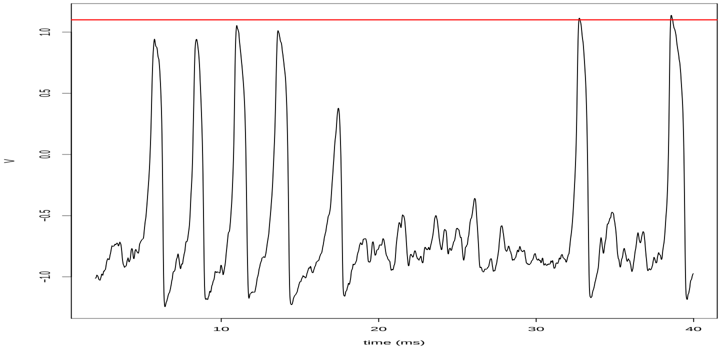
$$M_t(v) = \{s \leq t : V_s = v, U_t > 0\}$$



$v = 0.2$

Alternative definition: up-crossing process

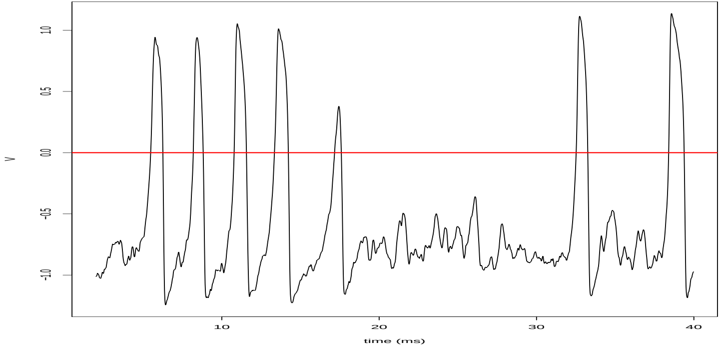
- For a level v, $M_t(v)$: number of up-crossings of V during interval $[0, t]$
  When v is too large, $M_t(v) = 0$



$$v = 1.1$$

Link with "spiking process"

- When v is large (not too large), $N_t = M_t(v)$



$$v = 0$$

Link with "spiking process"

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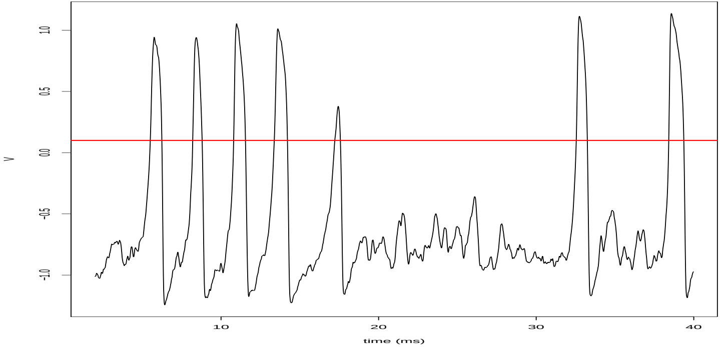

$v = 0.1$

Link with "spiking process"

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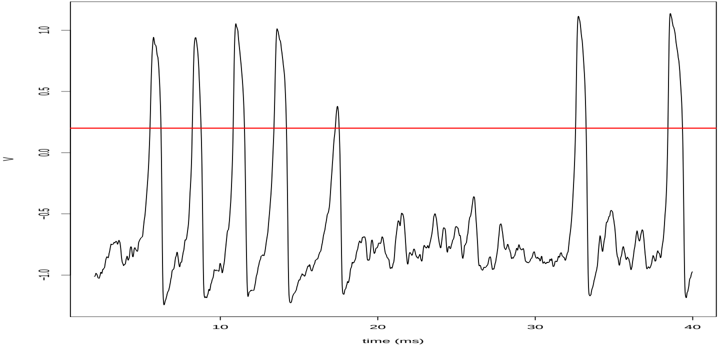

$v = 0.2$

Link with "spiking process"

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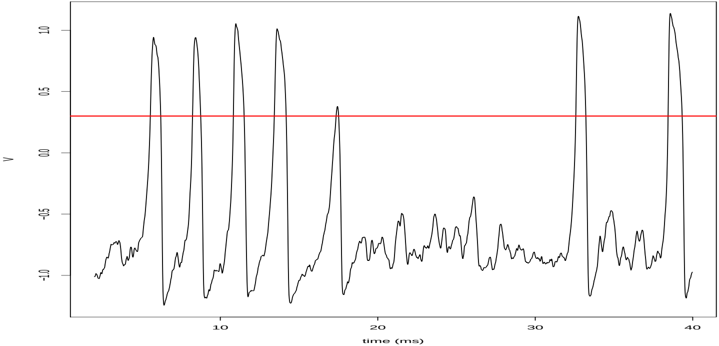

$v = 0.3$

Advantage from a mathematical point of view

Up-crossing process is a stochastic process that can be theoretically studied

Rice's formula

- Theoretical mean of the number of up-crossings in interval $[0, t]$:

$$\mathbb{E}\, M_t(v) = t \int_0^{\infty} u p(v, u) du$$

with p the stationary density

- What does that mean ?
  - Explicit expression for the mean number of "spikes" for certain values of v
  - Formula depends on the stationary distribution
  - $\rightarrow$ Can be estimated non-parametrically

Up-crossing rate

- Existence of the limit of the expected number of up-crossings by unit of time (ergodic theorem)

$$\frac{M_t(v)}{t} \to \int_0^\infty up(v,u)du \text{ a.s.}$$

Up-crossing rate

- Existence of the limit of the expected number of up-crossings by unit of time (ergodic theorem)

$$\frac{M_t(v)}{t} \to \int_0^\infty up(v,u)du \text{ a.s.}$$

- Allows to define the up-crossing rate for level v

$$\lambda(v) := \lim_{t\to\infty} \frac{M_t(v)}{t}.$$

Up-crossing rate

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- Allows to define the up-crossing rate for level v

$$\lambda(v) := \lim_{t\to\infty} \frac{M_t(v)}{t}.$$

  - v large, $\lambda(v) = 0$
  - For a set of values v, "$\lambda(v) = \rho$"

Distribution of up-crossings

- Recall that "length of Inter Up-Crossing Interval (IUCI)" is a random process
- Conditional probability of no up-crossing occurs in interval $[0, t]$, given that an up-crossing occurred at time zero

$$\begin{aligned}\Phi_v(t) &= \lim_{\tau\to 0} \frac{\mathbb{P}(1 \text{ up-crossing in}[-\tau,0] \text{ and no up crossing in } [0,t])}{\mathbb{P}(1 \text{ up-crossing in } [-\tau,0])} \\ &= \lim_{\tau\to 0} \frac{\mathbb{P}(M_{[-\tau,0]}(v) \geq 1, Cr_{[0,t]}(v) \leq 1)}{\mathbb{P}(1 \text{ up-crossing in } [-\tau,0])}\end{aligned}$$

- Distribution function of length of IUCI

$$F_v(t) = 1 - \Phi_v(t)$$

Main result

- Expectation of length between two successive up-crossings ("ISI") is the inverse of the up-crossing rate

$$\int_0^{\infty} t \, dF_v(t) = \frac{1}{\lambda(v)}$$

This gives a proof to the previous formula

$$< T >= \frac{1}{\rho}$$

- Explicit expression for the variance of the length between two successive up-crossings

3. Estimation

Quantities to be estimated

1. Stationary density p
2. Spiking rate $\lambda(v)$ and mean length of up-crossings interval
3. Variance of the length between two successive up-crossings
4. Parameters $\varepsilon, \beta, \gamma, \sigma$

3. Estimation

Quantities to be estimated

1. **Stationary density** p
2. **Spiking rate** $\lambda(v)$ **and mean length of up-crossings interval**
3. Variance of the length between two successive up-crossings
4. **Parameters** $\varepsilon, \beta, \gamma, \sigma$

3.1. Stationary density

- No explicit formula for p
- Solution of the Fokker-Planck equation

$$0 = -p - \frac{\partial}{\partial u}(b(v,u)p) + \frac{1}{2}\frac{\partial}{\partial u^2}(\sigma^2 p)$$

  - $b(v,u) = \frac{1}{\varepsilon}\left(u(1-\varepsilon-3v^2) - v(\gamma-1) - v^3 - (s+\beta)\right)$
  - Resolution of the PDE by finite difference
  - Require the values of the parameters
- Unstable scheme in spiking regime (ε small)

Alternative: non-parametric estimation of the stationary density

[Cattiaux, Leòn, Prieur, 2014-2015]

- **Idea**
  - Forget the form of the system
  - Learning/estimating p only from observations of the process (V_t, U_t)
  - Two cases: complete or partial observations

- **Complete observations**
  - both coordinates (V_t, U_t) at discrete times $i\Delta$, $i = 1, \ldots, n$
  - K a kernel function
  - $b = (b_1, b_2)$ a bandwidth
  - Estimator of p for any point $z = (z_1, z_2)$:

$$\tilde{p}_b(z) = \frac{1}{n} \sum_{i=1}^{n} K\left(\frac{V_i - z_1}{b_1}, \frac{U_i - z_2}{b_2}\right)$$

- **Incomplete observations**; only (V_t)
  - C_t **not observed** but, thanks to $dV_t = U_t dt$, can be replaced by

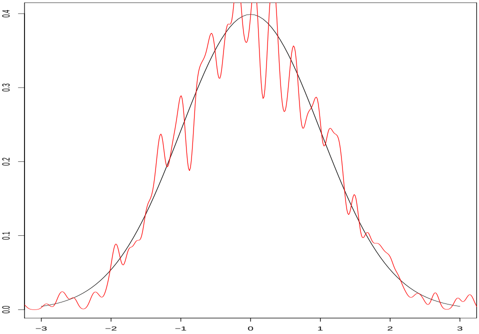
$$\bar{V}_i := \frac{V_{i+1} - V_i}{\Delta} = \frac{\int_{i\Delta}^{(i+1)\Delta} U_s ds}{\Delta} \approx U_{i\Delta}$$

  - Estimator of p

$$\hat{p}_b(z) = \frac{1}{n} \sum_{i=1}^{n} K\left(\frac{V_i - z_1}{b_1}, \frac{\bar{V}_i - z_2}{b_2}\right)$$

How choosing the bandwidth b

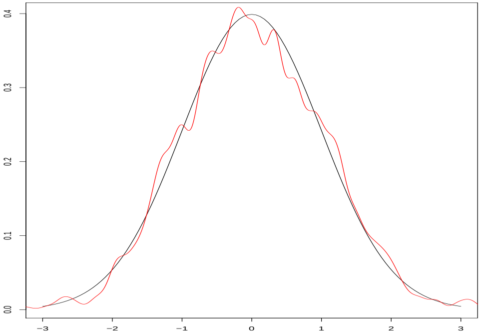
- b too small: large variance



$b = 0.05$

How choosing the bandwidth b

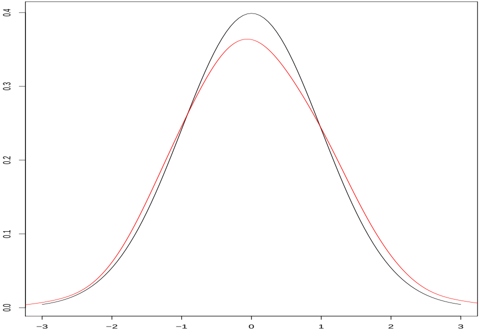
- b too small: large variance



$$b = 0.1$$

How choosing the bandwidth b

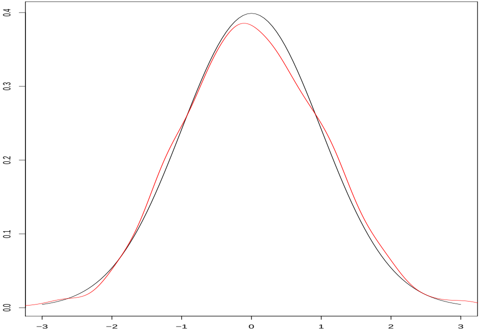
- b too large: large bias



$b = 0.4$

Ideal bandwidth

- Compromise bias-variance



$b = 0.228$

Data-driven procedure [Comte, Prieur, Samson, 2017]

- Selection criteria [Goldenshluger and Lepski, 2011; Lacour et al, 2016]

$$\tilde{b} = \arg\min_{b \in \mathcal{B}_n} \left(A(b) + V(b) \right),$$

  with
  - $A(b)$ mimicking the bias $(= \sup_{b' \in \mathcal{B}_n} \left(\|\tilde{p}_{b,b'} - \tilde{p}_{b'}\|^2 - V(b') \right)_+)$
  - $V(b)$ mimicking the variance $(= \kappa \frac{\|K\|_1^2 \|K\|^2}{n b_1 b_2} \sum_{i=0}^{n-1} \beta(i\delta))$

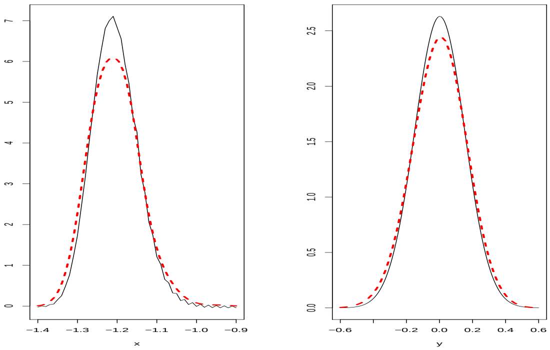
- Final estimator
  - $p_b = K_b * p$

$$\mathbb{E}(\|\tilde{p}_{\tilde{b}} - p\|^2) \leq C \inf_{b \in \mathcal{B}_n} \left(\|p - p_b\|^2 + V(b) \right) + C' \frac{\log(n)}{n\delta}$$

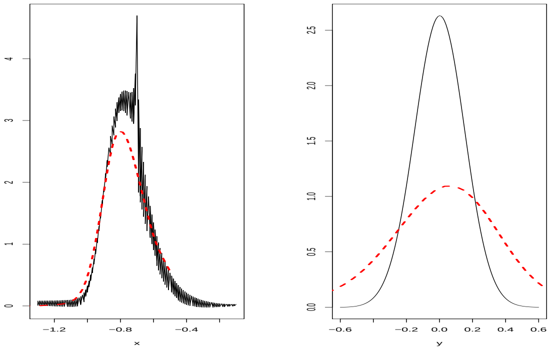
Same results in the partial case

Non-parametric estimation

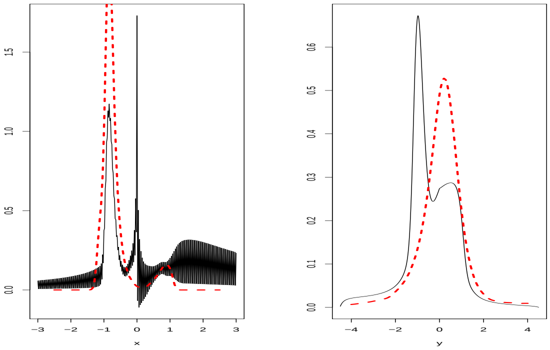
- Estimation of p when there is no spike ($\varepsilon = 0.5$)
- PDE solver in black, Kernel estimator in red



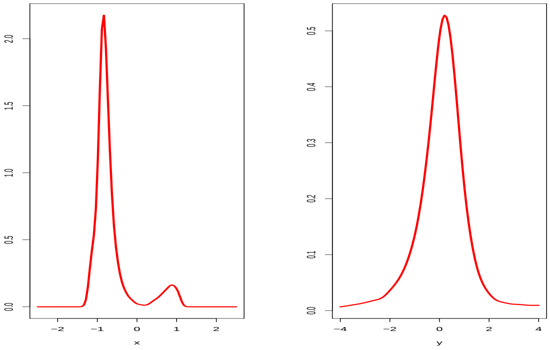
- Estimation of p with few spikes ($\varepsilon = 0.4$)
  - Unstability of the PDE solver



- Estimation of p with a lot of spikes ($\varepsilon = 0.1$)
  - Unstability of the PDE solver



- Estimation of p with a lot of spikes ($\varepsilon = 0.1$)



3.2 Estimation of the up-crossing rate

- Plug-in estimator

$$\hat{\lambda}(v) = \int_0^\infty u\hat{p}(v,u)\,du$$

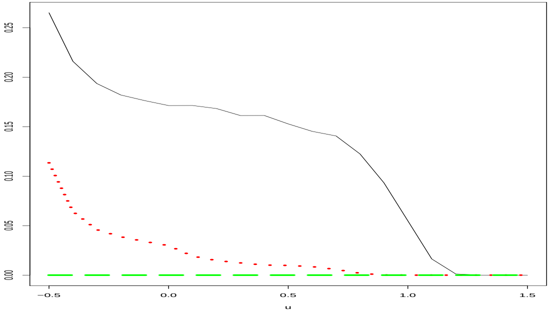
- Gaussian kernel

$$\hat{\lambda}(v) = \frac{\hat{b}_2}{2}\hat{p}^V(v) + \frac{1}{2}\frac{1}{n\hat{b}_1}\sum_{i=1}^{n} k\left(\frac{v - V_{i\delta}}{\hat{b}_1}\right)\bar{V}_{i\delta}$$

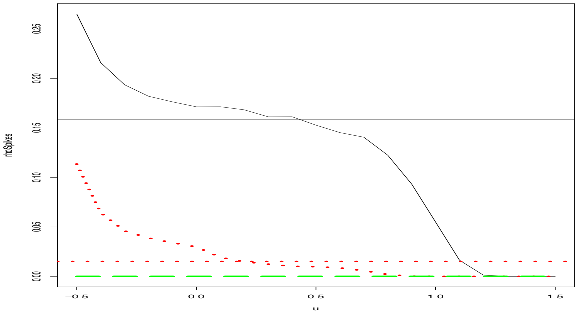
- Comparison with spiking rate

$$\rho = \lim \frac{N_t}{t}$$

- Black: $\varepsilon = 0.1$ (a lot of spikes)
- Red: $\varepsilon = 0.4$ (few spikes)
- Green: $\varepsilon = 0.5$ (no spikes)



- Black: $\varepsilon = 0.1$ (a lot of spikes)
- Red: $\varepsilon = 0.4$ (few spikes)
- Green: $\varepsilon = 0.5$ (no spikes)



3.3 Estimation of parameters

$$
\begin{aligned}
dV_t &= \frac{1}{\varepsilon}(V_t - V_t^3 - C_t - s)dt, \\
dC_t &= (\gamma V_t - C_t + \beta)\, dt + \tilde{\sigma} dB_t,
\end{aligned}
$$

Difficult because

- Hypoellipticity
- No explicit transition density of the SDE
- Hidden coordinate C

Ideal case of complete observations and noise on both coordinates $X_t = (V_t, C_t)$:

$$dX_t = b_\mu(X_t)dt + \Sigma dB_t, \quad \Sigma = \begin{pmatrix} \sigma_1 & 0 \\ 0 & \sigma_2 \end{pmatrix}$$

Discretization of the system (Euler-Maruyama) of $X_{i+1} = (V_{i+1}, U_{i+1})$:

$$X_{i+1} = X_i + \Delta b_\mu(X_i) + \sqrt{\Delta}\Sigma\eta_i, \quad \eta_i \sim_{iid} \mathcal{N}(0, I)$$

Minimum contrast estimator [Genon-Catolot, Jacod, 1993; Kessler 1996]
Set $\Gamma = \Sigma'\Sigma$.

$$\hat{\theta} = \arg\min_{\theta\in\Theta} \left(\sum_{i=1}^{n-1} (X_{i+1} - X_i - \Delta b_\mu(X_i))' \, \Gamma^{-1} \, (X_{i+1} - X_i - \Delta b_\mu(X_i)) + \sum_{i=1}^{n-1} \log\det\Gamma \right)$$

- $\hat{\mu}$, $\hat{\Gamma}$ asymptotically normal

What about hypoelliptic SDE ?

Impossible to apply previous estimator because

$$\Gamma = \begin{pmatrix} 0 & 0 \\ 0 & \sigma_2^2 \end{pmatrix} \quad \text{not invertible}$$

Idea: change of variable

- Assume ε known, and change the system with $U_t = \frac{1}{\varepsilon}(V_t - V_t^3 - C_t - s)$
- Litterature
  - Martingale estimating functions [Ditlevsen, Sorensen, 2004]
  - Gibbs sampler [Pokern et al, 2010]
  - Euler contrast [Gloter 2006, Samson, Thieullen, 2012];
  - Higher order contrast [Ditlevsen, Samson, work in progress]

Partial observations

- U_t **not observed** but can be replaced by

$$\bar{V}_i := \frac{V_{i+1} - V_i}{\Delta} = \frac{\int_{i\Delta}^{(i+1)\Delta} U_s ds}{\Delta} \approx U_{i\Delta}$$

- Contrast function with plug-in $\bar{V}$
  - $\mu = (\beta, \gamma, s)$

$$\hat{\theta} = \arg\min_{\theta \in \Theta} \left(\sum_{i=1}^{n-1} \frac{\left(\overline{V}_{i+1} - \overline{V}_i - \Delta b_\mu(V_{i-1}, \overline{V}_{i-1})\right)^2}{\Delta \sigma^2} + \sum_{i=1}^{n-1} \log \sigma^2 \right)$$

  - $\hat{\mu}$ is unbiased, asymptotically normal
  - $\hat{\sigma}$ is biased (because $\bar{V}_i$ is not Markovian)

Partial observations

- U_t **not observed** but can be replaced by

$$\bar{V}_i := \frac{V_{i+1} - V_i}{\Delta} = \frac{\int_{i\Delta}^{(i+1)\Delta} U_s ds}{\Delta} \approx U_{i\Delta}$$

- Contrast function with plug-in $\bar{V}$
  - $\mu = (\beta, \gamma, s)$

$$\hat{\theta} = \arg\min_{\theta\in\Theta} \left(\frac{3}{2} \sum_{i=1}^{n-2} \frac{\left(\overline{V}_{i+1} - \overline{V}_i - \Delta b_\mu(V_{i-1}, \overline{V}_{i-1})\right)^2}{\Delta \sigma_2^2} + \sum_{i=1}^{n-2} \log \sigma_2^2 \right)$$

  - $\hat{\mu}$ is unbiased, asymptotically normal
  - $\hat{\sigma}$ is unbiased, asymptotically normal

Parametric estimation assuming ε unknown

[Ditlevsen, Samson, work in progress]

What can not be applied

- Change of variable
- Euler contrast

Idea

- Higher order discrete scheme that propagates the noise to the first coordinate
- Contrast for complete observations as in the "ideal" case of non null
- Asymptotic results
  - Consistency of all parameters
  - $\hat{\varepsilon}$ is not asymptotically normal

Some estimation results obtained from 100 simulated data sets

		ε fixed	ε fixed	ε estimated
	True	New contrast	Euler Contrast	New contrast
ε	0.100	–	–	0.105 (0.010)
γ	1.500	1.523 (0.130)	1.499 (0.196)	1.592 (0.160)
β	0.800	0.821 (0.110)	0.779 (0.107)	0.866 (0.130)
σ	0.300	0.293 (0.008)	0.381 (0.038)	0.306 (0.020)

Conclusion/Perspectives

- Hypoelliptic FHN system
  - Existence of stationary density and non-parametric estimation
  - Link between the spiking rate and the mean length of ISI
  - Estimation of the "spiking" rate: still some issues with the complete distribution of ISI
  - Parametric estimation: still some issues with ε
    - Particle filter and EM algorithm
    - Optimal control theory
    - Local linearization of the SDE
- More complex neuronal systems
  - Link between spiking rates and ISI
  - Graphe of interaction in neural network for both intra and extra cellular data