Memory and hypoellipticity in neuronal models

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What this talk is about :

- What is the effect of memory in probabilistic models for neurons ?
- Study this in two classical models : the stochastic Hodgkin-Huxley model and a model of interacting Hawkes processes in high dimension.
- Why does memory lead to hypoellipticity ?
- What are the probabilistic and statistical consequences of this fact ?

The stochastic Hodgkin-Huxley model

Joint work with **M. Thieullen and R. Höpfner.**

Classically : HH-model = 4−dimensional deterministic model

$$(V_t, n_t, m_t, h_t), t \geq 0$$

for the membrane potential V of a single neuron, together with **gating variables** n, m, h that account for the **ion currents** of K^+ and Na^+−ions :

$$\begin{aligned} dV_t &= I_t dt - F(V_t, n_t, m_t, h_t) dt \\ dn_t &= [\alpha_n(V_t)(1-n_t) - \beta_n(V_t)\, n_t]\, dt \\ dm_t &= [\alpha_m(V_t)\,(1-m_t) - \beta_m(V_t)\, m_t]\, dt \\ dh_t &= [\alpha_h(V_t)\,(1-h_t) - \beta_h(V_t)\, h_t]\, dt, \end{aligned}$$

where $t \to I_t$ is some deterministic signal, and where

$$F(v,n,m,h) = g_K n^4 (v - E_K) + g_{Na}\, m^3 h (v - E_{Na}) + g_L (v - E_L).$$

The model - continued

• All conductances g_K, g_{Na}, g_L and equilibrium potentials $E_K, \ldots$ are explicitly known.

Also the voltage dependent activation and inactivation functions α, β :

$$\alpha_n(v) = \frac{0.1 - 0.01v}{\exp(1 - 0.1v) - 1}, \ldots :$$

not bounded, but analytic functions.

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• Hodgkin-Huxley (1952) : initiation and propagation of action potentials in the squid giant axon. Nobel price in medicine.

• Let us call the equations for the gating variables n, m, h **memory equations.**

• Indeed, for a fixed voltage trajectory $(V_t)_{t\geq 0}$, the equations for n, m, h are linear, and we obtain e.g.

$$n_t = n_0 e^{-\int_0^t (\alpha_n+\beta_n)(V_s)ds} + \int_0^t \alpha_n(V_u) e^{-\int_u^t (\alpha_n+\beta_n)(V_r)dr} du,$$

and similar formulas for the other gating variables...

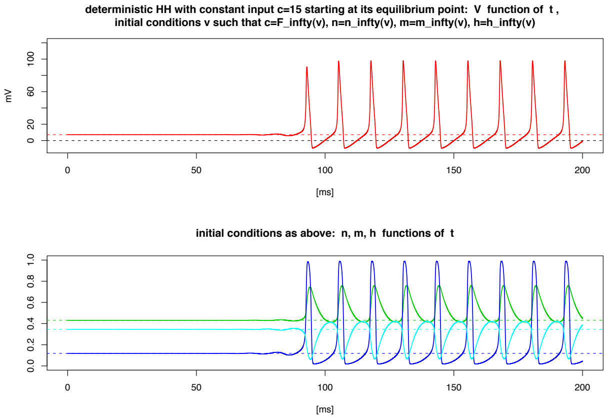


FIGURE: Deterministic HH with constant input $S = 15$ starting in a numerical approximation to its equilibrium point.

- Add noise to the system !
- Indeed : the neuron does certainly not receive the original deterministic signal :
  It receives input from its dendritic system.
- This system has a large number of synapses : they register spike trains from a huge number (about 10000!) of other neurons.

Noisy dendritic input

Höpfner 2007 : used kernel estimators to estimate drift and diffusion coefficient of the membrane potential process - away from spike times $\Rightarrow$ In some neurons, the input is well modeled by

$$d\xi_t = \nu \left(S(t) - \xi_t \right) dt + \gamma \, dW_t$$

Ornstein-Uhlenbeck process of mean-reverting type, where

$$t \to S(t)$$

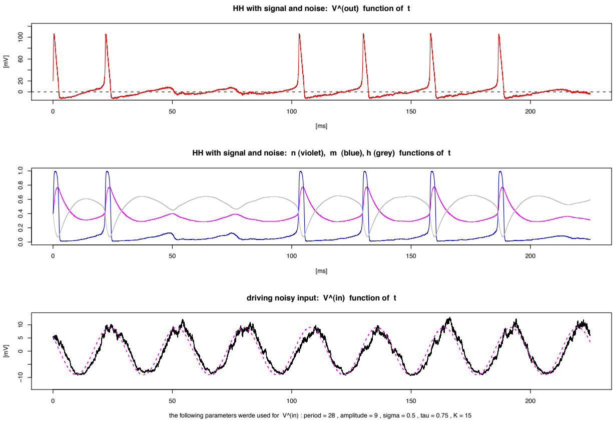
is some deterministic stimulus processed by the network. In other neurons, a CIR-process is a good model for the stochastic input.

Stochastic HH model

Stochastic Hodgkin-Huxley model with input $t \to S(t)$ given by

$$\begin{aligned}
dV_t &= d\xi_t - F(V_t, n_t, m_t, h_t)dt \\
dn_t &= [\alpha_n(V_t)(1-n_t) - \beta_n(V_t)\, n_t]\, dt \\
dm_t &= [\alpha_m(V_t)\,(1-m_t) \; - \; \beta_m(V_t)\, m_t]\, dt \\
dh_t &= [\alpha_h(V_t)\,(1-h_t) \; - \; \beta_h(V_t)\, h_t]\, dt \\
d\xi_t &= \nu\,(S(t) - \xi_t)\, dt \; + \; \gamma\, dW_t.
\end{aligned}$$

$5-$dimensional diffusion driven by $1-$dimensional Brownian motion present in ξ and in V. $S(t)$ supposed to be $T-$periodic signal, for some fixed periodicity T.


HH with signal and noise: V^(out) function of t
[mV]
0
20
60
100
0
50
100
150
200
[ms]
HH with signal and noise: n (violet), m (blue), h (grey) functions of t
0.0
0.2
0.4
0.6
0.8
1.0
0
50
100
150
200
[ms]
driving noisy input: V^(in) function of t
[mV]
−10
0
5
10
0
50
100
150
200
the following parameters werde used for V^(in) : period = 28 , amplitude = 9 , sigma = 0.5 , tau = 0.75 , K = 15

What we did with Reinhard and Michèle in a series of papers :

- We proved **limit theorems** for a large class of functionals of the process – under a certain condition of periodic recurrence.

- Analysis of **spiking patterns** in the neuron is then possible via SLLN. In particular : Glivenko-Cantelli theorem for the empirical ISI distributions.

- Tools : Periodic ergodicity induced by $T-$periodicity of the signal encoded in the drift, Nummelin- (or Doeblin-) type minorization condition based on existence of transition densities which are locally smooth.

This led us immediately to the notion of Hypoellipticity !

Hypoellipticity of the stochastic Hodgkin-Huxley model :

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&\dots \\
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\end{aligned}
$$

Noise only present in first and fifth variable - this is a **highly degenerate** five-dimensional diffusion.

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Noise only present in first and fifth variable - this is a **highly degenerate** five-dimensional diffusion. **What does Hypoelliptic mean ? ? ? ?**

• Degenerate diffusion are diffusions in dimension m (here, 5), driven by lower-dimensional $n-$dimensional Brownian motion (here, $n = 1$).

• Question : does the $n-$dimensional noise generate **density** of the process in the whole $m-$dimensional state space ?

If so, then we call the process **hypoelliptic**. (This is not exactly the definition of a *hypoelliptic diffusion generator*, but it is the basic idea.)

• What can be the problem in this degenerate case ?

A toy model

To fix ideas, consider a two-dimensional toy model with noise only in one component :

$$\begin{aligned} dX_t &= dW_t, X_0 = x, \\ dY_t &= f(X_t)dt, Y_0 = y, \end{aligned}$$

f smooth.

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f smooth. What is the problem here ?

First order approximation gives (for small t) :

$$\begin{pmatrix} X_t \\ Y_t \end{pmatrix} \approx \begin{pmatrix} W_t \\ 0 \end{pmatrix} + \begin{pmatrix} x \\ y + f(x)t \end{pmatrix}.$$

Brownian motion only in one coordinate : this vector **does not possess a two-dimensional Lebesgue density !**

So : need a second order approximation. Use Itô :

$$f(X_t) = f(x) + \int_0^t f'(X_s) dW_s + \frac{1}{2} \int_0^t f''(X_s) ds.$$

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Plug this in : $Y_t = y + \int_0^t f(X_s) ds$:

$$\begin{aligned} Y_t &= y + f(x)t + f'(x) \int_0^t \int_0^s dW_u \, ds + remainder \\ &= y + f(x)t + f'(x) \int_0^t (t-u) dW_u + remainder, \quad t << 1. \end{aligned}$$

Conclusion

$$\begin{pmatrix} X_t \\ Y_t \end{pmatrix} = \begin{pmatrix} W_t \\ f'(x) \int_0^t (t-u) dW_u \end{pmatrix} + \text{ remainder.}$$

$\uparrow$ Gaussian vector : has a two-dimensional density iff $f'(x) \neq 0$.

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Points x with $f'(x) \neq 0$ are points where the (weak) **Hörmander condition** holds. If $f'(x) = 0$, iterate the above argument. Sufficient : $\exists n : f^{(n)}(x) \neq 0$.

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The weak Hörmander condition is a condition which generalizes the well-known ellipticity condition. And it implies the hypo-ellipticity of the process.

A first comment on the structure of the covariance matrix

The Gaussian vector

$$\begin{pmatrix} W_t \\ f'(x) \int_0^t (t-u) dW_u \end{pmatrix}$$

has covariance matrix

$$\begin{pmatrix} t & f'(x)\frac{1}{2}t^2 \\ f'(x)\frac{1}{2}t^2 & (f'(x))^2\frac{1}{3}t^3 \end{pmatrix}.$$

• To keep in mind : for small t, this is of order $t^{3/2}$.

• the geometrical structure has changed, and the coordinates of the process **do not travel at the same speed.**

• the more iterations one needs to span the whole space, the worse this speed is.

Weak Hörmander condition for stochastic HH model

The **memory equations** for the gating variables n, m, h **feel** the noise only through the voltage variable V_t.

Weak Hörmander condition for stochastic HH model

The **memory equations** for the gating variables n, m, h **feel** the noise only through the voltage variable V_t. So we have to consider the derivatives with respect to v of $\alpha_n(v)$ etc....

- b_n, b_m, b_h : drift terms of n, m, h.

- Important quantity :

$$D(v, n, m, h) \ := \ \det \begin{pmatrix} \partial_v^2 b_n & \partial_v^3 b_n & \partial_v^4 b_n \\ \partial_v^2 b_m & \partial_v^3 b_m & \partial_v^4 b_m \\ \partial_v^2 b_h & \partial_v^3 b_h & \partial_v^4 b_h \end{pmatrix} (v, n, m, h).$$

Proposition

The weak Hörmander condition holds for all points (v, n, m, h, ζ) such that $D(v, n, m, h) \neq 0$.

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Proposition

The weak Hörmander condition holds for all points (v, n, m, h, ζ) such that $D(v, n, m, h) \neq 0$. This is an open set of full Lebesgue measure.

• We then checked that the above determinant is non-zero at certain attainable points of the stochastic HH model (in the sense of deterministic control).

• Using arguments from control theory (in particular, Arnold and Kliemann 1987), and from Nagano 1966, Susmann 1973 (*the weak Hörmander condition is transported by control paths, due to the analyticity of the coefficients of the system*)

Theorem (HLT 2016, to appear in Esaim P&S)

For the stochastic Hodgkin-Huxley system driven by an Ornstein-Uhlenbeck type process or a CIR type process, the weak Hörmander condition holds everywhere, and thus the process is hypoelliptic.

Summary

• Hypoellipticity of stochastic HH-model is induced by the absence of (Brownian) noise in the *gating* (or : *memory*) variables n, m, h.

• Even if we may assume these gating variables to be subject to noise as well, the *channel noise* is most likely not to be of the same type.

• Dealing with hypoelliptic rather than with elliptic diffusions has drastical consequences for any probabilistic study. Most important : **the control theory** is not at all established and has to be done "by hand".

Second example

Not any longer a model for a single neuron, but a system of interacting neurons.

Joint work with Susanne Ditlevsen (SPA, to appear in 2017)

A system of interacting neurons

• We consider a **large system of interacting Hawkes processes**, describing each one neuron. That is, we describe the successive appearences of spikes of a given neuron.

• This system is made of n populations, n is fixed.

• Each population k consists of N_k **neurons** described by their counting processes

$$Z_{k,i}(t), 1 \leq i \leq N_k.$$

• Within a population, all neurons behave in the same way. This is a mean-field assumption.

- Intensity of $i-$th neuron belonging to population k :

$$\lambda_{k,i}(t) = f_k \left(\sum_{l=1}^{n} \frac{1}{N_l} \sum_{1 \le j \le N_l} \int_{]0,t[} h_{kl}(t-s) dZ_{l,j}(s) \right).$$

- f_k = jump rate function of population k; *supposed to be Lipschitz continuous.*

- h_{kl} measures the influence of a typical neuron of population l on a typical neuron of population k; *supposed to be in* $L^2_{loc}(\mathbb{R}_+, \mathbb{R})$.

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- We are in a **mean field frame :** population l influences population k only through its **empirical measure.**

Mean field limit

In the $N \to \infty$ limit, a typical neuron of pop k spikes at rate λ_t^k :

$$\lambda_t^k = f_k \left(\sum_{l=1}^{n} \int_0^t h_{kl}(t-u) \lambda_u^l du \right), 1 \leq k \leq n.$$

Theorem (with S. Ditlevsen, SPA 2017)

For memory kernels h_{kl} which are Erlang kernels and for a specific interaction graph structure, the limit system has **oscillatory behavior***.*

This oscillatory behavior is mainly a consequence of the **memory** in the system (and of course also of the structure of the graph of interactions).

Hawkes memory

• Hawkes processes are truly infinite memory processes - the intensity depends on the whole history.

• Suppose $n = 1$ (only one population) and stochastic intensity (for fixed N, thus before passing to the limit)

$$\lambda(t) = f\left(\int_0^t h(t-s)d\bar{Z}_N(s)\right) =: f(X(t)), \quad \bar{Z}_N(s) = \frac{1}{N}\sum_{i=1}^N Z_i(s),$$

and h is an Erlang kernel :

$$h(t) = c\frac{t^m}{m!}e^{-\nu t}, \nu > 0, m \in \mathbb{N}_0, c \in \mathbb{R}.$$

That means : The delay of influence of the past is distributed. It takes its maximum at about m/ν time units back in the past.

Developping the memory - continued

- $\lambda(t) = f(X(t))$. We show that $X(t)$ is **Markov** and almost a **degenerate** diffusion process.
- Suppose e.g. $h(t) = cte^{-\nu t}$ (memory length $m = 1$) and define

$$h_1(t) := ce^{-\nu t}.$$

Then

$$X(t) = \int_0^t h(t-s) d\bar{Z}_N(s), \quad Y(t) = \int_0^t h_1(t-s) d\bar{Z}_N(s)$$

is a two dimensional Markov process with

$$dX_t = -\nu X_t + dY_t, \quad dY_t = -\nu Y_t dt + c\, d\bar{Z}_N(t).$$

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- For general Erlang kernels $h(t) = c\frac{t^m}{m!}e^{-\nu t}$ we obtain an $m+1-$dimensional process....

Diffusion approximation

We approximate the small jumps by a Brownian motion. In this way each neuron jumps at rate $f(\tilde{X}(t))$ where

$$\left\{ \begin{array}{rcl} d\tilde{X}(t) & = & -\nu\tilde{X}(t)dt + \tilde{Y}_t dt \\ d\tilde{Y}(t) & = & -\nu\tilde{Y}(t)dt + cf(\tilde{X}(t))dt \\ & & +\frac{c}{\sqrt{N}}\sqrt{f(\tilde{X}(t)}dB_t \end{array} \right\}.$$

• Can be extended to the general case of n populations and of general Erlang memory kernels.

• We obtain a diffusion of high dimension driven by only few (actually, n) Brownian motions.

• The **degeneracy** of this diffusion is once more due to the memory variables of the system.

• Due to the **cascade structure** of the drift - coming from the development of the memory - it is easy to show that the diffusion satisfies the weak Hörmander condition.

• This cascade structure (a coordinate does only depend on itself and the following coordinate) is reminiscent of Delarue-Menozzi (2010) (density estimates for hypo-elliptic diffusions describing chains of reactions).

On the covariance matrix

• In this specific system, if the Erlang kernel is of order m, then we have $m+1$ diffusion coordinates.

• The last is driven by Brownian motion : it travels at speed $t^{1/2}$.

• The before last one travels at speed $t^{3/2}$.

• And so on : the first at speed $t^{(2m+1)/2}$.

$\Rightarrow$ the process possesses a Lebesgue density, but its "geometry" is "flattened" compared to the elliptic case.

$\Rightarrow$ Moreover, it is not a priori clear that this density is positive – or more precisely, where exactly it is positive : Control problem !

More on the control problem

In the above cascade situation, the cost functional $V_t(x, y)$ of the process (in the sense of deterministic control : cost of steering the process from x to y within a time interval $[0, t]$) behaves as

$$V_t(x, y) \sim t|T_t^{-1}(\varphi_t(x) - y)|^2,$$

where

$$T_t = diag(t^{m+1}, t^m, \ldots, t)$$

and where $\varphi_t(x)$ is the associated deterministic flow with zero noise.

Coming back to our system studied with Susanne :

• Using a convenient Lyapunov-function and the control theorem (and ideas inspired by the work we did with Michèle Thieullen and Reinhard Höpfner on the stochastic Hodgkin-Huxley system)

$\Longrightarrow$ Under certain conditions on the structure of the graph of interactions :

$\exists$ attainable point (which is the unstable equilibrium of the limit dynamical system).

$\Longrightarrow$ diffusion is recurrent in the sense of Harris, with unique invariant probability measure μ^N.

Large deviations

• Limit system is attracted to non constant periodic orbit (limit cycle)...

• Presence of noise : diffusion may escape from a tube around the limit cycle - after longer and longer periods $\Longrightarrow$ natural to study the large deviations of the system. But :

As a consequence of the hypoellipiticity, classical results on control theory needed as main ingredient for sample path large deviations in the small noise regime, à la Freidlin-Wentzell, are not granted and have to be checked "by hand".

Theorem (Lö 2016)

$$\mu^N(D) \sim Ce^{-N[\inf_{x \in D} W(x)]},$$

where (in case of a periodic orbit Γ *and unstable equilibrium* x^**), the cost function is given by*

$$W(x) = V(\Gamma, x) \wedge [V(\Gamma, x^*) + V(x^*, x)].$$

Here, $V(x, y)$ *is the cost of stearing the process from* x *to* y *in any time.*

Final comments

– Refractory period and age dependence ?

– What about **Hypoellipticity** in the original Hawkes frame, without diffusion approximation (should be okay, Vandermonde determinant)

Höpfner, R., Löcherbach, E., Thieullen, M. (2014) : Strongly degenerate time inhomogeneous SDEs : densities and support properties. Application to a Hodgkin-Huxley system with periodic input. Bernoulli, to appear.

Höpfner, R., Löcherbach, E., Thieullen, M. (2016) : Ergodicity for a stochastic Hodgkin-Huxley model driven by Ornstein-Uhlenbeck type input. Annales de l'IHP **52**, No. 1, 483–501 (2016).

Höpfner, R., Löcherbach, E., Thieullen, M. (2016) : Ergodicity and limit theorems for degenerate diffusions with time periodic drift. Application to a stochastic Hodgkin-Huxley model. To appear in ESAIM P& S.

Ditlevsen, S., Löcherbach, E. (2017) : Multi-class oscillating systems of interacting neurons. SPA, to appear.

Thank you for your attention.