Probability for Neurosciences.

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Part 1. Channel noise for a single neuron

Conductance-based neuron models

A family of deterministic multidimensional models

$$
\begin{aligned}
C\frac{dV}{dt} &= -I_{ion}(V, w^{(1)}, \cdot, \cdot, \cdot, w^{(n)}) + I(t) \\
\frac{dw^{(j)}}{dt} &= \alpha_j(V)(1 - w^{(j)}) - \beta_j(V)w^{(j)}
\end{aligned}
$$

- $w^{(j)} \in [0, 1]$ probability that channels (or gates) of type j are open at time t,
- I_{ion} : the sum of ionic currents
- for type j ions, $I_j = G_j(w^{(1)}, \cdot, \cdot, \cdot, w^{(n)})(V - V_j)$ where V_j= reversal potential, G_j= varying conductance to be specified
- $I(t)$=external stimulus.

Deterministic 3D Morris-Lecar model

$$\begin{aligned}
C\frac{dV}{dt} &= I(t) - g_{Ca}u_{Ca}(V - V_{Ca}) - g_K u_K(V - V_K) - g_L(V - V_L),\\
\frac{du_{Ca}}{dt} &= (1 - \alpha_{Ca}(V))u_{Ca} - \beta_{Ca}(V)u_{Ca},\\
\frac{du_K}{dt} &= (1 - \alpha_K(V))u_K - \beta_K(V)u_K.
\end{aligned}$$

C is the membrane capacitance,
g_{Ca}, g_K are the maximal conductances,
V_{Ca}, V_K are the reversal potentials associated with ions Ca, K,
$I(t)$ is the input current.

3D Morris-Lecar (I)

2 types of ions : calcium and potassium

- current balance

$$C\frac{dV_t}{dt} + I_{\mathrm{Ca}} + I_{\mathrm{K}} + I_L = I$$

$$G_{\mathrm{Ca}} = g_{\mathrm{Ca}} u_{\mathrm{Ca}},\ G_{\mathrm{K}} = g_{\mathrm{K}} u_K,\ G_{\mathrm{L}} = g_{\mathrm{L}} = const.$$

u_{Ca} (resp. u_K) interpreted as proportion of open calcium (resp. potassium) channels

3D Morris-Lecar (II)

We use Morris-Lecar model with functions α, β given by

$$\begin{aligned}
\alpha_{Ca}(V) &= \frac{1}{2}\cosh\left(\frac{V-V_1}{2V_2}\right)\left(1+\tanh\left(\frac{V-V_1}{V_2}\right)\right)\\
\alpha_{K}(V) &= \frac{1}{2}\lambda_n\cosh\left(\frac{V-V_3}{2V_4}\right)\left(1+\tanh\left(\frac{V-V_3}{V_4}\right)\right)\\
\beta_{Ca}(V) &= \frac{1}{2}\cosh\left(\frac{V-V_1}{2V_2}\right)\left(1-\tanh\left(\frac{V-V_1}{V_2}\right)\right)\\
\beta_{K}(V) &= \frac{1}{2}\lambda_n\cosh\left(\frac{V-V_3}{2V_4}\right)\left(1-\tanh\left(\frac{V-V_3}{V_4}\right)\right)
\end{aligned}$$

2D Morris-Lecar

$$
\begin{aligned}
C\,\frac{dV}{dt} &= g_K\,\omega\,(V_K - V) + g_{Ca}\,m_\infty(V)\,(V_{Ca} - V) \\
\frac{d\omega}{dt} &= \alpha(V)(1-\omega) - \beta(V)\omega
\end{aligned}
$$

4D Hodgkin-Huxley (I)

3 types of gates : m and h (resp. n) for a sodium (resp. potassium) channel,

- current balance

$$C\frac{dV_t}{dt} + I_{\mathrm{Na}} + I_{\mathrm{K}} + I_L = I$$

- currents $I_j = G_j\,(V - V_j)$,

$$G_{\mathrm{Na}} = g_{\mathrm{Na}} m^3 h,\ G_{\mathrm{K}} = g_{\mathrm{K}} n^4,\ G_{\mathrm{L}} = g_{\mathrm{L}} = const.$$

- m, h, n are probability that gate of each type is open
- the probability that a sodium (resp. potassium) channel is open is $m^3 h$ (resp. n^4).

4D Hodgkin-Huxley (II)

$$\begin{aligned}
C\frac{dV_t}{dt} &= -g_{\mathrm{Na}}m^3h(V - V_{\mathrm{Na}}) - g_{\mathrm{K}}n^4(V - V_K) - g_{\mathrm{L}}(V - V_L) + I(t) \\
d\frac{dm_t}{dt}_t &= \alpha_m(V_t)(1 - m_t) - \beta_m(V_t)m_t \\
d\frac{dh_t}{dt}_t &= \alpha_h(V_t)(1 - h_t) - \beta_h(V_t)h_t \\
d\frac{dn_t}{dt}_t &= \alpha_n(V_t)(1 - n_t) - \beta_n(V_t)n_t
\end{aligned}$$

Set of constant values :

$$C = 1,$$

$$g_{\mathrm{K}} = 36, g_{\mathrm{Na}} = 120, g_{\mathrm{L}} = 0.3$$

$$V_{\mathrm{K}} = -12, V_{\mathrm{Na}} = 120, V_{\mathrm{L}} = 10.6$$

4D Hodgkin-Huxley (III)

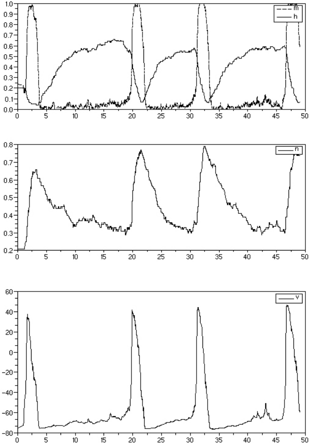
The opening/closing rates depend on V :

$$\alpha_n(V) = \frac{0.1 - 0.01\,V}{\exp(1 - 0.1\,V) - 1}, \quad \beta_n(V) = 0.125\exp(-V/80),$$

$$\alpha_m(V) = \frac{2.5 - 0.1\,V}{\exp(2.5 - 0.1\,V) - 1}, \quad \beta_m(V) = 4\exp(-V/18),$$

$$\alpha_h(V) = 0.07\exp(-V/20), \quad \beta_h(V) = \frac{1}{\exp(3 - 0.1\,V) + 1}.$$

The Hodgkin-Huxley Model : a fully coupled evolution



Common structure of conductance-based models

They are made of 2 parts :

- current balance for V,
- underlying stochastic gating mechanism of channels/gates for an **infinite** number of channels/gates.

However the number of gates/channels is finite.

Question : which stochastic version would be the most relevant and how to choose it ?

Two possible stochastic HH models (I)

The two states model : the building blocks are the *gates*.
Let N be the number of each type of channels (sodium and potassium),

- continuous component is V_N, the membrane potential of a neuron with this amount of channels
- any single gate is modeled by a two-state jump process with V_N dependent rates
- the jumping component u_N is the vector of proportions of open gates. For (HH), $u_N = (u_N^{(m)}, u_N^{(n)}, u_N^{(h)})$ where

$$u_N^{(m)}(t) = \frac{1}{N}\Sigma_{l=1}^{N} c_l^{(m)}(t)$$

where $c_l^{(m)}$ are jump processes in $\{ 0, 1 \}$ with rates $\alpha_m(V_N)$, $\beta_m(V_N)$. Idem for $u_N^{(n)}$, $u_N^{(h)}$.

Two possible stochastic HH models (II)

- Evolution of V_N, $\frac{dV_N}{dt} = f(V_N, u_N^{(m)}, u_N^{(n)}, u_N^{(h)})$ with

  $$f(v,p,q,r) = -g_{\mathrm{Na}} p^3 q (v - V_{\mathrm{Na}}) - g_{\mathrm{K}} r^4 (v - V_K) - g_{\mathrm{L}} (v - V_L)$$

- If $(u_N^{(m)}(0), u_N^{(n)}(0), u_N^{(h)}(0)) = (u_1, u_2, u_3)$ let v solve

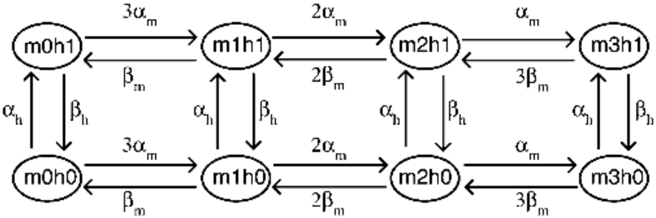
  $$\frac{dv}{dt} = f(v, u_1, u_2, u_3), \quad v(0) = V_N(0).$$

  Then the first jump time τ is defined by

  $$\mathbf{P}(\tau > t) = \mathrm{e}^{-N \int_0^t \Sigma_{j=1}^3 \beta_j(v(s))u_j + \alpha_j(v(s))(1-u_j)ds}.$$

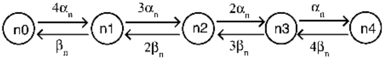
Two possible stochastic HH models (III)

Skaugen and Walloe : the building blocks are channels.



Gating of a sodium channel.

Two possible stochastic HH models (IV)



Gating of a potassium channel.

Two possible stochastic HH models (V)

Eight (resp. five) states for a sodium (resp. potassium) channel.

A single open state $m3h1$ (resp. $n4$).

- In this model $\frac{dV_N}{dt} = f(V_N,\, p_{N,\mathrm{Na}},\, p_{N,\mathrm{K}})$, with

  $$f(v,p,q,r) = -g_{\mathrm{Na}}\, p_{N,\mathrm{Na}}\,(v-V_{\mathrm{Na}}) - g_{\mathrm{K}}\, p_{N,\mathrm{K}}\,(v-V_{\mathrm{K}}) - g_{\mathrm{L}}(v-V_L),$$

- $p_{N,\mathrm{Na}}$ is the proportion of sodium channels in state $m3h1$,
- $p_{N,\mathrm{K}}$ the proportion of potassium channels in state $n4$.

The complete PDMP is $(V_N,\, p^{(j)})$ where $p^{(j)}$ are the proportions of channels in the total 13 possible states.

$N \to +\infty$ for the two types of PDMP sequences

(HH)-gates converges (u.c. compacts) to 4D HH.

(HH)-channels converges to a HH of dim. 14 whose first component V_t coincides with that of 4D HH only if initial conditions are related by

These convergence results can be proved with the classical methods about convergence of sequences of processes (cf. the courses by B. Cloez and J. Fontbona).

Piecewise Deterministic Markov Processes

Deterministic dynamics between successive random events

Data (cf. Davis) :

- a multidim. countable set K, an integer d
- $(f(\cdot, u))_{u\in K}$ family of vector fields
- $\lambda : \mathbf{R}^d \times K \to [0, 1]$ family of jump intensities
- $Q : B \times (\mathbf{R}^d \times K) \to [0, 1]$ family of jump measures.

Iterative construction of process $(X_t) = (Y_t, u_t)$

- Take initial value $X_0 = (Y_0, u_0)$
- Solve $\frac{dy(t)}{dt} = f(y(t), u_0); \quad y_0 = Y_0$
- Define T_1 such that

$$\mathbf{P}(T_1 > t) = \mathrm{e}^{-\int_0^t \lambda(y(s), u_0) ds}$$

- Define $\xi_1 \in \mathbf{R}^d \times K$ with law $Q(\cdot; (y(T_1), u_0))$ conditionally on T_1
- Define

$$\begin{array}{rcl} X_t & = & (y(t), u_0) \quad \text{if} \quad t < T_1 \\ X_{T_1} & = & \xi_1 \end{array}$$

PDMP as Markov processes

- (Y_t, u_t) is a Markov process
- Infinitesimal generator

$$\mathcal{L}h(x) = f(x)\nabla h(x) + \lambda(x)\int (h(\tilde{x}) - h(x))Q(d\tilde{x}, x)$$

  with $f(x)\nabla h(x) := f(y,u)\nabla_y h(y,u)$ if $x = (y,u)$.
- (Y_t) is not a Markov process
- Davis (1984,1993), Costa (1990), Jacobsen (2006), Costa-Dufour (2008)

The Fluid Limit Assumption

- Fluid Limit assumption in presence of jumps : *small jumps at high frequency.*
- For sequences of Markov jump processes in the fluid limit, LLN, CLT have been proved (Jacod, Kurtz) as well as CLT for exit times and exit points.
- Fluid Limit assumption for a sequence (X_N) :

  $$F_N(x) := \lambda_N(x) \int (z - x) Q_N(x, dz) \rightarrow F(x), \quad \forall x,$$

  when $N \rightarrow \infty$, where λ_N is the jump intensity, Q_N the jump measure of X_N.
- Fluid Limit provides LLN. Stronger assumption is required to prove CLT : convergence of

  $$G_N^{i,j}(x) = \alpha_N^2 \lambda_N(x) \int (z_i - x_i)(z_j - x_j) Q_N(x, dz)$$

Check Fluid Limit

For fully coupled systems of the form

$$\begin{aligned} \frac{dV_N}{dt} &= f(V_N, u_N) \\ u_N^{(i)} &= \frac{1}{N}\Sigma_{l=1}^{N} c_l^{(i)} \end{aligned}$$

- λ_N is proportional to N
- $\int (z-x)Q_N(x,dz)$ is proportional to $\frac{1}{N}$
- take $\alpha_N = \sqrt{N}$

Then both LLN and CLT are satisfied.

LLN and CLT

Let $x_N = (V_N, u_N)$ and $x = (V, u)$ solve

$$\begin{aligned} \frac{dV}{dt} &= f(V,u) \\ \frac{du^{(j)}}{dt} &= \alpha_j(V)(1-u^{(j)}) - \beta_j(V)u^{(j)} \end{aligned}$$

- LLN

$$\forall T > 0, \forall \delta > 0, \lim_{N \to +\infty} \mathbf{P}(\sup_{[0,T]} |x_N - x| > \delta) = 0$$

- CLT Set $b^{(j)}(x) = \alpha_j(V)(1-u^{(j)}) - \beta_j(V)u^{(j)}$.
  $\sqrt{N}(x_N - x)$ converges in distribution to $z = (z^v, z^{(j)})$ s.t.

$$\begin{aligned} dz_t^v &= \nabla f(x_t) \cdot z_t dt \\ dz_t^{(j)} &= \nabla b^{(j)}(x_t) \cdot z_t dt + q(x_t)^j dW_t^j \end{aligned}$$

- when each $u^{(j)} \in \mathbf{R}$, $q^j(x) = \sqrt{\alpha_j(V)(1-u^{(j)}) + \beta_j(V)u^{(j)}}$.

A comment on CLT

- Second CLT statement :

$$\sqrt{N}(u_N(t) - u_N(0) - \int_0^t b(V_N(s), u_N(s))ds)$$

  converges in distribution to $R = (\int_0^t q^j(x_s)dW_s^j)_{t\geq 0}$.
- Diffusion approximation for (V_N, u_N) by

$$\begin{aligned} d\tilde{V}_N &= f(\tilde{V}_N, \tilde{u}_N)dt \\ d\tilde{u}_N^{(j)} &= b^{(j)}(\tilde{V}_N, \tilde{u}_N)dt + \frac{1}{\sqrt{N}} q^j(\tilde{V}_N, \tilde{u}_N)dW_t^j \end{aligned}$$

A comment on exit time/point

Let ϕ of class C^1 such that $\phi(x(0)) > 0$. Denote $\dot{x} = F(x)$ and define

$$T_N := \inf\{t > 0; \phi(x_N(t)) \leq 0\}$$

$$T := \inf\{t > 0; \phi(x(t)) \leq 0\}$$

$$\pi(T) := -\frac{\nabla\phi(x(T)).z(T)}{\nabla\phi(x(T)).F(x(T))}$$

If $T < \infty$ and $\nabla\phi(x(T)).F(x(T)) < 0$, then convergence in distribution when $N \to \infty$:

$$\sqrt{N}(T_N - T) \to \pi(T)$$

$$\sqrt{N}(x_N(T_N) - x(T)) \to z(T) + \pi(T)F(x(T))$$

This can be used to study the variance of the *latency* time.

A comment on speed of convergence

With exponential inequalities for martingales we can prove the following

$$\limsup_{N\to\infty} \frac{1}{N} \log \mathbf{P}(\sup_{[0,T]} |x_N - x| > \delta) \leq -\frac{\delta \mathrm{e}^{-B(T)T}}{CT}$$

Example (I)

Consider **Model 1** with *channels* of a single type having 3 possible states (m_2 is the open state)

$$\mathrm{m}_0 \underset{\beta_\mathrm{m}(\mathrm{V})}{\overset{2\,\alpha_\mathrm{m}(\mathrm{V})}{\rightleftharpoons}} \mathrm{m}_1 \underset{2\beta_\mathrm{m}(\mathrm{V})}{\overset{\alpha_\mathrm{m}(\mathrm{V})}{\rightleftharpoons}} \mathrm{m}_2$$

and **Model 2** where each channel has two *gates* of a single type *m* having two possible states in $\{0, 1\}$ (channel is open when the two gates are open).

Example (II)

Corresponding deterministic limits :

to **Model 1 :** $(V(t), m_0(t), m_1(t), m_2(t))$,

$$\begin{aligned}
C\frac{dV}{dt} &= -g\, m_2(V - V_m) - g_L\,(V - V_L) \\
\frac{dm_2}{dt} &= -2\beta m_2 + \alpha m_1 \\
\frac{dm_1}{dt} &= 2\beta m_2 - (\alpha + \beta)m_1 + 2\alpha m_0 \\
\frac{dm_0}{dt} &= \beta m_1 - 2\alpha m_0.
\end{aligned}$$

to **Model 2 :** $(v(t), m(t))$,

$$\begin{aligned}
C\frac{dv}{dt} &= -g\, m^2(v - V_m) - g_L\,(v - V_L), \\
\frac{dm}{dt} &= (1 - m)\alpha(v) - m\beta(v),
\end{aligned}$$

Example (III)

If the initial conditions satisfy $V(0) = v(0)$,
$(m_0(0), m_1(0), m_2(0)) = ((1 - m(0))^2, 2m(0)(1 - m(0)), m(0)^2)$

then at any time $t > 0$,

$$\begin{aligned} V(t) &= v(t), \\ m_0(t) &= (1 - m(t))^2, \\ m_1(t) &= 2m(t)(1 - m(t)), \\ m_2(t) &= m(t)^2. \end{aligned}$$

In the sequel we assume that these conditions are satisfied.

Multiscale character of the previous models

In the (HH) above models the variable *m* is faster than the other variables : we replace α_m and β_m by $\frac{\alpha_m}{\epsilon}$ and $\frac{\beta_m}{\epsilon}$ for $\epsilon > 0$.

It is possible to perform a dimension reduction.

Reduction of deterministic HH

Let us denote

$$F(V,m,n,h) = -g_{\mathrm{Na}} m^3 h (V - V_{\mathrm{Na}}) - g_{\mathrm{K}} n^4 (V - V_K) - g_{\mathrm{L}} (V - V_L)$$

Then the reduced model (the $\epsilon \to 0$ limit) is 3D :

$$\begin{aligned} C\frac{dV_t}{dt} &= F(V, m_\infty(V), n, h) \\ \frac{dh_t}{dt} &= \alpha_h(V_t)(1 - h_t) - \beta_h(V_t) h_t \\ \frac{dn_t}{dt} &= \alpha_n(V_t)(1 - n_t) - \beta_n(V_t) n_t \end{aligned}$$

where $m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}$.

Reduction of (HH)-gates

The reduced model is again a PDMP :

h and n remain two states with rates α_h, β_h (resp. α_n, β_n).

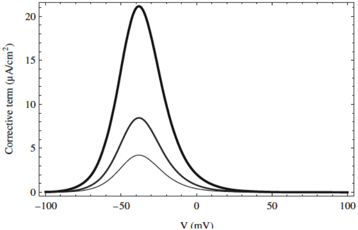
Evolution of V between jumps of h or n is

$$\frac{dV_t}{dt} = F(V, m_\infty(V), n, h) - g_{\mathrm{Na}}\, h\, (V - V_{\mathrm{Na}})\, K_N(V).$$

There is an additional term in $\frac{dV_t}{dt}$ which depends on the number N of sodium channels.

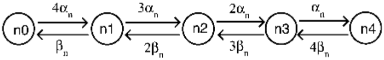
The additional drift in (HH)-gates

$$K_N(V) = \frac{3}{N_m} m_\infty(V)^2(1 - m_\infty(V)) + \frac{1}{N_m^2} m_\infty(V)(1 + 2m_\infty(V)^2).$$



Reduction of (HH)-channels

Again the reduced model is a PDMP,
2 states *sodium* channels : h has two states and rates α_h, β_h,
5 states *potassium* channels :



evolution of V between jumps of h or n is

$$\frac{dV_t}{dt} = -g_{\mathrm{Na}}\, m_\infty(V)^3\, h\,(V - V_{\mathrm{Na}}) - g_{\mathrm{K}}\, p_{\mathrm{K}}\,(V - V_{\mathrm{K}}) - g_{\mathrm{L}}(V - V_L),$$

where h is the proportion of open sodium channels,
and p_{K} the proportion of potassium channels in state $n4$.

Previous limits are LLN

Remark : we have encountered previously two limit results.

- $N \to \infty$, ϵ is fixed, (HH)-gates and (HH)-channels converge to deterministic HH type models,
- $\epsilon \to 0$, N is fixed, (HH)-gates and (HH)-channels converge to stochastic PDMP models.

In both results the convergence is in the following sense

$$\lim_{N \to +\infty} \mathbf{P}(\sup_{s \in [0,T]} |Z_k(s) - Z(s)| > \alpha) \to 0$$

for all $T > 0$, $\alpha > 0$ (resp. $\lim_{\epsilon \to 0}$) cf. the course by B. Cloez.

Associated CLT in ϵ (I)

In the sequel we focus on limits when $\epsilon \to 0$ for fixed N.

We can prove that (HH)-gates and (HH)-channels admit *switching diffusion* approximations. The CLT is read in the V_t evolution.

For (HH)-gates :

$$\begin{aligned} dV_t &= [F(V, m_\infty(V), h, n) - g_{\mathrm{Na}} h(V - V_{\mathrm{Na}}) K_N(v)]dt \\ &+ \sqrt{\epsilon}\, \sigma(V_t, h_t)\, dW_t. \end{aligned}$$

Note that $\sigma(V_t, h_t)$ does not depend on N_{Na}.

Associated CLT in ϵ (II)

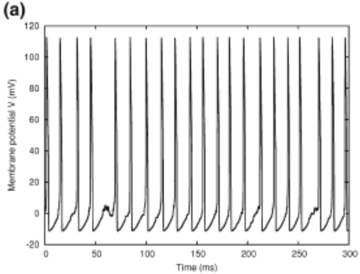
For (HH)-channels :

$$\begin{aligned} dV_t &= [-g_{\mathrm{Na}} m_\infty(V)^3 h(V - V_{\mathrm{Na}}) - g_{\mathrm{K}} p_{\mathrm{K}}(V - V_{\mathrm{K}}) - g_{\mathrm{L}}(V - V_L)]dt \\ &+ \sqrt{\frac{\epsilon}{N_{\mathrm{Na}}}}\, \sigma(V_t, h_t)\, dW_t. \end{aligned}$$

In this case the diffusion term depends on N_{Na}.

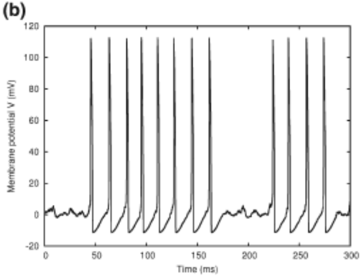
Combined effect of N and ϵ on ISI. (HH)-gates. (I)

10^4 gates h and n, $N = 30, \epsilon = 0.1$: periodicity



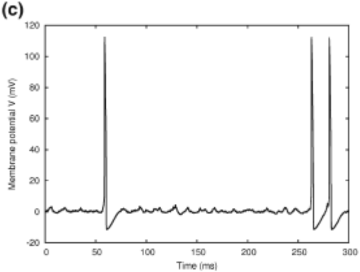
Combined effect of N and ϵ on ISI. (HH)-gates. (II)

$N = 70, \epsilon = 0.1$: bursting



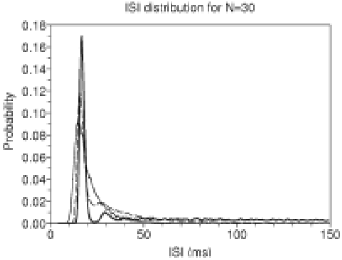
Combined effect of N and ϵ on ISI. (HH)-gates. (III)

$N = 120, \epsilon = 0.1$: small oscillation around equilibrium point, rare excursions.



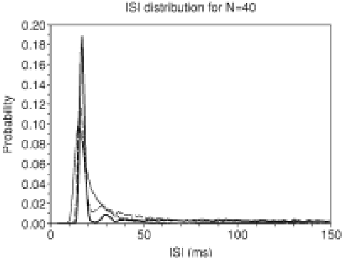
(HH)-channels (I)

$N = 30, \epsilon = 0.001$ (bold), $\epsilon = 0.01$ (dashed), $\epsilon = 0.1$ (thin) : no bursting for $\epsilon = 0.1$.



(HH)-channels (II)

$N = 40, \epsilon = 0.001$ (bold), $\epsilon = 0.01$ (dashed), $\epsilon = 0.1$ (thin) : no bursting for $\epsilon = 0.1$.



(Reference for this part

This part is based on the paper in collaboration with Khashayar PAKDAMAN and Gilles WAINRIB published in

- *J. Comput. Neuroscience*, 13 August 2011 (for the numerics part)
- *Advances in Applied Probability* (2010) and *Stochastic Processes and their Applications* (2012) for the mathematical proofs.

Part 2. Neuronal populations

Leaky Integrate and Fire Models

These models are 1D and composed of

- a *threshold* value V_F,
- the underthreshold evolution of the membrane potential described by an sde (mainly Ornstein-Uhlenbeck $dV_t = (-\frac{V_t}{\tau} + \mu)dt + \sigma dW_t$, or Cox-Ingersoll-Ross),
- the initial value V_0,
- the *reset* value : when the potential reaches the threshold it is instantaneously set back to the value V_0.

Compared to conductance-based models,

- LIF models contain less parameters,
- populations of LIF neurones are easier to simulate,
- however they are not biologically detailed.

A population of LIF neurons (I)

In two papers F. Delarue, J. Inglis, E. Tanré and S. Rubenthaler consider N neurons, for $i \in \{1, \cdot, \cdot, \cdot, N\}$,

$$V_t^i = V_0^i + \int_0^t b(V_s^i)ds + \frac{\alpha}{N}\sum_{j=1}^N M_t^j + W_t^i - M_t^i,$$

where M_t^i is the number of times neuron i has spiked before time t,

$$M_t^i = \sum_{k \geq 1} \mathbf{1}_{[0,t]}(\tau_k^i),$$

with

$$\tau_0^i := 0, \quad \tau_k^i := \inf\{t > \tau_{k-1}^i;\ V_{t-}^i \geq 1\}, \ \ \forall k \geq 1.$$

A population of LIF neurons (II)

- the potential at the soma of each neuron is a LIF model,
- In this model $V_F = 1$, reset value $V_R = 0$,

- the (τ_k) are the jump or reset times of V : each time V reaches the threshold, M (resp. V) is increased (resp. decreased) by 1 and V is instantaneously reset to $V_R = 0$,

- if one neuron in the system fires at some time t, the potential of any other neuron undergoes a jump proportional (with coefficient α) to the proportion of neurons firing simultaneously at that time t because of the interaction term $\frac{\alpha}{N} \sum_{j=1}^{N} M_t^j$.

- The W^i are independent Brownian motions.

A population of LIF neurons (III)

- Additional assumption : the initial values V_0^i are independent.

Delarue et al. address the question : does the system converge when $N \to +\infty$? Can we prove a propagation of chaos result for this model ?

Propagation of chaos holds if given a subset of k neurons, they are independent and follow the same law when $N \to +\infty$.

A population of LIF neurons (IV)

Then the *typical* behavior of a neuron in the population is given by the LLN limit.

Here a typical neuron should satisfy

$$V_t = V_0 + \int_0^t b(V_s)ds + \alpha\, E(M_t) + \sigma W_t - M_t \tag{1}$$

called the mean field evolution.

A population of LIF neurons (V)

Actually the process solution is the pair (V_t, M_t) satisfying (1) and (2)-(3) as follows

$$M_t = \sum_{k \geq 1} \mathbf{1}_{[0,t]}(\tau_k), \tag{2}$$

$$\tau_0 := 0, \quad \tau_k := \inf\{t > \tau_{k-1};\ V_{t^-} \geq 1\}, \ \forall k \geq 1. \tag{3}$$

Population density model

This is the PDE version of (1).

Suppose that $e(t) := E(M_t)$ is $\mathcal{C}^1$. Remember that $V_F = 1$, $V_R = 0$.

$$\partial_t \, p(t,y) + \partial_y \left((-y + \alpha \, e'(t)) \, p(t,y) \right) - \frac{1}{2} \partial_{yy} \, p(t,y) = \delta_0(y) \, e'(t)$$

on $]-\infty, 1[\times]0, +\infty[$,
with $p(t,1) = 0, \; p(t,-\infty) = 0, \; p(0,y) = p^0(y)$.

We have moreover $e'(t) = -\frac{1}{2} \, \partial_y \, p\,(t,1)$ since $p(t,x)dx$ is a probability density on $]-\infty, 1[$.

History of the model

Omurtag, Knight, Sirovich (2000) Nykamp, Tranchina (2000)
Somers et al. (1995)
Brunel, Hakim (1999, 2000)
Cai et al. (2006)
Caceres, Carrillo, Perthame (2011)
Dumont, Henry (2012, 2013)
Delarue et al. (2014, 2015),
Inglis, Talay (2015).

Propagation of chaos in Probability

Propagation of chaos for diffusions has been extensively studied in Probability by for instance by A. S. Sznitman, S. Méléard, C. Graham (cf. for instance Ecole d'été de Saint Flour 1991, LNM 1464 and C.I.M.E. Course, 1995, LNM 1627).

In the model considered by Delarue and coauthors, neurons interact through their hitting time of V_F.

This type of interaction does not fit the assumptions of these previous works.

The meaning of $e'(t)$

$e'(t) = \frac{d}{dt}\,\mathbf{E}(M_t) = -\frac{1}{2}\,\partial_y\, p\,(t,1)$ is the mean firing rate of the infinite network with $N = +\infty$.

$e'(t)$ very large, means that a large proportion of neurons in the network spike at that time t. The network is said to *synchronize* at time t.

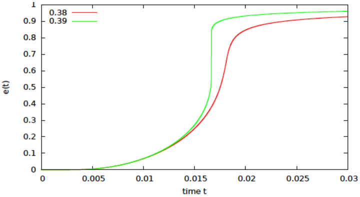
Corresponding mathematical meaning : if $e'(t) = +\infty$, the solution of (1) does not exist for times larger than t : there is a *blow-up*.

Example of result (I)

- $(V_t, M_t)_{t\in[0,T]}$ is a solution of (1)-(3) if $e \in \mathcal{C}^1([0,T])$ and (X_t) is a strong solution of (1).
- (cf. Delarue et al. (2014)) Let $X_0 = x_0 < 1$. There exists $\alpha_0 \in]0,1]$ depending on x_0 such that for all $\alpha \in]0,\alpha_0[$ and all $T > 0$, there is a solution on $[0,T]$ in the previous sense and it is unique.

Example of result (II)

Let $x_0 = 0.8$, $b \equiv 0$. Numerics (particle method) suggest that a global solution exists for $\alpha \leq 0.38$ but fails to exist for $\alpha \geq 0.39$.



A model without blow-up (I)

Problem :

- blow up is not biologically meaningful,
- instantaneous transmission from one neuron to the others is not either.

Inglis and Talay (2015) proposed another model. Note that their model allows for different synaptic weights and a non constant diffusion matrix.

A model without blow-up (II)

$$
\begin{aligned}
V_t^i &= V_0^i + H(t) + \int_0^t b(V_s^i)ds + \int_0^t \sigma(V_s^i)dW_s^i \\
&+ \sum_{j=1}^N \frac{J_{ij}}{S_i^N} \int_0^t G(t-s)M_s^j ds - M_t^i,
\end{aligned}
$$

where $S_i^N = \sum_{j=1}^N J_{ij}$, and as before

$$M_t^i = \sum_{k\geq 1} \mathbf{1}_{[0,t]}(\tau_k^i),$$

with

$$\tau_0^i := 0, \quad \tau_k^i := \inf\{t > \tau_{k-1}^i;\ V_{t-}^i \geq 1\}, \quad \forall k \geq 1.$$

A model without blow-up (III)

The $J_{ij} \geq 0$ are the synaptic weights.

The interaction term is $\sum_{j=1}^{N} \frac{J_{ij}}{S_i^N} \int_0^t G(t-s) M_s^j ds$ compared to $\frac{\alpha}{N} \sum_{j=1}^{N} M_t^j$ in the model of Delarue et al. Here there is *no* instantaneous transmission.

The kernel G is bounded and twice differentiable with bounded derivatives, and satisfies $G(0) = G'(0) = 0$.
Delarue et al. corresponds to $G = \delta_0$. It is not a particular case of Inglis, Talay.

We still have $V_t^i < 1$ a.s. for all i and t.

Motivation for the model without blow-up (I)

For simplicity ignore the axon part of a neuron.

- Dendritic tree : modeled as $\mathbb{R}$. The potential at a point ξ on the dendritic tree follows

$$\partial_t U(t,\xi) = \frac{1}{2}\partial_{\xi\xi} U(t,\xi) - \gamma U(t,\xi) + f(t,\xi),$$

  with $\gamma > 0$, $f(t,\xi)$ an applied current.

- Soma (located at $\xi = 0$) : the potential at the soma follows a LIF with an external current $I(t)$,

$$\begin{aligned} V_t &= V_0 + I(t) + \int_0^t b(V_s)ds + \int_0^t \sigma(V_s)dW_s \\ &- M_t, \end{aligned}$$

  where M_t is the number of spikes of the neuron in $[0,t]$ and $I(t)$ depends on the potential along the dendritic tree.

Motivation for the model without blow-up (II)

Now let us go back to the previous network, take neuron *i*. Then

- the potential at a point ξ on the dendritic tree of neuron *i*

$$\partial_t U^i(t,\xi) = \frac{1}{2}\partial_{\xi\xi} U^i(t,\xi) - \gamma U^i(t,\xi) + f^i(t,\xi),$$

- and the potential at the soma of neuron *i*

$$\begin{aligned} V_t^i &= V_0^i + I_i(t) + \int_0^t b(V_s^i)ds + \int_0^t \sigma(V_s^i)dW_s^i \\ &- M_t^i. \end{aligned}$$

Now $f^i(t,\xi)$ depends on the spike trains of neurons connected to neuron *i*.

Motivation for the model without blow-up (III)

- $I_i(t) := U^i(t,0)$ for all $t \geq 0$ (think to Ohm's law),
- $f^i(t,\xi)$ is taken as follows

$$f^i(t,\xi) = \frac{1}{S_i^N} \sum_{j=1}^{N} J_{ij}\, \rho(\xi) \sum_{k=1}^{\infty} \delta_0(t - \tau_k^j). \tag{4}$$

The first choice (more complicated) would be

$$f^i(t,\xi) = \sum_{j=1,\, j\neq i}^{N} \rho_{j\to i}(\xi) \sum_{k=1}^{\infty} \delta_0(t - \tau_k^j).$$

where $\rho_{j\to i}$ is the density of synapses on dendritic tree of i coming from presynaptic neuron j. Distribution of synapses is supposed homogeneous in (4) for simplicity.

Motivation for the model without blow-up (IV)

This leads to the coupled system

$$\begin{aligned}
\partial_t U^i(t,\xi) &= \frac{1}{2}\partial_{\xi\xi} U^i(t,\xi) - \gamma U^i(t,\xi) + \frac{1}{S_i^N}\sum_{j=1}^{N} J_{ij}\rho(\xi)\sum_{k=1}^{\infty}\delta_0(t-\tau_k^j) \\
V_t^i &= V_0^i + U^i(t,0) + \int_0^t b(V_s^i)ds + \int_0^t \sigma(V_s^i)dW_s^i - M_t^i.
\end{aligned}$$

Motivation for the model without blow-up (V)

It remains to deduce a self-contained system for the V^i, M^i from the previous coupled system.

This is done by expressing $U^i(t,0)$ (actually $U^i(t,\xi)$) using the Green kernel

$$\mathcal{G}(t,\xi) = \frac{1}{\sqrt{2\pi t}}\,\mathrm{e}^{-\gamma t}\,\mathrm{e}^{-\frac{1}{2}\xi^2},$$

that is

$$\begin{aligned} U^i(t,\xi) &= [\mathcal{G}(t,\cdot)\star U^i(0,\cdot)](\xi) \\ &+ \int_0^t \mathcal{G}(t-s,\xi'-\xi)\sum_{j=1}^{N}\frac{J_{ij}\rho(\xi')}{S_i^N}\sum_{k=1}^{\infty}\delta_0(t-\tau_k^j)d\xi' ds. \end{aligned}$$

Motivation for the model without blow-up (V)

Note that $\sum_{k=1}^{\infty} \delta_0(t - \tau_k^j) = \frac{d}{ds} M_s^j$. We obtain the *formal* expression

$$\begin{aligned} U^i(t,0) &= [\mathcal{G}(t,\cdot) \star U^i(0,\cdot)](0) \\ &+ \int_0^t [\mathcal{G}(t-s,\cdot) \star \rho](0) \frac{d}{ds} \sum_{j=1}^{N} \frac{J_{ij}}{S_i^N} M_s^j \, ds. \end{aligned}$$

Motivation for the model without blow-up (V)

The formal term is given a meaning through an integration by parts. To get rid of boundary conditions it is assumed that there are no synapses at the soma : $\rho(0) = 0$ as well as $\rho^{(k)}(0) = 0$. This leads to

$$\begin{aligned} V_t^i &= V_0^i + \int_0^t b(V_s^i)ds + \int_0^t \sigma(V_s^i)dW_s^i \\ &+ [\mathcal{G}(t,\cdot) \star U^i(0,\cdot)](0) \\ &+ \sum_{j=1}^N \frac{J_{ij}}{S_i^N} \int_0^t \frac{d}{ds}[\mathcal{G}(t-s,\cdot) \star \rho](0)\ M_s^j\, ds \\ &- M_t^i. \end{aligned}$$

Limit equation without blow-up

The limit of the previous interacting system should satisfy

$$\begin{aligned} V_t \quad = \quad & V_0 + \int_0^t b(V_s)ds + \int_0^t \sigma(V_s)dW_s \\ & + H(t) + \int_0^t G(t-s,\cdot)\,\mathbb{E}(M_s)\,ds - M_t, \end{aligned}$$

where

$$M_t = \sum_{k\geq 1} \mathbf{1}_{[0,t]}(\tau_k),$$

$$\tau_0 := 0, \quad \tau_k := \inf\{t > \tau_{k-1};\ V_{t^-} \geq 1\}.$$

In their paper Inglis and Talay show that indeed there is convergence when $N \to +\infty$ and that there is no blow-up for the limit equation.

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Delarue et al. :

- arXiv :1211.0299v4 [math.PR] 2 Jun 2014
- arXiv :1406.1151v3 [math.PR] 23 Jan 2015

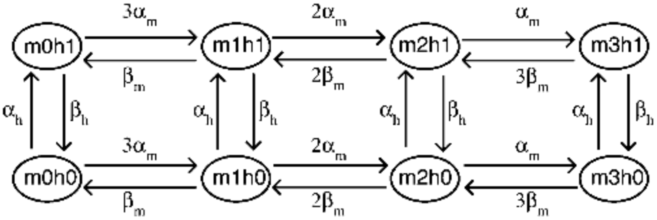
Talay, Inglis :

- arXiv :1409.8221v3 [math.PR] 6 Jan 2015

Part 3. Infinite dimensional PDMP models

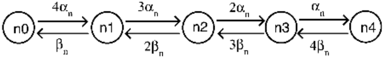
Reminder : gating mechanism of ionic channels (I)

Channels open and close at rates depending on membrane potential V : example of Hodgkin-Huxley model



for a sodium channel

Reminder : gating mechanism of ionic channels (II)



for a potassium channel

Reminder : channel noise

We want to model a neuron with a **finite** number of channels and study the impact of their stochastic gating mechanism :

channel noise

We also want to consider spatial models to take into account the **propagation** of the potential along the axon including **inhomogeneous repartition** of channels along the axon.

We want to handle the different time scales present in the gating mechanisms.

Deterministic Conductance-based Models (I)

Point models : multidimensional models

$$\begin{aligned} C\frac{dV}{dt} &= -I_{ion}(V, p^{(1)}, \cdot, \cdot, \cdot, p^{(n)}) + I(t) \\ \frac{dp_k^{(j)}}{dt} &= \sum_{i\neq k} \alpha_{i,k}(V) p_i^{(j)} - \alpha_{k,i}(V) p_k^{(j)} \end{aligned}$$

- $p_k^{(j)} \in [0, 1]$ probability that a channel of type j is in state k.
- I_{ion} : the sum of ionic currents
- $I(t)$= applied current (external stimulus).

Deterministic Conductance-based Models (II)

Ionic currents :

$$I_j = G_j(p^{(1)}, \cdot, \cdot, \cdot, p^{(n)})(V - V_j)$$

for type j channels, where V_j= reversal potential.

G_j= varying conductance
= proportion of channels in the open state.

Current balance equation :

$$C\frac{dV_t}{dt} = -\sum_j I_j + I$$

Example of Hodgkin-Huxley model

In the first course we introduced the Hodgkin-Huxley model,

- two types of channels : sodium and potassium
- 8 possible states for sodium channels, 5 possible states for potassium channels

- sodium open state is m_3h_1, potassium open state is n_4
- $p^{(1)}_{m_3h_1}$ (resp. $p^{(2)}_{n_4}$) the proportion of sodium (resp. potassium) channels in open state

$$G_{\mathrm{Na}} = g_{\mathrm{Na}} p^{(1)}_{m_3h_1},\ G_{\mathrm{K}} = g_{\mathrm{K}} p^{(2)}_{n_4},\ G_{\mathrm{L}} = g_{\mathrm{L}} = const.$$

Deterministic Conductance-based Models (III)

Hodgkin-Huxley model was originally a spatial models : in a simplified form,

$$\begin{aligned} C\frac{dV}{dt} &= \Delta V - I_{ion}(V, p^{(1)}, \cdot, \cdot, \cdot, p^{(n)}) + I(t) \\ \frac{dp_k^{(j)}}{dt} &= \sum_{i \neq k} \alpha_{i,k}(V) p_i^{(j)} - \alpha_{k,i}(V) p_k^{(j)} \end{aligned}$$

- here $V = V(t, x)$
- $p^{(j)} = p^j(t, x)$ since it is a function of $V(t, x)$: conductances vary with position x along the axon.

Piecewise Deterministic Markov Models or PDMP (I)

Deterministic dynamics between successive random events

We need characteristics (cf. Davis) :

- a countable set K (may be multidimensional), an integer d
- $(f(\cdot, p))_{u \in K}$ family of vector fields with values in $\mathbf{R}^d$
- $\lambda : \mathbf{R}^d \times K \to [0, 1]$ family of jump intensities
- $Q : B \times (\mathbf{R}^d \times K) \to [0, 1]$ family of jump measures.

Iterative construction of process $X_t = (U_t, p_t)$

- Take initial value $X_0 = (U_0, p_0)$
- Solve $\frac{dy(t)}{dt} = f(y(t), p_0); \quad y_0 = U_0$
- Define T_1 such that

$$\mathbf{P}(T_1 > t) = \mathrm{e}^{-\int_0^t \lambda(y(s),p_0)ds}$$

- Define $\xi_1 \in \mathbf{R}^d \times K$ with law $Q(\cdot;(y(T_1), p_0))$ conditionally on T_1
- Define

$$\begin{aligned} X_t &= (y(t), p_0) \quad \text{if} \quad t < T_1 \\ X_{T_1} &= \xi_1 \end{aligned}$$

Comments on PDMP

- same iterative construction applies with PDE instead of ODE
- the PDMP (U_t, p_t) is a Markov process
- (U_t) is not a Markov process
- (U_t) may have jumps too (for neuron models it is continuous : it is the membrane potential)

PDMP - HH Model (I)

Take N **channels** of each type (two types).

$$\begin{aligned} C\frac{dV_N}{dt} &= -g_{\mathrm{Na}} p_N^{m_3h_1}(V_N - V_{\mathrm{Na}}) - g_{\mathrm{K}} p_N^{n_4}(V_N - V_K) - g_L(V_N - V_L) \\ \frac{dp_N^k}{dt} &= \sum_{i \neq k} \alpha_{i,k}(V_N)p_N^i - \alpha_{k,i}(V_N)p_N^k \end{aligned}$$

where we consider the set of all possible state. There is no ambiguity on the type of channels : m_3h_1 is a possible state for sodium channels only.
$p_N^k(t)$ is the proportion of channels that are in state k at time t.

PDMP - Spatial Models (I)

- the axon is an interval D
- for each $n \in \mathbb{N}$, $\mathcal{P}_n$ is a partition of D in a finite collection of mutually disjoint intervals $D_{k,n}$ (the compartments)
- each compartment either contains no channel or a fixed deterministic number
- $\pi(n) :=$ the number of compartments $D_{k,n}$ containing channels
- $l(k,n)$ the total number of channels in $D_{k,n}$
- configuration of channels : $\Theta_i^{k,n}(t)$ is the number of channels in $D_{k,n}$ that are in state i at time t.

PDMP - Spatial Models (II)

Remember $\Theta_i^{k,n}(t) :=$ the number of channels located in $D_{k,n}$ that are in state i at time t.

- The jumping part of the PDMP is :

  $$z_i^n(\Theta^n(t)) := \sum_{k=1}^{\pi(n)} \frac{\Theta_i^{k,n}(t)}{l(k,n)} \mathbb{I}_{D_{k,n}}$$

  for each state i,
- $z^n \equiv 0$ on compartments with no channels,
- given configuration $\Theta_i^{k,n}$, one channel in $D_{k,n}$ switches from state i to state j at instantaneous rate

  $$\Theta_i^{k,n} \alpha_{ij} \Big(\frac{1}{|D_{k,n}|} \int_{D_{k,n}} V_t^n(x)\, dx \Big)$$

PDMP - Spatial Models (III)

The deterministic evolution between two successive jumps is given by a PDE.

Example of HH : $V_t^n(x)$ satisfies the PDE

$$\partial_t V^n(t,x) = \Delta V^n(t,x) - \sum_{i=1}^{2} g_i \, z_i^n(\Theta^n(t)) \, (V^n(t,x) - E_i)$$

where $i \in \{ 1, 3\}$ stands for the two open states $m_3 h_1$ and n_4 and E_i are the reversal potentials of Na and K.

General Mathematical Framework (I)

PDMP in Hilbert spaces : $X_t(\omega) = (U_t(\omega), \Theta_t(\omega))$ where

- $\Theta_t(\omega) \in K$ a countable set.
- For each $\theta \in K$, U_t satisfies an abstract evolution equation with unique solution

$$\dot{u} = A(\theta)\, u + B(\theta, u), \tag{5}$$

$A(\theta)$ a linear operator, $B(\theta, \cdot)$ a possibly nonlinear operator

General Mathematical Framework (II)

We obtain limit theorems (LLN, CLT) and Langevin approximation for sequences of PDMPs $(U^n, z^n(\Theta^n))$ when

$$\dot{U}_n = A(z^n(\theta^n))\, U_n + \; B(z^n(\theta^n), U_n)$$

where $z^n(\theta)$ is a finite dimensional vector, its dimension not depending on n.

Example of HH :

$$z_i^n(\Theta^n(t)) := \sum_{k=1}^{\pi(n)} \frac{\Theta_i^{k,n}(t)}{l(k,n)} \, \mathbb{I}_{D_{k,n}}$$

where the dimension of z^n is the number of open states the channels can be in.

Limit Theorems

LLN : the deterministic limit of the sequence $(U^n, z^n(\Theta^n))$ is (u, p) satisfying

$$\begin{aligned} \dot{u} &= A(p)\, u + B(p, u) \\ \dot{p}_j &= \textstyle\sum_{i \neq j} q_{ij}(u)\, p_i - q_{ij}(u)\, p_j := F_j(p, u) \end{aligned}$$

We also obtain a CLT and the Langevin approximation of $(U^n, z^n(\Theta^n))$ takes the form

$$\begin{aligned} d\tilde{U}^n_t &= \left(A(\tilde{p}^n_t)\tilde{U}^n_t + B(\tilde{p}^n_t, \tilde{U}^n_t)\right) dt \\ d\tilde{p}^n_t &= F(\tilde{p}^n_t, \tilde{U}^n_t)\, dt + \tfrac{1}{\sqrt{\alpha_n}} \sqrt{G(\tilde{U}^n_t, \tilde{p}^n_t)}\, dW_t \end{aligned}$$

Conditions on the partition (I)

The validity of LLN is expressed via two parameters of $\mathcal{P}_n$,

$$\delta_+(n) = \max_{k=1,\ldots,\pi(n)} \mathrm{diam}(D_{k,n}) \quad \text{and} \quad \ell_-(n) = \min_{k=1,\ldots,\pi(n)} l(k,n) :$$

If

- $\delta_+(n) \to 0$ and $\ell_-(n) \to \infty$ when $n \to \infty$
- and initial conditions $(U_0^n, z^n(\Theta_0^n))$ converge in probability to (u_0, p_0)

then Law of Large Numbers holds for the PDMP $(U^n, z^n(\Theta^n))$ which converges to (u, p).

Conditions on the partition (II)

Remember that

$$\delta_+(n) = \max_{k=1,\dots,\pi(n)} \operatorname{diam}(D_{k,n}) \quad \text{and} \quad \ell_-(n) = \min_{k=1,\dots,\pi(n)} l(k,n).$$

For the CLT additional parameters of $\mathcal{P}_n$ are needed :

$$\ell_+(n) := \max_{k=1,\dots,\pi(n)} l(k,n)\,,$$

$$\nu_+(n) := \max_{k=1,\dots,\pi(n)} |D_{k,n}|\,, \qquad \nu_-(n) := \min_{k=1,\dots,\pi(n)} |D_{k,n}|\,.$$

Conditions on the partition (III)

If, when $n \to \infty$,

- $\delta_+(n) \to 0$ and $\ell_-(n) \to \infty$
- $\frac{\ell_-(n)\,\nu_-(n)}{\ell_+(n)\,\nu_+(n)} \to 1$
- initial conditions $(U_0^n, z^n(\Theta_0^n))$ converge in probability to (u_0, p_0)

then Central Limit Theorem holds : $\left(\sqrt{\frac{\ell_-(n)}{\nu_+(n)}}\, M_t^n\right)_{t \geq 0}$ converges to a diffusion where M^n is the martingale part of $z^n(\Theta^n)$.

Comments

- only compartments which contain channels are used to establish LLN and CLL
- heterogeneities are possible with the limitation that $\frac{\ell_-(n)\,\nu_-(n)}{\ell_+(n)\,\nu_+(n)} \to 1$
- normalization coefficient of CLT depends on parameters of the partition $\mathcal{P}_n$
- size of the noise in Langevin approximation :

$$\sqrt{\frac{\nu_+(n)}{\ell_-(n)}}$$

Another family of infinite dimensional PDMP. Multiple time scales study. (I)

For a given scale $N \in \mathbb{N}^*$, we consider it is populated by N channels of different types (for Hodgkin-Huxley, Na, K),

located at sites $z_i \in \frac{1}{N}(\mathbb{Z} \cap N\,]0,1[)$.

For $z_i \in I_N$ consider $(\phi_{z_i}^{\mathcal{K}})$ a sequence of smooth functions approximating δ_{z_i}. The parameter $\mathcal{K}$ can be interpreted as a small area around z_i, when $\mathcal{K} \to 0$, the area shrinks to the point z_i itself. We will not write $\mathcal{K}$ in the sequel.

$$\partial_t V = \partial_{xx} V + \mathcal{I}$$

where $\mathcal{I}$ is the ionic current.

Another family of infinite dimensional PDMP. Multiple time scales study. (II)

A channel configuration is a vector $(r_i)_{i\in\{1,\cdot,\cdot,\cdot N\}}$ where $r_i = (c_i, z_i) \in \mathcal{S} \times I_N$ and $\mathcal{S}$ is the set of all possible states.

As before the current sources are single (or families of) ion channel(s) in open conducting states.

$$\mathcal{I}(r, V) = \frac{1}{N} \sum_{i=1}^{N} c_{r_i}(E_{r(i)} - \overline{V}_i)\,\phi_{z_i},$$

where $\overline{h}_i := \int_I h(x)\,\phi_{z_i}(x)\,dx$ for a function h.
Several time scales are naturally present. With A. Genadot we have proved averaging and associated CLT for this family of spatial PDMP.

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