On Spatially Extended Stochastic Models of Neurons.

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Conductance-based Point Models

A family of deterministic multidimensional models

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

- $w^{(j)} \in [0, 1]$ proportion of open channels (or gates) of type j
- 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
- $I(t)$= applied current (external stimulus). We will take $I(t) \equiv I$.

4D Hodgkin-Huxley

3 types of gates : m and h for sodium ions, n for potassium ions

- current balance

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

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

- m, h, n are proportion of open gates of each type
- underlying stochastic gating mechanism of fictive gates m, n, h for an **infinite** number of gates
- the proportion of open sodium channels (resp. potassium channels) is $m^3 h$ (resp. n^4)

3D Morris-Lecar

2 types of ions : calcium and potassium

- current balance

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

$$G_{\mathrm{Ca}} = g_{\mathrm{Ca}} u_1,\ G_{\mathrm{K}} = g_{\mathrm{K}} u_2,\ G_{\mathrm{L}} = g_{\mathrm{L}} = const.$$

  u_1 (resp. u_2) interpreted as proportion of open calcium (resp. potassium) channels

- underlying stochastic gating mechanism of channels Ca, K for an **infinite** number of channels

Conductance-based Spatial Models

A family of deterministic multidimensional models

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

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

Common Structure of Conductance-Based Models

They are made of 2 parts :

- the equation for V has standard form
- its coefficients describe a limiting behaviour : number of stochastic individuals (gates or channels) is infinite

We want to make these systems stochastic in order to study the fluctuations around the deterministic solution due to *channel noise*.

Piecewise Deterministic Markov Models or PDMP

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 $U_t \equiv$ the membrane potential which is continuous : take $U_{T_1} = y(T_1)$

PDMP as Stochastic Point Models (I)

For each $N \equiv$ the number of each type of gate/channels,

- continuous component is $U_N \equiv$ the membrane potential with this amount of gates/channels
- any single gate/channel is modeled by a two-state jump process with U_N dependent rates
- the jumping component p_N e.g. for Hodgkin-Huxley is $p_N = (p_N^{(m)}, p_N^{(n)}, p_N^{(h)})$ where

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

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

PDMP as Stochastic Point Models (II)

- ODE for U_N is

$$C\frac{dU_N}{dt} = \sum_{j=1}^{3} G_{N,j}(E_j - U_N)$$

- $G_{N,1} = \overline{g}_{\mathrm{Na}}(p_N^{(m)})^3 p_N^{(h)}$, $G_{N,2} = \overline{g}_{\mathrm{K}}(p_N^{(n)})^4$, $G_{N,3} = g_{\mathrm{L}} = const.$
- writing $\lambda(u_s, p_s) := \sum_{k=n,m,h} \beta_k(u_s)p_k(s) + \alpha_k(u_s)(1 - p_k(s))$ the law of T_1 is

$$\mathbf{P}(T_1 > t) = \mathrm{e}^{-N\int_0^t \lambda(u_s,p_s)ds}$$

Austin's Model(I)

T. Austin (2006) was the first to study mathematically a spatial PDMP :

- the axon is the interval $[0, 1]$
- N channels rgularly placed at $\frac{i}{N}$
- channels can be in a finite number of states e.g. "receptive to sodium ions and open"
- configurations of the N channels $r = r(i)$ satisfy

$$\Pr(r_{t+h}(i) = \eta | r_t(i) = \xi) = \alpha_{\xi,\eta}(U_t(\frac{i}{N}))h + o(h)$$

Austin's Model(II)

- membrane potential satisfies

$$\partial_t U = \Delta U + \frac{1}{N} \sum_{\xi} \sum_{i} \overline{g}_{\xi} \mathbf{1}_{\xi}(r(i))(E_{\xi} - U(\frac{i}{N}))\delta_{\frac{i}{N}}$$

- Austin proves a Law of Large Numbers when $N \to \infty$ with limit

$$\begin{aligned} \partial_t V &= \Delta V + \sum_{\xi} \overline{g}_{\xi} p_{\xi}(E_{\xi} - V) \\ \dot{p}_{\xi} &= \sum_{\eta \neq \xi} \alpha_{\eta,\xi}(V)\, p_{\eta} - \alpha_{\xi,\eta}(V)\, p_{\xi} \end{aligned}$$

PDMP as Stochastic Spatial Models (I)

Consider the deterministic membrane model on a spatial bounded domain D of the following form

$$\begin{aligned} \partial_t u &= \sum_{i,j=1}^{d} a_{ij}(x) u_{x_i x_j} + \sum_{i=1}^{m} g_i(x)\, p_i\, (E_i - u) \\ \dot{p}_j &= \sum_{i \neq j} q_{ij}(u)\, p_i - q_{ij}(u)\, p_j \end{aligned}$$

We can associate to it a sequence of PDMPs as follows

PDMP as Stochastic Spatial Models (II)

- For each $n \in \mathbb{N}$, $\mathcal{P}_n$ is a partition of D in a finite collection of mutually disjoint convex subsets $D_{k,n}$ (the compartments).
- Each compartment either contains no channel or a fixed deterministic number.
- $\pi(n) :=$ the number of compartments of $\mathcal{P}_n$ containing channels.
- $l(k, n)$ the total number of channels in $D_{k,n}$.

PDMP as Stochastic Spatial Models (III)

- Define first $\Theta_i^{k,n}(t) :=$ the number of channels located in $D_{k,n}$ in state i at time t. The jumping part of the PDMP is for $i \in \{1, \cdot, \cdot, \cdot, m\}$

$$z_i^n(\Theta^n(t)) := \sum_{k=1}^{\pi(n)} \frac{\Theta_i^{k,n}(t)}{l(k,n)} \mathbb{I}_{D_{k,n}} \in L^2(D)$$

- The continuous part U^n satisfies the pde

$$\partial_t U^n = \sum_{i,j=1}^{d} a_{ij}(x) U^n_{x_i x_j} + \sum_{i=1}^{m} g_i(x)\, z_i^n(\Theta^n(t))\,(E_i - U^n)$$

Comments

- $z^n \equiv 0$ on compartments with no channels
- jump rates : one channel in subdomain $D_{k,n}$ switches from state i to state j at instantaneous rate

$$\Theta_i^{k,n}(t) \cdot q_{ij}\Big(\frac{1}{|D_{k,n}|}\int_{D_{k,n}} U_t^n(x)\,dx\Big).$$

- $g_i(x) = \overline{g}\rho(x)$ is the *conductance density* at position x where $\rho(x)$ is the *channel density* at x (the number of channels by space unit around x), and $\overline{g}$ is the *single channel conductance*.

General Mathematical Framework (I)

For simplicity suppose that the underlying space ($\equiv$ the axon) is an interval I. Take K a countable set.
Consider a process $X_t(\omega) = (U_t(\omega), \Theta_t(\omega))$ where

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

$$\dot{u} = A(\theta)\, u + B(\theta, u) \tag{1}$$

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

General Mathematical Framework (II)

We consider sequences of PDMPs (U^n, Θ^n) where U^n solves

$$\dot{u} = A^n(\theta)\, u + B^n(\theta, u) \tag{2}$$

such that for each n

$$A^n(\theta)\, u \;=\; A(z^n(\theta))\, u, \quad B^n(\theta, u) \;=\; B(z^n(\theta), u) \tag{3}$$

where $z^n(\theta)$ is an m-dimensional vector and m does not depend on n.

General Mathematical Framework (II)

Example : PDMP Compartmental models

$$z_i^n(\Theta^n(t)) := \sum_{k=1}^{\pi(n)} \frac{\Theta_i^{k,n}(t)}{l(k,n)} \mathbb{I}_{D_{k,n}} \in L^2(D)$$

We look for limit theorems and Langevin approximation for the PDMP $(U^n, z^n(\Theta^n))$ where typically

$$\partial_t U^n = \sum_{i,j=1}^{d} a_{ij}(x) U^n_{x_i x_j} + \sum_{i=1}^{m} g_i(x)\, z_i^n(\Theta^n(t))\,(E_i - U^n)$$

The Deterministic Limit

In general it is the pair (u, p) satisfying

$$\begin{aligned} \dot{u} &= A(p)\,u + B(p,u), \\ \dot{p}_j &= F_j(p,u), \qquad\qquad j = 1, \ldots, m\,. \end{aligned}$$

For neuron models :

$$\begin{aligned} \partial_t u &= \sum_{i,j=1}^{d} a_{ij}(x) u_{x_i x_j} + \sum_{i=1}^{m} g_i(x)\, p_i\,(E_i - u) \\ \dot{p}_j &= \sum_{i \neq j} q_{ij}(u)\, p_i - q_{ij}(u)\, p_j \end{aligned}$$

LLN, TCL, Langevin for PDMP (I)

The proof of such results rely on the study of the jumping part $z^n(\Theta^n)$

$$z_j^n(\theta_t^n) = z_j^n(\theta_0^n) + \int_0^t D_{n,j}(s)ds + M_{n,j}(t)$$

more precisely on estimates for the martingale part $M_{n,j}$
Roughly :

- if for each j, M_j^n converges to 0 and and D_j^n to F_j we obtain LLN
- if moreover for $\alpha_n \to \infty$, the sequence $(\sqrt{\alpha_n} M^n)$ converges to a Gaussian process then CLT holds

LLN, TCL, Langevin for PDMP (II)

- the Langevin approximation of $(U^n, z^n(\Theta^n))$ takes the form

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

Comments

- general framework : the size of the jumps and their intensities (mean frequency) equilibrate
- types of convergence : for LLN, in probability uniformly on compacts in time, for CLT convergence in law
- for compartmental PDMP modelling neuronal membrane, convergence in LLN also holds in the mean
- processes take values in infinite dimensional spaces

Law of Large Numbers for Compartmental PDMP

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

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

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).

Central Limit Theorem for Compartmental PDMP (I)

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 :

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

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

Central Limit Theorem for Compartmental PDMP (II)

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.

Notation : M^n is the martingale part of $z^n(\Theta^n)$.

Comments I

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

Comments II

- another application to Wilson Cowan equation (M. Riedler work in progress)
- our results apply to multidimensional domains with heterogeneities
- fluctuations of the PDMP (not only its martingale part) and related linearized Langevin system
- PDMP are widely applicable

Bibliography

- the first mathematical paper about stochastic spatial Hodgkin-Huxley model : T. Austin (2006)
- Austin' s model with several time scales : A. Genadot (Univ. Pierre et Marie Curie) arXiv1109.6581
- PDMP in finite dimension, general theory : M. H. A. Davis (1993).
- PDMP in infinite dimension : E. Buckwar, M. Riedler (2010)
- intrinsic noise in neurons for point models G. Wainrib' s : PhD in particular K. Pakdaman., M. Thieullen, G. Wainrib (2010)