Local Asymptotic Normality for Stochastic Hodgkin-Huxley-Systems

Simon Holbach

Johannes Gutenberg-Universität Mainz

s.holbach@uni-mainz.com

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Classical Hodgkin-Huxley-System

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

with

- membrane potential V of a neuron
- deterministic periodic external input signal S
- internal gating variables n, m, h modeling activation of ion channels
- (explicit) smooth coefficient functions F, α_i, β_i

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Stochastic Hodgkin-Huxley-System

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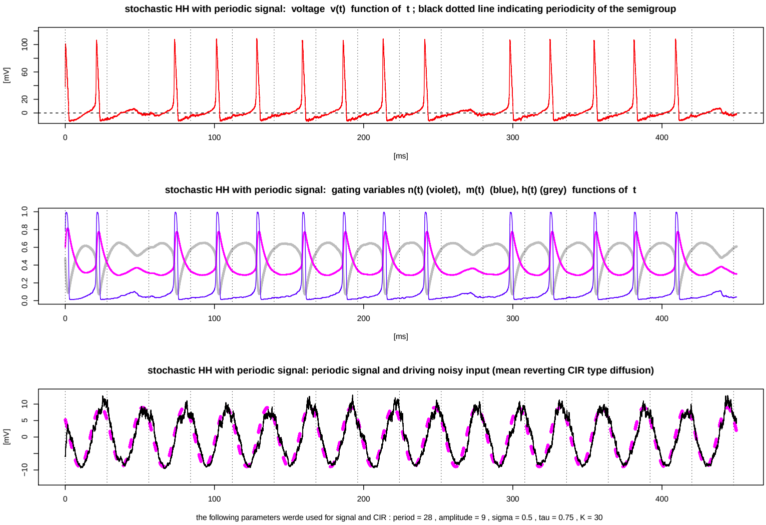
dm_t &= \left[\alpha_m(V_t)(1-m_t) - \beta_m(V_t)m_t\right]dt \\
dh_t &= \left[\alpha_h(V_t)(1-h_t) - \beta_h(V_t)h_t\right]dt \\
d\xi_t &= \gamma(S(t) - \xi_t)dt + \sigma(\xi_t)dW_t
\end{aligned}
$$

with

- membrane potential V of a neuron
- deterministic periodic external input signal S
- internal gating variables n, m, h modeling activation of ion channels
- (explicit) smooth coefficient functions F, α_i, β_i
- $\gamma > 0$ and $\sigma \in C_b^3$ bounded away from 0, W 1D Brownian Motion

Some Sample Paths



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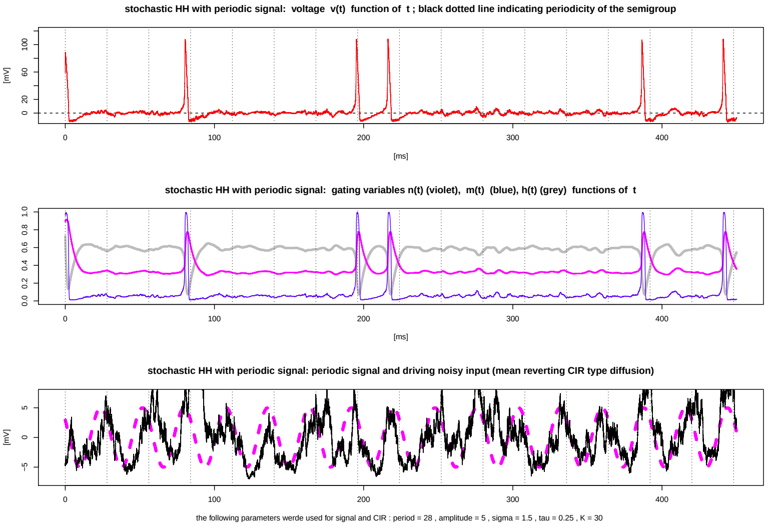

Introduce Parametrized Signal

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Then the equation for $X = (V, n, m, h, \xi)$ is of the form

$$dX_t = B_{(\vartheta,T)}(t, X_t)dt + \Sigma(X_t)dW_t$$

and its solution lives on $\mathbb{R} \times [0,1]^3 \times \mathbb{R}$ (if started there).

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Long-term goal:

Estimate (ϑ, T) from continuous observation not of X, but only of the membrane potential V.

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Immediate goal:

Prove LAN for the corresponding sequence of statistical experiments.

Likelihood-Ratios for Observation of X, V or ξ

Write $\mathbb{P}^{(\vartheta,T)}$ for the law on $C([0,\infty);\mathbb{R}^5)$ under which the canonical process $(\eta_t)_{t\geq 0}$ solves the stochastic Hodgkin-Huxley system starting from a fixed and deterministic $x_0 = (v_0, n_0, m_0, h_0, \xi_0)$.

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These lead to three different sequences of experiments

$$\Big(C([0,\infty);\mathbb{R}^5), \mathcal{F}_n^i, \Big\{\mathbb{P}^{(\vartheta,T)}|_{\mathcal{F}_n^i} \,\Big|\, (\vartheta, T) \in \Theta \times (0,\infty)\Big\}\Big), \quad n \in \mathbb{N}$$

where $i = 0, 1, 5$.

Likelihood-Ratios for Observation of X, V or ξ

However, as the parameters are only present in the drift term for the fifth (and thus also the first) equation and the local martingale part of X under $\mathbb{P}^{(\vartheta,T)}|_{\mathcal{F}^0_n}$ is given by

$$\Big(\int_0^{\cdot} \sigma(\xi_t)dW_t, 0, 0, 0, \int_0^{\cdot} \sigma(\xi_t)dW_t\Big)^\top,$$

we can conclude that for all $i \in \{0, 1, 5\}$ under $\mathbb{P}^{(\vartheta,T)}|_{\mathcal{F}^i_t}$

$$\log\left(\frac{d\mathbb{P}^{(\vartheta',T')}|_{\mathcal{F}^i_t}}{d\mathbb{P}^{(\vartheta,T)}|_{\mathcal{F}^i_t}}\right) \overset{d}{=} \gamma \int_0^t \frac{S_{(\vartheta',T')}(s) - S_{(\vartheta,T)}(s)}{\sigma(\xi_s)} dW_s - \frac{\gamma^2}{2} \int_0^t \left(\frac{S_{(\vartheta',T')}(s) - S_{(\vartheta,T)}(s)}{\sigma(\xi_s)}\right)^2 ds =: \Lambda_t^{(\vartheta',T')/(\vartheta,T)}.$$

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⇒ If LAN holds for *any* of these sequences, it holds for *all* of them.

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4. $\dot{S}\colon (\vartheta, T) \mapsto \dot{S}_{(\vartheta,T)}$ is $\mathbb{L}^2_{\text{loc}}$-continuous.
5. For each $(\vartheta, T) \in \Theta \times (0,\infty)$ there are $\alpha \in (0,1]$ and $\beta \in [0,(1+3\alpha)/2)$ such that for suitable $\varepsilon > 0$

$$\left\| \nabla_\vartheta S_{(\vartheta,T)} - \nabla_\vartheta S_{(\vartheta,T')} \right\|_{\mathbb{L}^2(0,t)} \leq C t^\beta \left| T - T' \right|^\alpha$$

for all $t > 0$, $T' \in (T-\varepsilon, T+\varepsilon)$ and some constant C that does not depend on T' or t.

Local Asymptotic normality

Fix $(\vartheta, T) \in \Theta \times (0, \infty)$. Suppose that for each $t > 0$ the matrix

$$J^{(\vartheta,T)}(t) = \gamma^2 \nu \left[\begin{pmatrix} \nabla_\vartheta S_\vartheta \\ -tT^{-2} S'_\vartheta \end{pmatrix} \begin{pmatrix} \nabla_\vartheta S_\vartheta \\ -tT^{-2} S'_\vartheta \end{pmatrix}^\top \right] \in \mathbb{R}^{(d+1)\times(d+1)}$$

is invertible (we will define the measure ν in a minute).

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Theorem (Local Asymptotic Normality)

With

$$I^{(\vartheta,T)} := \int_0^1 J^{(\vartheta,T)}(s)ds \quad \text{and} \quad \Delta_n^{(\vartheta,T)} := \gamma \delta_n \int_0^n \frac{\dot{S}_{(\vartheta,T)}(s)}{\sigma(\xi_s)} dW_s$$

we have $\Delta_n^{(\vartheta,T)} \xrightarrow{\mathcal{L}} \mathcal{N}\left(0, I^{(\vartheta,T)}\right)$ and

$$\Lambda_n^{(\vartheta_n,T_n)/(\vartheta,T)} = h_n^\top \Delta_n^{(\vartheta,T)} - \frac{1}{2} h_n^\top I^{(\vartheta,T)} h_n + o_{\mathbb{P}(\vartheta,T)}(1).$$

Tools for the Proof

- The *grid chain* $(\xi_{kT})_{k\in\mathbb{N}_0}$ is a time homogeneous Markov chain. Due to our assumptions it is positive Harris-recurrent and we write μ for its unique invariant probability measure.

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- The *path segment chain* $(\Xi_k)_{k\in\mathbb{N}_0}$ with

$$\Xi_k := \left(\xi_{(k-1)T+s}\right)_{s\in[0,T]}, \quad k \in \mathbb{N},$$
$$\Xi_0 \in C[0,T] \text{ arbitrary with } \Xi_0(T) = \xi_0,$$

  is a $C[0,T]$-valued time homogeneous Markov chain. It inherits positive Harris-recurrence from the grid chain and we denote its invariant probability measure by m.

Tools for the Proof

Strong Law of Large Numbers for Ξ (Höpfner, Kutoyants, 2010)

$(A_t)_{t\geq 0}$ increasing process, $F \in \mathbb{L}^1(m)$ nonnegative with

$$A_{kT} = \sum_{j=1}^{k} F(\Xi_j) \quad \text{for all } k \in \mathbb{N}.$$

Then

$$\frac{1}{t} A_t \xrightarrow{t\to\infty} \frac{1}{T} m(F) \quad \mathbb{P}^{(\vartheta, T)}\text{-a.s.}$$

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Apply this to show that for 1-periodic bounded measurable f and $m \in \mathbb{N}_0$

$$\frac{1}{t}\int_0^t \frac{f(s/T)}{\sigma^2(\xi_s)} ds \xrightarrow{t\to\infty} \int_0^1 f(s) \underbrace{\mu P_{0,sT}(\sigma^{-2}) ds}_{=:\nu(ds)} \quad \mathbb{P}^{(\vartheta,T)}\text{-a.s.}$$

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Apply this to show that for 1-periodic bounded measurable f and $m \in \mathbb{N}_0$

$$\frac{1}{n^{m+1}} \int_0^{tn} s^m \frac{f(s/T)}{\sigma^2(\xi_s)} ds \xrightarrow{n\to\infty} \frac{t^{m+1}}{m+1} \int_0^1 f(s) \underbrace{\mu P_{0,sT}(\sigma^{-2}) ds}_{=:\nu(ds)} \quad \mathbb{P}^{(\vartheta,T)}\text{-a.s.}$$

Main Step of the Proof

$$\left\langle \delta_n \int_0^{\cdot\, n} \frac{\dot S_{(\vartheta,T)}(s)}{\sigma(\xi_s)} dW_s \right\rangle_t = \delta_n^2 \int_0^{tn} \frac{\dot S_{(\vartheta,T)}(s)\dot S_{(\vartheta,T)}(s)^\top}{\sigma^2(\xi_s)} ds$$

$$= \int_0^{tn} \begin{pmatrix} n^{-1}\nabla_\vartheta S_\vartheta(\frac{s}{T})\nabla_\vartheta S_\vartheta(\frac{s}{T})^\top & n^{-2}\left(-sT^{-2}S'_\vartheta(\frac{s}{T})\nabla_\vartheta S_\vartheta(\frac{s}{T})\right) \\ n^{-2}\left(-sT^{-2}S'_\vartheta(\frac{s}{T})\nabla_\vartheta S_\vartheta(\frac{s}{T})\right)^\top & n^{-3}s^2T^{-4}S'_\vartheta(\frac{s}{T})^2 \end{pmatrix} \sigma^{-2}(\xi_s)ds$$

$$\xrightarrow{n\to\infty} \nu\left[\begin{pmatrix} t\nabla_\vartheta S_\vartheta \nabla_\vartheta S_\vartheta^\top & -\left(\frac{t^2}{2}T^{-2}S'_\vartheta \nabla_\vartheta S_\vartheta\right) \\ -\left(\frac{t^2}{2}T^{-2}S'_\vartheta \nabla_\vartheta S_\vartheta\right)^\top & \frac{t^3}{3}T^{-4}(S'_\vartheta)^2 \end{pmatrix}\right]$$

$$= \int_0^t \nu\left[\begin{pmatrix} \nabla_\vartheta S_\vartheta \\ -sT^{-2}S'_\vartheta \end{pmatrix}\begin{pmatrix} \nabla_\vartheta S_\vartheta \\ -sT^{-2}S'_\vartheta \end{pmatrix}^\top\right] ds$$

Example

- A simple example for a signal that satisfies the regularity assumptions is

$$S_{(\vartheta,T)}(s) = \sum_{k=0}^{l} \left(g_k(\vartheta) \sin\left(\frac{2k\pi s}{T}\right) + h_k(\vartheta) \cos\left(\frac{2k\pi s}{T}\right) \right)$$

with $l \in \mathbb{N}_0$ and $g_k, h_k \in C^1(\Theta)$ for all $k \in \{0, \ldots, n\}$.

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  with $l \in \mathbb{N}_0$ and $g_k, h_k \in C^1(\Theta)$ for all $k \in \{0, \ldots, n\}$.
- For $\sigma \equiv 1$ and the above signal with $l = d$, $h_k \equiv 0$ and g_k depending only on ϑ_k, the invertibility condition for $J^{(\vartheta,T)}(t)$ also holds.

Next Step

Construct estimator(s) for (ϑ, T) involving only V.

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