Estimation of Neuronal Hypoelliptic or Elliptic Multi-Dimensional Stochastic Models

Joint work with
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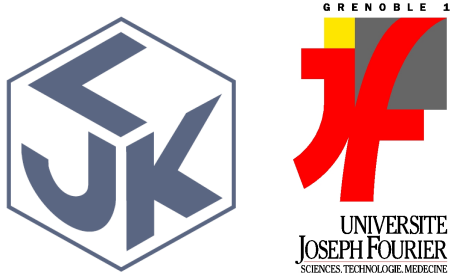


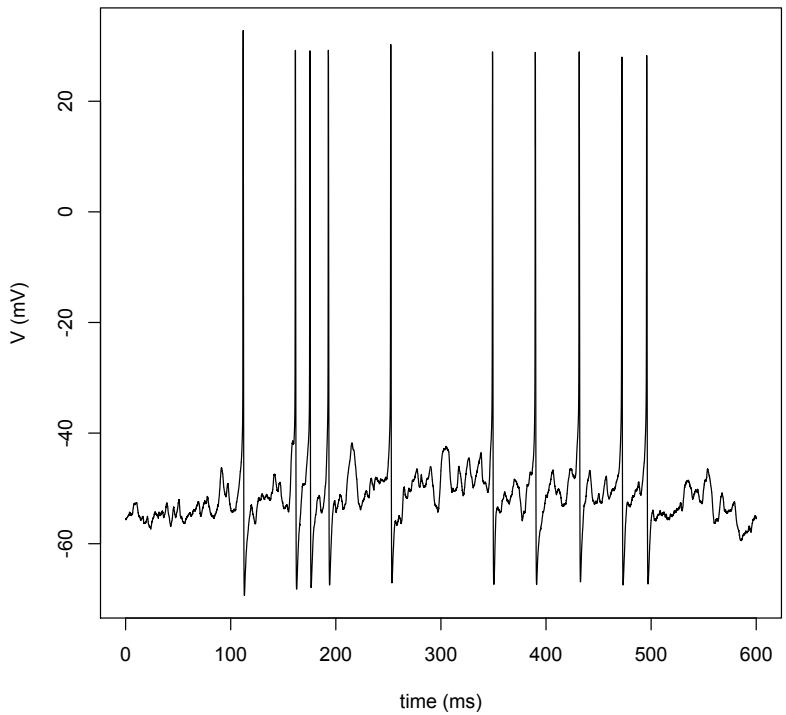
Intracellular recording data of one single neuron

Data

- Membrane potential
- High frequency ($\Delta = 0.1$ ms)

Objectives

- Neuronal modeling with stochastic models
- Parametric estimation/identification



Intracellular neuronal models

- One-dimensional stochastic model
  - Leaky Integrate-and-Fire model:

$$dV_t = \left(-\frac{1}{\tau} V_t + \mu(t) \right) dt + \sigma(V_t) dB_t$$

  - τ time constant, $\mu(t)$ input signal [Berg, Ditlevsen, Monier, Frégnac , ...]
  - No inherent generation of action potential

- Multi-dimensional stochastic models
  - Model with generation of spikes
    - Hodgkin-Huxley model [Hodgkin, Huxley, 1952]: 4 dimensional model
    - FitzHugh-Nagumo [FitzHugh, 1961]: 2 dimensional model
    - Morris Lecar model [Morris, Lecar, 1981]: 2 dimensional model
  - Two types of coordinates
    - One for the membrane potential V_t
    - the others for ion channel kinetics U_t

Deterministic neuronal model

Morris-Lecar model

$$\begin{aligned}\frac{dV_t}{dt} &= -g_{Ca} m_\infty(V_t)(V_t - V_{C_a}) - g_K U_t (V_t - V_K) - g_L(V_t - V_L) + I \\ \frac{dU_t}{dt} &= \alpha(V_t)(1 - U_t) - \beta(V_t) U_t\end{aligned}$$

FitzHugh-Nagumo model

$$\begin{aligned}\frac{dV_t}{dt} &= \frac{1}{\varepsilon}(V_t - V_t^3 - U_t - s) \\ \frac{dU_t}{dt} &= \gamma V_t - U_t + \beta\end{aligned}$$

Stochastic neuronal model

Hypoelliptic system

- Limit of Piecewise Deterministic Markov Process [Tuckwell, 88], [Pakdaman, Thieullen, Wainrib, 2010] when number of channels goes to infinity

$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt \\ dU_t &= b_2(V_t, U_t, \mu)dt + a_{\sigma_2}(V_t, U_t)dB_{2t} \end{aligned}$$

B_{2t}: Brownian motion

Elliptic system

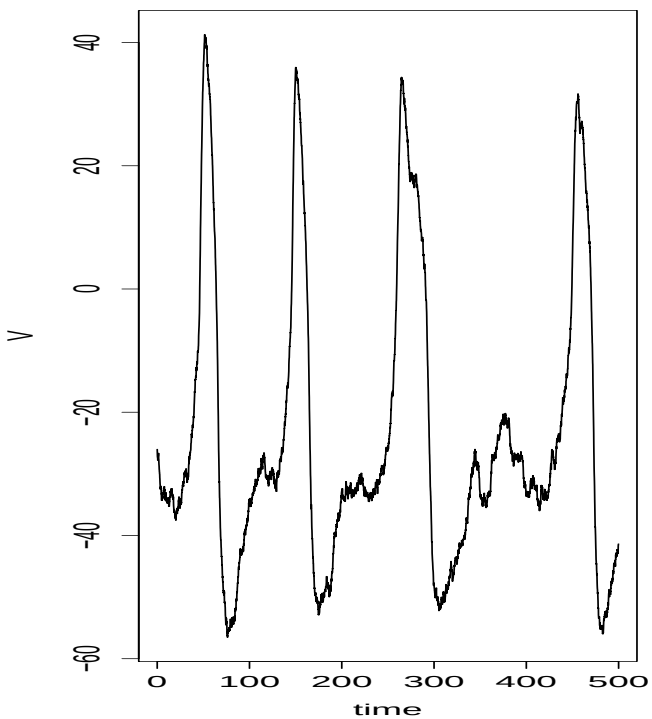
- Stochastic differential equation (SDE) [Ditlevsen, Greenwood, 2011]

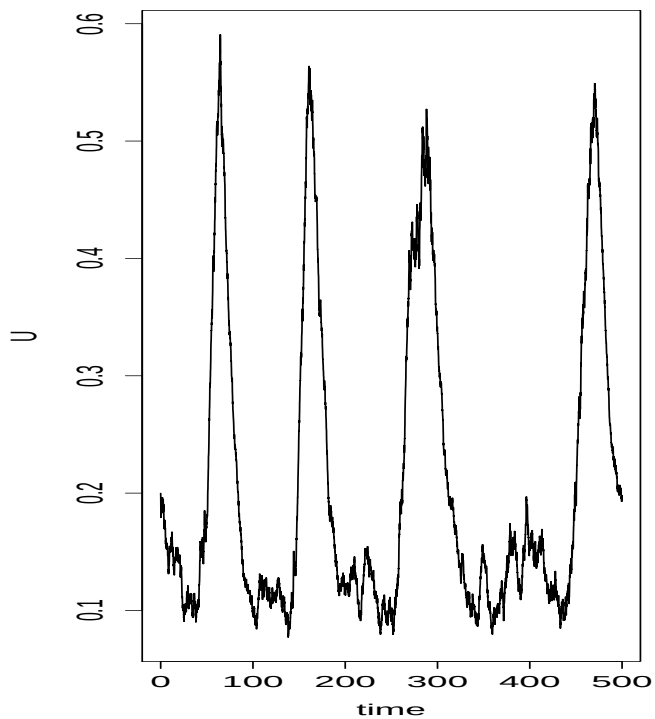
$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt + \sigma_1 dB_{1t} \\ dU_t &= b_2(V_t, U_t, \mu)dt + a_{\sigma_2}(V_t, U_t)dB_{2t} \end{aligned}$$

B_{1t}, B_{2t}: 2 independent Brownian motions

Morris-Lecar model

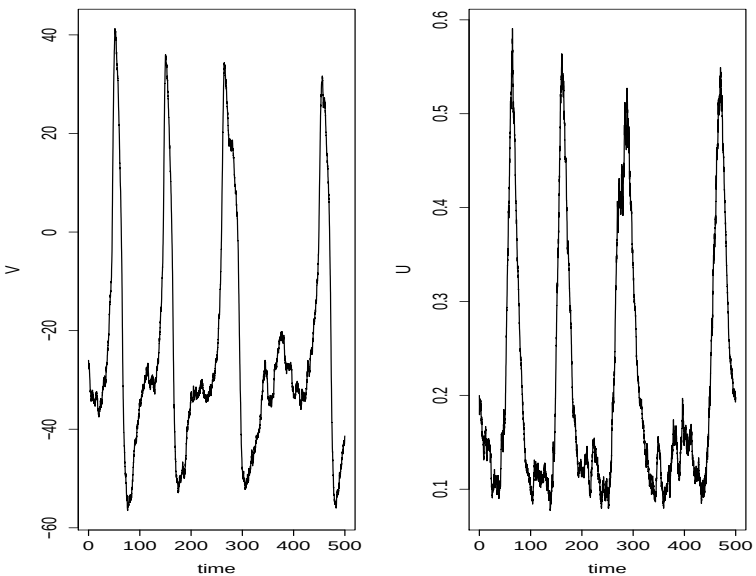
$$
\begin{aligned}
dV_t &= (-g_{Ca} m_\infty(V_t)(V_t - V_{C_a}) - g_K U_t (V_t - V_K) - g_L (V_t - V_L) + I)\, dt \\
&\quad + \sigma_1 dB_{1t}, \\
dU_t &= (\alpha(V_t)(1 - U_t) - \beta(V_t) U_t)\, dt + \sigma_2(V_t, U_t) dB_{2t}
\end{aligned}
$$

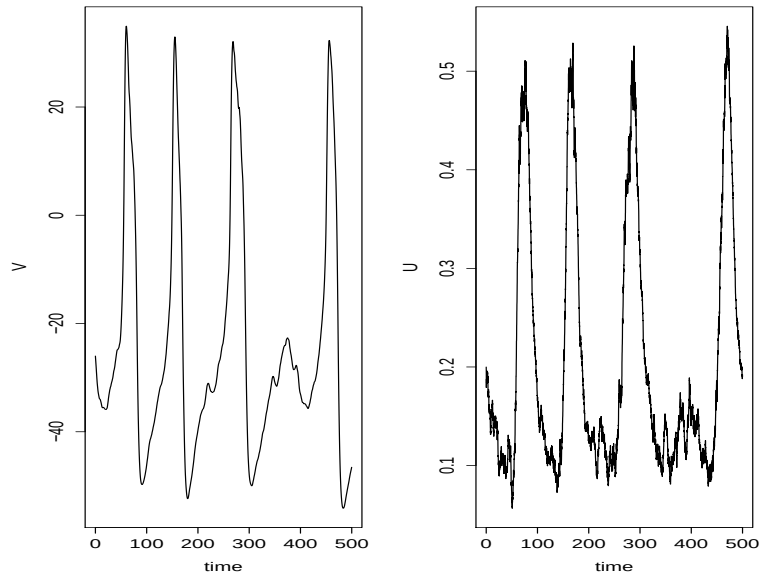


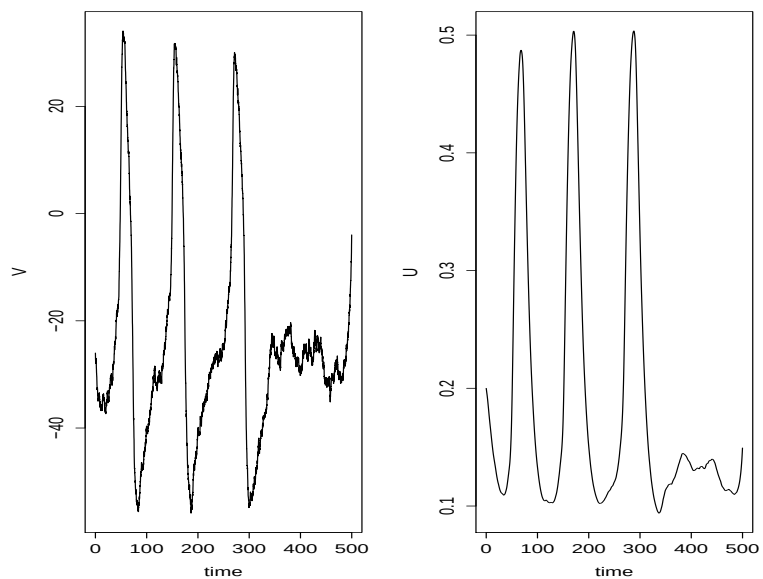


Effect of the noise

$\sigma_1 = 1, \sigma_2 = 0.3$







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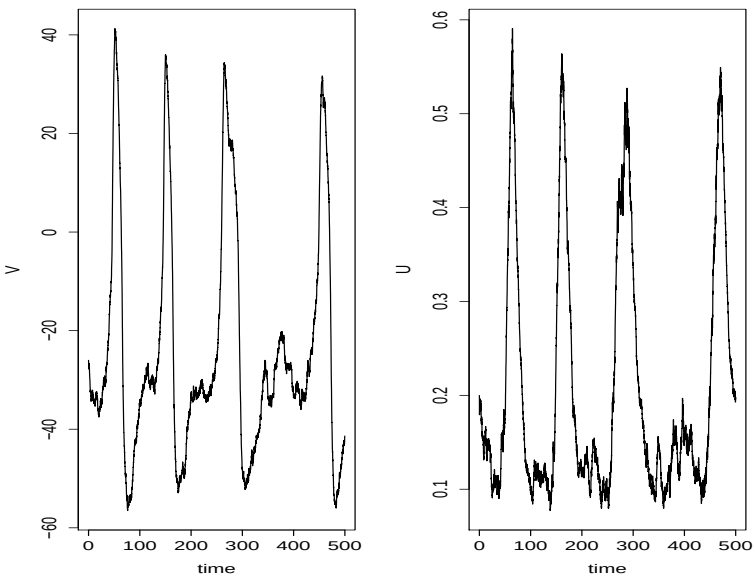
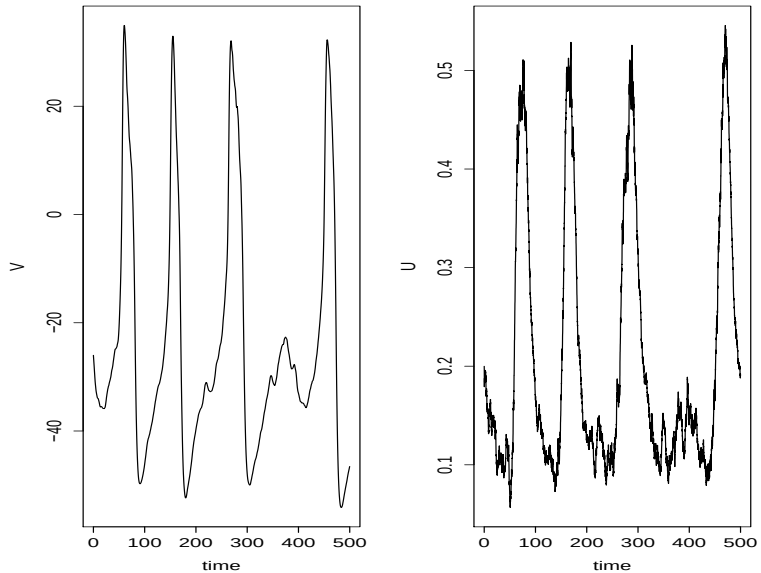
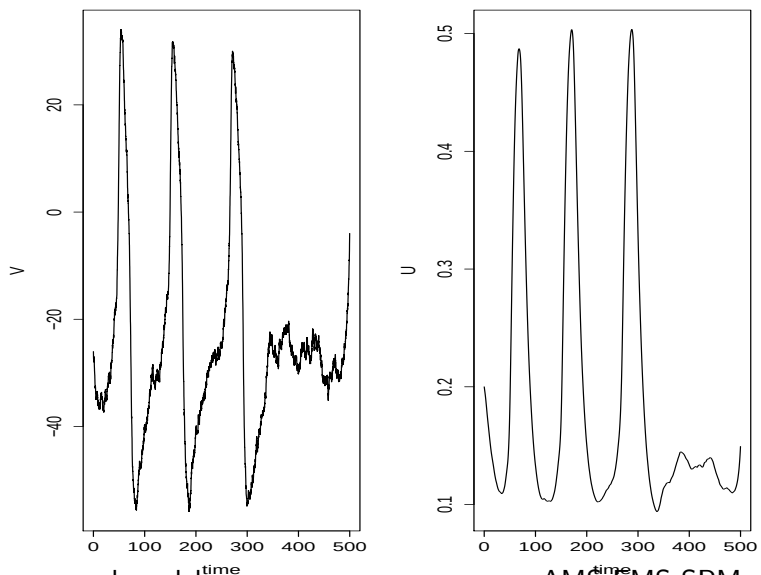


$\sigma_1 = 0$

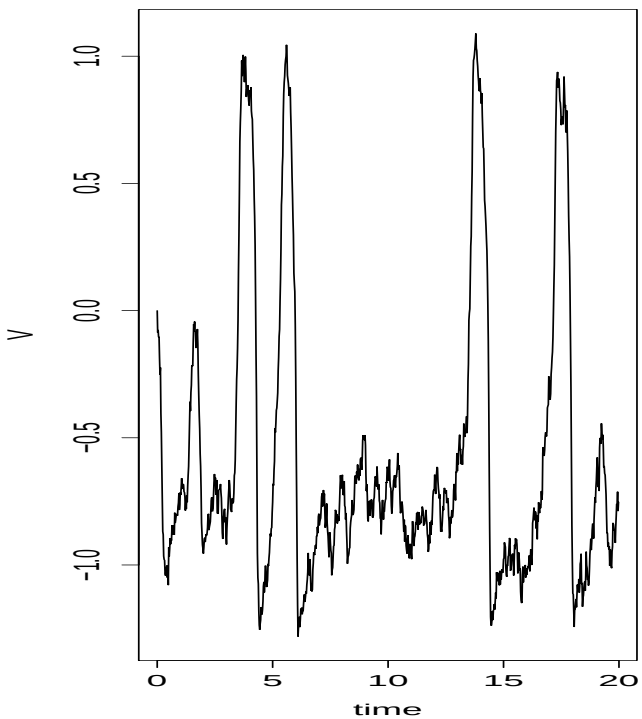


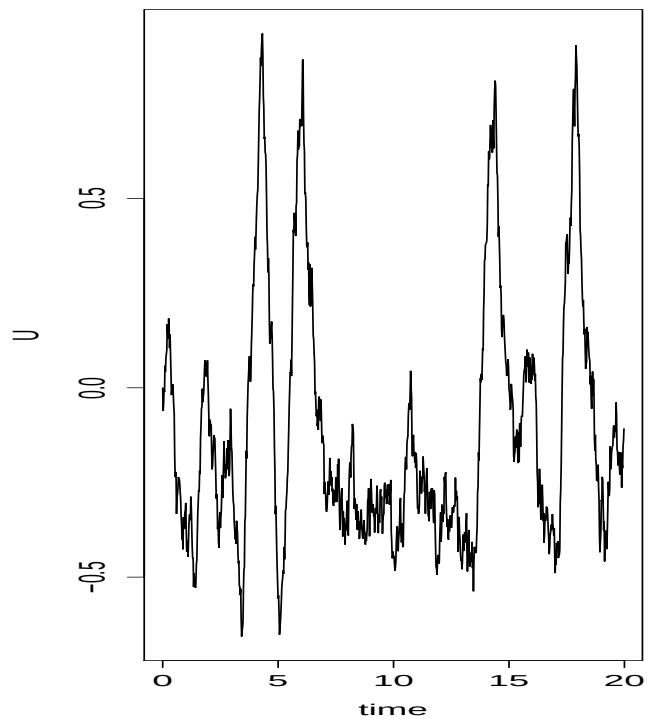
$\sigma_2 = 0$



FitzHugh-Nagumo model

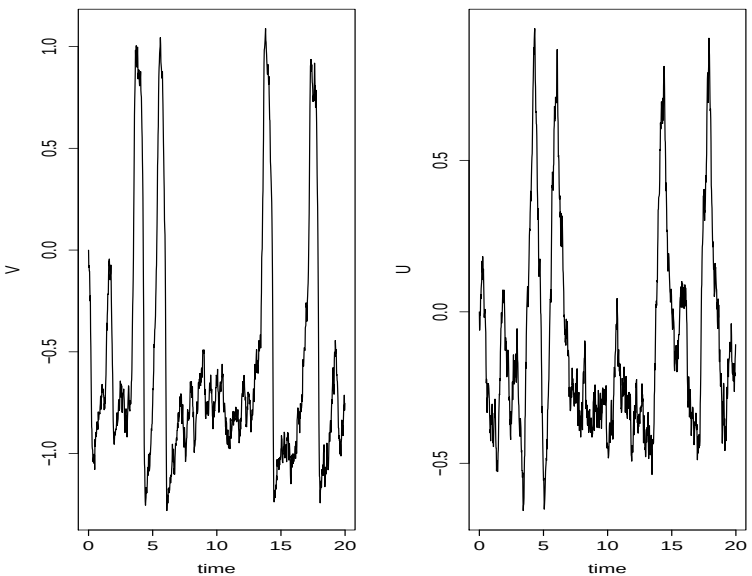
$$
\begin{aligned}
dV_t &= \frac{1}{\varepsilon}(V_t - V_t^3 - U_t - s)dt + \sigma_1 dB_{1t}, \\
dU_t &= (\gamma V_t - U_t + \beta)\, dt + \sigma_2 dB_{2t},
\end{aligned}
$$



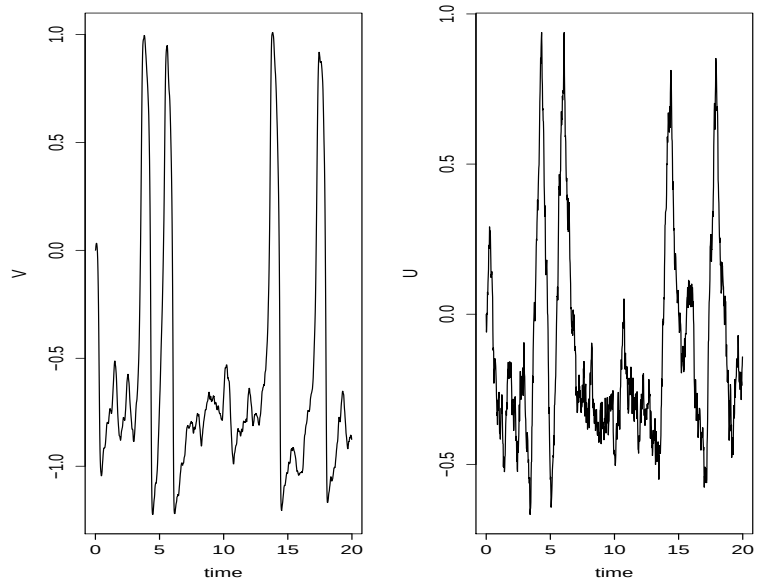


Effect of the noise

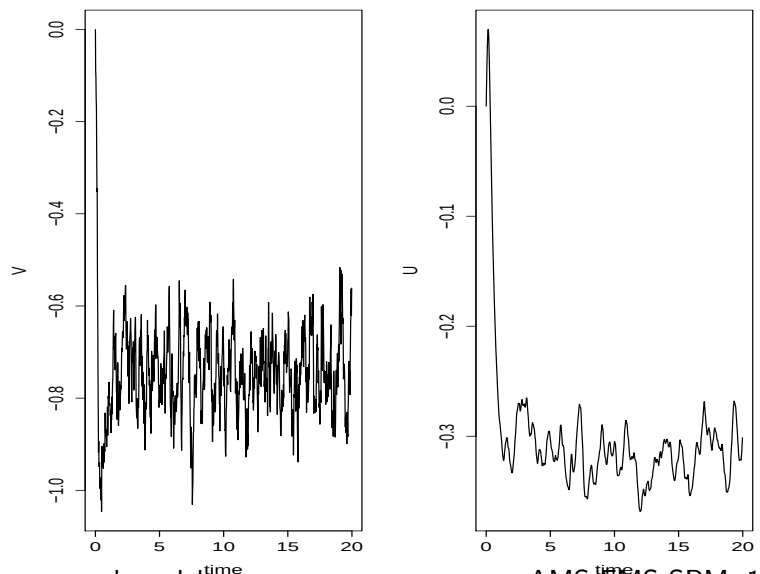
$\sigma_1 = 0.5, \sigma_2 = 0.3$



$\sigma_1 = 0$

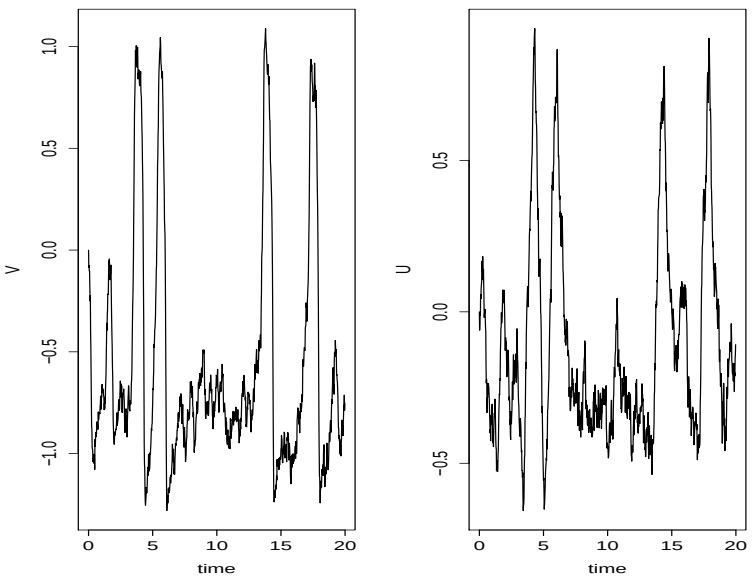


$\sigma_2 = 0$

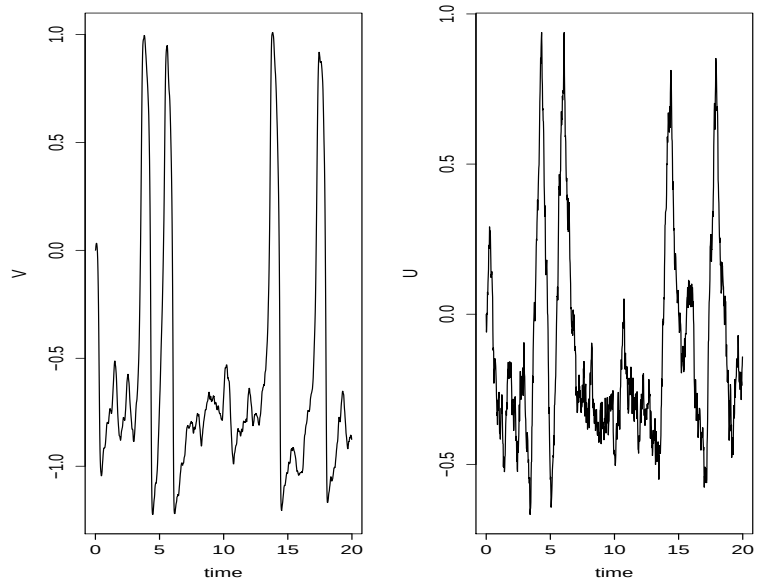


Effect of the noise

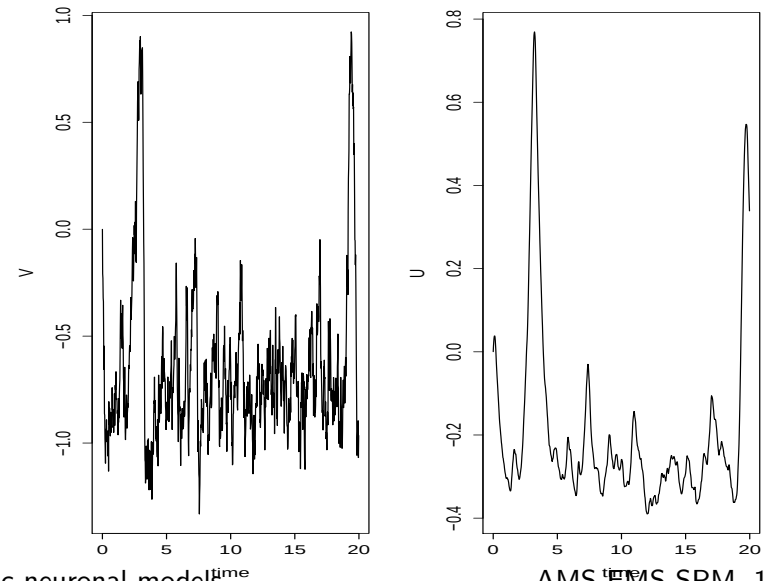
$\sigma_1 = 0.5, \sigma_2 = 0.3$



$\sigma_1 = 0$



$\sigma_1 = 0.7, \sigma_2 = 0$



Two models

Noise on both coordinates

$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt + \sigma_1 dB_{1t} \\ dU_t &= b_2(V_t, U_t, \mu)dt + \sigma_2 dB_{2t} \end{aligned}$$

Noise only on the second

$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt \\ dU_t &= b_2(V_t, U_t, \mu)dt + \sigma_2 dB_{2t} \end{aligned}$$

Questions:

- Can we estimate parameters from the data $V_{0:n} = (V_0, \ldots, V_n)$?
- Can we decide which model fits better the data ?

Parameter estimation

$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt + \sigma_1 dB_{1t} \\ dU_t &= b_2(V_t, U_t, \mu)dt + \sigma_2 dB_{2t} \end{aligned}$$

Estimation of parameters μ, σ_1, σ_2

- Data: discrete observations $V_{0:n} = (V_0, \ldots, V_n)$
- Hidden coordinate (U_t), possibly multi-dimensional

Difficult because

- No explicit transition density of the SDE
- Hidden states
- σ_1 may be fixed to 0 (hypoelliptic case)

Ideal case of complete observations and noise on both coordinates

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

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 $\Gamma = \Sigma'\Sigma$.

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

Consistence and asymptotic normality of $\hat{\theta}$

Estimation for partially observed SDE

Need to 'filter' the hidden component

Elliptic SDE

- EM algorithm + Kalman filter [Favetto, Samson, 2010], [Cuenod et al., 2011]
- EM algorithm + linearization of the SDE [Huys, Paninski, 2009]
- Bayesian approach [Fearnhead et al, 2008, Jensen et al, 2012]
- SAEM algorithm + particle filter [Ditlevsen, Samson, 2014]

Hypoelliptic SDE

- Assuming $dV_t = U_t dt$ and (U_t) autonomous:
  - Euler contrast [Gloter 2006];
  - Martingale estimating functions [Ditlevsen, Sorensen, 2004]
- Assuming $dV_t = U_t dt$ and (U_t) non autonomous:
  - Gibbs sampler [Pokern et al, 2010]
  - Euler contrast [Samson, Thieullen, 2012]
  - Non-parametric kernel estimator [Cattiaux et al, 2014, 2015]

Start with a Hamiltonian (hypoelliptic) SDE

$$\begin{aligned} dV_t &= U_t dt \\ dU_t &= b_2(V_t, U_t, \mu)dt + \sigma_2 dB_t \end{aligned}$$

U_t not observed but can be replaced by

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

Minimum contrast estimator [Samson, Thieullen, 2012]

$$\hat{\theta} = \arg\min_{\theta\in\Theta} \left(\frac{3}{2} \sum_{i=1}^{n-2} \frac{\left(\overline{V}_{i+1} - \overline{V}_i - \Delta b_2(V_{i-1}, \overline{V}_{i-1}, \mu)\right)^2}{\Delta\sigma_2^2} + \sum_{i=1}^{n-2} \log \sigma_2^2 \right)$$

Consistence and asymptotic normality of $\hat{\theta}$

General SDE

$$\begin{aligned} dV_t &= b_1(V_t, U_t, \mu)dt + \sigma_1 dB_{1t} \\ dU_t &= b_2(V_t, U_t, \mu)dt + \sigma_2 dB_{2t} \end{aligned}$$

Only V_i observed, U_i hidden

- Previous trick not available

- We want to filter U_i
  - Kalman filter when SDE is linear and Gaussian
  - **Particle filter/Sequential Monte Carlo** (SMC) for general SDE [Del Moral et al, 2001; Doucet et al, 2001; Chopin, 2004; ...]
  - Simulation of (a lot of) trajectories
  - Computation of their weights: their probability given the data

Computation of the weights

Require the knowledge of the transition density of the SDE

$$\begin{aligned} dV_t &= b_1(V_t, U_t)dt + \sigma_1 d\tilde{B}_t \\ dU_t &= b_2(V_t, U_t)dt + \sigma_2 dB_t \end{aligned}$$

Elliptic case

Euler scheme approximation

$$\begin{aligned} V_i &= V_{i-1} + \Delta b_1(V_{i-1}, U_{i-1}) + \sqrt{\Delta}\,\sigma_1\,\tilde{\eta}_i \\ U_i &= U_{i-1} + \Delta b_2(V_{i-1}, U_{i-1}) + \sqrt{\Delta}\sigma_2\eta_i \end{aligned}$$

$(\tilde{\eta}_i)$, (η_i) ind. centered Gaussian variables

- Explicit transition density of the approximate model

Hypoelliptic case

Euler scheme

$$\begin{aligned} V_i &= V_{i-1} + \Delta b_1(V_{i-1}, U_{i-1}) \\ U_i &= U_{i-1} + \Delta b_2(V_{i-1}, U_{i-1}) + \sqrt{\Delta}\sigma_2 \eta_i^2 \end{aligned}$$

No noise on the first coordinate $\Rightarrow$ degenerate weights in the particle filter

Perturbed Euler scheme [Bally, Talay, 1995]

$$\begin{aligned} \tilde{V}_i &= V_i + 1/\sqrt{i}\ \xi_i^1 \\ \tilde{U}_i &= U_i + 1/\sqrt{i}\ \xi_i^2 \end{aligned}$$

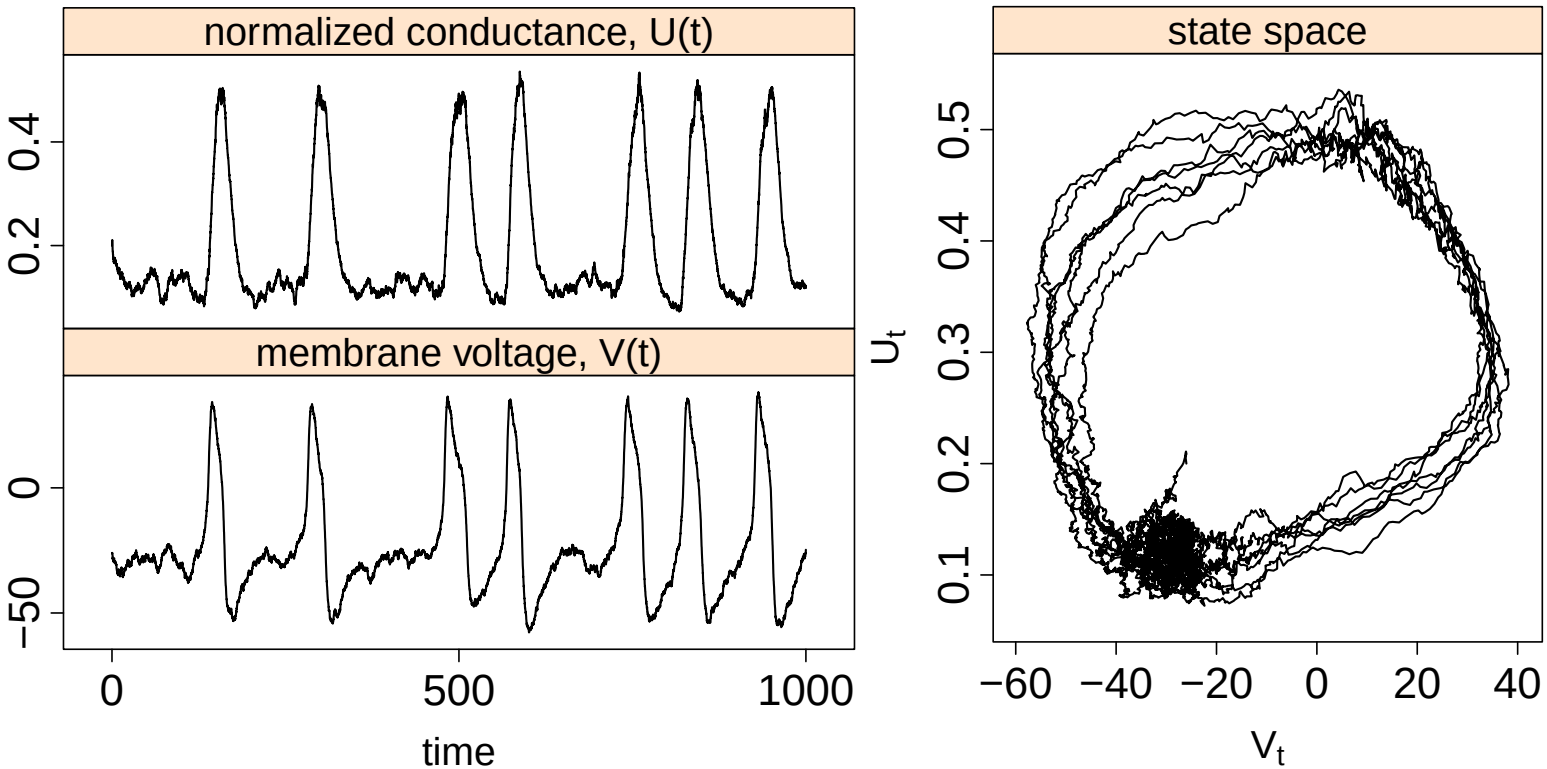
Measurement noise model $\Rightarrow$ Hidden Markov Model

Approximation with the 1.5 order scheme

$$\begin{aligned} V_i &= V_{i-1} + \Delta b_1(V_{i-1}, U_{i-1}) + \Delta^2\ g_1\ \eta_i^1 \\ U_i &= U_{i-1} + \Delta b_2(V_{i-1}, U_{i-1}) + \Delta^{1/2}\,\sigma_2\ \eta_i^2 + \Delta^{3/2}\,g_2\ \eta_i^1 \end{aligned}$$

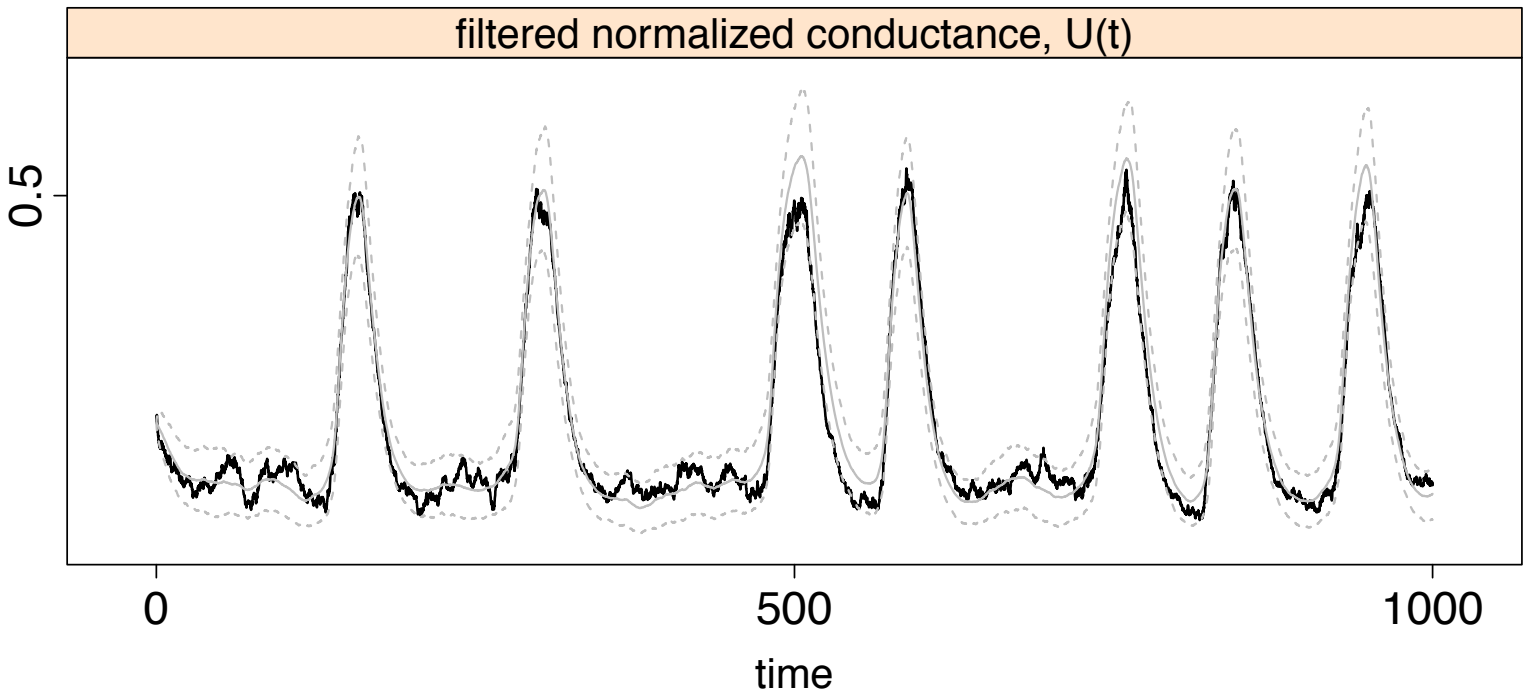
Noise on the first coordinate $\Rightarrow$ non degenerate weights in the particle filter

Simulations with the elliptic neuronal Morris-Lecar model



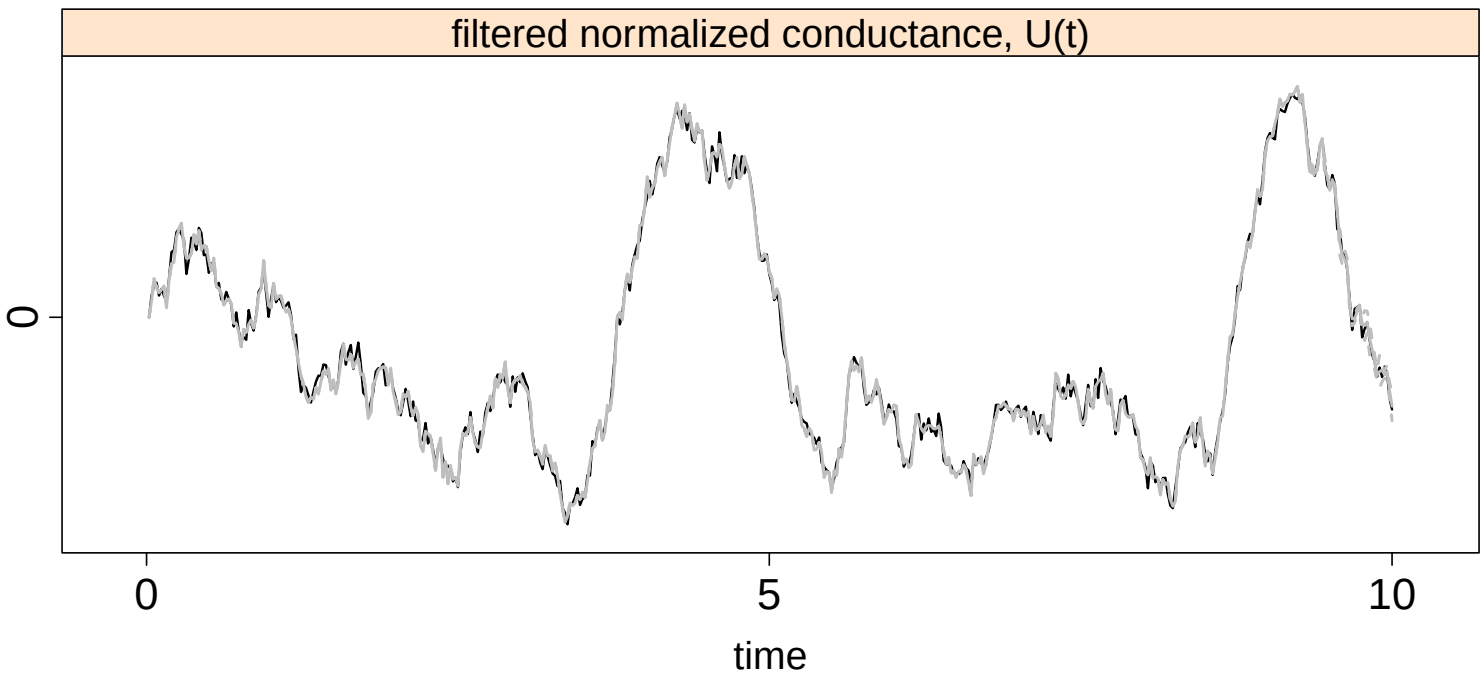
Filtering from $V_{0:n}$

Parameter θ fixed at the true value



Filtering with the hypoelliptic neuronal FitzHugh-Nagumo

Parameter θ fixed at the true value



Estimation of the parameters by maximum likelihood

Expectation-Maximization (EM) algorithm

- Likelihood non explicit, even with the discretisation scheme

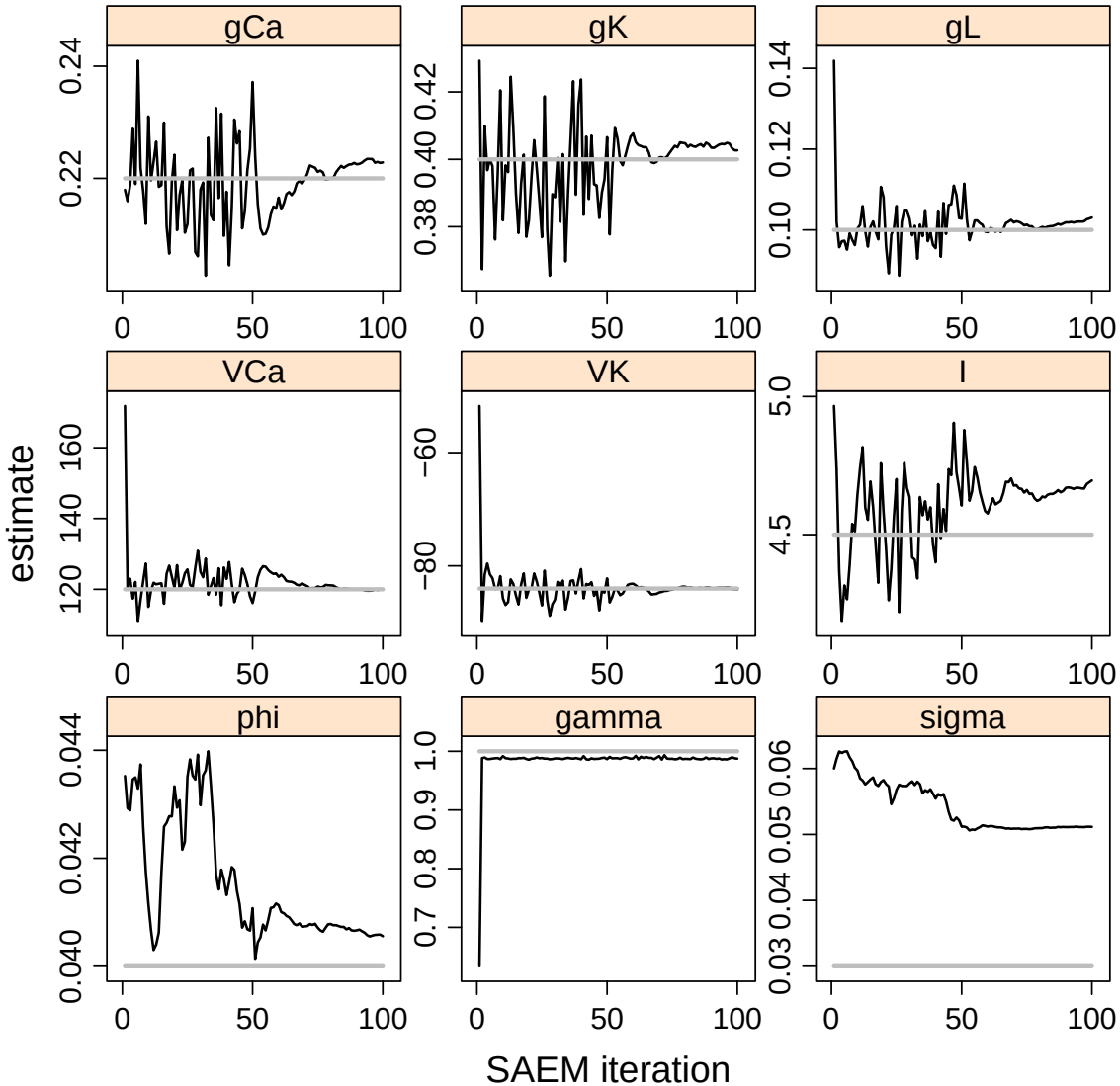
$$p_\Delta(V_{0:n};\theta) = \int \prod_{i=1}^{n} p_\Delta(V_i, U_i | V_{i-1}, U_{i-1};\theta) dU_{0:n}$$

- Incomplete data model
  - Observed data $(V_{0:n})$
  - Complete data $(V_{0:n}, U_{0:n})$

- SAEM algorithm [Delyon, Lavielle, Moulines, 1999, Ditlevsen, Samson, 2014], iteration m
  - *E Step*: computation of $Q_{m+1}(\theta) = \mathbb{E}_\Delta \left[\log p_\Delta(V_{0:n}, U_{0:n};\theta) \mid V_{0:n}, \widehat{\theta}_m \right]$ stochastic approximation with particle filter
  - *M Step*: update $\widehat{\theta}_{m+1} = \arg\max_\theta Q_{m+1}(\theta)$

- Convergence results [Wu, 1983]

SAEM-SMC on Morris-Lecar simulated data



- σ: not enough information in the membrane potential data

FitzHugh-Nagumo model

Elliptic system

	ϵ	γ	β	σ_1	σ_2
true	0.100	1.500	1.400	0.500	0.300
mean	0.110	1.556	1.438	0.459	0.289
SE	(0.01)	(0.21)	(0.16)	(0.01)	(0.04)

Hypoelliptic system

ϵ is fixed

	γ	β	σ_2
true	1.500	0.800	0.300
mean	1.523	0.821	0.293
SE	(0.13)	(0.11)	(0.01)

Perspectives

- Estimation for hypoelliptic system
  - 3-dim model or more: mean-field limit and diffusion approximation of interacting network
  - Theoretical results (convergence of the particle filter, SAEM, contrast estimator)
  - Which parameters can we estimate ?
  - R package
- Future:
  - Alternative with full Bayesian approach [joint work with S. Ditlevsen, A. Jensen, O. Papaspiliopoulos]
  - Tests to compare the models