A short teaser

MODELING with STOCHASTIC DIFFERENTIAL EQUATIONS and MIXED EFFECTS

Workshop on *Brain Dynamics and Statistics: Simulation versus Data*, (26/02/2017 - 03/03/2017, Banff, Alberta)

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Introduction

Differential equations are a frequently used tool for modeling the generating mechanisms behind longitudinal data. Often, the dynamics are complex and require multi-dimensional nonlinear models with several unknown parameters. Moreover, especially in biological systems, certain parameter values may vary across subjects and subject-specific models are asked for. Subject-wise parameter estimation can, however, be highly inefficient and unreliable if not enough subject-specific data is available (not enough repeated measurements). Thus, inference methods will lack sufficient power. The methodology of *random effects* allows data pooling and thereby facilitates more reliable estimation, while maintaining subject-specificity in modeling. The inclusion of stochasticity into the model itself, i.e., using *stochastic* differential equations (SDEs), adds further to the *robustness* of parameter inference, since the added system noise accounts for the (inherent) model uncertainty. We propose an approach for maximum-likelihood estimation in SDE models that include *mixed effects* (i.e., random and fixed effects). A striking (computational) benefit of the suggested approach is that the likelihood is *explicitly available* provided the parameters enter the drift term linearly. The model may, however, still be *nonlinear* in the state. This specific model class comprises a wide range of well-known statistical models (see below of some examples) and thus opens up for various applications, in particular in biology.
Covariates may be included as well to adjust for different experimental conditions or subject-specific information, such as age or gender.

Model

N independent r-dim. processes $X^i = (X^i_t)_{0\leq t\leq T^i}, i = 1, \ldots, N$, governed by the SDE

Applications

Modeling the neural excitability

The *Fitzhugh-Nagumo model* is a two-dimensional approximation of the four-dimensional Hodgkin-Huxley equations and often applied to model the regenerative firing mechanism in an excitable neuron. Neural firing is a complex interplay of numerous cell processes and to account for various unexplained noise sources, a stochastic FHN model can be considered (Jensen et al., 2012). Y represents the membrane potential of a neuron and Z the recovery.

$$
\begin{aligned}
dY_t &= \frac{1}{\varepsilon}\left(Y_t - Y_t^3 - Z_t + s\right) dt + \sigma_1 dW_{1,t},\\
dZ_t &= (\gamma Y_t - Z_t + \eta)\, dt + \sigma_2 dW_{2,t}.
\end{aligned}
$$

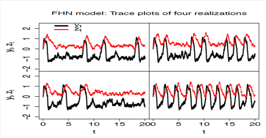
After the re-parametrization $\mu = (1/\epsilon, s/\epsilon, \gamma, \eta)$, the model for neuron i can be written as

$$
d\begin{pmatrix} Y^i_t \\ Z^i_t \end{pmatrix} = \left[\begin{pmatrix} 0 \\ Z^i_t \end{pmatrix} + \begin{pmatrix} Y^i_t - (Y^i_t)^3 - Z^i_t & 1 & 0 & 0 \\ 0 & 0 & Y^i_t & -1 \end{pmatrix}\right](\mu + \phi^i)\, dt + \Sigma\, dW^i_t
$$

with random effects $\phi^i \sim \mathcal{N}(0, \Omega)$ and unknown Ω.

Estimation results

	true value	$N=20$		$N=50$		$N=100$	
		rel. bias	RMSE	rel. bias	RMSE	rel. bias	RMSE
ϵ	0.10	0.002	0.035	0.003	0.022	0.003	0.016
s	0.50	-0.004	0.057	0.001	0.033	0.001	0.025
$1/\epsilon$	10.00	-0.001	0.352	-0.003	0.216	-0.003	0.154
s/ϵ	5.00	-0.006	0.240	-0.002	0.135	-0.002	0.104
γ	1.50	-0.000	0.050	-0.000	0.031	-0.001	0.024
η	1.20	-0.001	0.051	-0.001	0.031	0.000	0.022
	2.25	-0.065	0.731	-0.048	0.469	-0.017	0.340
diag(Ω)	1.00	-0.053	0.312	-0.025	0.197	-0.013	0.149
	0.04	-0.042	0.016	-0.035	0.010	-0.012	0.007
	0.04	-0.064	0.015	-0.007	0.010	-0.007	0.007

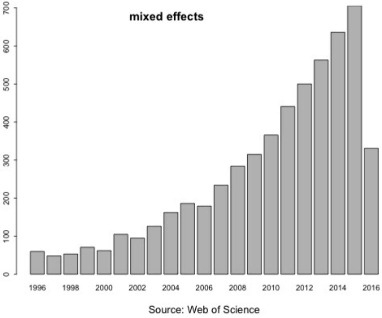


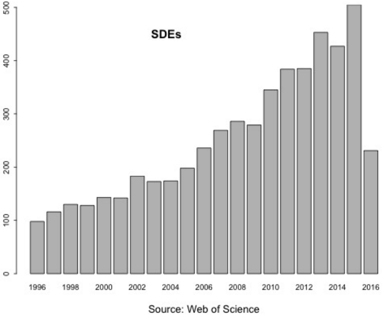
Trace plots of four realizations of the stochastic FHN model with random effects. The corresponding (rounded) realized parameter values of $\mu + \phi^i$ are (8.86,4.29,1.50,1.39), (10.16,7.49,1.73,1.40), (9.98,5.49,1.10,1.07), (9.26,5.17, 1.84, 1.01).

Take two popular modeling frameworks...

mixed effects

Stochastic differential equations





Showing: Number of publications by year (data accessed in early July 2016).

...and combine them

Data: Observations of N independent r-dim. processes $(X_t^i)_{0\leq t\leq T^i}$.

Data model:

(old) Stochastic differential equation (with fixed effects)

$$dX_t^i = F(t, X_t^i, \mu)dt + \Sigma(t, X_t^i)dW_t^i \rightsquigarrow \quad \textbf{estimate } \mu$$

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(new) Stochastic differential equation with mixed effects

fixed effect

random effect $\sim p(\phi^i; \vartheta)$

$$dX_t^i = F(t, X_t^i, \mu, \phi^i)dt + \Sigma(t, X_t^i)dW_t^i \rightsquigarrow \textbf{ estimate } \theta = (\mu, \vartheta).$$

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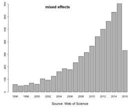
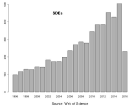
Actually, we can also include some covariate information (D_t^i)...:

$$dX_t^i = F(t, X_t^i, D_t^i, \mu, \phi^i)dt + \Sigma(t, X_t^i)dW_t^i$$

Two key reasons for increased popularity

(1) Both frameworks very useful - their combination all the more





hot · hot = even hotter

SDEs capture model insufficiencies, random effects enable pooling while still being subject-specific.

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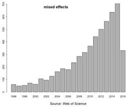

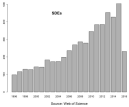

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SDEs capture model insufficiencies, random effects enable pooling while still being subject-specific.

(2) Both frameworks challenging - their combination all the more

Goal: obtain the MLE $\hat{\theta}_N = \arg\max_\theta L(\boldsymbol{X};\theta)$ $\theta = (\beta, \vartheta)$

Likelihood: $L(\boldsymbol{X};\theta) = \prod_{i=1}^N L(X^i;\theta) = \prod_{i=1}^N \int L(X^i;\beta,\phi^i)p(\phi^i;\vartheta)d\phi^i$

intractability · intractability = (intractability)^2

Good news for numerous applications

- In certain cases, the likelihood is **explicit**.
- Dynamics can be **non-linear** in the state.
- We can even include **covariate** information (gender, age, exp. condition, ...).
- Many well-known models fall into this certain class.
- The MLE is consistent and asymptotically normal (T fix, N large).
- We can do hypothesis testing.

Possible applications to neuroscience

(a) EEG data

- $\rightarrow$ avoid *averaging* over trials and/or subjects
- $\rightarrow$ keep "pooling", but *model* inter-trial / inter-subject variability with random effects

Data N subjects, J trials each, $X_t^i = (X_t^{i,1}, \ldots, X_t^{i,J})' \in \mathbb{R}^{r \cdot J}$,

$$dX_t^i = F(t, X_t^i, D_t^i, \mu, \phi^i)dt + \Sigma(X_t^i)dW_t^i$$

(b) Stochastic FHN model with mixed effects

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Hope to see you at my poster!