PSM: Population Stochastic Modelling

An R package for non-linear mixed-effects models based on stochastic differential equations

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Aim

- The use of stochastic differential equations (SDEs) in PK/PD models has been motivated in several articles [I-III]. The use of SDEs is practical when modelling systems with varying degrees of natural unpredictable variation. Many programs including NONMEM are based on ordinary differential equations and can handle SDEs only through additional implementations. A more user friendly alternative has previously been made available in Matlab [IV].
- This poster presents an R package that includes methods for handling NLME models based on SDEs.

Methods

The package is an implementation of the theoretical setup of NLME-SDE models also described by Overgaard et al [II]. The model specification is a continuous-discrete stochastic state-space model. The noise is assumed to be additive and normally distributed. The related covariance function might be time varying, but is assumed to be independent of the states. The individual model is

$$d\mathbf{x} = \mathbf{f}(\mathbf{x},\mathbf{u},t,\boldsymbol{\varphi})dt + \boldsymbol{\sigma} d\boldsymbol{\omega}_t$$

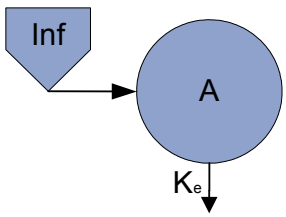
$$\mathbf{y}_k = \mathbf{g}(\mathbf{x},\mathbf{u},t,\boldsymbol{\varphi}) + \mathbf{e}_k$$

Where $\boldsymbol{\omega}_t$ is a standard wiener process with increments $\boldsymbol{\omega}_2 - \boldsymbol{\omega}_1 \in N(0, |t_2 - t_1|)$. The noise component in the system equations enables variation to be split in system and observation noise.
The individual likelihood function is evaluated by the (extended) Kalman Filter.
The FOCE approximation is used to calculate the likelihood for the NLME component of the model setup.

General Description	PSM Component
Stochastic State Space System	Linear / Non-Linear `Matrices/Functions`
Initial State value	`X0`
Observation noise	`S`
System noise	`SIG`
Parameters to be optimized	`ModelPar`
Individual param.	`h`
Data	`Time, Y, U, Dose`

Figure 1. Deconvolution of infusion

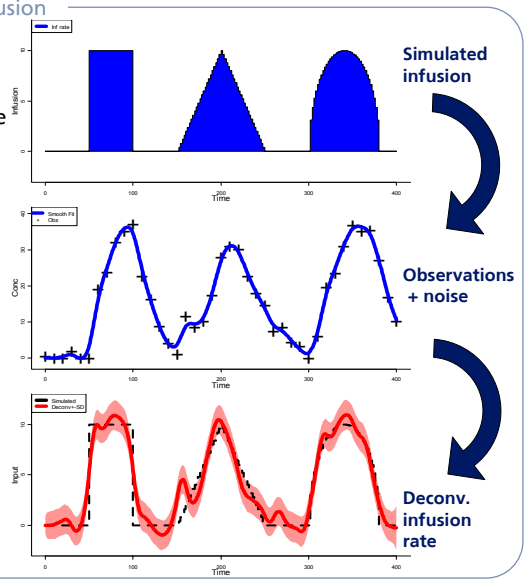
Example: An Iv-infusion system is simulated with a known infusion rate profile.
The kinetic system is assumed to be known and the infusion rate is determined by deconvolution [V].



$$dA = (Inf - Ke \cdot A)dt$$

$$dInf = \sigma d\omega_t$$

$$y_k = A_k / V + e_k \qquad e_k \in N(0,S)$$



PSM Package

The implementation is done in R with some core functions implemented in FORTRAN. The main functionality is available through 3 functions operating on a model specification, data and parameters.
The package is able to handle multivariate observations, covariates, different dosing regimes and missing observations.

• Simulation
`PSM.simulate` simulates states and observations for a model. The state trajectories are simulated by a simple Euler scheme with predefined time increments and observation times.

• Estimation
`PSM.estimate` performs a maximum likelihood based estimation of the population parameters.

The optimization is a quasi-Newton based algorithm optionally with boundaries on the parameters. The confidence intervals for the estimated parameters can also be calculated.

• Smoothing
`PSM.smooth` creates the smoothed estimates of states and observations based on all data at all times. The feature is available both for linear and non-linear models.

The PSM package provides a flexible framework for working with NLME-SDE models and the usage of R provides additional functionality at hand.

Furthermore the PSM package can easily be used for deconvolution purposes as shown in figure 1.

Get Started

To get started download and install R and install PSM by typing:

```
>install.packages("PSM")
```

Further documentation and help can be found by

```
>help("PSM")
```
or
```
>vignette("PSM")
```

Summary

- The R package PSM enables the use of stochastic differential equations in non-linear mixed-effects models.
- It provides a flexible framework as models are based on specification of differential equations
- Data handling, visualization and modelling can be performed in R.
- More material and information can be found at

www.imm.dtu.dk/psm

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References

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