

Hierarchical Stochastic Pharmacokinetic Models

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Features of PK/PD analysis

- Biological system is inherently stochastic (due to physiological differences) and time continuous.
- Additional measurement error.
- Irregularly spaced data / Unbalanced designs / Missing data.
- Population / Individual level modelling

Bayesian Inference

- Hierarchical modeling / Borrowing strength across individuals.
- General non-linear diffusion framework.
- MCMC implementation:
 - Data augmentation scheme.
 - Reparametrisation required to avoid reducibility of the chain.

ODEs vs SDEs models

Traditionally PK/PD modeling utilizes Ordinary Differential Equations (ODEs) to describe the dynamics of the drug concentration X , e.g.

$$\frac{dX_t}{dt} = -\kappa t \rightarrow X_t = X_0 e^{-\kappa t}$$

Hence, κ is *deterministically* related to X .

The use of Stochastic Differential Equations (SDEs) extend ODE models by explicitly incorporating system noise, e.g.

$$dX_t = -\kappa dt + \sigma(t, X_t, \theta) dW_t$$

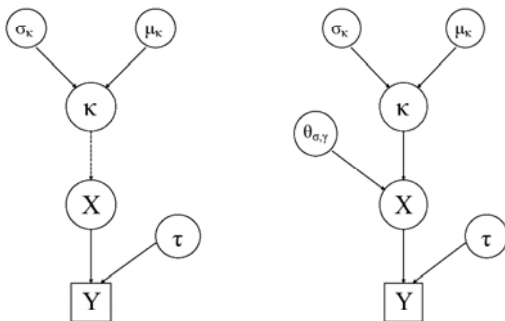


Figure 1: Graphical representations of ODE (left) and SDE (right) based single compartment models.

Discernible characteristics of PK/PD models with SDEs

- Mean behavior remains intact.
- Naturally disentangles system from measurement error.
- Ability to account for structural misspecification.
- Probabilistic framework for model determination.

Example: 1 Compartment model

We simulated data from the model below for $I=20$ and average J of 13.

$$Y_{ij} \sim N(X_{it}, \tau^2), i = 1, \dots, I, j = 1, \dots, J_i$$

$$dX_{it} = -\kappa_i X_{it} dt + \sigma X_{it}^\gamma dW_t$$

$$\kappa_i \sim N(\mu_\kappa, \sigma_\kappa^2)$$

with non-informative priors. The results are shown below:

	Posterior Median	Posterior Mean	Posterior SD	True Value
μ_κ	1.586	1.587	0.082	1.5
σ_κ	0.329	0.337	0.064	0.3
σ	0.812	0.780	0.163	0.7
γ	0.423	0.435	0.0824	0.5
τ	0.1293	0.134	0.0731	0.2

Table 1: Posterior summaries from simulated data analysis.

Note: Each value of γ corresponds to a different transition density for X ($\gamma=0.5$: non-central Chi-Square, $\gamma=1$: log-Normal). This approach may be seen as model averaging.

Future Directions

- Extensions to multi-compartmental models.
- Applications (i.e. Bioequivalence assessment).
- Model choice – inclusion of covariates.
- Alternative PK/PD models