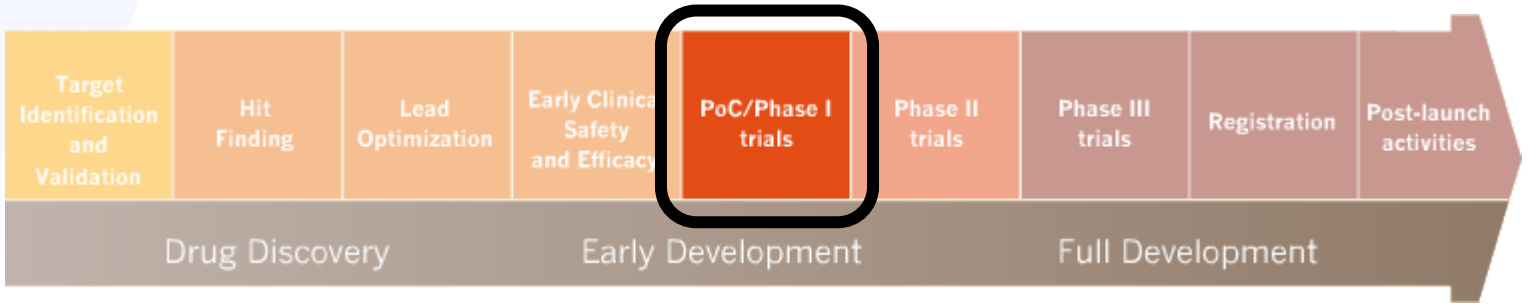
Phase I clinical trials

Nonparametric modelling of dose escalation data: Population Smoothing Splines

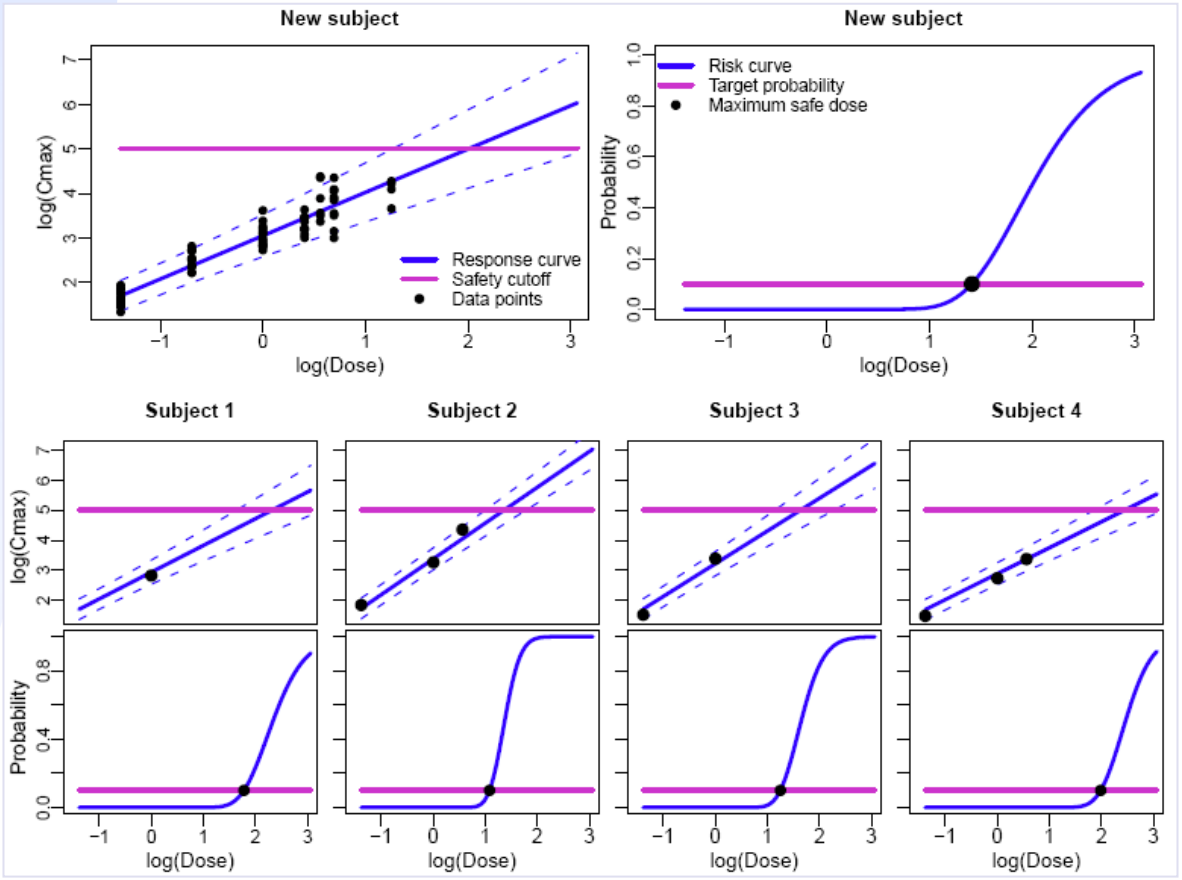
In collaboration with

GlaxoSmithKline



Phase I – Parametric dose escalation

Example: dose escalation study of an antidepressant drug



A. Russu *et al*. Bayesian population approaches to the analysis of dose escalation studies. Submitted to *Computer Methods and Programs in Biomedicine*

Phase I – Population Smoothing Splines

Fact

Parametric models (power, E_{max}, ...) are widely used in pharmacometrics: simple, but not flexible enough

Few available data $\Rightarrow$ high chance of *model misspecification*

Idea from Machine Learning: Gaussian Processes

Model-free and *smooth* alternative to parametric approaches

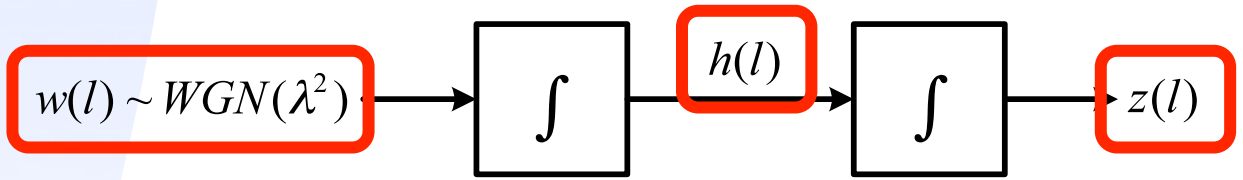
Can be adapted to population analyses: *Population Smoothing Splines*

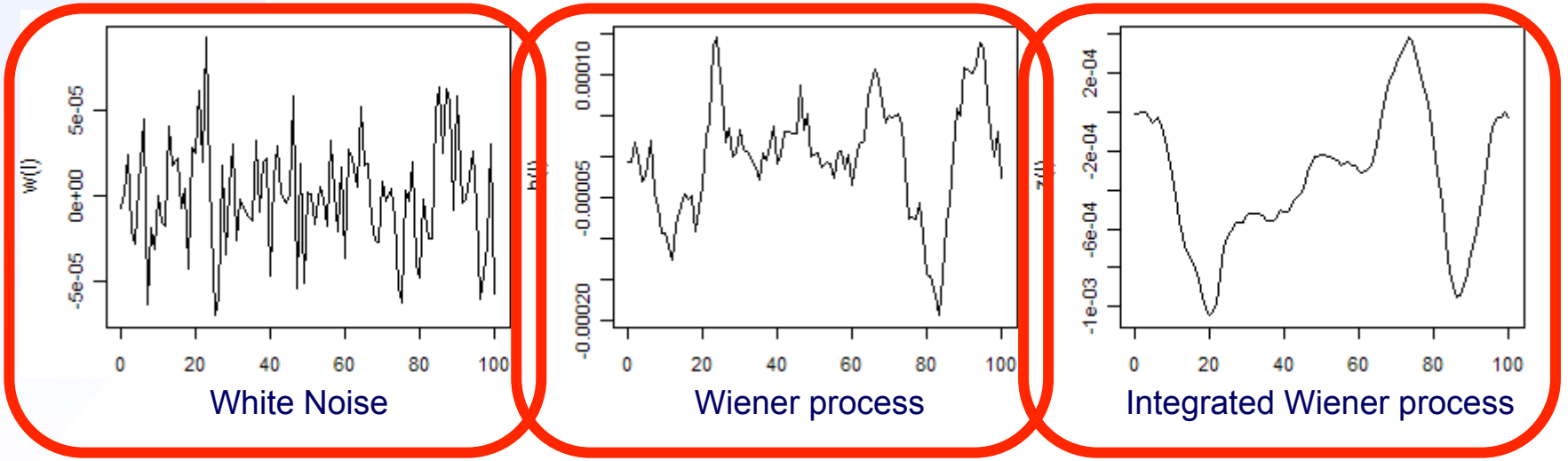
Phase I – Population Smoothing Splines

Gaussian Process model

Integrated Wiener process: white gaussian noise, integrated twice

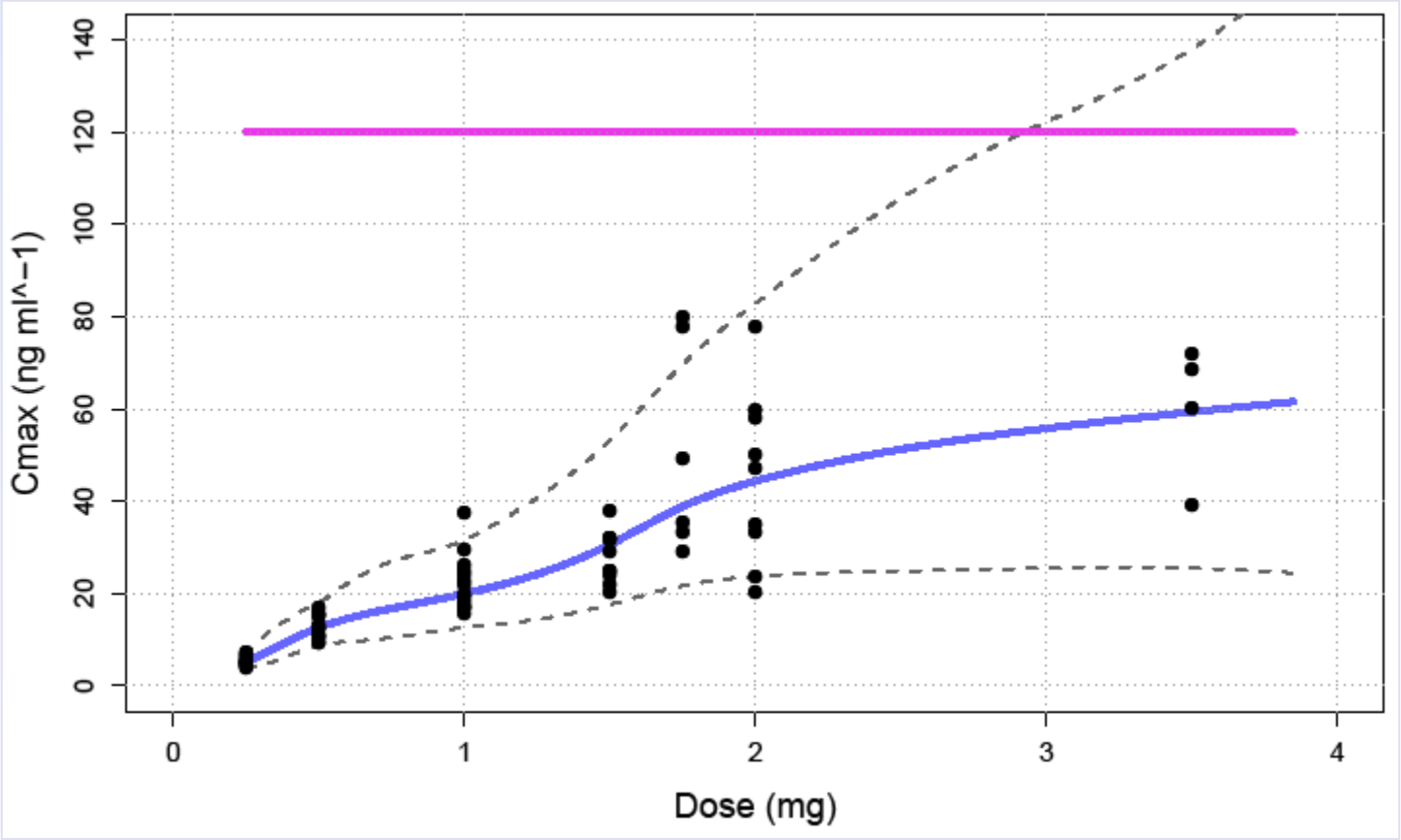
Population approach: typical curve + individual curve





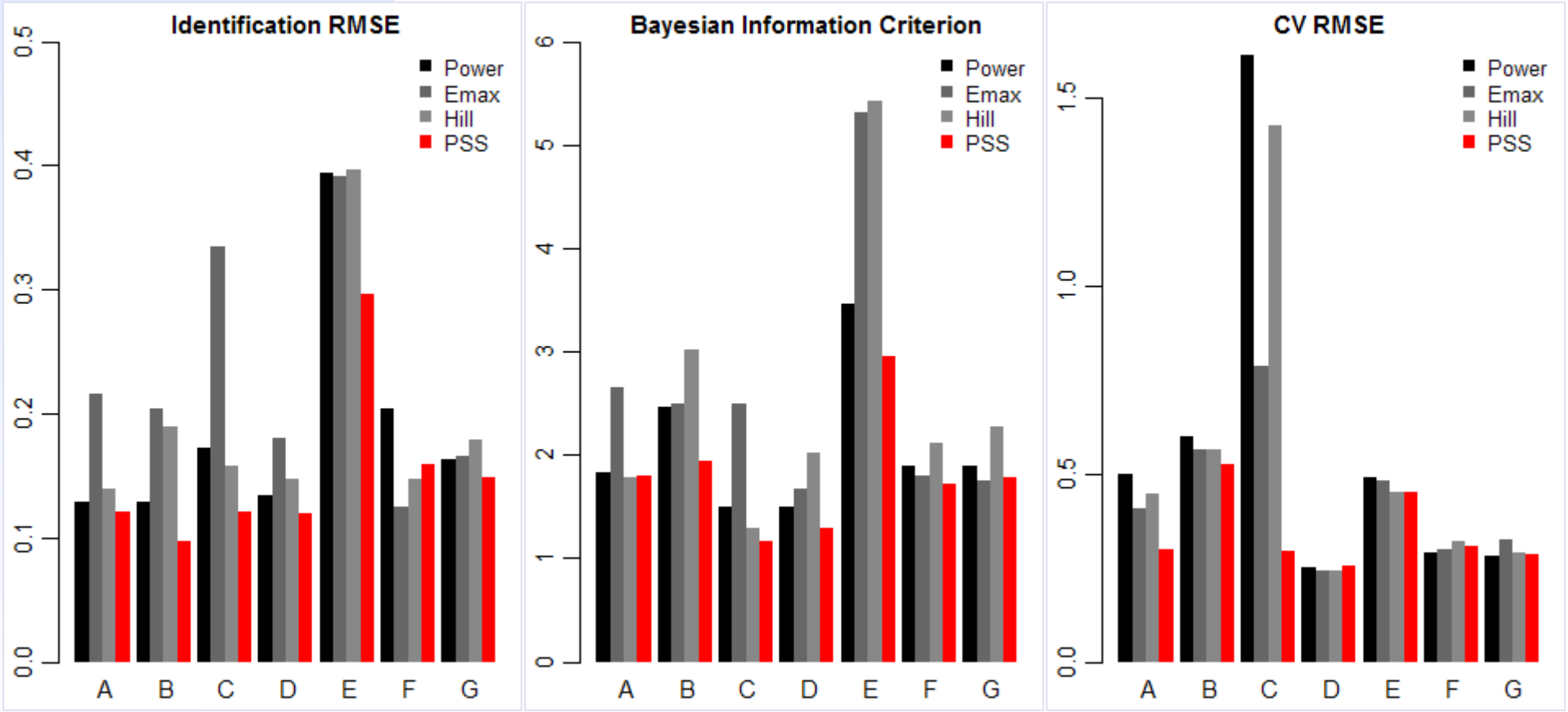
Phase I – Population Smoothing Splines

Example: dose escalation study (population distribution)



Phase I – Population Smoothing Splines

Performances on experimental datasets



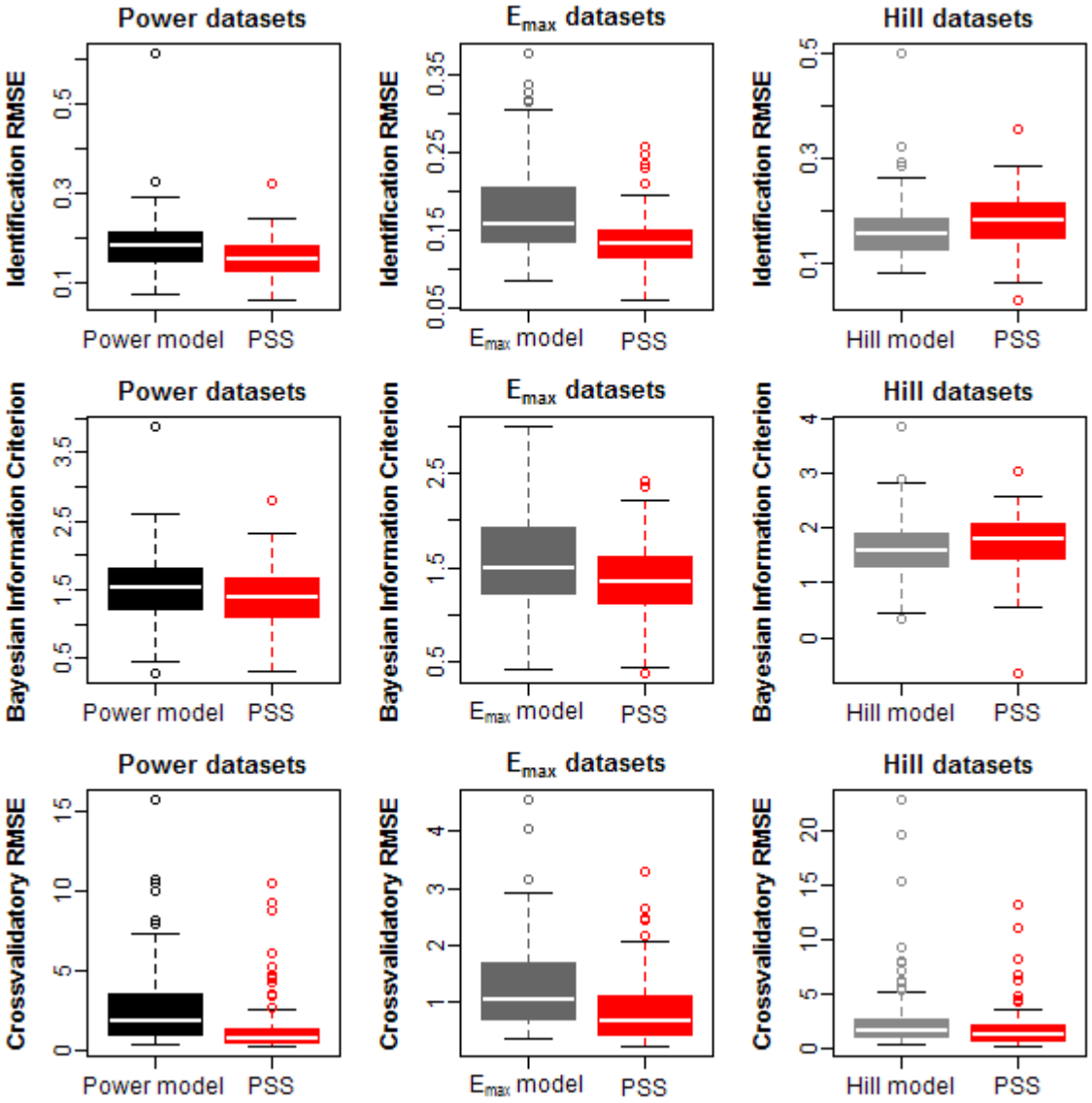
A. Russu *et al*. Bayesian population modelling of Phase I dose escalation studies: a Gaussian process approach. Submitted to *IEEE Transactions on Biomedical Engineering*

Phase I – Population Smoothing Splines

Simulated benchmark

1. Generate 300 synthetic datasets with:
   - Power model
   - E_{max} model
   - Hill model
2. Fit each generating model and PSS to data of the generating models
3. Evaluate:
   - Identification RMSE
   - Bayesian Information Criterion
   - Crossvalidatory RMSE

   of generating model *vs* PSS



A. Russu *et al*. Bayesian population modelling of Phase I dose escalation studies: a Gaussian process approach. Submitted to *IEEE Transactions on Biomedical Engineering*

Phase I – Population Smoothing Splines

Previous state-of-the-art

Widespread use of parametric models despite misspecification issues

R. Jelliffe *et al*. Population pharmacokinetic and dynamic models: parametric (P) and nonparametric (NP) approaches," in *Proc. 14th IEEE Symp. Computer-Based Med. Syst*., 407–412, 2001

Key achievements

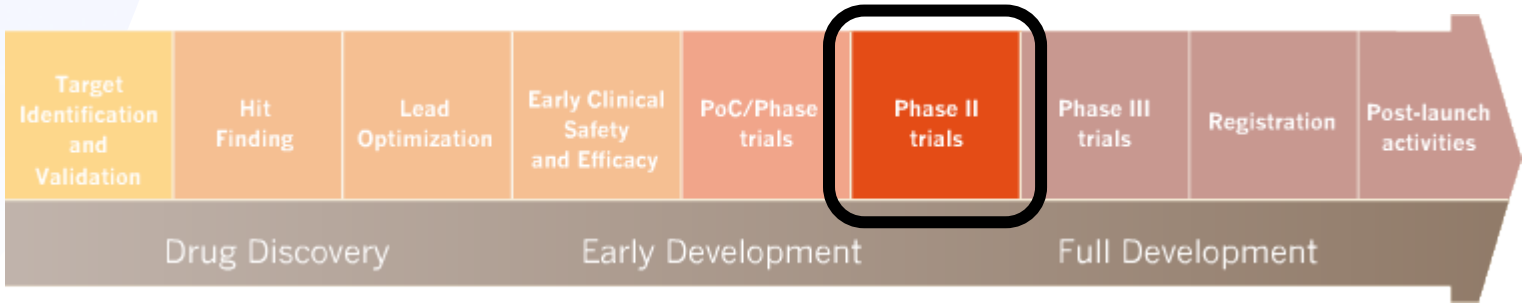
- Development of a flexible and smooth population method
- Robust extrapolation (crossvalidation)
- Simulated benchmark: excellent performances of PSS with respect to the true models

Phase II clinical trials

Joint population modelling of clinical response and dropout

In collaboration with

GlaxoSmithKline



Phase II – Joint model of response & dropout

Clinical studies in depression

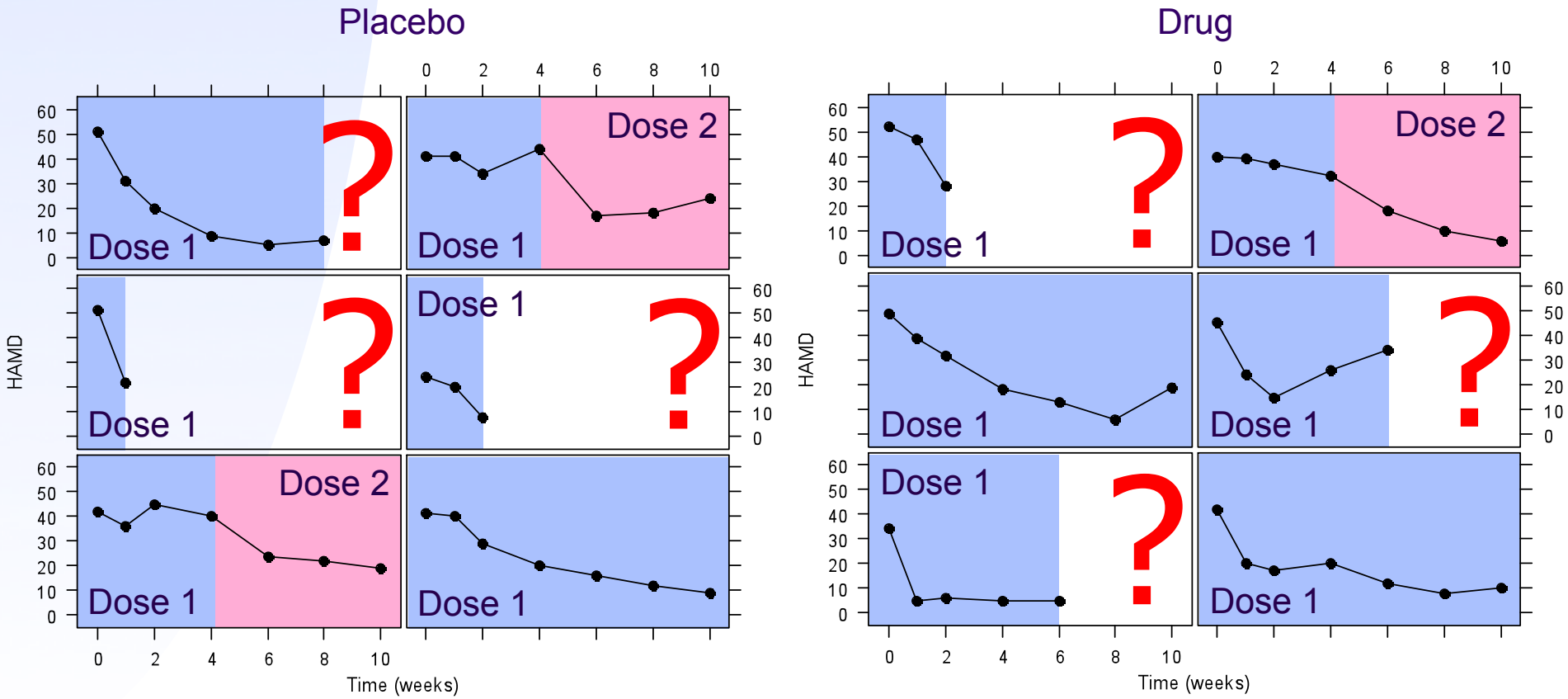
- Main tool to evaluate depression: Hamilton Rating Scale for Depression (HAMD)
- Questionnaire based on 17 items:
  - Sadness
  - Sense of guilt
  - Insomnia
  - Anxiety
  - Suicidal thoughts
  - ...

Phase II – Joint model of response & dropout

Example of a depression dataset

Complication 1: dropout events

Complication 2*:* possible dose escalation at a given week (*flex-design*)

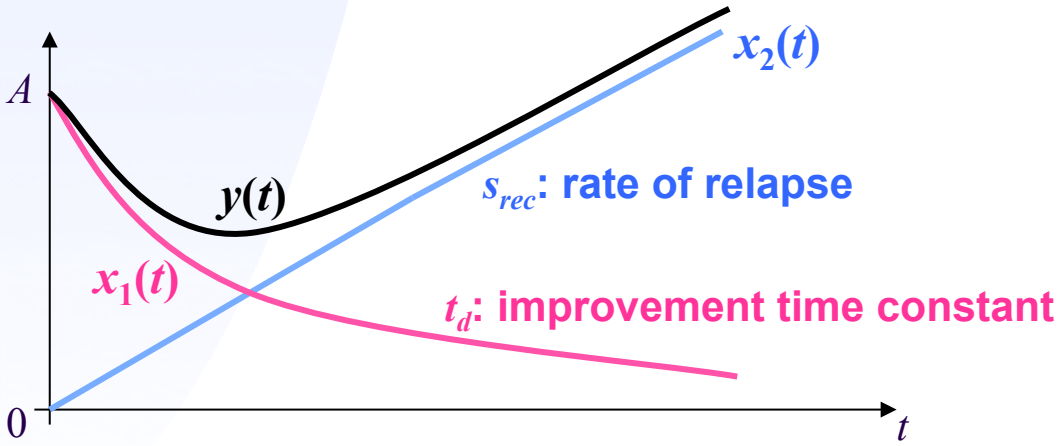


Phase II – Joint model of response & dropout

A joint modelling approach

HAMD time-course model

$$\begin{cases} \dot{x}_1(t) = -\frac{b}{t_d^b} x_1(t) t^{b-1} & x_1(0) = A \\ \dot{x}_2(t) = s_{rec} & x_2(0) = 0 \\ y(t) = x_1(t) + x_2(t) & \\ z(t_k) = y(t_k) + \varepsilon & \end{cases}$$



Dropout model

Hazard function (T: dropout time)

$$h(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid t \le T)}{\Delta t}$$

Cumulative hazard

$$H(t) = \int_0^t h(u)du$$

Survival function

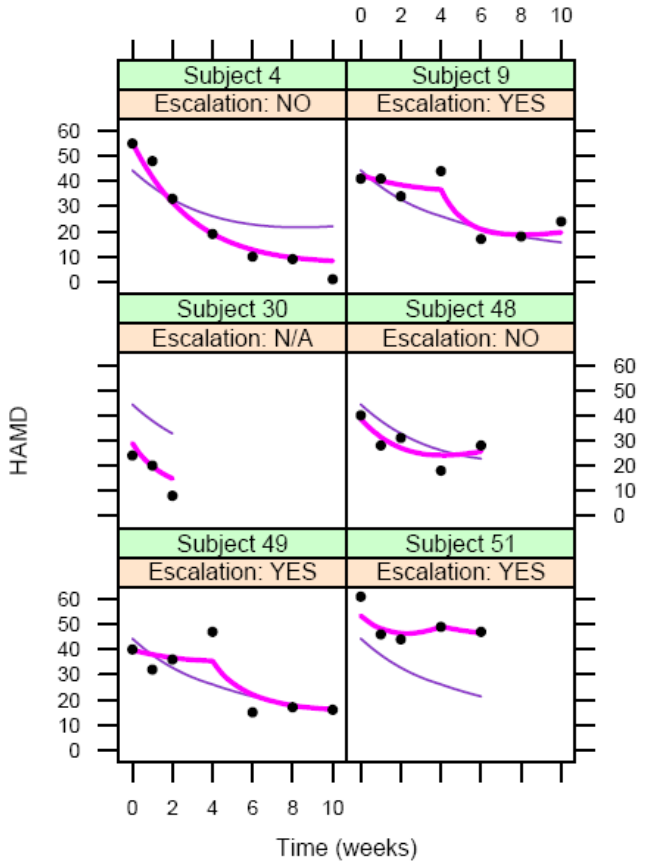
$$S(t) = e^{-H(t)}$$

A. Russu *et al*. Disease and dropout modelling in depression trials: a state-space approach. 6th International Symposium on Measurement and Kinetics of In Vivo Drug Effects, 2010
A. Russu *et al*. Integrated model for clinical response and dropout in depression trials: a state-space approach. Population Approach Group in Europe (PAGE) 19th Meeting, 2010

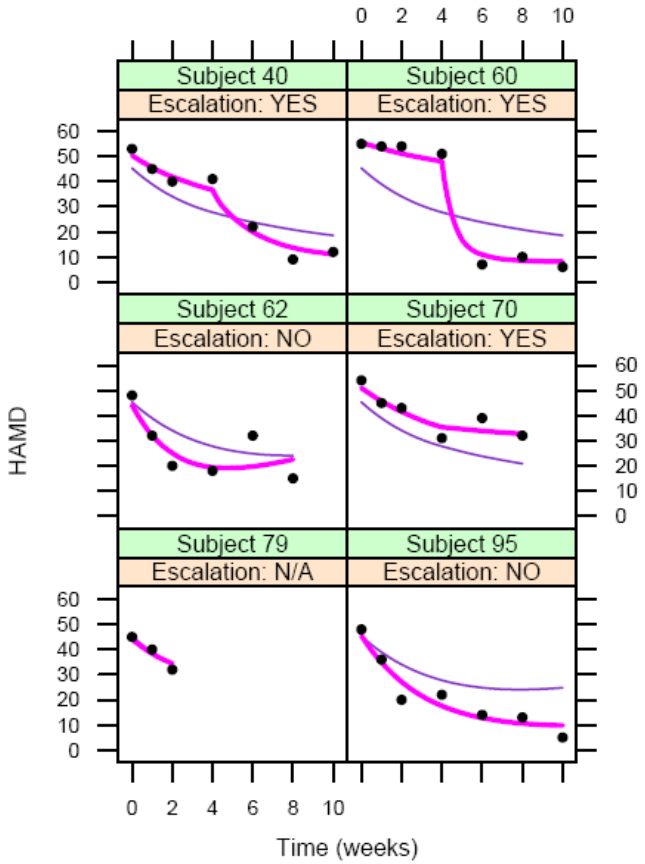
Phase II – Joint model of response & dropout

Fitting of HAMD data

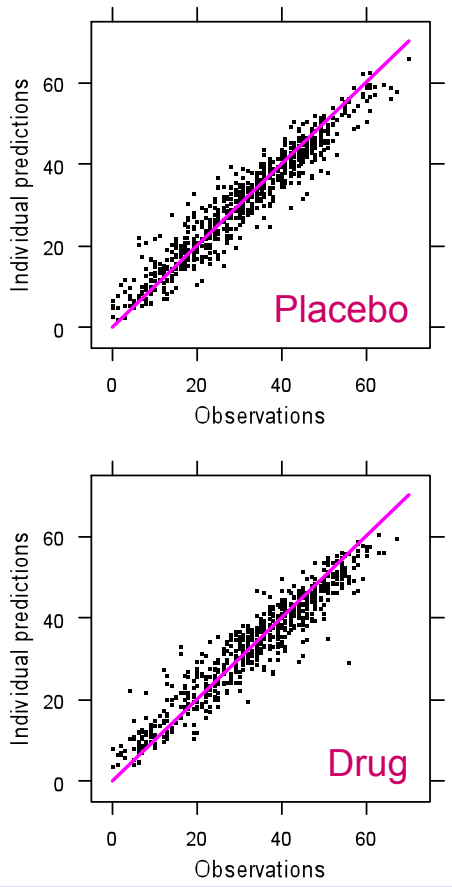
Placebo arm



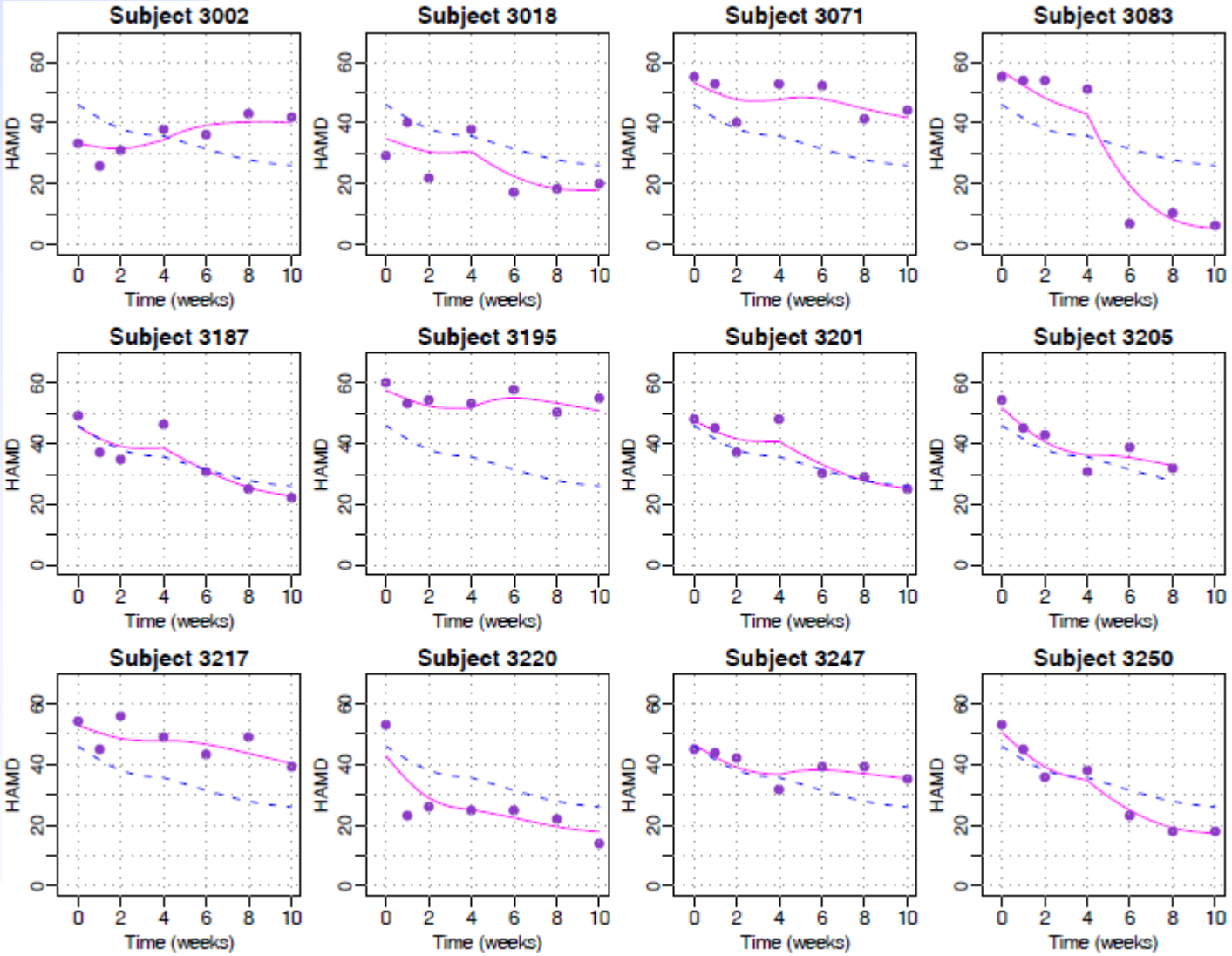
Drug arm



Goodness-of-fit



Subset of individual fittings



Visual Predictive Check