Università di Pavia

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Integrated model for clinical response and dropout in depression trials: a state-space approach

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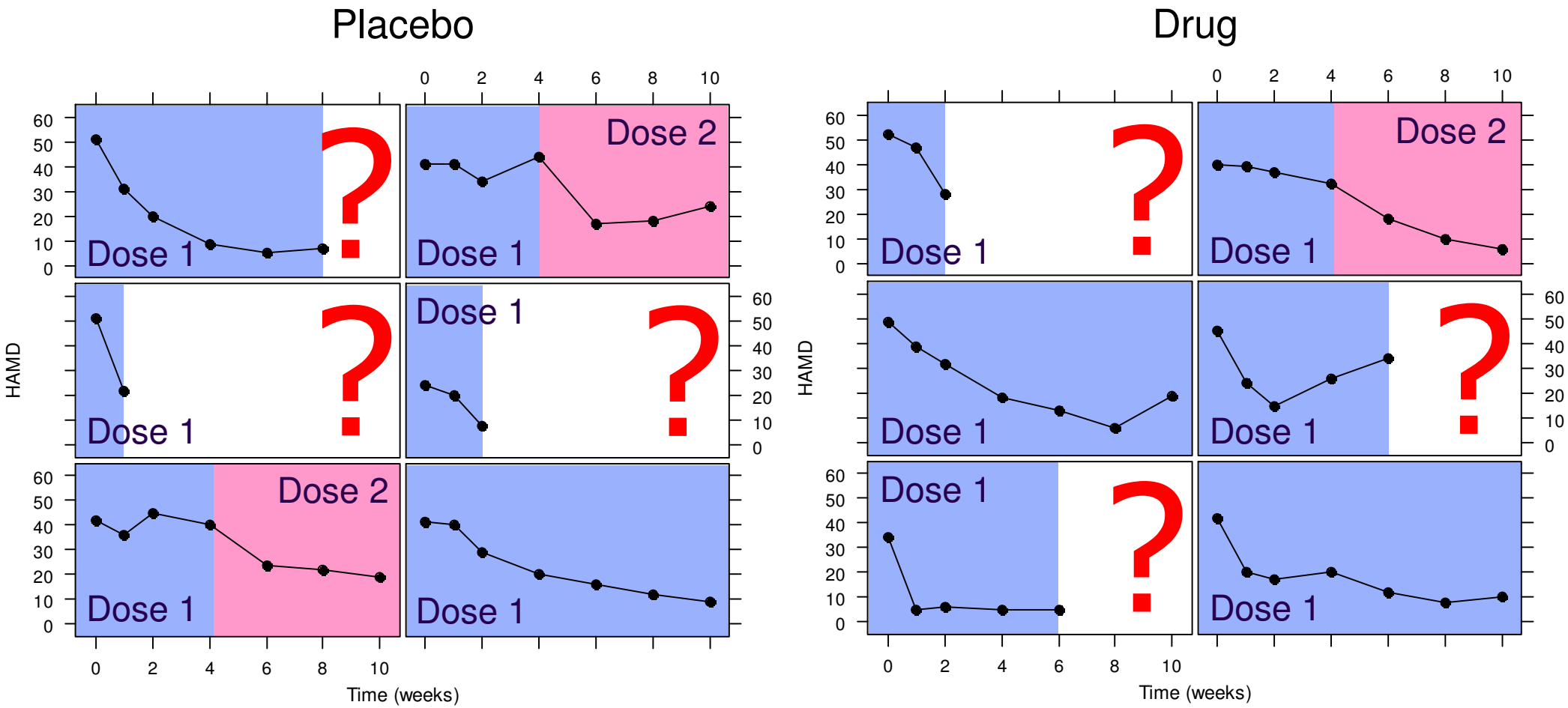
Population Approach Group Europe 19th Meeting

Motivation

Example of a depression dataset

Dropout events

Flex-design: possible dose escalation at a given week



Motivation

1. Response modelling:
   - How to formulate a suitable mathematical model for depression data?

2. *Flex-design*, i.e. possible dose escalations during the study:
   - How to handle them?

3. Dropout modelling:
   - How to handle dropout events?
   - Is there an interaction between the response model and the dropout model?

Outline

1. Modelling the HAMD score: a state-space approach
2. Modelling dropout
3. Results
4. Conclusion

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Modelling HAMD: a state-space approach

Algebraic models

- Inverse Bateman: $y(t) = A - B(e^{-t/t_{onset}} - e^{-t/t_{recovery}})$
- Polynomial function: $y(t) = a + bt + ct^2$
- Mixed Weibull-linear function: $y(t) = Ae^{-(t/t_d)^b} + s_{rec}t$
- …

However...

- Empirical models: just a description of data
- How to handle the *flex-design*?

Modelling HAMD: a state-space approach

State-space concept

$x(t)$: vector of variables
summarising the patient's health state at time t

Fundamental property of state-space models[1]

Given the state $x(t^*)$ and an evolution law f for $t > t^*$,
future states are completely determined:

$$x(t+dt) = x(t) + f(x(t))dt$$

$$\dot{x}(t) = f(x(t))$$

Also, $x(t)$ is a continuous function of t

[1] Kalman, R.E., Falb, P.L., and Arbib, M.A. (1969), Topics in Mathematical System Theory, McGraw-Hill, New York

Modelling HAMD: a state-space approach

Example 1

$$x(t) = HAMD(t)$$

Applies when the score at time t summarises all past history and is sufficient to determine future response to treatment

One state variable: *1st order* model

Modelling HAMD: a state-space approach

Example 2

2 patients A and B, with same HAMD at time t^*, respond differently to same therapy starting at t^* because A was ameliorating and B was worsening:
the trend matters

2nd order model (two state variables):

$$x(t) = \begin{bmatrix} x_1(t) \\ x_2(t) \end{bmatrix} = \begin{bmatrix} HAMD(t) \\ \frac{d}{dt} HAMD(t) \end{bmatrix}$$

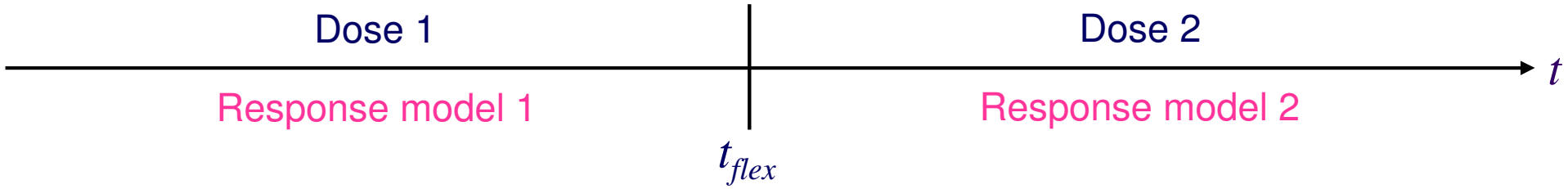
Latent variable that accounts for trend at time t

More general models are possible

Modelling HAMD: a state-space approach

One of the advantages of state-space approach

Modelling change of dose (*flex-design*)



How to concatenate the two models?

Use

$$\dot{x}(t) = f_1(x(t)) \quad t \le t_{flex}$$

to compute

$$\bar{x} = x(t_{flex})$$

Use

$$\dot{x}(t) = f_2(x(t)) \quad t > t_{flex}$$

with initial condition

$$x(t_{flex}) = \bar{x}$$

t_{flex}

Modelling HAMD: a state-space approach

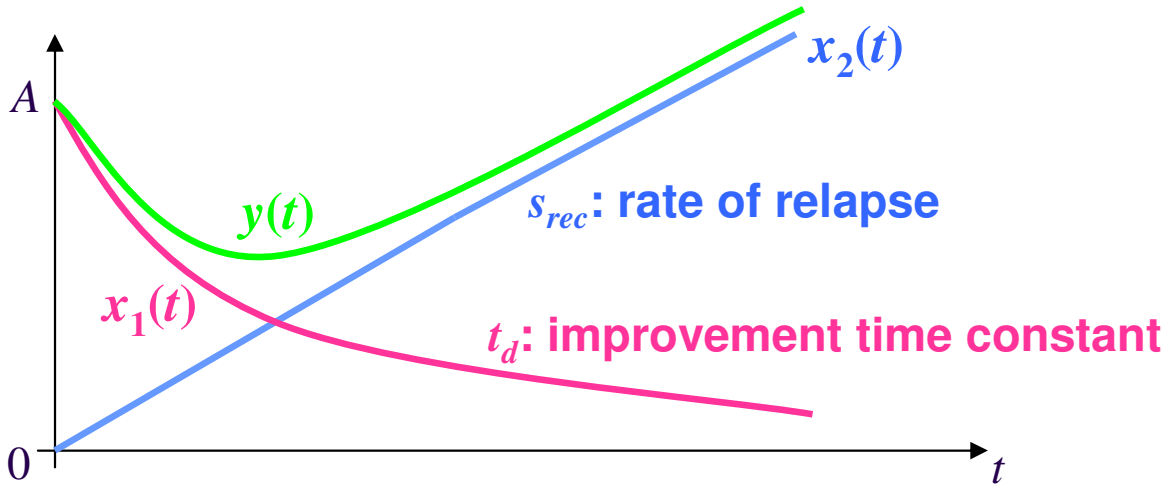
Application: mixed Weibull-linear model[1]

State-space formulation

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

Solution

$$\begin{cases} x_1(t) = A e^{-(t/t_d)^b} \\ x_2(t) = s_{rec} t \\ y(t) = x_1(t) + x_2(t) \\ z(t_k) = y(t_k) + \varepsilon \end{cases}$$

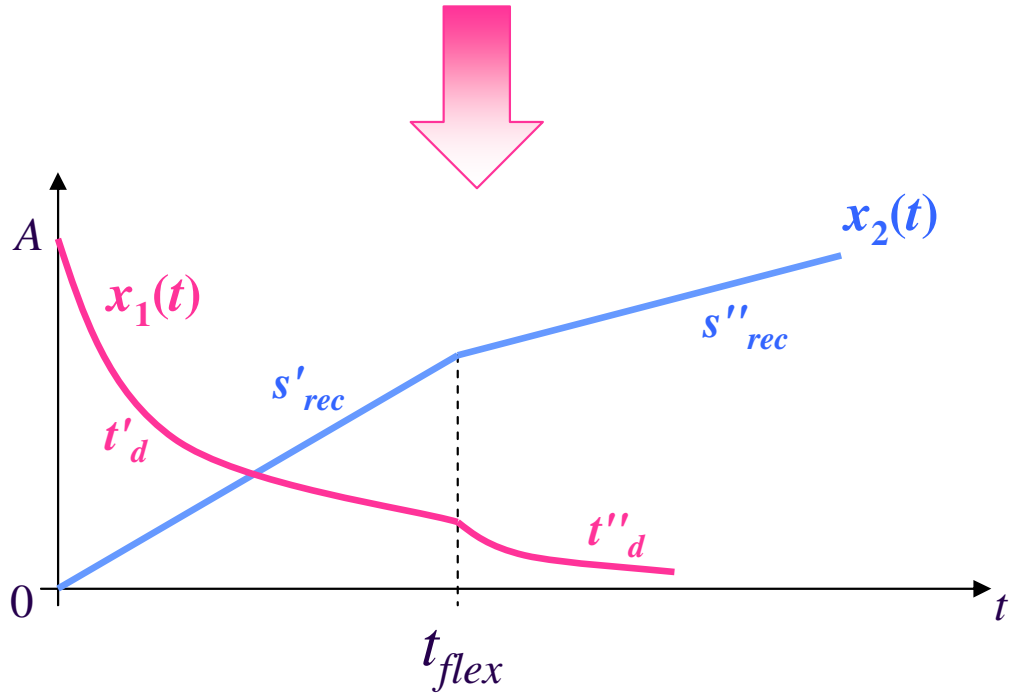


[1] Gomeni R. et al., *European Journal of Pharmaceutical Sciences*, 36, 4–10, 2009

Modelling HAMD: a state-space approach

Handling the *flex-design*: *flexible* parameters

$$t_d = \begin{cases} t_d^{'} & 0 \le t \le t_{flex} \\ t_d^{''} & t > t_{flex} \end{cases} \qquad s_{rec} = \begin{cases} s_{rec}^{'} & 0 \le t \le t_{flex} \\ s_{rec}^{''} & t > t_{flex} \end{cases}$$



Discontinuity of parameters, but continuity of $x_1(t)$ and $x_2(t)$

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Modelling dropout

- T : time-to-dropout (interval or right censored)
- Hazard function: $h(t) = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t \mid t \le T)}{\Delta t}$
- Cumulative hazard: $H(t) = \int_0^t h(u)du$
- Survival function: $S(t) = e^{-H(t)}$

Modelling dropout

Completely Random Dropout (CRD)[1]

$$h(t) = \alpha\lambda(\lambda t)^{\alpha-1}$$

Random Dropout (RD)[1]

$$h(t) = \alpha\lambda(\lambda t)^{\alpha-1} \cdot e^{\theta f(z)}$$

Informative Dropout (ID)[1]

$$h(t) = \alpha\lambda(\lambda t)^{\alpha-1} \cdot e^{\theta f(y)}$$

[1] Hu C. & Sale M., *Journal of Pharmacokinetics and Pharmacodynamics*, 30, 83–103, 2003

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Results

GlaxoSmithKline study SND103285:

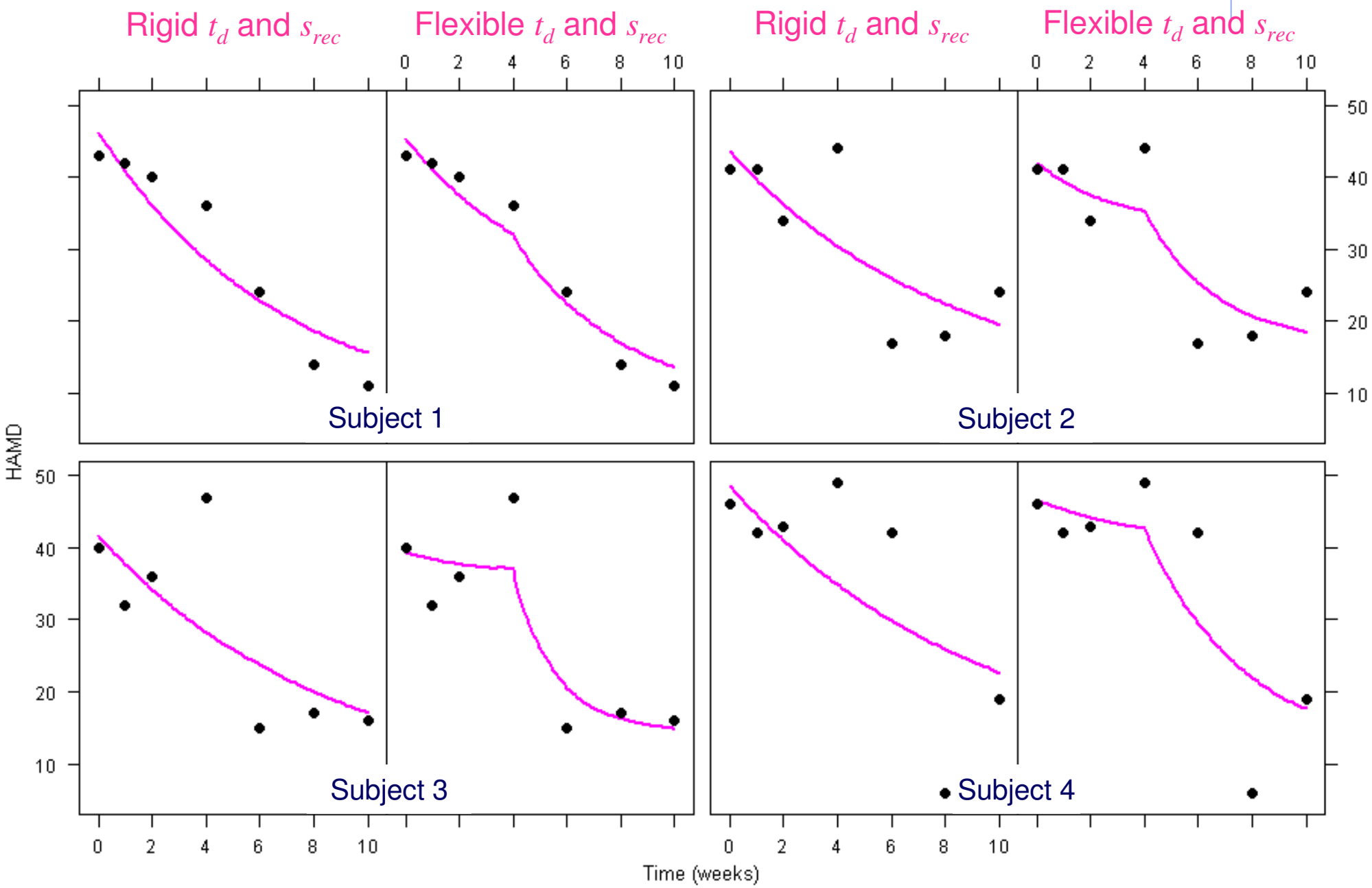
- Phase II,
- 10-week,
- Randomized,
- Double-blind,
- Flexible-dose (decision at week 4)

depression trial comparing GSK372475 (1.5 and 2.0 mg/day) and placebo

Software implementation:

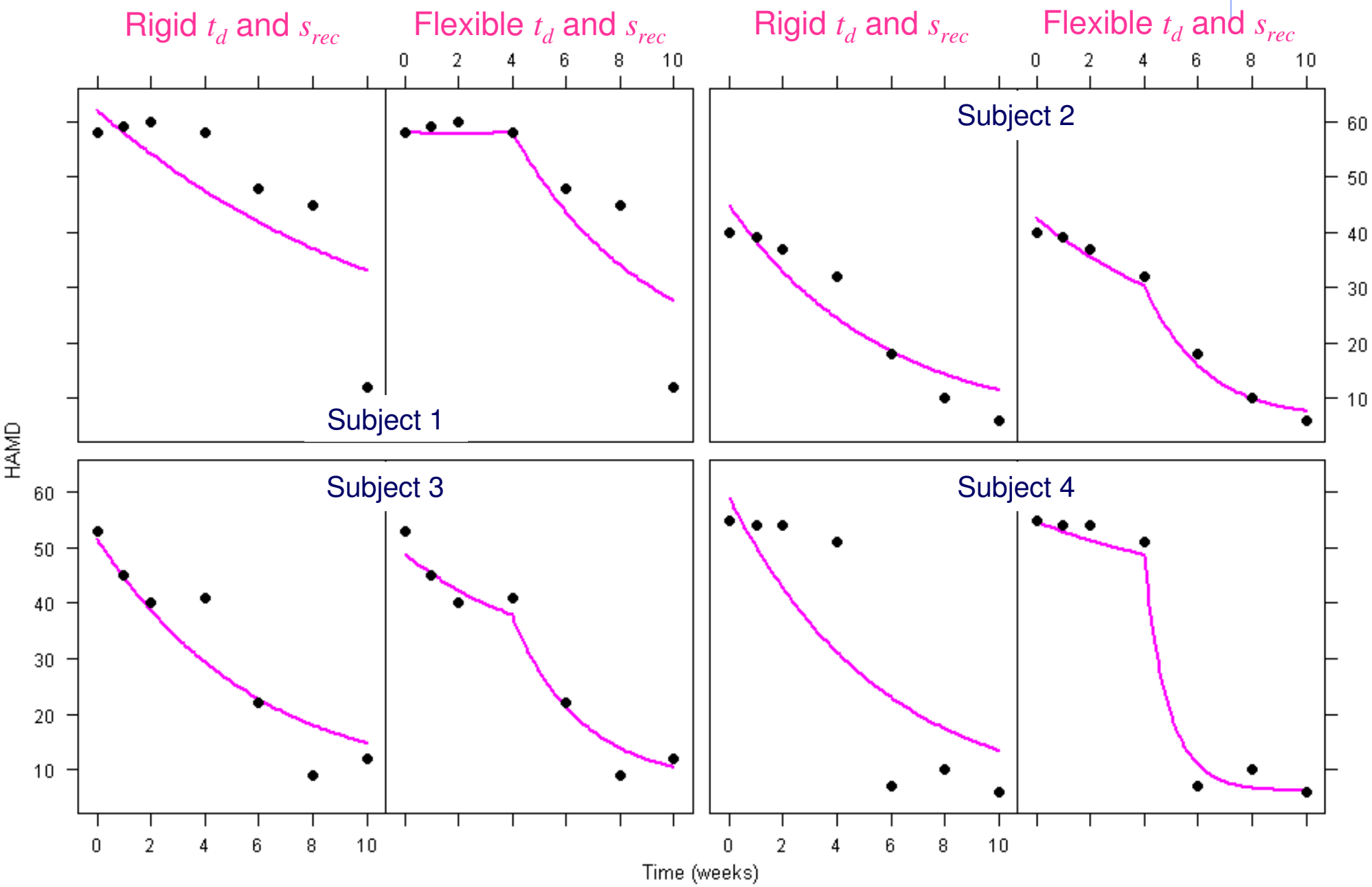
- R 2.10.0: pre-processing and graphical output
- WinBUGS + WBDiff: Markov Chain MonteCarlo estimation

Results: effect of dose escalation (placebo)



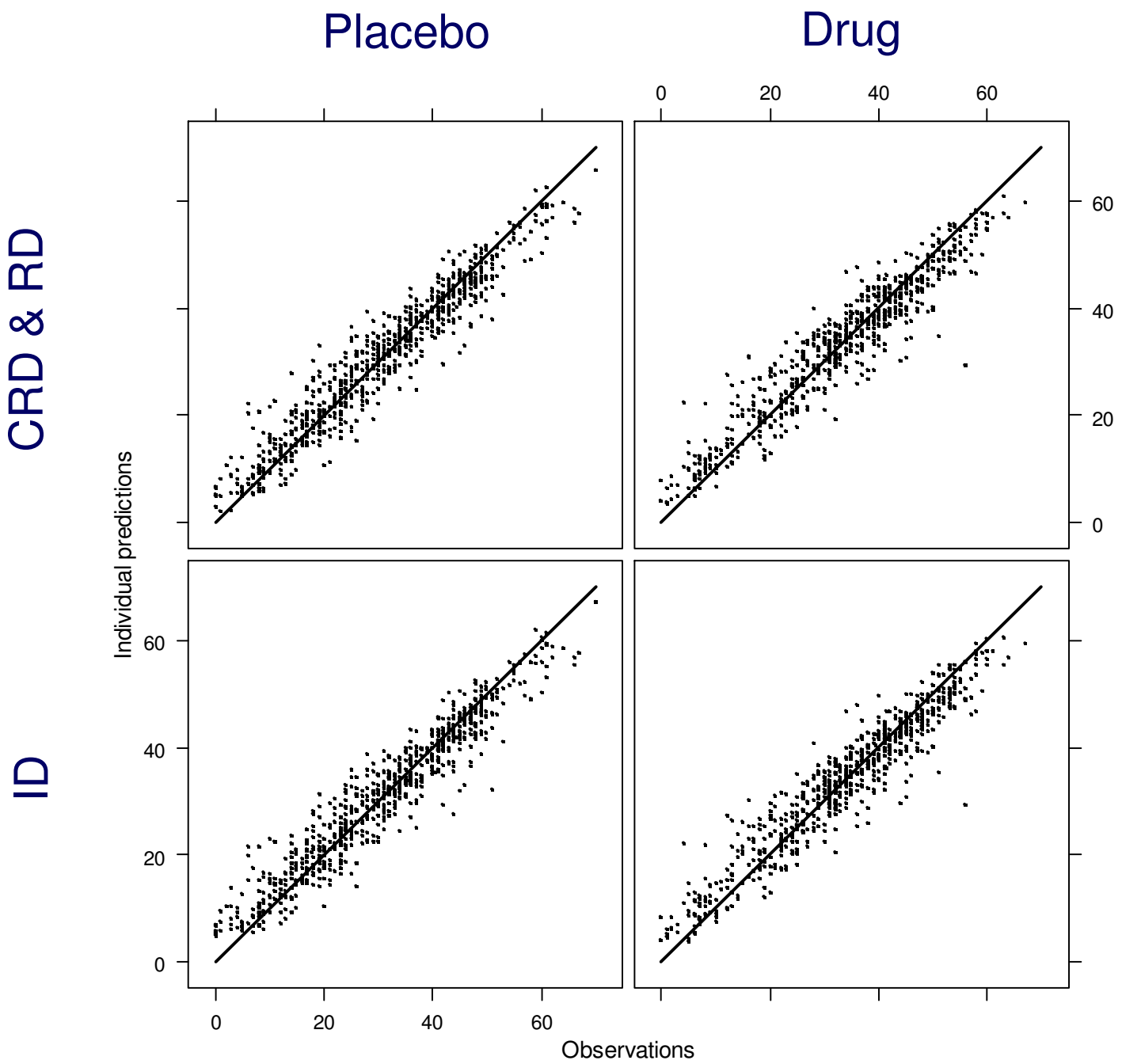
DIC: 4990.640 (no flex) *vs* 4856.200 (flex)

Results: effect of dose escalation (GSK372475)

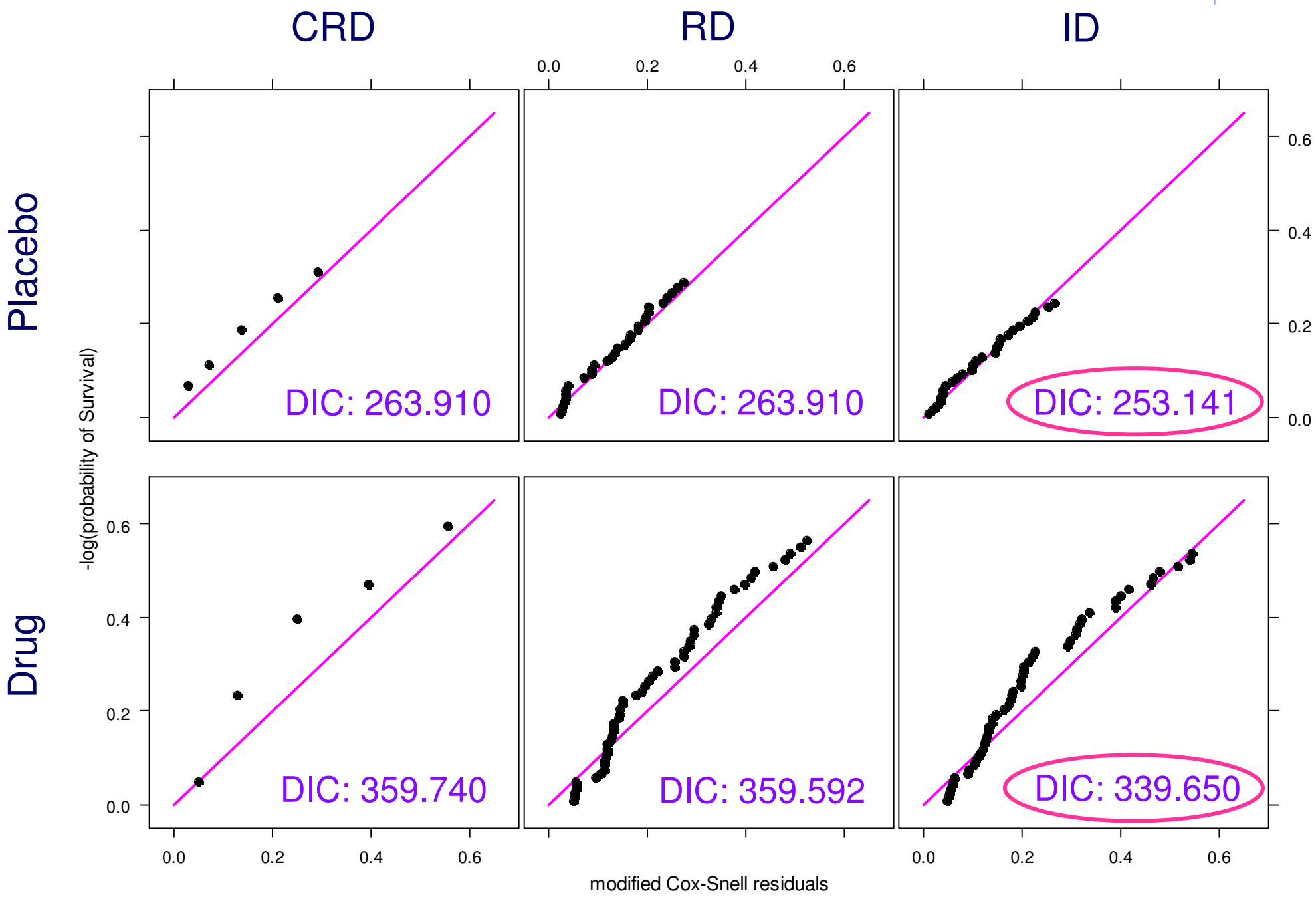


DIC: 4711.810 (no flex) *vs* 4587.440 (flex)

Results: HAMD goodness-of-fit



Results: Cox-Snell residuals and DIC



Results: wrap-up

- HAMD time course:
  - In presence of flexible dosing scheme, response is better described by the flexible model (switch t'_d to t''_d and s'_{rec} to s''_{rec})
- Placebo arm:
  - RD and ID are more adequate than CRD (Cox-Snell residuals)
  - $\Rightarrow$ Dropout is well explained by the HAMD course
- GSK372475 arm:
  - ID fits best (dropout DIC)
  - Residuals suggest misspecification of the hazard model
  - Could be solved by integrating safety/tolerability (see also Lalovic *et al.*, PAGE 16, 2007)

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Conclusion

1. State-space approach: rigorous management of discontinuities in the dosing regimen

2. Straightforward extension to more complex problems and/or further states (e.g. dx/dt, HAMD subscales, ...)

3. Covariates for the dropout model can be searched for in the state space

Acknowledgements

Giuseppe De Nicolao
(PhD supervisor)

Thank you for your attention

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A last remark

VPCs were not shown…

…Why?

Answer

To perform a correct VPC, the decision on dose change must be also simulated

⇓

All factors affecting this decision should be modelled (future work)