Challenges and opportunities in the analysis of clinical data

Statistics seminar, Department of Mathematics, King's College London

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Introduction

Introduction: Motivation

A lot of information is available

➔ Electronic medical records

Introduction: Motivation

A lot of information is available

➔ Electronic medical records

Different types of information

➔ Baseline characteristics
➔ Longitudinal outcomes
➔ Time-to-event outcomes

Introduction: Examples

Applications

- ➔ Heart valve
- ➔ Stroke
- ➔ Cystic Fibrosis

Introduction: Examples

Applications

- ➔ Heart valve
  - ◇ Aortic gradient
  - ◇ Aortic regurgitation
  - ◇ Time-to death/reoperation
- ➔ Stroke
- ➔ Cystic Fibrosis

Introduction: Examples

Applications

- ➔ Heart valve
- ➔ Stroke
  - ◇ Extremity performance
  - ◇ Limb strength
- ➔ Cystic Fibrosis

Introduction: Examples

Applications

- ➔ Heart valve
- ➔ Stroke
- ➔ Cystic Fibrosis
  - ◇ FEV_1
  - ◇ BMI
  - ◇ Time-to death/exacerbation

Introduction: Common practice

Separate analysis

➔ Each longitudinal outcome

➔ Survival outcomes

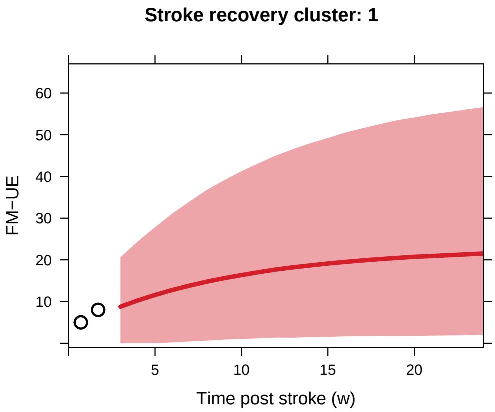
Introduction: Common practice

Separate analysis - Stroke data

- ◇ 412 patients
- ◇ Outcome of interest:

  Fugl–Meyer

van der Vliet, R., Selles, R. W., Andrinopoulou, etc (2020). Predicting upper limb motor impairment recovery after stroke: a mixture model. Annals of Neurology, 87(3), 383-393.



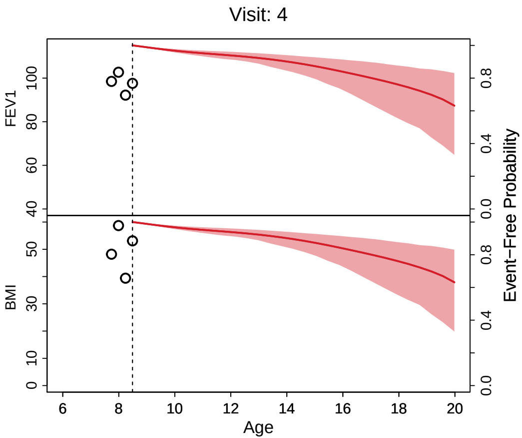
Introduction: Extensions

Combined analysis - Cystic Fibrosis data

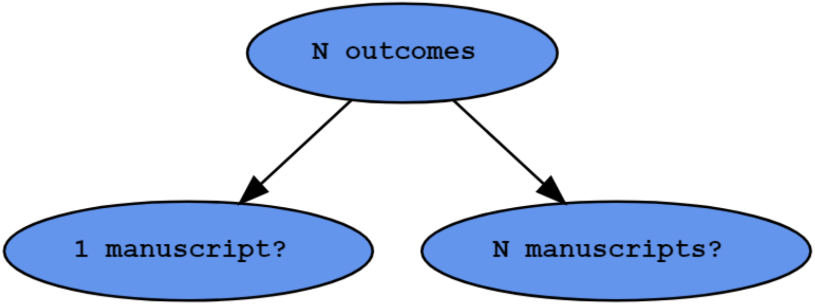
- 17,100 patients
- Outcomes of interest:

  FEV_1
  BMI
  weight-for-age
  height-for-age
  time-to first exacerbation

Andrinopoulou, E. R., Clancy, J. P., & Szczesniak, R. D. (2020). Multivariate joint modeling to identify markers of growth and lung function decline that predict cystic fibrosis pulmonary exacerbation onset. BMC pulmonary medicine, 20, 1-11.



Introduction: Challenges and Opportunities



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Combined analysis - Heart valve data

- ➔ 296 patients
- ➔ Association of Aortic Gradient with time-to-death/reoperation
  - ◇ Aortic Gradient is measured with error

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Combined analysis - Heart valve data

➔ 296 patients

➔ Association of Aortic Gradient with time-to-death/reoperation

◇ Aortic Gradient is measured with error

◇ Different features of Aortic Gradient

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Statistical Models

Statistical Models

Let's assume that we have a longitudinal outcome

Statistical Models: Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^{\top}(t)\beta_1 + z_{1i}^{\top}(t)b_{1i} + \epsilon_{1i}(t)$$

where

- $b_{1i} \sim N(0, D)$
- $\epsilon_{1i}(t) \sim N(0, \Sigma_{1i})$

Statistical Models: Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^{\top}(t)\beta_1 + z_{1i}^{\top}(t)b_{1i} + \epsilon_{1i}(t)$$

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- $\epsilon_{1i}(t) \sim N(0, \Sigma_{1i})$

Let's assume that we have two longitudinal outcomes

Statistical Models: Multivariate Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \epsilon_{1i}(t)$$
$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

where

- $b_i^\top = (b_{1i}^\top, b_{2i}^\top) \sim N(0, D)$

Statistical Models: Multivariate Mixed Models

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where

- $b_i^\top = (b_{1i}^\top, b_{2i}^\top) \sim N(0, D)$

Challenge: Quantify the association between y_1 and y_2

Statistical Models: Multivariate Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^{\top}(t)\beta_1 + z_{1i}(t)^{\top} b_{1i} + \alpha m_{2i}(t) + \epsilon_{1i}(t)$$
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where

- α denotes the association

Statistical Models: Multivariate Mixed Models

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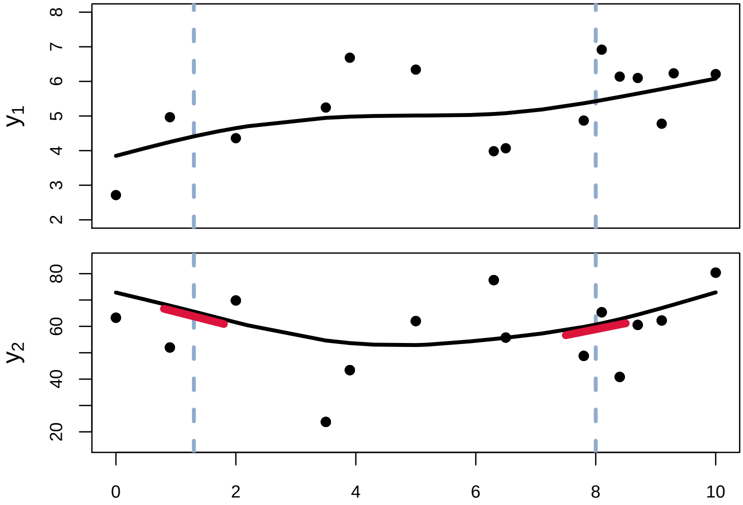
where

- α denotes the association

Challenge: Is that our only option?

Statistical Models: Multivariate Mixed Models



Statistical Models: Multivariate Mixed Models

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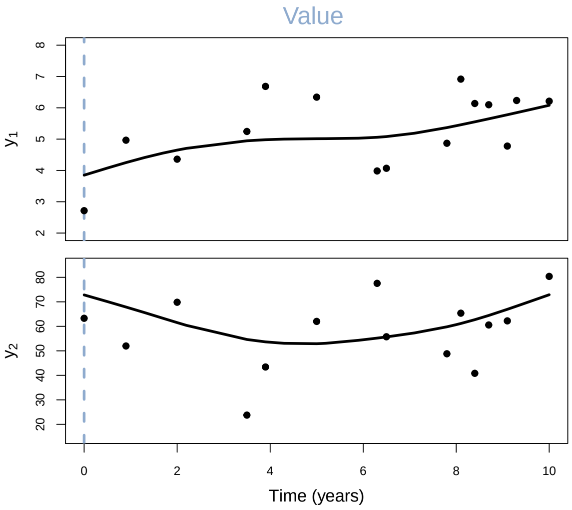
$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha \ f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

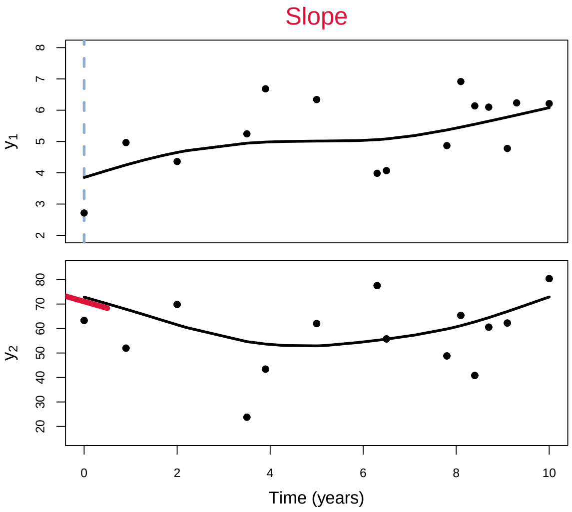
where

- α denotes the association
- $\mathcal{M}_{2i}(t)$ denotes the history of the true unobserved longitudinal process up to time point t

Statistical Models: Multivariate Mixed Models



Statistical Models: Multivariate Mixed Models



Statistical Models: Multivariate Mixed Models

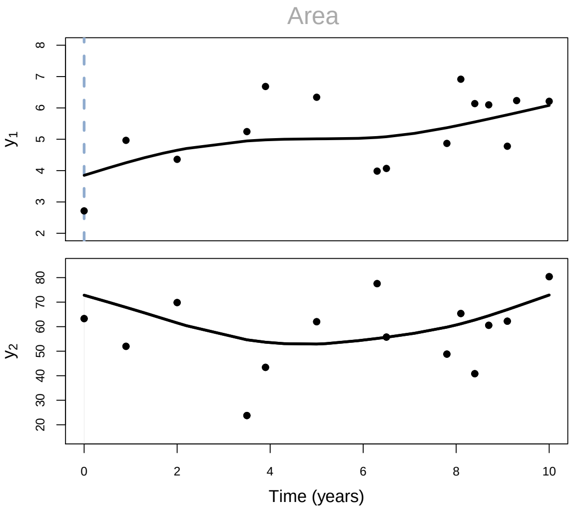
$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha \frac{d}{dt} m_{2i}(t) + \epsilon_{1i}(t),$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t),$$

where

- α denotes the association

Statistical Models: Multivariate Mixed Models



Statistical Models: Multivariate Mixed Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha \int_0^t m_{2i}(s)dt + \epsilon_{1i}(t),$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t),$$

where

- α denotes the association

Let's assume that we have a longitudinal and a survival outcome

Statistical Models: Joint Models

➔ Naive joint analysis

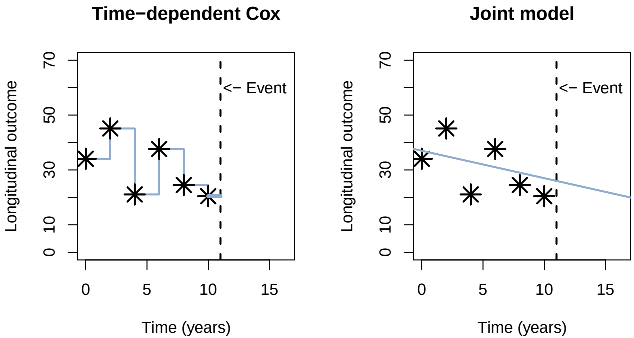
- ◇ Cox model using the last observation
- ◇ Time-dependent Cox model

Data is discarded!

Statistical Models: Joint Models

- ➔ Naive joint analysis
  - ◇ Cox model using the last observation
  - ◇ Time-dependent Cox model

Time-dependent Cox models are suitable only for exogenous covariates!



Statistical Models: Joint Models

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_i^\top(t)b_i + \epsilon_i(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha m_i(t)]$$

where

- α denotes the association

Statistical Models: Joint Models

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_i^\top(t)b_i + \epsilon_i(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \sum_{j=1}^{J} \alpha_j f_j\{\mathcal{M}_i(t)\}]$$

where

- α_j denotes the association
- Shrinkage

Andrinopoulou, E. R.,& Rizopoulos, D. (2016). Bayesian shrinkage approach for a joint model of longitudinal and survival outcomes assuming different association structures. Statistics in medicine, 35(26), 4813-4823.

Let's assume that we have two longitudinal and a survival outcome

Statistical Models: Multivariate Joint Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \epsilon_{1i}(t)$$

$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha_{S1} f\{\mathcal{M}_{1i}(t)\} + \alpha_{S2} f\{\mathcal{M}_{2i}(t)\}],$$

where

- α_{S1} and α_{S2} denote the associations

What about the association between the longitudinal outcomes?

Statistical Models: Multivariate Joint Models

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$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha_L f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$
$$y_{2i}(t) = m_{2i}(t) + \epsilon_{2i} = x_{2i}^\top(t)\beta_1 + z_{2i}(t)^\top b_{2i} + \epsilon_{2i}(t)$$

$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha_S f\{\mathcal{M}_{1i}(t)\}]$$

where

- α_S denotes the survival association
- α_L denotes the longitudinal association

Statistical Models: Multivariate Joint Models

$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha_L \, f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$

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where

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Statistical Models: Multivariate Joint Models

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$$y_{1i}(t) = m_{1i}(t) + \epsilon_{1i} = x_{1i}^\top(t)\beta_1 + z_{1i}(t)^\top b_{1i} + \alpha_L f\{\mathcal{M}_{2i}(t)\} + \epsilon_{1i}(t)$$
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$$h_i(t) = h_0(t)[\gamma^\top w_i + \alpha_S f\{\mathcal{M}_{1i}(t)\}]$$

where

- α_S denotes the survival association
- α_L denotes the longitudinal association

Simulations

Simulations

Multivariate Mixed Models

Simulations: Scenario

Simulate

→ **Outcome 1**

Linear time
Treatment
Value of outcome 2

→ **Outcome 2**

Linear time

Simulations: Scenario

Simulate

➔ **Outcome 1**

Linear time
Treatment
Value of outcome 2

➔ **Outcome 2**

Linear time

Fit

➔ **Outcome 1**

Linear time
Treatment
~~Value of outcome 2~~

➔ **Outcome 2**

Linear time

Simulations: Scenario

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Simulate

➔ **Outcome 1**

Linear time
Treatment
Value of outcome 2

➔ **Outcome 2**

Linear time

Fit

➔ **Outcome 1**

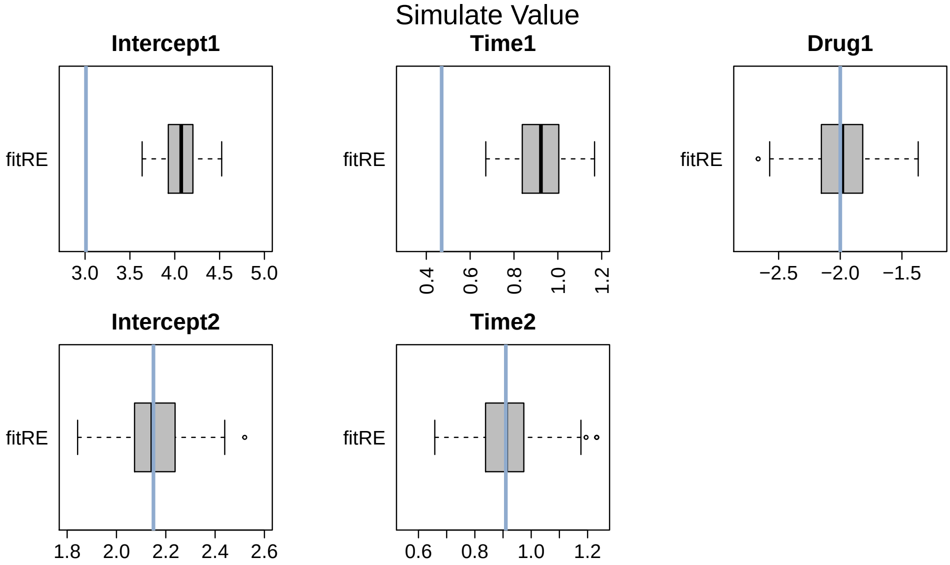
Linear time
Treatment
~~Value of outcome 2~~

➔ **Outcome 2**

Linear time

All models were fitted under the Bayesian framework

Simulations: Results



Simulations: Scenario

Simulate

➔ **Outcome 1**

Linear time
Treatment
Value of outcome 2

➔ **Outcome 2**

Linear time

Fit

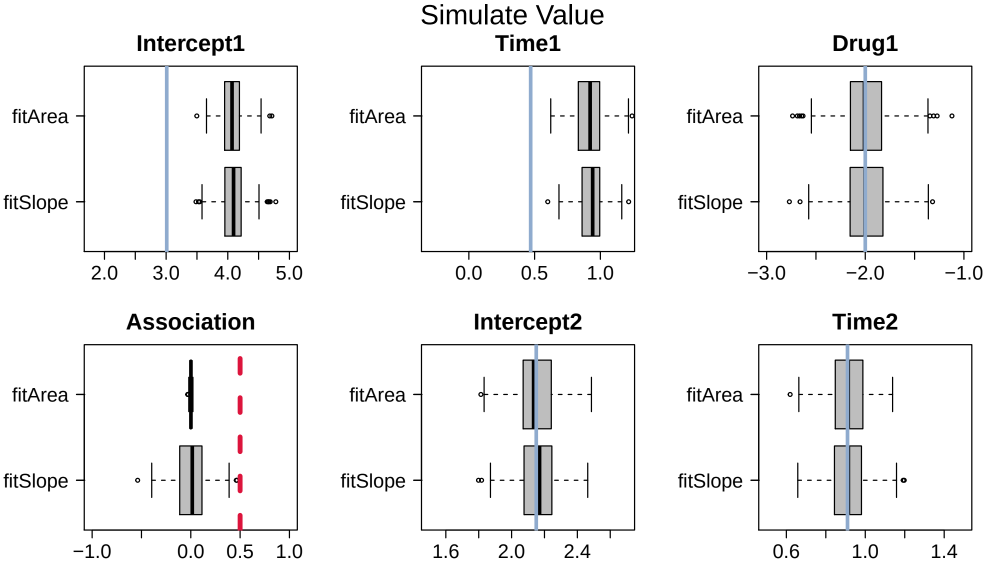
➔ **Outcome 1**

Linear time
Treatment
Slope/Area of outcome 2

➔ **Outcome 2**

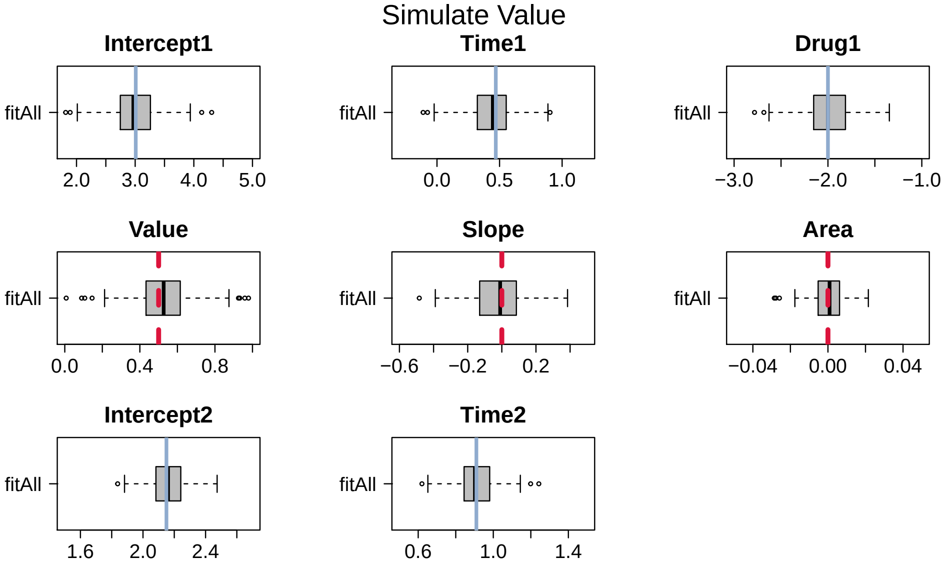
Linear time

Simulations: Results

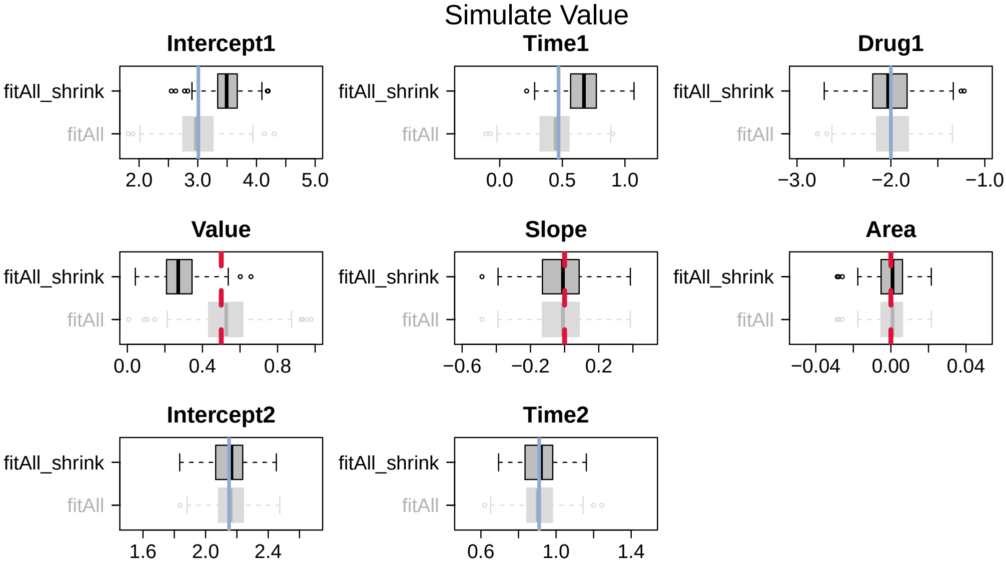


What if we fit all functional forms

Simulations: Results



Simulations: Results



Let's investigate a more complicated scenario

Simulations: Scenario

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Simulate

→ **Outcome 1**

Non linear time
Treatment
Value of outcome 2
Slope of outcome 2

→ **Outcome 2**

Non linear time

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Simulations: Scenario

Simulate

→ **Outcome 1**

Non linear time
Treatment
Value of outcome 2
Slope of outcome 2

→ **Outcome 2**

Non linear time

Fit

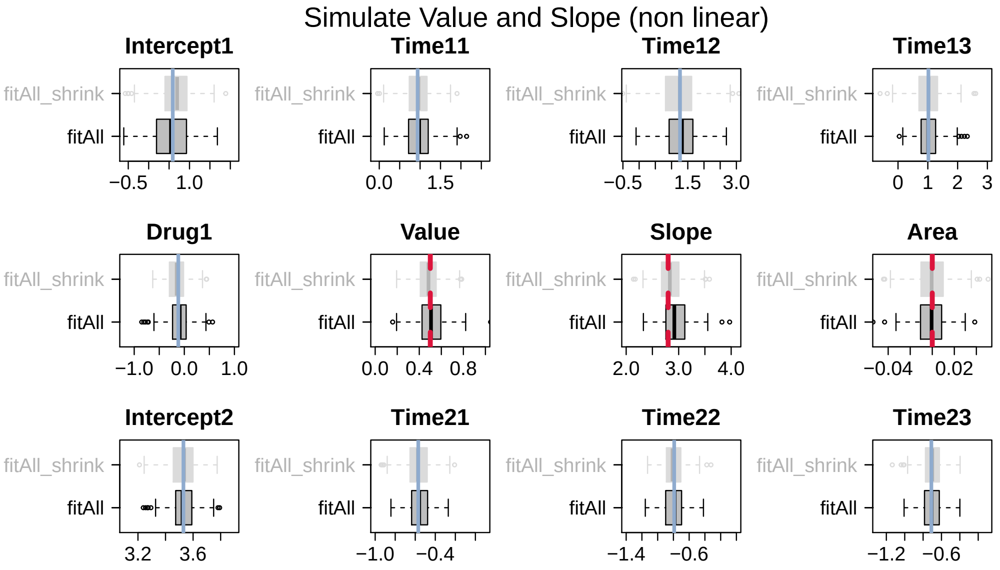
→ **Outcome 1**

Non linear time
Treatment
Value of outcome 2
Slope of outcome 2
Area of outcome 2

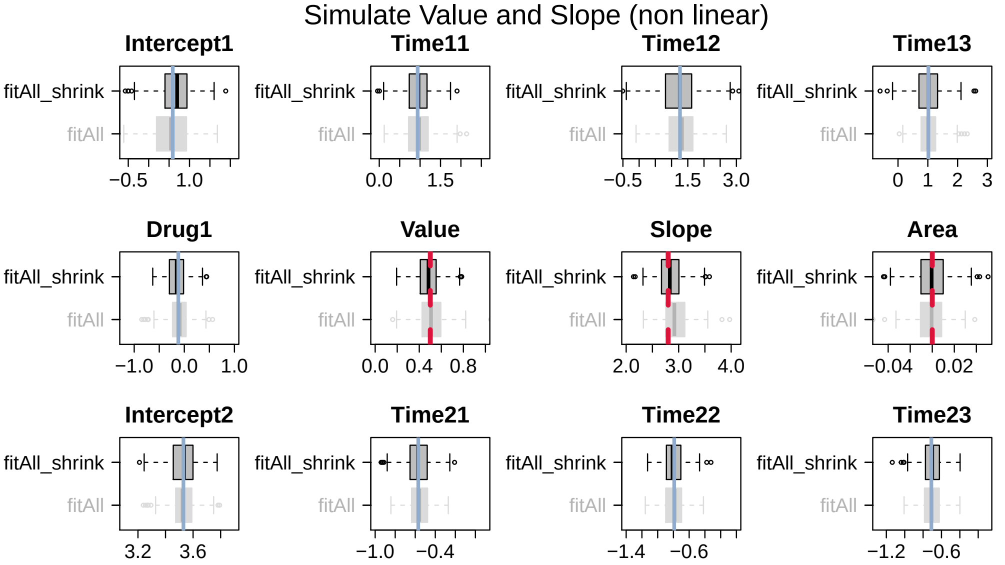
→ **Outcome 2**

Non linear time

Simulations: Results



Simulations: Results



Joint Models

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Simulations: Scenario

Simulate

→ **Longitudinal outcome**

Non linear time
Treatment

→ **Survival outcome**

Treatment
Value of longitudinal outcome

Simulations: Scenario

Simulate

➔ **Longitudinal outcome**

Non linear time
Treatment

➔ **Survival outcome**

Treatment
Value of longitudinal outcome

Fit

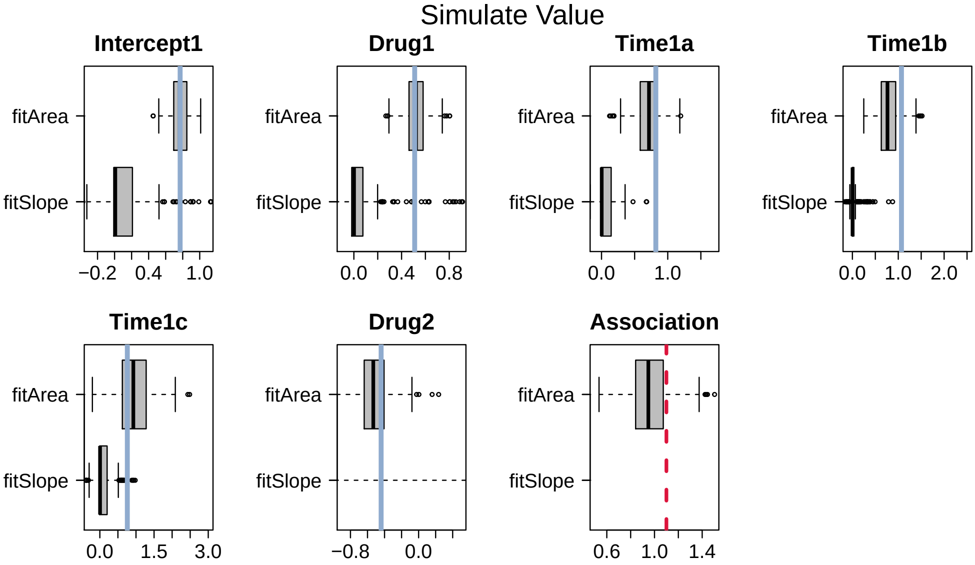
➔ **Longitudinal outcome**

Non linear time
Treatment

➔ **Survival outcome**

Treatment
Slope/Area of longitudinal outcome

Simulations: Results



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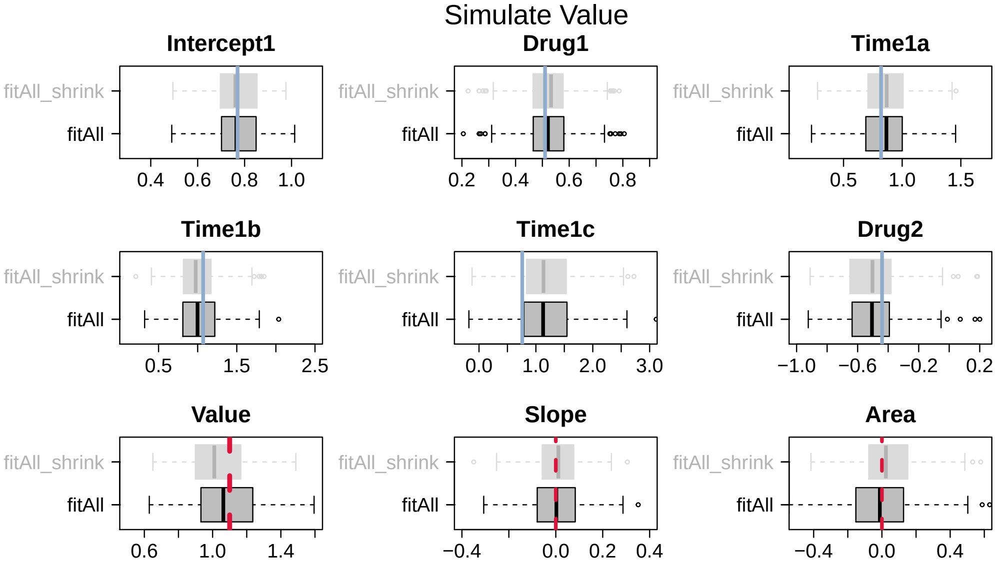
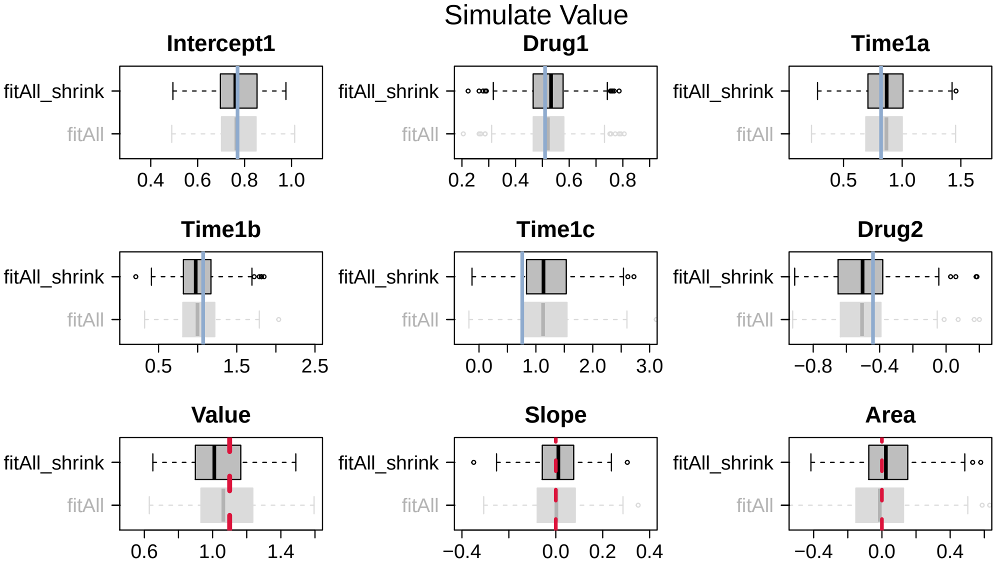
What if we fit all functional forms

Simulations: Results



Simulations: Results



Let's combine everything

Simulations: Scenario

Simulate

➔ **Longitudinal outcome 1**

Non linear time
Treatment
Value of longitudinal outcome 2

➔ **Longitudinal outcome 2**

Linear time

➔ **Survival outcome**

Treatment
Value of longitudinal outcome 1

Simulations: Scenario

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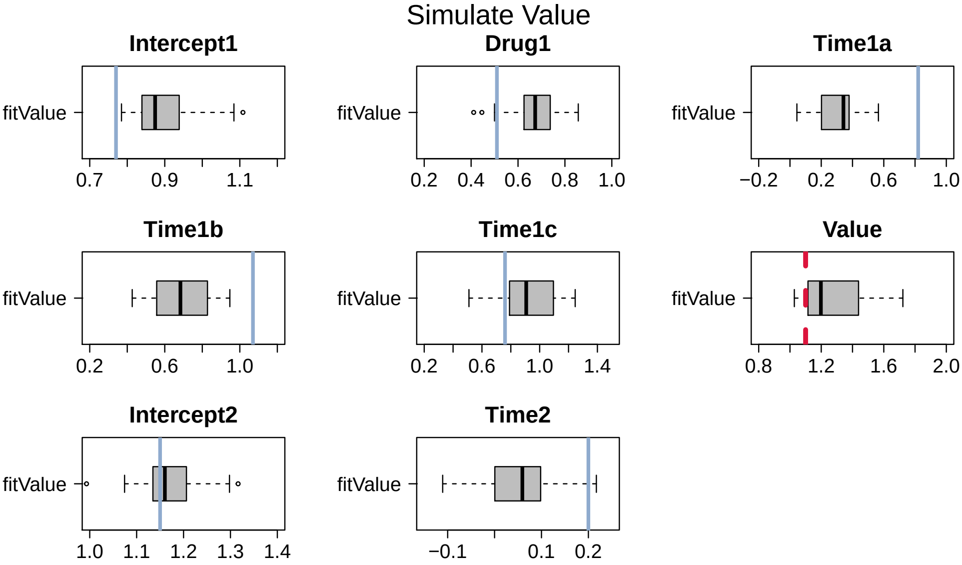
Simulate

- ➔ **Longitudinal outcome 1**
  - Non linear time
  - Treatment
  - Value of longitudinal outcome 2
- ➔ **Longitudinal outcome 2**
  - Linear time
- ➔ **Survival outcome**
  - Treatment
  - Value of longitudinal outcome 1

Fit

- ➔ **Longitudinal outcome 1**
  - Non linear time
  - Treatment
  - ~~Value of longitudinal outcome 2~~
- ➔ **Longitudinal outcome 2**
  - Linear time
- ➔ **Survival outcome**
  - Treatment
  - Value of longitudinal outcome 1

Simulations: Results



Software

Software: R

➔ Joint models

- ◇ JMbayes, JMbayes2, JM
- ◇ joineR, joineRML
- ◇ frailtypack
- ◇ stan_jm
- ◇ lcmm
- ◇ bamlss
- ◇ JointAI

➔ Multivariate mixed models

- ◇ lcmm
- ◇ brms
- ◇ MCMCglmm
- ◇ JointAI

Summary and Discussion

Summary and Discussion

➔ A lot of information is available

➔ Correlation between outcomes

Summary and Discussion

➔ A lot of information is available

➔ Correlation between outcomes

➔ Challenges and opportunities

- ◇ Functional forms

Summary and Discussion

➔ A lot of information is available

➔ Correlation between outcomes

➔ Challenges and opportunities

- ◇ Functional forms

➔ Future steps

- ◇ Dynamic predictions

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Thank you for your attention!

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