

Challenges and opportunities of combined analysis of multiple outcomes in longitudinal studies

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International Society for Clinical Biostatistics, 23-27 August, 2020

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

Applications

- Heart valve
- Stroke
- Cystic Fibrosis

Applications

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

Applications

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

Applications

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

Separate analysis

- Each longitudinal outcome
- Survival outcomes

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

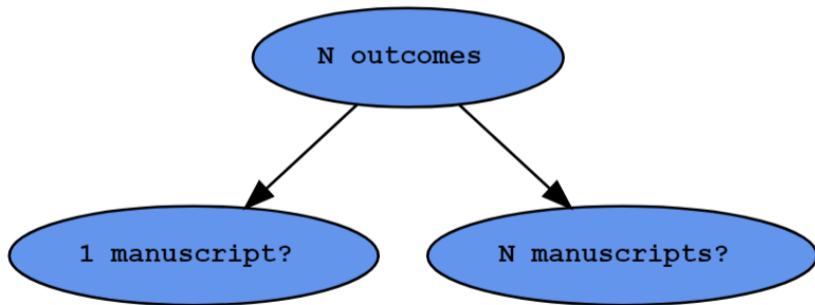
BMI

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.



Combined analysis - Heart valve data

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

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

Statistical Models

Statistical Models

Let's assume that we have a longitudinal outcome

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

where

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

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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

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

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Challenge: Quantify the association between y_1 and y_2

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

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- ◇ α denotes the association

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Challenge: Is that our only option?

Statistical Models: Multivariate Mixed Models

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

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Challenge: Is that our only option?

Statistical Models: Multivariate Mixed Models

Statistical Models: Multivariate Mixed Models

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

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_i^\top(t)b_{1i} + \epsilon_i(t)$$

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

where

- ◇ α denotes the association

Statistical Models: Joint Models

$$y_i(t) = m_i(t) + \epsilon_i = x_i^\top(t)\beta + z_{1i}^\top(t)b_i + \epsilon_i(t)$$

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

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

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

where

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

What about the association between the longitudinal outcomes?

Statistical Models: Multivariate Joint Models

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

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where

- ◇ 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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Simulations

Simulations

Multivariate Mixed Models

Simulate

→ Outcome 1

Linear time

Treatment

Value of outcome 2

→ Outcome 2

Linear time

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

Simulate

→ Outcome 1

Linear time

Treatment

Value of outcome 2

→ Outcome 2

Linear time

Fit

→ Outcome 1

Linear time

Treatment

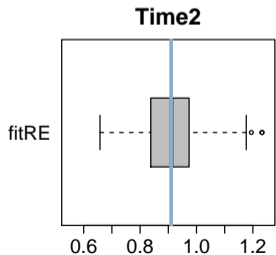
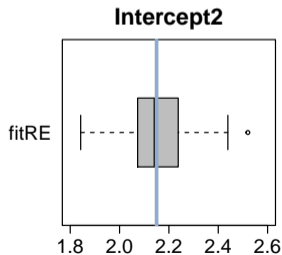
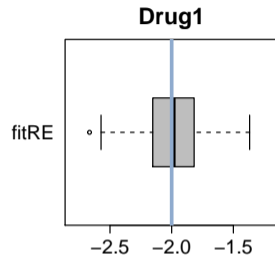
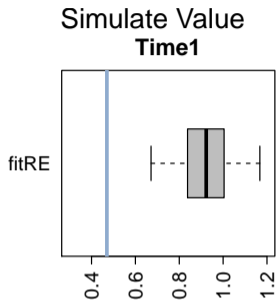
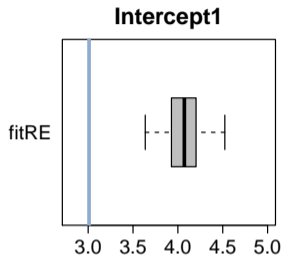
~~Value of outcome 2~~

→ Outcome 2

Linear time

All models were fitted under the Bayesian framework

Simulations: Results



Simulate

→ Outcome 1

Linear time

Treatment

Value of outcome 2

→ Outcome 2

Linear time

Fit

→ Outcome 1

Linear time

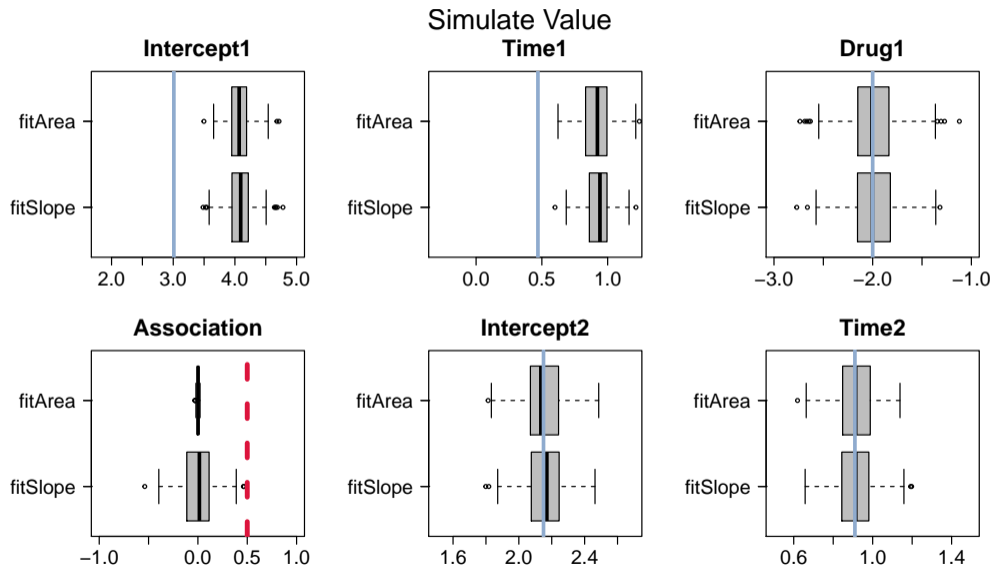
Treatment

Slope/Area of outcome 2

→ Outcome 2

Linear time

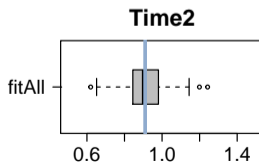
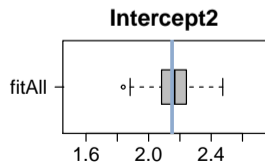
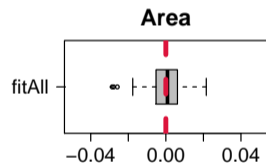
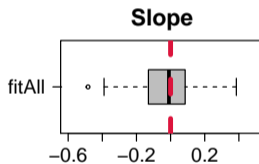
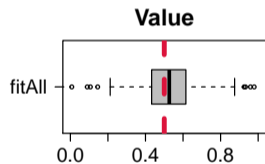
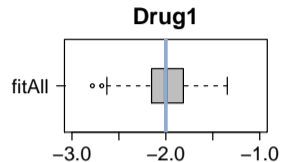
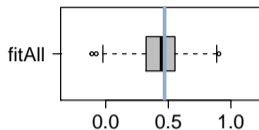
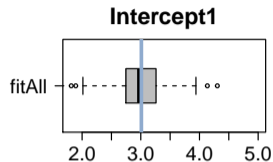
Simulations: Results



What if we fit all functional forms

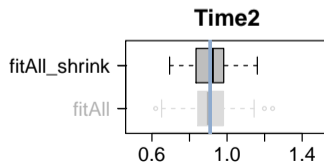
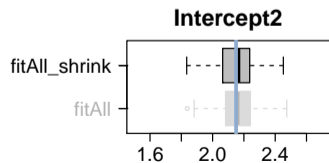
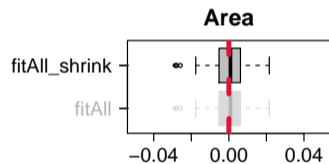
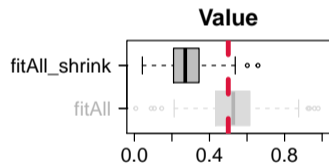
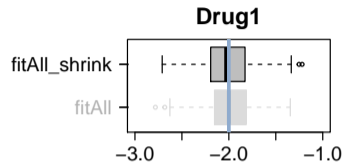
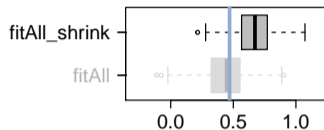
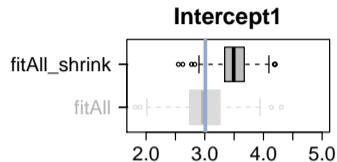
Simulations: Results

Simulate Value



Simulations: Results

Simulate Value



Joint Models

Simulate

→ Longitudinal outcome

Non linear time

Treatment

→ Survival outcome

Treatment

Value of longitudinal
outcome

Simulate

→ **Longitudinal outcome**

Non linear time
Treatment

→ **Survival outcome**

Treatment
Value of longitudinal
outcome

Fit

→ **Longitudinal outcome**

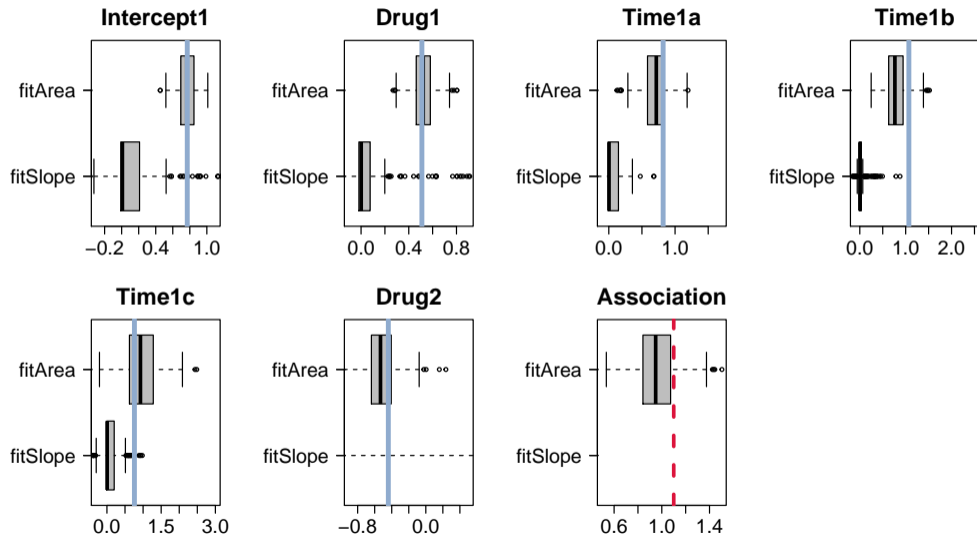
Non linear time
Treatment

→ **Survival outcome**

Treatment
Slope/Area of longitudinal
outcome

Simulations: Results

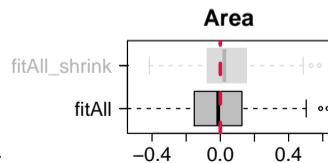
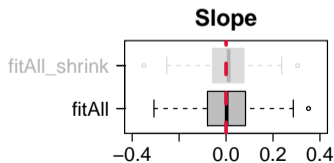
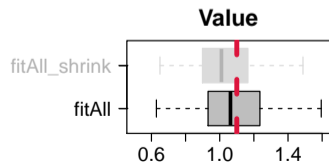
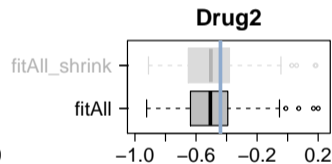
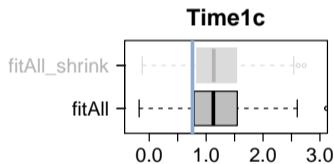
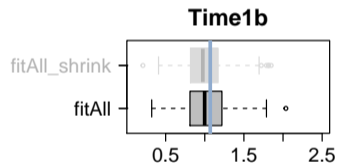
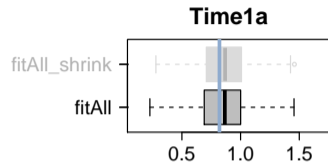
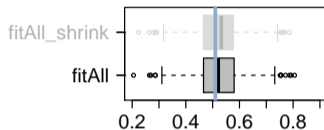
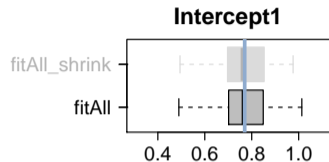
Simulate Value



What if we fit all functional forms

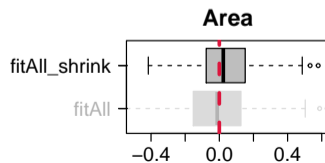
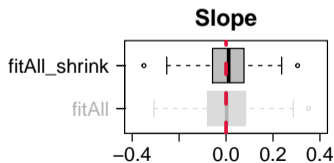
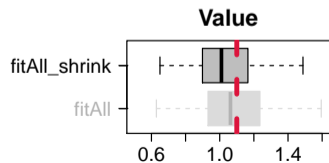
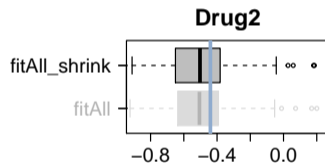
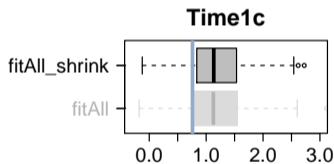
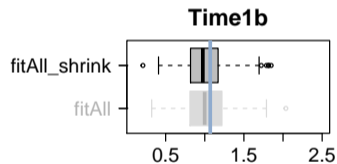
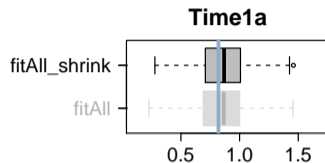
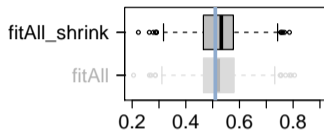
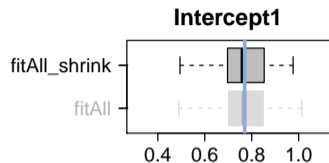
Simulations: Results

Simulate Value



Simulations: Results

Simulate Value



Let's combine everything

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

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

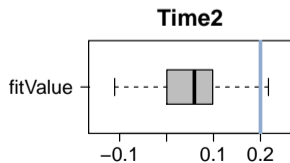
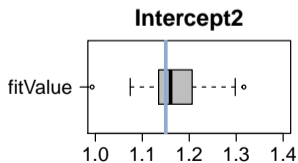
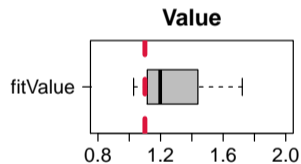
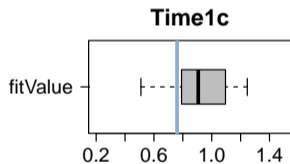
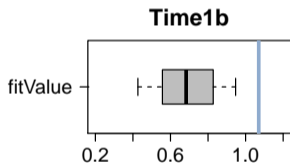
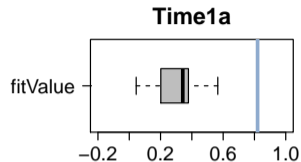
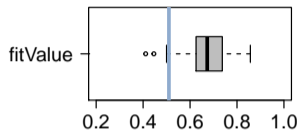
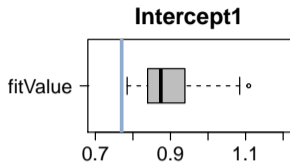
→ Survival outcome

Treatment

Value of longitudinal outcome 1

Simulations: Results

Simulate Value Drug1



Software

→ Joint models

- ◇ JMbayes, JM
- ◇ joinerR, joinerRML
- ◇ 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

- A lot of information is available
- Correlation between outcomes

- Challenges and opportunities
 - ◇ Functional forms

Thank you for your attention!

The slides are available at: <https://www.erandrinopoulou.com>