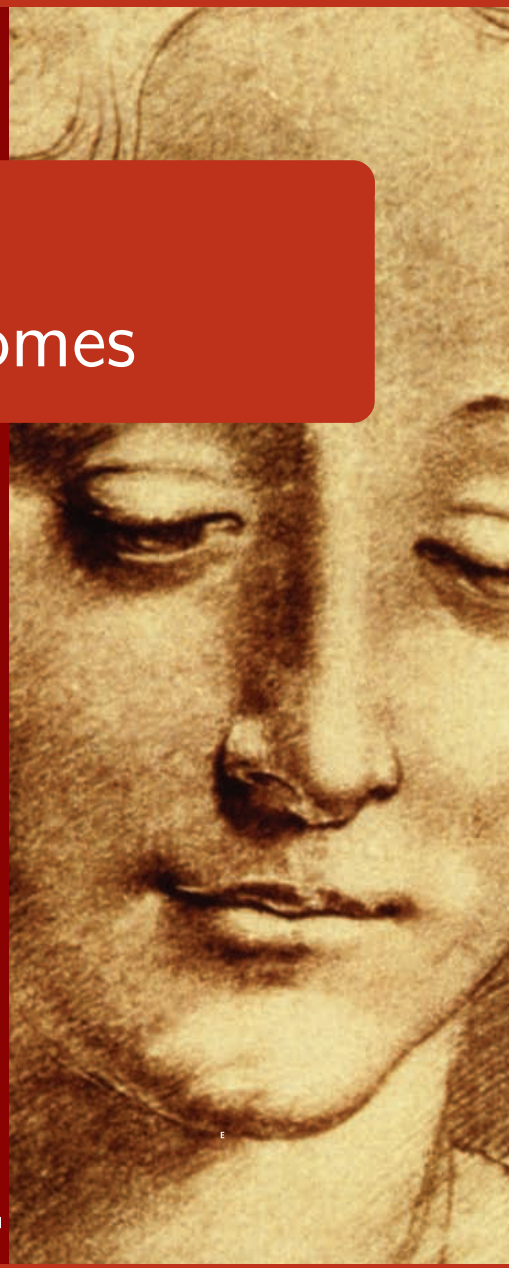
Extensions in Joint Modeling of Survival and Longitudinal Outcomes



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Outline

Introduction

Setting

- Longitudinal responses collected together with event history data for each patient
- Example: CD4 cell counts taken at different time points related to time to death
- Such data need to be jointly analyzed
  - to properly account for the association between longitudinal an survival processes
- When focus on longitudinal outcome:
  events cause nonrandom dropout
- When focus on event times:
  longitudinal responses is internal time-dependent covariate
  - cannot be simply included in relative risk model

Introduction: What Instead of Joint Modeling?

Focus on Event Time outcome: standard approaches

- Use only the last available measurement: valuable information discarded
- Time-dependent Cox model: assumes that time-dependent covariate process is exogenous

Definition: Exogenous time-dependent covariate

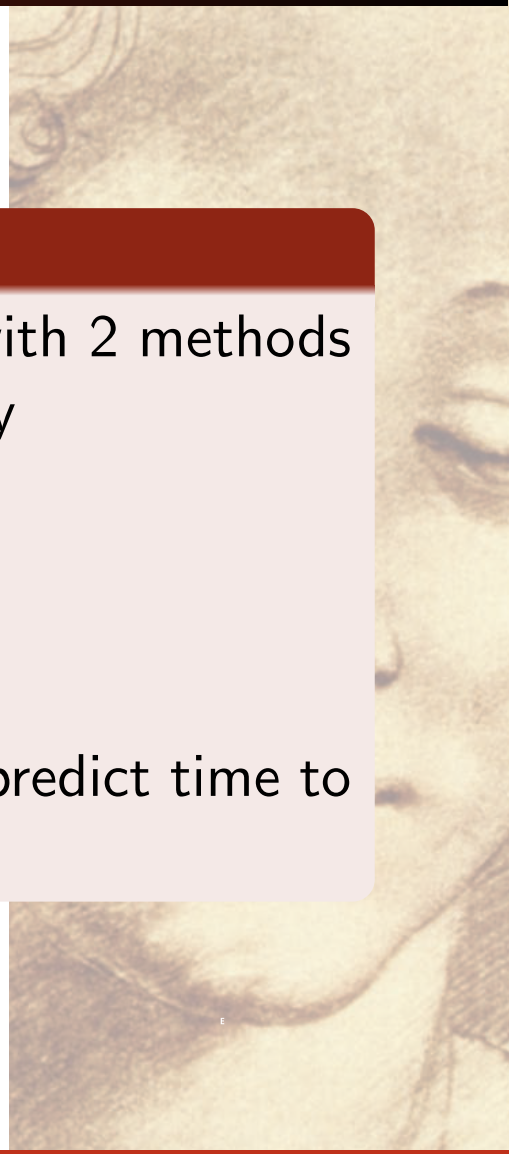
- Kablfeisch and Prentice: path at future time point t not affected by the occurrence of event at time $s \leq t$
- Only applies in some circumstances, e.g. environmental factors
- Does not hold for biomarkers!
- Measurement error

Introduction

Focus on longitudinal outcome

- Consider different types of processes that may cause missingness in longituidnal response:
- Little and Rubin: Missing Completely At Random (MCAR), Missing At Random (MAR), Missing Not At Random (MNAR)
- Under MNAR dropout process cannot be ignored: joint distribution of the dropout and longitudinal processes needs to be modeled
- Use pattern mixture, selection or shared parameters models
- First two approaches mainly applies for discreet time, last can handle both discreet and continuous time-to-dropout
- In this thesis only last approach considered

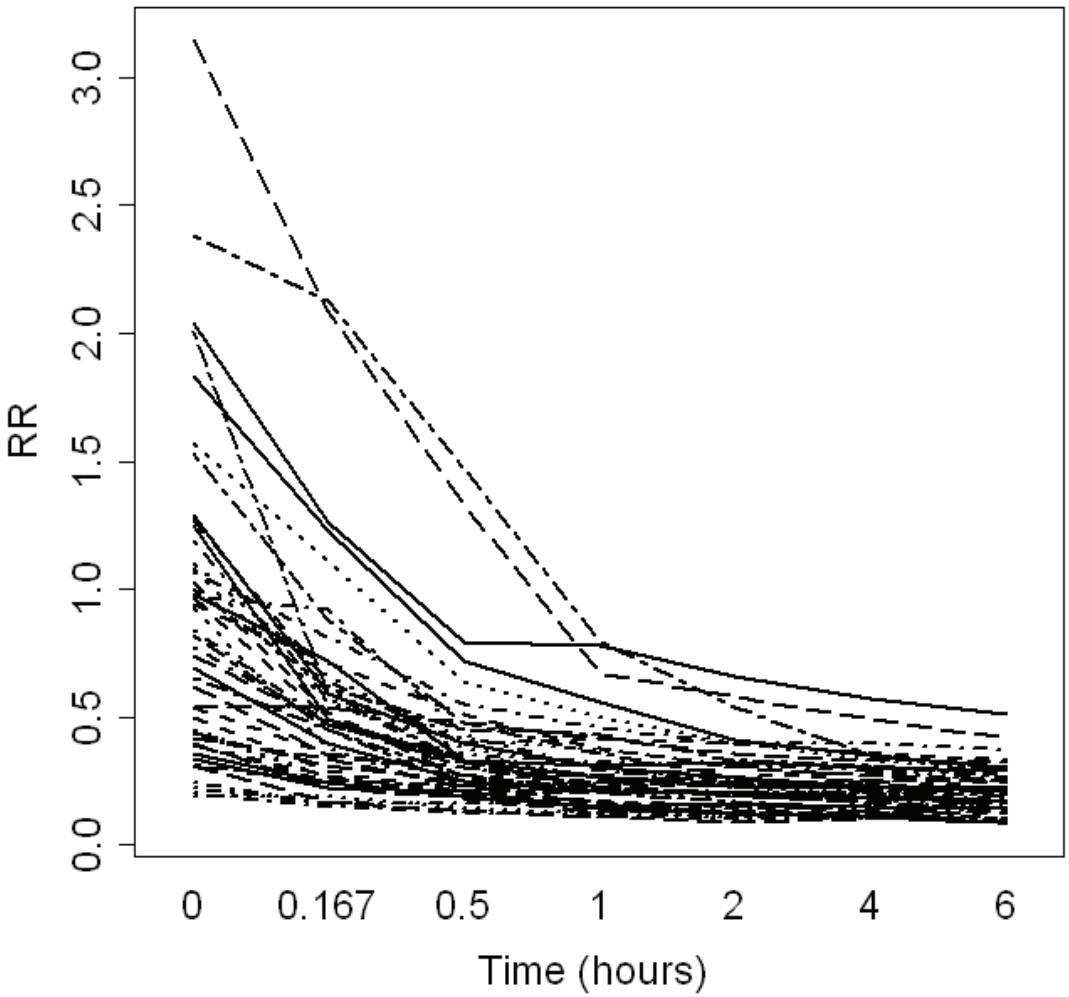
Motivating Data Sets



Renal Data

- Prospective trial on kidney-transplant patients with 2 methods of kidney storage prior to transplantation surgery
- Cold storage vs machine perfusion (MP)
- Only MP arm analysed
- Nonlinear resistance level (RR): kidney flow
- Aim: use RR (and some baseline covariates) to predict time to allograft failure

Motivating Data Sets



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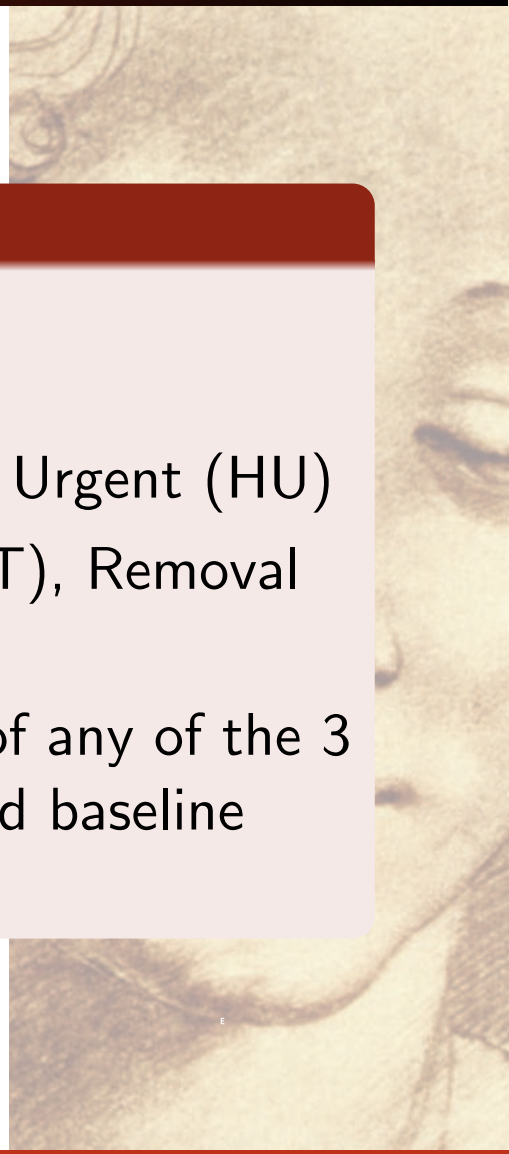
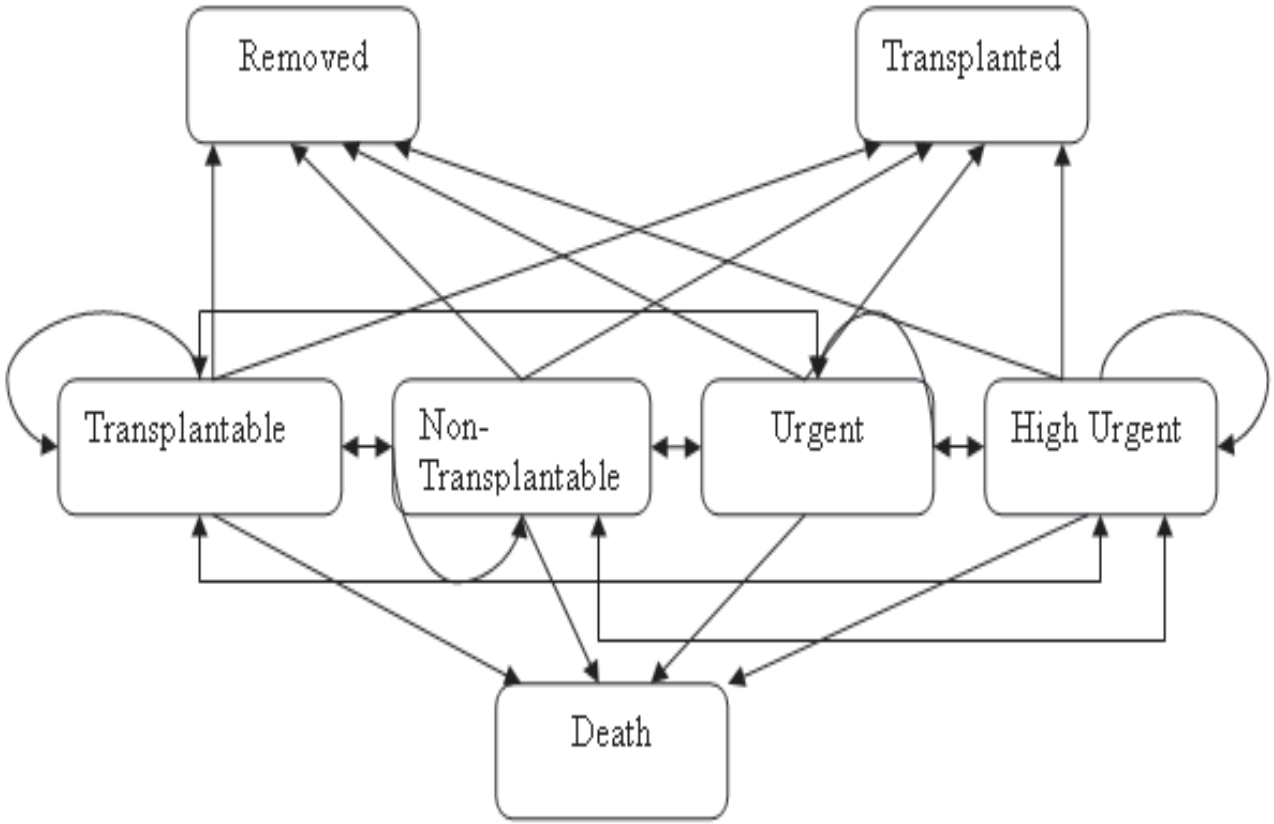


Heart Data

- 2921 heart recipients on waiting list
- Each classified to states: Transplantable (T), Non-Transplantable (NT), Urgent (U) and High Urgent (HU)
- Competing risks: Death (D), Transplantaion (TT), Removal (R)
- Aim: predict future state and estimate the risk of any of the 3 competing events using the available history (and baseline covariates)

Motivating Data Sets

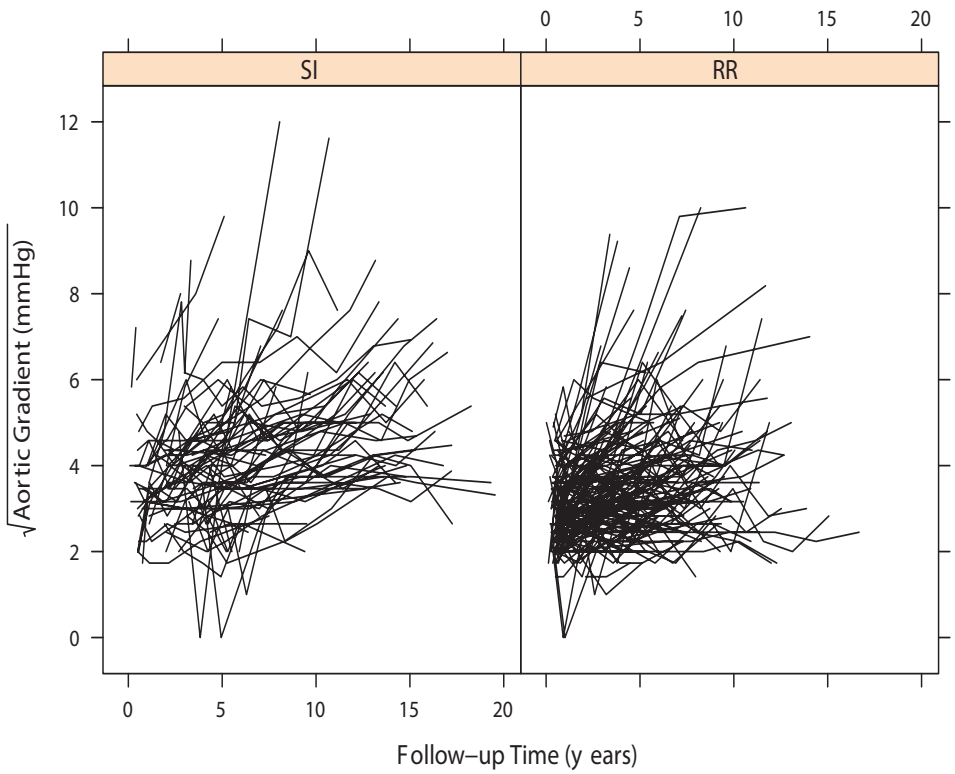


Motivating Data Sets

Aortic Data

- Valve stenosis (AS) is a disease of heart valves
- 285 AS patients received human tissue valve in aortic position
- Patients received sub-coronary implantation (SI) or root replacement (RR)
- Using velocity of blood through valve pressure gradient across valve can be calculated (aortic gradient)
- Aim : predictions of re-operation-free survival using longitudinal aortic gradient (and baseline covariates)
- Composite event: re-operation or death (no competing risks here)

Motivating Data Sets



Joint Modeling: What Is New in The Thesis?

Chapter 2: Two-Stage Procedure

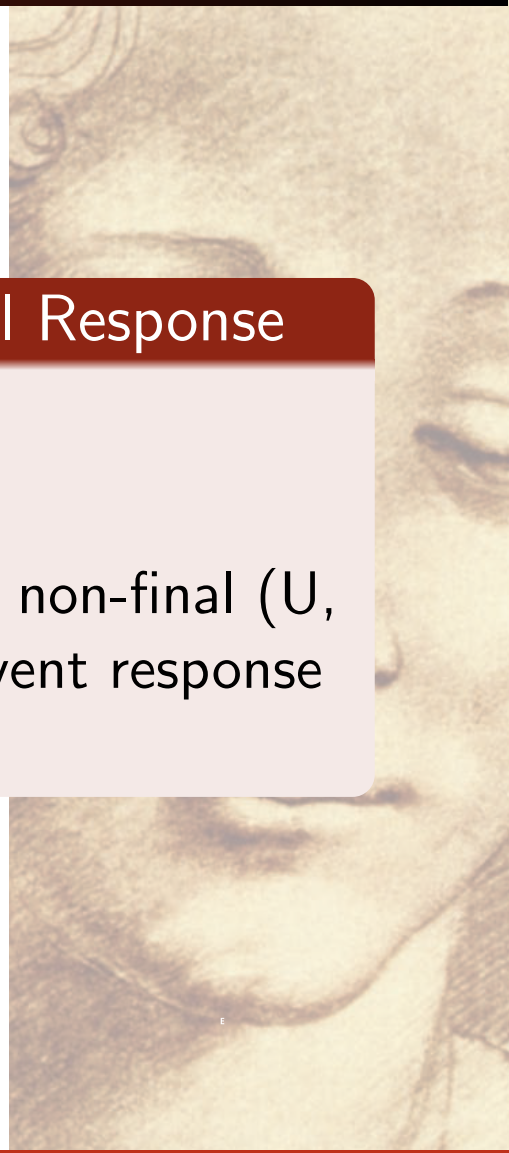
- Applied for Renal Data
- Longitudinal responses taken before actual follow-up for time-to-event initiated
- Survival will not affect longitudinal process, measurement error remains
- 1st step: summarize longitudinal information with nonlinear mixed-effects model
- 2nd step: include Empirical Bayes estimates of subject-specific parameters as predictors in Cox model
- To correct for plug-in uncertaininty: Monte Carlo approach to sample from the posterior distribution of the random effects given the observed data

Joint Modeling: What is New in The Thesis?

Chapter 3: Multi-State Models for Nominal Longitudinal Response

- Applied for Heart Data
- Simple method for modeling of nominal longitudinal response in presence of competing risks
- Pseudo-values approach of Andersen et al. applied for Aalen-Johansen estimator of state occupation probabilities
- Pseudo-values: uses idea of jackknife statistic constructed for non-parametric estimator
- Simpler and straightforward alternative comparing to other non-standard methods available for non-Markov models

Joint Modeling: What is New in The Thesis?



Chapter 4: Joint Models for Nominal Longitudinal Response

- Applied for Heart Data
- Alternative to multi-state models approach
- Bayesian model for joint modeling of categorical non-final (U, HU, T, NT) longitudinal statuses and time-to-event response with competing risks (D, R, TT)

Joint Modeling: What is New in The Thesis?

Chapter 4: Submodel for Nominal Longitudinal Response

- multinomial logit mixed model to model probabilities of states $s = U, HU, T, NT$
- $logit(P(Y_i(t) = s_r)) = w_{ir}(t) = x_i^T(t)a_r + z_i^T(t)b_{ir}$, $r = 1, 2, \ldots, R-1, \qquad i = 1, 2, \ldots N$
- $b_{ir}^T = (b_{i1}^T, b_{i2}^T, \ldots, b_{ir}^T)$, $b_{ir} \sim N(0, \Sigma_r)$
- $x_i(t)$ -vector of covariates
- $z_i(t)$ - design vector for random effects

Joint Modeling: What is New in The Thesis?

Chapter 4: Submodel for Survival Response

- $T_{i1}^*, T_{i2}^*, \ldots, T_{iK}^*$ - true failure times for individual i
- We observe only $T_i = \min(T_{i1}^*, T_{i2}^*, \ldots, T_{iK}^*, C_i)$, C_i -censoring time, Δ_i -failure ind.
- Relative risk submodel for each cause of failure k:
- $\lambda_{ik}(t) = \lim_{s \to 0} \mathrm{P}(t \leq T_i^* < t + s, \Delta_i = k \mid T_i^* \geq t)/s =$
- $= \lambda_{0k}(t) \exp(\gamma_k^T b_i + \beta_k^T v_i)$, $k = 1, \ldots, K$, $b_i^T = (b_{i1}^T, b_{i2}^T, \ldots, b_{ir}^T)$
- v_i - baseline covariates
- sharing all random effects b_i with multinomial logit model
- cause-specific baseline hazards $\lambda_{0k}(t)$ modeled as piecewise constant function

Joint Modeling: What is New in The Thesis?

Chapter 4: Joint Models for Nominal Longitudinal Response

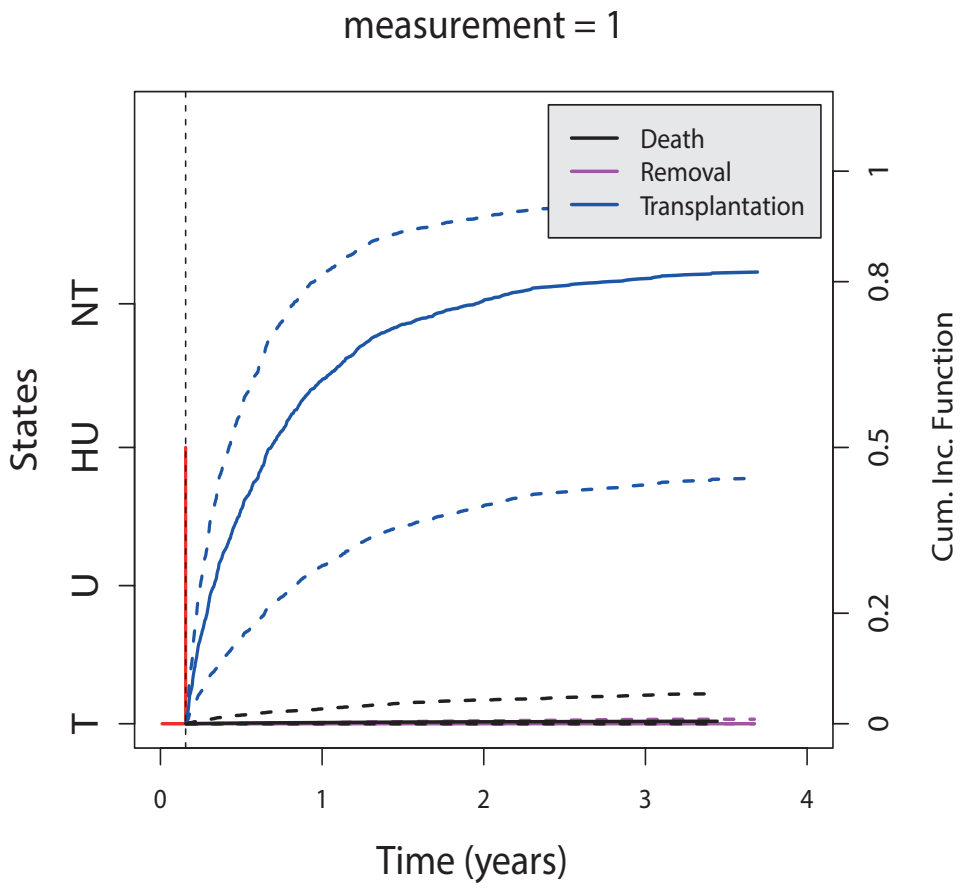
- Bayesian model used for dynamic predictions
- Dynamic Predictions: update prediction of the risk of event based on current available longitudinal profile
- Monte Carlo approach used to update cumulative incidence functions (CIF)
- 1st step: sample from posterior distribution of random effects
- 2nd step: update CIF
- Different parametrizations of Bayesian joint model examined

Joint Modeling: What Is New In The Thesis?

Chapter 5: Joint Models versus Landmarking

- Applied for Aortic Data
- Comparison of joint modeling technique for making dynamic prediction with landmarking
- Landmarking: survival probabilities from a Cox model fitted to patients still at risk at time point of interest (landmark time)
- Different measures of discrimination and calibration presented
- Different parametrizations of joint models examined

Dynamic Predictions Tool



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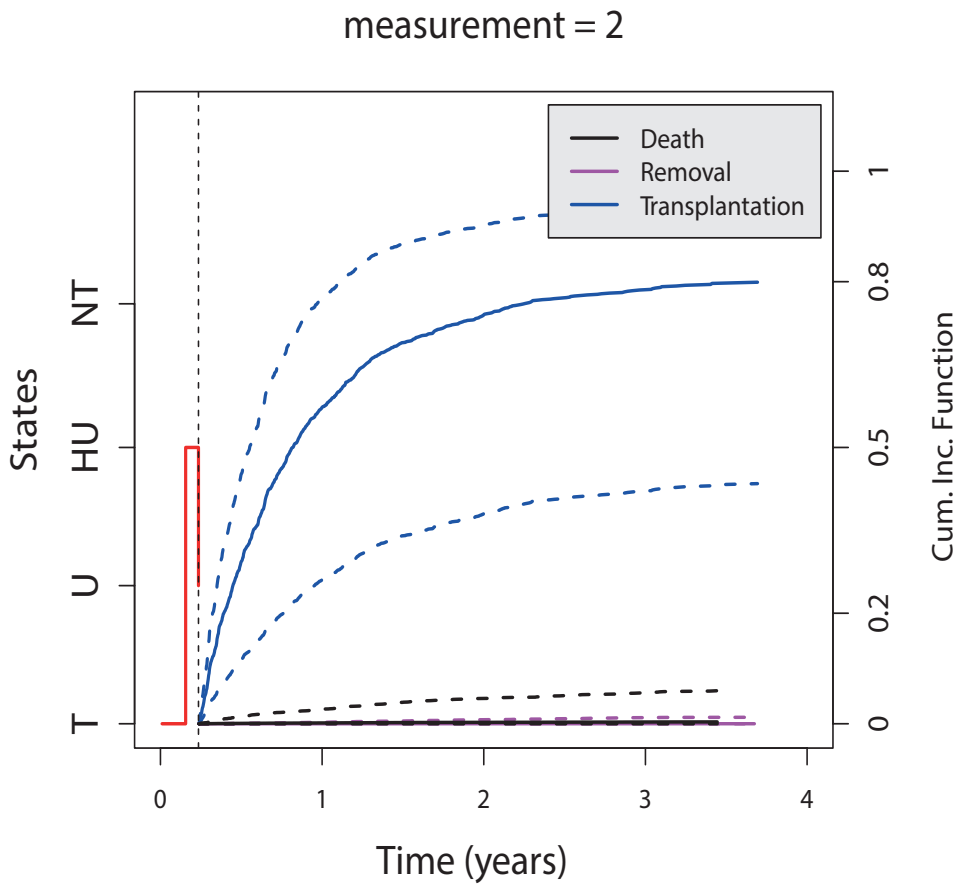

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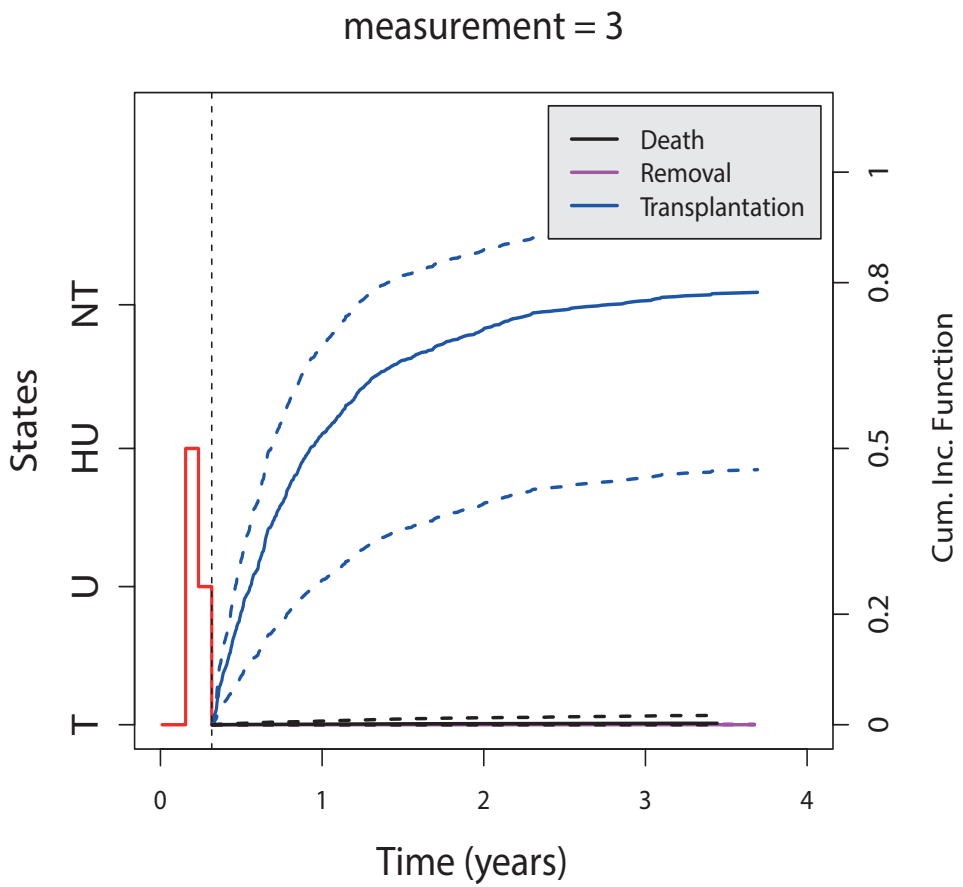

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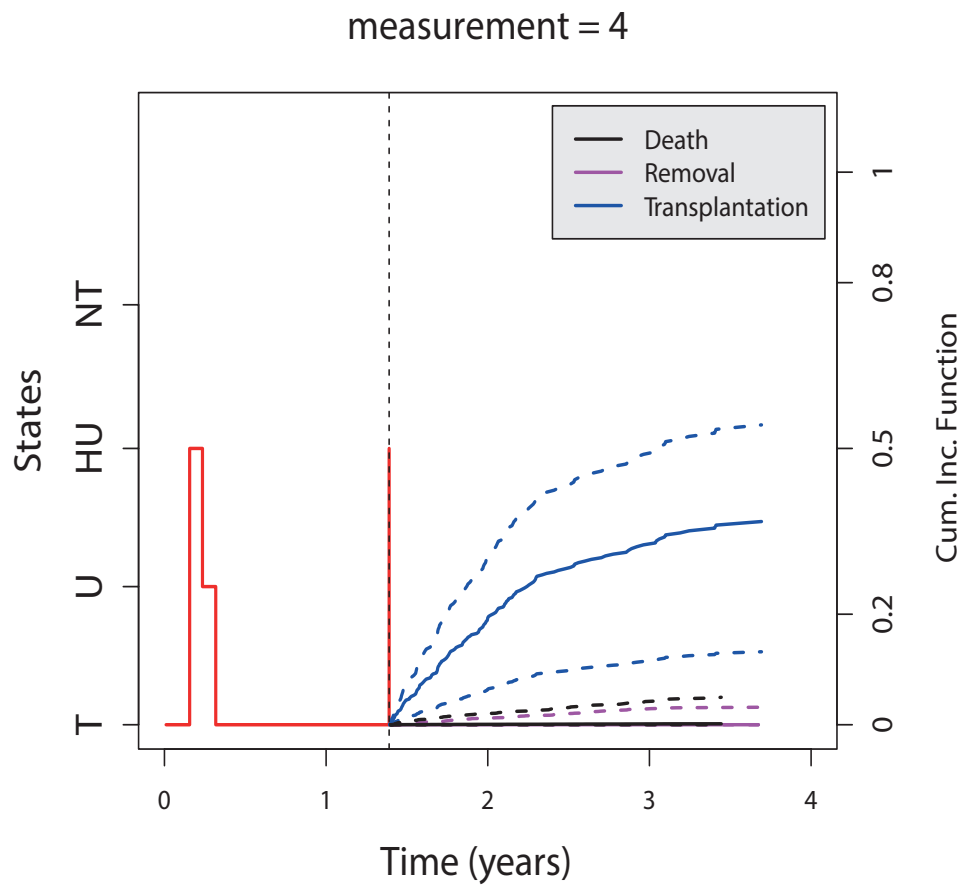

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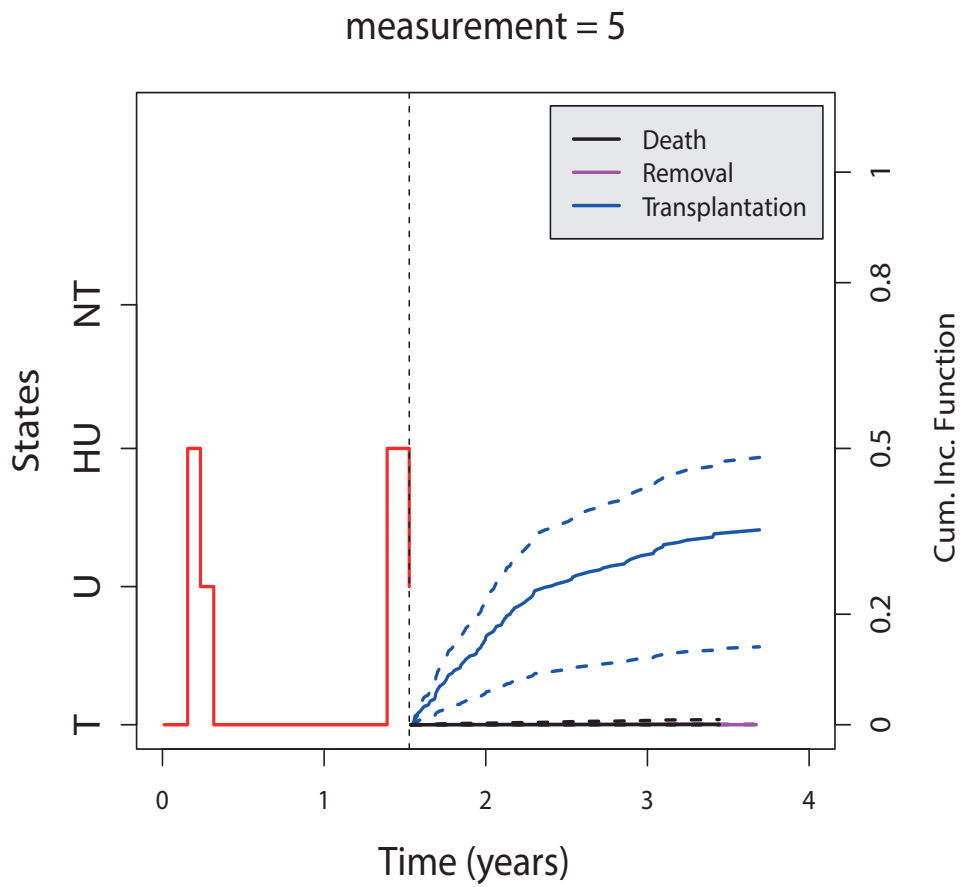

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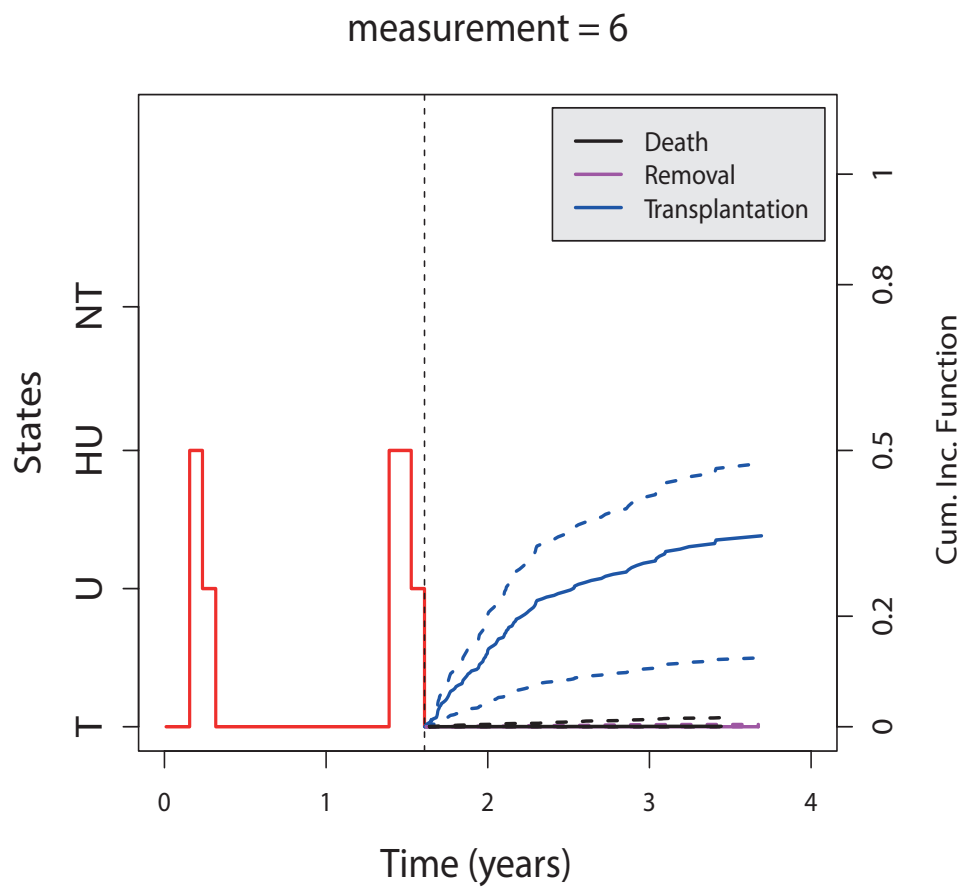

Dynamic Prediction Tool Implementation

- Dynamic predictions: easy to use through www
- R code can be implemented using *shiny* R package

Dynamic Prediction Tool Implementation

Input Patient

Choose a bloodgroup:
A

Choose a gender:
Male

Choose an IC group:
IC

Disease:
DCM

Age:
50

Number of measurments:
3

Measurement 1

Characteristics | Longitudinal & CIF Plot | All plots | Data

	response	status	time	person	gender	age	blood	IC	disease
1	4	T	0.027359781121751	1	Male	50	A	IC	DCM
2	1	NT	0.136798905608755	1	Male	50	A	IC	DCM
3	3	U	0.820793433652531	1	Male	50	A	IC	DCM

Download data

```
[1] "Not updated"
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Measurement 1
T

Time 1 (days):
10

Measurement 2
NT

Characteristics | Longitudinal & CIF Plot | All plots | Data

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[1] "Finished"
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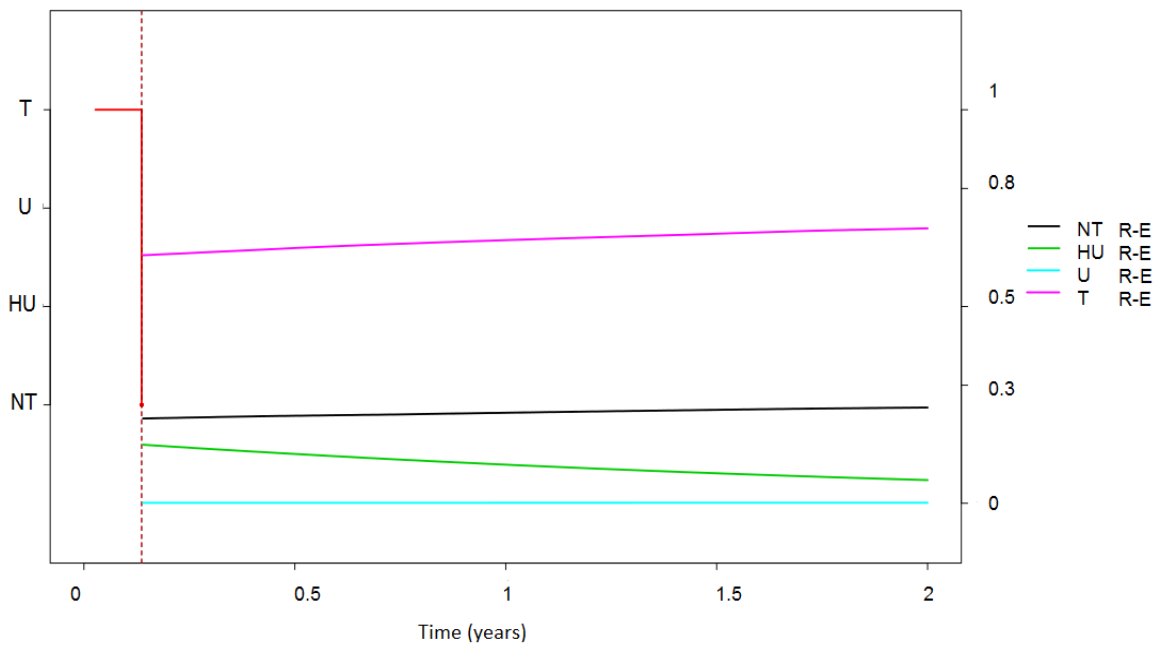

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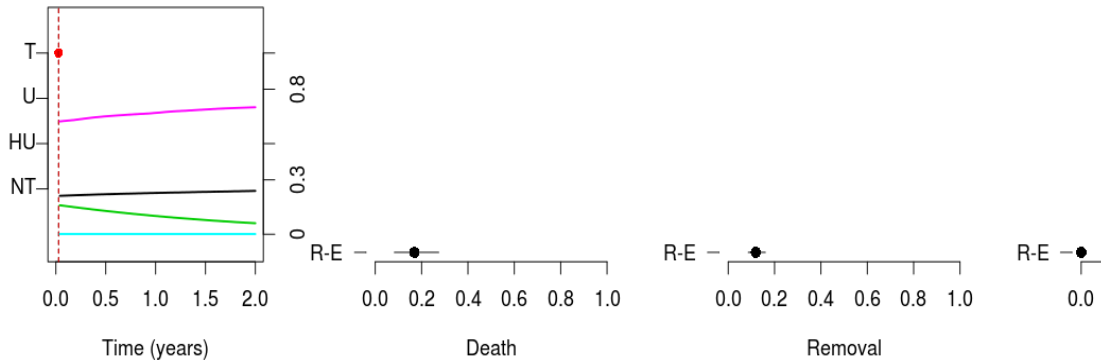

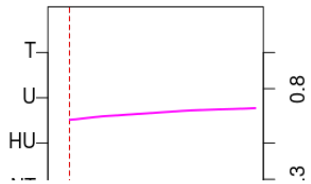

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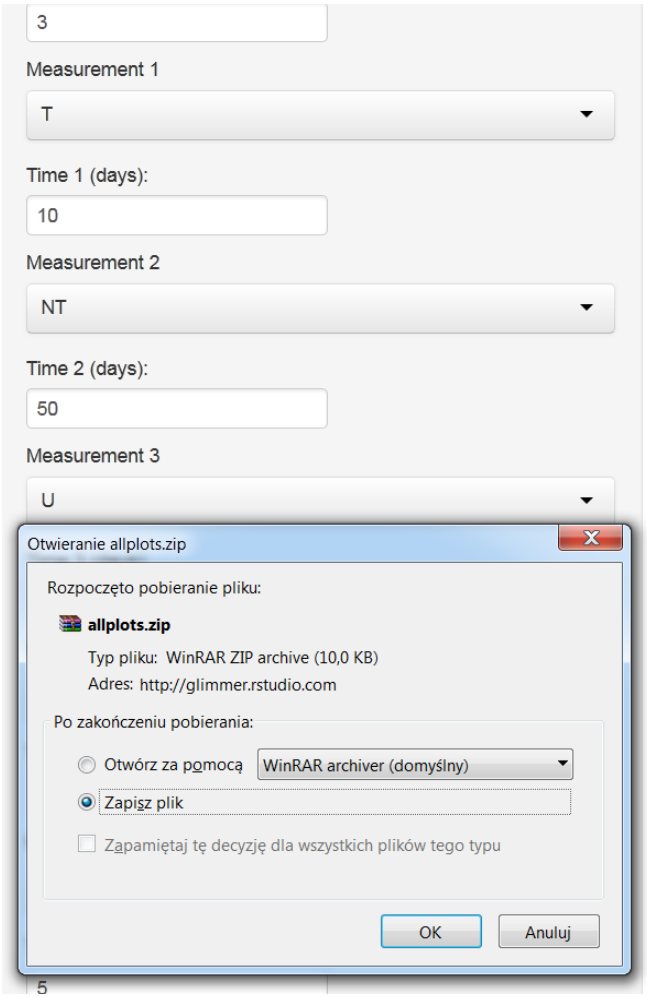
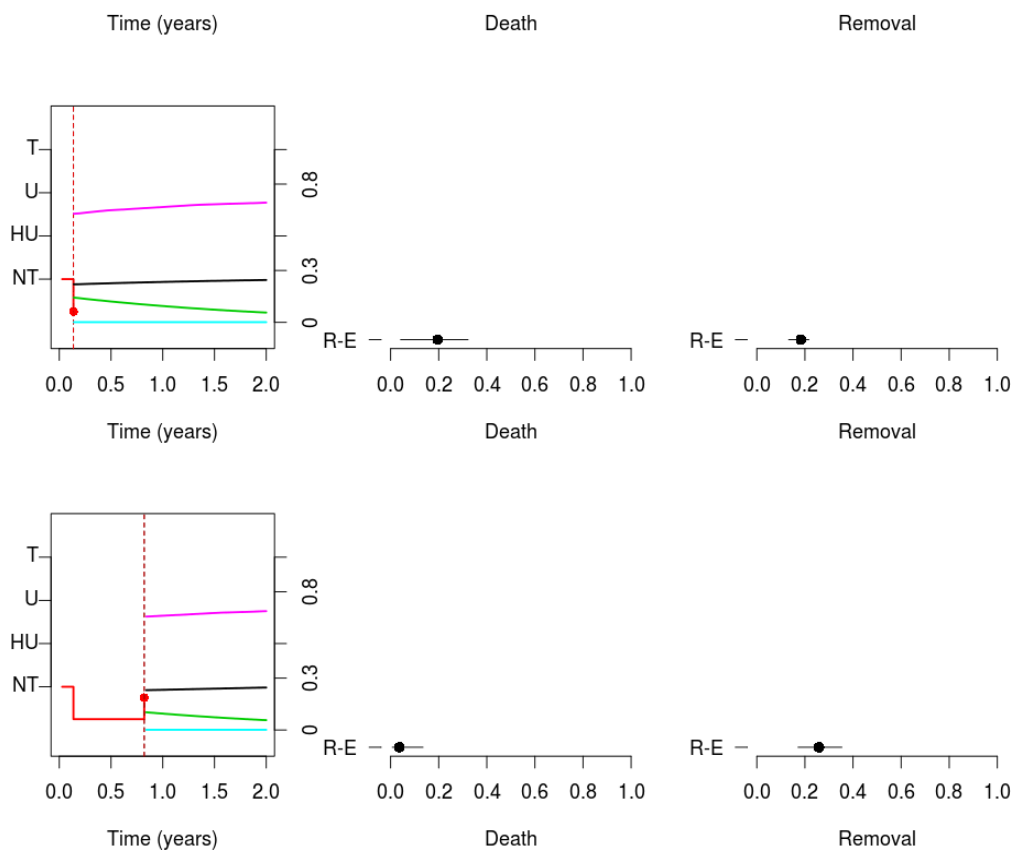
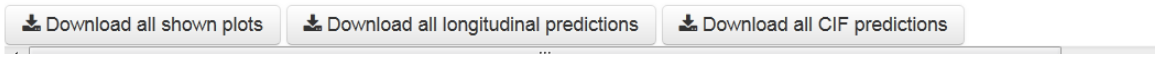


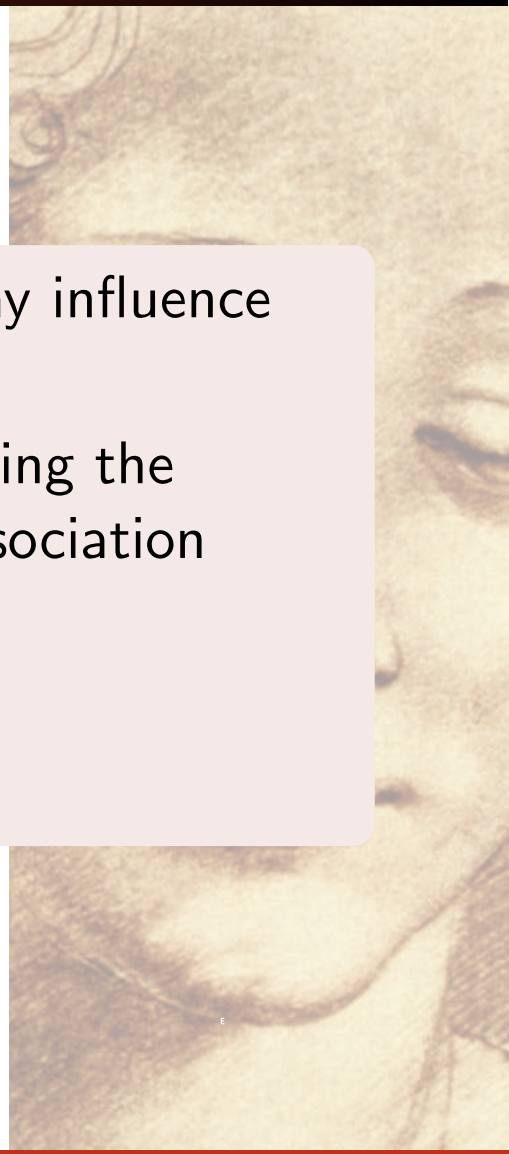




Several Assumptions

- Visiting and censoring processes assumed noninformative
- Chapter 3: under MAR, joint modeling approach allows for ignorable visiting and censoring processes
- Much more complicated when using multi-state modeling approach
- Conditional independence : longitudinal and survival processes independent conditional on shared terms
- When violated MAR does not hold
- Normal distribution for the random effect: influences only their prior distribution, not a problem for large number of measurements per subject
- Sensitivity analysis recommended anyway

Conclusions



- Chapter 4: parametrization for a joint model may influence predictions, mainly for the survival part
- Chapter 4: misspecification of joint model omitting the time-dependent terms more severe for strong association between survival and longitudinal process
- Which model is the best?
- Sensitivity analysis again

Conclusions /Future Work

- Model selection problem in joint modeling still under investigation
- Problems with residuals due to dropout: reference distribution of residuals not certain
- Solution 1: use multiple imputation idea to impute missing patterns and apply standard diagnostics
- Solution 2: Bayesian model averaging
- Solution 3: use measures from Chapter 5 (calibration and discrimination of predictions)
- Measures from Chapter 5 need to be developed for competing risks setting

THANK YOU!

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