The Landmark Approach: An Introduction and Application to Dynamic Prediction in Competing Risks

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Outline

Landmarking

Origin of landmarking

- Origin: debate on the effect of response to chemotherapy on survival (Anderson JR, Cain KC, Gelber RD, 1983, *J Clin Oncol* **1**, 710-719)
- Common way of analysis: make two groups, a "responder" group and a "non-responder" group and compare survival between these two groups
- Problem with this approach: a potential responder will only belong to the "responder" group if he/she survives until time of response
- Individuals in the responder group are immortal for some time, this gives them an unfair survival advantage: immortal time bias

Time-dependent covariates

- The problem comes in a number of disguises
  - Effect of recurrence on survival in cancer
  - Effect of transplant failure on survival in transplant studies
  - Effect of compliance on recurrence
  - Effect of drug-specific adverse events on recurrence
  - Effect of winning an Oscar on survival for US actors (*Ann Intern Med*)
- Unfortunately the incorrect approach is still prevalent in medical journals

Correct approaches

- Crucial issue: "responder" versus "non-responder" is something that is not known at baseline
- When studying survival, it is not allowed to make groups based on something that will happen in the future
- Two alternatives proposed
  - Time-dependent covariate
  - Landmark
    - Consider response at fixed point in time (landmark)
    - Remove patients with event (or censored) before landmark from analysis

Dynamic prediction

- Prediction is often well known from start treatment/diagnosis/...
- Depends on patient characteristics known at baseline
- Patient comes back for regular (6 months eg) checks
  - Baseline covariates have not changed
  - But event history (clinical events) may have changed
  - Biomarkers ...
- As a result, prognosis will have changed
  - Also if patient has had *no* events
- Prediction needs to be updated (dynamic prediction)

US Health and Retirement Study (HRS)

- HRS: number of nationally representative cohorts
- Here only oldest cohort (AHEAD) used, born before 1923, aged 70 and older in 1993
- Outcome of interest: overall survival; time scale is age
- Time-fixed covariates Z at entry: gender, education, BMI, smoking
- Time-dependent covariate

$$Z_{\mathrm{ADL}}(t) = \begin{cases} 1, & \text{if subject is ADL-disabled at age } t; \\ 0, & \text{otherwise.} \end{cases}$$

  - Basic Activities of Daily Living (walking, bathing, dressing, toileting, feeding), disabled if "with difficulty" for ≥ 1 item

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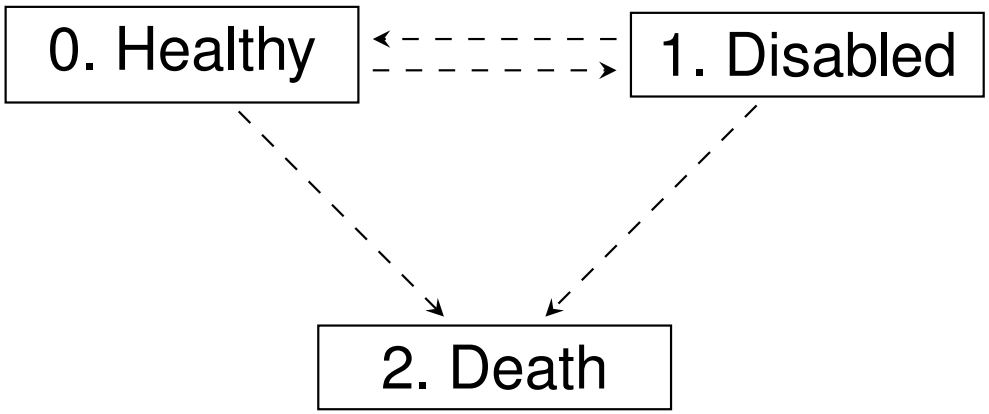
- Objective: dynamic prediction of survival of at least 10 years beyond age s, with given ADL-disability status at age s and given covariates

Covariates

Covariate	N	(%)
Gender		
Male	1564	(39%)
Female	2468	(61%)
Education		
Less than high school	1736	(43%)
High school	1212	(30%)
Some college	1084	(27%)
BMI		
≤ 25	2244	(56%)
25 – 30	1388	(34%)
> 30	390	(10%)
Smoking		
Never	1997	(50%)
Past	1683	(42%)
Current	324	(8%)

Multi-state approach

- Multi-state model; process $X(t)$ in time, taking values
  - 0: alive without ADL disability
  - 1: alive with ADL disability
  - 2: dead



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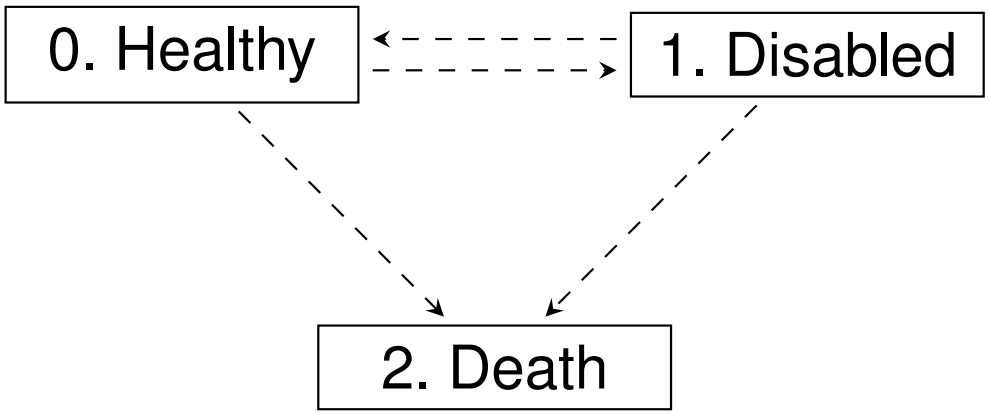
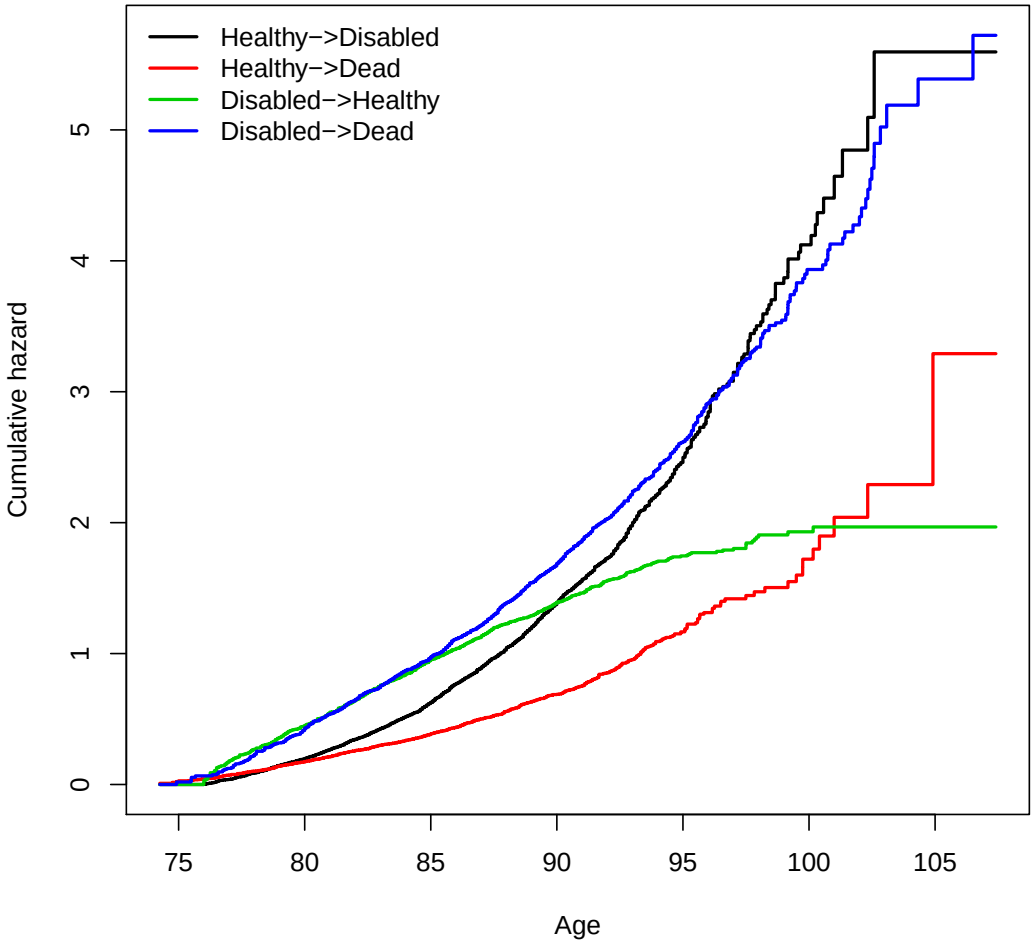


- Reversible illness-death model
- Objective: estimation of $P(X(s+w) < 2 | X(s) = 0, Z^*)$ and $P(X(s+w) < 2 | X(s) = 1, Z^*)$ for given Z^*

Estimated transition hazards



Dynamic prediction for the multi-state model

If the Markov assumption holds

- There are no easy closed-form expressions for the prediction probabilities (because the multi-state model is reversible)
- The Aalen-Johansen estimator can be used to obtain estimates of prediction probabilities but is laborious
- Implemented in **`mstate`**

Otherwise

- If the Markov assumption does not hold, we would have to use (micro-)simulation
  - In our data, there is evidence that history of ADL-disability increases disability rate ($\Rightarrow$ violation of Markov assumption)

Dynamic prediction and landmarking

- Idea to use landmarking for dynamic prediction stems from van Houwelingen (2007)
- Suppose we want to estimate the probability, given alive at age 80, of survival until age 90

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  - We would select a subset of the data, consisting of everyone alive at age 80 (a landmark data set)
  - And simply count how many are alive at age 90 and calculate proportion
  - If there is censoring, we would estimate the probability using Kaplan-Meier
  - If there are also covariates involved, we could incorporate them in a Cox model

Landmarking in general terms

For each of a set of landmark time points $s \in [s_0, s_1]$

- Construct corresponding landmark data set, by selecting all individuals at risk at s
- Define $Z(s)$: current vector of predictors, including intermediate events (depends on landmarking time point s)
- Fit simple Cox model

$$\lambda(t \mid Z(s), s) = \lambda_0(t \mid s) \exp(\beta(s)^\top Z(s))$$

  for $s \leq t \leq t_{\text{hor}}$, enforcing administrative censoring at t_{hor}
- After having obtained estimates $\hat{\beta}(s)$ and $\hat{\Lambda}_0(t \mid s)$:
- Estimate of prediction probability $P(T > t_{\text{hor}} \mid T > s, Z^*(s))$ is then given by $\exp(-\exp(\hat{\beta}(s)^\top Z^*(s))\hat{\Lambda}_0(t_{\text{hor}} \mid s))$

Robustness

- Note: for fixed s and t_{hor}, the Cox model

$$\lambda(t \mid Z(s), s) = \lambda_0(t \mid s) \exp(\beta(s)^\top Z(s))$$

  uses $Z(s)$ as time-fixed covariates and $\beta(s)$ as time-fixed covariate effects
- Xu & O'Quigley (2000) and van Houwelingen (2007): *even if the effect of $Z(s)$ is time-varying*, the above model give accurate (dynamic) predictions provided
  - Administrative censoring is enforced at t_{hor} during estimation of the Cox model
  - Prediction is only used at t_{hor}

Combining information

- Estimate parameters by fitting simple Cox model

$$\lambda(t \mid Z(s), s) = \lambda_0(t \mid s) \exp(\beta(s)^\top Z(s))$$

  for $s \leq t \leq t_{\text{hor}}$, enforcing administrative censoring at t_{hor}
- Can be done for each landmark point separately
- But we would expect the coefficients $\beta(s)$ to depend on s in a smooth way
- Can use splines or parametric model, eg

$$\beta(s) = \beta_0 + \beta_1 s$$

How to implement it

- Fitting this combined model can be done using standard software
  - Stack the landmark data sets
  - Stratify by landmark
- Estimated coefficients are correct, but for standard errors we need correction for the fact that data of the same patient are used repeatedly
  - Sandwich estimators (Lin & Wei, 1989)
- Baseline hazard estimated by Breslow estimator
- Depends on s unless both $Z(s)$ and $\beta(s)$ are constant

Baseline hazards

- Baseline hazards for different landmark time points s may be combined
- To add more structure and to make it easier to interpret the models
- We may assume a model

$$\lambda_0(t \mid s) = \lambda_0(t) \exp(\theta(s))$$

  with $\theta(s_0) = 0$ for identifiability
- In our application we take

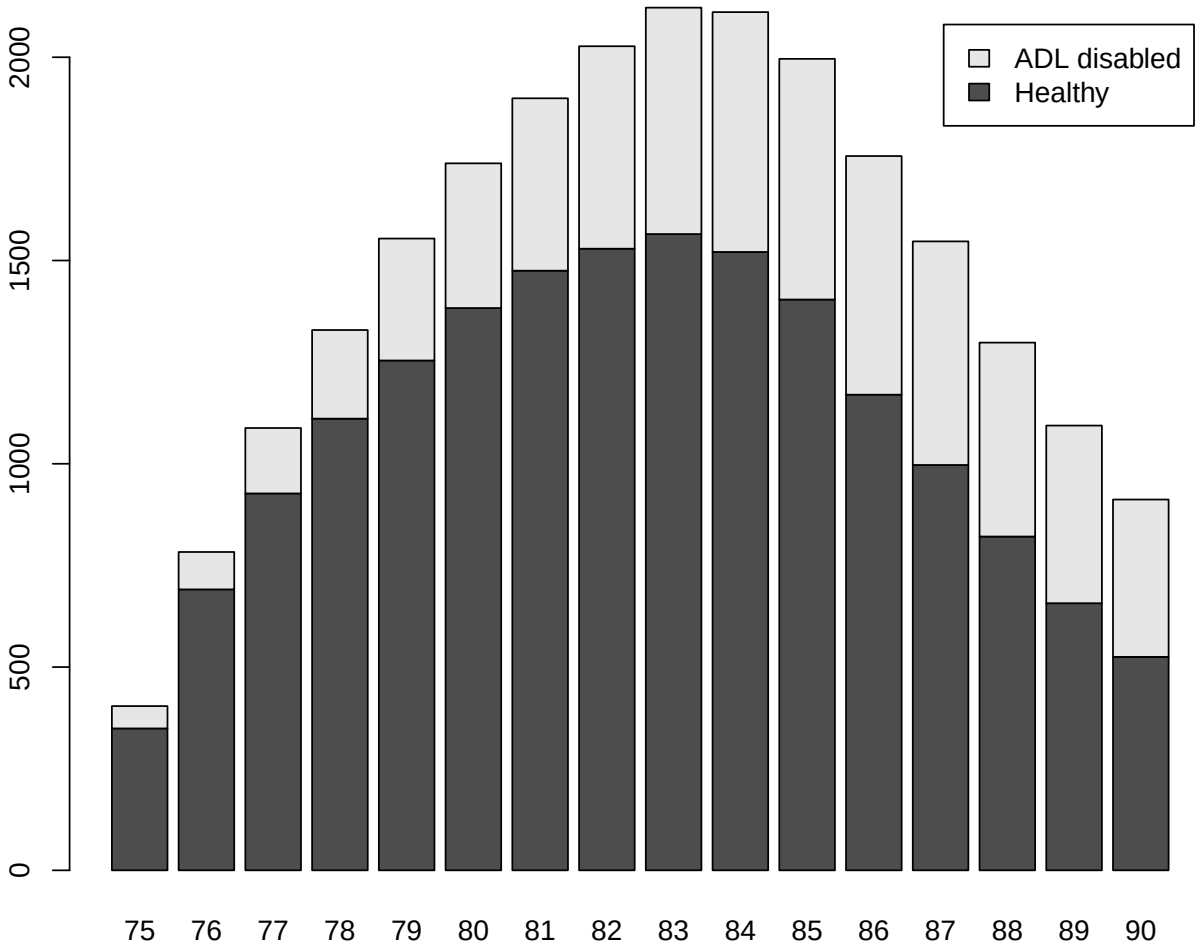
$$\theta(s) = \theta_1 s + \theta_2 s^2$$

- Model can be fitted directly by applying a simple Cox model to the stacked data set
- Landmark time s not used as stratifying variable but as covariate

Set-up

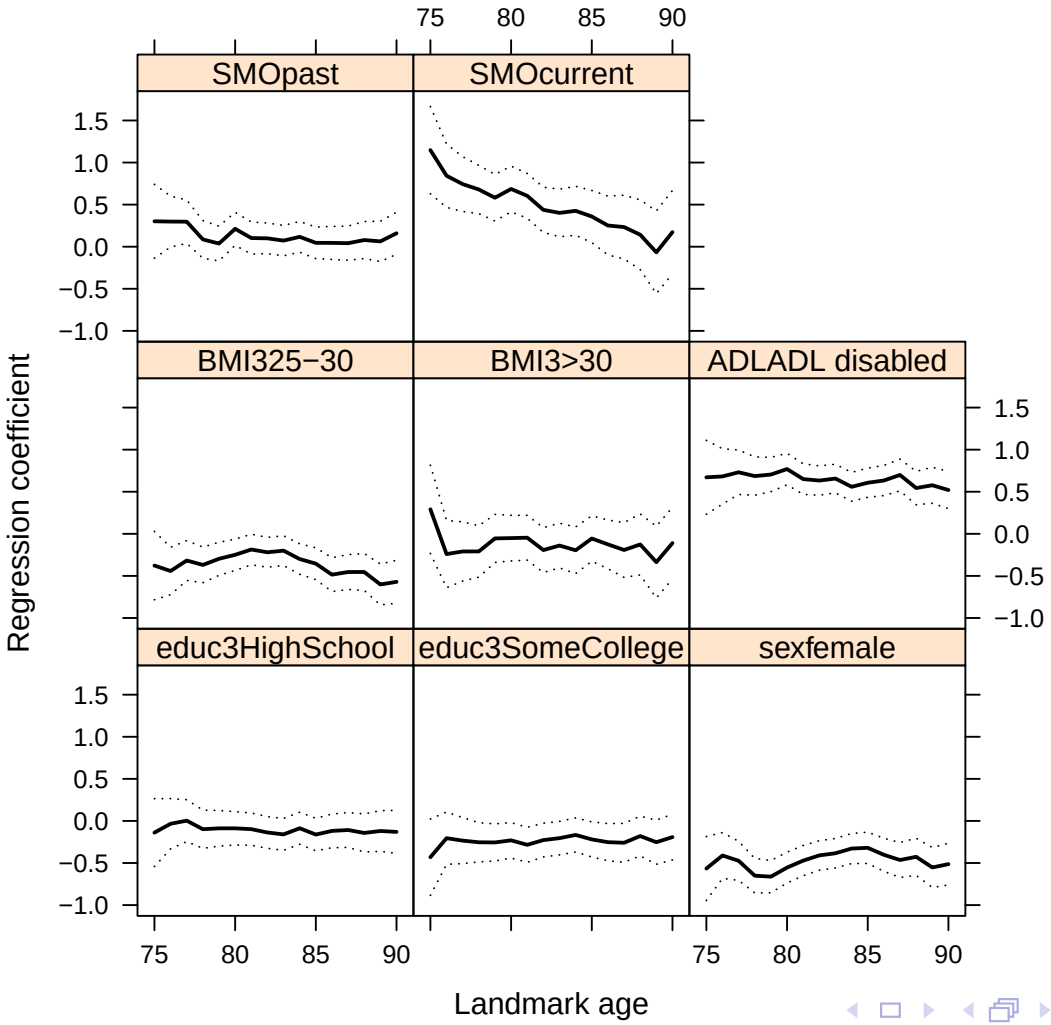
- Endpoint is survival in a window of fixed width $w = 10$ years from the moment of prediction
- Landmark time points used: 16 points, equally spaced, from age 75 to age 90
- For each landmark (prediction) time point, construct landmark data set, containing all relevant information needed for the prediction
- In all data sets we take all patients still at risk (alive), compute the current value of ADL-disability, and set the horizon at $t_{\text{hor}} = t_{\text{LM}} + 10$ years
- At each landmark point we fit a simple Cox model on $(t_{\text{LM}}, t_{\text{hor}})$ and use that to obtain a prediction of survival at $t_{\text{hor}} + 10$

The landmark data sets



Regression coefficients

Regression coefficients with 95% confidence intervals

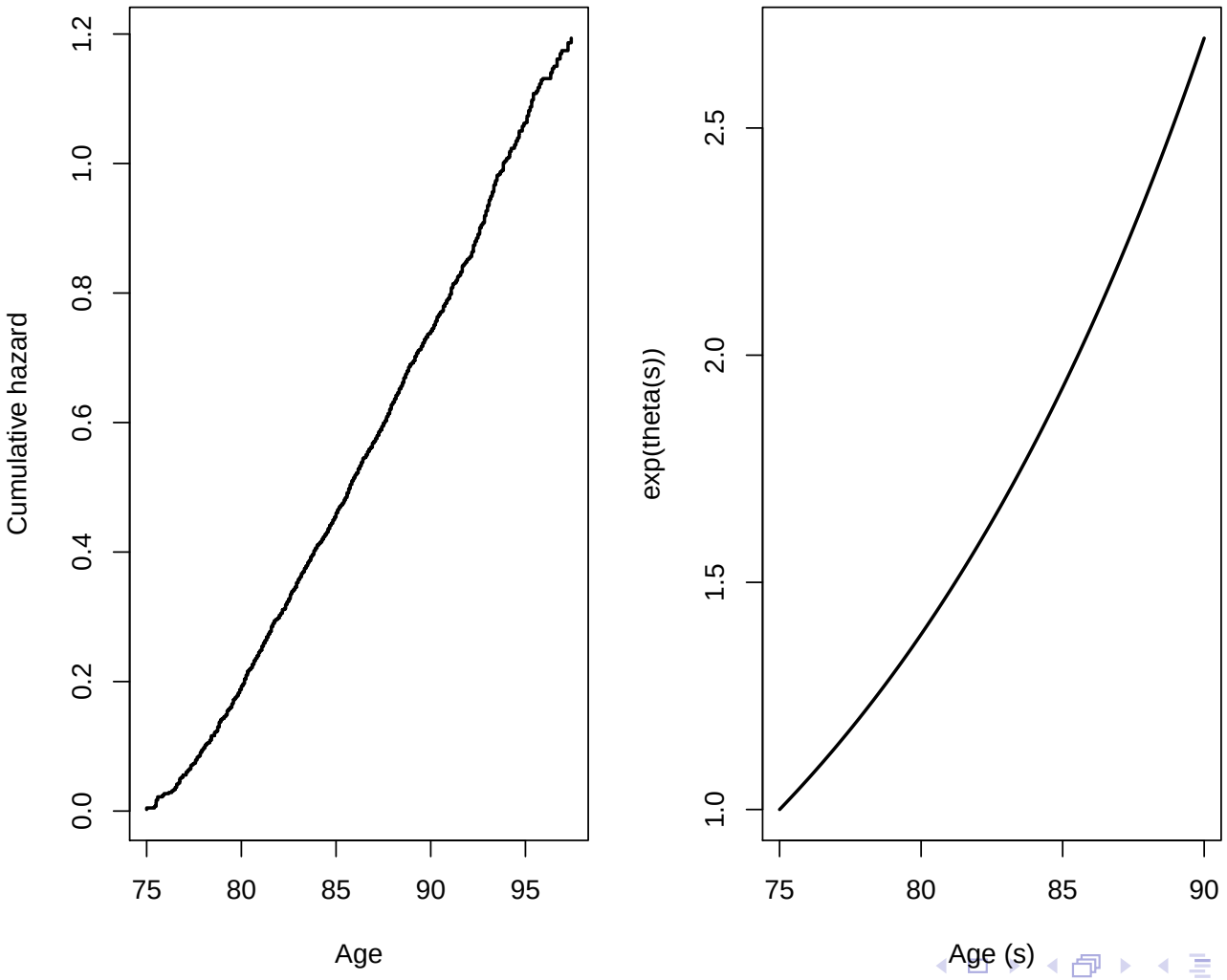


Landmark super model

Covariate	Category	B	SE
Gender	Female	-0.465	0.063
Education	High school	-0.111	0.068
	College	-0.234	0.072
BMI	25–30	-0.344	0.065
	> 30	-0.135	0.098
ADL	ADL disabled	0.636	0.050
Smoking	Past smoker	0.389	0.166
	$\times \bar{s}$	-1.020	0.586
	$\times \bar{s}^2$	0.739	0.506
	Current smoker	1.024	0.205
	$\times \bar{s}$	-1.460	0.810
	$\times \bar{s}^2$	0.538	0.794
$\theta(s)$	$\bar{s}$	0.971	0.424
	$\bar{s}^2$	0.021	0.356

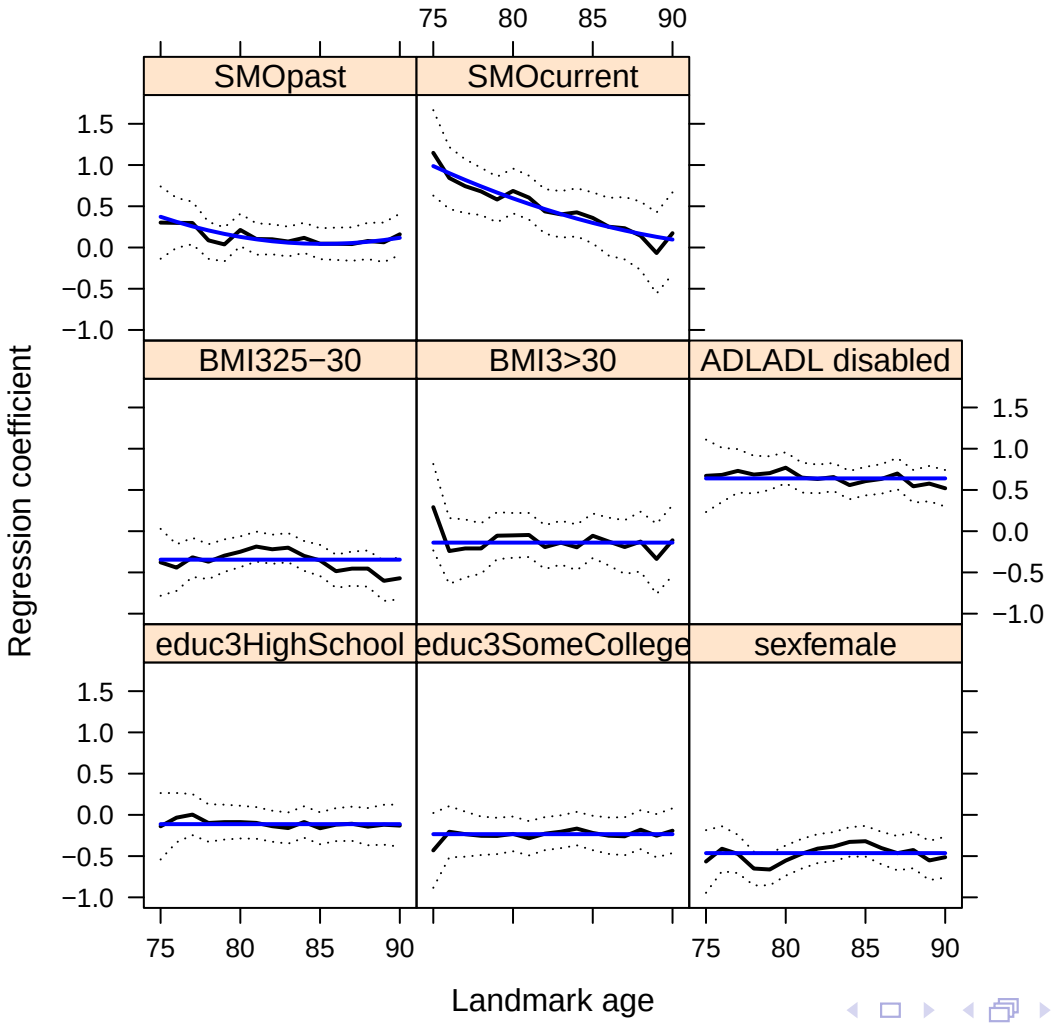
$\bar{s} = (s - 75)/15$

With corresponding baselines

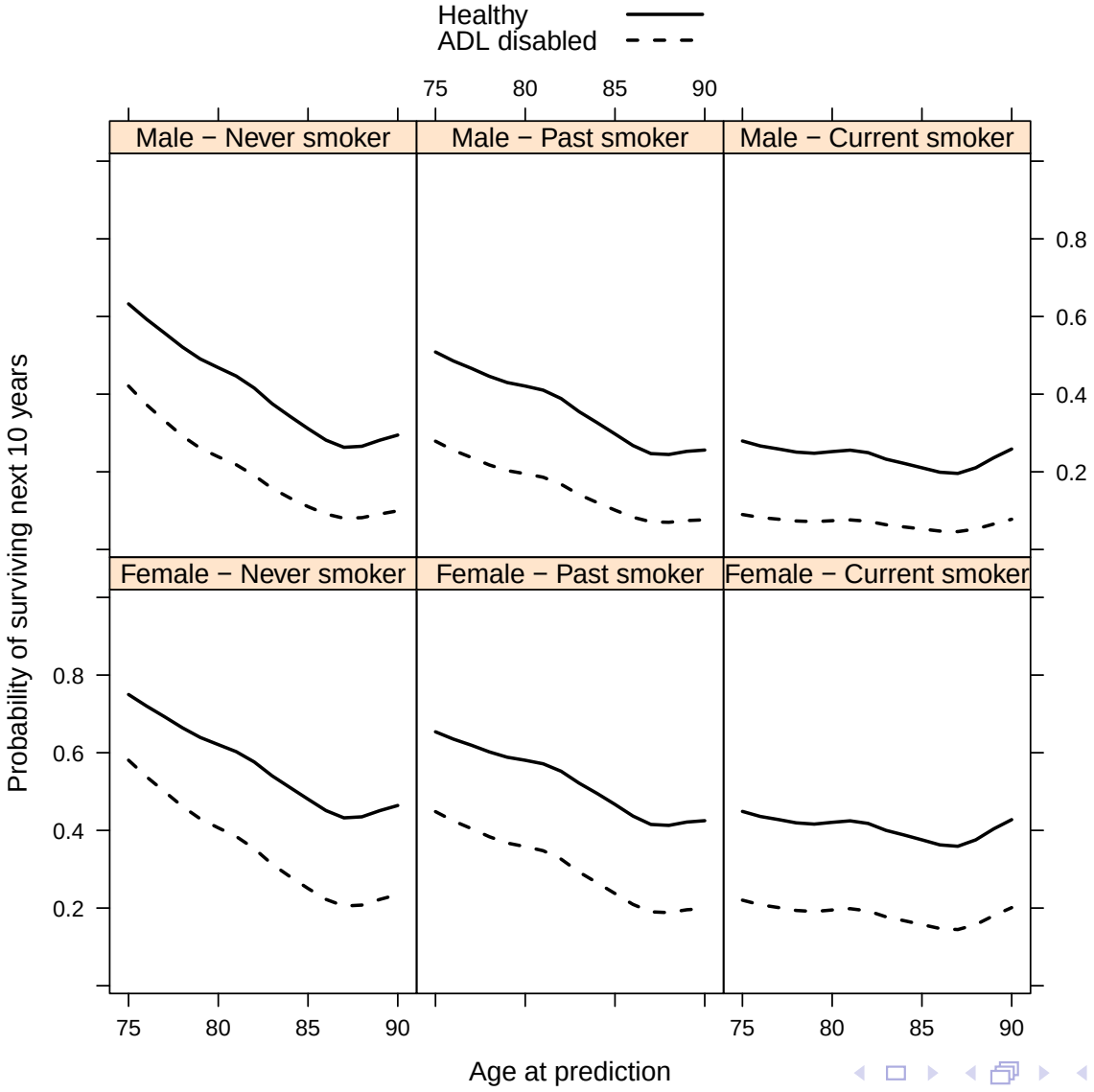


Regression coefficients

Blue lines are the (landmark-varying) supermodel effect estimates



Dynamic predictions from the landmark super model



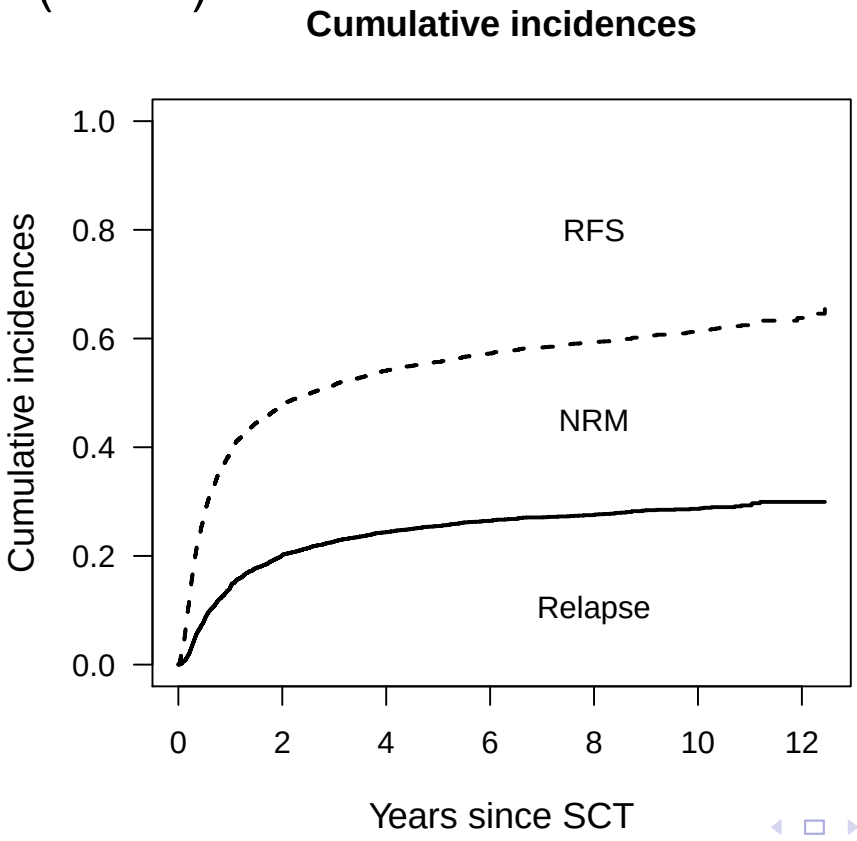
Software

dynpred

- It is not so difficult to write your own code in the statistical package of your choice
- In R, package **dynpred** is available on CRAN (`cran.r-project.org`)
  - The companion package of the book "Dynamic Prediction in Clinical Survival Analysis" by Hans van Houwelingen and myself (Chapman & Hall)
  - Functions available to create landmark data sets, applying administrative censoring at horizon (*cutLM*), and to calculate dynamic "death within window" curves (*Fwindow*)
- On the book website `http://www.msbi.nl/DynamicPrediction`, R code (using the **dynpred** package) of all the analyses in the book is available for download

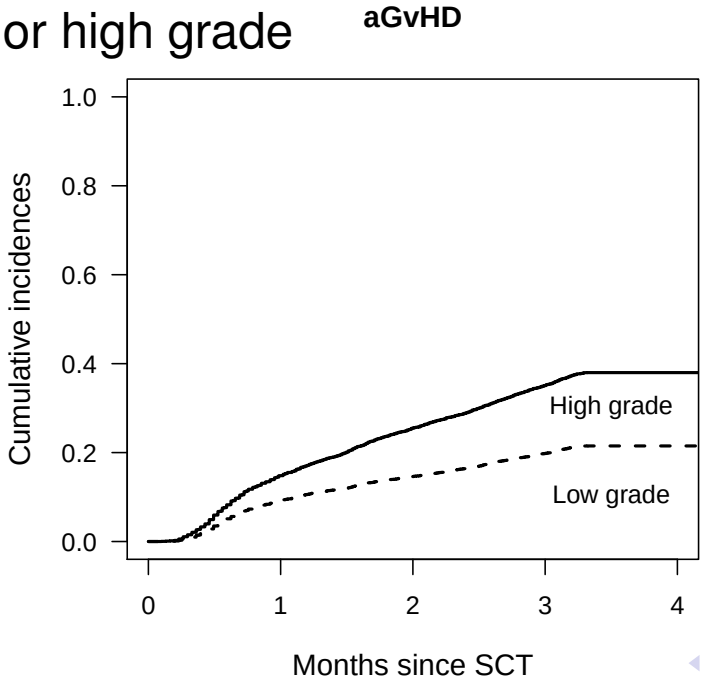
Data (EBMT)

- 5582 CML patients with transplantation (SCT) between 1997 and 2003
- Two competing risks: "**relapse**" (Rel) and "**non-relapse mortality**" (NRM)



Events of interest

- Objective:
  - To give prognosis of the disease/recovery process after SCT for a patient with a given post-transplant history
- Prediction to be based on covariates
  - Baseline: year of SCT, risk score (low, medium, high)
  - Time-dependent: Acute Graft-versus-Host-Disease (aGvHD)
    - Low or high grade



Time-dependent covariates

- Define

$$Z_{\text{low}}(t) = \mathbf{1}\{\text{occurrence of low grade aGvHD before time } t\}$$
$$Z_{\text{high}}(t) = \mathbf{1}\{\text{occurrence of high grade aGvHD before time } t\}$$

Objective

- For a patient, alive without relapse at time s after SCT, with given covariates $Z^*(s)$, what is the probability that he/she will
  - have had relapse before time $s + w$
  - have died without relapse before time $s + w$
- In our application: w is five years

Competing risks: notation

- J types of failure
- $\tilde{T}$ time of failure, C censoring time, $T = \min(\tilde{T}, C)$
- D: type of failure, $\Delta = D$ if failure occurred, 0 otherwise
- $Z(t)$ vector of covariates (possibly time-dependent)
- We observe $(T_i, \Delta_i, Z_i(\cdot))$ for individual i
- Assume censoring is independent of $(\tilde{T}, D)$ given covariates
- Cumulative incidences

$$F_j(t|s) = P(T \leq t, D = j | T > s)$$

Landmarking and competing risks

Approach based on cause-specific hazards

- Select a number of landmark time points
- For landmark time point s
  - Construct landmark data set, by selecting subjects at risk at s; denote by $\mathcal{D}_s$
  - Define $Z(s)$: current (at s) vector of predictors
  - Fit Cox models on the cause-specific hazards

$$\lambda_j(t \mid Z(s), s) = \lambda_{j0}(t \mid s) \exp(\beta_j(s)^\top Z(s))$$

  - Obtain estimates $\hat{\beta}_j(s)$ and $\hat{\lambda}_{j0}(t \mid s)$
  - For given (new) patient calculate patient-specific $\hat{\lambda}_j(t \mid Z^*(s), s) = \hat{\lambda}_{j0}(t \mid s) \exp(\hat{\beta}_j(s)^\top Z^*(s))$
  - Calculate

$$\hat{F}_j(t \mid Z^*(s), s) = \int_s^t \hat{\lambda}_j(u \mid Z^*(s), s) \hat{S}(u - \mid Z^*(s), s) du$$

Cause-specific hazards approach

- Cortese & Andersen (2010) looked at fixed set of landmark time points and over the whole future
  - No administrative censoring applied
- Nicolaie et al. (2012): interested in fixed width predictions
  - To be obtained at a continuum of prediction time points
  - Administrative censoring applied (robust against violations of proportional hazards)
  - Super models, combining different landmark models in one, were used
- For both approaches
  - Covariate effects are expressed in terms of the rates (cause-specific hazards), not directly on the risks (cumulative incidences)
- Fine-Gray type approach combined with landmarking
  - Done in Cortese & Andersen (2010) approach (straightforward, because no super models)
  - Not directly for Nicolaie et al. (2012)

Modeling: intuition from complete data

Fix cause of interest j and fix s

- For individual i within $\mathcal{D}_s$, the *survivors* at s, define

$$Y_i = \mathbf{1}\{T_i \leq s + w, D_i = j\}$$

- Expectation of Y_i in $\mathcal{D}_s$ is $P(T_i \leq s + w, D_i = j \mid T_i > s)$
- General idea: specify a model for $\mu_i(\beta) = E(Y_i | T_i > s, Z_i)$
- For some link function g, postulate

$$g(\mu_i(\beta)) = \beta_0(s) + \beta^\top(s)\mathbf{Z}_i(s)$$

- Score equation from binomial likelihood

$$\sum_{i=1}^{n_s} \frac{\partial \mu_i(\beta)}{\partial \beta} \cdot \frac{1}{\mu_i(1-\mu_i)} \cdot [y_i - \mu_i] = 0$$

Obtaining dynamic predictions

- For a new patient with covariate vector $\mathbf{Z}^*$
- Estimate of $P(T \leq s + w, D = j | T > s, \mathbf{Z}^*(s))$ is

$$\widehat{F}_j(s + w | \mathbf{Z}^*(s),\ s) = g^{-1}(\widehat{\beta}_0(s) + \widehat{\beta}^\top(s)\mathbf{Z}^*(s)),$$

- Its variance is estimated consistently by

$$\left(\frac{\mathrm{d}g^{-1}(x)}{\mathrm{d}x}\right)^2_{|x=\widehat{\beta}^\top \mathbf{Z}^*} \cdot (\mathbf{Z}^*)^\top \cdot \widehat{\mathrm{var}}(\widehat{\beta}) \cdot \mathbf{Z}^*$$

(delta-method)

Dynamic pseudo-observations

- Recall
$$Y_i = \mathbf{1}\{T_i \leq s + w, D_i = j\}$$
- Unfortunately, not available for censored patients !
- Define the dynamic pseudo-observation

$$\hat{\theta}_{is} = n_s \hat{F}_j(s + w|s) - (n_s - 1)\hat{F}_j^{(-i)}(s + w|s),$$

where

$$\hat{F}_j(s + w|s) = \sum_{s < t_i \leq s+w} \frac{d_{ij}}{n_i} \cdot \hat{S}(t_i - |s),$$

with

- d_{ij} = no of cause j events at t_i; n_i = no at risk at t_i

Properties of dynamic pseudo-observations

No censoring

$$\hat{\theta}_{is} = \mathbf{1}\{T_i \leq s + w, D_i = j\}$$

Properties of dynamic pseudo-observations

No censoring

$$\hat{\theta}_{is} = \mathbf{1}\{T_i \leq s + w, D_i = j\}$$

With censoring

- **(P1)** $\hat{\theta}_{is}$ is asymptotically independent of $\hat{\theta}_{ls}$ for individuals $i \neq l$ as $n_s \to \infty$
- **(P2)** $\hat{\theta}_{is}$ is asymptotically independent of $\hat{\theta}_{ls'}$ for individuals $i \neq l$ and landmark time points $s \neq s'$ as $n_s, n_{s'} \to \infty$
- **(P3)** $E\left[\hat{\theta}_{is} | T_i > s, \mathbf{Z}_i\right]$ equals asymptotically its theoretical counterpart $\mathbf{E}\left[\mathbf{1}\{T_i \leq s + w, D_i = j\} | T_i > s, , \mathbf{Z}_i\right]$ as $n_s \to \infty$

(Follow more or less directly from results in Graw et al. (2009).)

Censored data

Fixed s

- $Y_i = \mathbf{1}\{T_i \leq s + w, D_i = j\},\ i \in \mathcal{D}_s$ not observed
- Retain score equations and replace y_i by pseudo-observations $\hat{\theta}_{is}$
- The quasi-score equation is

$$\sum_{i=1}^{n_s} \frac{\partial \mu_i(\beta)}{\partial \beta} \cdot \frac{1}{\mu_i(1-\mu_i)} \cdot [\hat{\theta}_{is} - \mu_i] = 0$$

- Estimating equations are asymptotically unbiased ($\Rightarrow$ asymptotic normality of $\hat{\beta}$)
- Note: we calculate only one pseudo-observation per individual

Obtaining dynamic predictions

- For a new patient with covariate vector $\mathbf{Z}^*$
- Estimate of $P(T \leq s + w, D = j | T > s, \mathbf{Z}^*(s))$ is

$$\widehat{F}_j(s + w | \mathbf{Z}^*(s),\ s) = g^{-1}(\widehat{\beta}_0(s) + \widehat{\beta}^\top(s)\mathbf{Z}^*(s)),$$

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(delta-method)

Super models: setup

- Define a set of landmark time points $0 \leq s_1 < \ldots < s_K \leq \tau$
- Construct the corresponding landmark data sets $\mathcal{D}_k := \mathcal{D}_{s_k}$
- Define the dynamic pseudo-observation $\widehat{\theta}_{ik}$ of individual i at time $s_k + w$
- Note again: only one per subject per s_k (namely at $s_k + w$)
- Define
$$\hat{\theta}_i = (\hat{\theta}_{ik},\ k \in \mathcal{L}_i),\ \mathcal{L}_i \subset \{1, \ldots, K\}$$
- Longitudinal vector $\hat{\theta}_i$ *truncated by death* (Kurland & Heagerty 2005)

Super models

- Define $\mu_{ik} = \mu_i(s_k) = P(T_i \leq s_k + w, D_i = j \mid T_i > s_k)$
- GLM
$$g(\mu_{ik}|Z_i(s_k)) = \beta_0(s_k) + \beta^\top(s_k)\mathbf{Z}_i(s_k),$$
- Choose smooth model for l^{th} component of $\beta(s)$
$$\beta_l(s) = \beta_l^\top h_l(s) \qquad \Rightarrow \qquad \beta(s) = H(s)\beta$$
- The quasi-score equation for regression parameter β is
$$U(\beta) = \sum_{i=1}^{n} U_i(\beta) = \sum_{i=1}^{n} \frac{\partial \mu_i(\beta)}{\partial \beta} \cdot V_i^{-1}(\widehat{\theta}_i - \mu_i) = 0$$
- Asymptotic unbiasedness of these estimation equations follows (only for independence working correlation!)

Dynamic prediction in super models

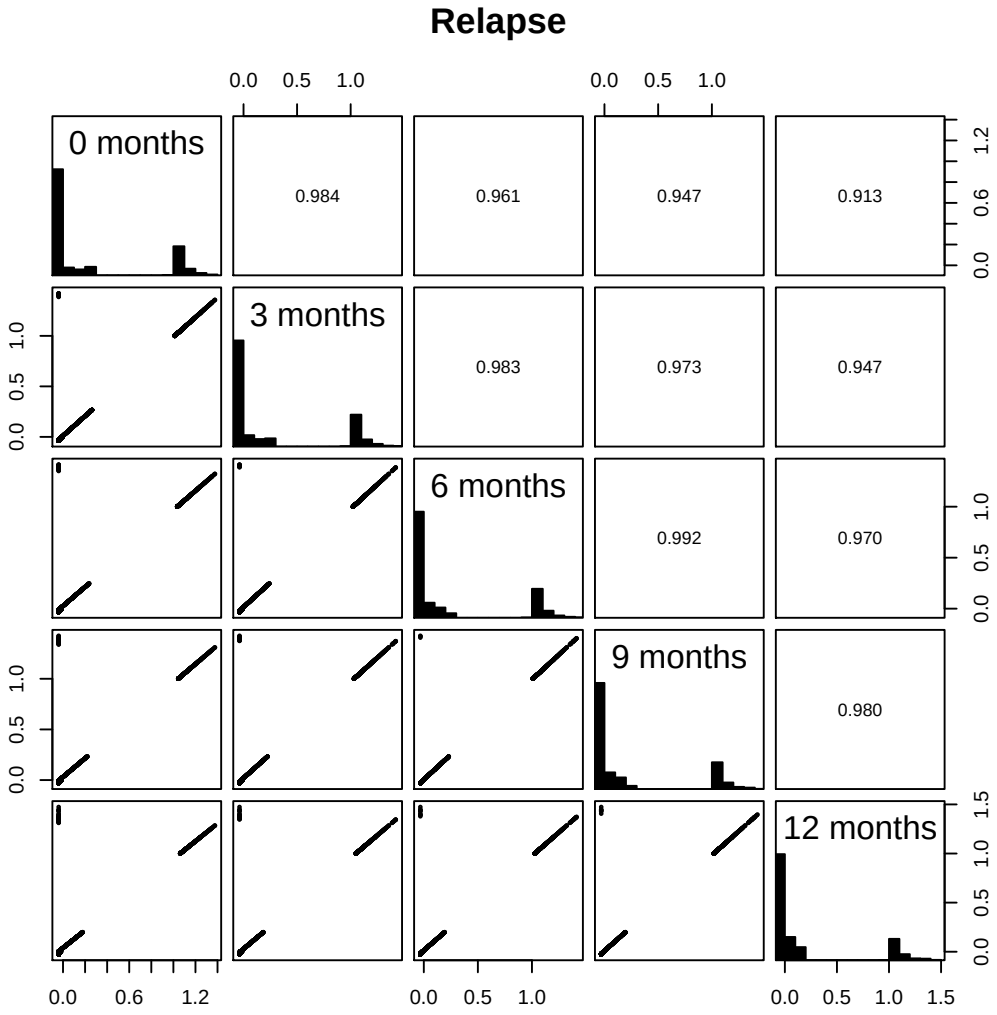
- For a new patient with covariate vector $\mathbf{Z}^*$
- The estimate of $P(T \leq s + w, D = j | T > s, \mathbf{Z}^*(s))$ is

$$\widehat{F}_j(s + w | \mathbf{Z}^*,\ s) = g^{-1}(\widehat{\beta}_0(s) + \widehat{\beta}^\top(s)\mathbf{Z}^*(s)),$$

  with $\widehat{\beta}(s) = H(s)\hat{\beta}$
- Its variance is estimated consistently by

$$\left(\frac{\mathrm{d}g^{-1}(x)}{\mathrm{d}x}\right)^2_{|x=(\widehat{\beta})^\top \mathbf{Z}^*} \cdot (\mathbf{Z}^*)^\top \cdot H(s) \cdot \widehat{\mathrm{var}}(\widehat{\beta}) \cdot H(s)^\top \cdot \mathbf{Z}^*$$

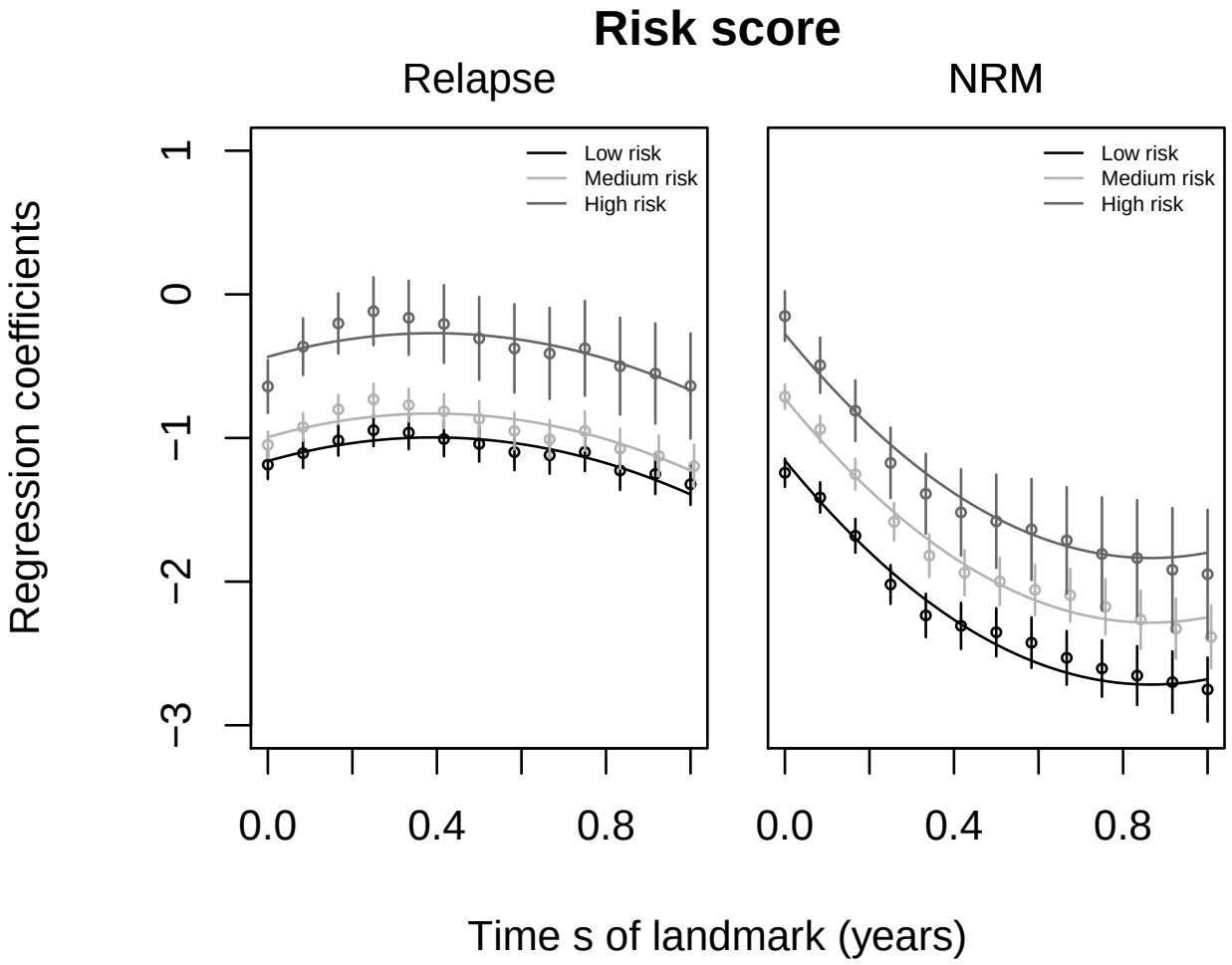
Scatter-plot



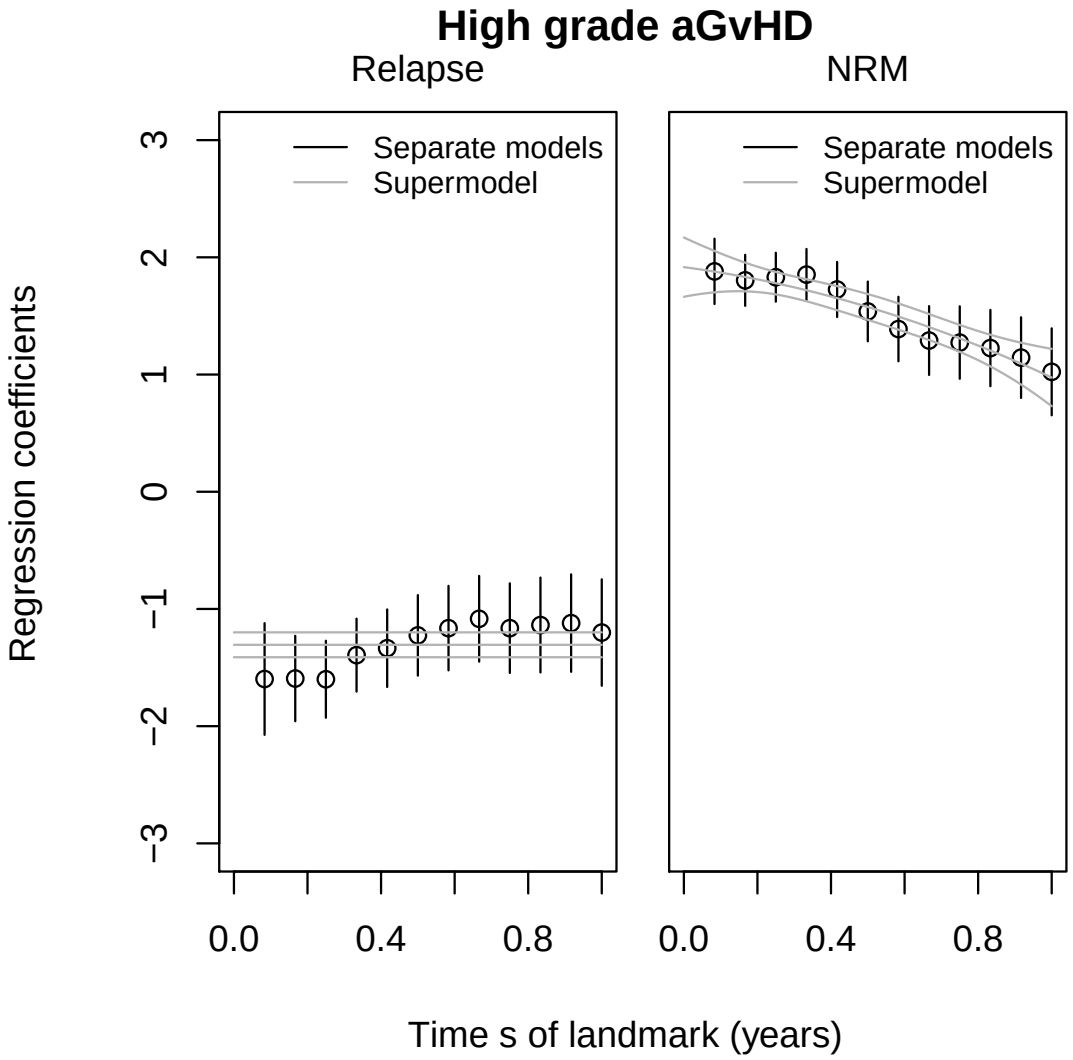
Model

Covariate	Relapse		NRM	
	$\widehat{\beta}$	SE($\widehat{\beta}$)	$\widehat{\beta}$	SE($\widehat{\beta}$)
Intercept				
Constant	-1.160	0.027	-1.156	0.029
s	0.839	0.126	-3.603	0.165
s^2	-1.072	0.129	2.080	0.183
Year of transplantation				
Constant	0.530	0.126	-0.591	0.125
s	-1.165	0.657	1.604	0.718
s^2	0.553	0.678	-1.079	0.766
Risk score				
Low risk				
Medium risk	0.166	0.022	0.431	0.025
High risk	0.725	0.039	0.880	0.042
Low grade aGvHD				
Constant	-0.490	0.030	0.168	0.102
s			2.032	0.461
s^2			-1.738	0.436
High grade aGvHD				
Constant	-1.305	0.054	1.916	0.129
s			-0.416	0.579
s^2			-0.524	0.545

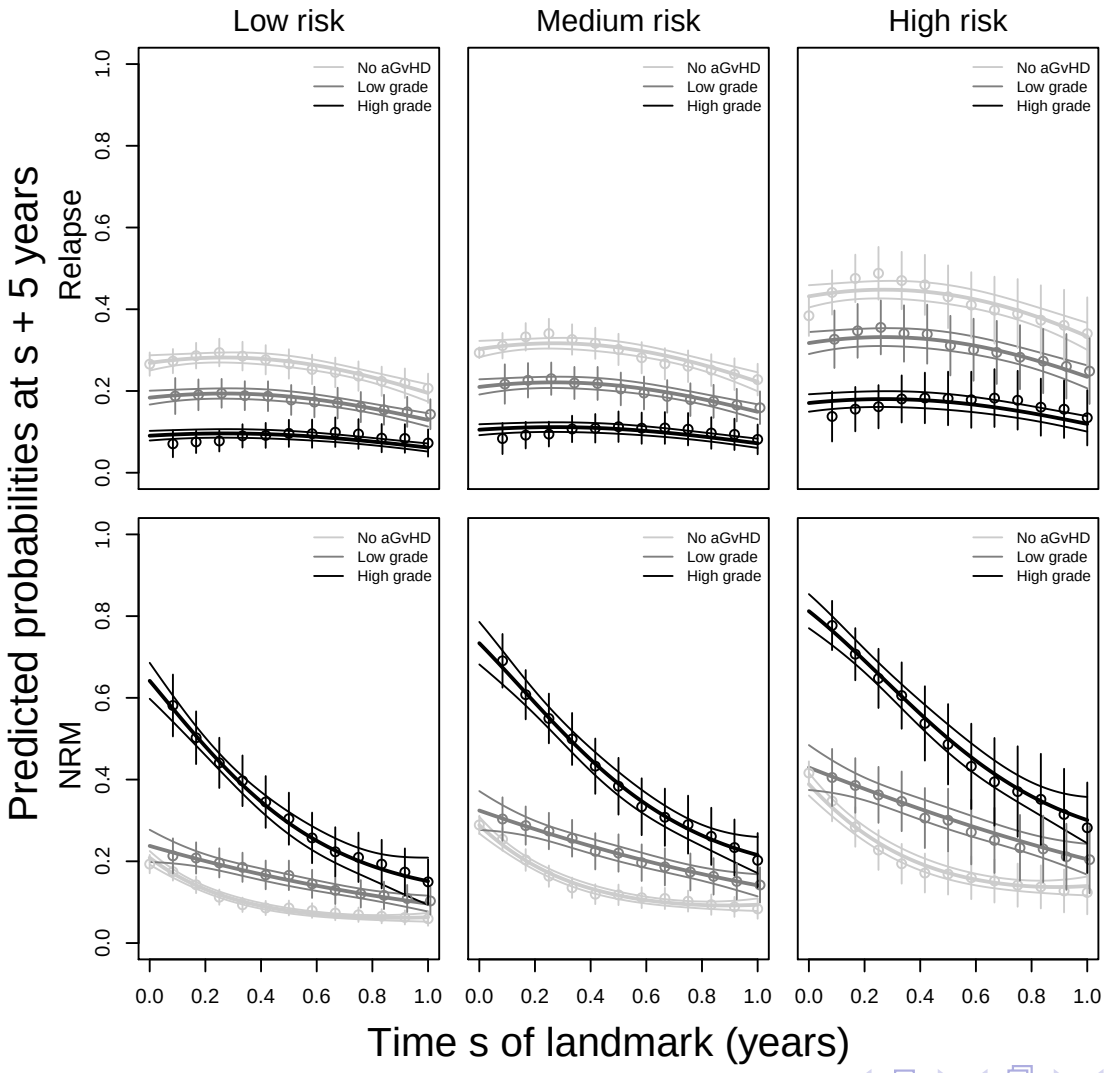
Regression coefficients of EBMT risk score



Regression coefficients of aGvHD



5-yr prediction probabilities



Discussion

- For each landmark time point s_k we only use (need) dynamic pseudo-observations at one fixed horizon $(s_k + w)$
- No proportional hazards assumptions needed
- Gain in robustness
- But possible loss of efficiency
- Method is direct and straightforward to implement in GEE software (especially using the **`pseudo`** package)
- Correlation structure of dynamic pseudo-observations is ignored in the estimating equations of the super models

Discussion (general)

Advantages of standard approach

- It is standard
- There is software
- You gain biological understanding (hopefully) by modeling the effects of covariates on transitions

Advantages of landmarking

- It is more direct; no need for complicated formulas for prediction
- Predictions obtained from multi-state model may be off the mark if assumptions are violated or if model fit is not good
- Sparse model (considerably fewer parameters than multi-state model)

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