# Introduction to BART with time-to-event outcomes

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# Outline

- Motivation: advanced lung cancer prognosis
- Survival analysis with BART
- Motivation: diabetes and recurrent hospital admissions
- Recurrent events with BART
- Motivation: liver transplant waiting list
- Competing risks

# Survival analysis with Cox Proportional Hazards

Cox 1972 *JRSS-B*

Data: $(s_i, \delta_i, x_i)$

$\mathbf{0} = t_{(0)} < \cdots < t_{(J)} < \infty$: distinct ordered death, $s_i$, times

$$(0, t_{(1)}] \ldots (t_{(J-1)}, t_{(J)}]$$

$$\lambda(t, x_i) = \lambda_0(t) e^{\beta' x_i}$$ Linear proportionality

$$[\beta | \lambda_0(t)] = \prod_i \frac{e^{\beta' x_i}}{\sum_{j \in R(t_i)} e^{\beta' x_j}}$$ Partial Likelihood

$$\hat{S}_0(t) = e^{-\hat{\Lambda}_0(t)} \text{ where } \hat{\Lambda}_0(t) = \sum_{t_i \le t} \frac{\delta_i}{\sum_{j \in R(t_i)} e^{\hat{\beta}' x_i}}$$

$$\hat{S}(t, x_i) = \hat{S}_0(t)^{\exp(\hat{\beta}' x_i)}$$

# Survival analysis with BART

Sparapani et al. 2016 *Statistics in medicine*

$$\mathbf{0} = t_{(0)} < \cdots < t_{(K)} < \infty : \text{distinct ordered, } s_i, \text{ times}$$

$$y_{ij}|p_{ij} \overset{\text{ind}}{\sim} \mathbf{B}\left(p_{ij}\right) \text{ where } j = 1, \ldots, J_i = \arg\min_j s_i \leq t_{(j)}$$

$$y_{ij} = \delta_i \mathbf{I}\left(j = J_i\right)$$

$$p_{ij} = p\left(t_{(j)}, x_{ij}\right) \text{ where } x_{ij} = x_i\left(t_{(j)}\right)$$

$$= \Phi\left(f\left(t_{(j)}, x_{ij}\right)\right) \text{ where } f \overset{\text{prior}}{\sim} \text{BART}$$

$$[y|p] = \prod_{i=1}^{N} \prod_{j=1}^{J_i} p_{ij}^{y_{ij}} \left(1 - p_{ij}\right)^{1-y_{ij}} \quad \text{Likelihood}$$

$$S\left(t_{(j)}, x_{ij}\right) = \mathbf{P}\left[t > t_{(j)}|x_{ij}\right] = \prod_{j' \leq j} \left(1 - p_{ij'}\right)$$

Discrete time intensity model $\Rightarrow$ longitudinal binary BART

# Survival analysis with BART and inference

We generate samples of $f$ from the posterior with MCMC

$$\hat{f}(t,x) = M^{-1}\sum_m f_m(t,x) \qquad \text{Estimate } f$$

$$\hat{S}(t,x) = M^{-1}\sum_m S_m(t,x) \qquad \text{Survival function}$$

$$(S_{0.025}(t,x), S_{0.975}(t,x)) \qquad \text{95\% Credible Interval}$$

$$RI(t,x_n(t),x_d(t)) = \frac{p(t,x_n(t))}{p(t,x_d(t))} \qquad \text{Relative Risk or Intensity}$$

$$= \frac{\Phi(f(t,x_n(t)))}{\Phi(f(t,x_d(t)))}$$

# Survival analysis with BART and Friedman's partial dependence function

Friedman 2001 *AnnStat*

$f(t,x) = f(t,x_S,x_C)$ BART function where $x = [x_S, x_C]$

$$f(t,x_S) = \mathrm{E}_{x_C}\left[f(t,x_S,x_C)|x_S\right]$$

$$\approx N^{-1}\sum_i f(t,x_S,x_{iC})$$

$$f_m(t,x_S) \equiv N^{-1}\sum_i f_m(t,x_S,x_{iC})$$

$$\hat{f}(t,x_S) \equiv M^{-1}\sum_m f_m(t,x_S)$$

# surv.bart and mc.surv.bart input and output

```
post=surv.bart(x.train, times=times, delta=delta,
    ..., ndpost=M, keepevery=10) or
post=mc.surv.bart(x.train, times=times, delta=delta,
    ..., ndpost=M, keepevery=10, mc.cores=2, seed=99)
```

Input vector `times` with $K$ distinct values and `x.train`: $x_i$

$$\begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_N \end{bmatrix}$$

Output `post`, of type `survbart` which is essentially a list of matrices including: `post$surv.train`: $\hat{S}_m(t_{(j)}, x_i)$

$$\begin{bmatrix} \hat{S}_1(t_{(1)},x_1) & \dots & \hat{S}_1(t_{(K)},x_1) & \dots & \hat{S}_1(t_{(1)},x_N) & \dots & \hat{S}_1(t_{(K)},x_N) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \hat{S}_M(t_{(1)},x_1) & \dots & \hat{S}_M(t_{(K)},x_1) & \dots & \hat{S}_M(t_{(1)},x_N) & \dots & \hat{S}_M(t_{(K)},x_N) \end{bmatrix}$$

# `surv.pre.bart` input and output

```
post <- surv.pre.bart(times, delta, x.train,
    x.test=x.train)
```

Output a list containing the data transformed such as

matrix `pre$tx.train` and vector `pre$y.train`:

$$\begin{bmatrix} t_{(1)} & x_1 \\ \vdots & \vdots \\ t_{(J_1)} & x_1 \\ \vdots & \vdots \\ t_{(1)} & x_N \\ \vdots & \vdots \\ t_{(J_N)} & x_N \end{bmatrix} \quad \begin{bmatrix} y_{11} = 0 \\ \vdots \\ y_{1J_1} = \delta_1 \\ \vdots \\ y_{N1} = 0 \\ \vdots \\ y_{NJ_N} = \delta_N \end{bmatrix}$$

N.B. for `pre$tx.test` $J_i = K$

# `predict.survbart` input and output

```
pred <- predict(post, pre$tx.test, mc.cores=1, ...)
```

Input matrices: `x.test`: $x_i$

$$\begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_Q \end{bmatrix}$$

Output `pred` of type `survbart` with `pred$surv.test`: $\hat{S}_m(t_{(j)}, x_i)$

$$\begin{bmatrix} \hat{S}_1(t_{(1)},x_1) & \dots & \hat{S}_1(t_{(K)},x_1) & \dots & \hat{S}_1(t_{(1)},x_Q) & \dots & \hat{S}_1(t_{(K)},x_Q) \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \hat{S}_M(t_{(1)},x_1) & \dots & \hat{S}_M(t_{(K)},x_1) & \dots & \hat{S}_M(t_{(1)},x_Q) & \dots & \hat{S}_M(t_{(K)},x_Q) \end{bmatrix}$$

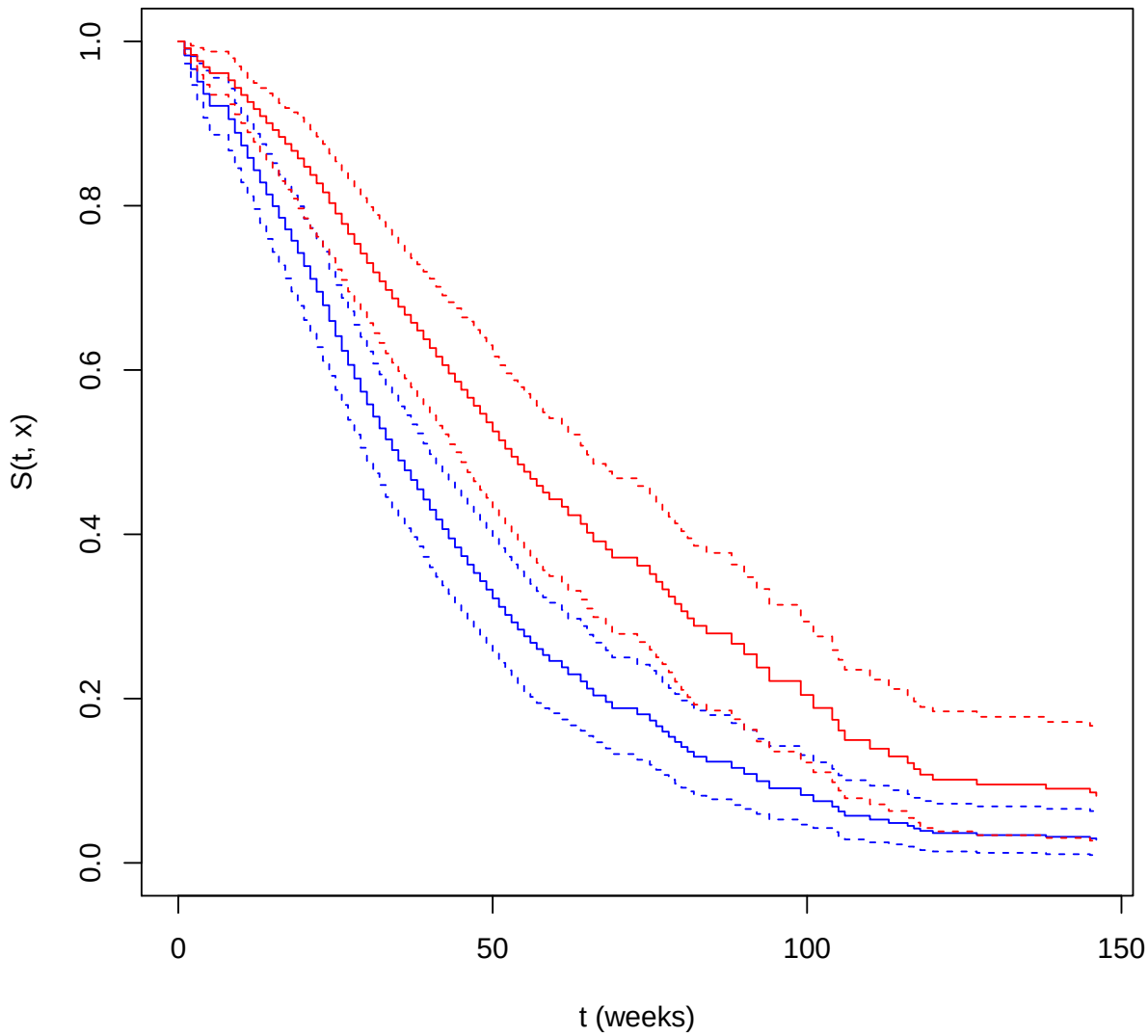
# Survival analysis: advanced lung cancer prognosis

Loprinzi et al. 1994 *JCO*

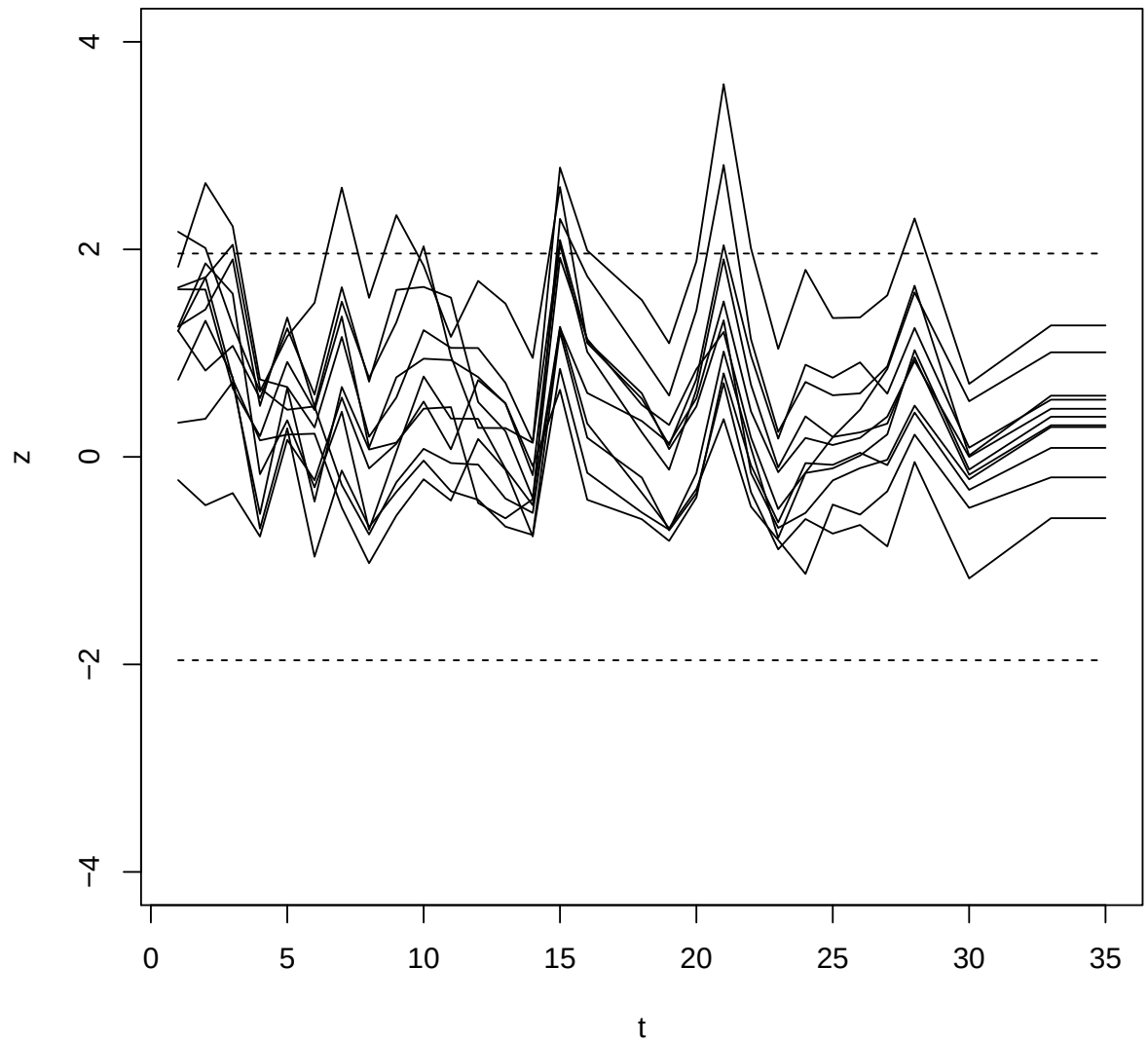
- The North Central Cancer Treatment Group surveyed 228 advanced lung cancer patients
- Study focused on prognostic variables
- Patient responses paired with some clinical variables
- We control for age, gender and Karnofsky performance score as rated by the physician
- We will compare males to females with Friedman's partial dependence function
- `lung` data set in the **BART** R package

```
system.file('demo/lung.surv.bart.R', package='BART')
system.file('demo/geweke.lung.surv.bart.R',
package='BART')
```

# Friedman's partial dependence function with 95% credible intervals: M (blue) vs. F (red)



# Geweke convergence diagnostics: Advanced lung cancer example



# Geweke convergence diagnostics: live demonstration

- `system.file('demo/geweke.surv.bart.R', package='BART')`
- Simulated data set: $N = 100, P = 20$
- $t_i \sim \mathbf{Wei}\left(2, \mathbf{e}^{f(x_i)}\right)$
- adapted from Friedman's five-dimensional test function *Annals of Statistics 1991*
- $f(x_i) = 3 + \sin(\pi x_1 x_2) - 2(x_3 - 0.5)^2 + x_4 - 0.5x_5$
- 20% censoring

# Diabetes and recurrent hospital admissions

- We have IRB approval to study a cohort of newly diagnosed diabetes patients from a single health care system
- We have the electronic health records (EHR) for these patients from 2007-2012: prior records may, or may not, be available
- EHR are an omnibus of digital health care information
- We focus on 82 covariates: patient demographics, health insurance, health care charges, diagnoses, procedures, anti-diabetic therapy, laboratory values and vital signs
- By its nature, EHR data is fundamentally time-varying
- EHR covariates are occasionally missing even when carrying the last value forward
- Imputed 15 continuous variables with Sequential BART (Xu, Daniels & Winterstein 2016 *Biostatistics*)

# Diabetes and recurrent hospital admissions

- 488 patients followed 5 years from 2008-2012
  the survival rate was high 0.939 (noninformative censoring)
  yet experienced a high rate of hospital admissions: 525 total
- For diabetes, which covariates increase the risk of admission? What about the number of previous admissions or an acutely recent admission?
- What are the functional forms of the covariates i.e. linear, quadratic, logarithm, etc.? Are the covariate effects additive or multiplicative?
- Are there interactions? Are these effects constant with respect to time, i.e., proportionality assumption?
- We want to avoid precarious restrictive assumptions hence we chose to use Bayesian Additive Regression Trees (BART)

# Recurrent event analysis with BART

Data: $(s_i, t_{i1}, \ldots, t_{iN_i}, x_i(t))$

$(0, t_{(1)}] \ldots (t_{(K-1)}, t_{(K)}]$: grid of distinct ordered times, $t_{ik}$

$$y_{ij}|p_{ij} \overset{\text{ind}}{\sim} \mathrm{B}(p_{ij}) \qquad j = 1, \ldots, J_i$$

$$y_{ij} = \max_{k=1,\ldots,N_i} \mathrm{I}\left(t_{ik} = t_{(j)}\right)$$

$$p_{ij} = \Phi(f(t_{(j)}, x_{ij})) \qquad f \overset{\text{prior}}{\sim} \mathbf{BART}$$

$$[y|p] = \prod_{i=1}^{N} \prod_{j=1}^{J_i} p_{ij}^{y_{ij}} (1 - p_{ij})^{1-y_{ij}} \qquad \text{Likelihood}$$

$$\Lambda(t_{(j)}, x_{ij}) = \int_0^{t_{(j)}} \mathrm{d}\Lambda(t, x_i(t)) = \sum_{j'=1}^{j} p_{ij'}$$

Discrete time intensity model $\Rightarrow$ longitudinal binary BART

# Semi-Markov process and conditional independence

- $(t_{i1}, \ldots, t_{iN_i})$ are not independent; rather, they are conditionally independent given $x_i(t)$ and the event history which is denoted by $N_i(t)$
- $N_i(t)$ is the counting process of events and $N_i \equiv N_i(s_i)$ When $N_i = 0$, then $t_{iN_i} = t_{i0} \equiv 0$
- Semi-Markov process, i.e., condition on summaries of the event history just prior to time $t$ which is denoted by $t-$

| | |
|---|---|
| Counting process just prior to time $t$ | $N_i(t-)$ |
| Sojourn time from the last event | $v_i(t) \equiv t - t_{iN_i(t-)}$ |

$$y_{ij}|p_{ij} \overset{\text{ind}}{\sim} \mathrm{B}\,(p_{ij})$$

$$p_{ij} = \Phi(f(t_{(j)}, \widetilde{x}_{ij}))$$

$$\text{where } \widetilde{x}_{ij} = \left[v_i(t_{(j)}), N_i(t_{(j-1)}), x_{ij}\right]$$

# Diabetes and recurrent hospital admissions

| | Patients | | Admissions | |
|---|---|---|---|---|
| Number of Admissions | 488 | | 525 | |
| 0 | 308 | (63.0) | 0 | |
| 1 | 79 | (16.2) | 79 | (15.0) |
| 2-3 | 50 | (10.3) | 115 | (21.9) |
| 4-16 | 51 | (10.5) | 331 | (63.1) |

# Diabetes and recurrent hospital admissions

- We focus on 82 covariates: patient demographics, health insurance, health care charges, diagnoses, procedures, anti-diabetic therapy, laboratory values and vital signs
- These covariates are inherently time-dependent and occasionally missing even when carrying the last value forward
- Imputed 15 continuous variables with Sequential BART
  8 lab values and 7 vital signs
  Xu, Daniels & Winterstein 2016 *Biostatistics*
- Variable selection: Decoupling Shrinkage and Selection (DSS)
  Hahn & Carvalho 2015 *JASA*; McCulloch et al. 2015 JSM
- Divided the cohort at random into training and validation sets
- Risk agonists: insulin treatment, peripheral vascular disease (PVD) and the number of previous admissions, $N_i(t-)$

# Diabetes and recurrent hospital admissions

| | Patients | | Admissions | |
|---|---|---|---|---|
| Gender | 488 | | 525 | |
| M | 216 | (44.3) | 228 | (43.4) |
| F | 272 | (55.7) | 297 | (56.6) |
| Race | 488 | | 525 | |
| Black | 174 | (35.7) | 265 | (50.5) |
| White | 314 | (64.3) | 260 | (49.5) |
| Age | 488 | | 525 | |
| Mean, SD | 60.9 | 15.0 | 60.3 | 15.7 |
| ZIP3 area | 488 | | 525 | |
| 532/urban | 378 | (77.5) | 454 | (86.5) |
| 530/suburb | 110 | (22.5) | 71 | (13.5) |
| Insurance and Age | 488 | | 525 | |
| Government 65+ | 191 | (39.1) | 224 | (42.7) |
| Government <65 | 138 | (28.3) | 208 | (39.6) |
| Commercial <65 | 143 | (29.3) | 71 | (13.5) |
| Other <65 | 16 | ( 3.3) | 22 | ( 4.2) |

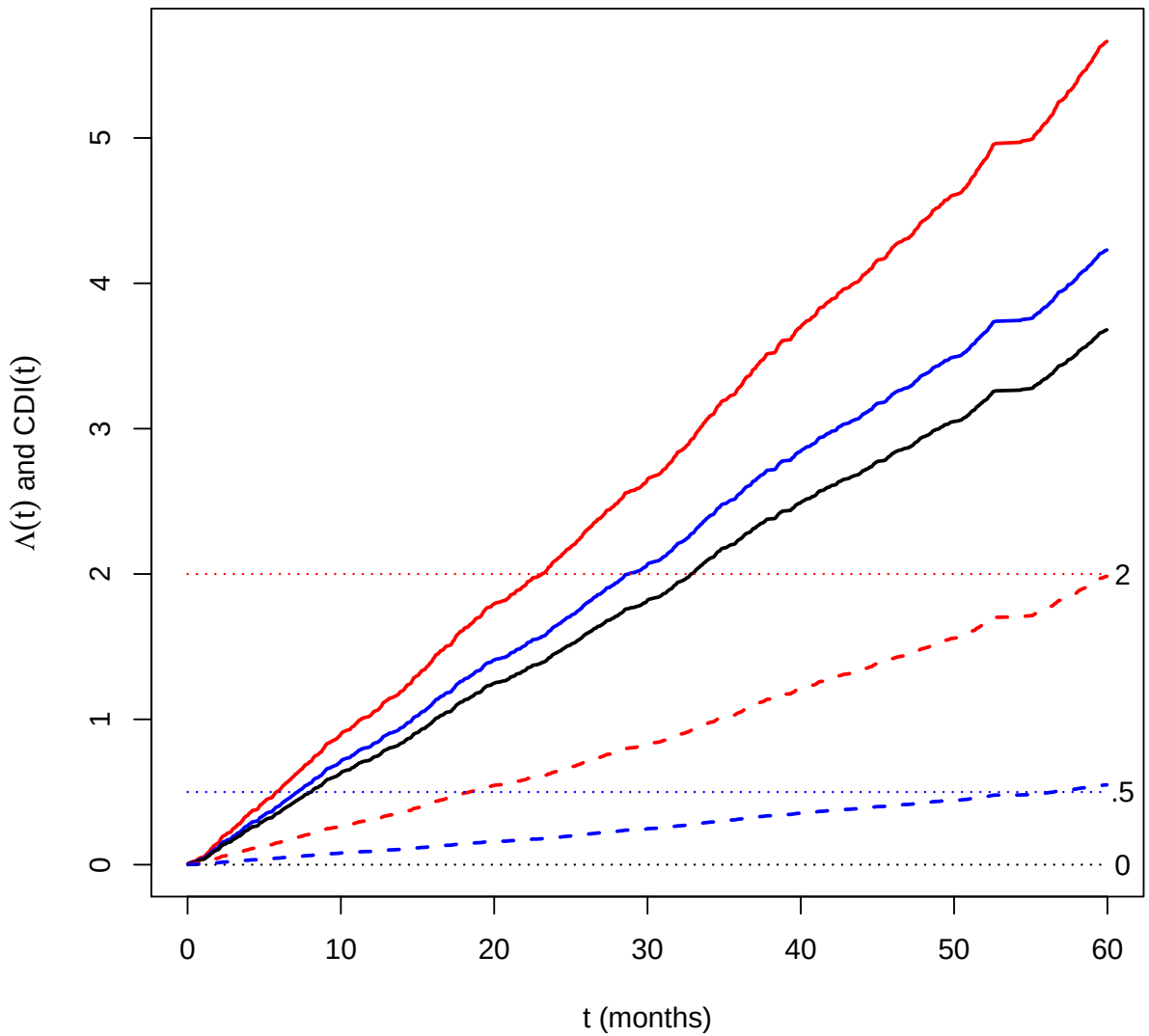
# Diabetes and recurrent hospital admissions

| | Patients | | Admissions | | Relative Intensity | 95% Credible Interval |
|---|---|---|---|---|---|---|
| Insulin | 488 | | 525 | | 2.39 | 1.56, 3.25 |
| Yes | 206 | (42.2) | 391 | (74.5) | | |
| No | 282 | (57.8) | 134 | (25.5) | | |
| PVD | 488 | | 525 | | 2.90 | 2.00, 3.89 |
| Yes | 272 | (55.7) | 488 | (93.0) | | |
| No | 216 | (44.3) | 37 | ( 7.0) | | |
| | | | | | partial dependence function | |

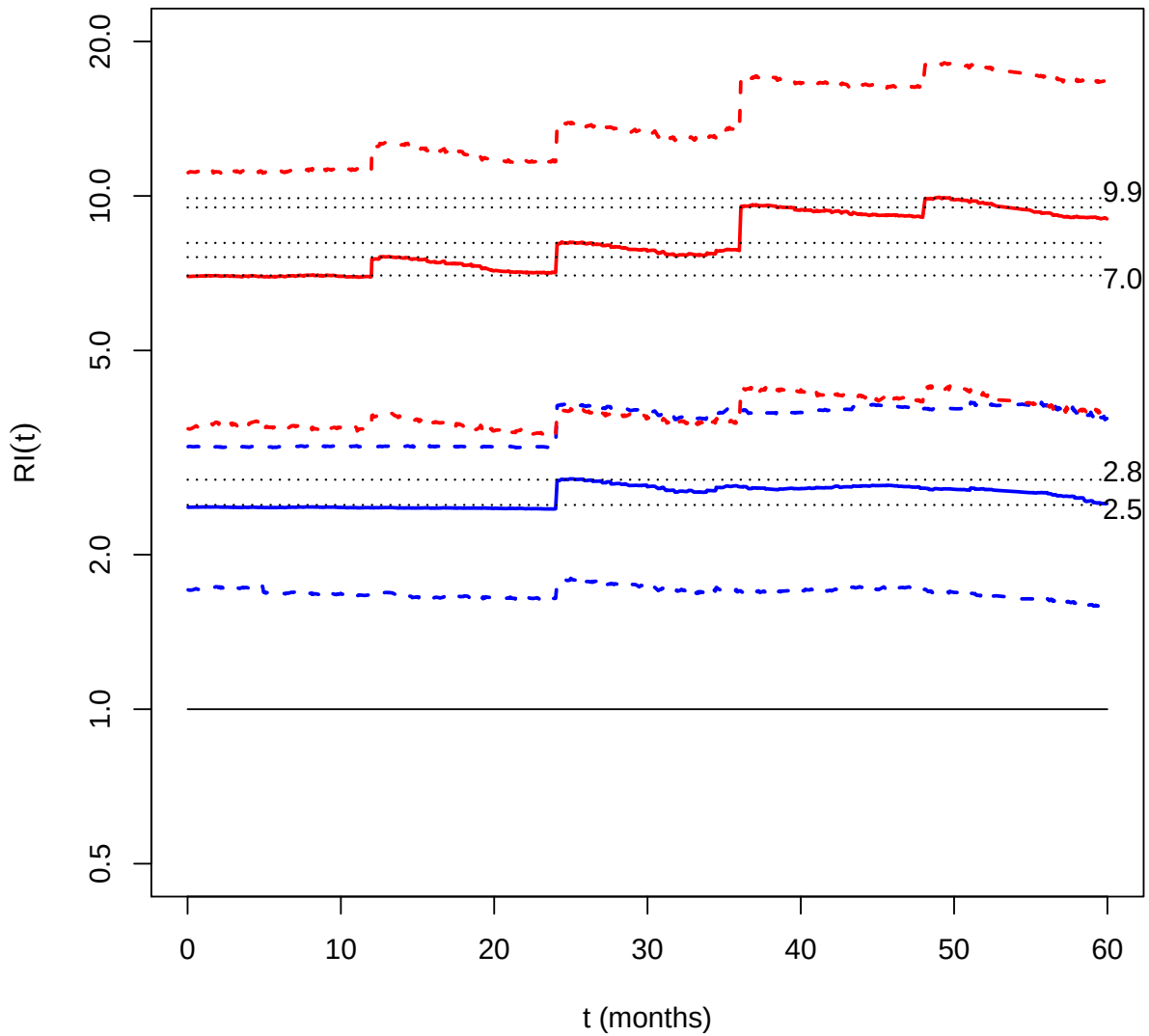
# Hospital admission risk profiles

| Risk | Insulin | PVD | $N_i(t)$ with time in months 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|---|---|
| Low | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Medium | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 |
| High | 1 | 1 | 0 | 1 | 2 | 3 | 4 | 4 |

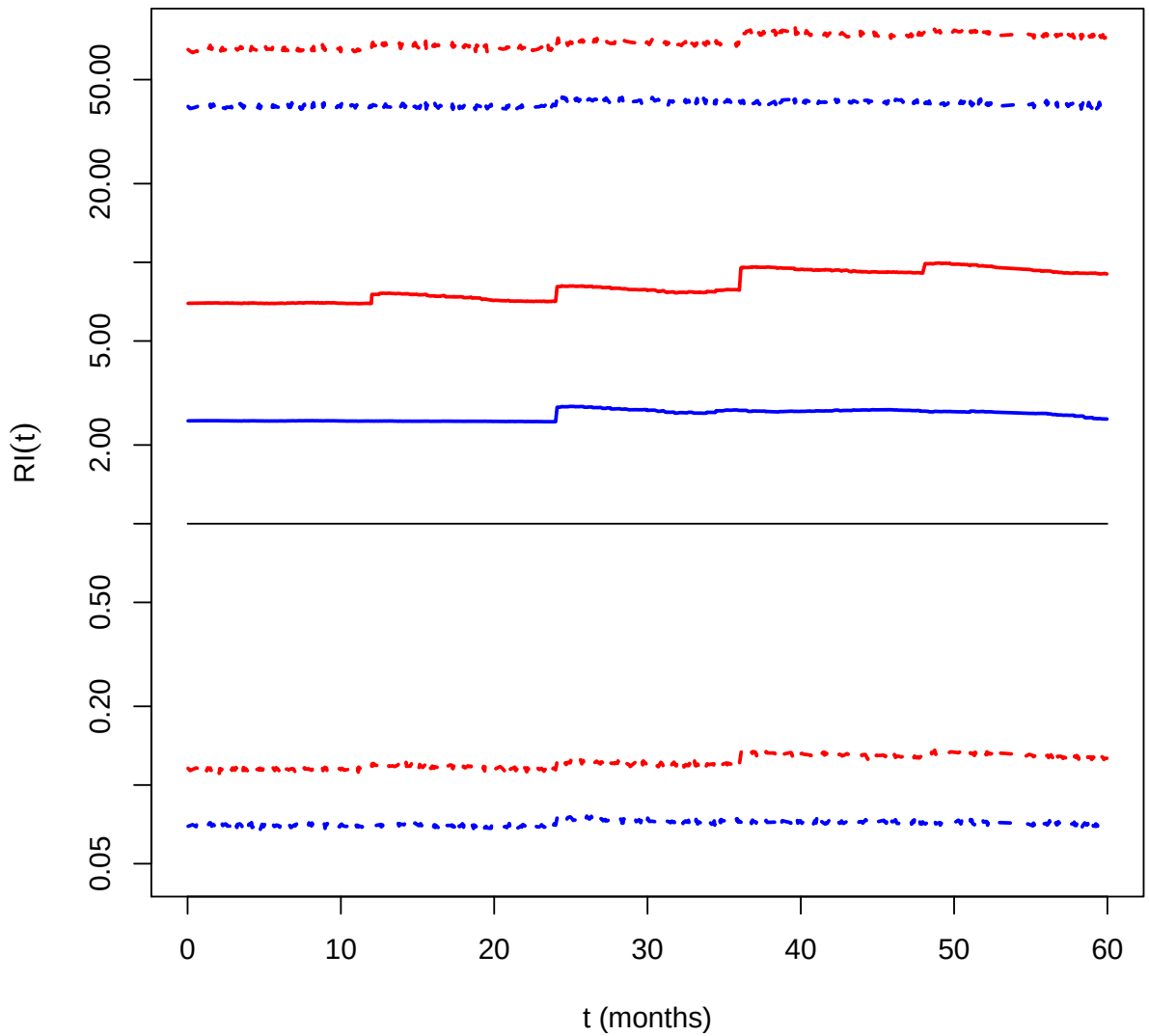
# Risk profiles: Cumulative Intensity partial dependence function



# Risk profiles: Relative Intensity and 95% Credible Intervals partial dependence function



# Risk profiles: Relative Intensity & 95% Prediction Intervals partial dependence function



# Diabetes and hospital admission risk

- Some diabetes patients are at high risk for hospital admission
  - diagnosed with PVD
  - prescribed insulin therapy
  - with a recent hospital admission
  - and/or several previous hospital admissions
- Health policy implications: Diabetic patients' health care post-discharge should be carefully orchestrated to ensure the delivery of quality clinical care which maximizes healthy outcomes while preventing adverse events and costly unnecessary hospital admissions
- **BART** package contains a roughly 20% random sample
  50 patients from training: `ydm20.train` & `xdm20.train`
  50 patients from validation: `xdm20.test`
- complete data set at `http://www.mcw.edu/FileLibrary/Groups/Biostatistics/TechReports/TechReports5175/tr064.tar`.

# Diabetes and hospital admission risk

- Acknowledgments and Disclaimers

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# Competing risks

Data: $(s_i, \delta_i, x_i(t))$ where $\delta_i \in \{0, 1, 2\}$

$0 = t_{(0)} < \cdots < t_{(K)} < \infty$: distinct ordered, $s_i$, times

$$
\begin{aligned}
y_{1ij} &= \mathrm{I}(\delta_i = 1)\,\mathrm{I}(j = J_i),\ j = 1, \ldots, J_i \\
y_{1ij} | p_{1ij} &\sim \mathrm{B}(p_{1ij}) \\
p_{1ij} &= \Phi(f_1(t_{(j)}, x_{ij})) \text{ where } f_1 \sim \text{BART} \\
y_{2ij} &= \mathrm{I}(\delta_i = 2)\,\mathrm{I}(j = J_i),\ j = 1, \ldots, K_i \\
&\quad \text{where } K_i = J_i - \mathrm{I}(\delta_i = 1) \\
y_{2ij} | p_{2ij} &\sim \mathrm{B}(p_{2ij}) \\
p_{2ij} &= \Phi(f_2(t_{(j)}, x_{ij})) \text{ where } f_2 \sim \text{BART}
\end{aligned}
$$

$$
[y|p] = \prod_{i=1}^{N} \left( \prod_{j=1}^{J_i} p_{1ij}^{y_{1ij}} (1 - p_{1ij})^{1 - y_{1ij}} \right)
$$

$$
\times \left( \prod_{j=1}^{K_i} p_{2ij}^{y_{2ij}} (1 - p_{2ij})^{1 - y_{2ij}} \right) \text{ Likelihood}
$$

# Competing risks

$$S(t, x_i(t)) = 1 - F(t, x_i(t)) = \prod_{j=1}^{k} (1 - p_{1ij})(1 - p_{2ij})$$

$$\text{where } k = \arg\max_j \left[ t_{(j)} \leq t \right]$$

$$F_1(t, x_i(t)) = \int_0^t S(u-, x_i(u-)) \lambda_1(u, x_i(u)) \mathrm{d}u$$

$$= \sum_{j=1}^{k} S(t_{(j-1)}, x_i(t_{(j-1)})) p_{1ij}$$

$$F_2(t, x_i(t)) = \int_0^t S(u-, x_i(u-)) \lambda_2(u, x_i(u)) \mathrm{d}u$$

$$= \sum_{j=1}^{k} S(t_{(j-1)}, x_i(t_{(j-1)})) (1 - p_{1ij}) p_{2ij}$$

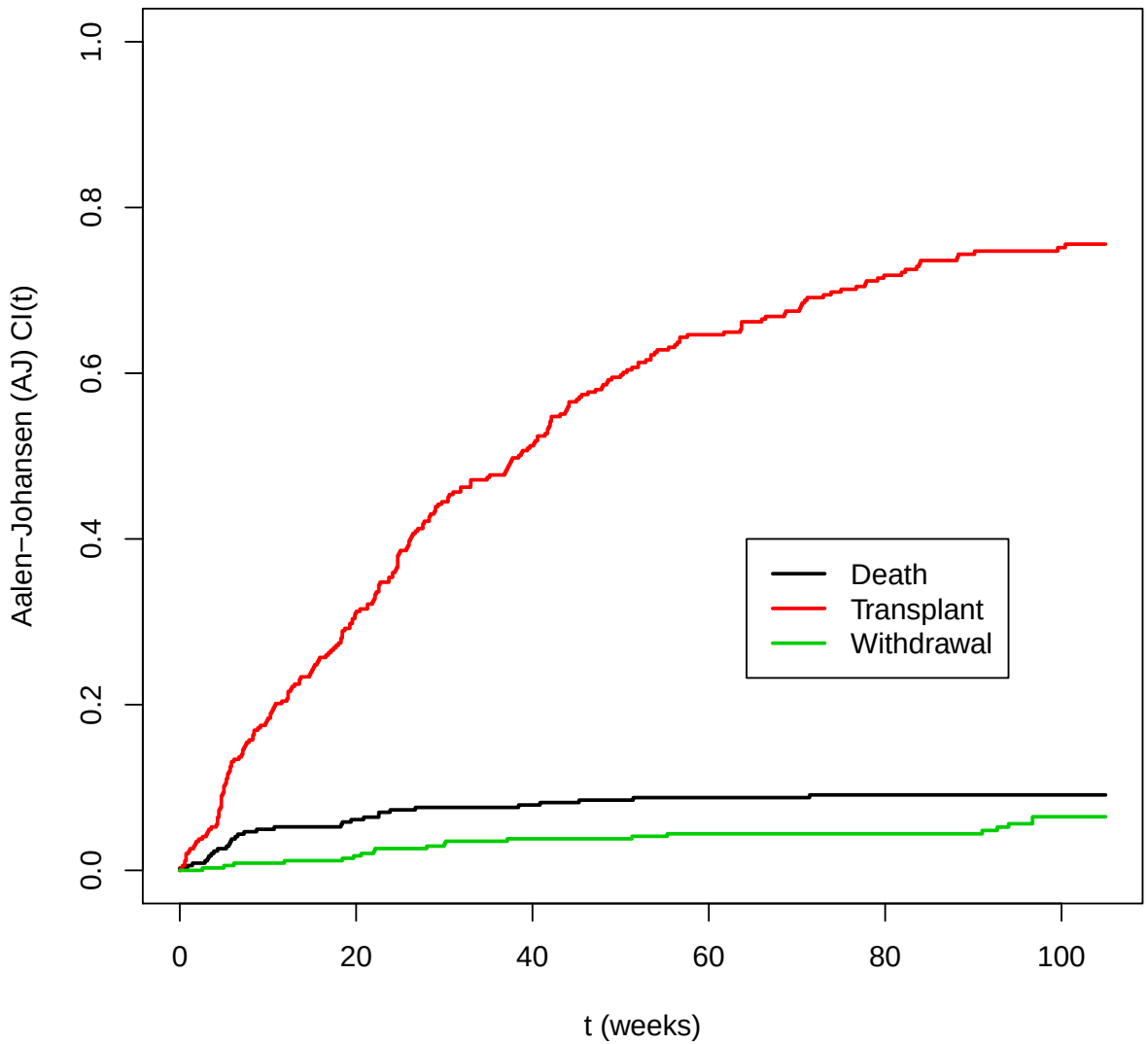
# Liver transplant

Kim et al. 2006 *Hepatology*

- Mayo Clinic Liver transplant waiting list data from 1990-1999
- During this period, liver allocation policy was flawed
- Donor livers from subjects with blood type O can be used by patients with A, B, AB or O blood types, whereas an A, B, AB liver can only be used by an A, B, AB recipient respectively
- Type O subjects on the waiting list were at a disadvantage since the pool of competitors was larger for type O donor livers
- Current policies have evolved and now depend on each individual patient's risk and need which are assessed and updated regularly while a patient is on the waiting list
- However, the overall donor liver shortage remains acute today
- `transplant` data set in **BART** R package: $N = 815$
- `system.file('demo/liver.crisk.bart.R', package='BART')`

# Liver transplant Competing Risks for Type O patients

## Aalen-Johansen estimator available in **survival** R package



# Liver transplant Competing Risks for Type O patients
# Aalen-Johansen and BART