

# Joint Modelling of Longitudinal Measurements and Survival Outcomes

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# Outline

- **Joint modelling:**
  - what is it?
  - why do it?
- **Modelling longitudinal measurements**
- **Modelling survival outcomes**
- **Joint modelling**
  - transformation models
  - random effects models
- **Examples**
- **Conclusions**

## Joint modelling: what is it?

- Subjects  $i = 1, \dots, m$ .
- Longitudinal measurements  $Y_{ij}$  at times  $t_{ij}$ .
- Times-to-event  $S_i$  (possibly censored).
- Baseline covariates  $x_i$ .
- Parameters  $\theta$ .

$$[Y, S | x, \theta]$$

## AIDS data

- Data from RCT of three different drug regimes for HIV+ patients.
  - 1 = zidovudine, 600mg
  - 2 = didanosine, 500mg
  - 3 = didanosine, 750mgTotal  $n = 913$  subjects.
- $S$  = time of progression to AIDS or death
- $Y$  = time-sequence of CD4 measurements (weeks 0, 2, 6, 12, 18, 24)
- $S > 24$  for most subjects (long-term follow-up)
- 334 observed event-times, 579 censored

## Schizophrenia data

- Data from placebo-controlled RCT of drug treatments for schizophrenia:
  - Placebo
  - Haloperidol (standard)
  - Risperidone (novel)

Total  $n = 517$  subjects.

- $Y =$  PANSS measurement (weeks -1, 0, 1, 2, 4, 6, 8)
- $S =$  dropout time
- High dropout rates:

week	-1	0	1	2	4	6	8
missing	0	3	9	70	122	205	251
proportion	0.00	0.01	0.02	0.14	0.24	0.40	0.49

- Dropout rate also treatment-dependent ( $P > H > R$ )

## Heart surgery data

- RCT to compare two types of artificial heart-valve
  - homograft
  - stentless
- $Y$  = time-sequence of left-ventricular-mass-index (LVMI)
- $S$  = time of death

Is a patient's longitudinal LVMI profile predictive of their survival prognosis?

## Joint modelling: why do it?

To analyse survival time  $S$ , whilst exploiting correlation with an imperfectly measured, time-varying risk-factor  $Y$

Example: AIDS data

- interest is in time to progression/death
- but long latency period implies heavy censoring
- hence, joint modelling improves inferences about marginal distribution  $[S]$

To analyse a longitudinal outcome measure  $Y$  with potentially informative dropout at time  $S$

Example: Schizophrenia data

- interest is reducing mean PANSS score
- but informative dropout process would imply that modelling only  $[Y]$  may be misleading

Because the relationship between  $Y$  and  $S$  is of intrinsic interest

Example: heart surgery data

- long-term build-up of left-ventricular muscle mass may increase hazard for fatal heart-attack
- hence, interested in modelling relationship between survival and subject-level LVMI

Scientific goal affects choice of statistical model/method?

# Modelling longitudinal measurements

## The Gaussian linear model

- $(Y_{ij}, t_{ij}) : j = 1, \dots, n_i; i = 1, \dots, m \quad \mu_{ij} = \mathbf{E}[Y_{ij}]$
- $Y_i = (Y_{i1}, \dots, Y_{in_i}) \quad Y = (Y_1, \dots, Y_m)$
- $t_i = (t_{i1}, \dots, t_{in_i}) \quad t = (t_1, \dots, t_m)$

$$Y \sim \text{MVN}\{X\beta, V(\phi)\}$$

$$V(\phi) = \begin{bmatrix} V_1 & 0 & \dots & 0 \\ 0 & V_2 & \dots & \vdots \\ \vdots & \dots & & 0 \\ 0 & \dots & 0 & V_m \end{bmatrix}$$

## Modelling longitudinal measurements

### Specifying the covariance structure

$$Y_{ij} = \mu_{ij} + U_i + W_i(t_{ij}) + Z_{ij}$$

Corresponds to within-subject variance matrices

$$V_i = \nu^2 J + \sigma^2 R(t_i) + \tau^2 I$$

where  $R(t_i)$  has elements  $R_{jk} = \rho(|t_{ij} - t_{ik}|)$ .

# Modelling longitudinal measurements

## The variogram

$$V(u) = \frac{1}{2} \text{Var}\{Y(t) - Y(t - u)\}$$

- useful data-analytic tool for irregularly spaced, incomplete data
- theoretical form for model on previous slide

$$V(u) = \tau^2 + \sigma^2\{1 - \rho(u)\}$$

## Modelling survival outcomes

Fundamental tool is the hazard function,

$$h(s) = f(s) / \{1 - F(s)\}$$

## Modelling strategies

- **Proportional hazards**

$$h_i(s) = h_0(s)\theta_i \quad \theta_i = \exp(\mathbf{x}'_i\beta)$$

- **Accelerated life**

$$F_i(s) = F_0(\theta_i s) \quad \theta_i = \exp(\mathbf{x}'_i\beta)$$

- **Frailty**

$$h_i(s) = h_0(s)\theta_i U_i \quad \theta_i = \exp(\mathbf{x}'_i\beta) \quad U_i \sim G(u)$$

## Modelling strategies (continued)

- **Parametric**

$$S \sim f(s; \theta) \quad \theta_i = \exp(\mathbf{x}'_i \boldsymbol{\beta})$$

- $S \sim \text{Gamma}(\lambda, \kappa)$  : proportional hazards ( $\kappa$  known)

- $\log S \sim \text{N}(\mu, \sigma^2)$  : accelerated life

- $S \sim \text{Weibull}(\lambda, \delta)$  : proportional hazards and accelerated life

## Joint modelling

### Considerations to inform choice of approach

- focus on questions of primary scientific interest
- interpretability of model parameters
- statistical efficiency
- diagnostic checks for assumptions about effects of primary interest
- robustness to departures from assumptions about effects not of primary interest
- ease of implementation
- reduction to standard methods when there is no association

## Joint modelling

### Transformation models

$$(\log S, Y) \sim \text{MVN}(\mu, \Sigma)$$

- $\mu = (\mu_S, \mu_Y)$
- $\Sigma = \begin{bmatrix} \sigma^2 & \gamma' \\ \gamma & V(\phi) \end{bmatrix}$
- subjects provide independent replicates of  $(\log S, Y)$

## Transformation models: the likelihood function

### Standard result:

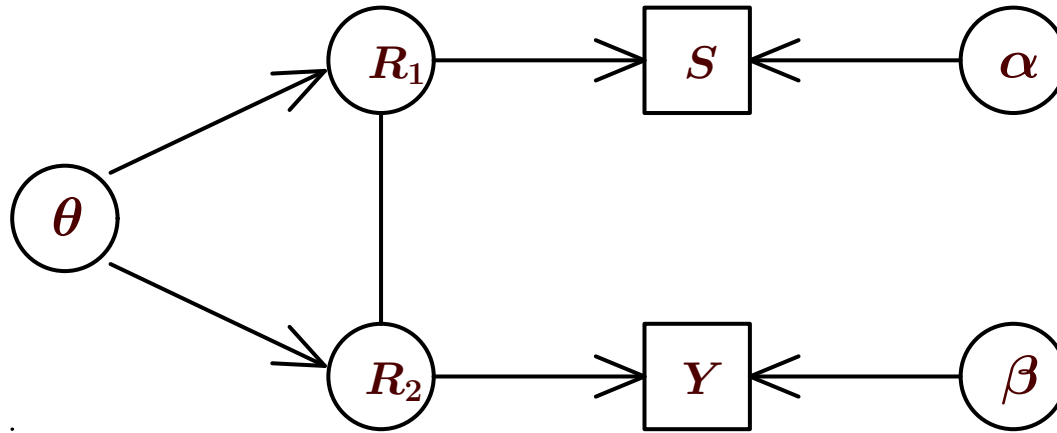
- $\log S|Y \sim N(\mu_{S|Y}, \sigma_{S|Y}^2)$
- $\mu_{S|Y} = \mu_S + \gamma'V(\phi)^{-1}(Y - \mu_Y)$
- $\sigma_{S|Y}^2 = \sigma^2 - \gamma'V(\phi)^{-1}\gamma$

### Likelihood contribution from $i$ th subject:

- uncensored  $S_i$ :  
  $[Y_i] \times [\log S_i|Y_i]$  (multivariate Gaussian pdf)
- censored  $S_i$ :  
  $[Y_i] \times \{1 - \Phi((\log S_i - \mu_{S|Y_i})/\sigma_{S|Y})\}$  (pdf times tail probability)

## Joint modelling

### Random effects models



# Formulation of random effects models

## Latent stochastic process

Bivariate Gaussian process  $R(t) = \{R_1(t), R_2(t)\}$

- $R_k(t) = D_k(t)U_k + W_k(t)$
- $\{W_1(t), W_2(t)\}$ : bivariate stationary Gaussian process
- $(U_1, U_2)$ : multivariate Gaussian random effects

Bivariate process  $R(t)$  is realised independently between subjects

## Measurement sub-model

$$Y_{ij} = \mu_i(t_{ij}) + R_{1i}(t_{ij}) + Z_{ij}$$

- $Z_{ij} \sim \text{N}(0, \tau^2)$
- $\mu_i(t_{ij}) = X_{1i}(t_{ij})\beta_1$

## Hazard sub-model

$$h_i(t) = h_0(t)\mathcal{F}\{X_2(t)\beta_2 + R_{2i}(t)\}$$

- $h_0(t)$  = non-parametric baseline hazard
- $\eta_2(t) = X_{2i}(t) + R_{2i}(t)$  = linear predictor for hazard
- typical choice  $\mathcal{F}(\cdot) = \exp(\cdot)$

## Random effects models: the likelihood function

- conditional independence:  $S \perp Y | R$
- standard Gaussian marginal:  $[Y], L_1(\theta; Y)$
- Gaussian conditional:  $[R|Y]$
- standard conditional:  $[S|R], L_2(\theta; S|R)$
- selection factorisation

$$\begin{aligned} [Y, S] &= \int [Y, S, R] dR \\ &= \int [Y] [R|Y] [S|R, Y] dR \\ &= [Y] \int [R|Y] [S|R] dR \end{aligned}$$

$$L(\theta; Y, S) = L_1(\theta; Y) \times \mathbf{E}_{R|Y}[L_2(\theta; S|R)]$$

## Evaluating the likelihood function

$$L(\theta; Y, S) = L_1(\theta; Y) \times \mathbf{E}_{R|Y}[L_2(\theta; S|R)]$$

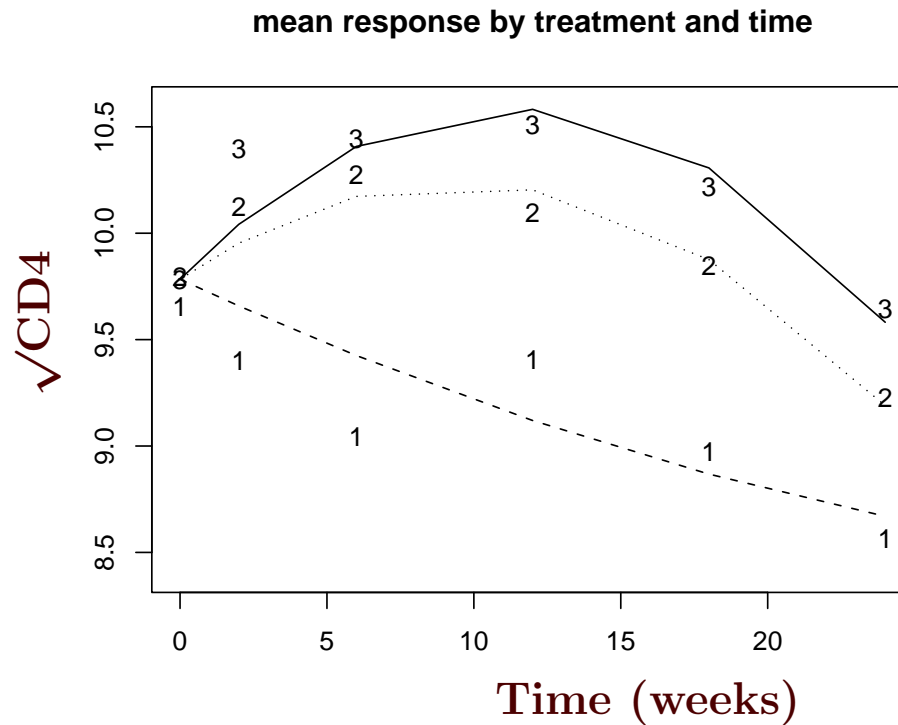
- $R$  is infinite-dimensional, but
- non-parametric specification of  $h_0(\cdot)$  implies we only need  $R$  at event-times
- Monte Carlo evaluation of expectation term
- explicit EM evaluation possible in useful special cases (eg Wulfsohn and Tsiatis, 1997)

## Examples

- AIDS data (transformation model)
- Schizophrenia data (random effects model)
- Heart surgery data (random effects model?)

# AIDS data

## Mean square-root CD4



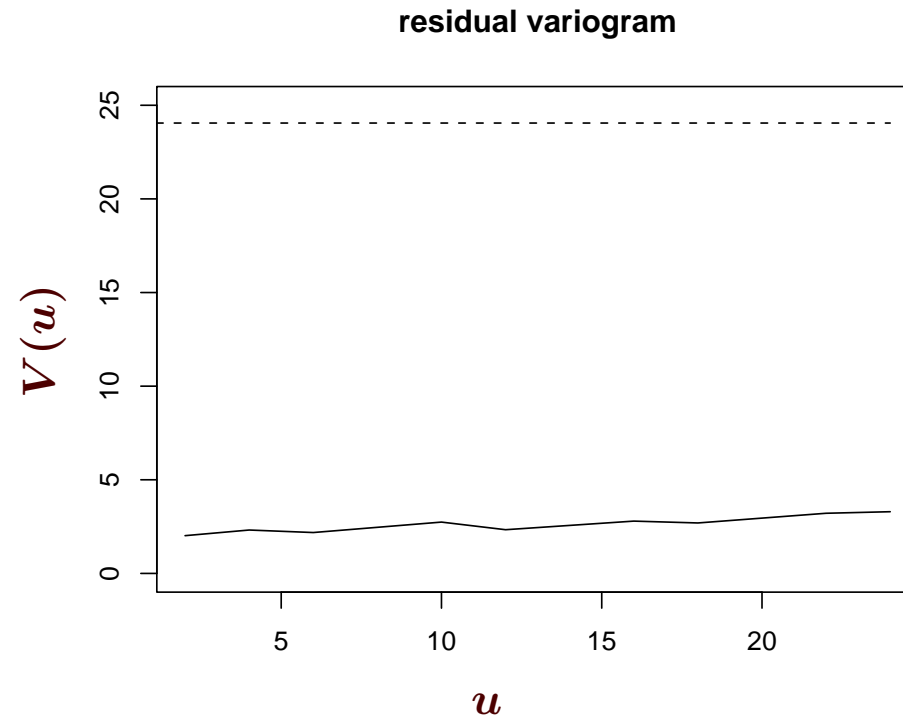
Fitted lines are quadratics with common intercept

## Covariance structure

- Variance matrix of OLS residuals from saturated treatments-by-times model

17.94	18.26	18.53	18.80	18.47	18.01
18.26	22.86	21.02	21.32	20.94	20.57
18.53	21.02	23.95	22.47	22.02	21.76
18.80	21.32	22.47	25.01	22.60	22.54
18.47	20.94	22.02	22.60	24.67	22.20
18.01	20.57	21.76	22.54	22.20	24.64

- Variogram tells similar story: dominant source of variation is between subjects



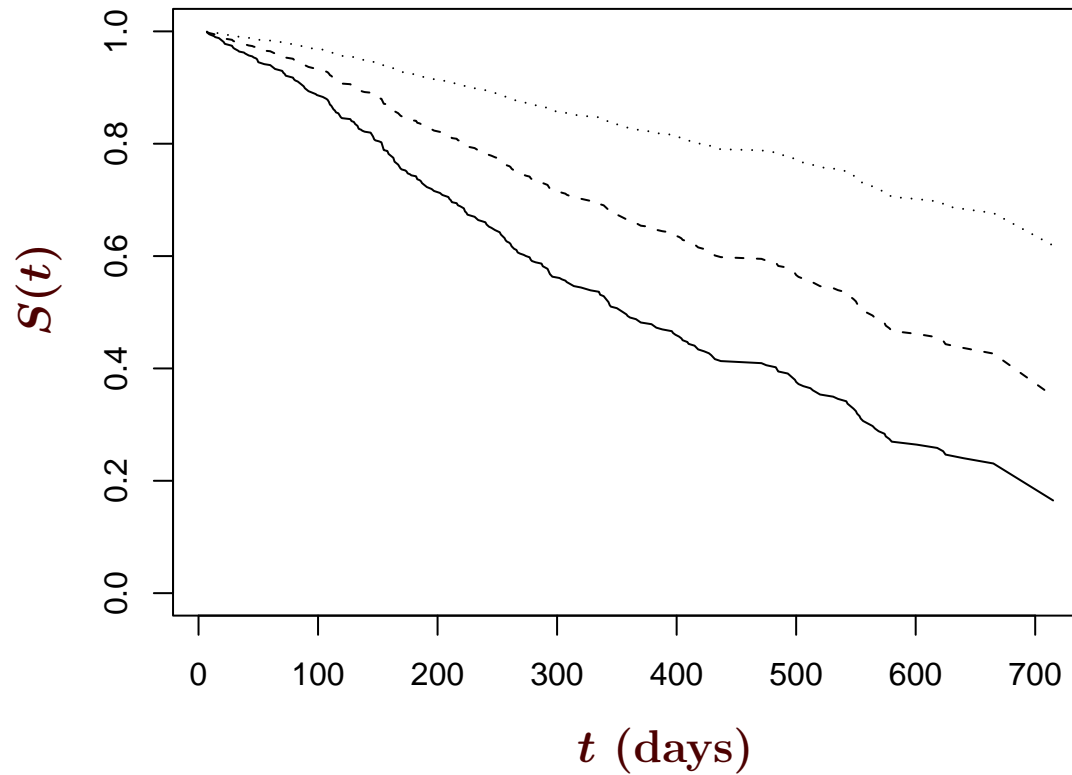
$R(t)$  = residual at time  $t$

$$V(u) = \frac{1}{2} \text{Var}\{R(t) - R(t - u)\}$$

# AIDS data

## Baseline CD4 and time to progression/death

Fitted  $S(t)$  at quartiles of baseline CD4



## Model formulation

- exchangeable covariance structure for  $Y$
- non-parametric specification of  $\text{Cov}(\log S, Y)$
- mean  $\sqrt{\text{CD4}}$  quadratic in time within each treatment group
- linear covariate adjustments

## Maximum likelihood estimation

- **Treatment contrasts:**

$\theta_{2-1}, \theta_{3-1}$  : contrasts in mean  $\log S$

$\theta_{2-1}^*, \theta_{3-1}^*$  : contrasts in mean  $Y$  at 24 weeks

Scale	parameter	estimate	std. error	correlation
$\log S$	$\theta_{2-1}$	0.351	0.129	
	$\theta_{3-1}$	0.222	0.126	0.486
$Y$	$\theta_{2-1}^*$	0.981	0.439	
	$\theta_{3-1}^*$	1.003	0.362	0.423

- Covariance structure

$$\text{Var}(Y) = \tau^2 I + \nu^2 J$$

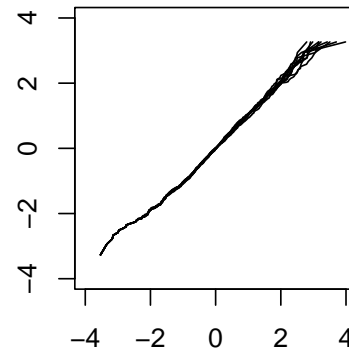
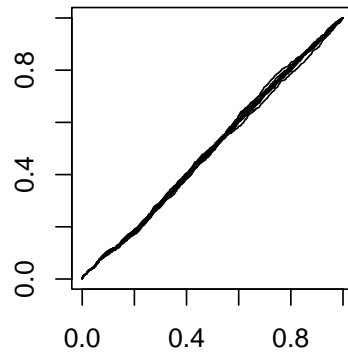
$$\text{Var}(\log S) = \sigma^2$$

$$\text{Corr}(\log S, Y_j) = \rho_j$$

Parameter	estimate	std. error
$\tau^2$	2.432	0.057
$\nu^2$	16.723	0.808
$\sigma^2$	1.653	0.145
$\rho_1$	0.428	0.038
$\rho_2$	0.468	0.035
$\rho_3$	0.467	0.035
$\rho_4$	0.457	0.036
$\rho_5$	0.520	0.035
$\rho_6$	0.509	0.038

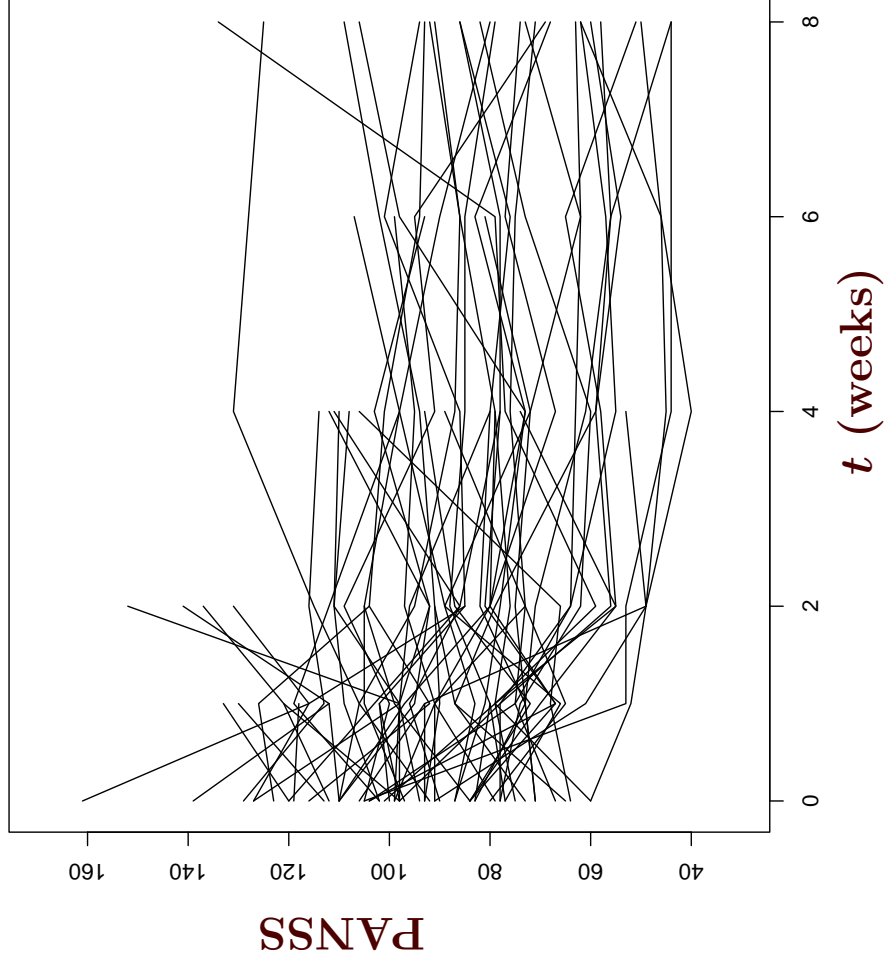
## Goodness-of-fit

- Focus on conditional distribution of  $\log S$  given  $Y$
- Gaussian P-P and Q-Q plots with multiple imputation of censored  $\log S$



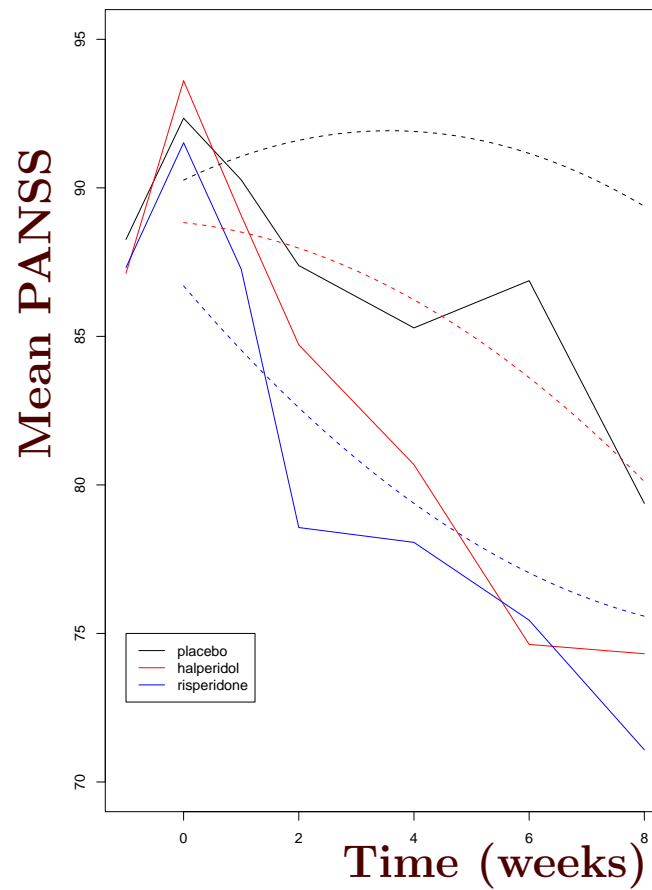
## Schizophrenia data

PANSS responses from haloperidol arm

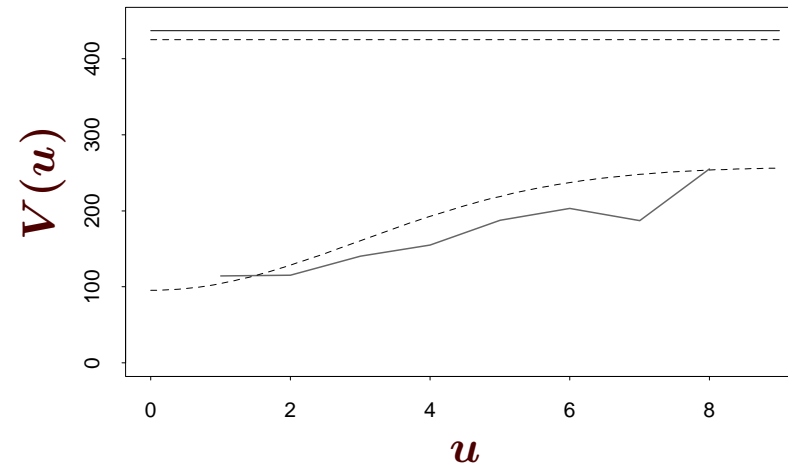


# Schizophrenia data

## Mean response

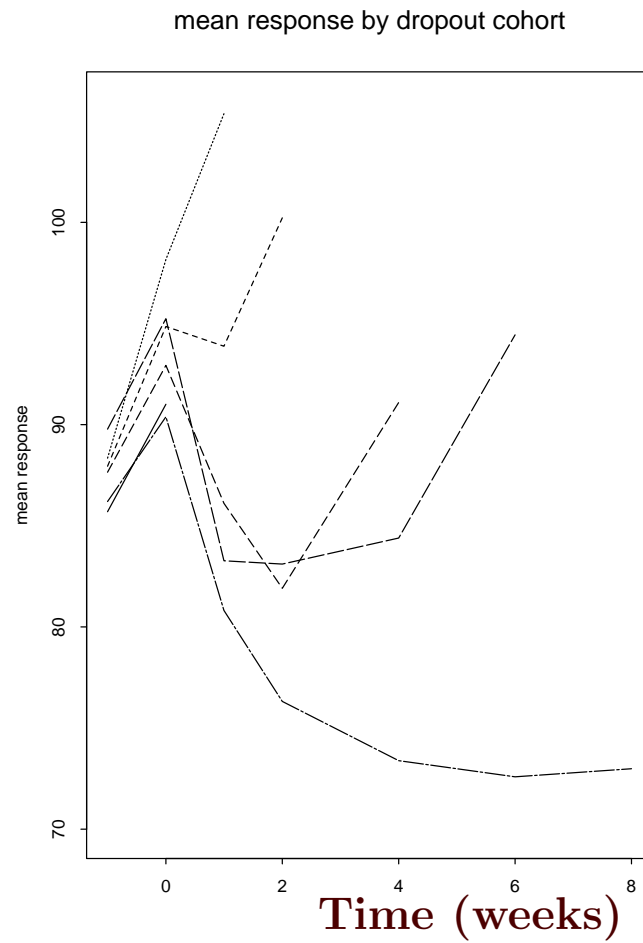


## Empirical and fitted variograms



Apparently fits well, but hard to distinguish empirically from random intercept and slope model.

# Mean response by dropout cohort



## Model formulation

### Measurement sub-model

For subject in treatment group  $k$ ,

$$\mu_i(t) = \beta_{0k} + \beta_{1k}t + \beta_{2k}t^2$$

$$Y_{ij} = \mu_i(t_{ij}) + R_{1i}(t_{ij}) + Z_{ij}$$

### Hazard sub-model

For subject in treatment group  $k$ ,

$$h_i(t) = h_0(t) \exp\{\alpha_k + R_{2i}(t)\}$$

Latent process

Two choices for measurement process component

$$R_1(t) = U_1 + W_1(t)$$

$$R_1(t) = U_1 + U_2 t$$

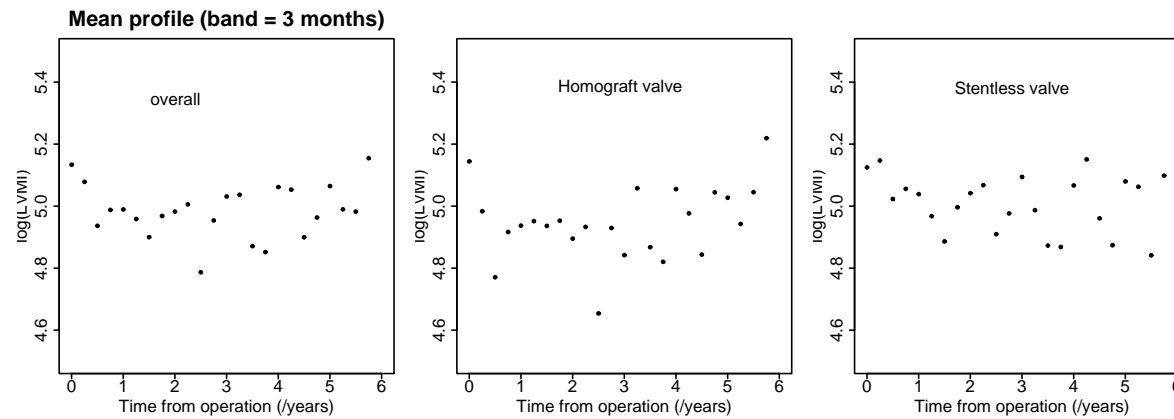
And for hazard process component

$$R_2(t) = \gamma_1 R_1(t)$$

$$R_2(t) = \gamma_1 (U_1 + U_2 t) + \gamma_2 U_2$$

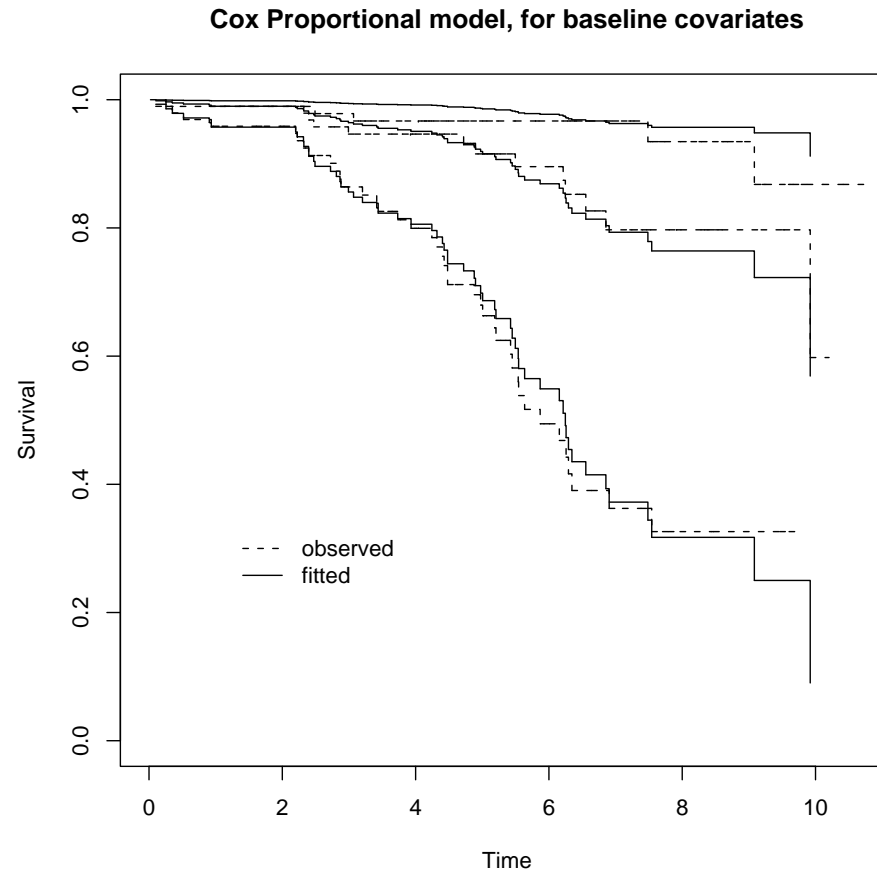
# Heart surgery data

## Mean log-LVMI response profiles



# Heart surgery data

## Survival curves adjusted for baseline covariates



# Heart surgery data

## Hypothesis

- subjects who regress after surgery (increasing LVMI) are at greater risk of heart attack

## Exploratory analysis

- overall mean  $\log(\text{LVMI})$  decreases initially after surgery, then remains approximately constant
- but some patients regress (increasing LVMI)
- time-averaged  $\log(\text{LVMI})$  is associated with increased hazard

## Random effects joint model for heart surgery data

$$Y_{ij} = \begin{cases} \mu(t_{ij}) + A_i + W_i(t_{ij}) + Z_j & : t \leq \tau \\ \mu(t_{ij}) + (A_i + \{B_i(t - \tau)\}) + W_i(t_{ij}) + Z_j & : t > \tau \end{cases}$$

$$h_i(t) = h_0(t) \exp(x'_i \beta + B_i)$$

- surgery has immediate beneficial effect on all patients
- patient outcomes diverge after time  $\tau$  post-surgery
- hazard for survival depends on **slope** of LVMI after time  $\tau$

## Conclusions

- Choice of model/method should relate to scientific purpose.
- Simple models/methods are useful when exploring a range of modelling options, for example to select from amongst potential covariates.
- Complex models/methods are useful when seeking to understand subject-level stochastic variation.
- Flat likelihoods are common: different models may fit the data almost equally well.
- We need an R library.

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