Joint models for discrete longitudinal outcomes in ageing research

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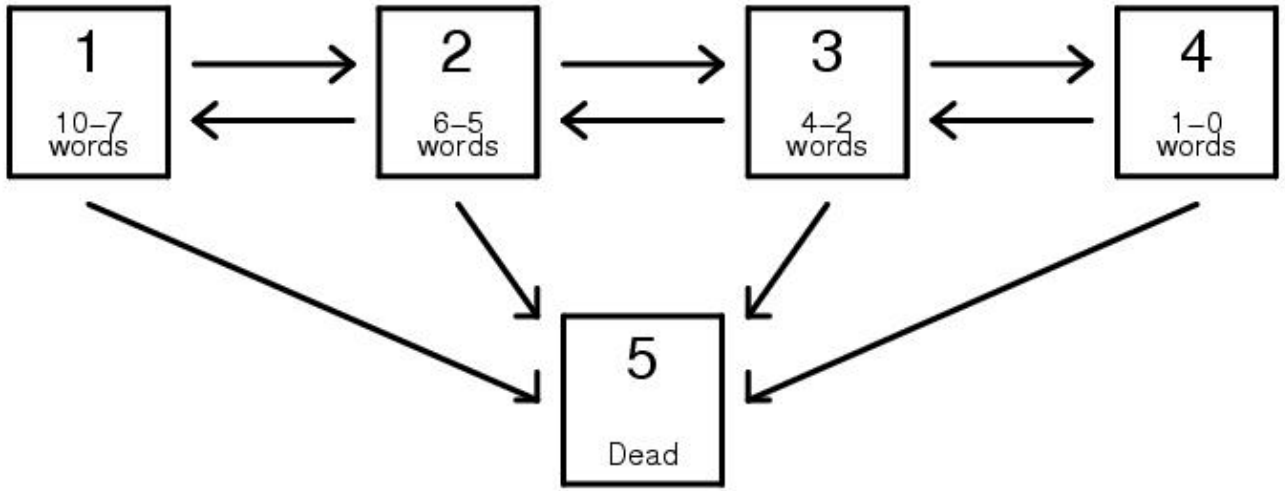
1. Research interest & data
2. Multi-state survival models
3. Joint models using a shared-parameter approach
4. Conclusion

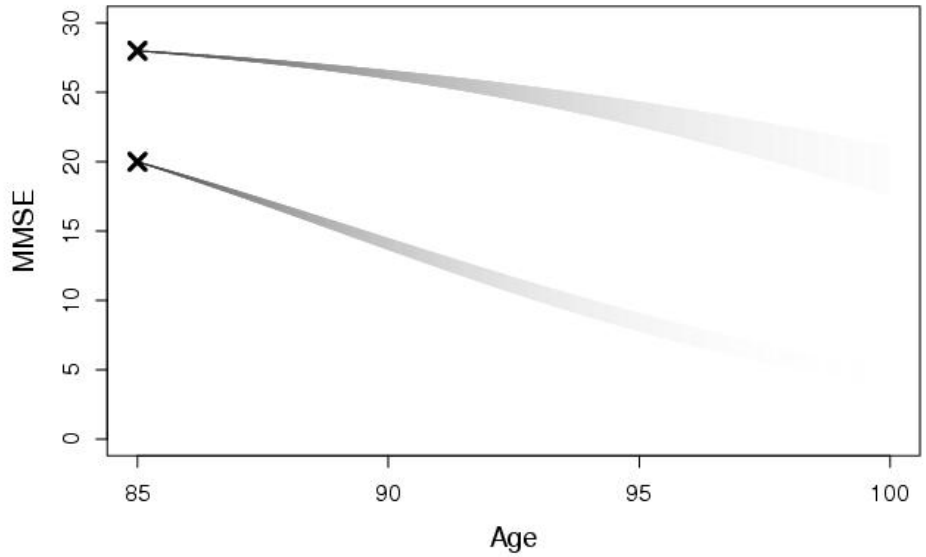
1. Research interests & data

- UK population is ageing
- Statistical modelling of the ageing process is of interest: understanding and prediction
- Wider scope of modelling: planning future health care
- Today: cognitive function. Response often discrete

- Analysis of longitudinal data for ageing processes cannot ignore dropout due to death
- One option: use a multi-state survival model
- Example for number of words remembered:



- Another option: link a model for the process of interest with a model for survival
- Example: cognitive function using the Mini-Mental State Examination (MMSE). Ceiling effects very common



MMSE prediction

Fade out for survival probability

Random effects link measurement model and survival

Longitudinal data

- MRC Cognitive Function and Ageing Study (CFAS, `www.cfas.ac.uk`)
- Cambridge City over-75s Cohort Study (CC75C, `www.cc75c.group.cam.ac.uk`)
- English Longitudinal Study of Ageing (ELSA, `www.ifs.org.uk/ELSA`)

2. Multi-state survival models

- Using theory for continuous-time stochastic process
- Regression models for transition intensities (hazards)
- Approximate time-dependency by piecewise-constant intensities
- Likelihood for interval-censored data constructed using transition probabilities for time intervals. Known time of death can be accounted for

(Cox & Miller 1965; Kalbfleisch & Lawless 1985; Jackson 2011)

- Regression models
  - Individual i at age t_i
  - Hazard model for transition from state r to state s is

$$h_{rs}(t_i) = h_{rs.0}(t_i) \exp(\boldsymbol{x}_i^\top \boldsymbol{\beta}_{rs})$$

  - Parametric baseline hazards can be chosen from, e.g.,

$$\begin{aligned} \text{Weibull:} \quad h_{rs.0}(t) &= \lambda_{rs}\tau_{rs}t^{\tau_{rs}-1} \\ \text{Gompertz:} \quad h_{rs.0}(t) &= \lambda_{rs}\exp(\xi_{rs}t) \end{aligned}$$

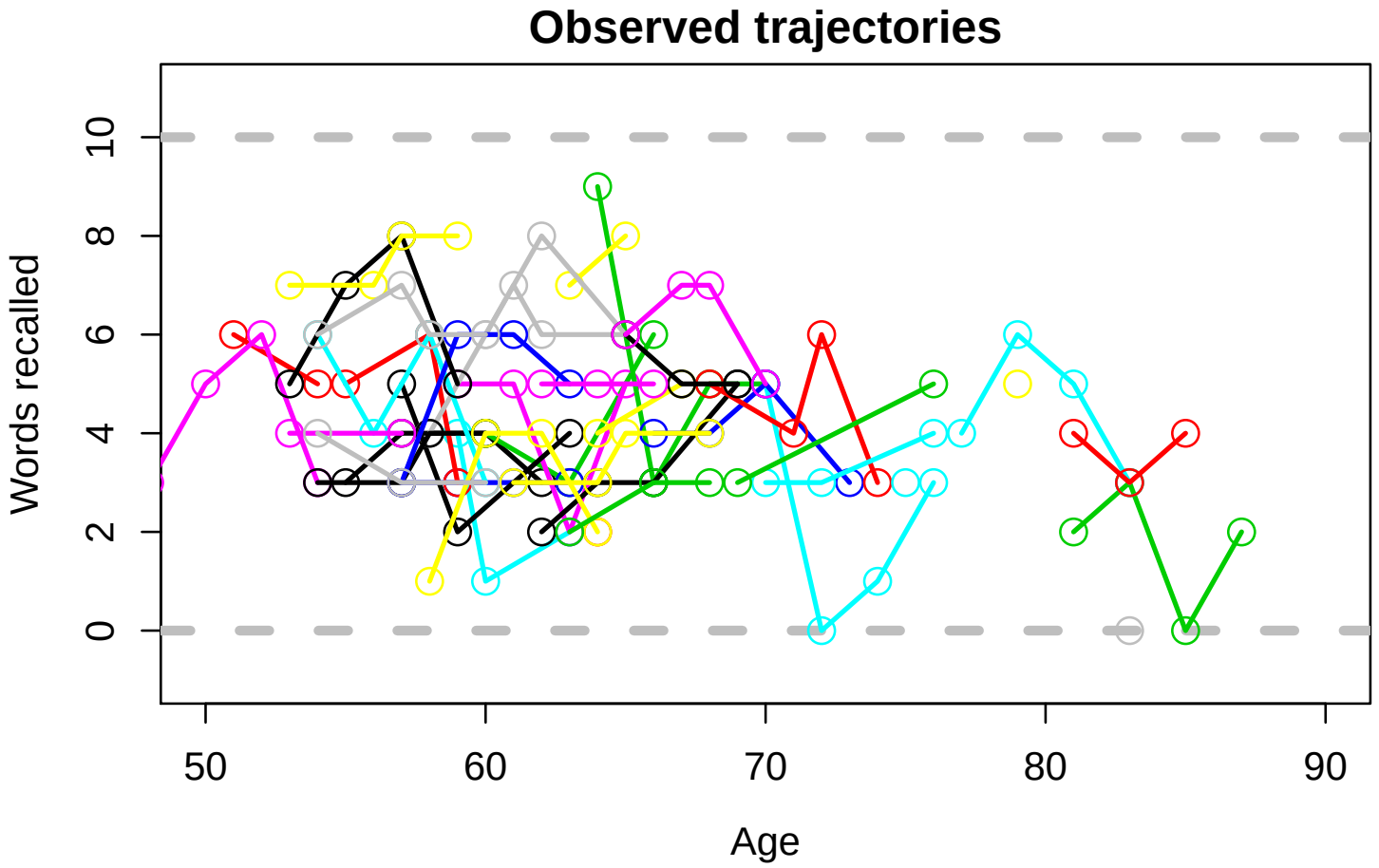
  - Choose parametric shape because of prediction

- Approximate shape by piecewise-constant intensities
  - Example: for observation times $t_{i1}, t_{i2}, t_{i3}, t_{i4}$ hazards are held constant within $(t_{i1}, t_{i2}]$, $(t_{i2}, t_{i3}]$, and $(t_{i3}, t_{i4}]$
  - When time between end of follow-up and death is long, impose grid (Van den Hout & Matthews 2009)
- For maximum likelihood, transition probabilities derived from transition intensities using the Kolmogorov differential equations (Cox & Miller 1965)
- Use scoring algorithm (extension of Kalbfleisch & Lawless 1985)

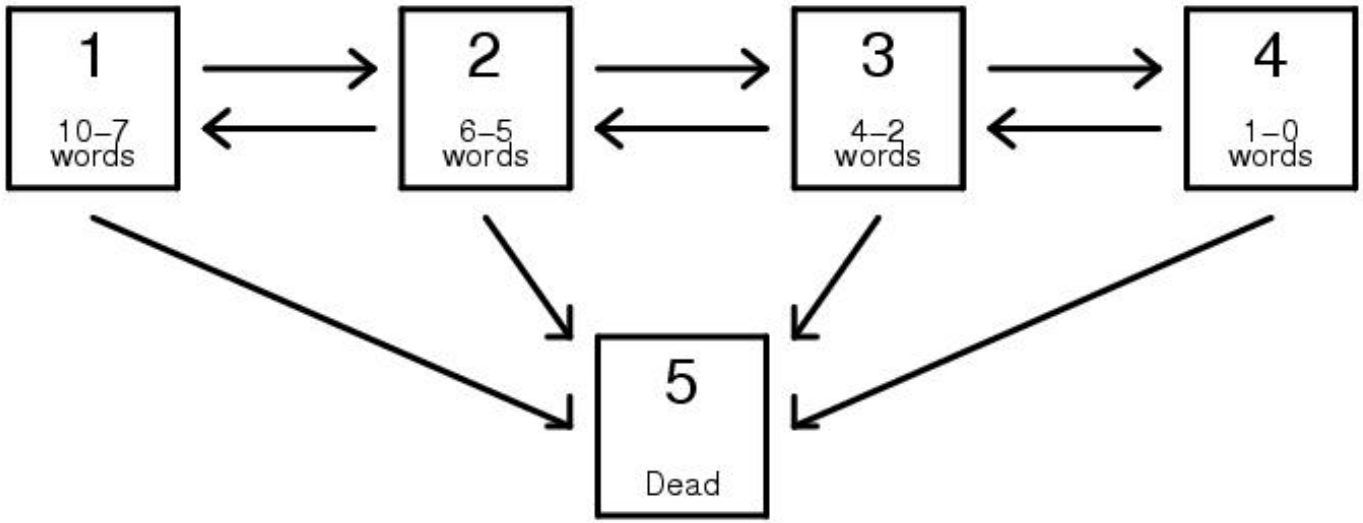
Application

- English Longitudinal Study of Ageing (ELSA)
- Info on health, economic position, and quality of life. Data in waves 1 - 4 (2002-2009). Age 90^+ is censored
- Subsample $N = 1000$, with 6 individuals with censored age, and 157 with only one observation
- Sample size in application 837. With 463 women and 374 men. Dropout due to death is about 11%

- Response is the number of words remembered in a recall from a list of ten



- Living states defined using number of words remembered in the recall



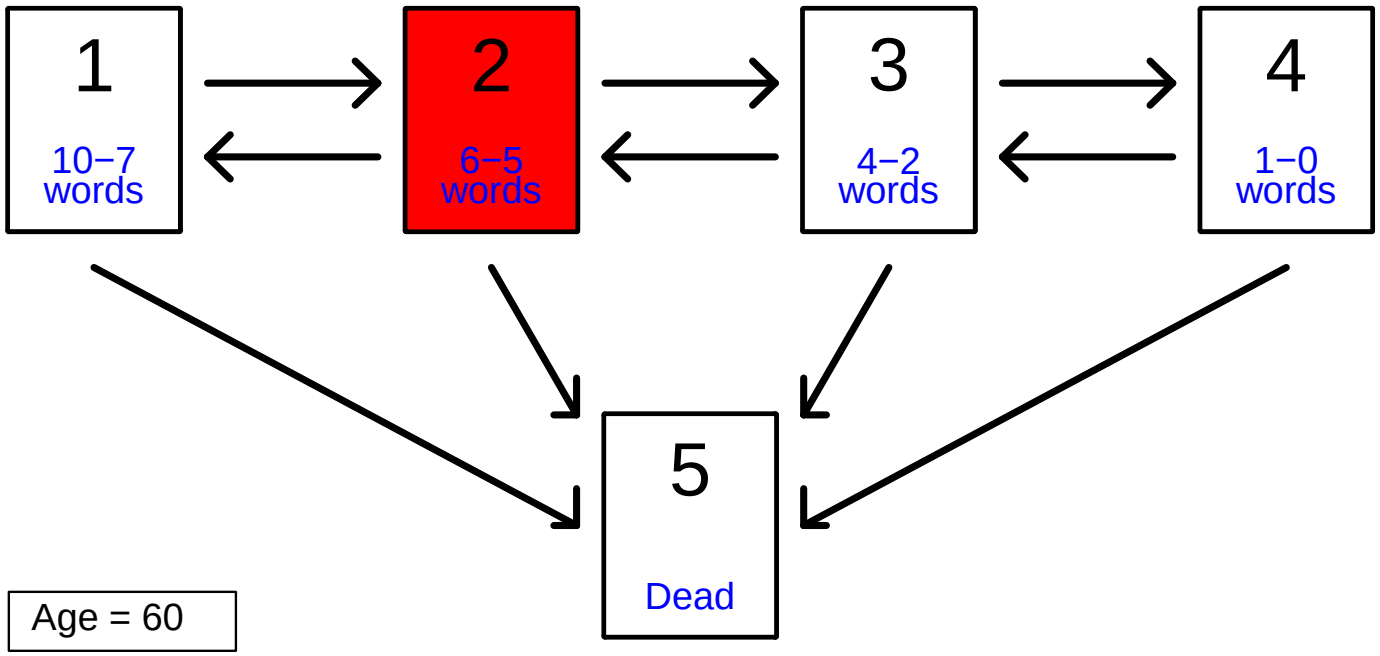
- AIC prefers Gompertz hazards for the forward transitions between living states and Weibull for death:

$$q_{rs}(t) = \exp\left(\beta_{rs.0} + \xi_{rs}t + \beta_{rs.1}Sex + \beta_{rs.2}Education\right) \quad \text{for } (r,s) \in \{(1,2),(2,3),(3,4)\}$$

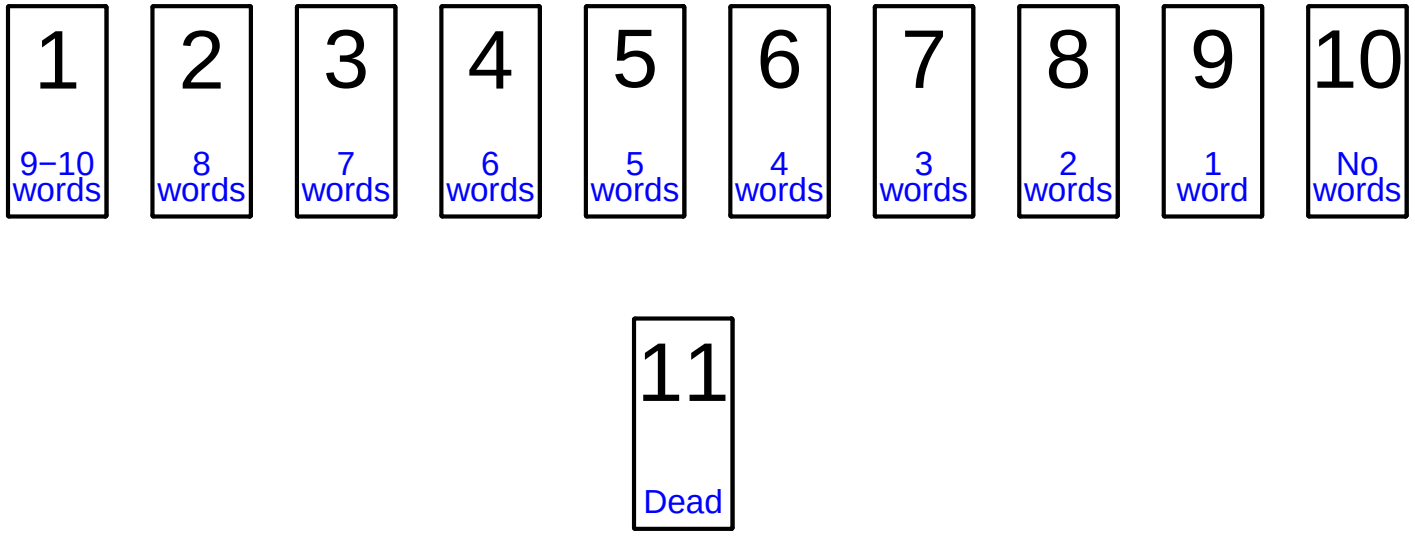
$$q_{rs}(t) = \exp\left(\beta_{rs.0}\right) \quad \text{for } (r,s) \in \{(2,1),(3,2),(4,3)\}$$

$$q_{rD}(t) = \tau_D t^{(\tau_D - 1)} \exp\left(\beta_{rD.0} + \beta_D Sex\right), \quad \text{for } r \in \{1,2,3,4\}$$

- Ageing associated with decline of cognitive function
- More education associated with a lower risk of moving to states 2 or 3
- Parametric model:
  - Can estimate transition probabilities for any start state and specified time interval
  - Can estimate duration of stay per state (residual life expectancies)

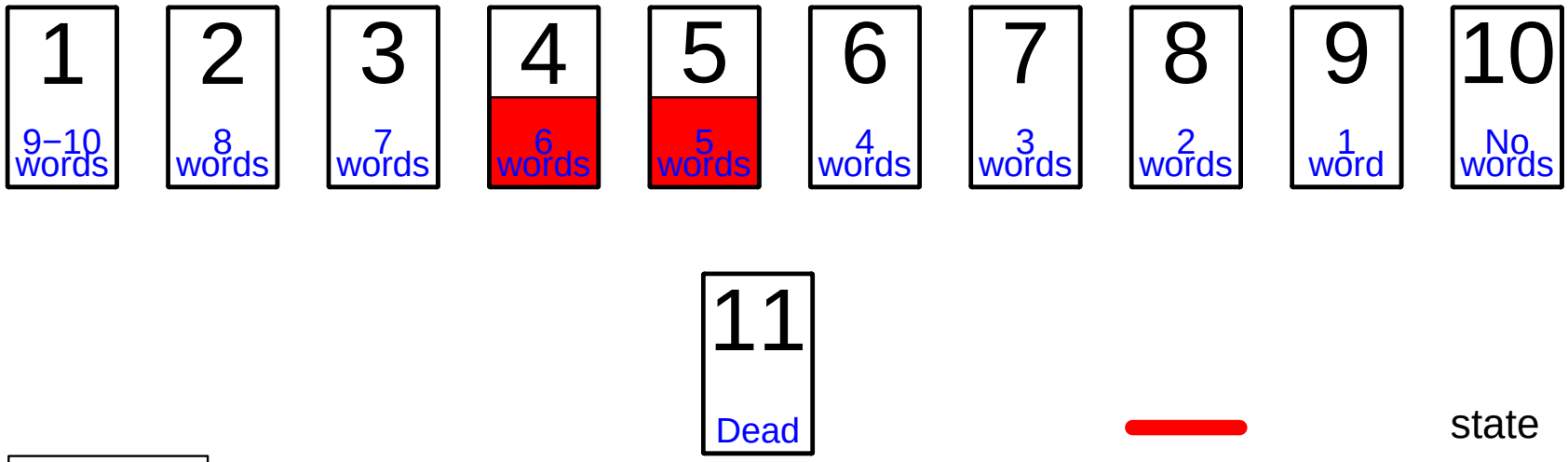

1
10−7
words
2
6−5
words
3
4−2
words
4
1−0
words
5
Dead
Age = 60

- Extend number of states:



- Example of a model:

$$
\begin{aligned}
q_{rs}(t) &= \exp(\alpha_0 + \xi t + \alpha_1 r) && \text{for } (r, s = r + 1) \\
q_{rs}(t) &= \exp(\beta) && \text{for } (r, s = r - 1) \\
q_{rD}(t) &= \tau_D t^{(\tau_D - 1)} \exp(\gamma)
\end{aligned}
$$


1
9–10 words
2
8 words
3
7 words
4
6 words
5
5 words
6
4 words
7
3 words
8
2 words
9
1 word
10
No words
11
Dead
Age = 60
state
last living state

3. Joint models using a shared-parameter approach

With Graciela Muniz

MRC Unit for Lifelong Health and Ageing, London

- Joint models used for continuous longitudinal measurements in the presence of dropout during follow-up
- Today's joint models builds upon an established framework (Rizopoulos 2012; Fitzmaurice et al. 2009, Ch. 13-16)
- Extension to deal with specific features of modelling of cognitive function in the older population

- Typically, cognitive function is measured with a questionnaire test with an integer scale

  In the applications: MMSE sum score $\in \{0, 1, 2, ..., 30\}$, and recall of words $\in \{0, 1, ..., 10\}$

- Specific features of our joint models:

  i) Non-linear mixed-effects model instead of linear

  ii) Parametric survival model instead of semi-parametric

  iii) Age as time scale: delayed entry (left truncation)

- For individual i, with response y_{ij} at time t_{ij} the **measurement model** has linear predictor

$$\begin{aligned} \eta_{ij} &= \beta_{0i} + \beta_{1i} t_{ij} + \boldsymbol{X}_i \gamma \\ \beta_{0i} &= \beta_0 + b_{0i} \\ \beta_{1i} &= \beta_1 + b_{1i} \qquad \boldsymbol{b}_i = (b_{0i}, b_{1i}) \sim N(\mathbf{0}, \boldsymbol{\Sigma}) \end{aligned}$$

- Discrete outcome: The logit link for binomial distribution or for beta-binomial distribution

- Beta-binomial has an extra variance parameter θ — here assumed to be the same for all individuals

- Beta-binomial distribution for Y defined by probability of success μ, variance parameter θ, and m trials:

$$\mathbb{E}[Y] = m\mu \quad \text{and } \mathrm{Var}[Y] = m\mu(1-\mu)\left(1 + \frac{(m-1)\theta}{(1+\theta)}\right)$$

- Observation-specific random effect in a binomial regression model: don't switch to beta-binomial

- Cluster-specific random effects: switching may work

- The binomial regression model is generalised linear mixed model, the beta-binomial is not (Agresti 2002)

- Given $\boldsymbol{\beta_i} = (\beta_0 + b_{0i}, \beta_1 + b_{1i})$, the **hazard model** is

$$h_i(t) = h_0\left\{t | g_0(\alpha_0, \boldsymbol{\beta}_i, t)\right\} \exp\{g(\alpha, \boldsymbol{\beta}_i, t) + \boldsymbol{x}_i^* \gamma^*\}$$

- Examples of parametric shapes for the baseline are

$$\begin{aligned} \text{Weibull:} \quad h_0(t) &= \lambda \tau t^{\tau - 1} \\ \text{Gompertz:} \quad h_0(t) &= \lambda \exp(\xi t) \end{aligned}$$

- g_0 and g are is functions of fixed and random effects

- Random effects $\boldsymbol{b}_i$ are *shared* by measurement model and hazard model

- The **hazard model** (again) is

$$h_i(t) = h_0\{t|g_0(\alpha_0, \boldsymbol{\beta}_i, t)\}\exp\{g(\alpha, \boldsymbol{\beta}_i, t) + \boldsymbol{x}_i^*\boldsymbol{\gamma}^*\}$$

- Using $g(\alpha, \boldsymbol{\beta}_i, t) = \alpha(\beta_{0i} + \beta_{1i}t)$

  – and the Gompertz defines a Gompertz model:

$$\begin{aligned} h_i(t) &= \exp\{\gamma_0^* + \xi t + \alpha(\beta_{0i} + \beta_{1i}t)\} \\ &= \exp\{(\gamma_0^* + \alpha\beta_{0i}) + (\xi + \alpha\beta_{1i})t\} \end{aligned}$$

  – and the exponential defines a Gompertz model:

$$h_i(t) = \exp\{(\gamma_0^* + \alpha\beta_{0i}) + \alpha\beta_{1i}t\}$$

- Marginal likelihood assuming independence given the random effects. For individual i with age at baseline t_{i1} and death or right censoring at t_i

$$L_i(\boldsymbol{\omega}|t_{i1}) = \int p(t_i|\boldsymbol{b}_i, t_{i1}, \delta_i, \boldsymbol{\omega}) p(\boldsymbol{y}_i|\boldsymbol{b}_i, \boldsymbol{\omega}) p(\boldsymbol{b}_i|t_{i1}, \boldsymbol{\omega}) d\boldsymbol{b}_i$$

$$= \int h(t_i|\boldsymbol{b}_i, \boldsymbol{\omega})^{\delta_i} P(T \geq t_i|T > t_{i1}, \boldsymbol{b}_i, \boldsymbol{\omega}) \left\{ \prod_j p(y_{ij}|\boldsymbol{b}_i, \boldsymbol{\omega}) \right\} p(\boldsymbol{b}_i|t_{i1}, \boldsymbol{\omega}) d\boldsymbol{b}_i$$

$$= \int h(t_i|\boldsymbol{b}_i, \boldsymbol{\omega})^{\delta_i} P(T \geq t_i|\boldsymbol{b}_i, \boldsymbol{\omega}) \left\{ \prod_j p(y_{ij}|\boldsymbol{b}_i, \boldsymbol{\omega}) \right\} \frac{p(\boldsymbol{b}_i|\boldsymbol{\omega})}{P(T \geq t_{i1}|\boldsymbol{\omega})} d\boldsymbol{b}_i$$

where $\boldsymbol{\omega}$ is vector with population parameters

(*cf.* Jensen *et al.* 2004; Rondeau *at al.* 2006)

- For Gompertz with λ_i and ξ_i

$$P(T \geq t_i | \boldsymbol{b}_i, \boldsymbol{\omega}) = \exp\Big[- \lambda_i \xi_i^{-1} \{\exp(\xi_i t_i) - 1\}\Big]$$

- Maximisation in R using Gaussian quadrature and a multi-purpose optimiser

- For estimation of random effects: maximum aposterior (MAP) estimation

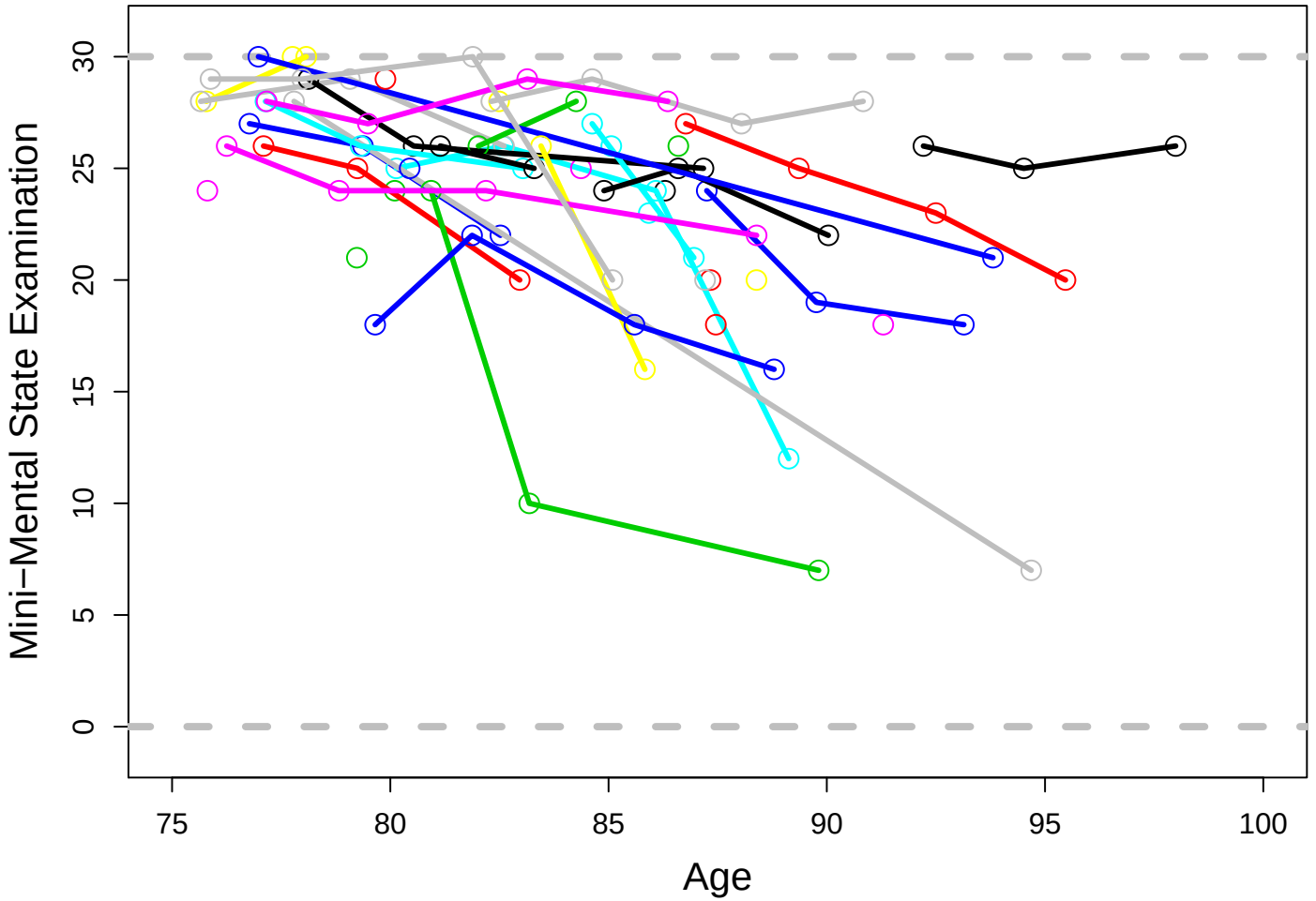
- Alternative: Bayesian inference using a Gibbs sampler, with Metropolis steps to draw values from the conditional distributions. (Can't do this in WinBUGS)

Two applications

- CC75C with $N = 1932$. All death times available. Of interest: how change of cognitive function over time affects survival

- ELSA. Dropout due to death is 11%. Of interest: effect of gender on cognitive change over time when controlling for education

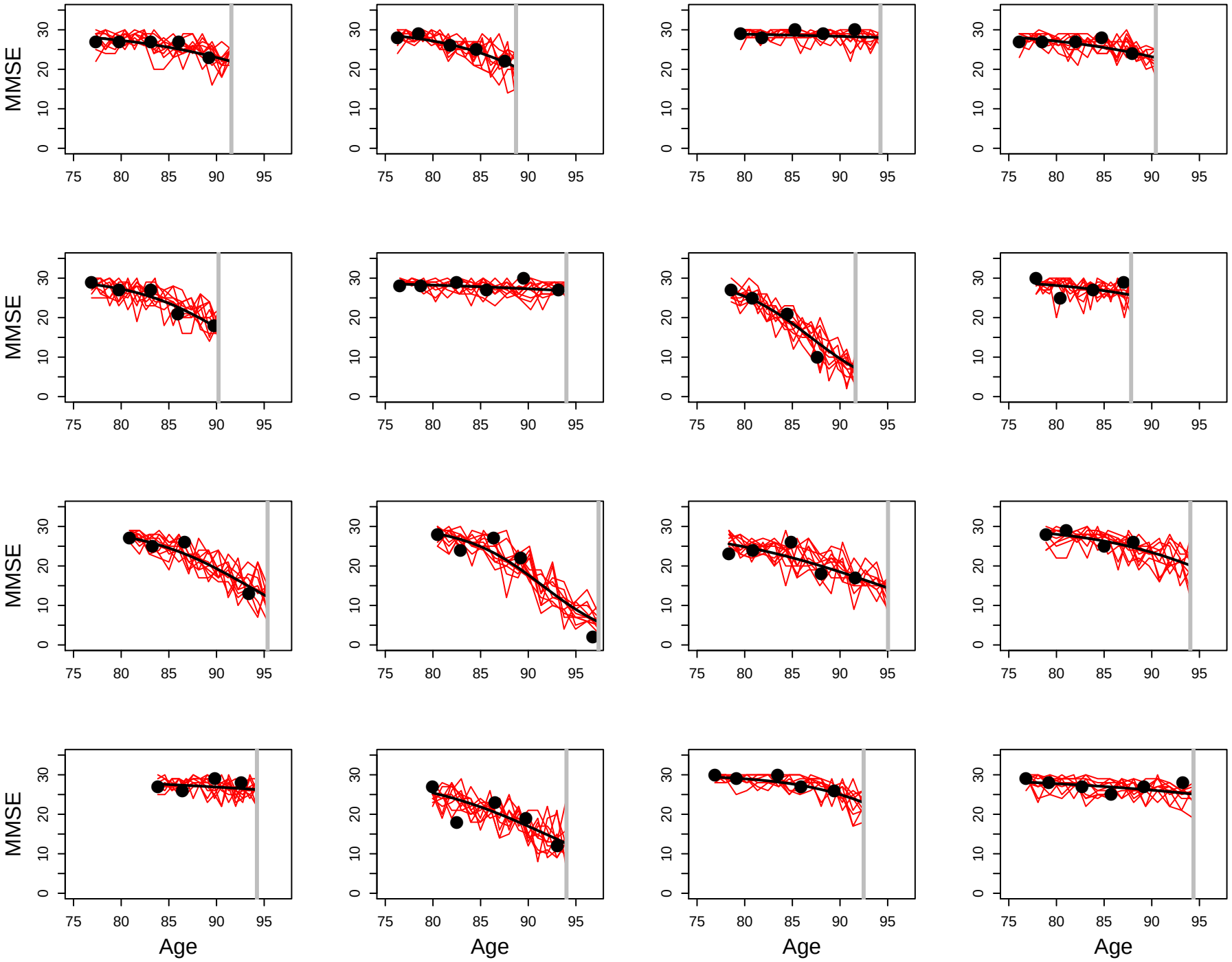
CC75C


Mini−Mental State Examination
0
5
10
15
20
25
30
75
80
85
90
95
100
Age

- 698 men and 1234 women. Mean age at baseline is 81
- Covariates `sex` (0/1 for women/men) and `educ` (0/1 for less than 10yrs of education/10yrs or more)
- AIC prefers beta-binomial regression and Gompertz hazard

$$\begin{aligned} \eta_{ij} &= \beta_{0i} + \beta_{1i} t_{ij} \\ h_i(t) &= \exp\{\gamma_0^* + \alpha\beta_{0i} + (\xi + \alpha\beta_{1i})t + \gamma_1^* \texttt{sex}_i + \gamma_2^* \texttt{educ}_i\} \end{aligned}$$

- Next slide: Fit to individual data for a random subset of 16 individuals (including simulated trajectories)


MMSE
0
10
20
30
75
80
85
90
95
Age

- Model (again) with $\beta_{0i} = \beta_0 + b_{0i}$ and $\beta_{1i} = \beta_1 + b_{1i}$

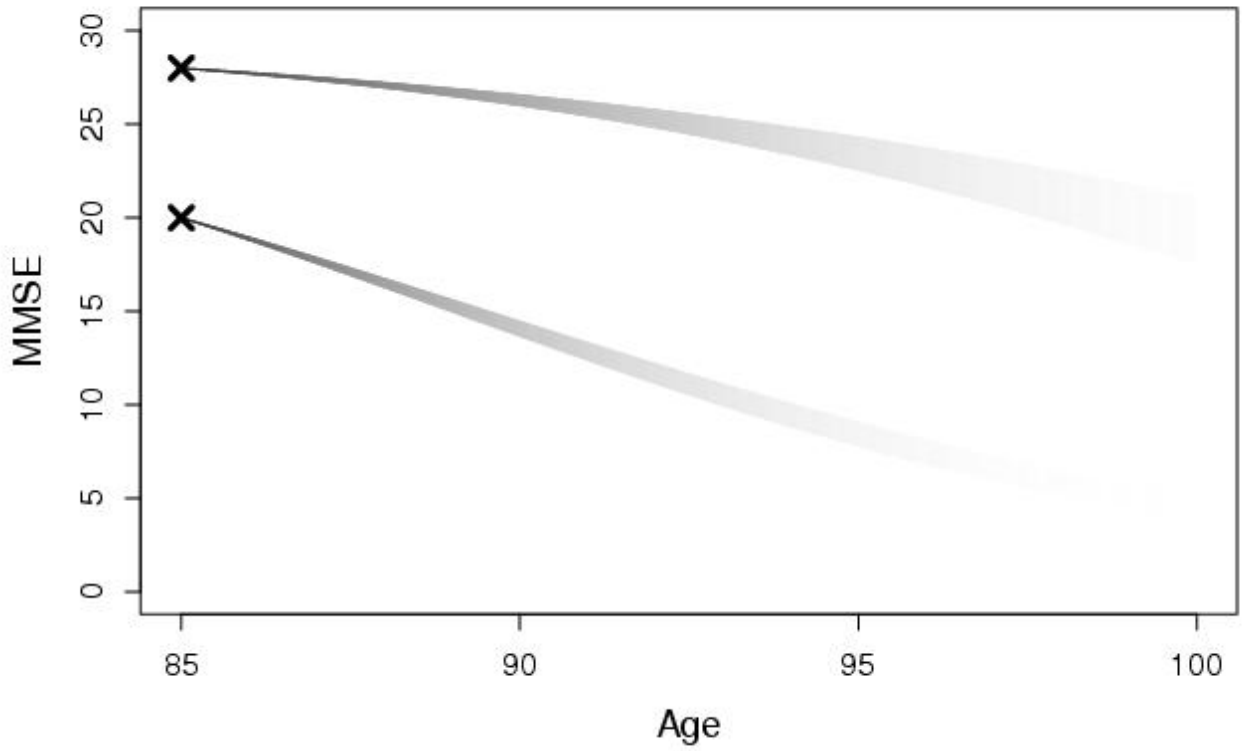
$$\begin{aligned} \eta_{ij} &= \beta_{0i} + \beta_{1i} t_{ij} \\ h_i(t) &= \exp\{\gamma_0^* + \alpha\beta_{0i} + (\xi + \alpha\beta_{1i})t + \gamma_1^* \texttt{sex}_i + \gamma_2^* \texttt{educ}_i\} \end{aligned}$$

- Time scale t is age minus 70 years

- Some results: $\widehat{\beta}_1 = -0.16$ $(-0.17; -0.15)$, $\widehat{\gamma}_1^*, \widehat{\gamma}_2^* > 0$, $\widehat{\alpha} = -0.42$ $(-0.48; -0.35)$

- Negative α implies that having better cognitive function as measured by the MMSE is associated with a smaller hazard and thus with better survival

- Prediction given MMSE at a specified age is possible
- Example



ELSA

- Data in waves 1 - 4 (2002-2009)
- The 167 individuals with censored age (90^{+}) are removed. Resulting sample size is 11627
- Dropout due to death is around 11%
- Baseline: 6533 women and 5094 men
- Response $\in \{0, 1, ..., 10\}$ is number of words remembered in a recall from a list of ten

- Binomial regression and Gompertz hazard

$$\begin{aligned}\eta_{ij} &= \beta_{0i} + \beta_{1i}t_{ij} + \gamma_1 \texttt{sex}_i + \gamma_2 \texttt{educ}_i + \gamma_3(\texttt{sex}_i \times t_{ij}) + \gamma_4 \texttt{yob}_i \\ h_i(t) &= \exp\{\gamma_0^* + \alpha\beta_{0i} + (\xi + \alpha\beta_{1i})t + \gamma_1^* \texttt{sex}_i + \gamma_2^* \texttt{bmi}_i\},\end{aligned}$$

  where men $\equiv$ 1, more education $\equiv$ 1. Year of birth minus 1900, BMI coded -2, -1, 0, 1, 2, 3

- Time scale t is age minus 30 years

- Model has AIC = 148333. Switching to beta-binomial regression: AIC = 148233

- Model (again), with men $\equiv 1$, more education $\equiv 1$:

$$\begin{aligned}\eta_{ij} &= \beta_{0i} + \beta_{1i}t_{ij} + \gamma_1 \texttt{sex}_i + \gamma_2 \texttt{educ}_i + \gamma_3(\texttt{sex}_i \times t_{ij}) + \gamma_4 \texttt{yob}_i \\ h_i(t) &= \exp\{\gamma_0^* + \alpha\beta_{0i} + (\xi + \alpha\beta_{1i})t + \gamma_1^* \texttt{sex}_i + \gamma_2^* \texttt{bmi}_i\}\end{aligned}$$

$$\begin{aligned}\widehat{\beta}_1 &= -0.002\ (0.002) & \widehat{\gamma}_1 &= -0.067\ (0.051) \\ \widehat{\gamma}_3 &= -0.004\ (0.002) & \widehat{\gamma}_1^* &= \ \ 0.539\ (0.062) \\ & & \widehat{\alpha} &= -0.161\ (0.043)\end{aligned}$$

- Fit based on MAP OK. Extrapolation not so good

- Age range is quite wide relative to length of follow-up

4. Conclusion

- Using sum score: Varying success probabilities across questions is OK for the binomial. Dependence is not
- Possible alternative: Item Response Theory models (with J-P Fox)
- Alternatives for discrete sum score and ceiling effects:
  - Proust-Lima et al (2009) use transformation
  - Hutton & Stanghellini (2009) use censored skew-normal distributions

- For longitudinal discrete outcome data: multi-state survival models and joint models can take dropout due to death into account

- Distribution of test sum scores is often skewed: use of the normal distribution for the outcome is problematic

- Presented framework is flexible w.r.t. other distributions or random-effects structures