A Multi-Stage Stochastic Model in the Analysis of Longitudinal Dementia Data

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May 12, 2018

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Introduction

- Four stages: normality, memory-impaired intermediate, dementia and death without dementia.
- Motivation: to estimate the transitional probabilities and to discover risk factors.
- To analyze longitudinal data, we develop the likelihood function based on a first order Markov chain model.
- We extend from typical illness-death model to a stochastic model consisting of four stages, and construct a reversible transition model between normality and memory-impaired intermediate.

Notation

- $X(s)$: the stage at time s
  $\pi_{jl}(s,t) = P(X(t)=l|X(s)=j)$
  $\lambda_{jl}(t) = \lim_{\Delta t \to 0} \frac{P[X(t+\Delta t)=l|X(t)=j]}{\Delta t} = \lim_{\Delta t \to 0} \frac{\pi_{jl}(t,t+\Delta t)}{\Delta t}$
- Consider time-homogeneous models: $\lambda_{jl}(t)$ is independent of t, that is, $\lambda_{jl}(t) = \lambda_{jl}$, for any t.
  $\pi_{jl}(T) = \pi_{jl}(s, s+T) = \pi_{jl}(0,T)$
  $\pi'_{jl}(T) = \lim_{\Delta t \to 0} \frac{\pi_{jl}(s,s+T+\Delta t) - \pi_{jl}(s,s+T)}{\Delta t}$
  $\lambda_j = \sum_{l \neq j} \lambda_{jl}$

Kolmogrov's Backward Equation (for continuous-time Markov chain)

$$\pi_{jl}(T+\Delta t) - \pi_{jl}(T) = \sum_{k} \pi_{jk}(\Delta t)\pi_{kl}(T) - \pi_{jl}(T)$$

$$= \sum_{k \neq j} \pi_{jk}(\Delta t)\pi_{kl}(T) - (1 - \pi_{jj}(\Delta t))\pi_{jl}(T)$$

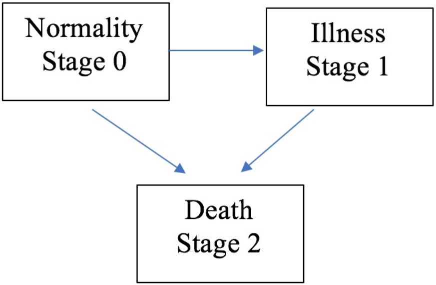
$$\lim_{\Delta t \to 0} \frac{\pi_{jl}(T+\Delta t) - \pi_{jl}(T)}{\Delta t}$$

$$= \lim_{\Delta t \to 0} \{ \sum_{k \neq j} \frac{\pi_{jk}(\Delta t)}{\Delta t} \pi_{kl}(T) - \frac{(1 - \pi_{jj}(\Delta t))}{\Delta t} \pi_{jl}(T) \}$$

$$\pi'_{jl}(T) = \sum_{k \neq j} \lambda_{jk}\pi_{kl}(T) - \lambda_j \pi_{jl}(T) \qquad \text{(KB)}$$

Illness-death Model

- Model Structure



Illness-death Model

- Transitional Probability Matrix

$$\begin{pmatrix} \pi_{00} & \pi_{01} & \pi_{02} \\ 0 & \pi_{11} & \pi_{12} \\ 0 & 0 & 1 \end{pmatrix}$$

Illness-death Model

$$\pi'_{jl}(T) = \sum_{k \neq j} \lambda_{jk}\pi_{kl}(T) - \lambda_j \pi_{jl}(T) \qquad \text{(KB)}$$

$$\Rightarrow \begin{cases} \pi'_{00}(T) = -\lambda_0 \pi_{00}(T) \\ \pi'_{11}(T) = -\lambda_1 \pi_{11}(T \\ \pi'_{01}(T) = \lambda_{01}\pi_{11}(T) - \lambda_0 \pi_{01}(T) \end{cases}$$

$$\pi_{00}(0) = \pi_{11}(0) = 1, \ \pi_{01}(0) = 0$$

Illness-death Model

- The transitional probabilities are

$$\pi_{00}(T) = e^{-\lambda_0 T}$$

$$\pi_{01}(T) = \frac{\lambda_{01}}{\lambda_0 - \lambda_1}[e^{-\lambda_1 T} - e^{-\lambda_0 T}]$$

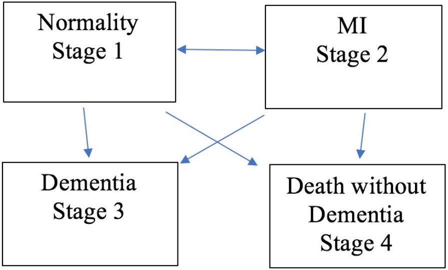
$$\pi_{02}(T) = 1 - \pi_{00}(T) - \pi_{01}(T)$$

$$\pi_{11}(T) = e^{-\lambda_1 T}$$

$$\pi_{12}(T) = 1 - \pi_{11}(T)$$

Song et.al (2011) Model

- Model Structure



Song et.al (2011) Model

- Transitional Probability Matrix

$$\begin{pmatrix} \pi_{11} & \pi_{12} & \pi_{13} & \pi_{14} \\ \pi_{21} & \pi_{22} & \pi_{23} & \pi_{24} \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

Song et.al (2011) Model

$$\pi'_{jl}(T) = \sum_{k \neq j} \lambda_{jk}\pi_{kl}(T) - \lambda_j \pi_{jl}(T) \qquad \text{(KB)}$$

$$\pi'_{11}(T) = \lambda_{12}\pi_{21}(T) - \lambda_1\pi_{11}(T)$$

$$\pi'_{21}(T) = \lambda_{21}\pi_{11}(T) - \lambda_2\pi_{21}(T)$$

$$\pi'_{12}(T) = \lambda_{12}\pi_{22}(T) - \lambda_1\pi_{12}(T)$$

$$\pi'_{22}(T) = \lambda_{21}\pi_{12}(T) - \lambda_2\pi_{22}(T)$$

$$\pi'_{13}(T) = \lambda_{12}\pi_{23}(T) + \lambda_{13} - \lambda_1\pi_{13}(T)$$

$$\pi'_{23}(T) = \lambda_{21}\pi_{13}(T) + \lambda_{23} - \lambda_2\pi_{23}(T)$$

Song et.al (2011) Model

$$\pi_{11}(T) = \frac{\lambda_2 - \lambda_1 + k}{2k} e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - \frac{\lambda_2 - \lambda_1 - k}{2k} e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T}$$

$$\pi_{12}(T) = \frac{\lambda_{12}}{k}(e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T})$$

$$\pi_{13}(T) = \frac{\lambda_{13}}{k}(e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T})$$

$$\pi_{14}(T) = 1 - \pi_{11}(T) - \pi_{12}(T) - \pi_{13}(T)$$

Song et.al (2011) Model

$$\pi_{21}(T) = \frac{\lambda_{21}}{k}\left(e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T}\right)$$

$$\pi_{22}(T) = \frac{\lambda_1 - \lambda_2 + k}{2k} e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - \frac{\lambda_1 - \lambda_2 - k}{2k} e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T}$$

$$\pi_{23}(T) = -\frac{\lambda_{13}}{\lambda_{12}} + \frac{\lambda_{13}(\lambda_1 - \lambda_2 + k)}{2\lambda_{12}k} e^{\frac{-(\lambda_1+\lambda_2)+k}{2}T} - \frac{\lambda_{13}(\lambda_1 - \lambda_2 - k)}{2\lambda_{12}k} e^{\frac{-(\lambda_1+\lambda_2)-k}{2}T}$$

$$\pi_{24}(T) = 1 - \pi_{21}(T) - \pi_{22}(T) - \pi_{23}(T)$$

where $k = \sqrt{(\lambda_1 - \lambda_2)^2 + 4\lambda_{12}\lambda_{21}}$

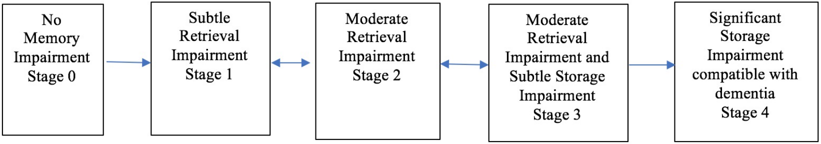
SOMI Model, Grober et.al (2018)

- Stages classification

Stages of Objective Memory Impairment (SOMI)	Free Recall Scores	Total Recall Scores
0 No Memory Impairment	>30	>46
1 **(aMCI)** Subtle Retrieval Impairment	25-30	>46
2a **(Prodromal)** Moderate Retrieval Impairment	20-24	>46
2b **(Prodromal)** Moderate Retrieval Impairment and Subtle Storage Impairment		44-46
3 Significant Storage Impairment compatible with dementia	<20	33-43

SOMI Model, Grober et.al (2018)

- Model Structure



SOMI Model, Grober et.al (2018)

- Transitional Probability Matrix

$$\begin{pmatrix} \pi_{00} & \pi_{01} & \pi_{02} & \pi_{03} & \pi_{04} \\ 0 & \pi_{11} & \pi_{12} & \pi_{13} & \pi_{14} \\ 0 & \pi_{21} & \pi_{22} & \pi_{23} & \pi_{24} \\ 0 & \pi_{31} & \pi_{32} & \pi_{33} & \pi_{34} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

SOMI Model, Grober et.al (2018)

$$\pi'_{jl}(T) = \sum_{k \neq j} \lambda_{jk}\pi_{kl}(T) - \lambda_j \pi_{jl}(T) \qquad \text{(KB)}$$

$$\pi'_{00}(T) = -\lambda_0 \pi_{00}(T)$$

$$\pi'_{01}(T) = \lambda_{01}\pi_{11}(T) + \lambda_{02}\pi_{21}(T) + \lambda_{03}\pi_{31}(T) - \lambda_0\pi_{01}(T)$$

$$\pi'_{11}(T) = \lambda_{12}\pi_{21}(T) + \lambda_{13}\pi_{31}(T) - \lambda_1\pi_{11}(T)$$

$$\pi'_{21}(T) = \lambda_{21}\pi_{11}(T) + \lambda_{23}\pi_{31}(T) - \lambda_2\pi_{21}(T)$$

$$\pi'_{31}(T) = \lambda_{31}\pi_{11}(T) + \lambda_{32}\pi_{21}(T) - \lambda_3\pi_{31}(T)$$

$$\pi'_{02}(T) = \lambda_{01}\pi_{12}(T) + \lambda_{02}\pi_{22}(T) + \lambda_{03}\pi_{32}(T) - \lambda_0\pi_{02}(T)$$

SOMI Model, Grober et.al (2018)

$$\pi'_{12}(T) = \lambda_{12}\pi_{22}(T) + \lambda_{13}\pi_{32}(T) - \lambda_1\pi_{12}(T)$$
$$\pi'_{22}(T) = \lambda_{21}\pi_{12}(T) + \lambda_{23}\pi_{32}(T) - \lambda_2\pi_{22}(T)$$
$$\pi'_{32}(T) = \lambda_{31}\pi_{12}(T) + \lambda_{32}\pi_{22}(T) - \lambda_3\pi_{32}(T)$$
$$\pi'_{03}(T) = \lambda_{01}\pi_{13}(T) + \lambda_{02}\pi_{23}(T) + \lambda_{03}\pi_{33}(T) - \lambda_0\pi_{03}(T)$$
$$\pi'_{13}(T) = \lambda_{12}\pi_{23}(T) + \lambda_{13}\pi_{33}(T) - \lambda_1\pi_{13}(T)$$
$$\pi'_{23}(T) = \lambda_{21}\pi_{13}(T) + \lambda_{23}\pi_{33}(T) - \lambda_2\pi_{23}(T)$$
$$\pi'_{33}(T) = \lambda_{31}\pi_{13}(T) + \lambda_{32}\pi_{23}(T) - \lambda_3\pi_{33}(T)$$

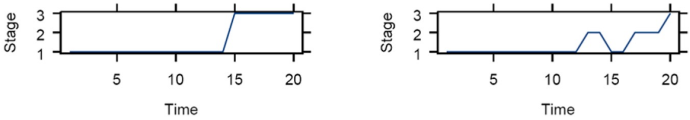
Likelihood

- Our model formulation can be used for both continuous and discrete-time Markov processes.
- We concentrate here on the discrete case in which we observe study participants at equally spaced time points (study waves).

Likelihood

- Let k denote a time point of observation, $k = 0, 1, 2, ..., K$; $k = 0$ to denote study baseline.
- Define the following random variable:
  $y_i^{(k)}(jl) = 1$ if a subject i is in stage j at time k and in stage l at time $(k+1)$;
  $y_i^{(k)}(jl) = 0$ otherwise, for $0 \leq k \leq K-1$.

Likelihood (first-order Markov transitional probability and time-independent transitional hazard rates)



$$L = \prod_{i=1}^{n} \prod_{k=0}^{K-1} \pi_{11}(k, k+1)^{y_i^{(k)}(11)} \pi_{12}(k, k+1)^{y_i^{(k)}(12)}$$

$$\pi_{13}(k, k+1)^{y_i^{(k)}(13)} \pi_{14}(k, k+1)^{y_i^{(k)}(14)} \pi_{21}(k, k+1)^{y_i^{(k)}(21)}$$

$$\pi_{22}(k, k+1)^{y_i^{(k)}(22)} \pi_{23}(k, k+1)^{y_i^{(k)}(23)} \pi_{24}(k, k+1)^{y_i^{(k)}(24)}$$

Likelihood

- Since the π_{jl}'s are functions of the transitional hazards, λ_{jl}, parameter estimates of λ_{jl} can be computed by using maximum likelihood methods.
- We will use ordinal logistic regression to investigate what covariates have significant influence on the transition.

Reference

- Grober, E., Veroff, A.E. and Lipton, R.B., 2018. Temporal unfolding of declining episodic memory on the Free and Cued Selective Reminding Test in the predementia phase of Alzheimer's disease: Implications for clinical trials. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring.
- Song, C., Kuo, L., Derby, C.A., Lipton, R.B. and Hall, C.B., 2011. Multi-stage transitional models with random effects and their application to the Einstein aging study. Biometrical Journal, 53(6), pp.938-955.
- Harezlak, J., Gao, S. and Hui, S.L., 2003. An illness–death stochastic model in the analysis of longitudinal dementia data. Statistics in medicine, 22(9), pp.1465-1475.
- Ross, S.M., 1985. Introduction to probability models (No. 519.2 R826 1985). Academic Press.