Modeling Progressive Disease Using Longitudinal Panel Data with Applications to Alzheimer's Disease

Jacquelyn Neal and Dandan Liu
Vanderbilt University, Department of Biostatistics

Introduction

- Alzheimer's disease (AD) is a progressive disorder with no cure
- Three major clinical stages: Normal cognition, mild cognitive impairment (MCI), dementia/Alzheimer's disease
- MCI definition is broad and allows MCI - Normal transitions[1]
- Often exclude reverters, a source of pathological information
- Best treatment available is to delay the onset of later stages
- Identifying individuals with highest risk of progression is necessary for providing best treatment options and testing interventions in clinical trials
- Predicting the probability an individual will progress along disease pathway helps identify the highest-risk patients
- AD progression is continuous over time, but assessment is completed at annual exam
- Repeated measurements at pre-scheduled times, panel data
- Interval-censored data to investigate transitions between stages

Alzheimer's Disease Progression

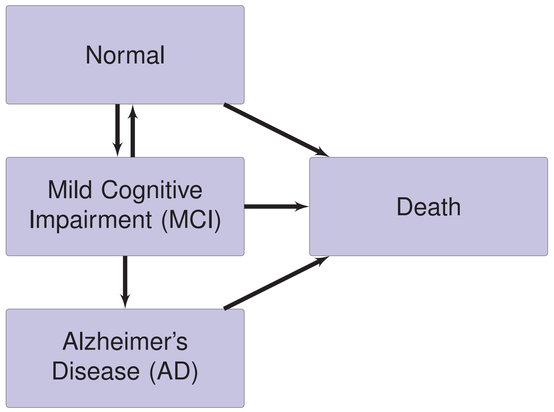

Figure 1: Progression between AD stages

National Alzheimer's Coordinating Center (NACC)

- Uniform Data Set (UDS) defines a common set of clinical observations collected longitudinally on participants at Alzheimer Disease Centers (ADCs)
- Information on 30,000+ participants from 31 ADCs since 2005
- Majority are white, female, and have more than 3 follow-up visits
- 6329 normal participants, 10.2% converted to MCI or AD, 3% died
- 2740 MCI participants, 36.2% converted to AD, 4.8% died
- Cognitive complaint is predictor of interest
- 4-levels: "No Complaint" (referent), "Self Complaint", "Informant Complaint", or "Both Complaint"

Observed Transition Paths between Visits Using NACC Data

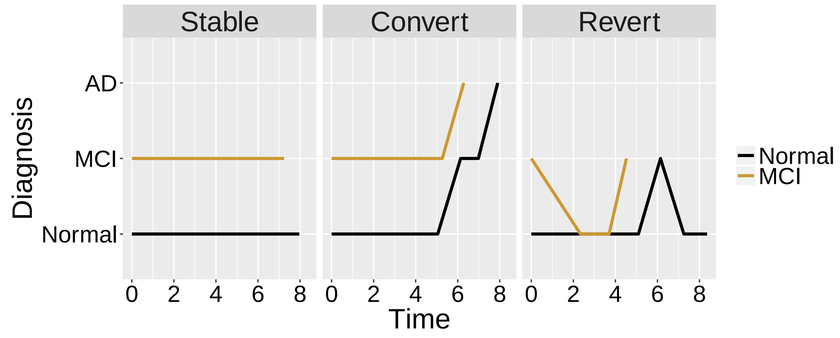

Figure 2: Example Disease Paths of NACC Participants

Multi-state Model Specifications

Figure 1 illustrates a multi-state model in continuous time, though the process is observed in discrete time, introducing interval-censoring to the model. We specify the intensity matrix $\boldsymbol{Q}$, the matrix of individual transition intensities for consecutive visits, $q_{rs}(t, z(t))$, for each pair of states (r, s). The process also depends on $z(t)$, a matrix of covariate values for each individual[2].

$$q_{rs}(t, z(t)) = \lim_{\delta t \to 0} P(S(t + \delta t) = s | S(t) = r)/\delta t \quad (1)$$

$$q_{rr} = -\sum_{s \neq r} q_{rs} \quad (2)$$

$$P(t) = exp(tQ) \quad (3)$$

$$q_{rs}(z(t)) = q(0)_{rs}\, exp(\beta_{rs}^T z(t)) \quad (4)$$

1. Intensity represents instantaneous risk of moving from state r to state s, defined in equation (1)
2. Intensities form $\boldsymbol{Q}$, a matrix whose rows sum to zero, with diagonal entries defined by equation (2)
3. Using equation (3) above, transition probabilities can be calculated from $\boldsymbol{Q}$
4. Transition intensities modeled as a function of predictors using equation (4)

Multi-state Model Assumptions

- Markov Assumption
  - Aim: Test Markov assumption by incorporating past history of MCI into model
  - $q_{rs}(Z_t, \mathcal{F}_t) = q_{rs}(Z_t)$, $\mathcal{F}_t$ is full history
  - Future state depends only on the current state, not on the full sequence of previous events
- Time-Homogeneous Assumption
  - $P(u, t + u) = P(t)$
  - Transition matrix P is the same at each time point
  - Transition probabilities at k^{th} step computed as P^k
  - Necessary for panel data to give closed form of likelihood function due to interval-censoring

Multi-state Model Results

Models chosen to compare traditional method (Model 1) with the inclusion of reverters (Model 2), and to compare these methods with incorporating prior history of MCI (Model 3) to address the Markov assumption:

- Model 1: Traditional baseline normal longitudinal dataset
- Model 2: Model 1 plus data from MCI participants that revert
- Model 3: Model 2 plus adjustment for prior MCI history

Table 1: Hazard ratios for baseline self complaint only

	Model 1	Model 2	Model 3
Normal - MCI	2.64 (2.10,3.33)	2.38 (1.92,2.96)	1.85 (1.48,2.32)
Normal - Death	0.15 (0.00,10.98)	0.22 (0.02,2.97)	0.30 (0.04,2.46)
MCI - Normal	1.93 (1.27,2.92)	1.18 (0.82,1.71)	1.04 (0.69,1.57)
MCI - AD	1.20 (0.63,2.27)	1.19 (0.63,2.23)	1.48 (0.81,2.71)
MCI - Death	0.30 (0.03,3.18)	0.34 (0.02,4.59)	0.13 (0.004,4.24)
AD - Death	3.18 (0.62,16.24)	2.82 (0.51,15.72)	2.99 (0.63,14.13)

Table 2: Hazard ratios for baseline both complaints

	Model 1	Model 2	Model 3
Normal - MCI	3.50 (2.74,4.47)	3.55 (2.80,4.49)	2.41 (1.87,3.12)
Normal - Death	0.41 (0.07,2.27)	0.59 (0.16,2.17)	0.53 (0.12,2.39)
MCI - Normal	0.99 (0.60,1.63)	1.21 (0.87,1.69)	1.19 (0.81,1.77)
MCI - AD	1.51 (0.81,2.83)	1.03 (0.57,1.87)	1.79 (0.98,3.26)
MCI - Death	0.51 (0.09,2.84)	0.39 (0.08,1.97)	0.33 (0.05,1.98)
AD - Death	1.18 (0.22,6.30)	1.00 (0.20,4.97)	1.08 (0.21,5.43)

Results of note:

- Hazard ratios consistent comparing between levels of complaint
- Model 1 overestimates the hazard ratio for MCI-Normal for self-complaint
- 11.6 (9.1,14.9): Hazard ratio for Normal - MCI when adjusting for past history

Discussion

- Advantages
  - Models the transition intensities between stages, transformed into hazard ratios
  - Flexible choice in $\boldsymbol{Q}$ allows for model approximating biological process
- Disadvantages
  - Requires assumption that all history is contained in previous diagnosis, disregards full disease history
  - All participants must have same initial state
- Previous studies use cross-sectional methods which treat transition between normal cognition and MCI the same as MCI to AD
- Potential method: Partly Conditional Model[3]
  - Flexible selection of past history to use in predicting future disease progression
  - Can incorporate baseline normal and MCI participants in same model

References

1. Gifford, K.A., Liu, D., Lu, Z., Tripodis, Y., Cantwell, N.G., Palmisano, J., Kowall, N. and Jefferson, A.L., 2014. The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults. Alzheimer's and Dementia, 10(3), pp.319-327.
2. Jackson, C.H., 2011. Multi-state models for panel data: the msm package for R. Journal of Statistical Software, 38(8), pp.1-29.
3. Pepe, M.S. and Couper, D., 1997. Modeling partly conditional means with longitudinal data. Journal of the American Statistical Association, 92(439), pp.991-998.