Adaptive Analysis of Adherence Data for HIV+ Subjects

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Overview

• the study and its adherence data to be analyzed
  – both electronically monitored and self-reported adherence data
• the modeling process for adherence over time
  – adaptive Poisson regression and adaptive repeated measures
• electronically monitored adherence patterns for selected individual subjects
• consistency of MEMS adherence with prescribed adherence
  – and compared to baseline self-reported adherence
• mean self-reported adherence for all subjects
  – by time, gender, and treatment group
• assessment of gender effects on chance for high adherence
• the change in mean self-reported adherence for all subjects
• summary
ATHENA Project

- randomized clinical trial of HIV+ subjects on HAART
  - 172 eligible subjects
  - 50.6% (87) randomized to a home-based nursing intervention
    - control group received standard nursing care
  - 51.7% (89) male
- used Medication Event Monitoring System (MEMS) caps
  - all medications controlled by the caps were prescribed at 2 per day
  - MEMS data available for 164 (95.3%) of the eligible subjects
    - consisting of over 75,000 openings on over 66,000 days for 186 caps
- removed periods not truly reflective of subject adherence
  - when subjects not fully responsible for taking medications
    - e.g., when in prison, the hospital, an in-patient drug facility, etc.
  - or when subjects were off medications on provider order
  - usable data left for 161 (93.6%) of the eligible subjects

used MEMS IV caps and MEMS Version 2.61 software
Self-Reported Adherence Data

• adherence was also measured at each interview as the overall percentage of prescribed antiretroviral medications self-reported to have been taken within the prior 3 days
  – subjects were interviewed up to 7 times at 3 month intervals apart
  – 784 total self-reported adherence values available
  – from 171 (99.4%) of the eligible subjects

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Example Subject

• used a single cap for 419 days, opening it 836 times
  – an overall cap opening rate of 1.995 openings per day
  – very close to the prescribed rate of 2 per day
  – but how consistent was this subject's adherence over time?

• self-reported adherence was always 100%
  – at each of 5 interviews (at 0, 3, …, 12 months)

• to visualize the subject's MEMS data
  – partition the cap usage period into 100 equal-sized intervals
    • of 4.19 days each
  – compute grouped opening counts/rates for each interval
  – plot these rates over time
Example Subject

- subject has a very consistent pattern of openings over time close to the prescribed rate
- to characterize the adherence pattern
  - fit a smooth nonparametric function of time to the data
  - using Poisson regression
    - since modeling counts/rates
    - adaptively chosen using heuristic search based on cross-validation scores for distinguishing between models
Example Subject

- selected model is constant at about 2 openings per day
- to measure how close the MEMS pattern is to the prescribed rate
  - compare likelihood scores for MEMS adherence and prescribed adherence
  - measure of % consistency of MEMS adherence with prescribed adherence
  - equals 100% in this case
- agrees with self-reported adherence of 100% at each of 5 interviews
Modeling Process

• adaptive Poisson regression of MEMS adherence data
  – for each subject, adaptively chose a polynomial in an arbitrary number of arbitrary powers of time
  – heuristic search through such models to uncover an effective one
  – based on likelihood cross-validation (LCV) scores
  – measure consistency of MEMS with prescribed adherence
    • take the ratio of likelihood scores and convert it to a percentage
      (changed from earlier use of LCV scores; gives a more accurate depiction of consistency)

н, see paper in Statistics in Medicine, 2004; 23:783-801

• adaptive repeated measures modeling of self-reported adherence data
  – the same search process applied to linear mixed models with compound symmetry covariance (or exchangeable correlations)
    • the standard repeated measures covariance structure
  – but to data for all subjects combined rather than each separately
  – modeling dependence on time, gender, and treatment group
Selected MEMS Adherence Patterns

**Improving Adherence**  
93.9% Consistency

**Declining Adherence**  
77.6% Consistency

**Oscillating Adherence**  
12.7% Consistency

**Low Adherence**  
0.1% Consistency
Adherence Distributions

- % consistency
  - bimodal distribution for 161 subjects with usable MEMS data remaining after adjustment
  - peaks at the ends
    - at low (≤10%) and high (>90%) adherence levels
  - nearly uniform in between
    - and at risk for drug resistance
- baseline self-reported adherence
  - highly inflated with about 2 out of every 3 of 171 subjects reporting levels over 90%
  - otherwise fairly evenly spread out
Self-Reported Adherence by Time, Gender, and Treatment Group

- mean baseline adherence significantly
  - higher for males than females \((p<0.01)\)
  - lower for intervention than control group \((p=0.03)\) even though randomized
  - but not if only baseline data are analyzed

- mean adherence over time
  - is constant for the control group
  - increases for the intervention group from baseline to a constant post-baseline level

- gender effect persists post-baseline but intervention overcomes baseline treatment group differences

- does the gender effect result in an increased chance for consistently high levels of post-baseline adherence?
  - with consistently high meaning over 95% at all available post-baseline times

![Graph showing self-reported adherence by time, gender, and treatment group.](image)
High Adherence by Gender

- consistently high post-baseline self-reported adherence (>95% whenever available after baseline; 151 subjects)
  - differs significantly ($\chi^2$, p=0.04) by gender
  - chance for males 16% more than for females
- high % consistency (>90%; 161 subjects)
  - also differs significantly ($\chi^2$, p=0.04) by gender
  - difference in chance (14%) about the same
- gender effects exist using both adherence measures and are of comparable sizes
- but adherence to antiretroviral medications typically does not vary with gender

R. Scherer, Adherence in Resource Poor Settings, presentation at Elements of Success Conference, 2004
- is there an explanation?
Stratified Consistently High Post-Baseline Self-Reported Adherence

- for consistently high post-baseline self-reported adherence, the gender effect is actually a gender-within-intervention-group effect
  - significant (extended Mantel-Haenszel, p=0.04) difference by gender within treatment strata
  - more control males have consistently high adherence levels than females (56% vs. 45%), but not significantly ($\chi^2$, p=0.36) more
  - intervention males significantly ($\chi^2$, p=0.05) more likely than females (63% vs. 39%) to have consistently high adherence levels

- an intervention effect on consistently high post-baseline self-reported adherence is likely if its impact is improved for females
  - significant (p=0.03) if 1/3 more intervention females (from 39% to 72%) had high levels

- similar results hold for high % consistency
Change in Self-Reported Adherence

- mean self-reported adherence improves from baseline for the intervention but not the control group
  - mean change is zero for the control group and significantly (p=0.01) nonzero for the intervention group
  - using an adaptive repeated measures model with possible nonlinear dependence on time within gender and treatment groups
- improves by the constant amount of 7.6% for all post-baseline times
- there is no gender effect
- currently extending the methods to be able to conduct a similar analysis of % consistency between interviews
Summary

• adaptive modeling methods can be used to model MEMS and self-reported adherence data
  – adaptive Poisson regression applied to MEMS data
    • for individual subjects generating % consistency scores or for all subjects
  – adaptive repeated measures applied to self-reported data
    • for all subjects possibly categorized into groups (e.g., by gender)
• self-report provides an inflated assessment of adherence compared to % consistency of prescribed/MEMS adherence
  – but increases in adherence of similar sizes can occur for both
• ATHENA intervention increased self-reported adherence, but females were lower at baseline, so only males had an increased chance for consistently high adherence levels
  – intervention females may then be more at risk for drug resistance
  – a gender-sensitive revised intervention with increased effectiveness for females has the potential for significant improvement in the chance for high adherence for both genders combined