Considerations for Analysis of Data Collected by Wearable Digital Health Technology in Clinical Trials

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Outline

- Wearable Accelerometer measuring Activity
  - Missing Data
  - Different Follow-up Time
  - Statistical Methods
- Case Study: Sleep measurement
  - Week day vs weekend variation
  - Missing Data
- Case Study: Circadian Variation

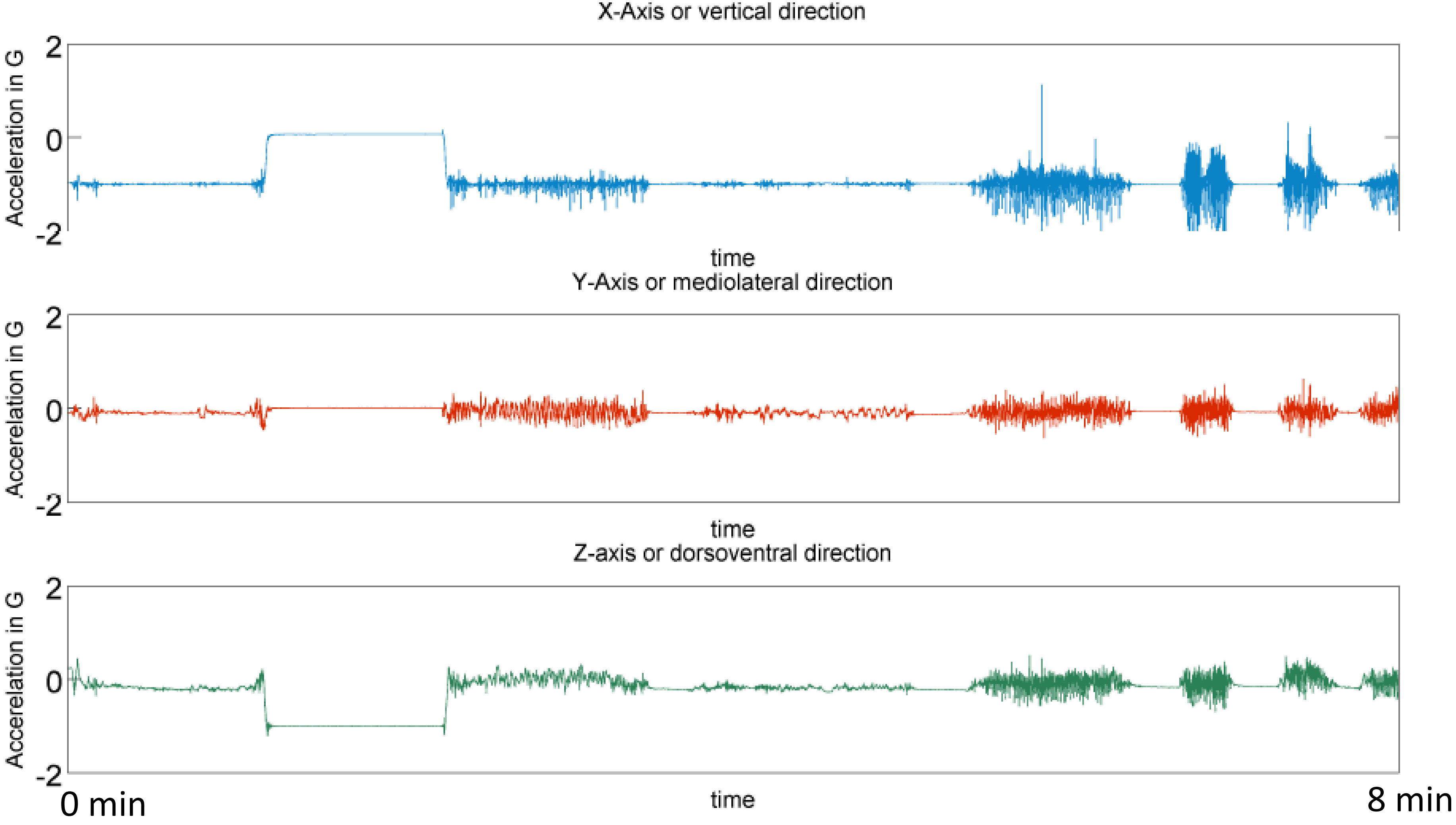
Digital Health Technology

- Digital Health Technology (DHT)
  - Broad category of technology relating to health applications
- Focus in this presentation on DHTs measuring clinical endpoints or physiological data in clinical studies
- Examples:
  - Smart watches
  - Continuous blood glucose monitors (CBGM)
  - Activity monitors (accelerometers)
- CDRH’s DHCoE: https://www.fda.gov/medical-devices/digital-health-center-excellence

Activity Data

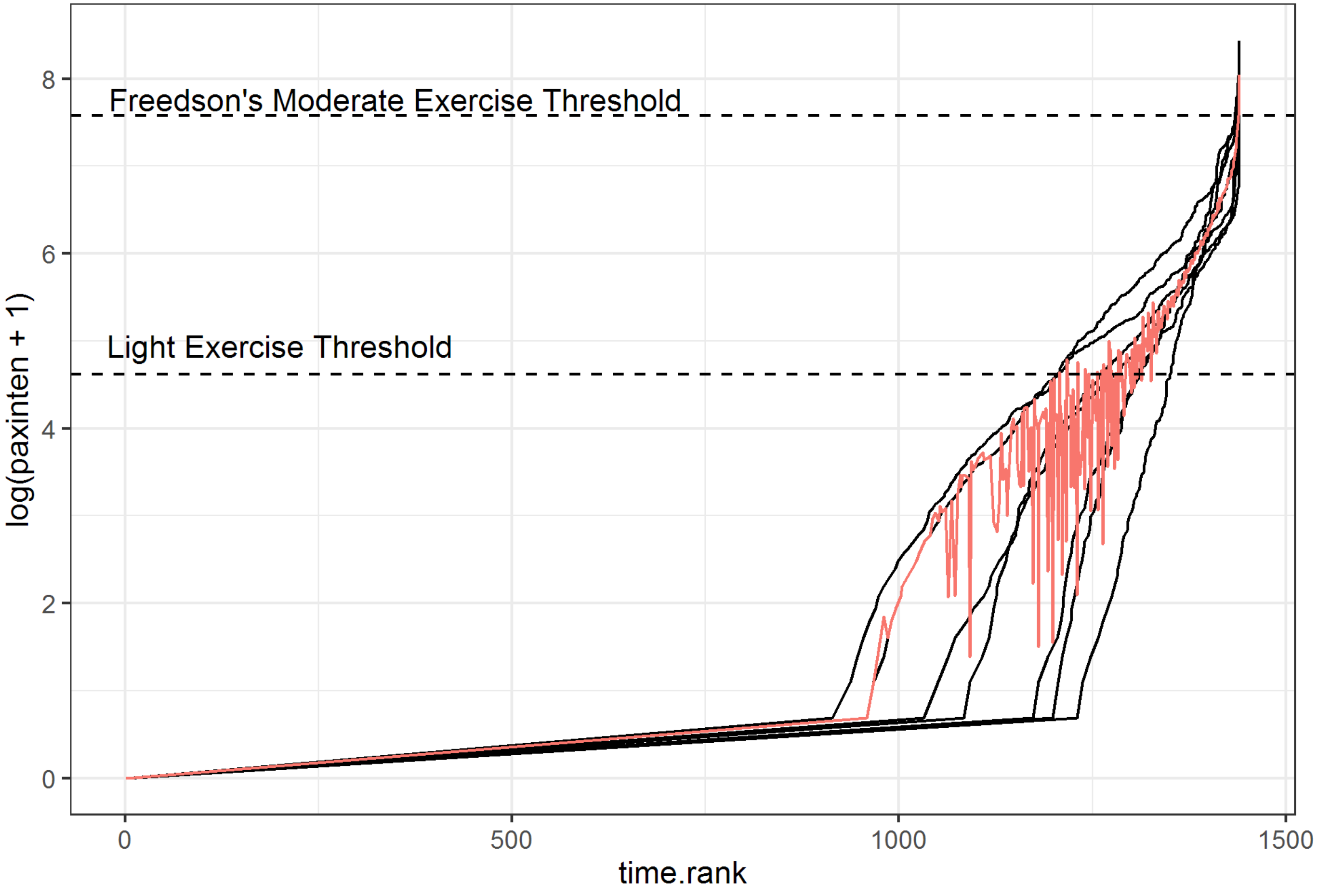
- A wearable accelerometer is used to measure free living exercise
  - Data is recorded when the device is worn
  - Aggregated into 1 minute epochs
  - At least 1440 data points per day
- Periods without recorded activity
  - Sleep?
  - Not wearing the device?
- Patients may wear the device for different times each day
- What may happen? How does it effect statistical analysis?

Movement Data from Acceleration Sensors



Gyllensten, IC, Physical Activity Recognition in Daily Life using a Triaxial Accelerometer, Master's Thesis, 2010.

Example Daily Activity Counts



- Sample subject from NHANES 2003-2004 dataset
- Each curve – activity count at a minute
- Red curve is mean of daily curves
- How to summarize?
  - The entire curve?
  - Features of the curve?

Two Frameworks

Functional Data Analysis

- Considers the data, $Y_{ij}(t)$, to be continuous in time measured: daily, hourly, sub-hourly
- Assumes model:
  $$Y_{ij}(t, X_i) = F_j(t, X_i) + e_i(t)$$
- Where,
  - $F_j(t, x_i)$ is the functional response for the jth treatment arm
    - May include random effects for subjects
  - X_i is any covariates
  - $e_i(t)$ is the error
    - May be white noise or correlated noise
- How to determine treatment effect?

Longitudinal Summary Statistics

- Considers the data, $\tilde{Y}_{ijs}$, to be summaries of the observed $Y_{ij}(t)$ measured at time points such as: weekly, monthly, etc
- Potential model:
  - Mixed effects models with random effects for subject’s trajectories
  - Marginal model using an unstructured or structured covariance matrix to address within patient correlation
  - Generalized estimating equations
- Does the summary statistical and model capture the relevant treatment effect?

CASE STUDY – ACTIVITY DATA AND MISSINGNESS

Activity Data as a Study Endpoint

- Consider an investigation drug X that is hypothesized to improve exercise
- Patients are followed for 6 weeks
- Can a wearable accelerometer measure exercise?
- Endpoint is related to daily total exercise change over 6 weeks
  - Total steps?
  - Time spent in moderate to vigorous physical activity?
  - Walking speed?
- What time scale for baseline exercise and Week 6 exercise?

Verification and Validation of DHT measurements

- Addresses the question “Does the DHT measure what it proports to measure?”
- A property of how the DHT takes the measurements
- Examples:
  - How accurate and precise are measurements of blood glucose measurements from a CGBM?
  - How accurate and precise are measurements of acceleration in an activity monitor?

Verification and Validation of DHT measurements

- Addresses the question "Does the DHT measure the clinical endpoint in the target population?"
- Depends on the outcome, patient population, DHT, etc.
- May require studies in target population
- Examples:
  - How accurate and precise are functions of measurements (e.g., time in range) of blood glucose from a CGBM?
  - Is a step measured by the DHT a step in a Parkinson's disease patient?
  - Are activity thresholds capturing a patient's physical function?

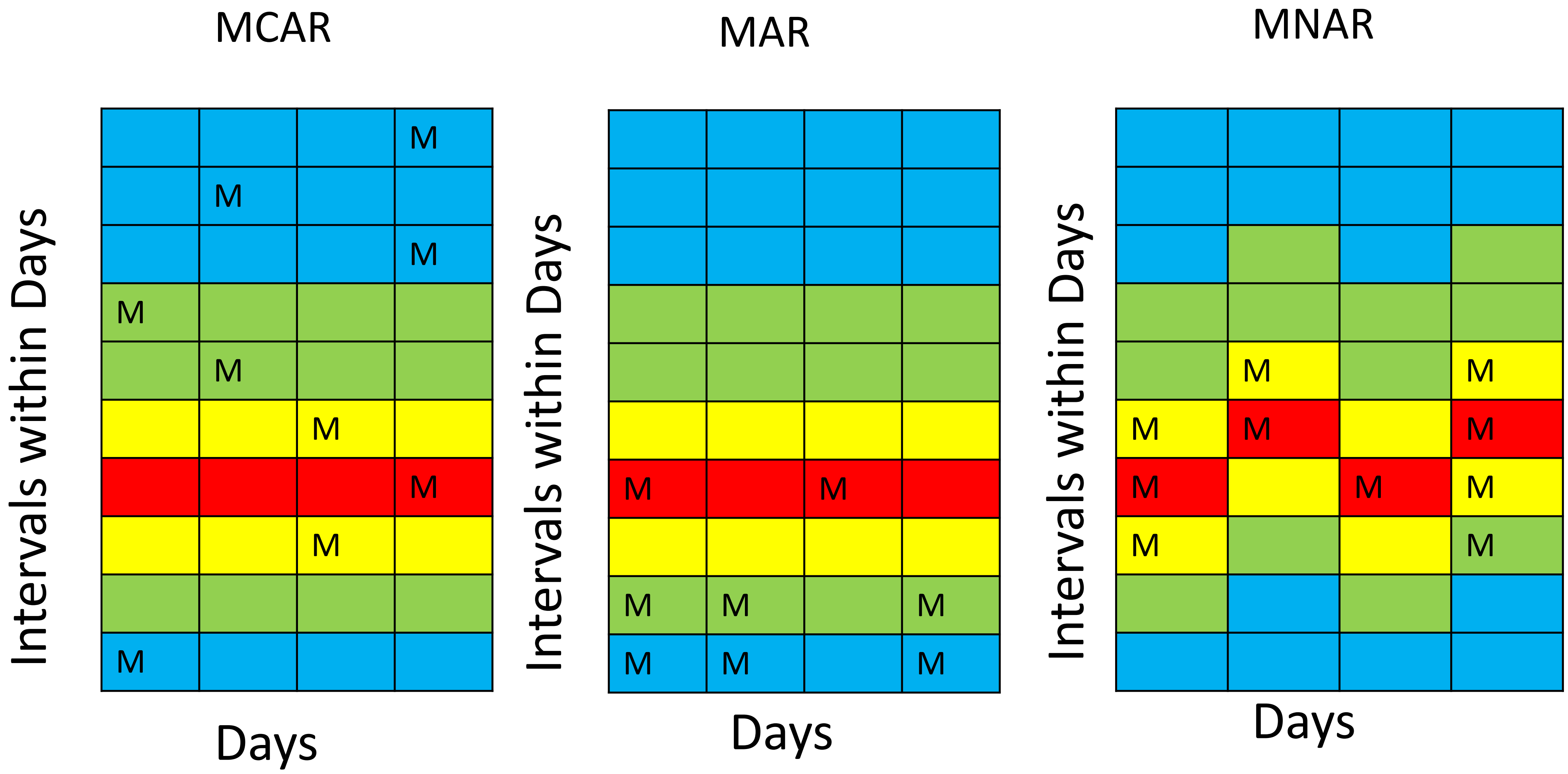
Potential Statistical Analyses

- ANCOVA
  - Use baseline and 6 week exercise data
  - Missing data: Unbiased estimates under MCAR assumption for missing data
- MMRM on the weekly summarized data
  - Uses every week of data
  - Missing data: Unbiased estimates under MAR assumption for longitudinal and MCAR for within day and week measurements
- Mixed model on the daily summarized data
  - Uses every day of data
    - How to incorporate non-linear temporal effects?
  - Missing data: Unbiased estimates under MAR assumption for missing days and MCAR for within day measurements
- Other methods?

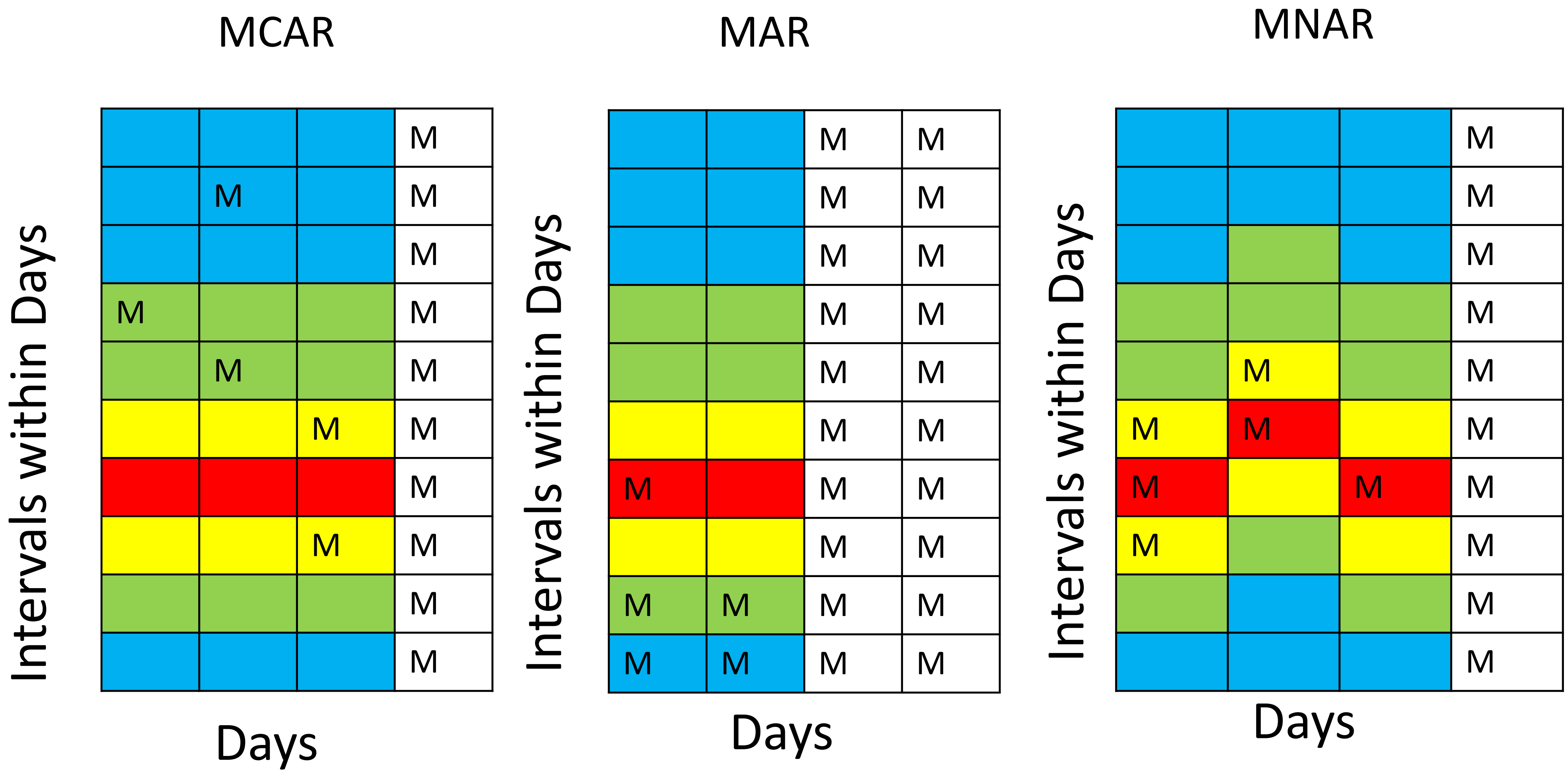
How data can go missing

- Missing data can occur at multiple time scales (minute, day, week, etc)
- At the minute scale:
  - DHT does not record the physical quantity
  - Patient removes DHT to go swimming
  - Etc
- At the day scale:
  - Patient is feeling sick and does not put on the DHT
- At the week scale:
  - Patient drops out of the study

Missing Data in Activity Data – Within Day



Missing Data in Activity Data – Monotone Dropout and Within Day



A Common Approach for Activity Data

- Calculate daily activity summary endpoint A_{day} if
  - Patient wears accelerometer for at least T hours
    - T is often 8, 10, or 12 hours
    - Consider this a valid day
- Calculate weekly activity summary endpoint A_{week} if
  - Patient has at least W (often 3-4) valid weekday measurements
  - Patient has at least U (often 1) valid weekend measurements
- Some proposals include standardizing A_{day} to a common day length
- This method assumes that missing epochs are missing at random (MCAR)
  - Is this justifiable?

Alternative Approaches

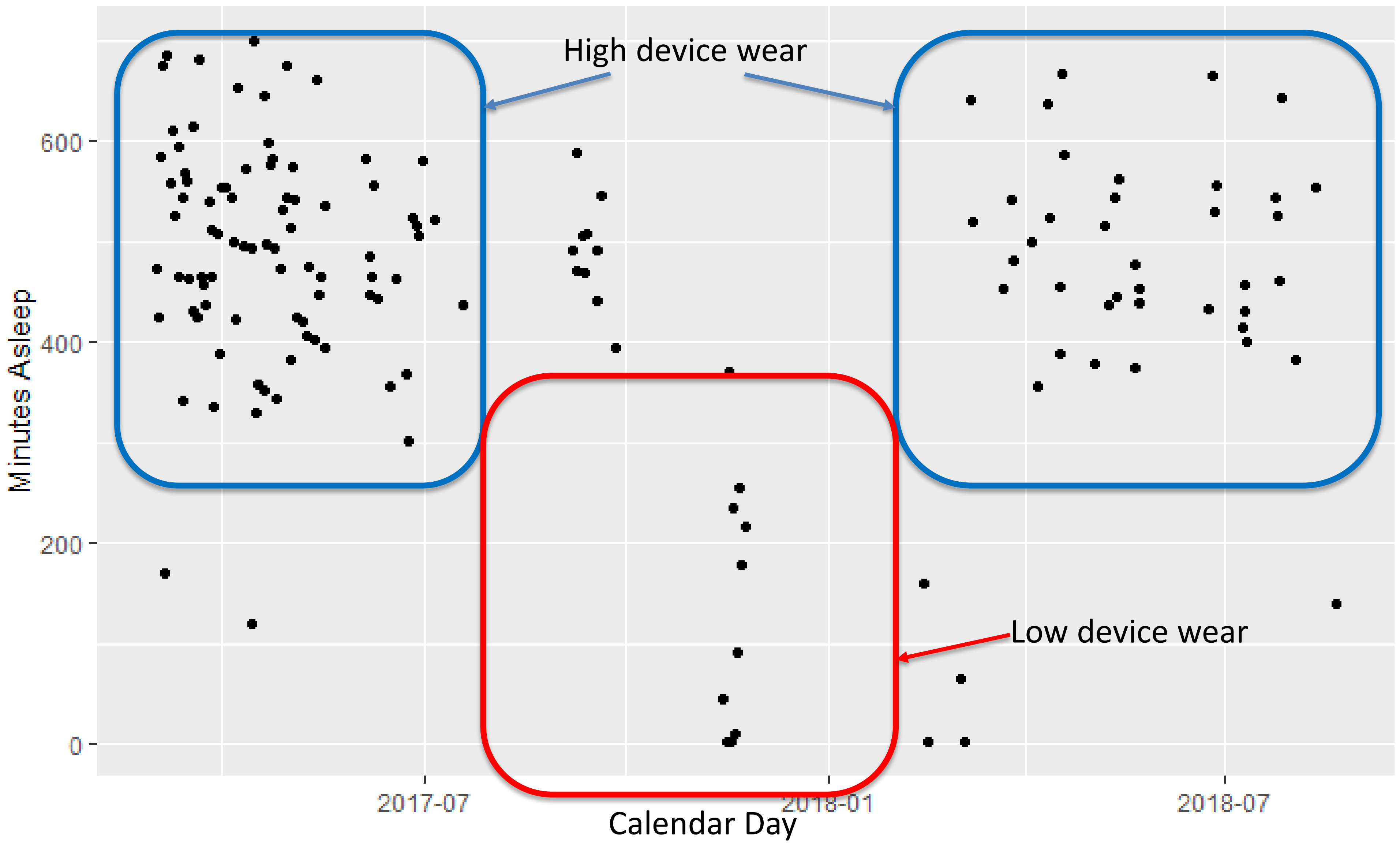
- Imputation by borrowing between days
- Censoring partial day observations
- Imputation by fitting smooth functions within each day

CASE STUDY - SLEEP

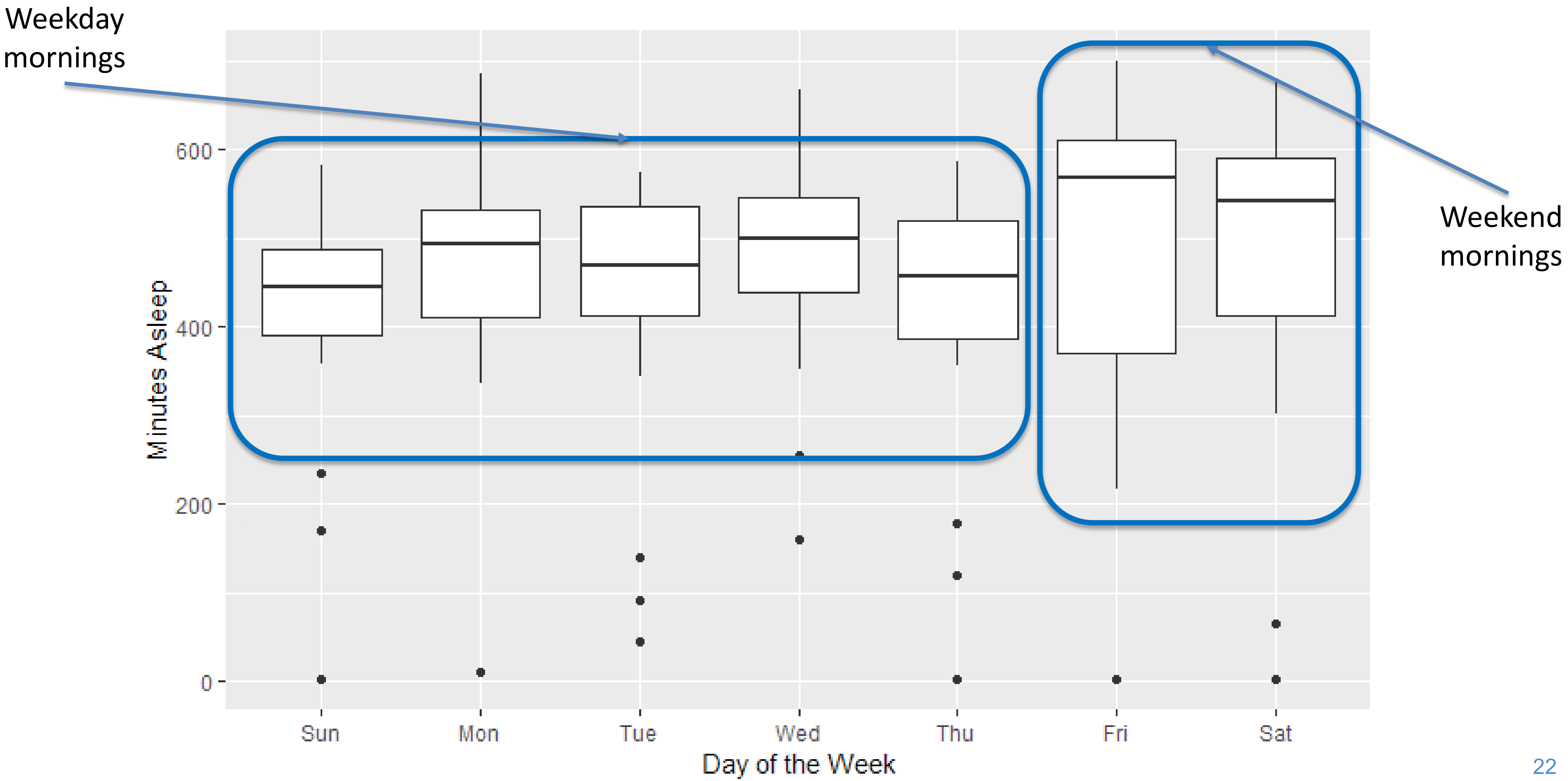
Total Sleep Time

- Measure of how long a person sleeps during the night
- Usually measured with polysomnography (PSG)
  - PSG determines sleep/awake by measuring brains electrical activity
  - Read by expert readers
- Can motion detected by an accelerometer be processed to determine time spent sleeping?
  - Algorithms classify each time epoch into sleep/awake using motion data
  - Utility depends on sensitivity and specificity of this classification
  - Provides daily sleep data

Total Sleep Time Derived from Acceleration Sensor



Weekday to Weekend Variability In Total Sleep Time



Weekday to Weekend Variation - Sleep

- Case Study on:
  - Analysis of the longitudinal evolution of the daily sensor data
- Illustrate an approach to analyzing longitudinal evolution using total sleep time (TST) as a summary measure of daily sensor data
  - Compare changes in TST between a new sleep medication to placebo over four weeks
  - Focus on modeling the linear trend in TST in both groups
  - Use all observed data
  - Calculation of TST at specific time points conducted after statistical modeling
- Framework extends to multiple sleep parameters and functional models

Case Study - Sleep

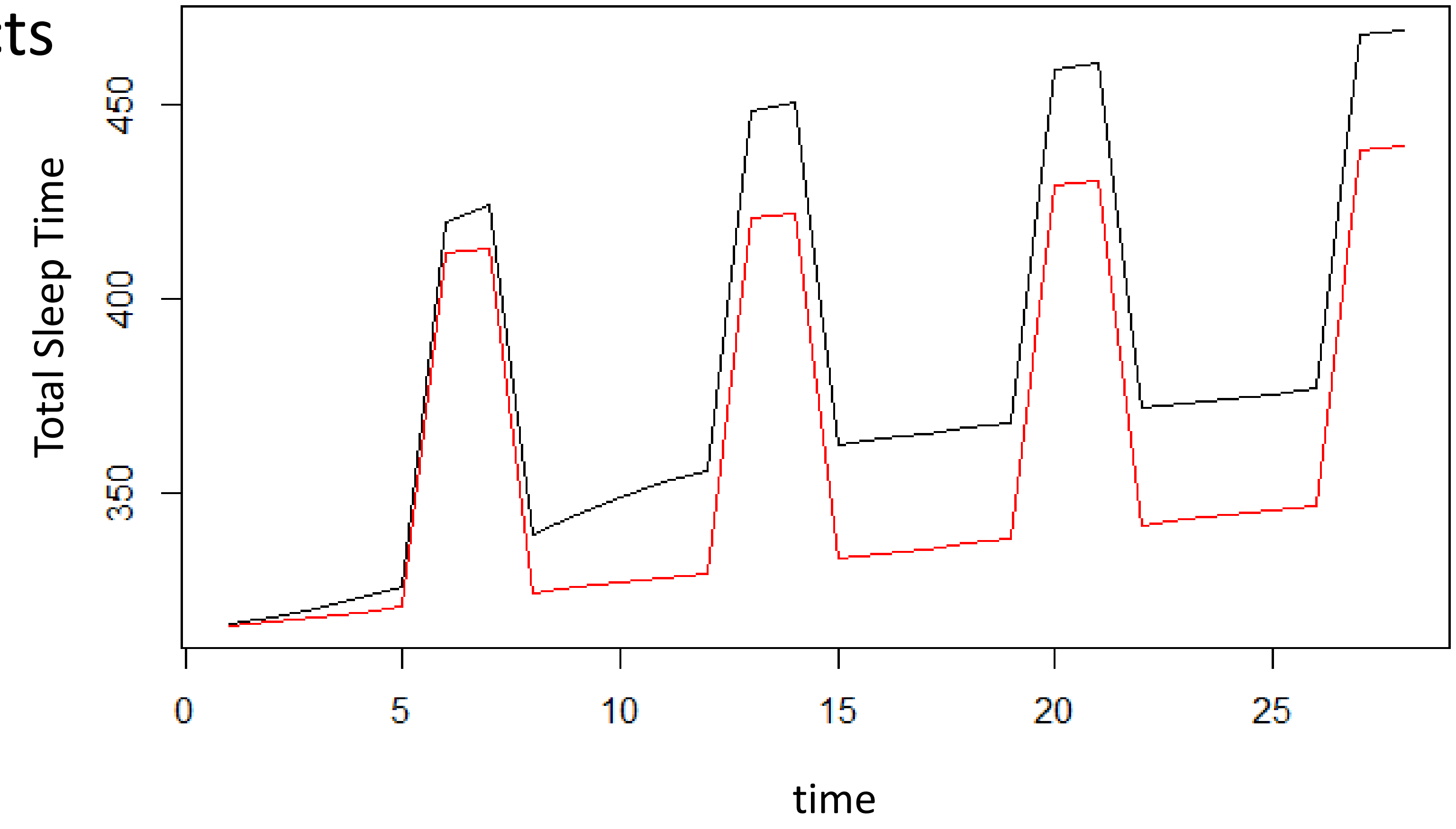
- Simulated data:
  - 300 patients
  - 30 minute improvement in TST by day 15
  - Similar change in TST to several NDAs submitted to FDA
  - Complete data vs. Monotone dropout
- Measure treatment effect by:
  - Difference in TST at four weeks
    - Estimate after modeling vs. calculate average before modeling (NA if any day missing)
  - Average TST trajectory in each group – model on the linear part of the trend
- Use two statistical models
  - Linear mixed model
    - Linear functional form of time with random slopes and adjustment of day of week
    - Factor for week with days correlated within week and adjustment of day of week
    - Factor for week and no adjustment for day of week in the model
  - Generalized estimating equation (GEE) model – robust to misspecification of covariance between days

Case Study - Sleep

- True treatment effect

$$F(t|TRT = active) - F(t|TRT = plb) = \frac{a}{1 + \mathrm{e}^{\{-b(t-c)\}}}$$

- Weekend effects are factors



Linear mixed model 1

$$Y_{ikl}(t_j) = \beta_0 + b_{0,i} + (\beta_1 + b_{1,1})t_j + \beta_2 \times TST_{baseline,i} + (\beta_3+\gamma_1 t_j) \times TRT_k + \sum_{l=1}^{7} \delta_l I(day_{il} = l) + \epsilon_{ikl}(t_j)$$

$$(b_0, b_1) \sim N(0, \mathbf{G}), \mathbf{G} = \begin{pmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{pmatrix}$$

$$\epsilon_{ikl}(t_j) \sim N(0, \sigma_\epsilon^2 \boldsymbol{I})$$

$$(b_0, b_1) \perp \epsilon_{ikl}(t_j)$$

i indexes the patient
k indexes the treatment arms
j is the observed days
l indexes the day of the week

(b_0, b_1): patient level random intercept and slop
$\epsilon_i(t_j)$: error

<u>Fixed Effects:</u>
β_0: intercept
β_1: time effect
β_2: baseline TST effect
β_3: treatment effect
γ_1: treatment by time effect
δ_l: day effect

Linear Mixed Model 2

$$Y_{ijkl} = \beta_0 + \beta_1 \times TST_{baseline,i} + \beta_2 \times TRT_k + \sum_{j=1}^{W} \alpha_j I\left(week_j = j\right) +$$

$$\sum_{j=1}^{W} \sum_{k=1}^{1} \gamma_{jk} I\left(week_j = j\right) \times TRT_k +$$

$$\sum_{l=1}^{7} \delta_l I(day_{il} = d) + \epsilon_{ijkl} \qquad \epsilon_{ijkl} \sim N\left(0, \begin{pmatrix} \Sigma_{11} & \cdots & \rho_2 \\ \vdots & \ddots & \vdots \\ p_2 & \cdots & \Sigma_{WW} \end{pmatrix}\right)$$

$$\Sigma_{jj} = \sigma^2 \begin{pmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & & \rho \\ \vdots & & \ddots & \vdots \\ \rho & \rho & \cdots & 1 \end{pmatrix}$$

<u>Fixed Effects:</u>

α_j: week effects

All other terms defined previously

Linear Mixed Model 3

$$Y_{ijk}$$

$$= \beta_0 + \beta_1 \times TST_{baseline,i} + \beta_2 \times TRT_k + \sum_{j=1}^{W} \alpha_j I\left(week_j = j\right)$$

$$+ \sum_{j=1}^{W} \sum_{k=1}^{1} \gamma_{jk} I\left(week_j = j\right) \times TRT_k + \epsilon_{ijkl}$$

$$Y_{ijk} = \frac{1}{7} \sum_{l=1}^{7} Y_{ijkl}$$

$$\epsilon_{ijk} \sim N\left(0, \begin{pmatrix} \sigma_{11} & \sigma_{12} & \cdots & \sigma_{1W} \\ \sigma_{21} & \sigma_{22} & & \sigma_{2W} \\ \vdots & & \ddots & \vdots \\ \sigma_{W1} & \sigma_{W2} & \cdots & \sigma_{WW} \end{pmatrix}\right)$$

All other terms defined previously

Generalized Estimating Equation (GEE)

$$Y_{ikl}\left(t_j\right) = \beta_0 + (\beta_1)t_j + \beta_2 \times TST_{baseline,i} + (\beta_3 + \gamma_1 t_j) \times TRT_i + \sum_{l=1}^{7} \delta_l I(day_{il} = d) + \epsilon_{ikl}\left(t_j\right)$$

Working correlation matrix is AR(1)
Standard errors estimated with sandwich estimator
All other terms defined previously

Generalized Estimating Equation (GEE)

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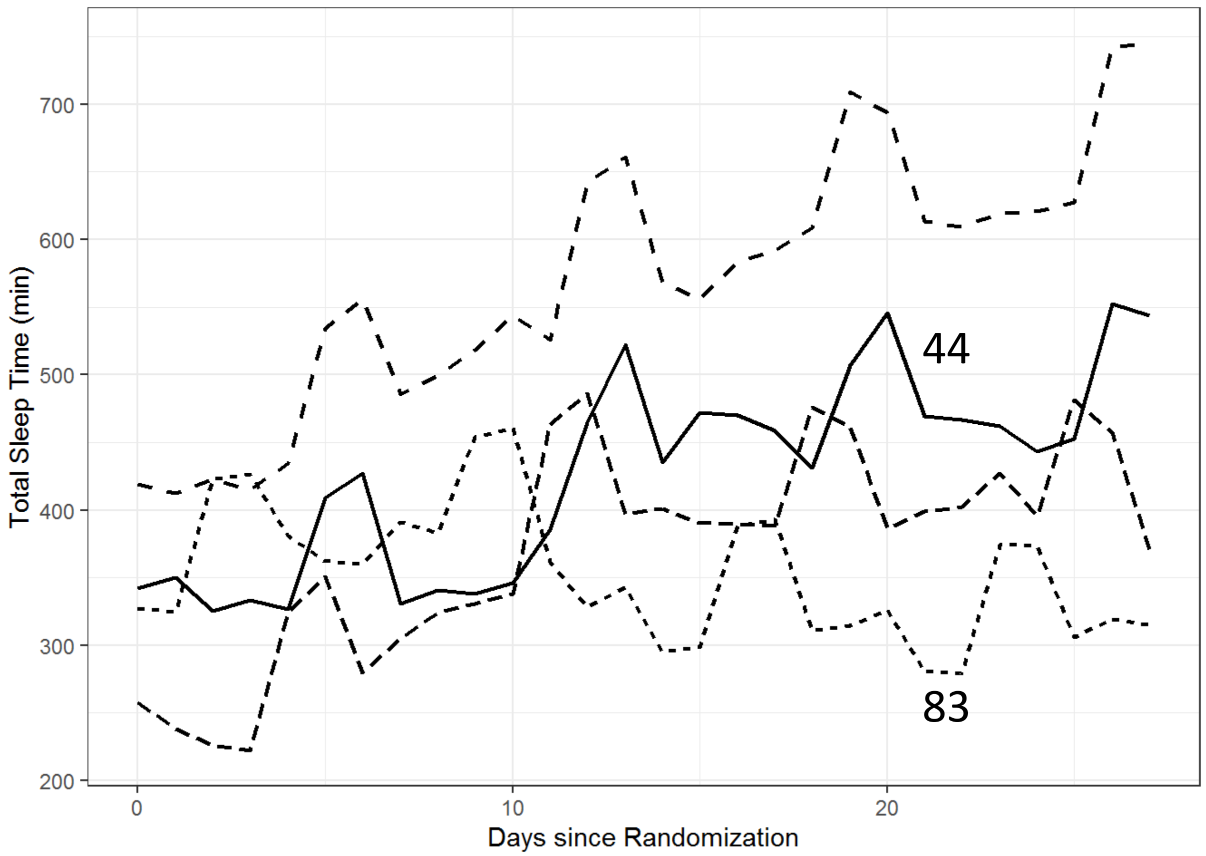
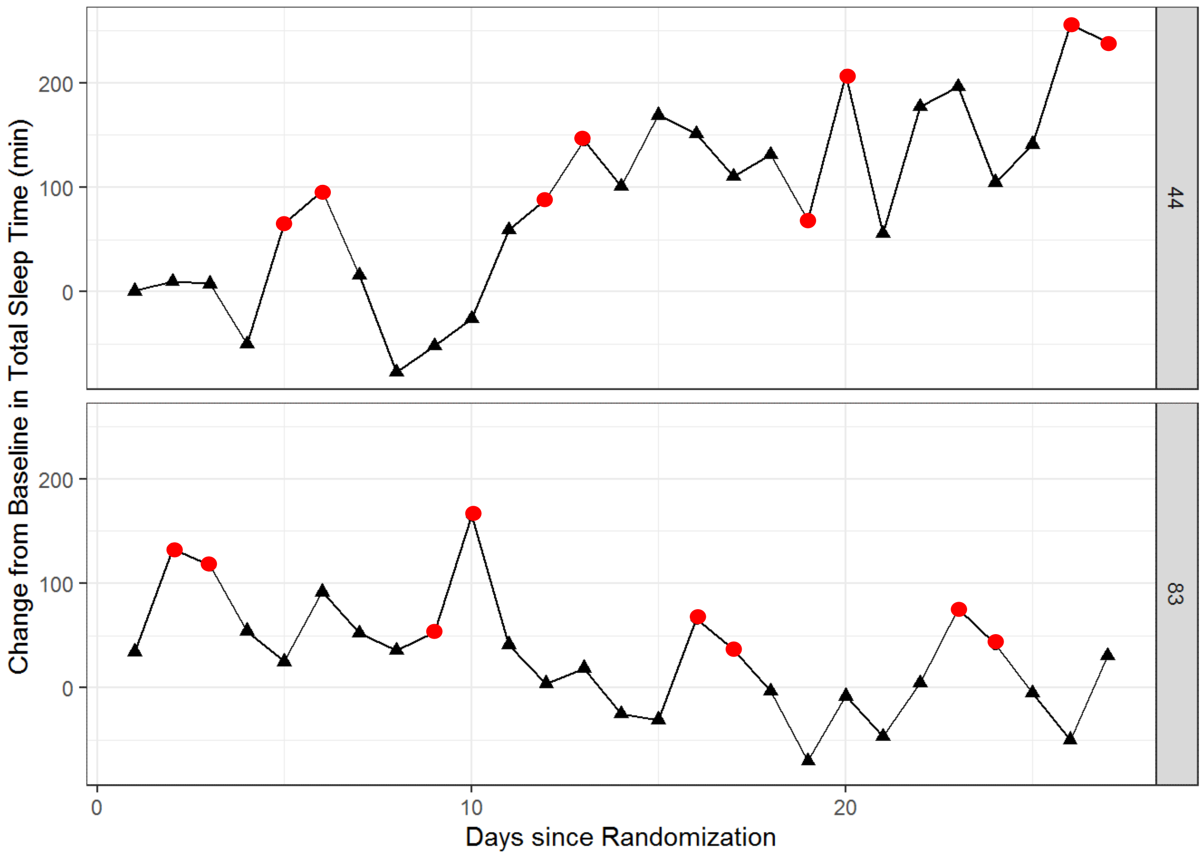
Simulated Clinical Trial – The Data

Example Subjects



Subject Specific Change from Baseline in TST

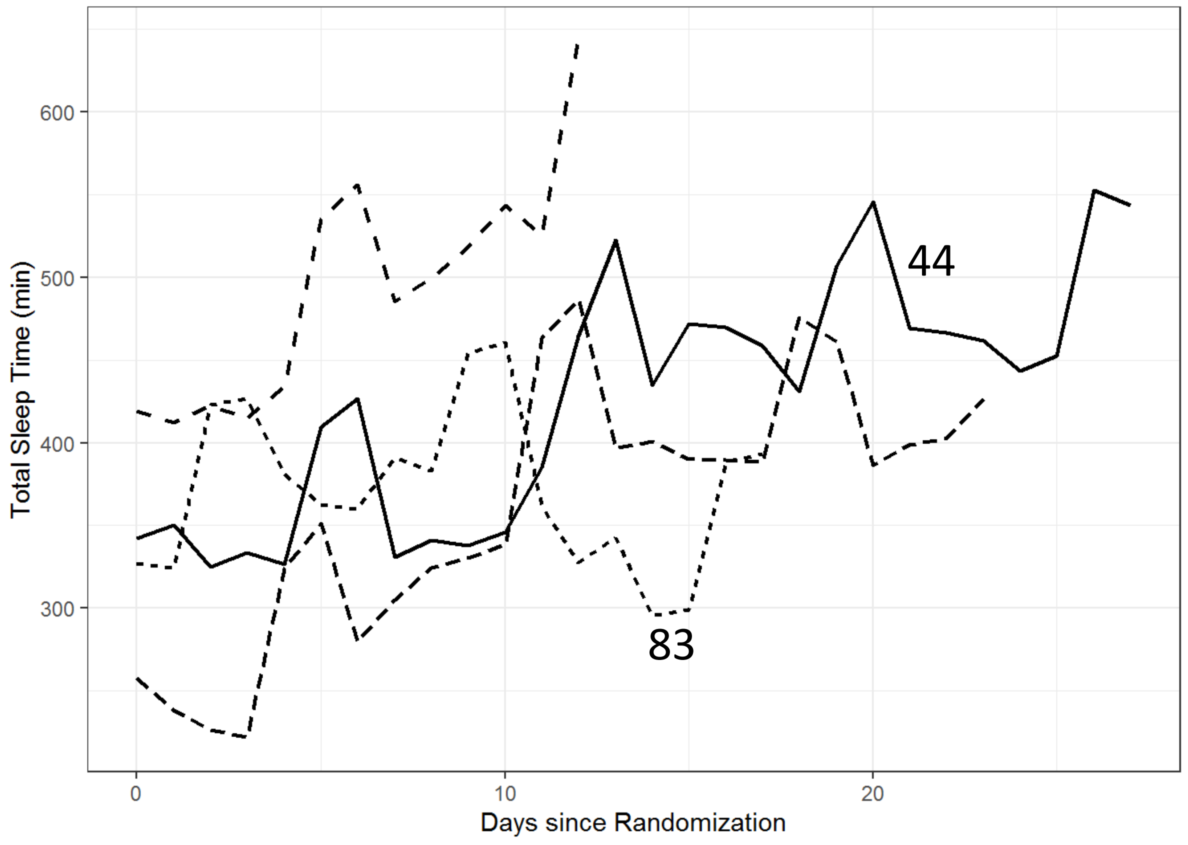


Triangles – Weekday

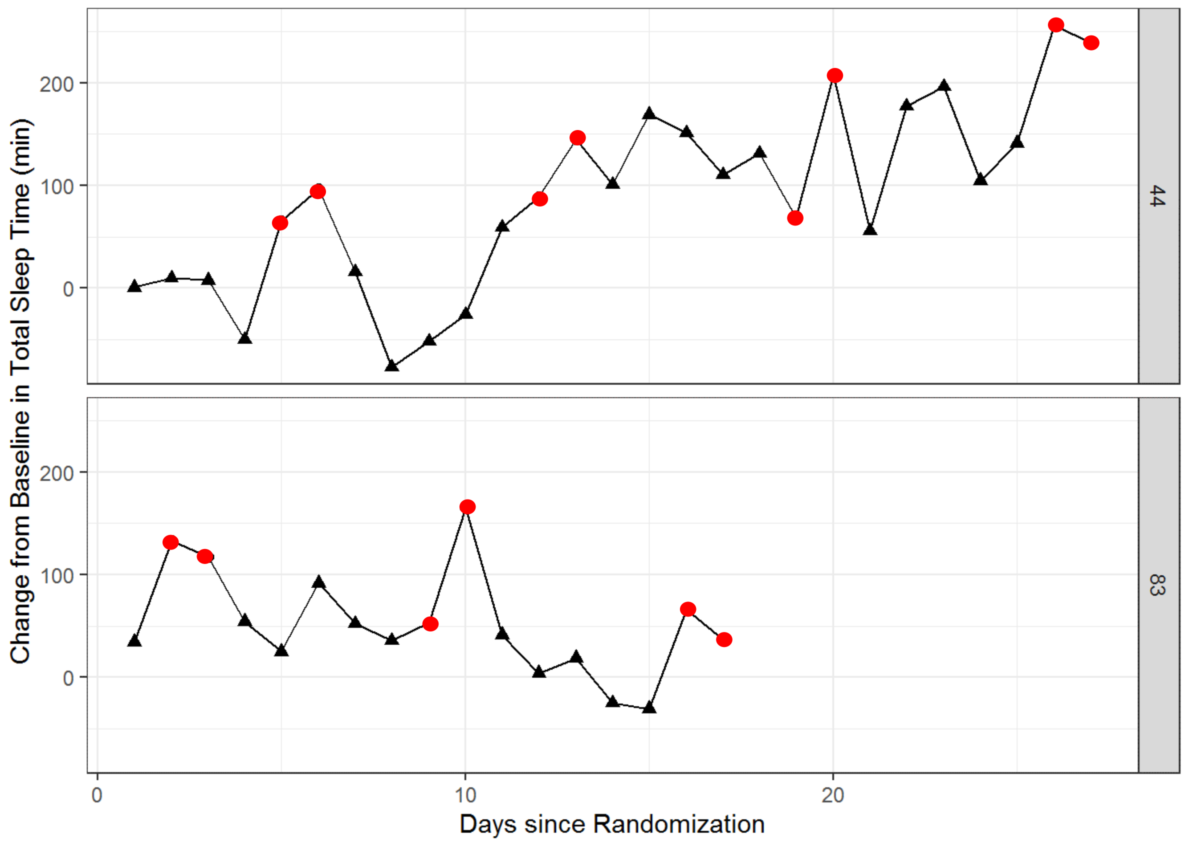
Red Circles - Weekend

Simulated Clinical Trial – The Data with Dropout

Example Subjects



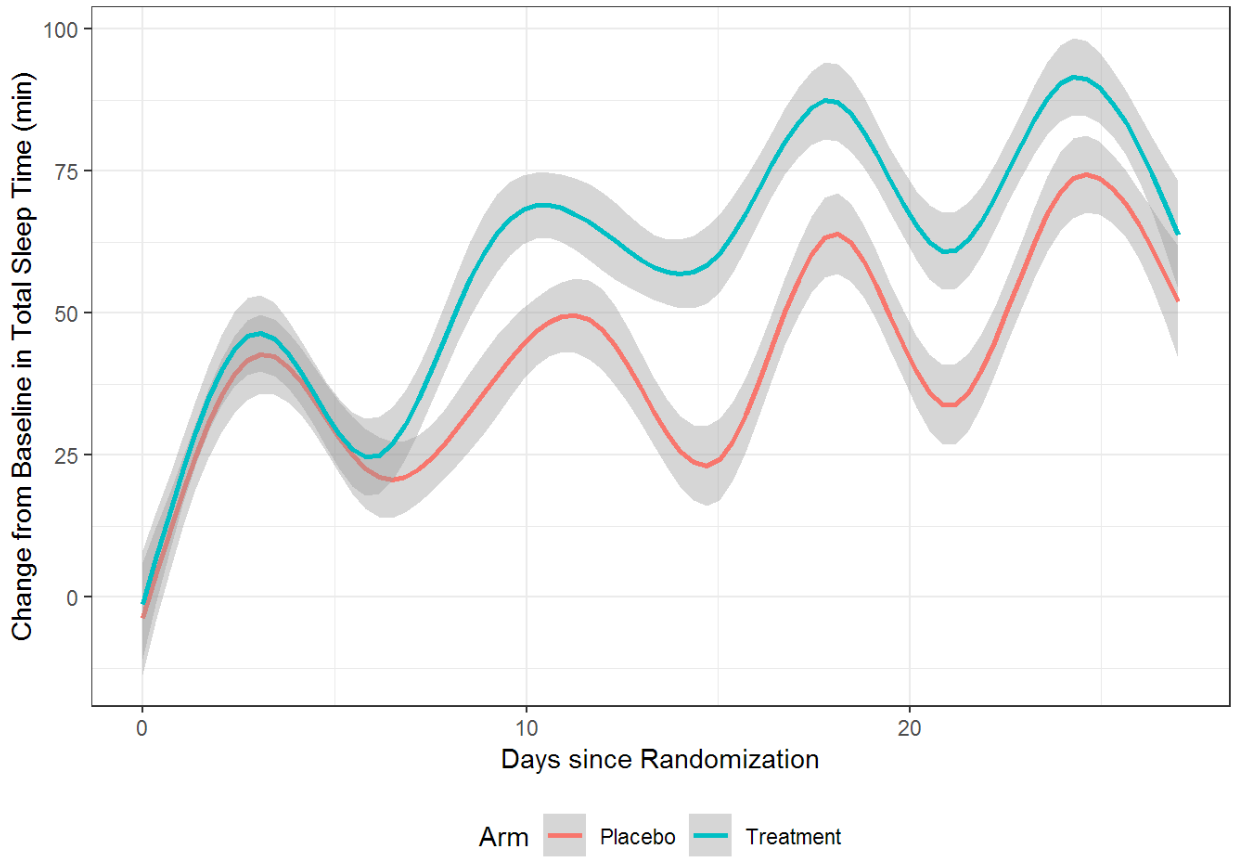
Subject Specific Change from Baseline in TST



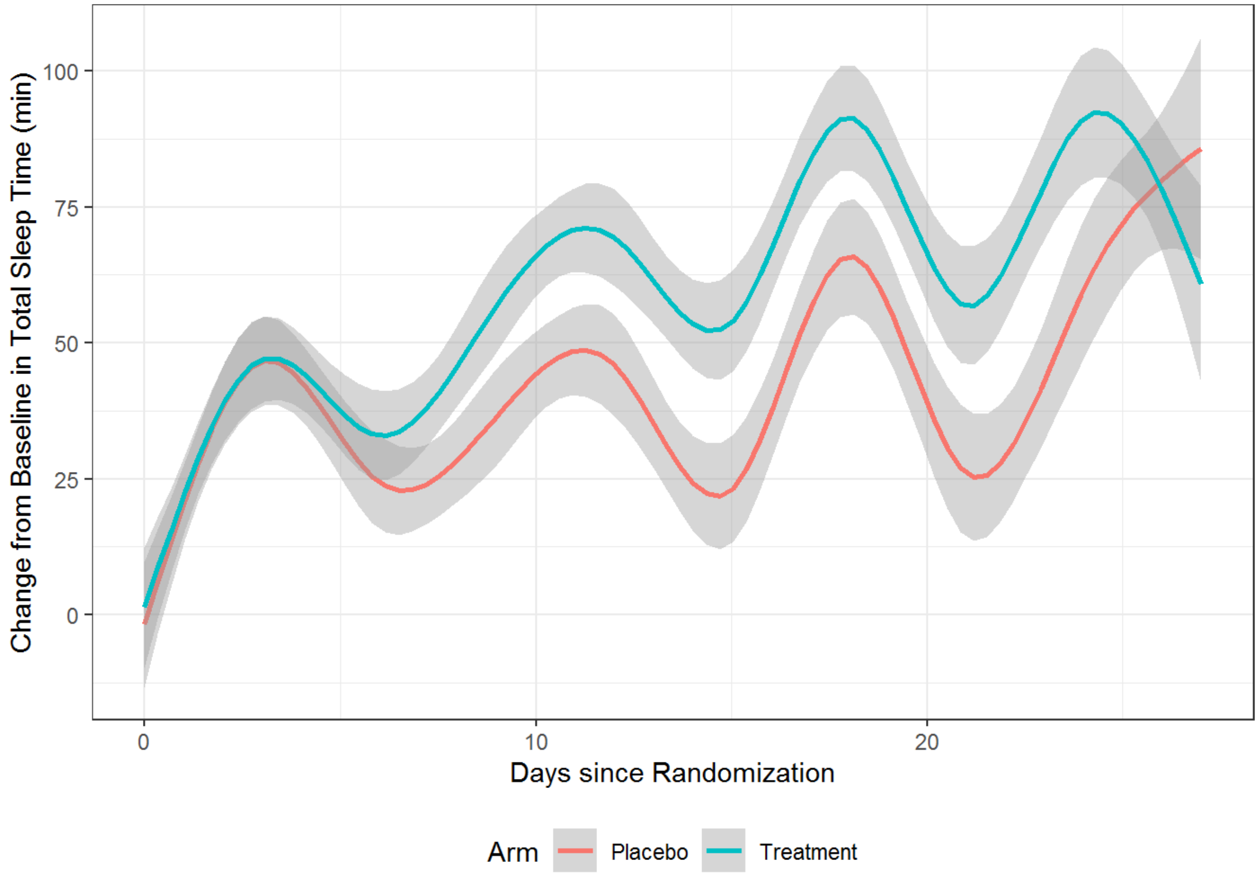
Triangles – Weekday
Red Circles - Weekend

Population Average Total Sleep Time Trajectories

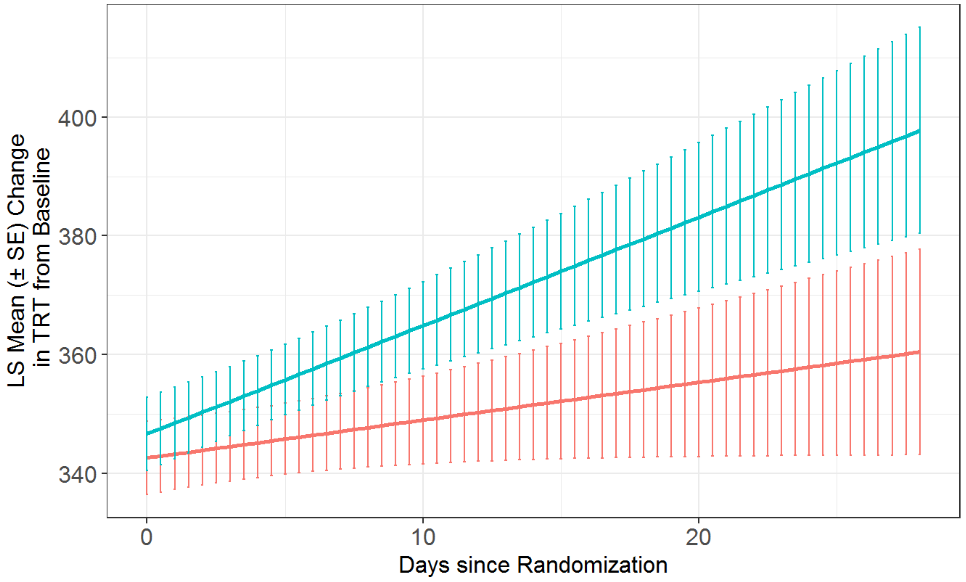
Complete Data



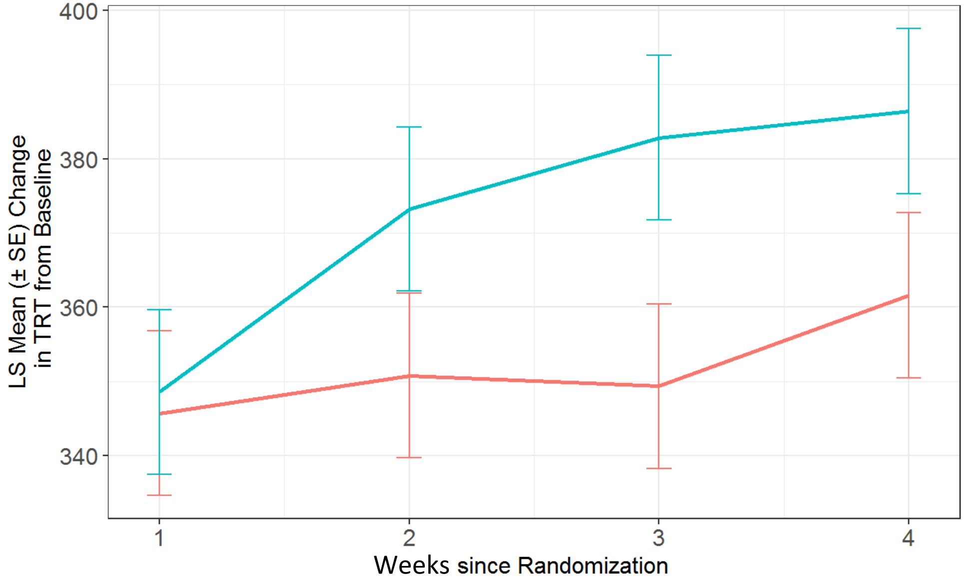
Monotone Dropout



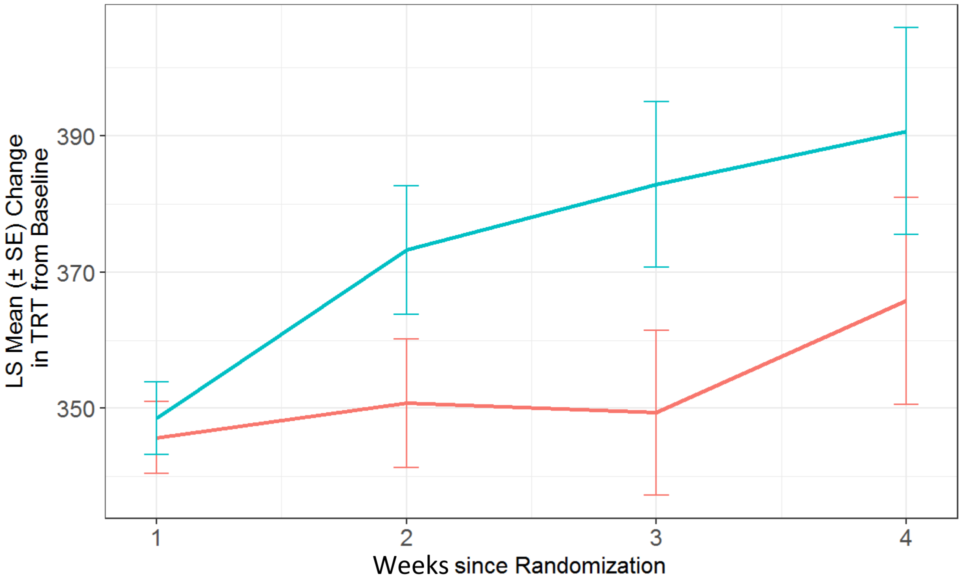
Complete Data



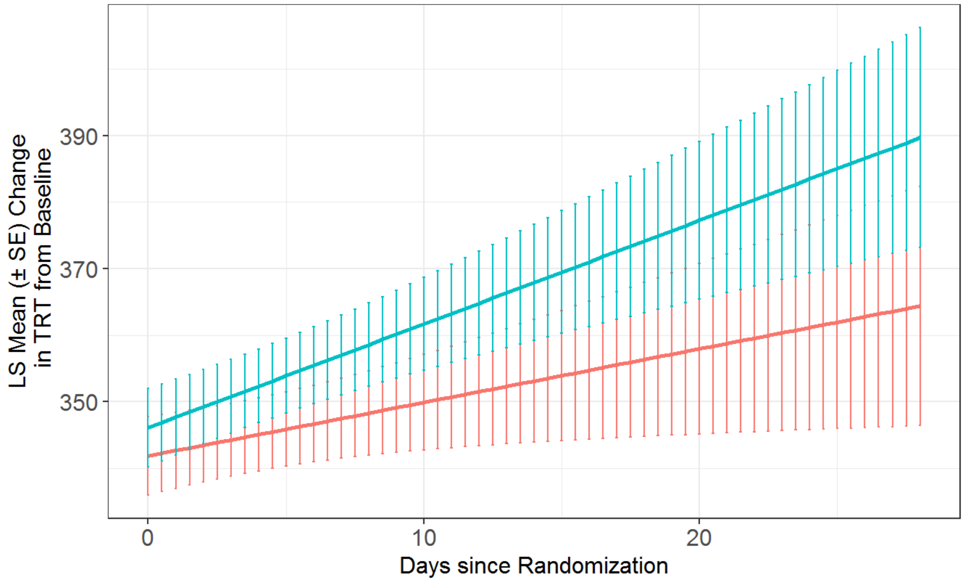
LMM1 – Linear Function of Time



LMM2 – Factor for week including days

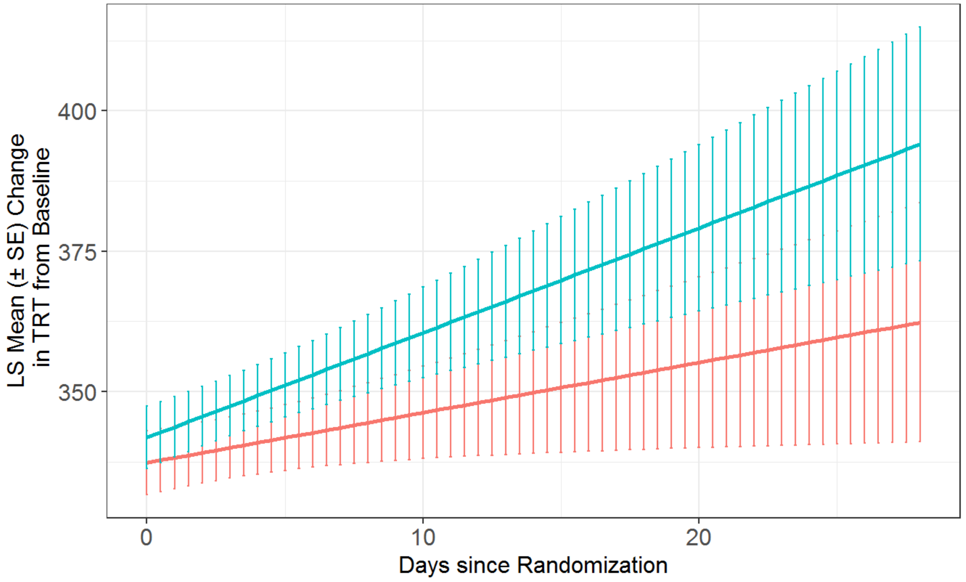


LMM3 – Pre-model averaging for week

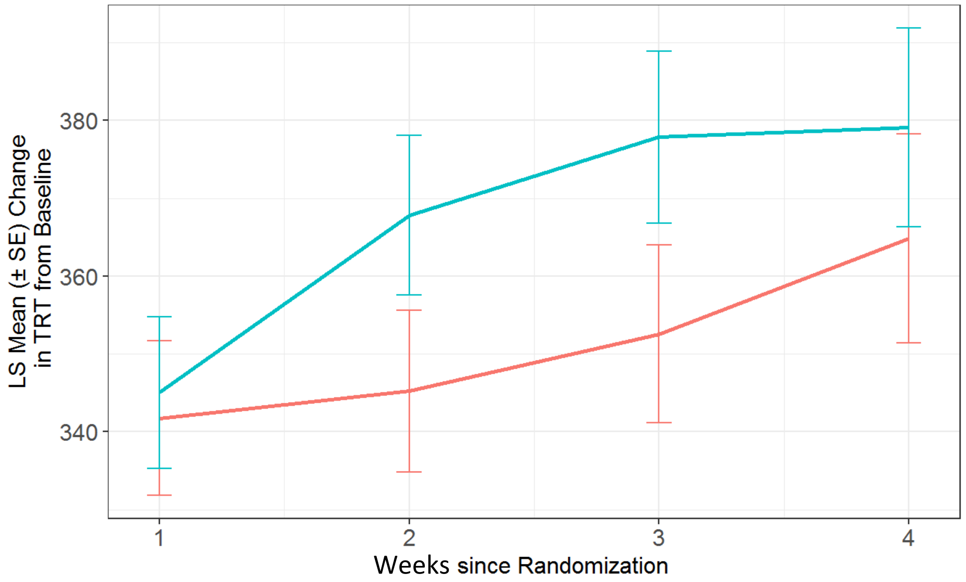


GEE – Linear Function of Time

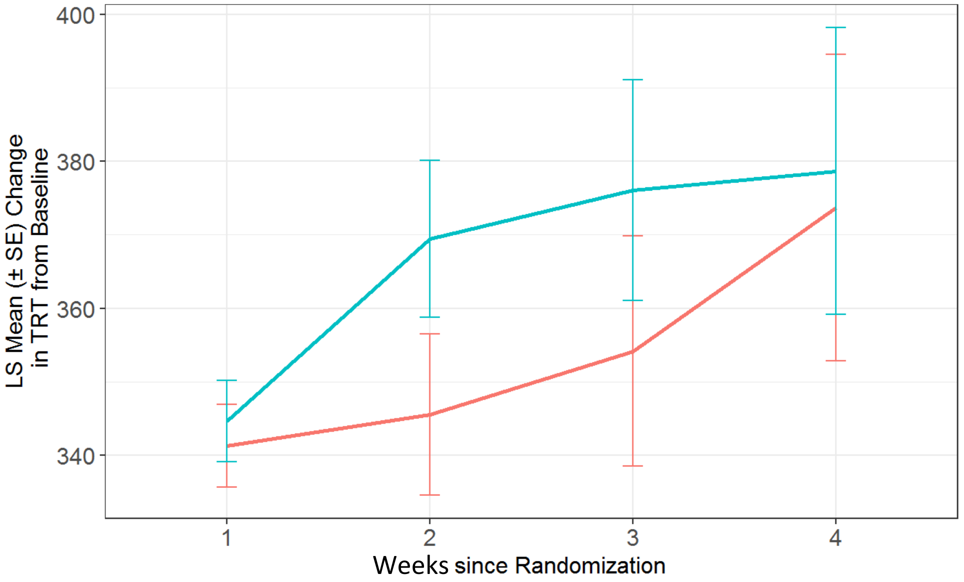
Monotone Dropout



LMM1 – Linear Function of Time



LMM2 – Factor for week including days



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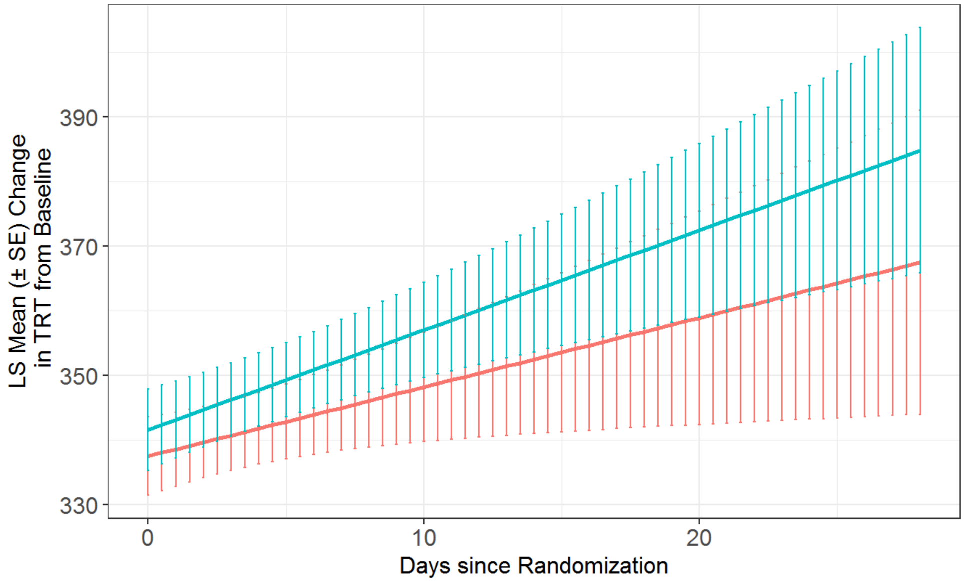


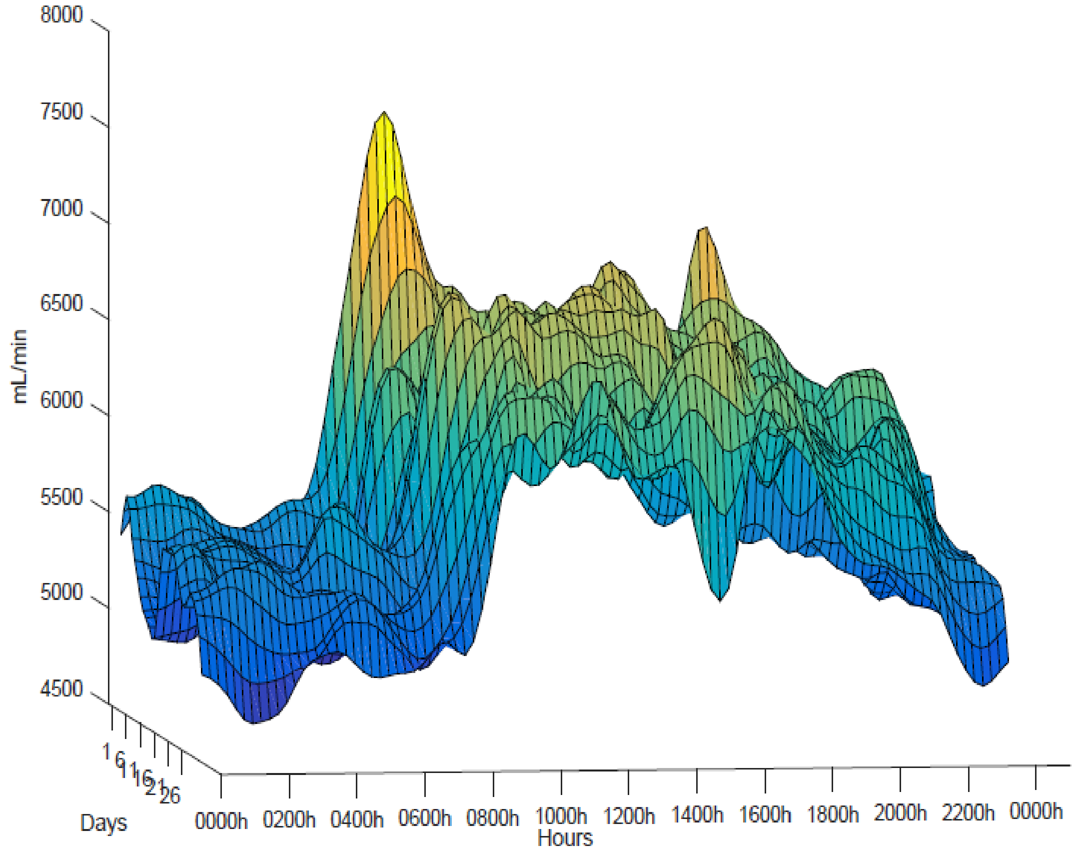
GEE – Linear Function of Time

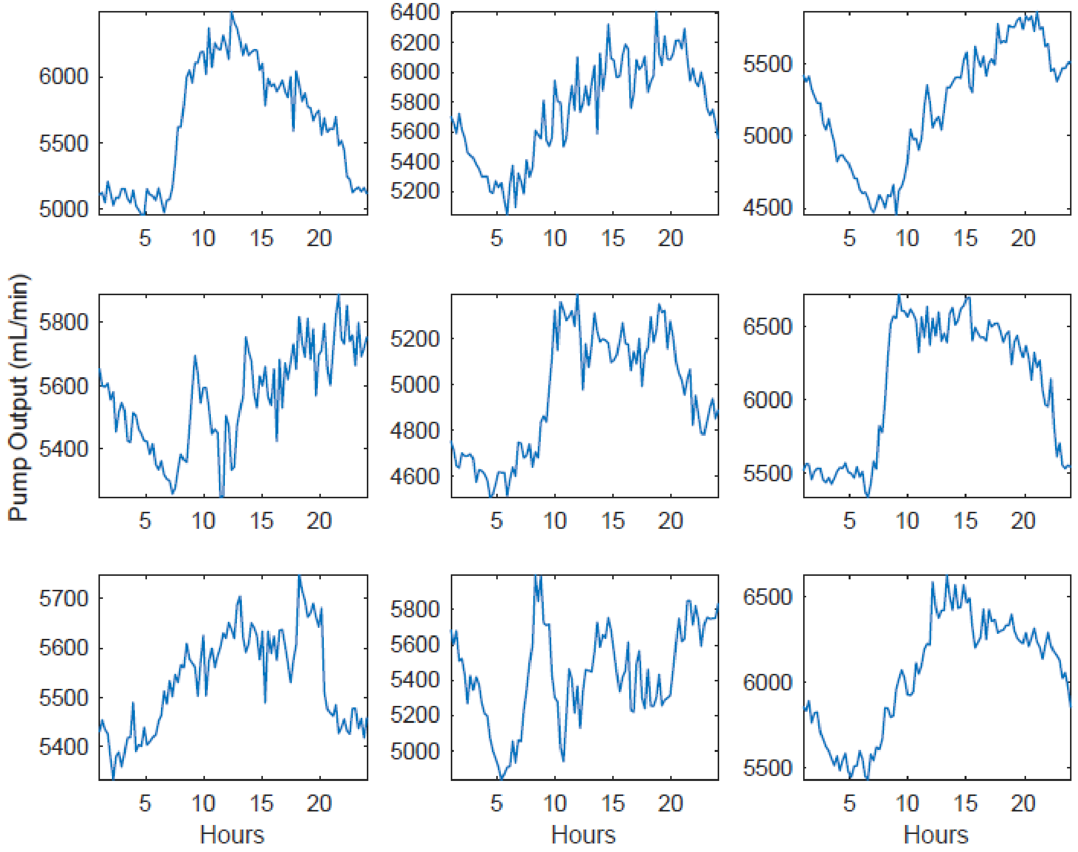
Estimated Treatment Effects

	Model	Complete Data				Monotone Dropout			
		Estimated Daily Δ (min)	95% Confidence Interval		p-value	Estimate Daily Δ (min)	95% Confidence Interval		p-value
TST difference at Day 28	LMM1 – Linear Function of Time and random slopes with day term	37.3	12.8	61.8	0.003	31.8	2.0	61.5	0.037
	GEE – Linear Function of Time and AR1 working correlation with day term	25.3	0.93	49.7	0.041	17.3	-12.9	47.5	0.262
TST difference at Week 4	LMM2 – Week as Factor with day term	24.8	9.1	40.6	0.002	14.3	-4.3	32.79	0.131
	LMM3 – Pre-averaged week without with day term	24.9	3.4	46.4	0.023	5.0	-23.6	33.6	0.347

CASE STUDY – CIRCADIAN VARIATION

An Important Feature:
Circadian Variation in Sensor Data

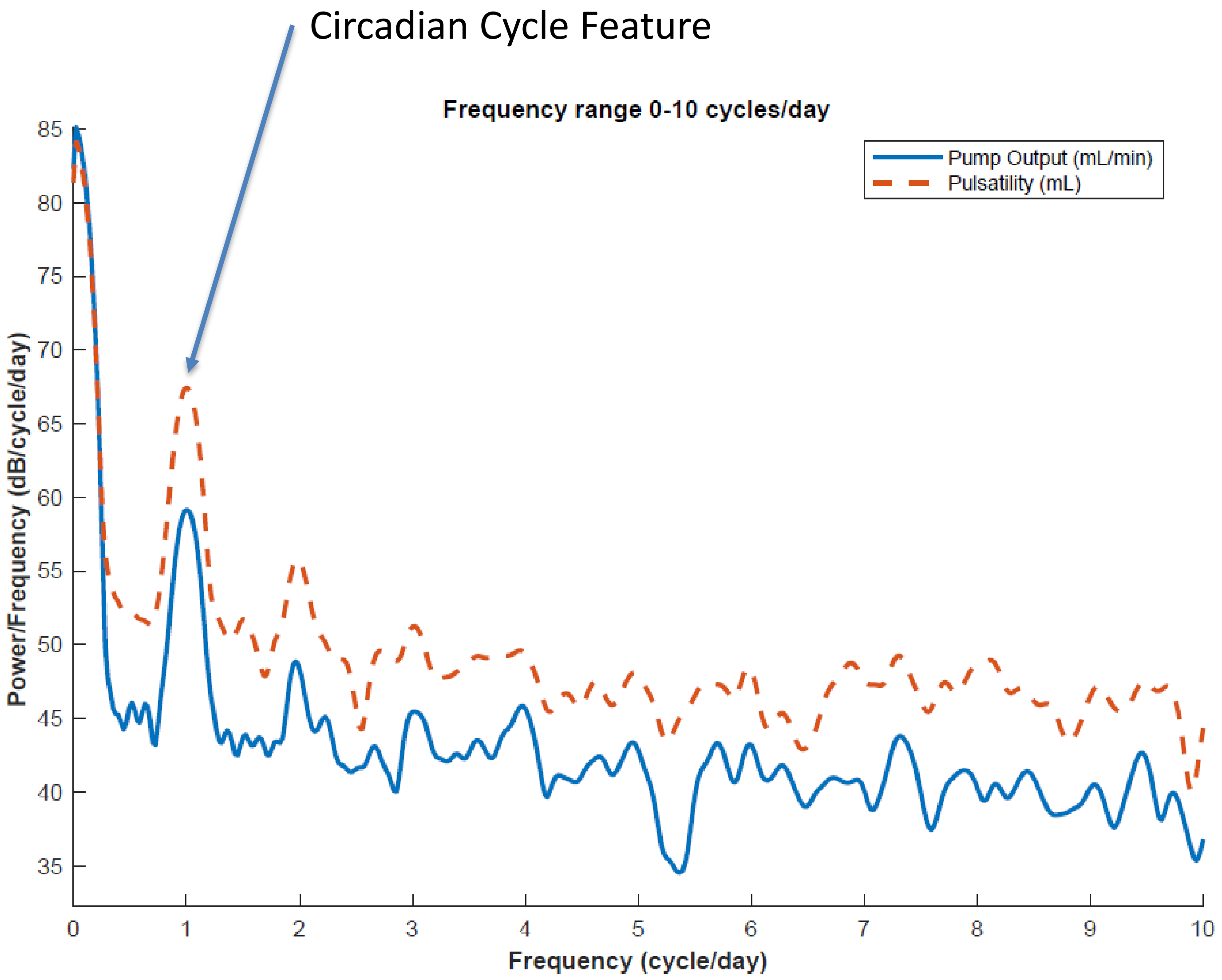




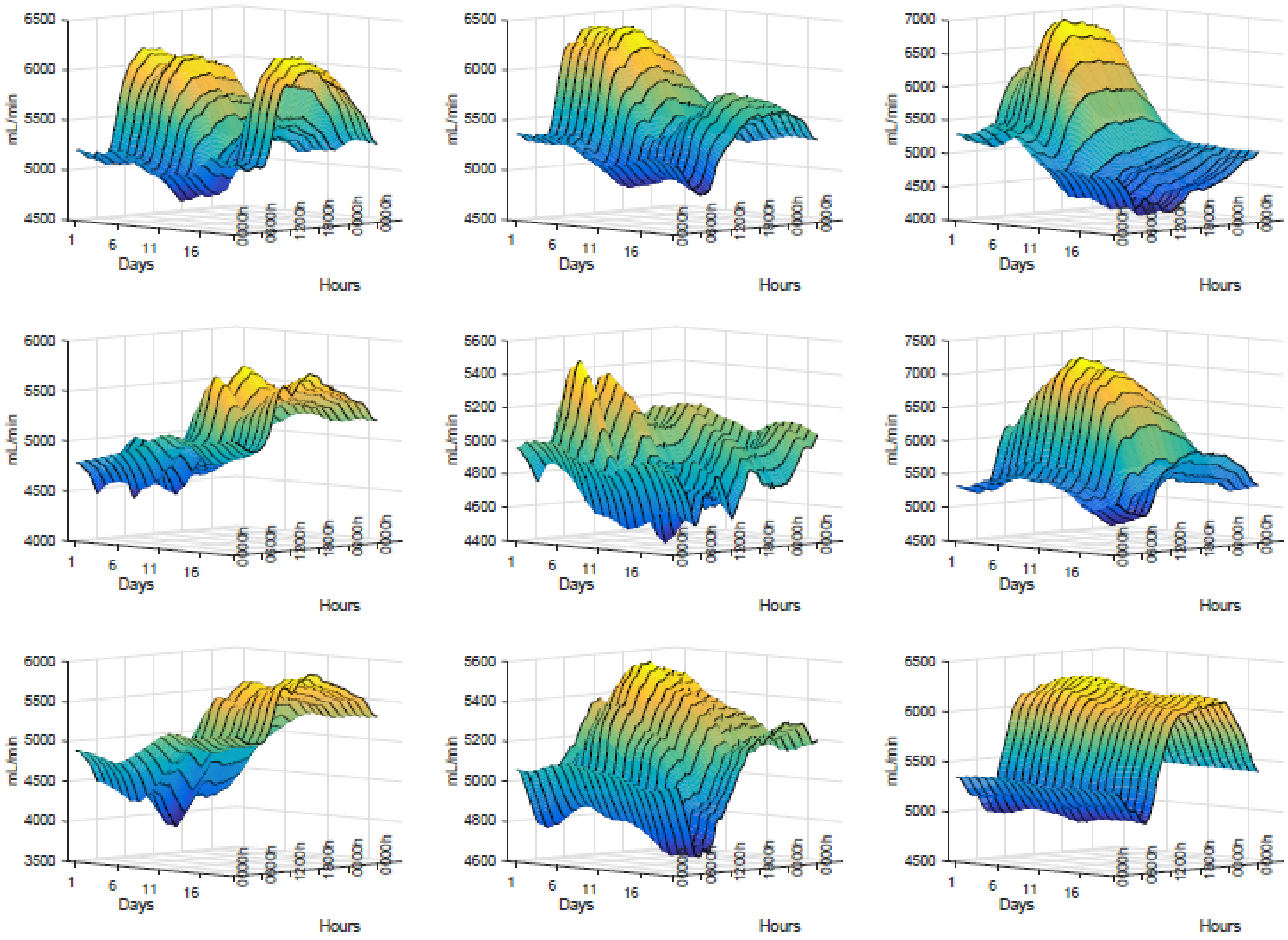
- Blood flow data from a ventricular assist device recorded every 15 min.
- Circadian patterns present in multiple types of sensor data

Extracting Features – Fourier Transform

- Focuses on periodic features in a signal
  - Represents the strength of a signal over a range of frequencies
  - Signals with circadian variation have a peak at 1 cycle/day



Longitudinal Evolution of Circadin Variation



Conclusions

- Missing data approaches can affect both the mean and standard error estimation
- Different models can provide useful information even when mis-specified
- Need to conduct model assessment
- Need to conduct model diagnostics
- Need to develop and conduct assessments of missing data approaches

References

- Catellier DJ et al, Imputation of missing data when measuring physical activity by accelerometry. *Med Sci Sports Exerc*. 2005;37(11 Suppl):S555-S562. doi: 10.1249/01.mss.0000185651.59486.4e
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