

Statistical Concerns for the Analysis of Data Collected by Wearable Digital Health Technology in Clinical Trial

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

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

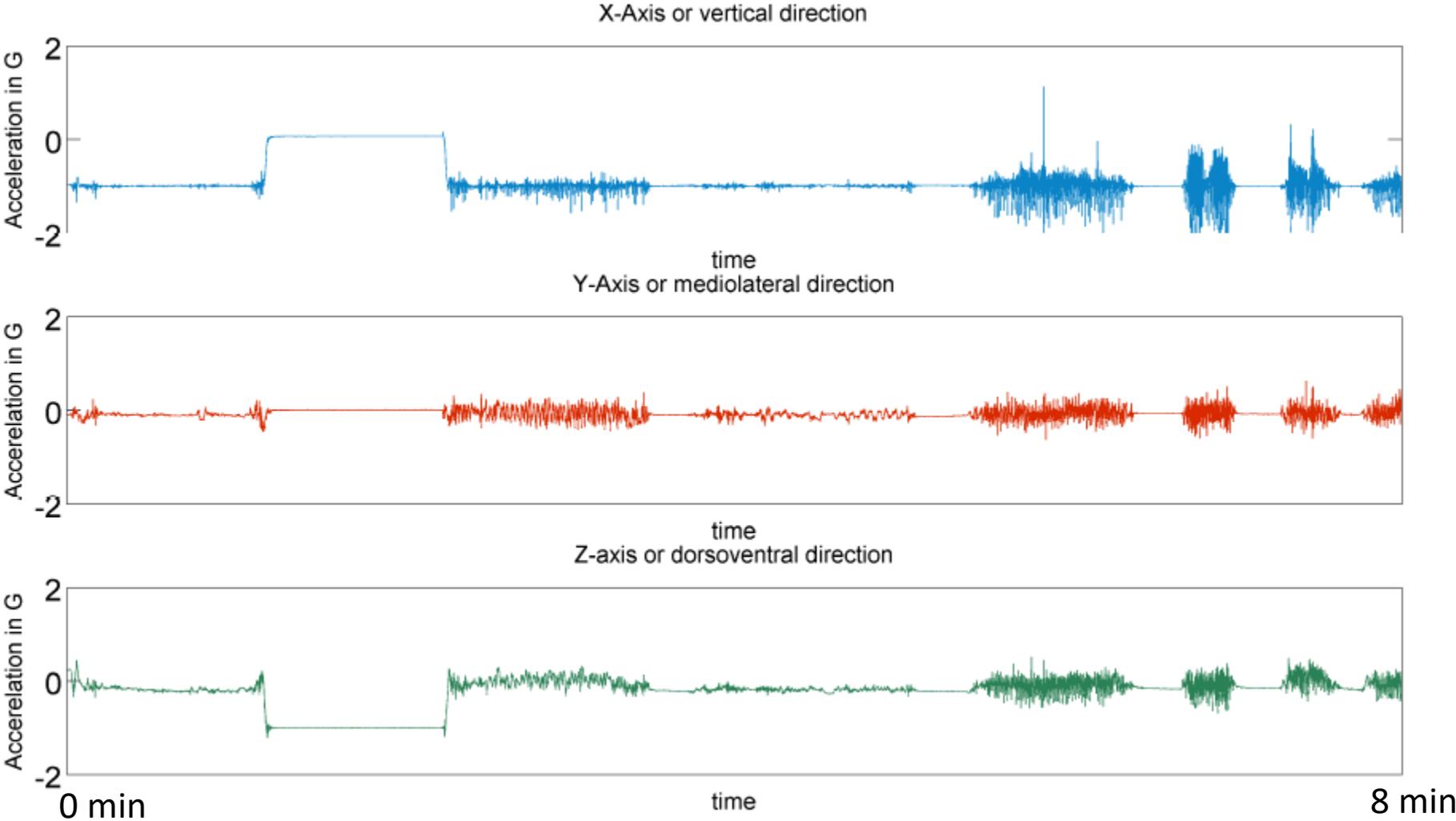
Digital Health Technology

- 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)

Activity Data

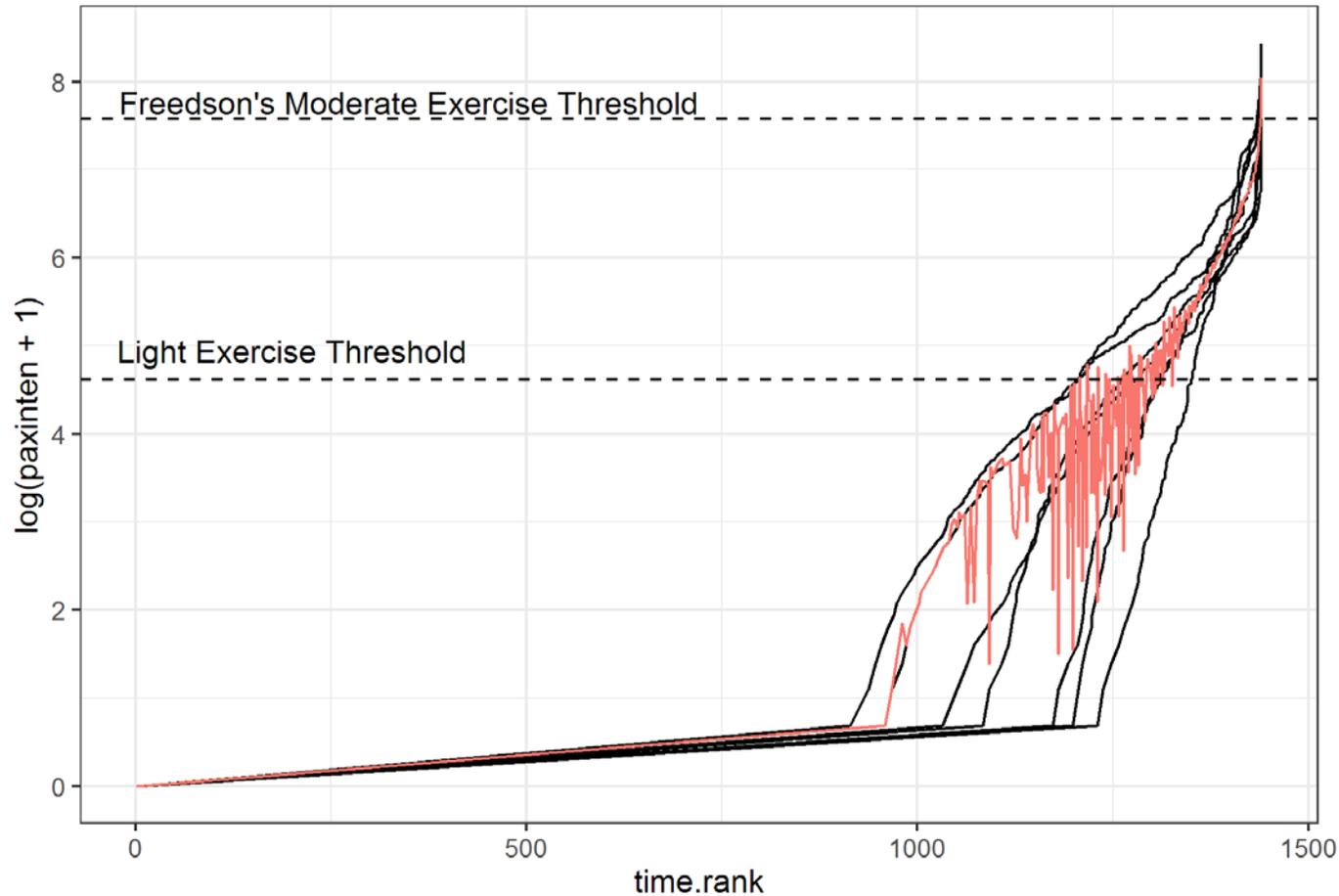
- A wearable accelerometer is used to measure free living exercise
 - Data is recorded when the device is worn
 - Aggregated into 1 minute epochs
 - At least 1440 data points per day
- Periods without recorded activity
 - Sleep?
 - Not wearing the device?
- Patients may wear the device for different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

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 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?

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
 - Missing data: Unbiased estimates under MAR assumption for missing days and MCAR for within day measurements
- Other methods?

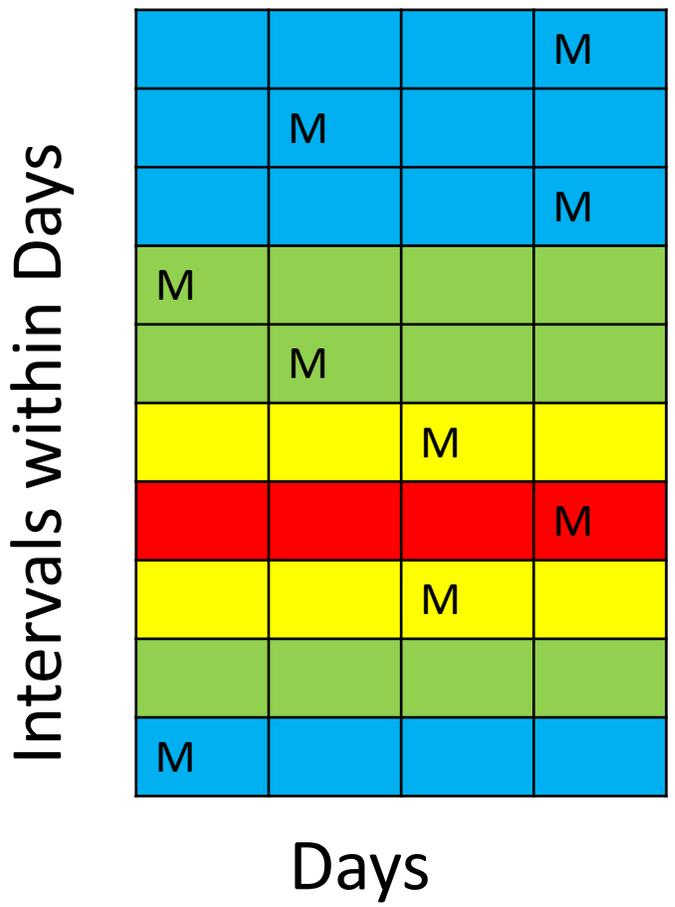
How data can go missing

- 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

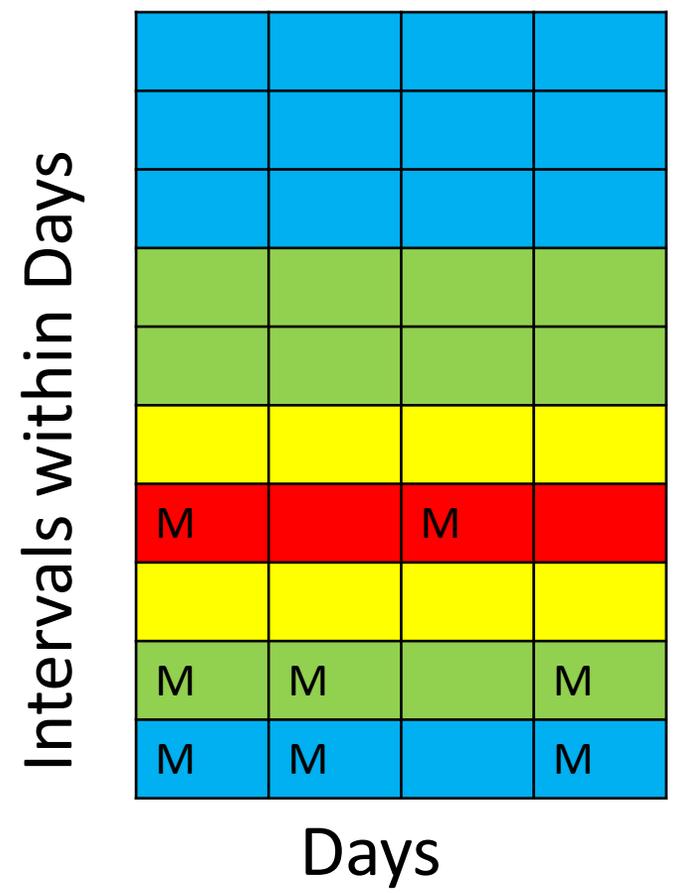
Missing Data in Activity Data – Within Day



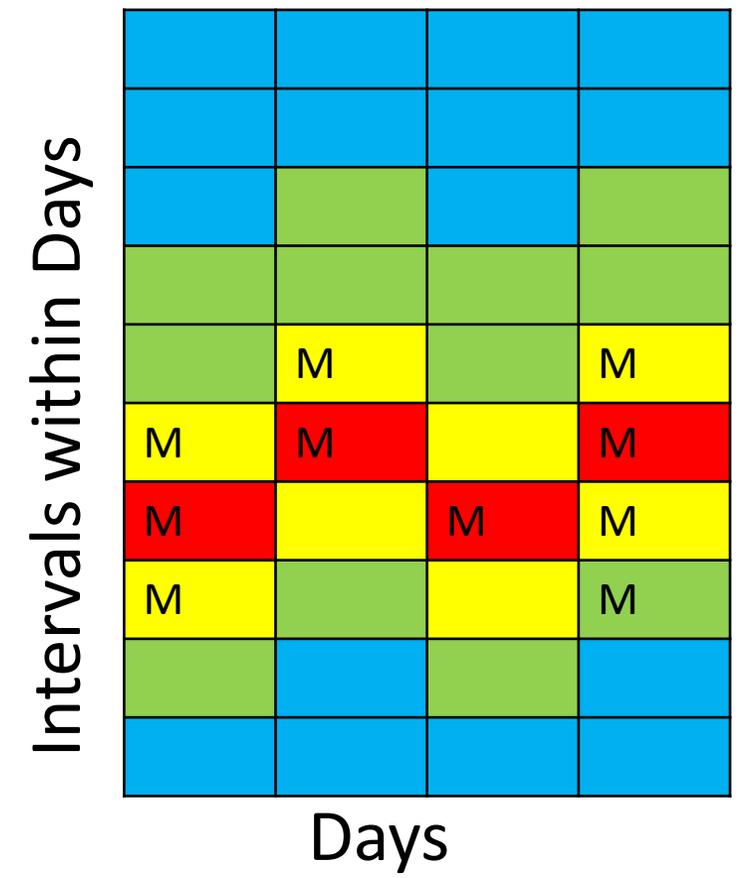
MCAR



MAR



MNAR



Missing Data in Activity Data – Monotone Dropout and Within Day

MCAR

MAR

MNAR

Intervals within Days

			M
	M		M
			M
M			M
	M		M
		M	M
			M
		M	M
			M
			M

Intervals within Days

		M	M
		M	M
		M	M
		M	M
		M	M
		M	M
		M	M
M		M	M
		M	M
M	M	M	M
M	M	M	M

Intervals within Days

			M
			M
			M
			M
			M
	M		M
M	M		M
M		M	M
M			M
			M
			M

Days

Days

Days

A Common Approach for Activity Data

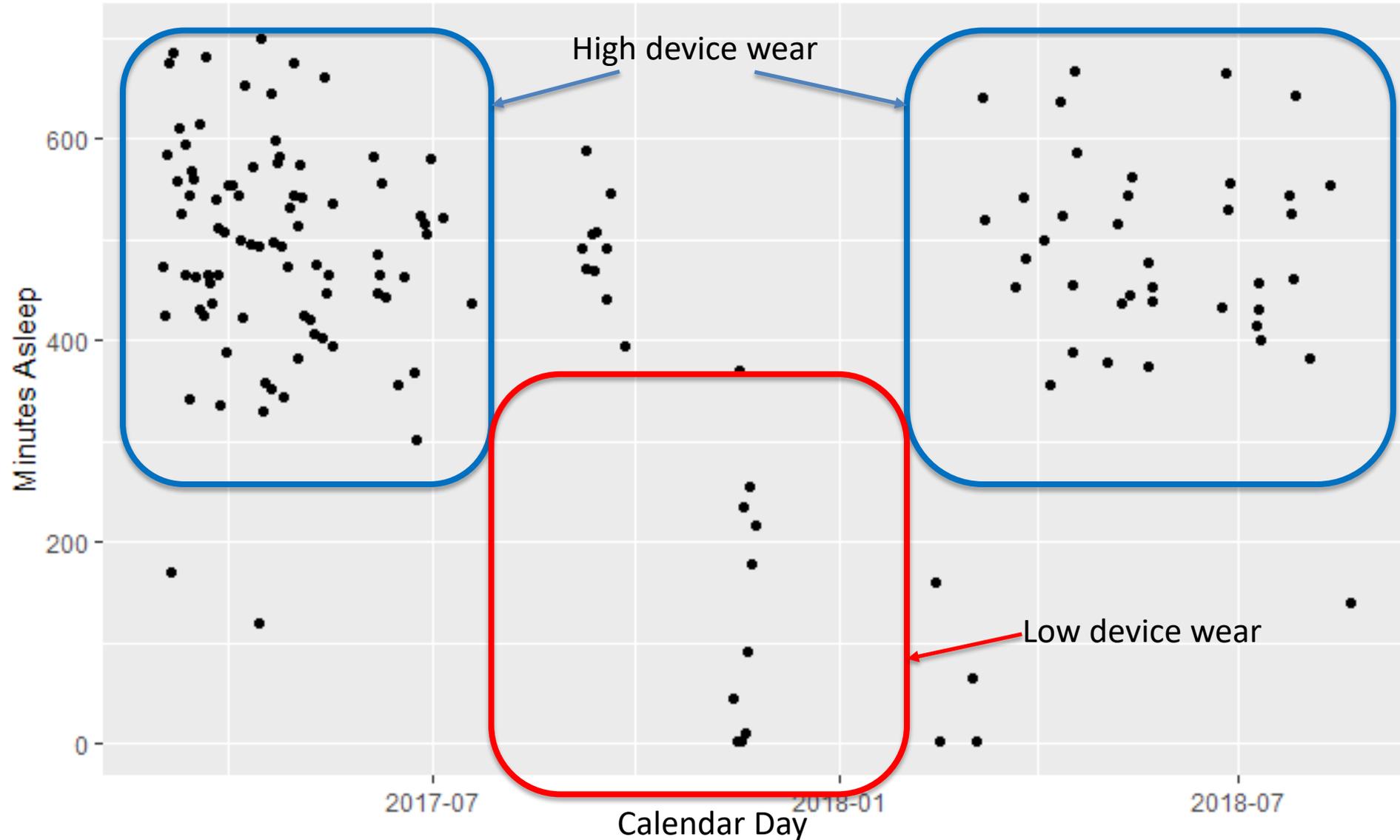
- Calculate daily activity summary endpoint A_{day} if
 - Patient wears accelerometer for at least T hours
 - T is often 8, 10, or 12 hours
 - Consider this a valid day
- Calculate weekly activity summary endpoint A_{week} if
 - Patient has at least W (often 3-4) valid weekday measurements
 - Patient 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?

CASE STUDY - SLEEP

Total Sleep Time

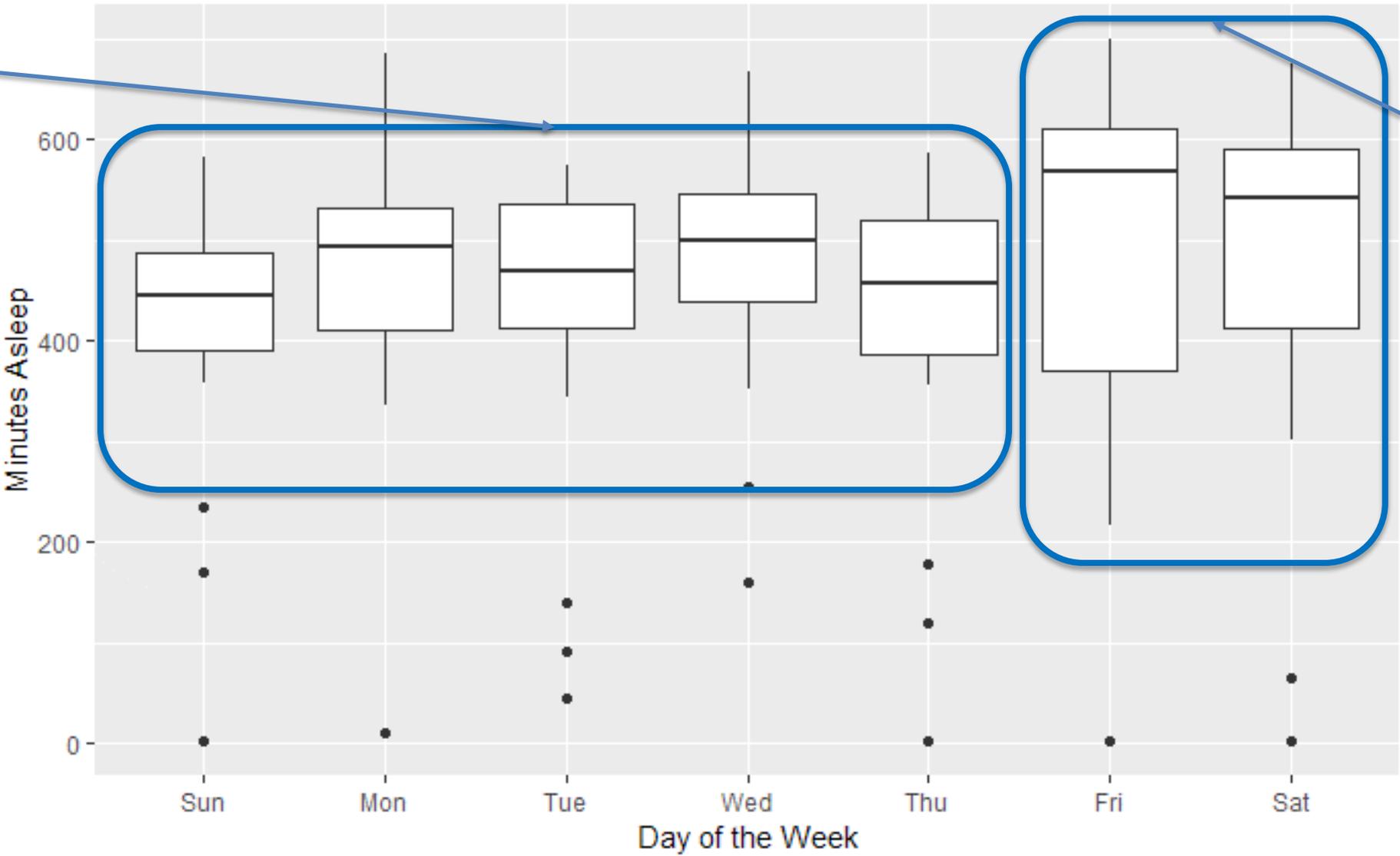
- Measure of how long a person sleeps during the night
- Usually measured with polysomnography (PSG)
 - PSG determines sleep/awake by measuring brains electrical activity
 - Read by expert readers
- Can motion detected by an accelerometer be processed to determine time spent sleeping?
 - Algorithms classify 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 mornings



Weekend mornings

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

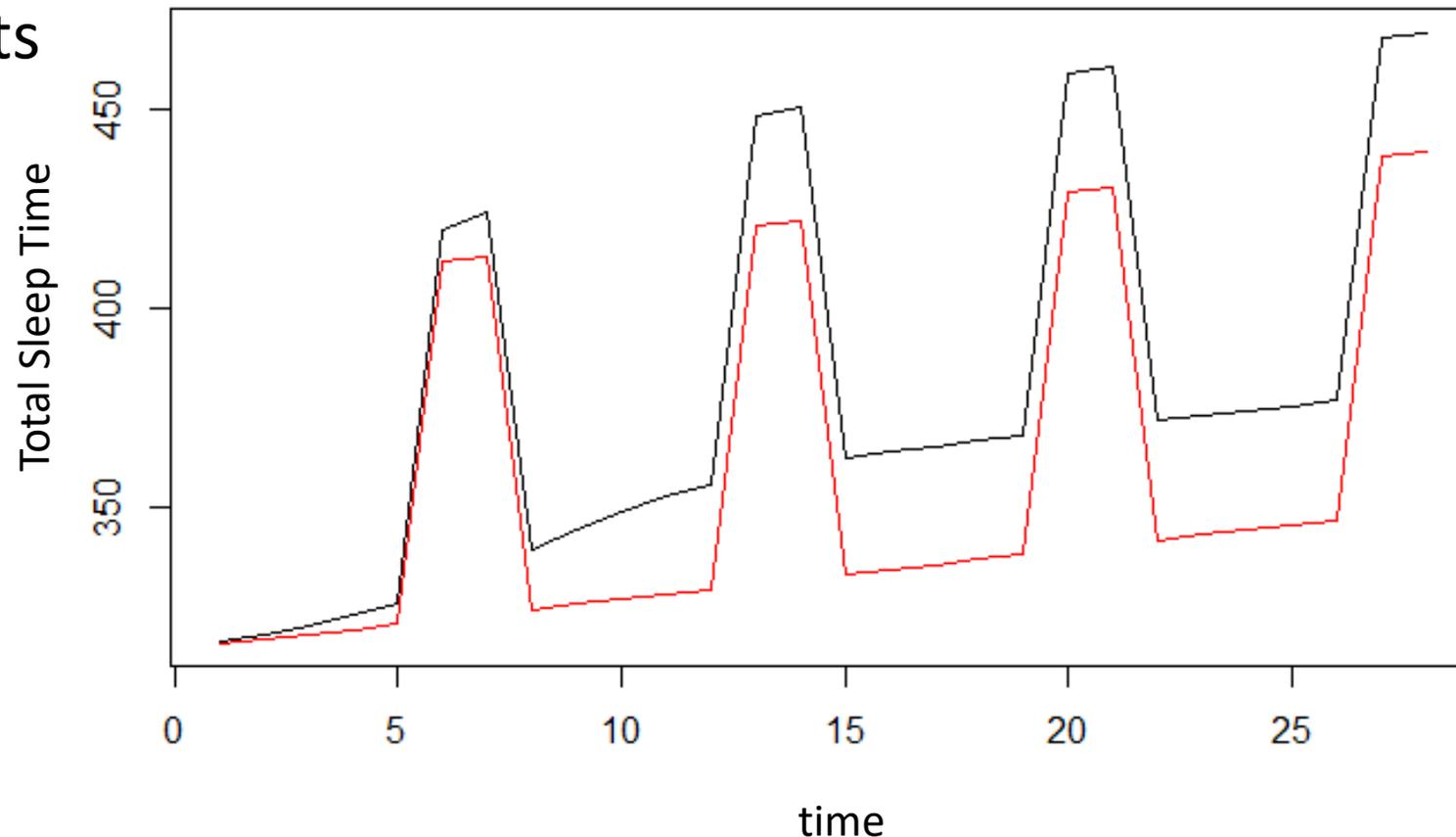
- Simulated data:
 - 300 patients
 - 30 minute improvement in TST by day 15
 - Similar change in TST to several NDAs submitted to FDA
 - Complete data vs. Monotone dropout
- Measure treatment effect by:
 - Difference in TST at four weeks
 - Estimate after modeling vs. calculate average before modeling (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

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

- Weekend effects are factors



Linear mixed model 1

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

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

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

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

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 slope

$\epsilon_i(t_j)$: error

Fixed Effects:

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

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

$$\sum_{j=1}^W \sum_{k=1}^1 \gamma_{jk} I(\text{week}_j = j) \times TRT_k +$$

$$\sum_{l=1}^7 \delta_l I(\text{day}_{il} = d) + \epsilon_{ijkl}$$

$$\epsilon_{ijkl} \sim N \left(0, \begin{pmatrix} \Sigma_{11} & \cdots & \rho_2 \\ \vdots & \ddots & \vdots \\ p_2 & \cdots & \Sigma_{WW} \end{pmatrix} \right)$$

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

Fixed Effects:

α_j : week effects

All other terms defined previously

Linear Mixed Model 3

$$\begin{aligned}
 Y_{ijk} &= \beta_0 + \beta_1 \times TST_{baseline,i} + \beta_2 \times TRT_k + \sum_{j=1}^W \alpha_j I(\text{week}_j = j) \\
 &+ \sum_{j=1}^W \sum_{k=1}^1 \gamma_{jk} I(\text{week}_j = j) \times TRT_k + \epsilon_{ijkl}
 \end{aligned}$$

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

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

All other terms defined previously

Generalized Estimating Equation (GEE)



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

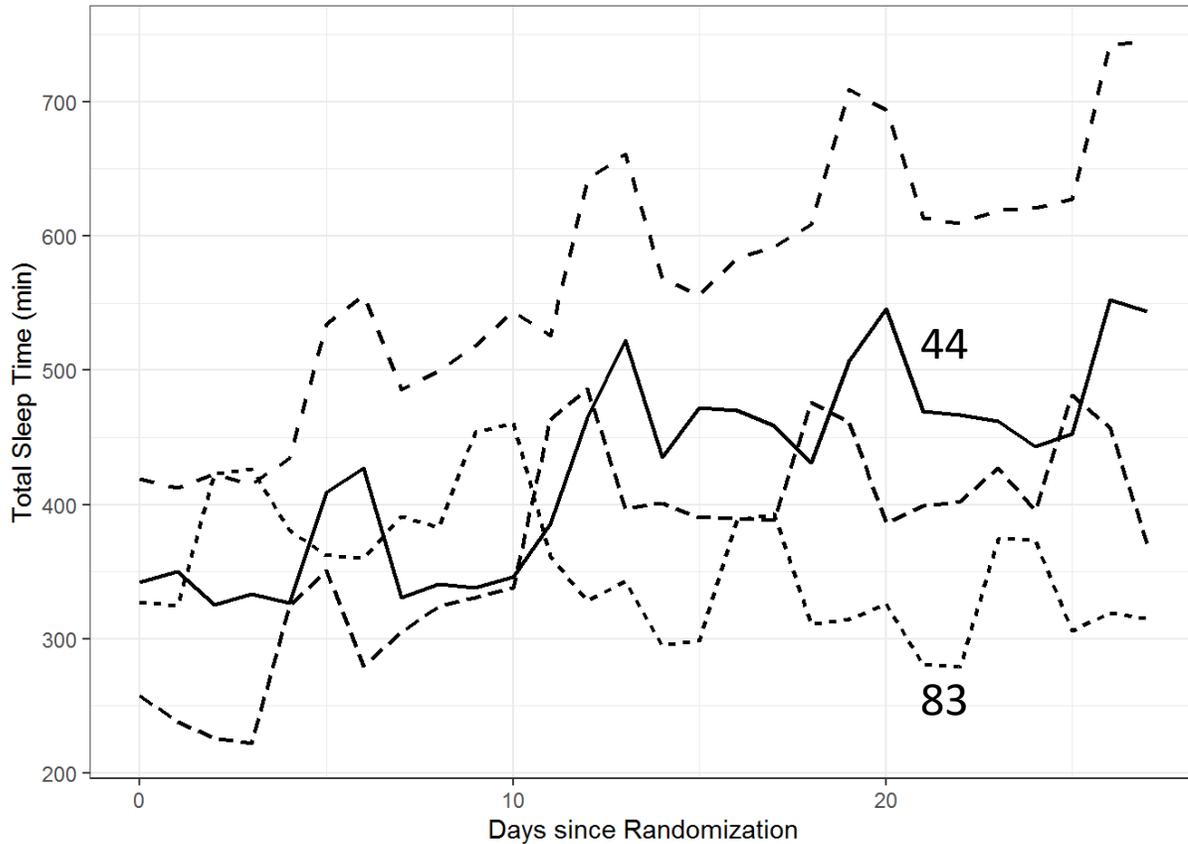
Working correlation matrix is AR(1)

Standard errors estimated with sandwich estimator

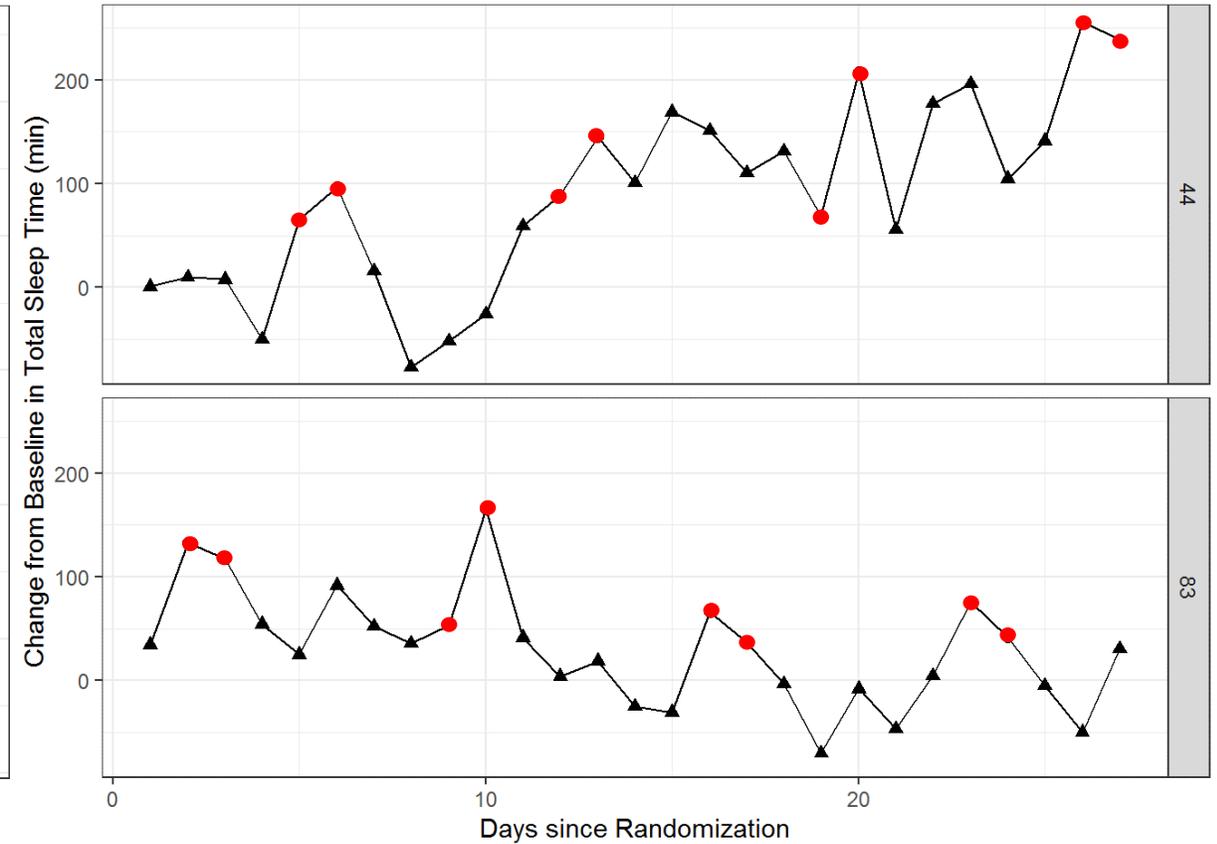
All other terms defined previously

Simulated Clinical Trial – The Data

Example Subjects



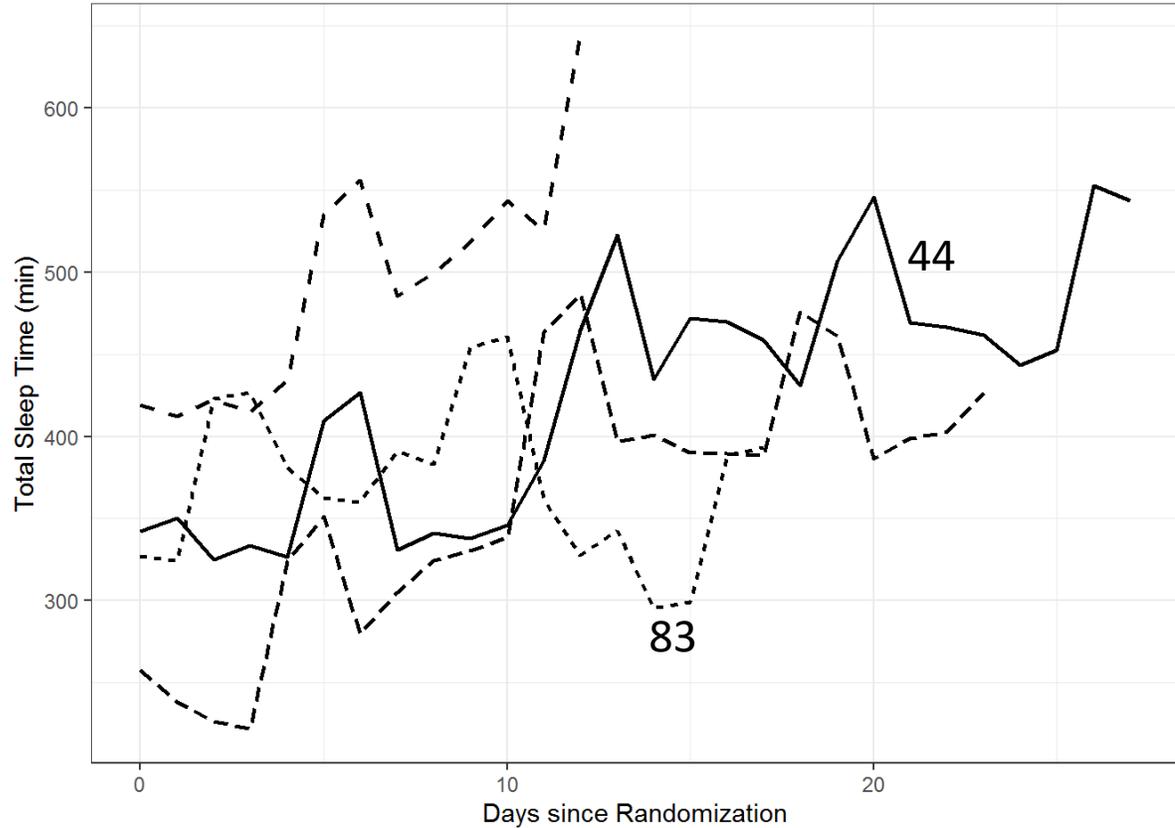
Subject Specific Change from Baseline in TST



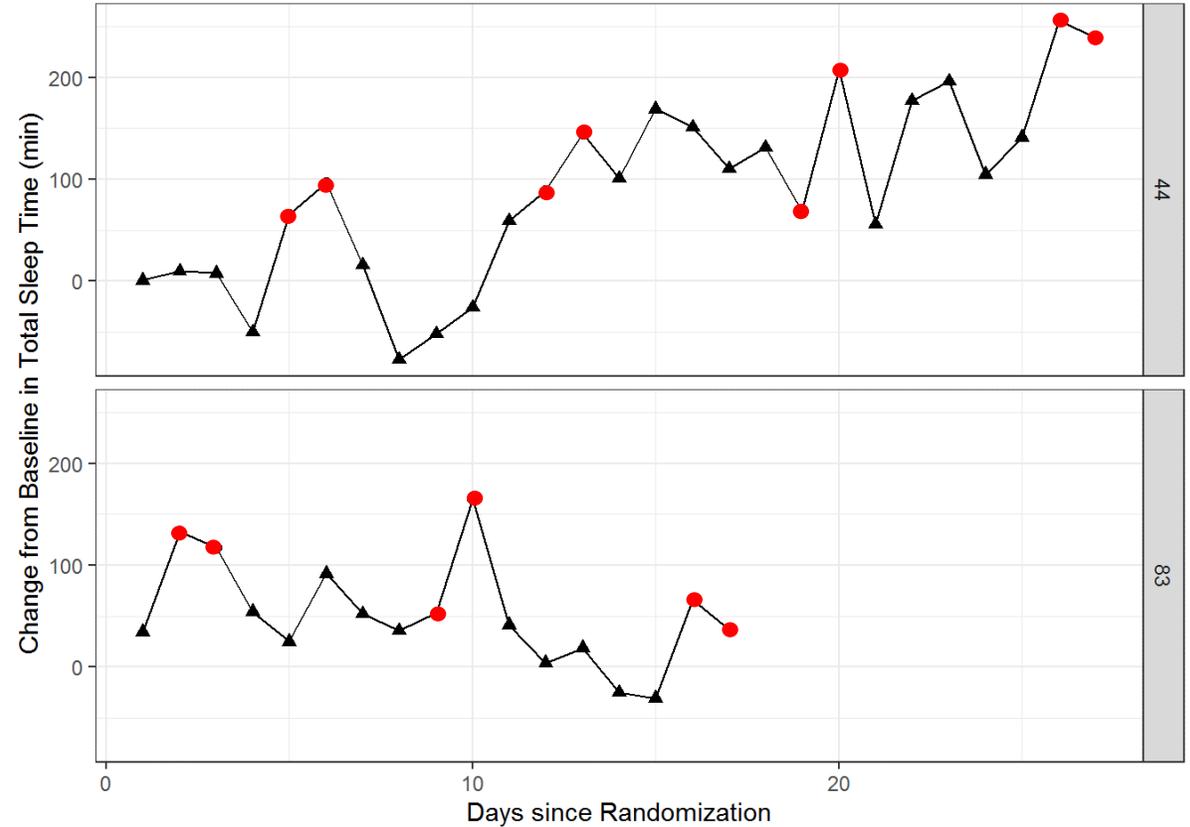
Triangles – Weekday
Red Circles - Weekend

Simulated Clinical Trial – The Data with Dropout

Example Subjects



Subject Specific Change from Baseline in TST

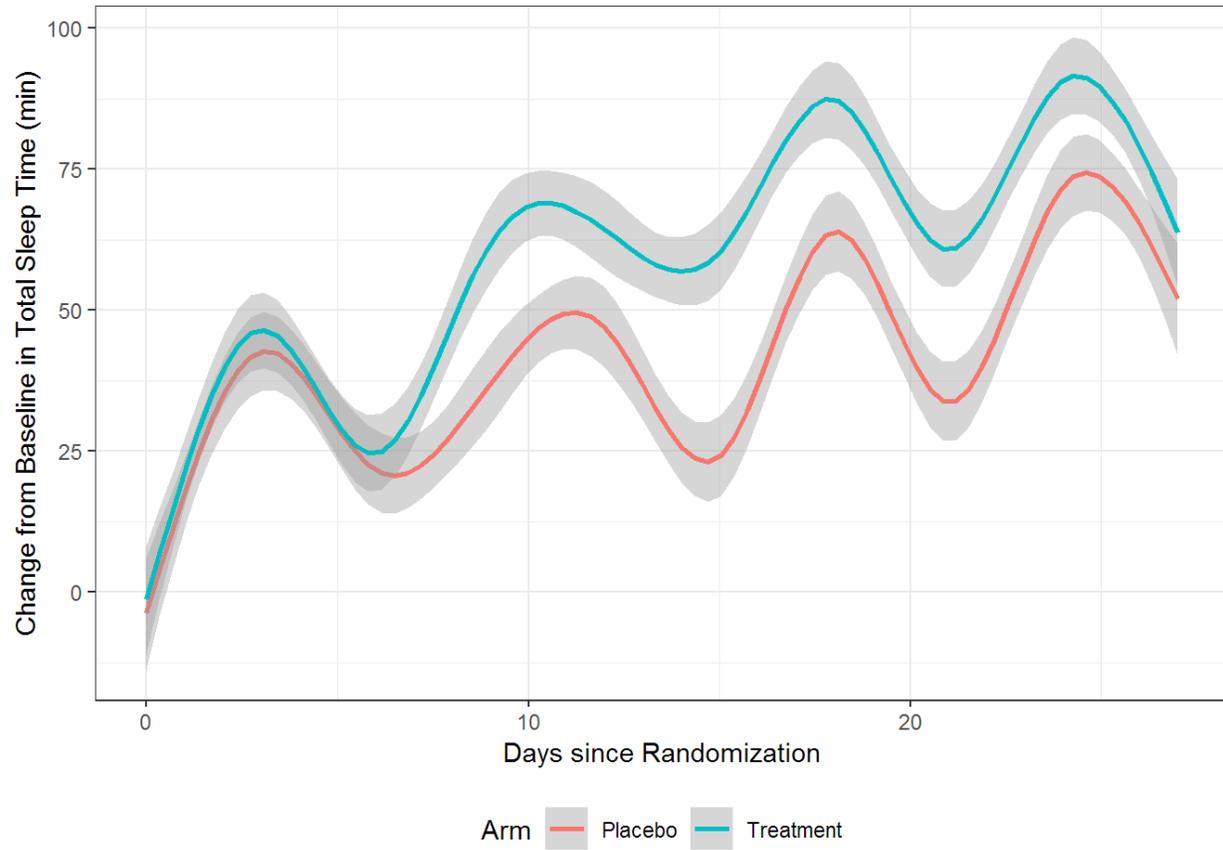


Triangles – Weekday
Red Circles - Weekend

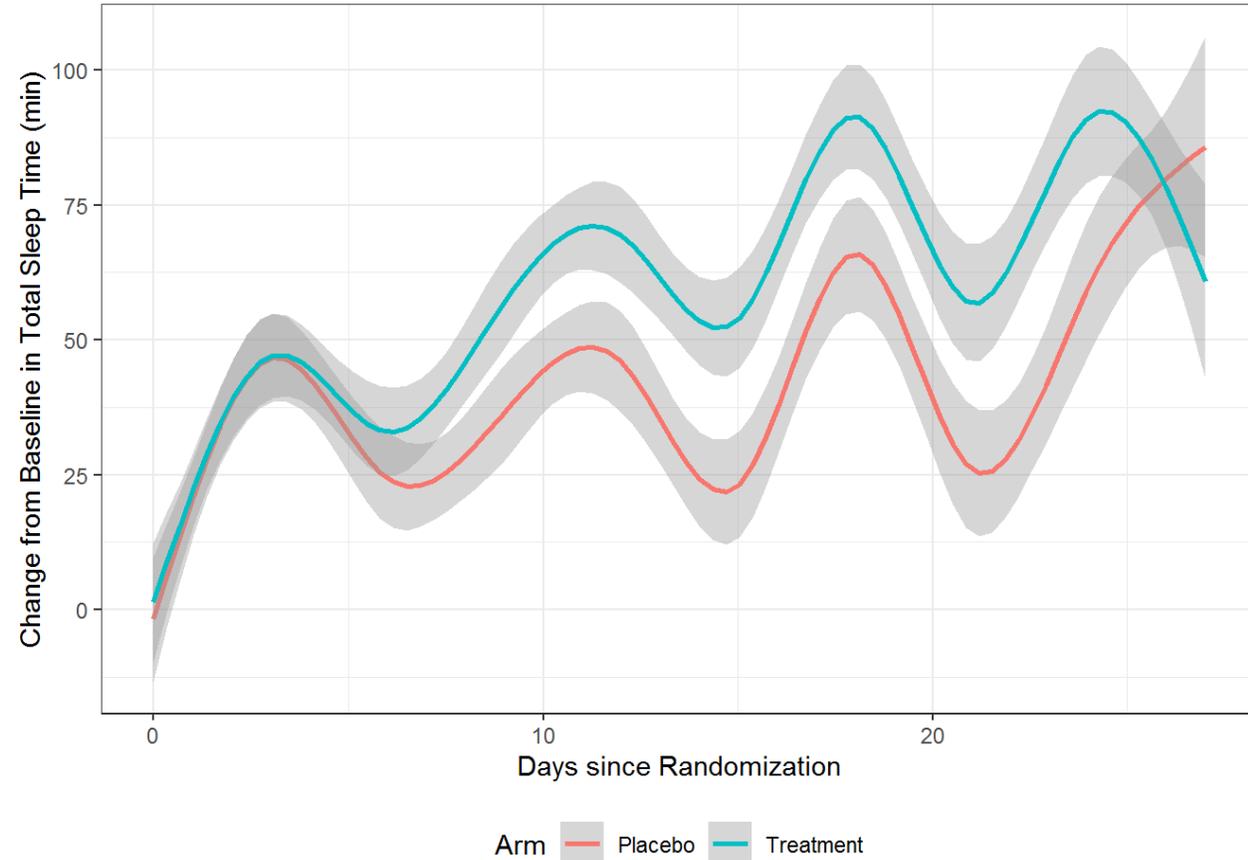
Population Average Total Sleep Time Trajectories

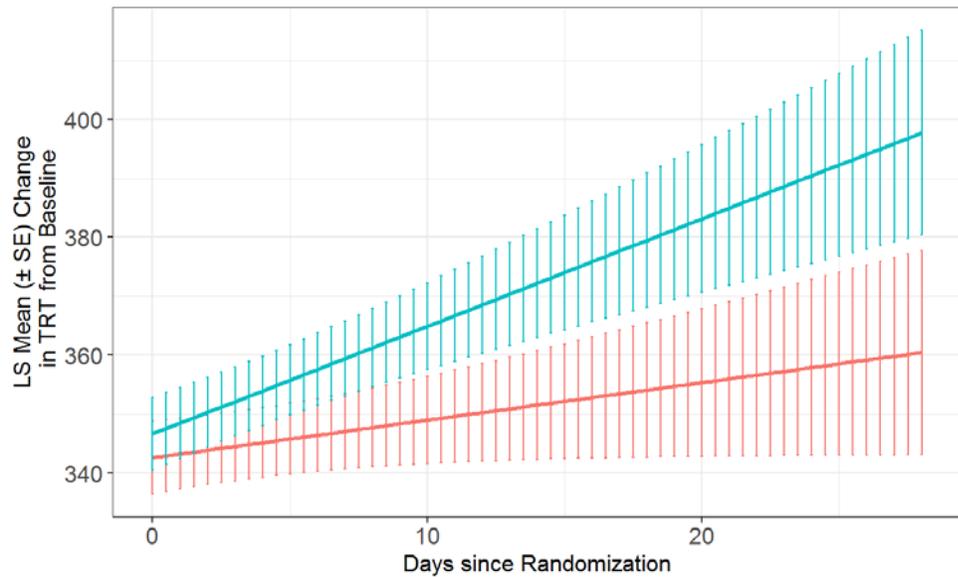


Complete Data

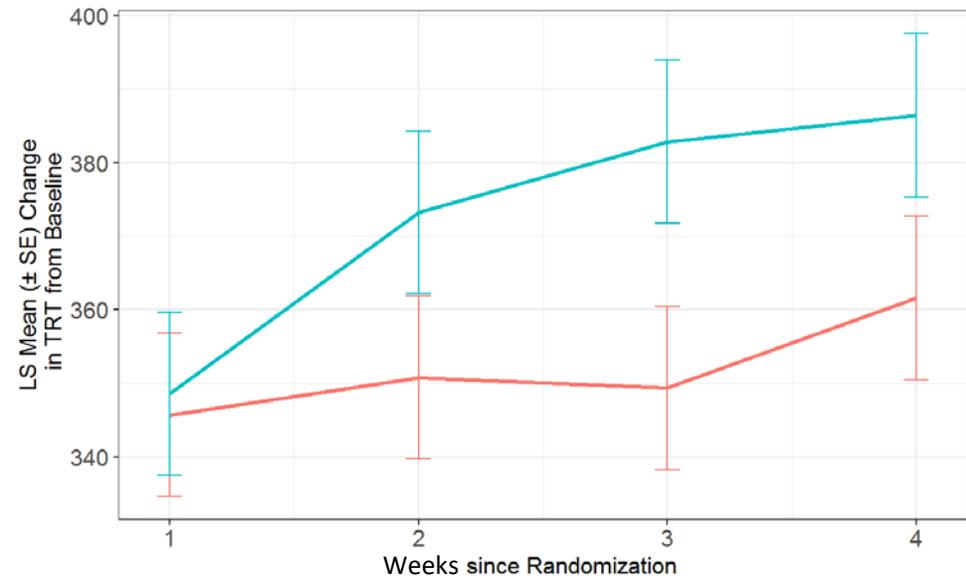


Monotone Dropout

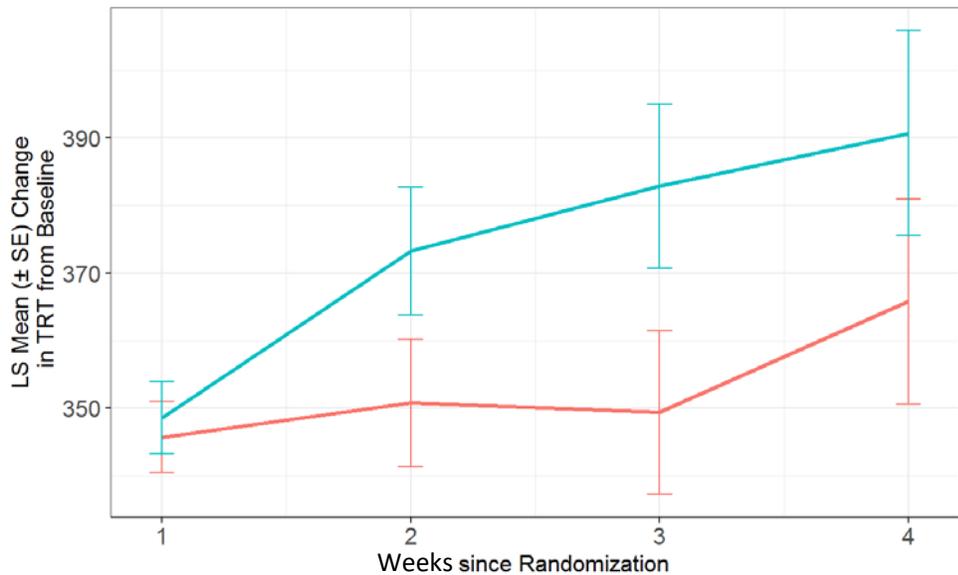




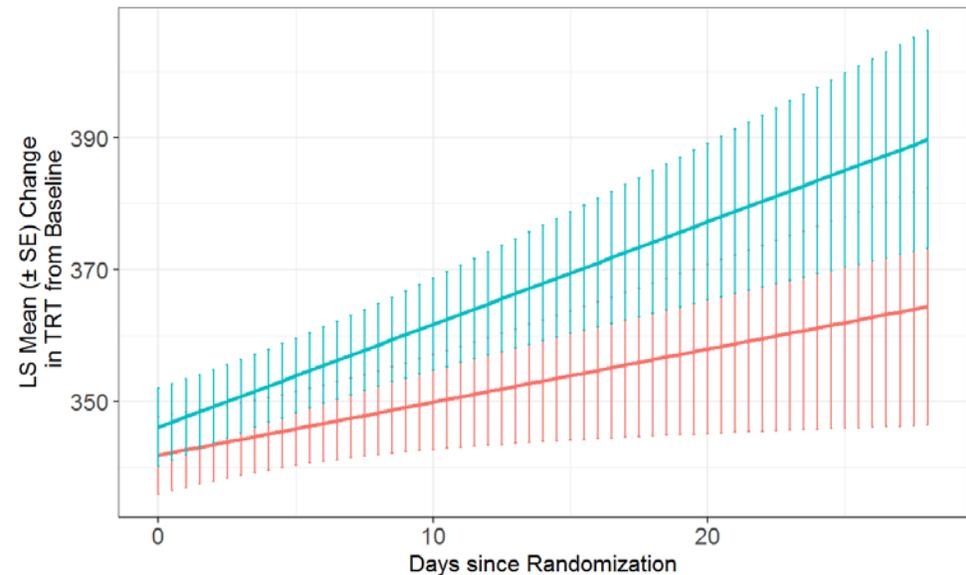
LMM1 – Linear Function of Time



LMM2 – Factor for week including days

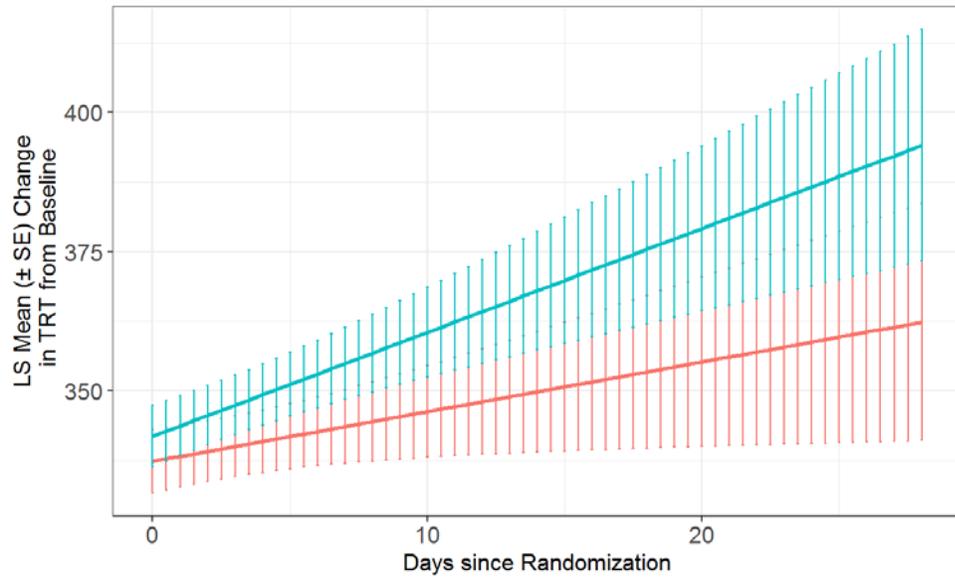


LMM3 – Pre-model averaging for week

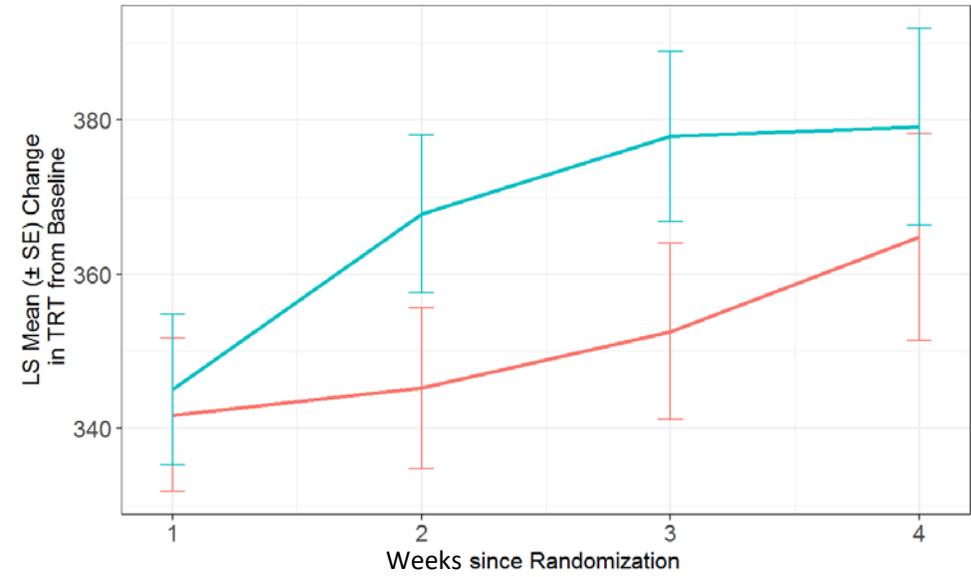


GEE – Linear Function of Time

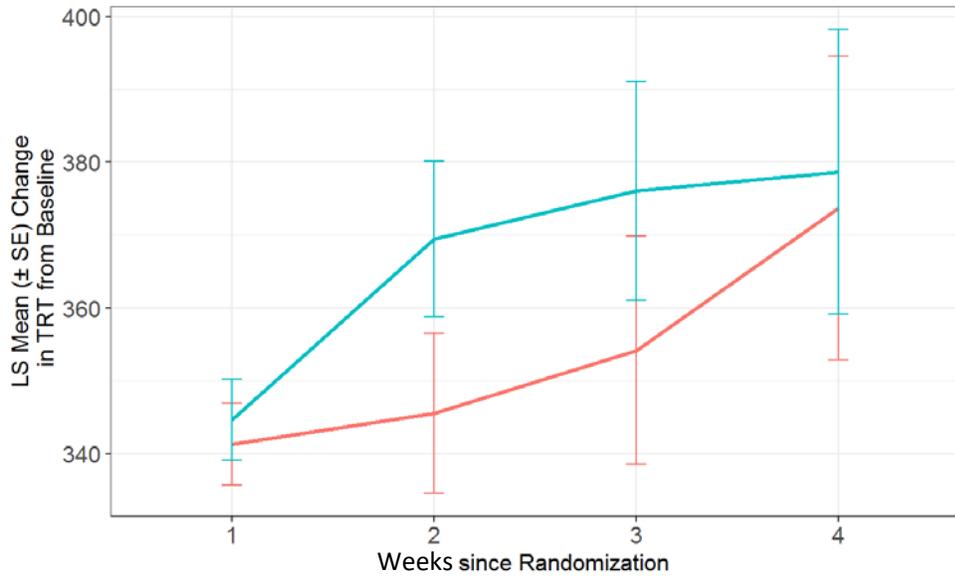
Monotone Dropout



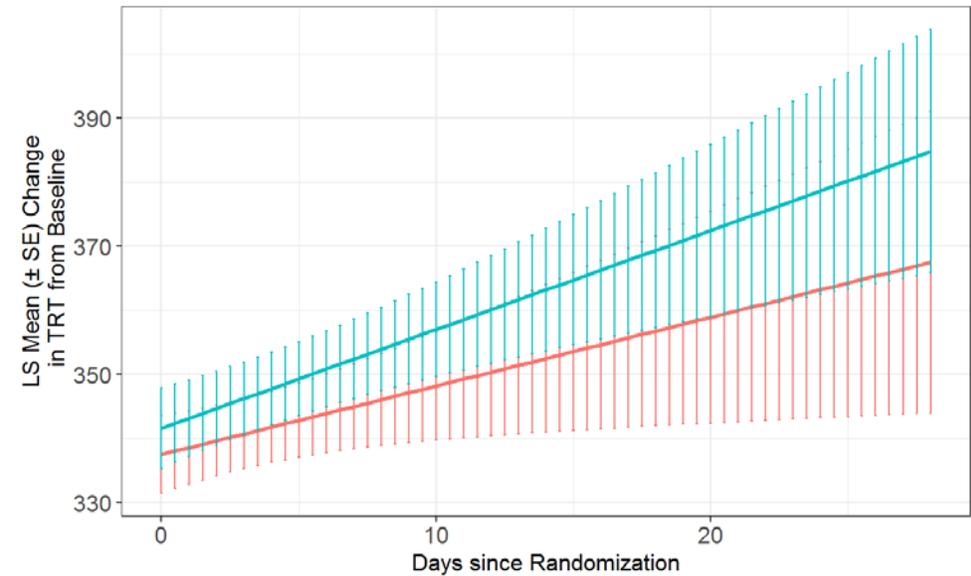
LMM1 – Linear Function of Time



LMM2 – Factor for week including days



LMM3 – Pre-model averaging for week



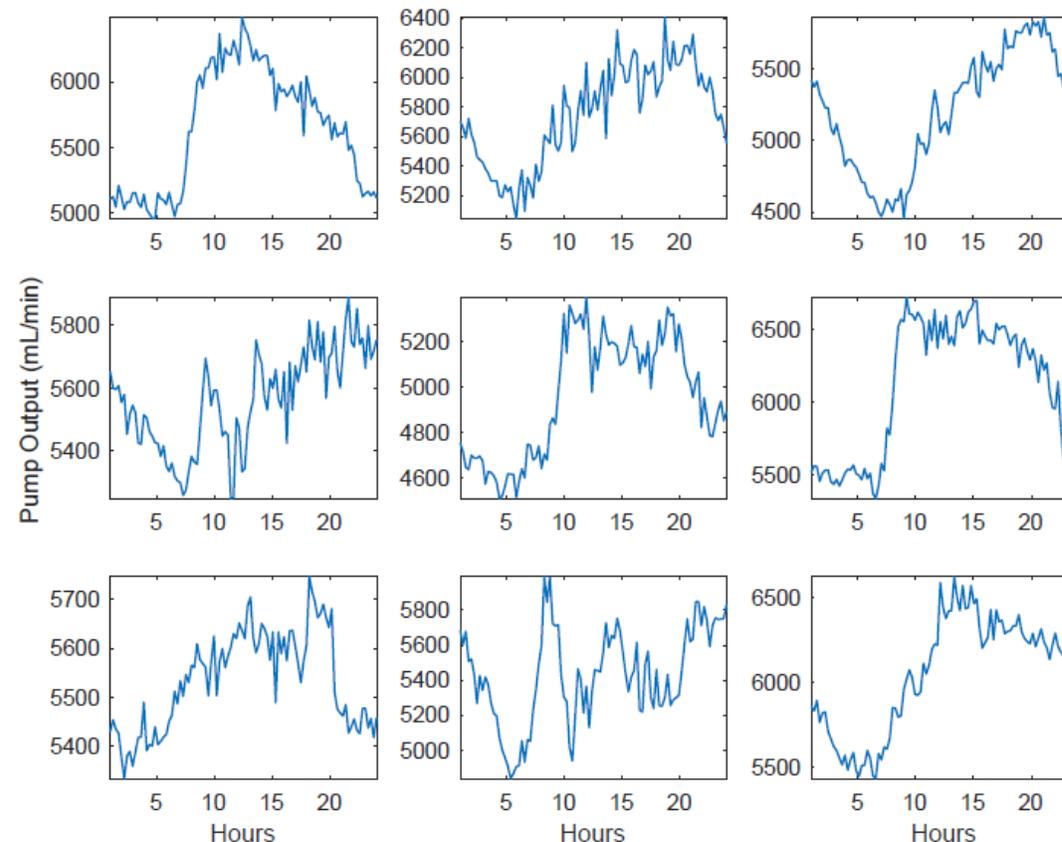
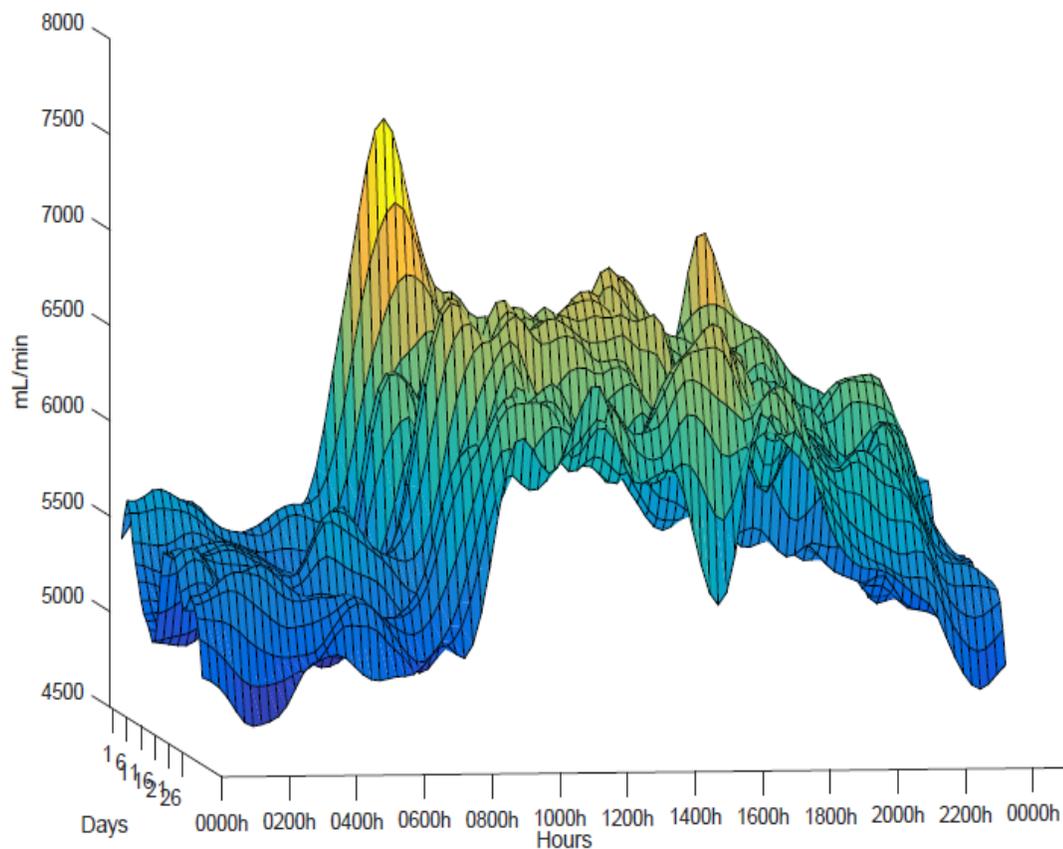
GEE – Linear Function of Time

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

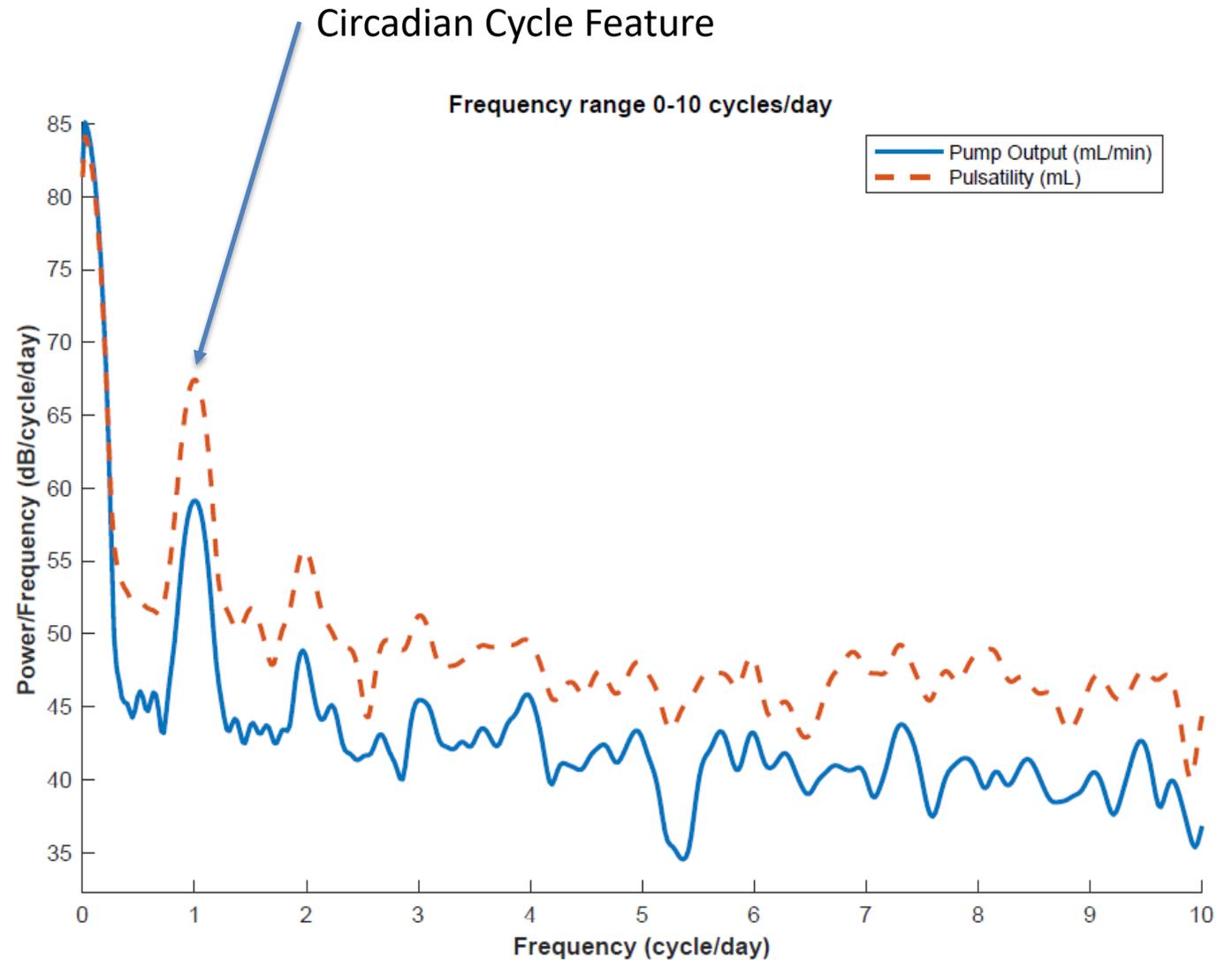
An Important Feature: Circadian Variation in Sensor Data



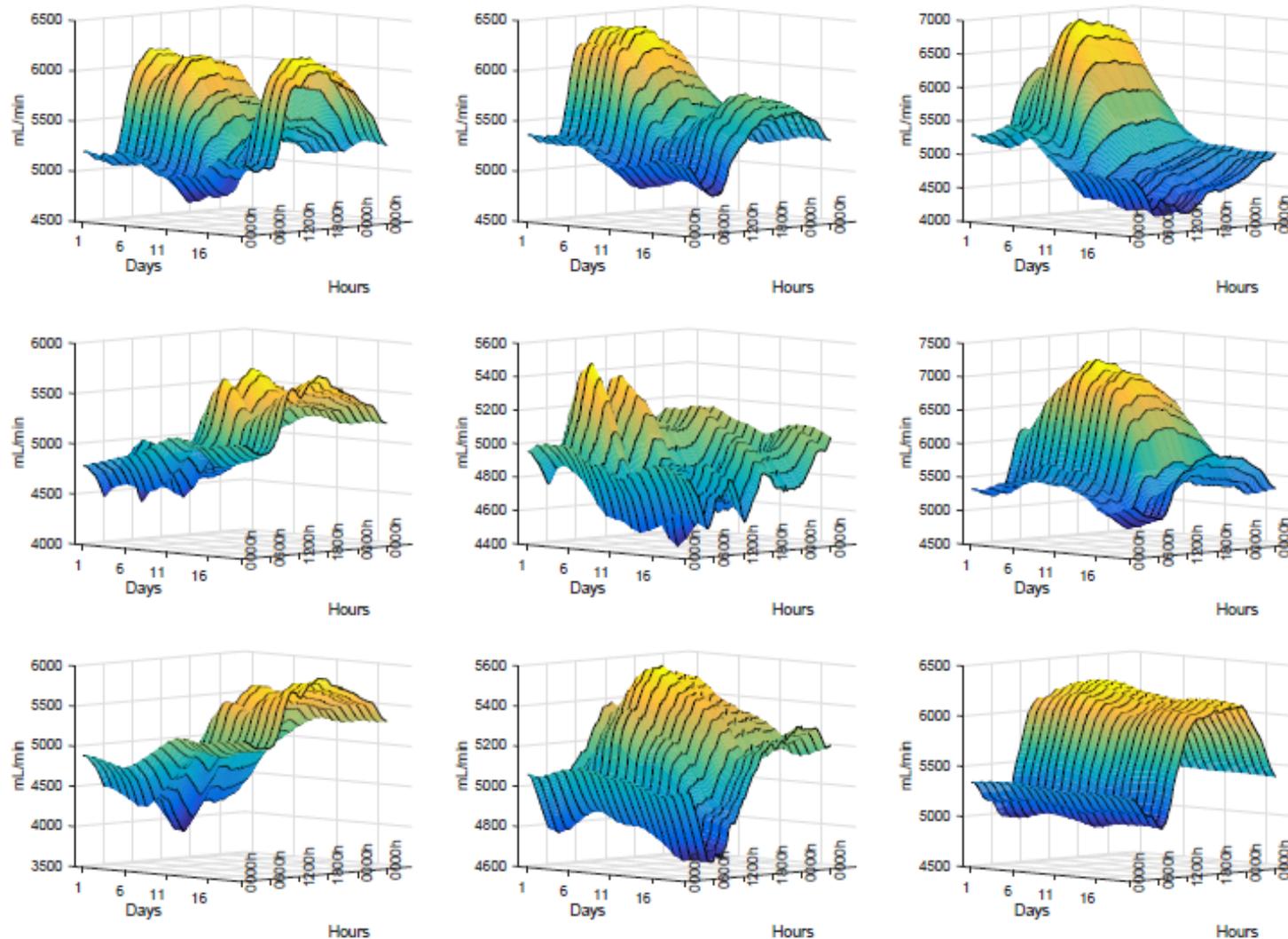
- Blood flow data from a ventricular assist device recorded every 15 min.
- Circadian patterns present in multiple types of sensor data

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 misspecified
- 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](https://doi.org/10.1249/01.mss.0000185651.59486.4e)
- Song J et al, A semiparametric model for wearable sensor-based physical activity monitoring data with informative device wear, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 287–298. doi: <https://doi.org/10.1093/biostatistics/kxx073>
- Byrom B and Rowe DA, Measuring free-living physical activity in COPD patients: Deriving methodology standards for clinical trials through a review of research studies, *Contemporary Clinical Trials*, Volume 47, 2016, Pages 172-184. doi: <https://doi.org/10.1016/j.cct.2016.01.006>.

