Wearables: non-functional approaches

JSM 2019

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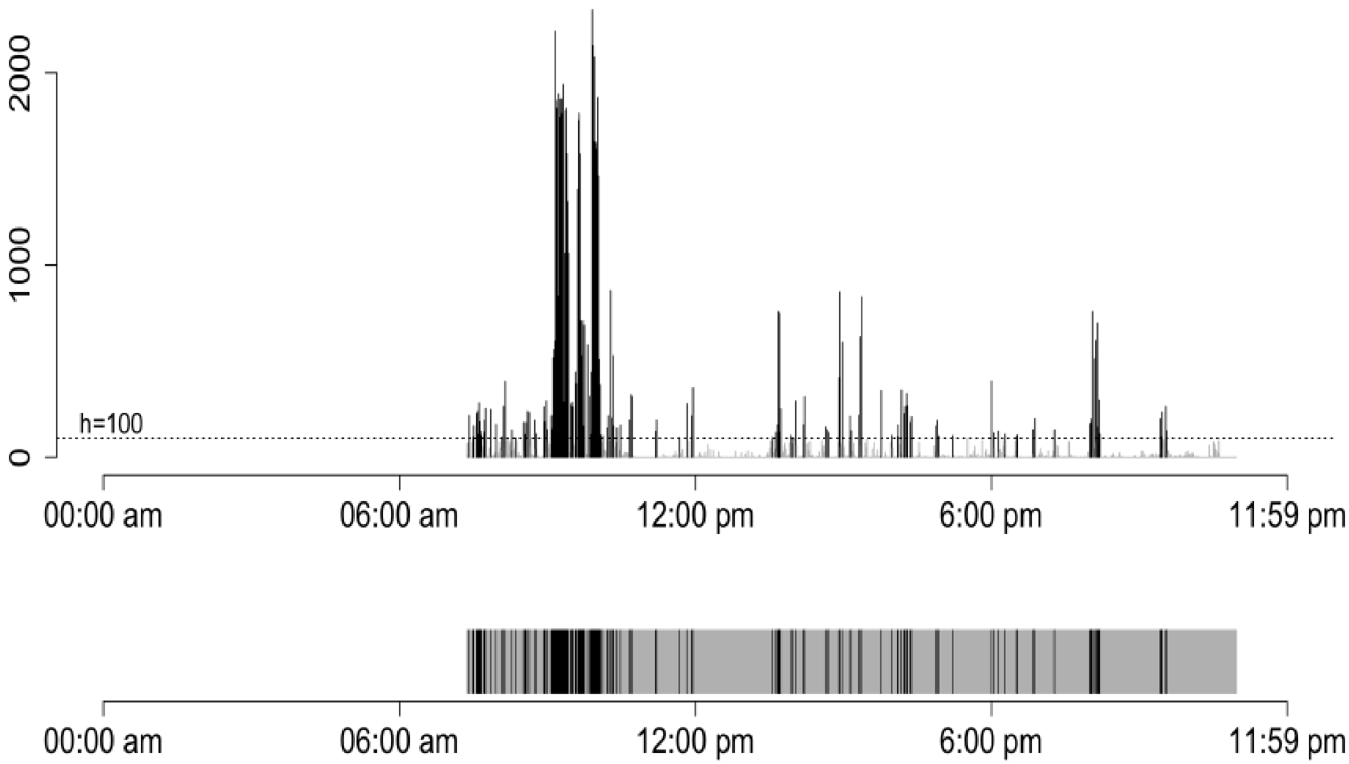
Overview

- Review of PA, SL, CR
- PA: Fragmentation
- SL: Review, summary measures, mid-point
- CR: parametric and non-parametric approaches
- JIVE for PA, SL, CR
- Adding contexts: EMA/Electronic diaries

Fragmentation



Fragmentation

Nonparametric

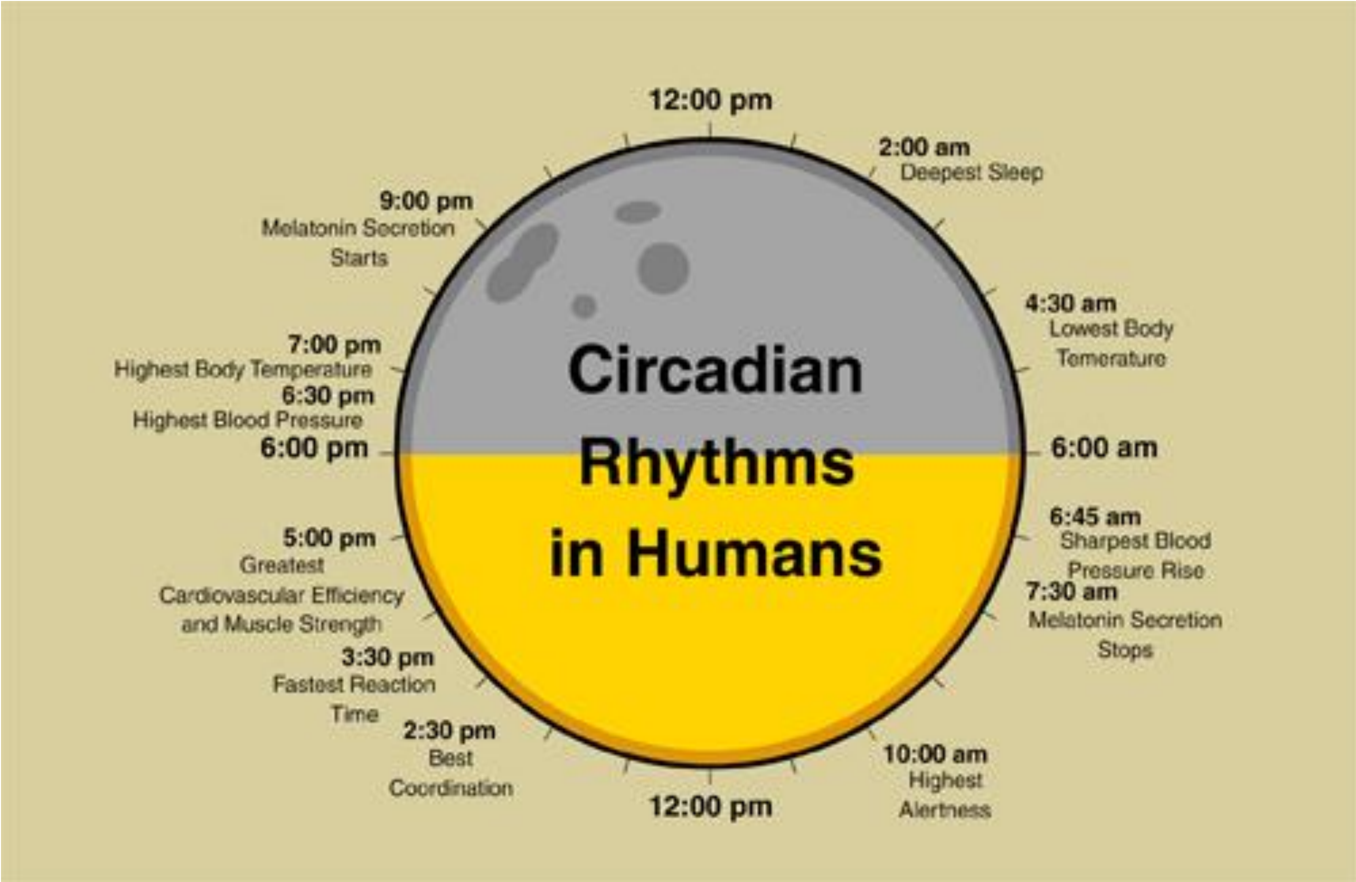
Metrics	Interpretation	Definition	Estimation
AAC (μ)	average duration	Ed_i	$\frac{T}{n}$
nAAC ($^*\mu$)	normalized average	$\frac{Ed_i}{*d}$	$\frac{T}{*dn}$
Gini (g)	normalized variability	$\frac{E\lvert d_i - d_j\rvert}{2\mu}$	$\frac{\sum_{ij} \lvert d_i - d_j\rvert}{2n\sum_t d_t}$
AH ($\bar{h}$)	average hazard	$h(t) = \frac{F'(t)}{1-F(t)}$	$\bar{h} = \frac{1}{m}\sum_{t\in\mathcal{D}} \hat{h}(t)$

Systematic Derivation	$I_\psi(\hat{F}) = \int_0^{*d} \psi(\hat{F}(t))dt$
AAC	$\hat{\mu} = \int_0^{*d}(1-\hat{F}(t))dt$
nAAC	$\hat{^*\mu} = \frac{1}{*d}\int_0^{*d}(1-\hat{F}(t))dt$
Gini	$\hat{g} = \frac{1}{\hat{\mu}}\int_0^{*d}\hat{F}(t)(1-\hat{F}(t))dt$
AH	$\bar{h} = \frac{1}{*d}\int_0^{*d}\frac{\hat{F}(t)-\hat{F}(t-1)}{1-\hat{F}(t-1)}dt$

References:

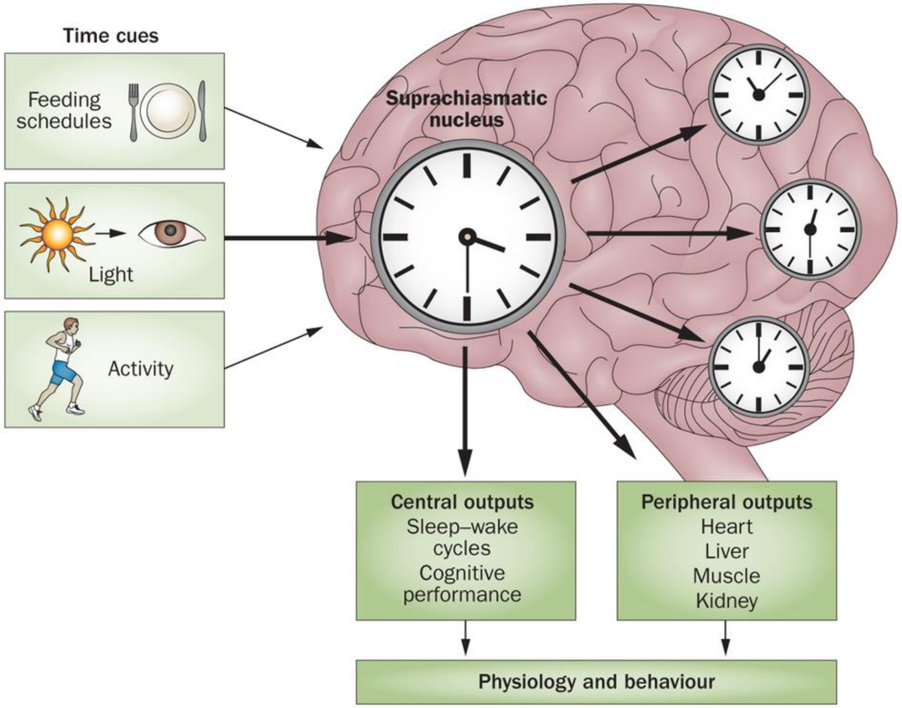
- Di, J., Leroux, A., Urbanek, J., Varadhan, R., Spira, A., Schrack, J., Zipunnikov, V. Patterns of Sedentary and Active Time Accumulation Are Associated with Mortality in US adults: The NHANES Study https://www.biorxiv.org/content/biorxiv/early/2017/08/31/182337.full.pdf

Circadian Clock



Circadian Clock

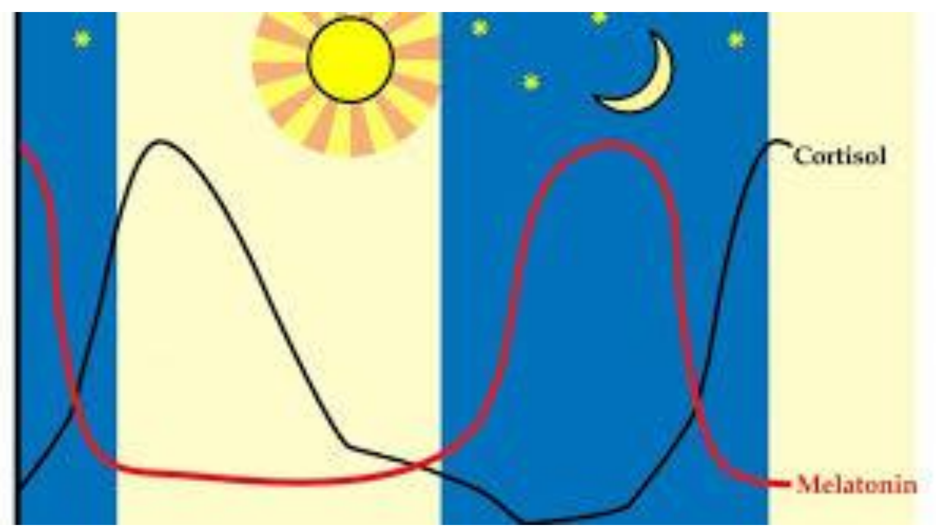
- **Suprachiasmatic nucleus** (SCN) is a small region hypothalamus
- SCN receives input from melanopsin-containing ganglion cells in retina
- SCN modulates core body temperature and production of hormones (cortisol and melatonin)
- SCN allows entrainment of daily rhythms to the 24-hour cycles in nature
- Circadian dysregulation leads to circadian rhythm sleep disorders



Circadian Rhythmicity and Disregulation

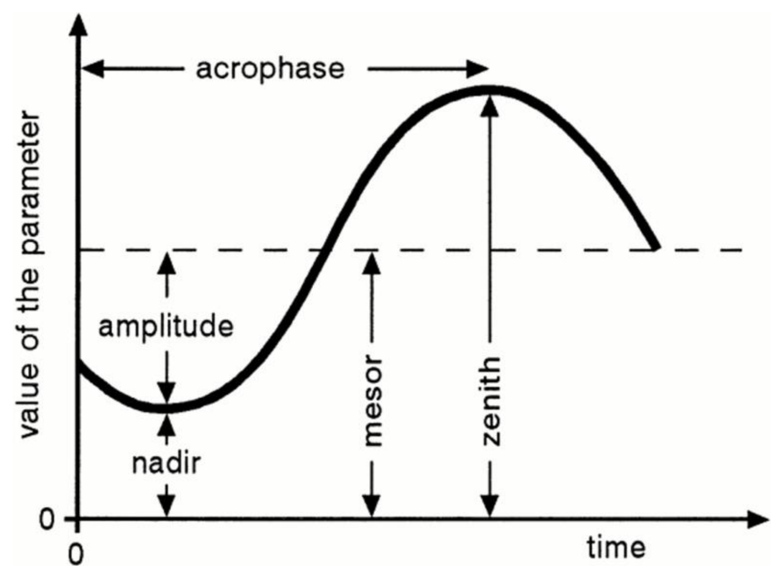
Circadian markers (hard to measure)

- Melatonin
- Cortisol
- Core body temperature

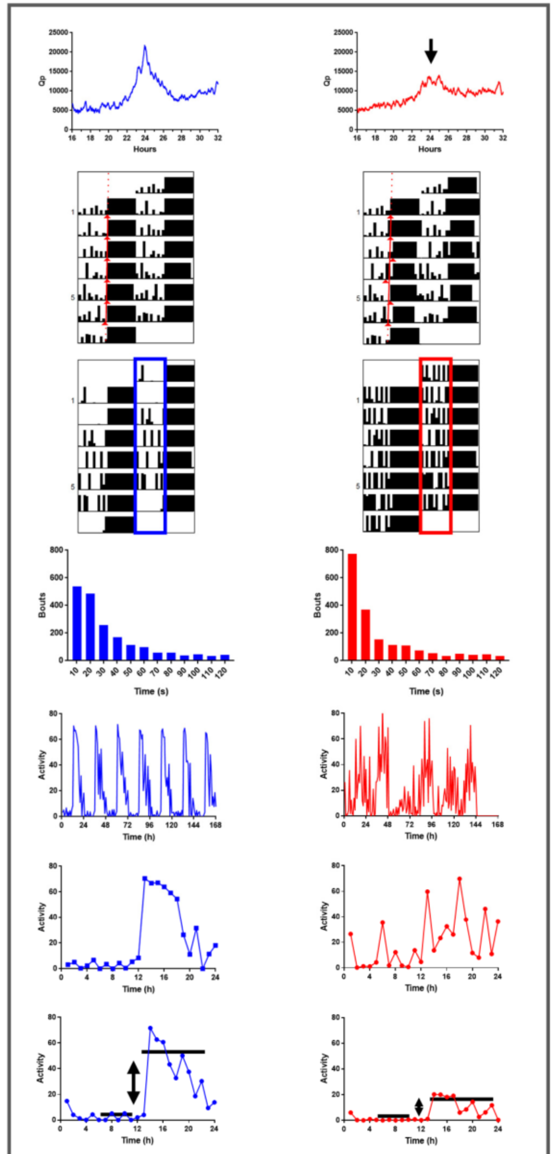


Circadian Rhythmicity (Actigraphy)

- Cosinor-based models (period, amplitude, phase, phase-shifts)
- Wavelet-based methods (time-frequency transformations)
- Nonparametric methods: IV, IS, RA;



NORMAL DISRUPTED

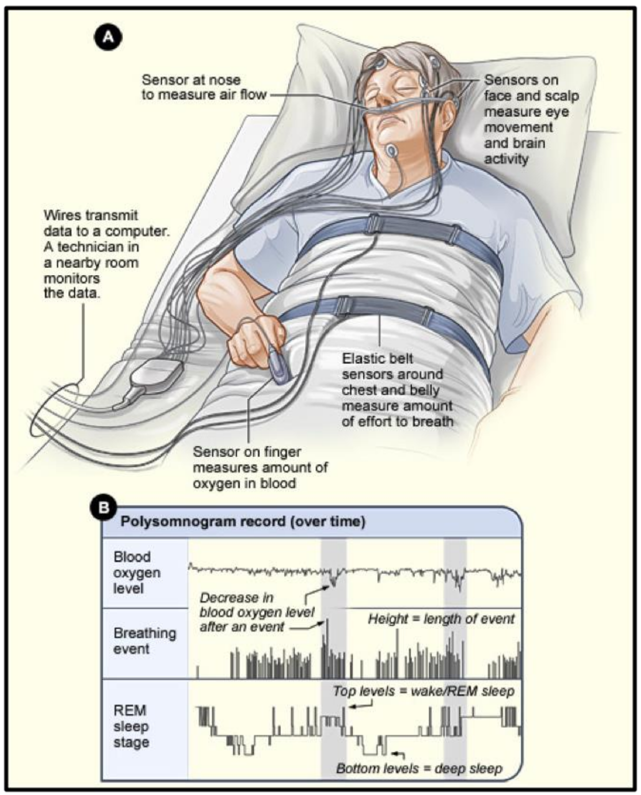


Periodogram power	Decreased power
Activity onset	Increased variance
Light phase activity	Increased light phase activity
Activity bouts	More bouts of short duration
Interdaily stability	Low IS
Intradaily variability	High IV
Relative amplitude	Decreased RA

Telling the Time with a Broken Clock: Quantifying Circadian Disruption in Animal Models
Laurence A. Brown † , Angus S. Fisk †, Carina A. Pothecary and Stuart N. Peirson; Biology (MDPI)

Sleep (PSG)

• Polysomnography (golden standard)



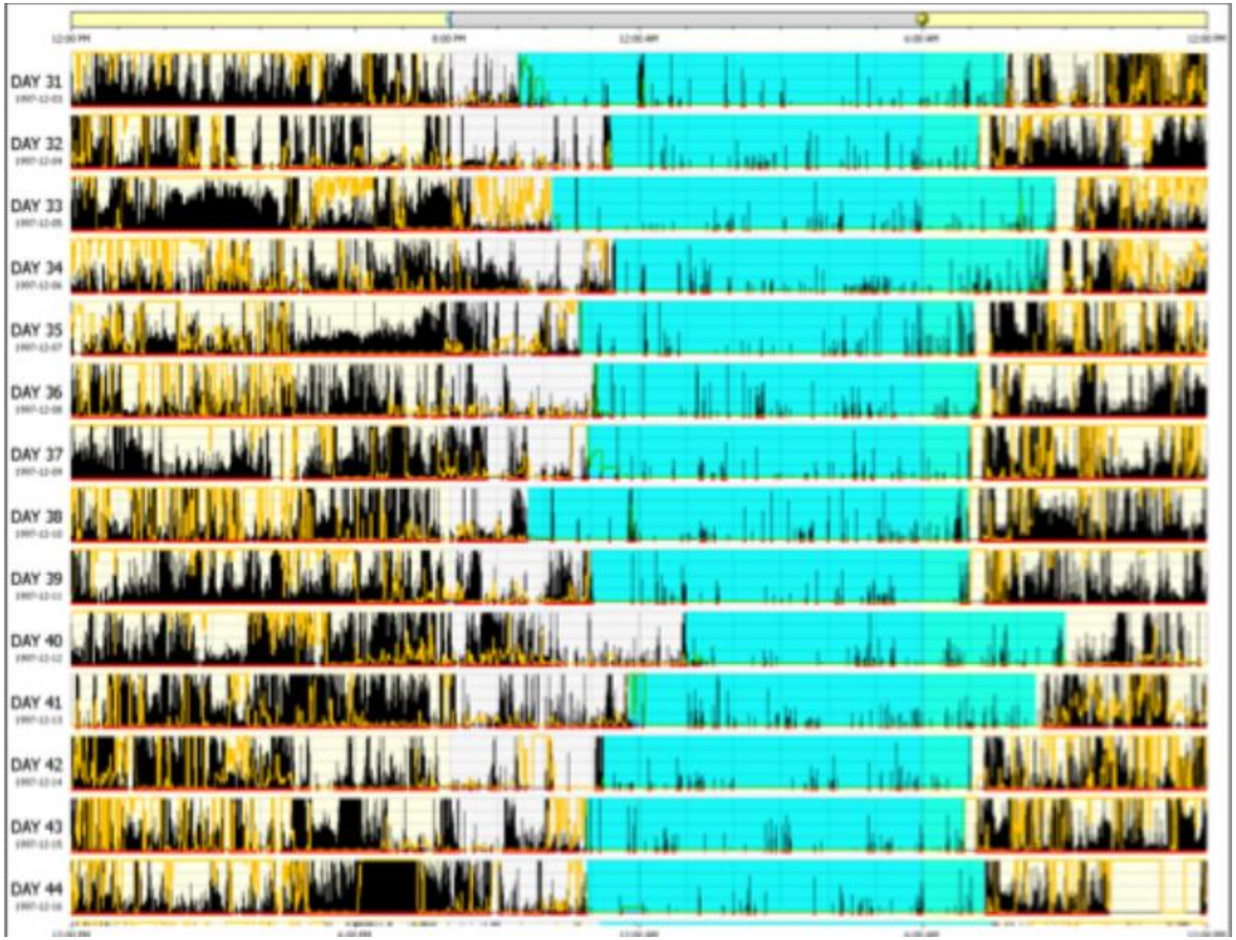
Clinical Report:

- Time in REM, NREM (1,2,3)
- Desaturation summaries
- Fragmentation

Limitations:

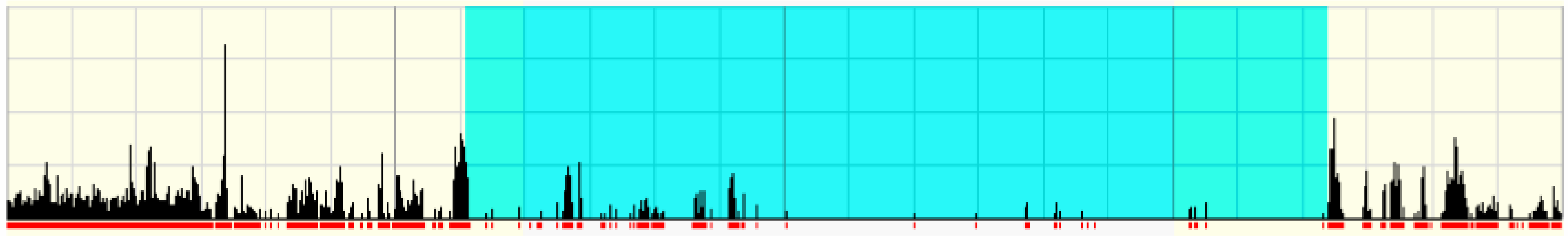
- Invasive
- Impractical for ambulatory applications

Sleep (Actigraphy)

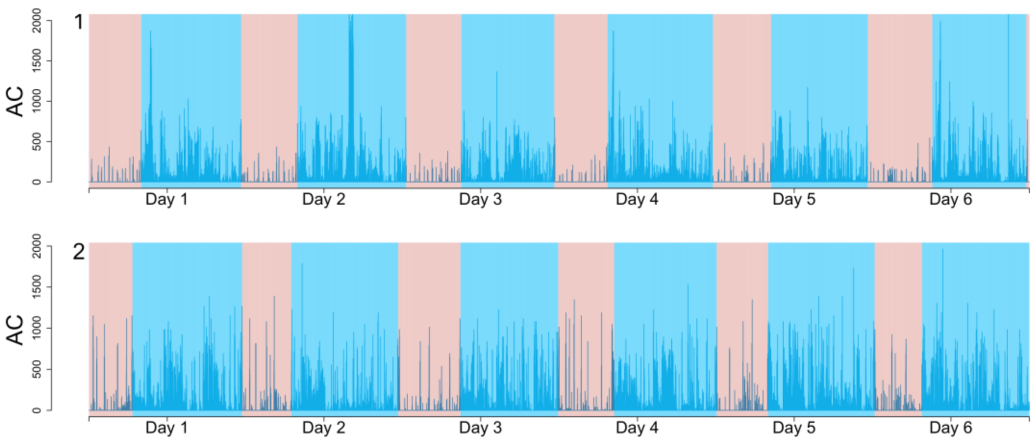


Actigraphy-Measured Sleep Quality

- Summaries
  - Total Sleep Time (TST)
  - Wake After Sleep Onset (WASO)
  - Number of Wake Bouts
  - Sleep Efficiency (SEFF)
  - Sleep Onset Latency
- Major Limitations
  - cannot discriminate between sleep stages
  - No oxygenation information

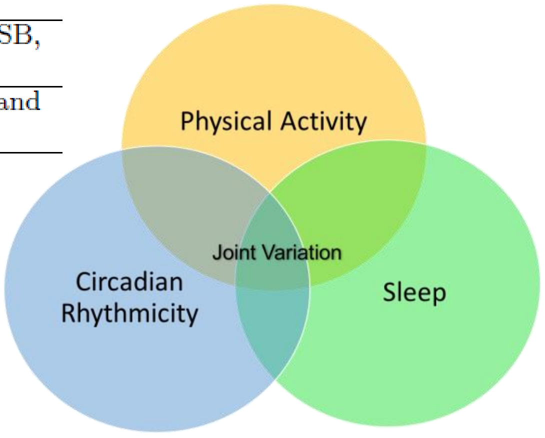


Joint and Individual Modelling of Sleep, Physical activity, Circadian Rhythmicity



Domain-specific Features

Domains	Thresholds	Features
PA	50,100	TAC, TLAC, LTAC, TST, pST, μ, λ, g, α
SL	20,40	SOL, SEFF, WASO, pWT, NWB, AWB, TSLT, pSLT, NSB, WSTP
CR	-	min, mesor, amplitude, α, β, ϕ, RA, IV (at both minute and hourly level), fPC_1, fPC_2,..., fPC_{10}



Baltimore Longitudinal Study of Aging

- 415 BLSA participants (aged 24 – 96 y.o.)
- 7 consecutive 24-hour periods measured with Actiwatch-2
- Days with more than 5% daily missing data (72) were excluded. Subjects with fewer than 3 days of valid days were excluded
- Features were averaged across days

Multi-Domain Data

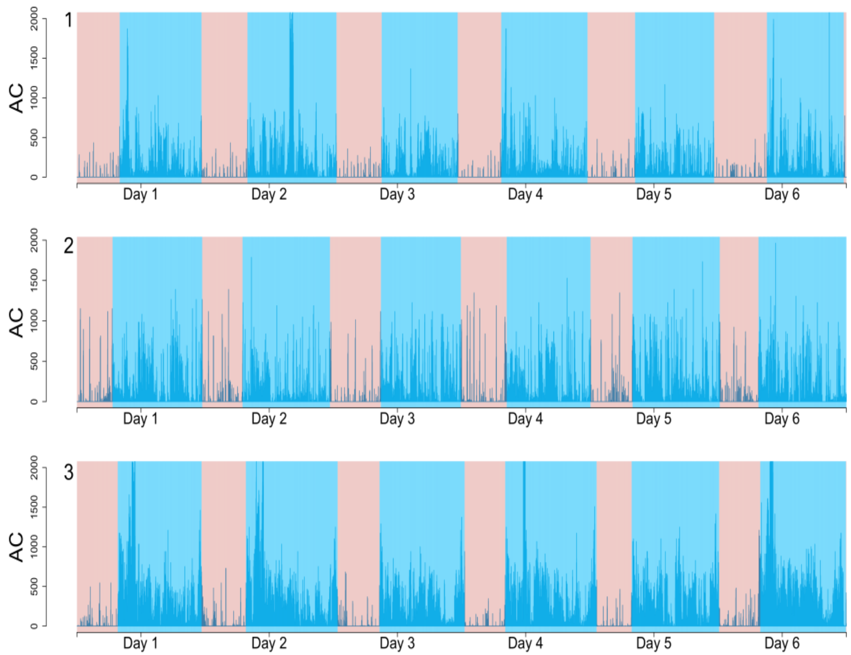


Figure 9. 24-hour measurement for 6 days from BLSA

- Continuous actigraphy measurement enables us to study
  - Physical activity (PA): waking period

  e.g. sedentary behavior and its accumulation patterns are risk factors for a wide range of diseases and mortality.

  - Sleep (SL): night time sleeping period

  e.g. sleep has been shown to be associated with cognitive function and neurodegenerative disease.

  - Circadian rhythms: 24 hour oscillation

  e.g. misalignment of circadian rhythm is associated with adverse metabolic and cardiovascular consequences.

- Guided by specific questions, researches typically focus on one of the three domains without considering the joint dependence of features within and between the domains.

- It becomes crucial to understand the joint effect of all three domains

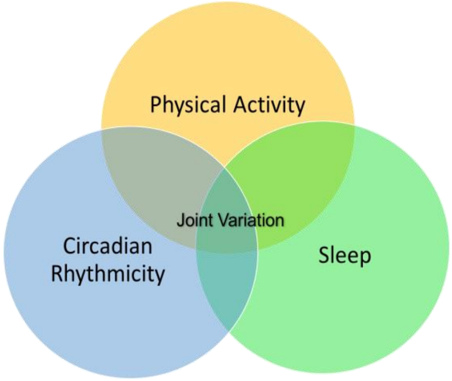
Multivariate within Each Domain

Domains	Threshold	Features
PA	50, 100	TAC, TLAC, LTAC, TST, WT, pST, μ, λ, g, α, $\bar{h}$
SL		TiB, SOL, SEFF, WASO, pWT, NWB, AWB, TSLT, pSLT, NSB, ImmbT, pImmb, NImmbB, AImmbB, TMT, pMT, NMB, AMB, N1ImmbB, p1ImmbB, Fragment
CR	Original scale Log-transformed	mesor, amp, acrophase, fPC1-6, IV, RA

- The list of features can be easily expanded with new summaries or by applying different thresholds.
- For multivariate data, dimension reduction can eliminate redundancy and capture most of relevant information.

Interdependency and Heterogeneity

- Interdependency: same 24-hour cycles from the same group of subjects.
- Heterogeneity: domains represent different physiological systems.



Joint and Individual Variation Explained (JIVE)

$$\mathbf{Y}^1 = J^1 + A^1 + \epsilon^1 = \Phi_J^1 \Gamma_J + \Phi_A^1 \Gamma_A^1 + \epsilon^1$$
$$\vdots$$
$$\mathbf{Y}^\mathbf{D} = J^D + A^D + \epsilon^D = \Phi_J^D \Gamma_J + \Phi_A^D \Gamma_A^D + \epsilon^D$$

- Joint Structure: $\mathbf{J} = \begin{bmatrix} J^1 \\ \vdots \\ J^D \end{bmatrix}$, with score Γ_J and loading Φ_J, rank(**J**) = r
- Individual structures: A^d, with scores Γ_A^d and loading Φ_A^d, rank(A^d) =r_d
- Orthogonality constraint: $\mathbf{J}A^{d^T} = 0$ (joint pattern unrelated to the individual pattern)

Lock, E.F., Hoadley, K.A., Marron, J.S. and Nobel, A.B., 2013. Joint and individual variation explained (JIVE) for integrated analysis of multiple data types. *The annals of applied statistics*, *7*(1), p.523.

Scientific Applications: Model Gait Speed with Scores

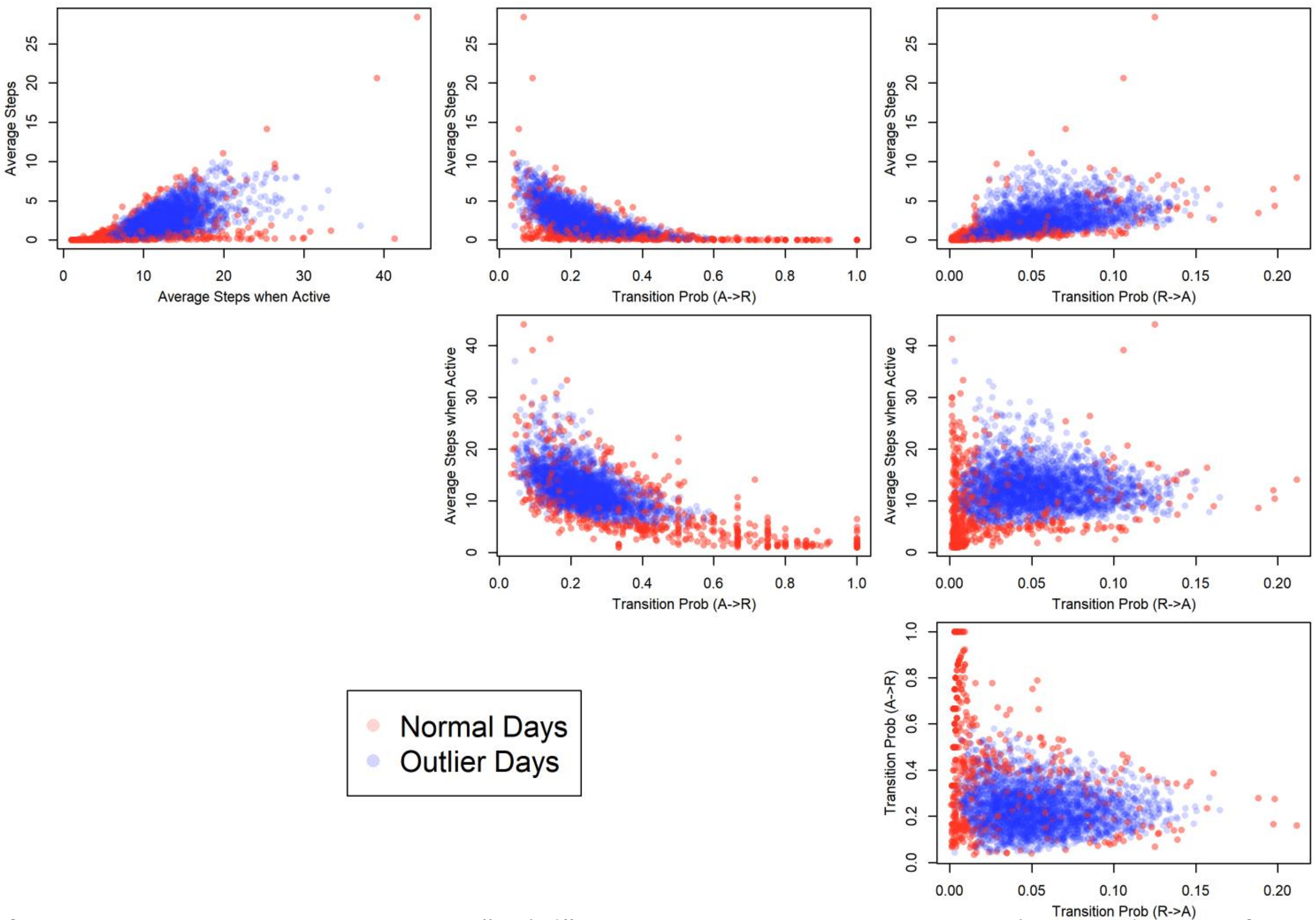
Predictors	Beta	95% CI	P Values	Predictors	Beta	95% CI	P Values
JT-PC1	**0.13**	**(0.04, 0.22)**	**0.0048**	SL-PC3	-0.141	(-0.32, 0.04)	0.13
JT-PC2	0.084	(-0.002, 0.17)	0.056	SL-PC4	-0.178	(-0.47, 0.11)	0.23
JT-PC3	-0.04	(-0.13, 0.05)	0.37	CR-PC1	-0.003	(-0.09, 0.08)	0.93
PA-PC1	-0.035	(-0.12, 0.05)	0.41	CR-PC2	-0.07	(-0.15, 0.02)	0.11
PA-PC2	**0.155**	**(0.07, 0.24)**	**0.0006**	CR-PC3	0.023	(-0.06, 0.11)	0.59
PA-PC3	-0.07	(-0.16, 0.016)	0.11	CR-PC4	0.03	(-0.05, 0.11)	0.48
SL-PC1	**-0.203**	**(-0.33, -0.08)**	**0.0012**	CR-PC5	-0.01	(-0.1, 0.08)	0.82
SL-PC2	0.043	(-0.04, 0.13)	0.32				

- The model is adjusted by age, gender, and BMI (adj-R2 = 0.24)
- PA-PC2 and SL-PC1 are highly loaded on activity and sleep fragmentation. (adj-R2 = 0.34)

References:

- Di, J., Spira, A., Bai, J., Urbanek, J., Leroux, A., Wu, M., Resnick, S., Simonsick, E., Ferrucci, L., Schrack, J. and Zipunnikov, V., 2019. Joint and Individual Representation of Domains of Physical Activity, Sleep, and Circadian Rhythmicity. *Statistics in Biosciences*, pp.1-32.

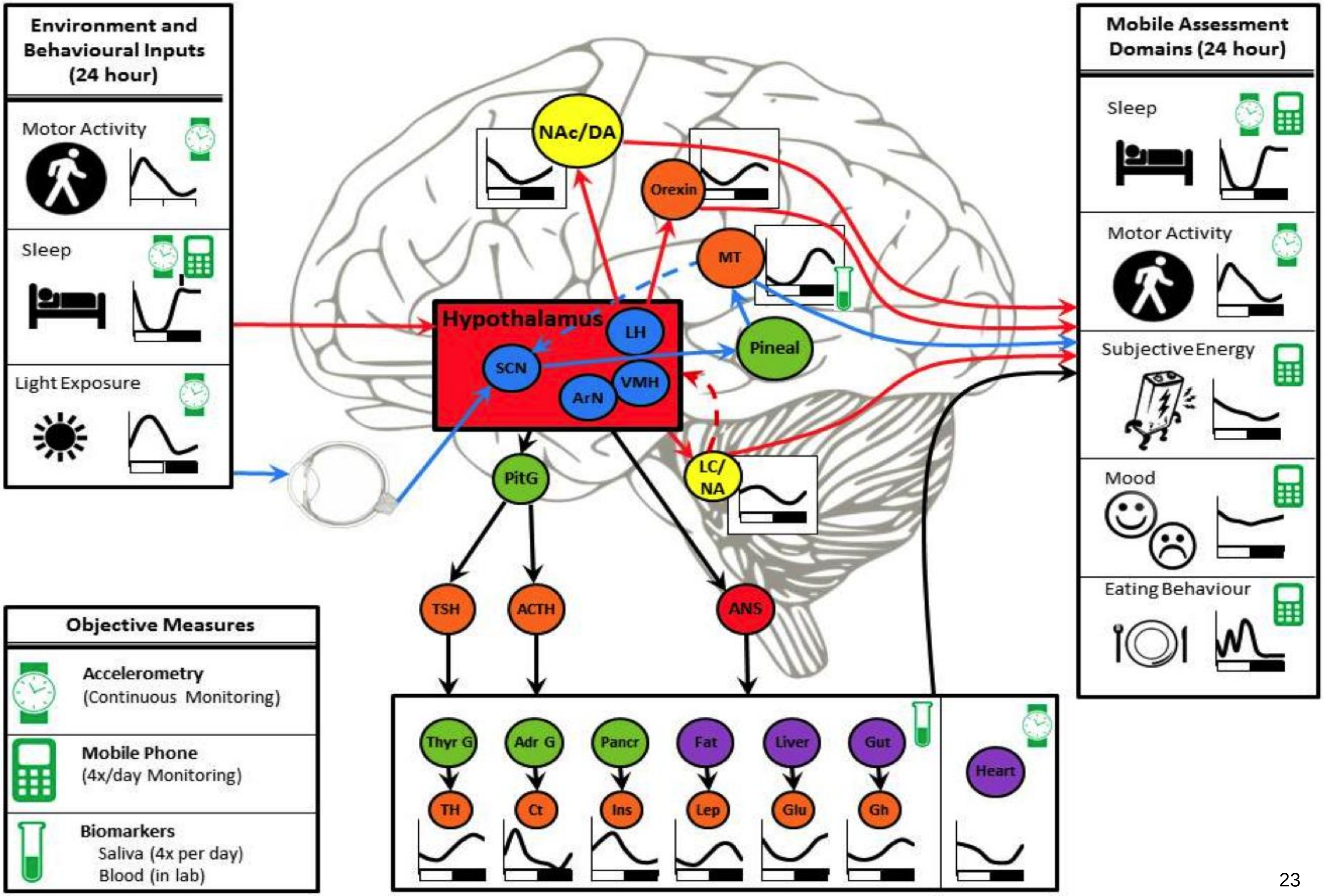
Automatically Detecting Outlying Days



Methods for Step Count Data: Determining "Valid" Days using Support Vector Machine and Quantifying Fragmentation of Walking Bouts (submitted to Gait and Posture)

Lisa Reider, Jiawei Bai, Daniel Scharfstein, Vadim Zipunnikov

EMA data



Environment and Behavioural Inputs (24 hour)
Motor Activity
Sleep
Light Exposure
Mobile Assessment Domains (24 hour)
Sleep
Motor Activity
Subjective Energy
Mood
Eating Behaviour
NAc/DA
Orexin
MT
Hypothalamus
LH
SCN
ArN
VMH
Pineal
PitG
LC/NA
TSH
ACTH
ANS
Thyr G
Adr G
Pancr
Fat
Liver
Gut
Heart
TH
Ct
Ins
Lep
Glu
Gh
Objective Measures
Accelerometry
(Continuous Monitoring)
Mobile Phone
(4x/day Monitoring)
Biomarkers
Saliva (4x per day)
Blood (in lab)

EMA Data

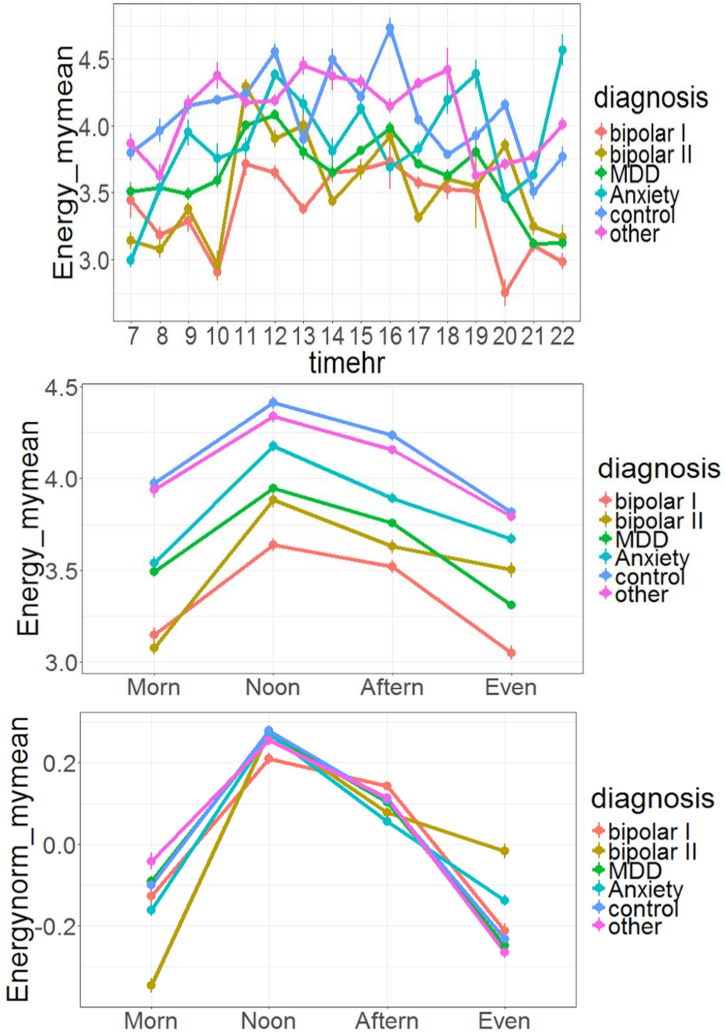
Challenges:

- Normalization of subject-specific interpretation of the scales (1-7, 1-10)
- Continuous modelling of ordinal scales
- Mixed data types: exponential family
- Daily observations: weekly patterns
- Bringing context: work/work-free days, etc
- Subject-specific vs population-level modeling/prediction

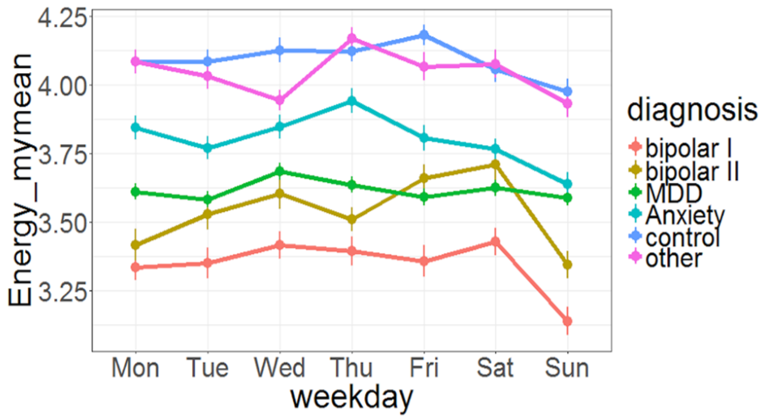
Important considerations

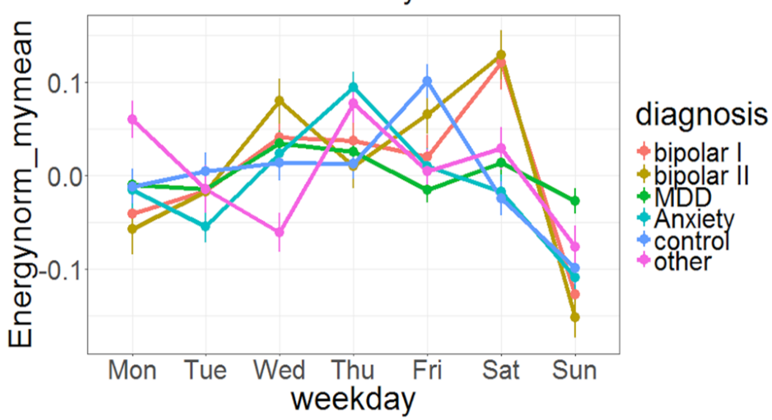
1. Normalize to the subject-specific internal clock
2. Estimate subject-specific diurnal pattern
3. Understand subject-specific weekly pattern
4. Do subject-specific normalization of the measurement (AC, subjective scores)
5. The subject-specific norm is defined by 1-4.
6. Dynamic deviations from the subject-specific norm (defined by 1-4) can be used for dynamic prediction

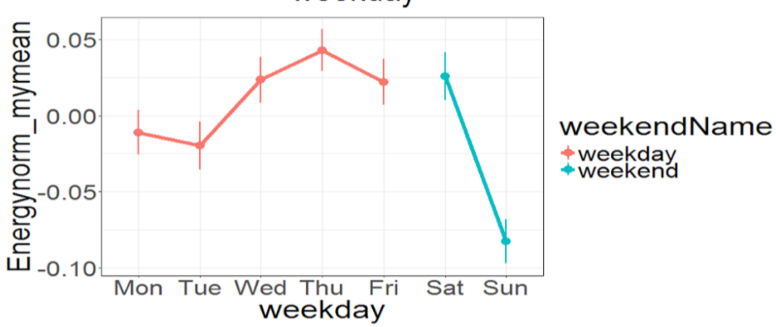
Steps 1 and 2: internal (wake) time and diurnal patterns



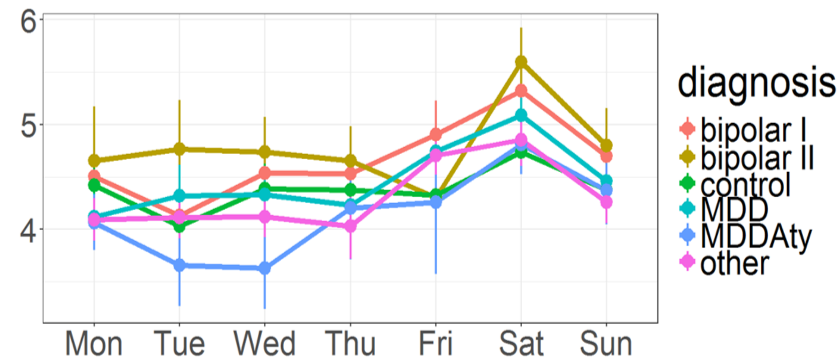
Step 3: Subject-specific weekly patterns







Sleep Midpoint Raw Scores



Sleep Midpoint Normalized