Functional Data Analysis Approach for Individual Causal Mediation Analysis in N-of-1 Mobile Health Studies

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Motivation

Sleep is an essential factor for physical and mental health, however, has historically been hard to observe

Mobile health studies have developed new technology for observing sleep patterns over a long follow-up within participant's daily home life

Digital devices (such as wrist actigraph) generate **dense** across time and **noisy raw data**

- Common to use scalar overnight values to summarize (such as sleep duration)

Functional data analysis provides an intuitive approach to summarize intensive longitudinal data by viewing data as **functional units with added noise** instead of scalar measurement

- Most common in settings with independent functional units measured

Bipolar Longitudinal Study (BLS)

- Mobile health study from McLean Hospital
- Extreme **heterogeneity** between participants → **N-of-1 approach**

Wrist actigraph collects physical activity levels

Mobile phone collects daily responses to survey on symptoms, mood, and behaviors

Here we focus on a participant with bipolar spectrum disorder and a follow-up of approximately 2.5 years

FPCA with N-of-1 approach

Functional Principal Component Analysis (FPCA) is a common tool for dimension reduction, where functional units are decomposed into a **mean function, loadings, and functional principal components**.

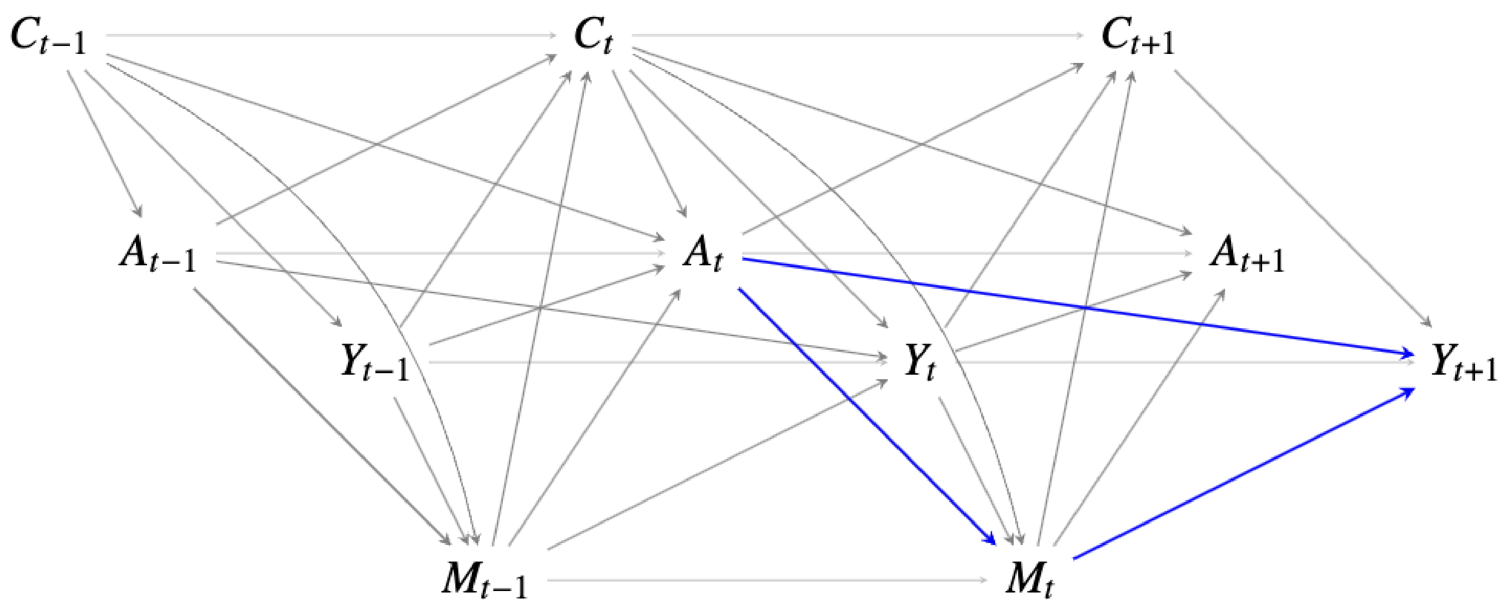
We employ FPCA to analyze overnight wrist actigraphy data representing sleep for a **single participant's** longitudinal data

– Note data will violate independence assumptions traditionally made in FPCA

Objective

Evaluate the role of **sleep as a mediator** between today's **self-reported stress** and tomorrow's **positive mood**

Mediation Causal Framework



Y_{t+1}: Outcome (pos mood)

M_t: Mediator (sleep)

A_t: Exposure (stress)

C_t: Covariates

Under above framework, adjustment set $\mathrm{X_t} = \{C_t, A_{t-1}, Y_{t-1}, Y_t, M_{t-1}\}$ is sufficient for A_t to Y_{t+1}, M_t to Y_{t+1}, and A_t to M_t

Causal estimands

Natural direct effect: $NDE = E\left(Y_{t+1}^{a_t, M_t^{a^*}} - Y_{t+1}^{a_t^*, M_t^{a^*}}\right)$

Natural indirect effect: $NIE = E\left(Y_{t+1}^{a_t, M_t^{a_t}} - Y_{t+1}^{a_t, M_t^{a_t^*}}\right)$

Total effect: $TE = E\left(Y_{t+1}^{a_t, M_t^{a_t}} - Y_{t+1}^{a_t^*, M_t^{a_t^*}}\right)$

We assume positivity, consistency, no unmeasured exposure-outcome, mediator-outcome, nor exposure-mediator confounding and no descendant of the exposure is a confounder for the mediator-outcome relationship.

Causal estimation

To estimate the effects of interest, we assume linearity, stationarity and Markovian independence, such that we fit linear models:

$$E(Y_{t+1}|a_t, m_t, x_t) = \theta_0 + \theta_1 a_t + \theta_2' m_t + \theta_3' x_t$$

And for each k = 1, …, K mediator $M_{t,k}$

$$E\left(M_{t,k}\middle|a_t, x_t\right) = \beta_{0,k} + \beta_{1,k} a_t + \beta_{2,k}' x_t$$

Then we can estimate:

$$NDE = \theta_1(a - a^*);$$

$$NIE = \left(\sum_{k=1}^{K} \theta_{2,k}{}'\beta_{1,k}\right)(a - a^*);$$

$$TE = NDE + NIE = \left(\theta_1 + \sum_{k=1}^{K} \theta_{2,k}{}'\beta_{1,k}\right)(a - a^*)$$

Objective

Evaluate the role of sleep as a mediator between today's self-reported stress and tomorrow's positive mood

We consider defining sleep as:

- Sleep duration in hours (as identified via DPSleep pipeline)
- Scores for functional principal components that explain 95% of variance in overnight minute-by-minute wrist actigraph data

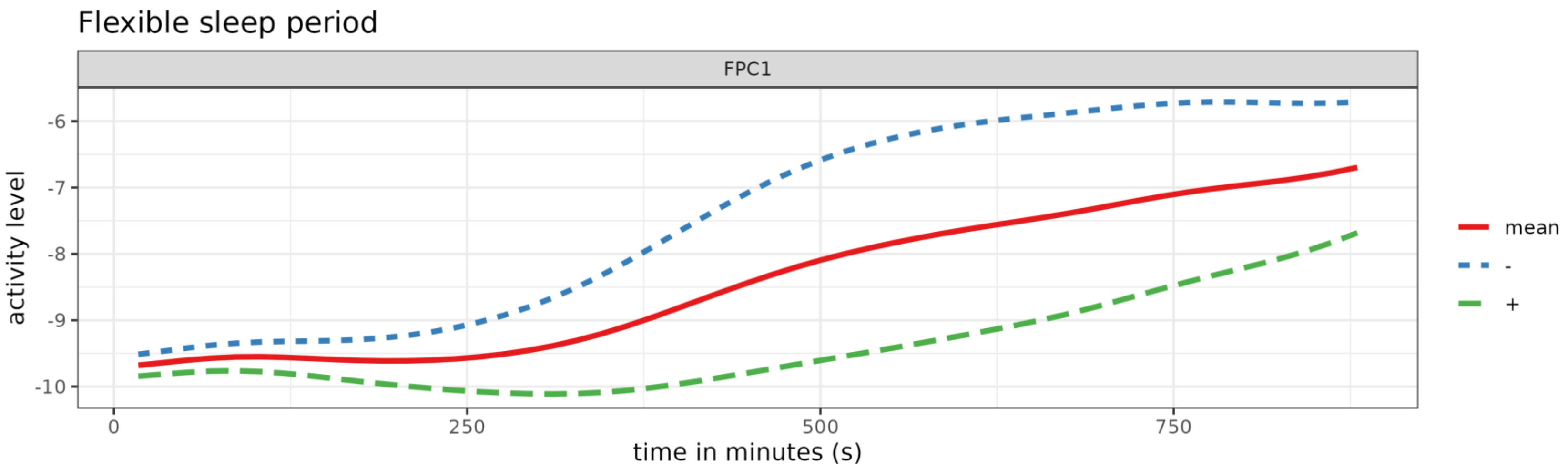
FPCA sleep period

We want M_t to reflect only sleep behavior, not all actigraphy data, and to ensure temporal order of A_t, M_t, and Y_{t+1}

Set overnight sleep period as time of sleep onset for that given night to that time plus 90th percentile of sleep duration for the individual (14.7 hours)

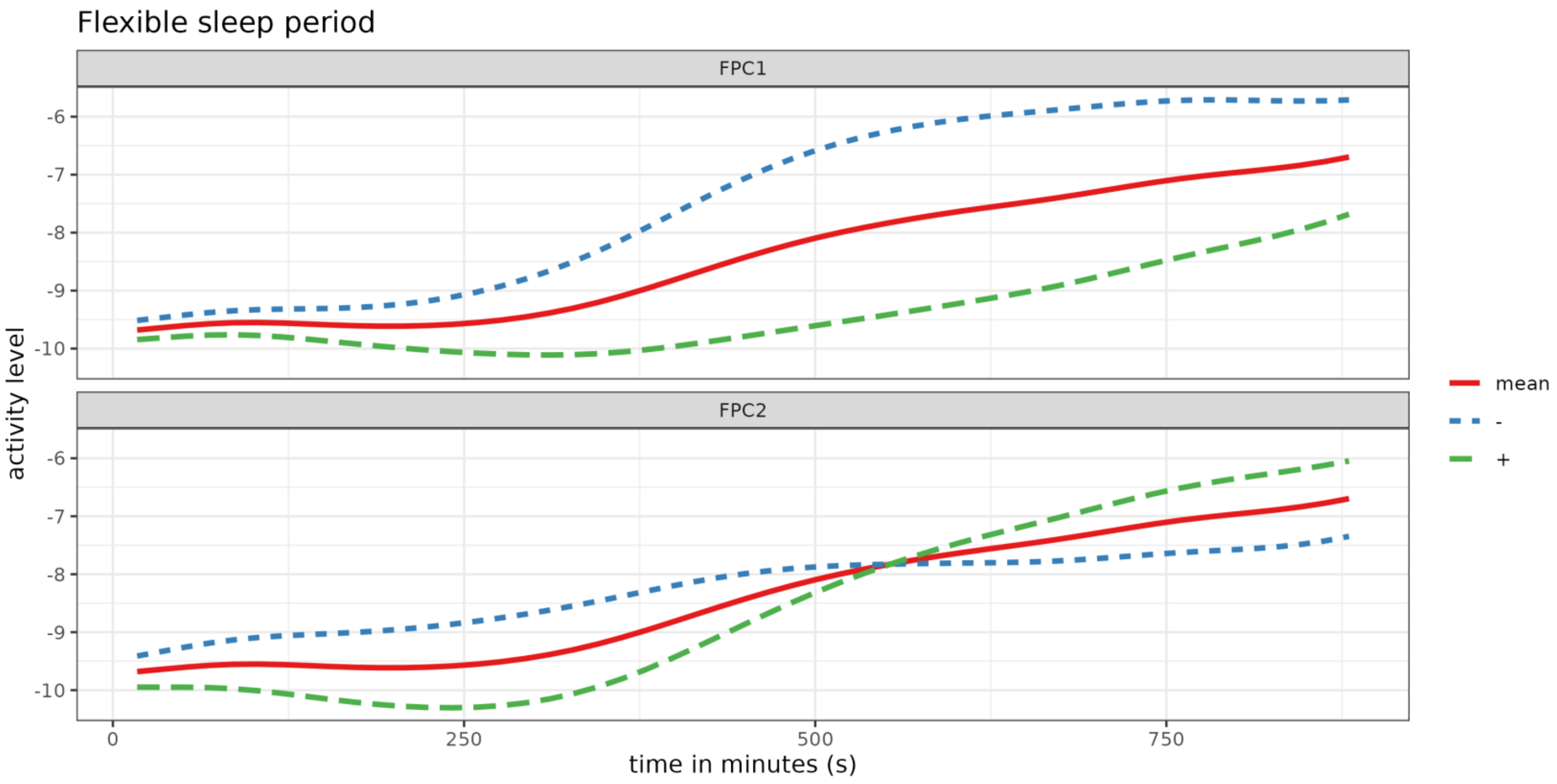
- This should capture variance in activity levels while asleep and overall duration

Functional Principal Components



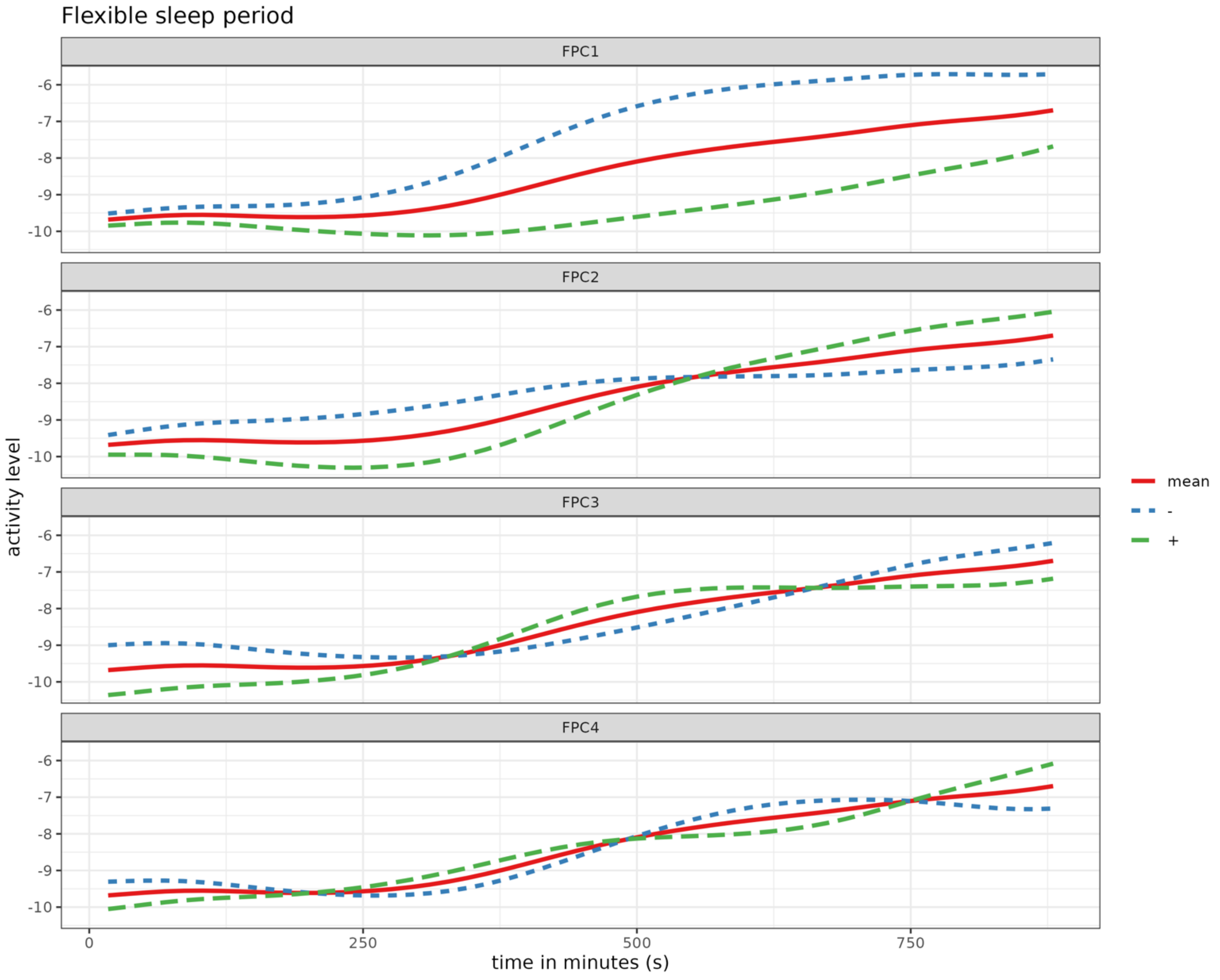
First FPC reflects earlier or later wake up and explains 71% of the variance.

Functional Principal Components



Second FPC explains 16% of the variance and reflects variability in activity during sleep, and later in the morning.

Functional Principal Components



Relation between sleep and positive mood

term	estimate	95% CI low	95% CI high	p-value
sleep duration	-0.310	-0.432	-0.188	<0.001
loading 1	-0.031	-0.044	-0.018	<0.001
loading 2	0.018	-0.009	0.044	0.188
loading 3	0.009	-0.024	0.043	0.588
loading 4	0.054	0.012	0.095	0.012

Table: θ_2' terms depending on sleep measurement resulting from

$$E(Y_{t+1}|a_t, m_t, x_t) = \theta_0 + \theta_1 a_t + \theta_2' m_t + \theta_3' x_t$$

Note no terms for $\beta_{1,k}$ significant from models for

$$E\left(M_{t,k}\middle|a_t, x_t\right) = \beta_{0,k} + \beta_{1,k} a_t + \beta_{2,k}' x_t$$

Mediation results

M	effect	estimate	95% CI low	95% CI high
sleep duration	NDE	0.508	-2.467	3.482
	NIE	0.241	-0.050	0.531
	TE	0.748	-2.317	3.814
FPC	NDE	-0.143	-3.029	2.742
	NIE	0.572	-0.042	1.186
	TE	0.429	-2.469	3.327

Direct, indirect, and total effect of stress reported as “Extremely" compared to “Very slightly stressed or not at all" on the next day's positive mood

Conclusion and next steps

Demonstrate that FPCA can be used with N-of-1 data and identifies additional important signal that is lost when using a scalar definition of sleep

No significant results for stress - theory that stress must accumulate over time

Limitations of assumptions of stationarity, linear relationships, no unmeasured confounding

Potential use of registration to describe vertical and horizontal variance in watch actigraphy data

Need for extension of FPCA to setting with temporally correlated functional units

Thank you!

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