“Wearable and Implantable Technology (WIT) with Biopharmaceutical Applications”

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Financial Disclosure

Professor Crainiceanu is consulting with Bayer and Johnson and Johnson on methods development for wearable and implantable computing with applications to clinical trials. Relevant financial relationships have been disclosed through the Johns Hopkins University eDisclose system.

The presentation contains references to devices used by research collaborators of Dr. Crainiceanu for illustration purposes. The devices and the studies presented here are not related to the consulting work of Dr. Crainiceanu. Dr. Cainiceanu has no conflict of interest related to these devices.

Examples of studies using wearable devices

Large observational studies

NHANES, UK Biobank, BLSA, EPIC, REGARDS, ARIC, BRHS, MACS, Maastricht Study, WHI/OPACH, mMARCH

Clinical trials

STURDY, ACHIEVE, BECT/BHS, COPTR, LIFE, TAAG, WHS, RT-CGM, JDRF-CGM, mSToPS

Ranking predictors of five-year all-cause mortality in the US

Rank	Variable	AUC	Rank	Variable	AUC
1	**TAC**	**0.770**	**16**	**sPC6**	**0.657**
2	Age	0.757	**17**	**$TLAC_{6\text{-}8am}$**	**0.633**
3	**$TLAC_{8\text{-}10pm}$**	**0.753**	**18**	Education	0.611
4	**MVPA**	**0.748**	**19**	Drinking	0.593
5	**$TLAC_{4\text{-}6pm}$**	**0.740**	**20**	Smoking	0.574
6	**$TLAC_{12\text{-}2pm}$**	**0.735**	**21**	CHF	0.569
7	**ASTP**	**0.734**	**22**	BMI	0.550
8	**$TLAC_{10am\text{-}12pm}$**	**0.734**	**23**	Cancer	0.559
9	**$TLAC_{2\text{-}4pm}$**	**0.730**	**24**	Diabetes	0.556
10	**ST**	**0.728**	**25**	Gender	0.554
11	**TLAC**	**0.722**	**26**	Stroke	0.548
12	**$TLAC_{8\text{-}10am}$**	**0.684**	**27**	CHD	0.548
13	Mobil. Prob.	0.672	**28**	Race	0.514
14	**$TLAC_{8\text{-}10pm}$**	**0.671**	**29**	**$TLAC_{12am\text{-}2am}$**	**0.519**
15	**SATP**	**0.660**	**30**	**Wear time**	**0.459**

NHANES 2003-2006, age: 50-84, total: 2969, cases: 294, controls: 2675

Getting the organized NHANES accelerometry data

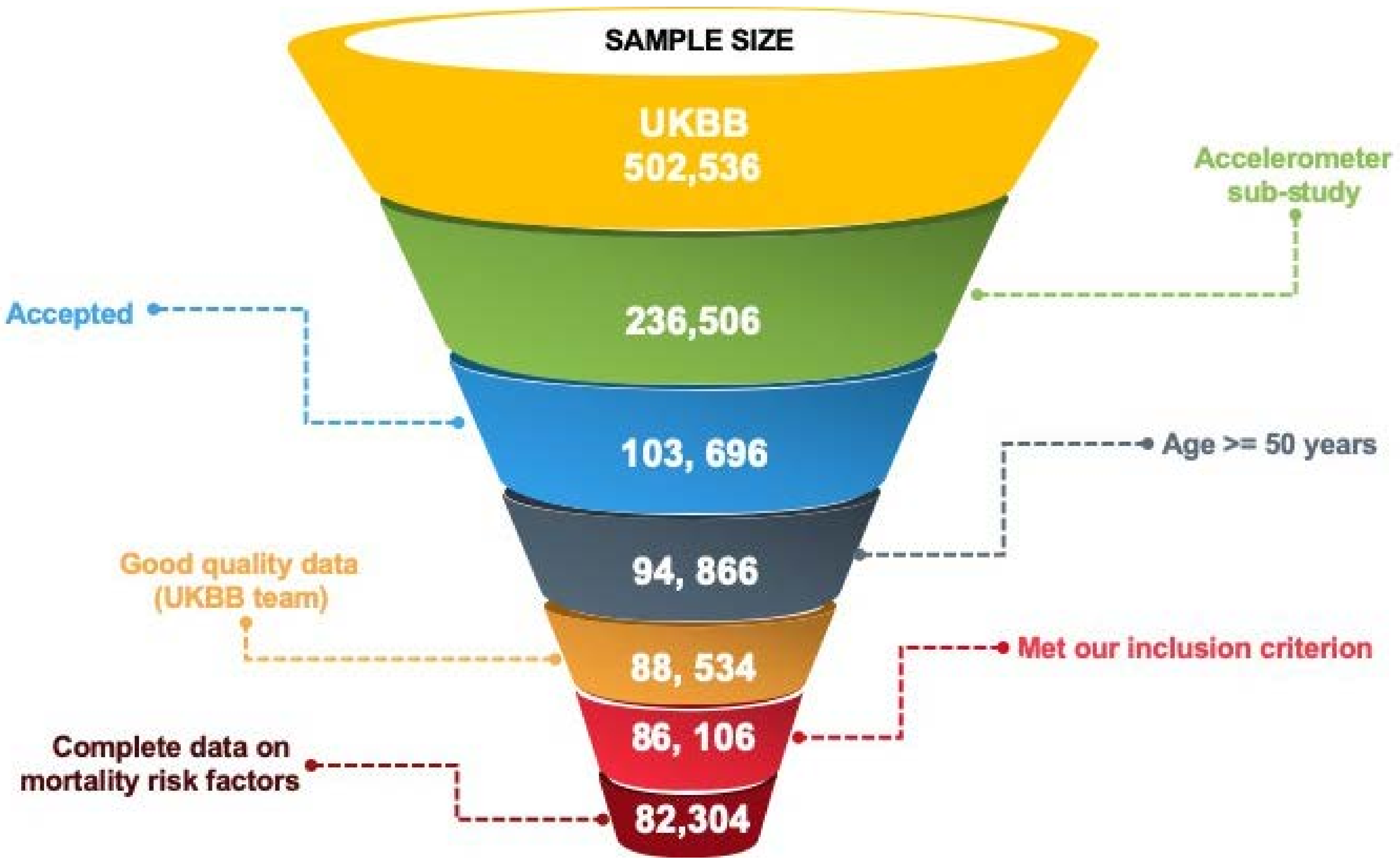
- NHANES data package (*rnhanesdata*):

  https://github.com/andrew-leroux/rnhanesdata

- Installing the rnhanesdata

  devtools::install_github(andrew-leroux/rnhanesdata)

UK Biobank accelerometry at a glance



Ranking predictors of time to death in the UK

Rank	Variable	C	Rank	Variable	AUC
1	**TA**	**0.685**	**16**	**$TLA_{10am-12pm}$**	**0.609**
2	**MVPA**	**0.681**	**17**	SR Disability	0.601
3	**RA**	**0.674**	**18**	**LIPA**	**0.601**
4	**M10**	**0.673**	**19**	SR Health	0.598
5	**TLA_{4-6pm}**	**0.671**	20	**TLA_{8-10pm}**	**0.596**
6	Age	0.669	21	**TLA_{8-10am}**	**0.596**
7	**TLA_{6-8pm}**	**0.653**	22	Gender	0.590
8	**TLA**	**0.653**	23	Smoking	0.586
9	**ST**	**0.652**	24	High BP	0.581
10	**TLA_{2-4pm}**	**0.647**	25	**DARE**	**0.579**
11	**TLA_{12-2pm}**	**0.638**	26	Walk speed	0.577
12	**ABT**	**0.625**	27	**L5**	**0.573**
13	**ASTP**	**0.618**	28	**TLA_{2-4am}**	**0.566**
14	**SATP**	**0.616**	29	BMI	0.566
15	**SBT**	**0.610**	30	**TLA_{6-8am}**	**0.551**

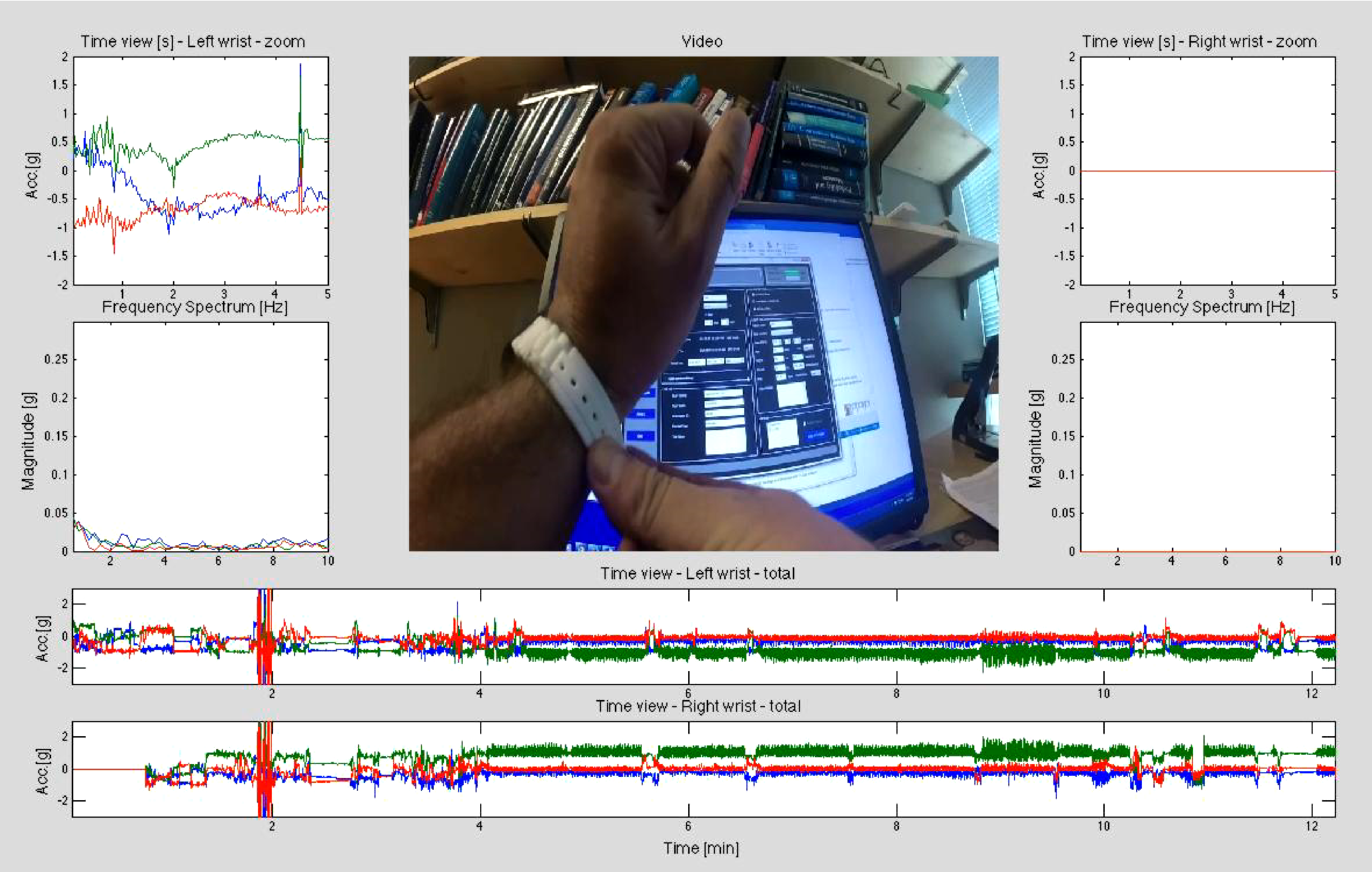
UK Biobank, age: 50+, total: 82,304, cases: 849, follow-up: 258,364 py

How much does activity add to known mortality risk factors?

Stopping Rule: $\delta C \geq 0.001$			
Variable	Cumulative Concordance	δC	$\hat{\beta} \pm 2\text{SE}(\hat{\beta})$
Age	0.669	0.669	0.077 (0.065, 0.089)
Self-reported overall health	0.701	0.032	
Excellent			-0.071 (-0.278, 0.136)
Fair			0.178 (0.001, 0.355)
Poor			0.531 (0.244, 0.819)
Cigarette Smoker	0.714	0.013	
Former			0.122 (-0.026, 0.270)
Current			0.851 (0.642, 1.059)
Gender (male)	0.723	0.009	0.295 (0.149, 0.440)
Longstanding illness/disability	0.730	0.006	0.300 (0.144, 0.456)
Cancer	0.733	0.003	0.406 (0.208, 0.603)
High blood pressure	0.735	0.002	0.175 (0.029, 0.322)
Injury/illness within past 2 years	0.737	0.002	0.319 (0.123, 0.515)
Relative amplitude (RA)	0.758	0.021	-0.276 (-0.341, -0.212)
TLA 4-6PM	0.760	0.002	-0.219 (-0.297, -0.141)

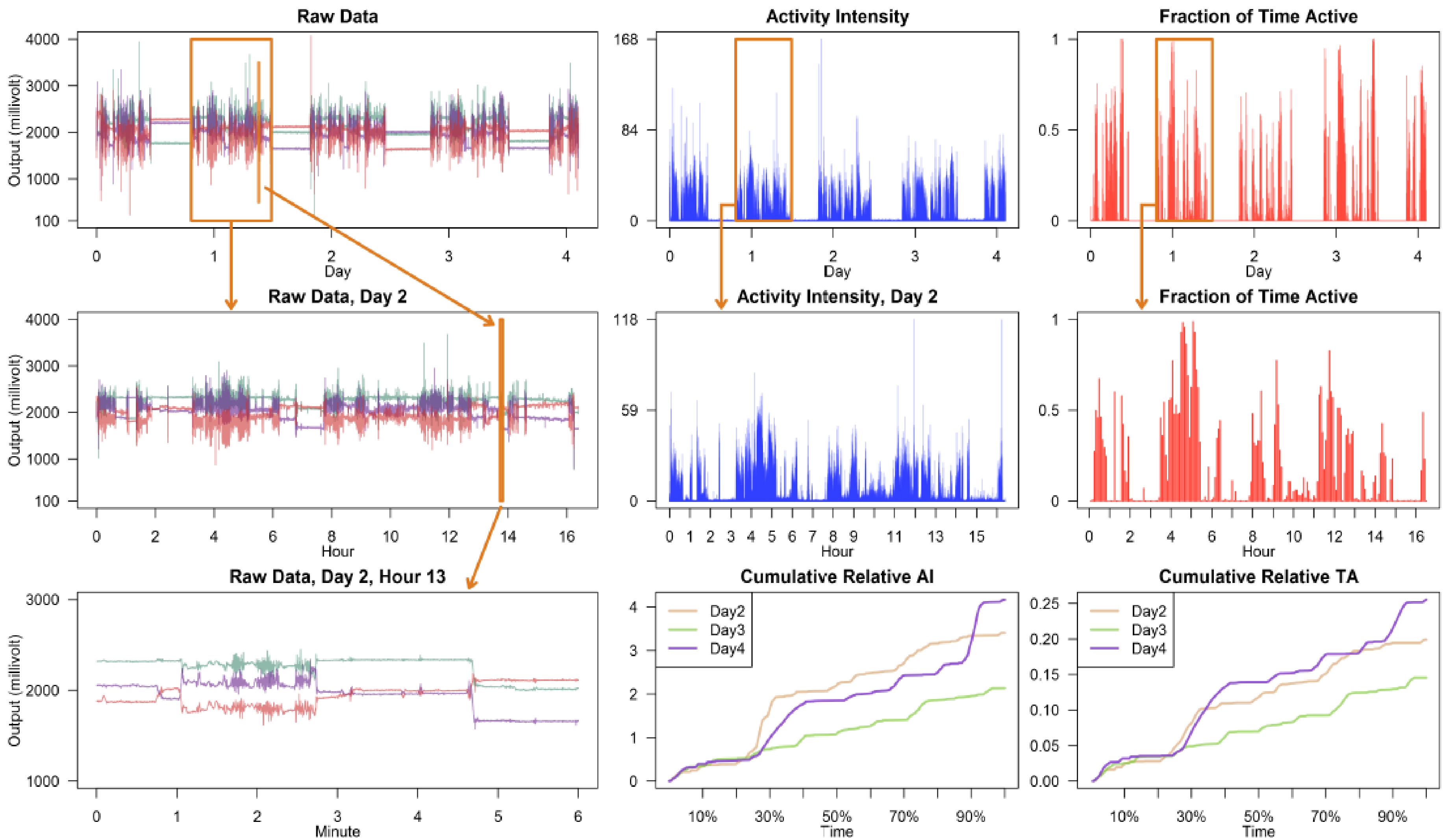
What kind of sensors?

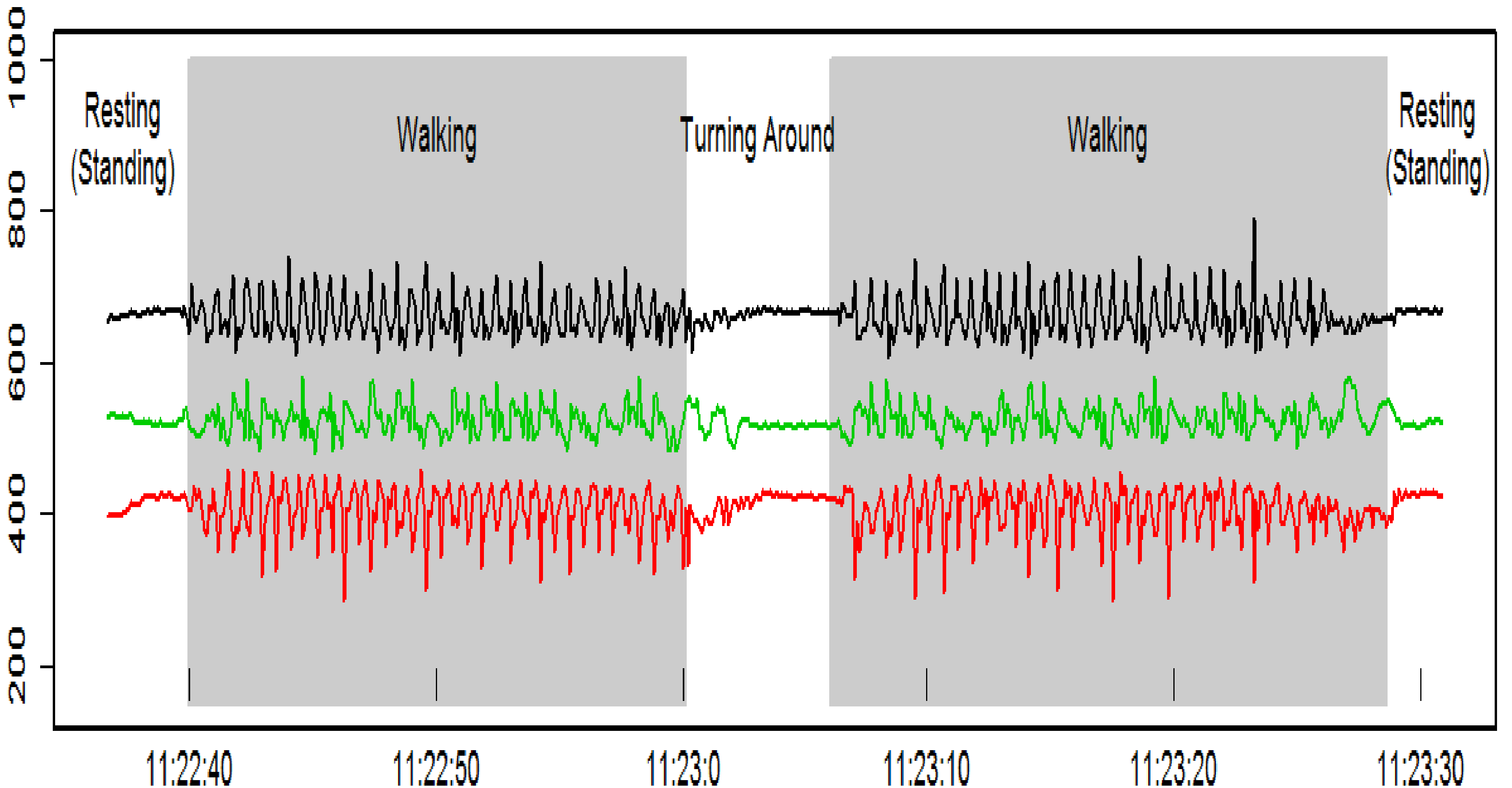
Understanding measurement

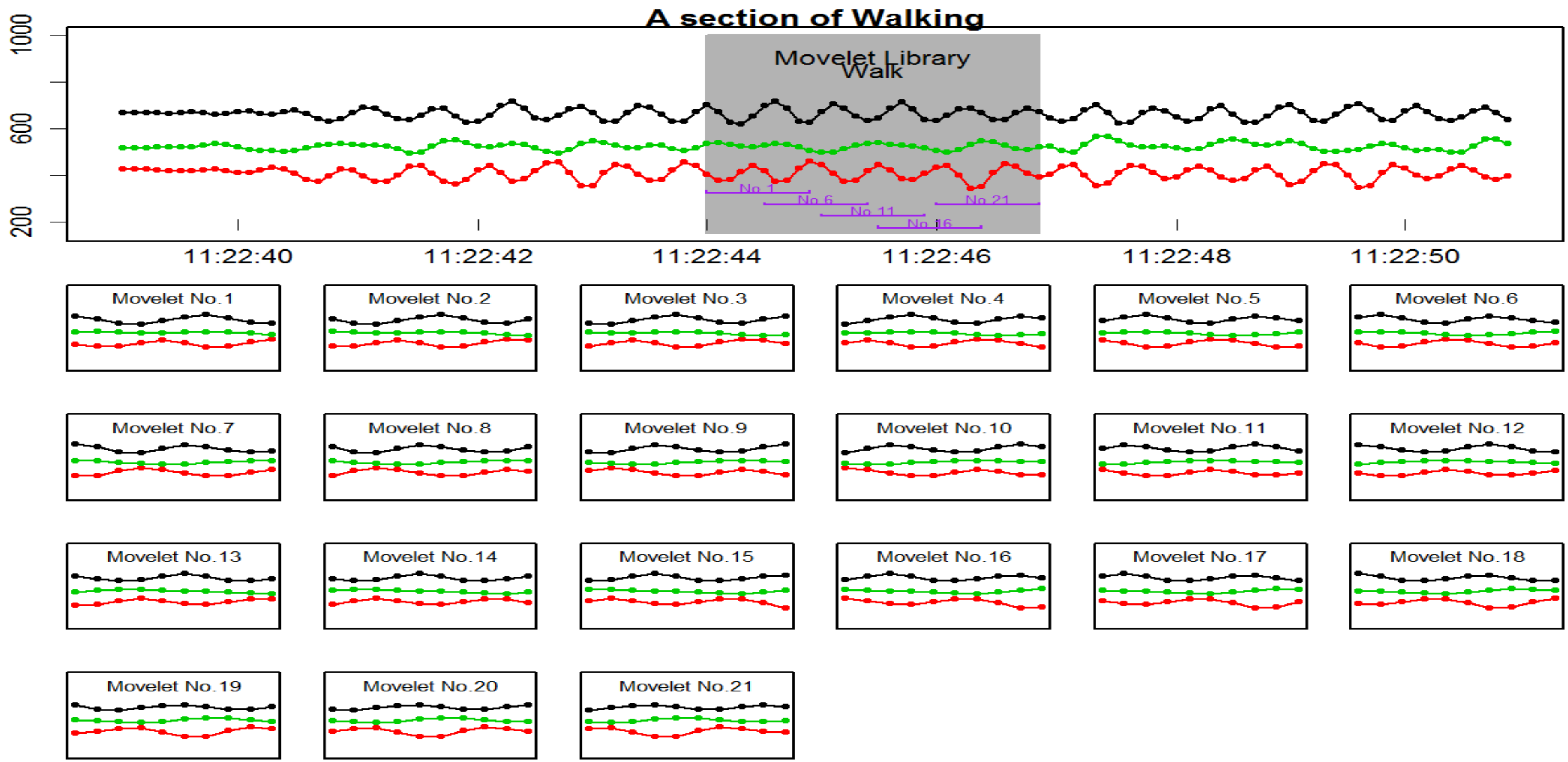


Time view [s] - Left wrist - zoom
Video
Time view [s] - Right wrist - zoom
Acc.[g]
Frequency Spectrum [Hz]
Magnitude [g]
Time view - Left wrist - total
Time view - Right wrist - total
Time [min]

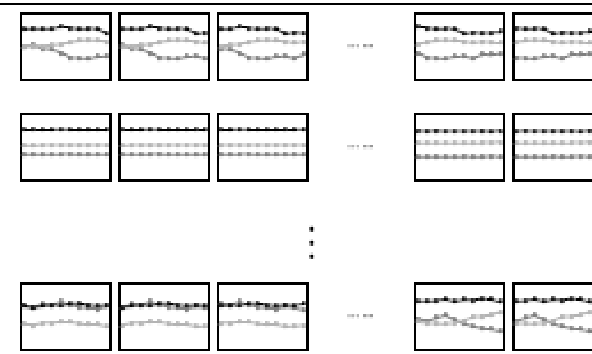
Micro- and macro-level data



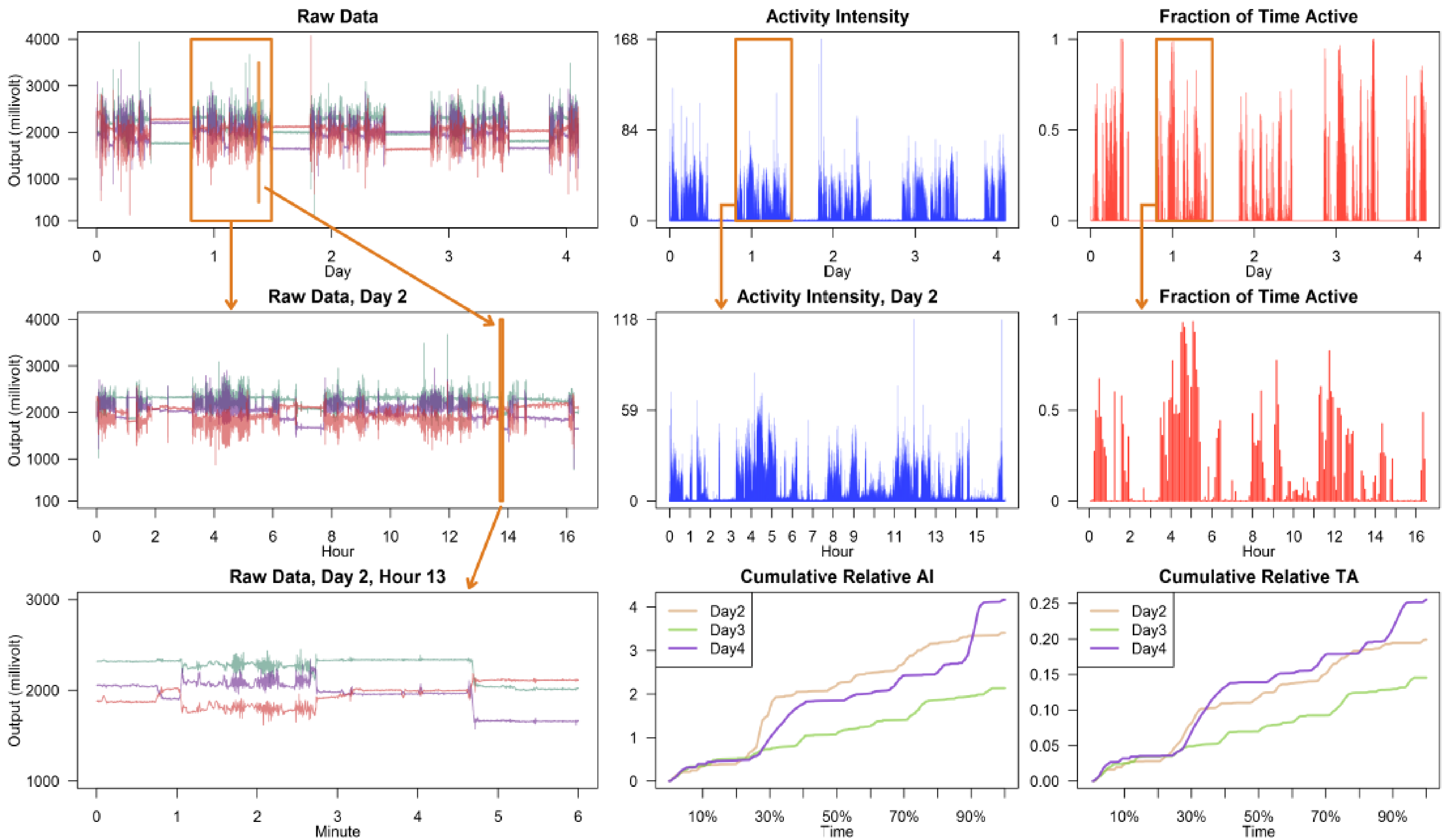

1000
800
600
400
200
Resting
(Standing)
Walking
Turning Around
Walking
Resting
(Standing)
11:22:40
11:22:50
11:23:0
11:23:10
11:23:20
11:23:30



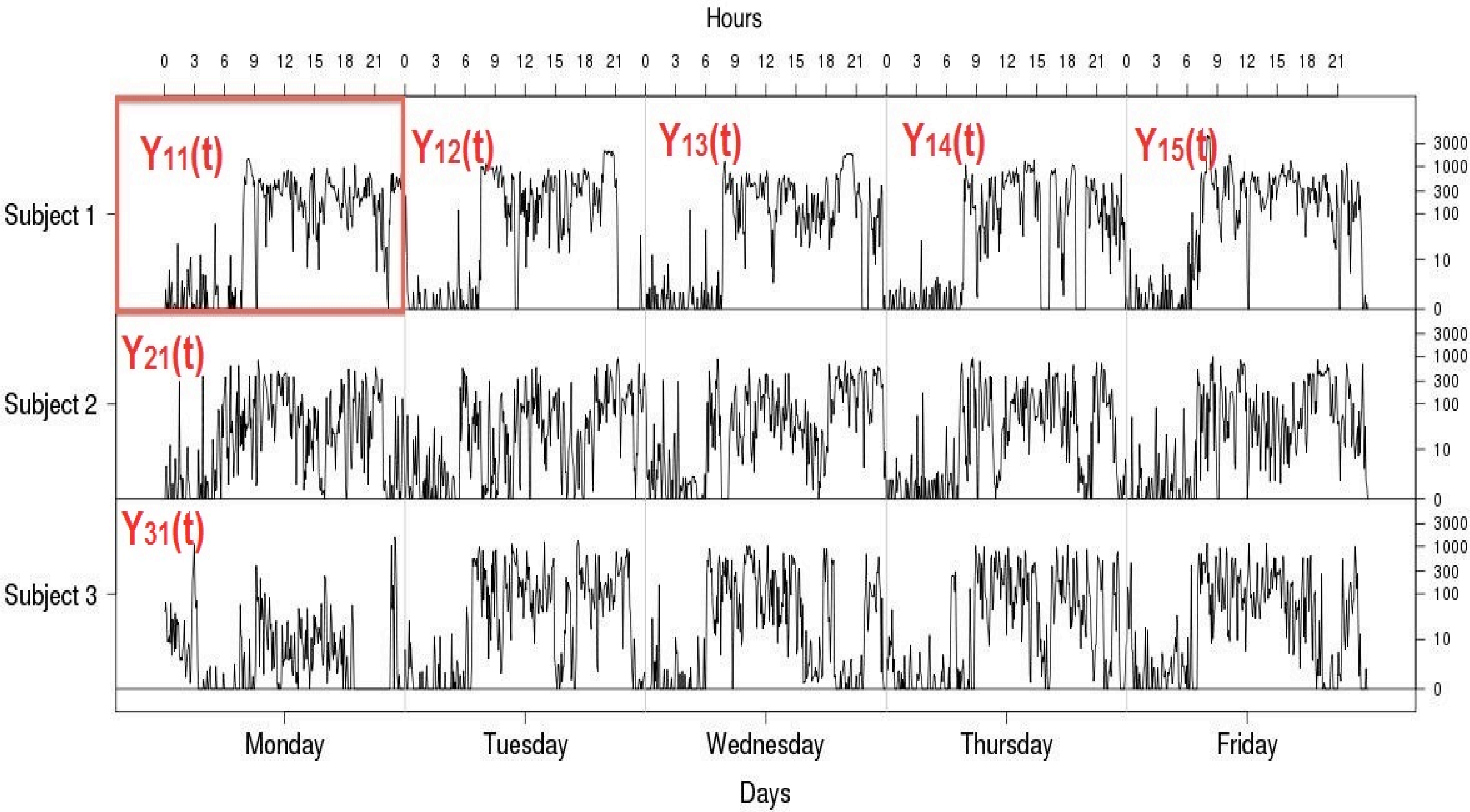
Chapter	Activity	Movelets
$\mathcal{C}_1$	Activity 1	$\{M_i(t) : L_i(t) = \text{Act}_1\}$
$\mathcal{C}_2$	Activity 2	$\{M_i(t) : L_i(t) = \text{Act}_2\}$
$\vdots$	$\vdots$	$\vdots$
$\mathcal{C}_A$	Activity A	$\{M_i(t) : L_i(t) = \text{Act}_A\}$



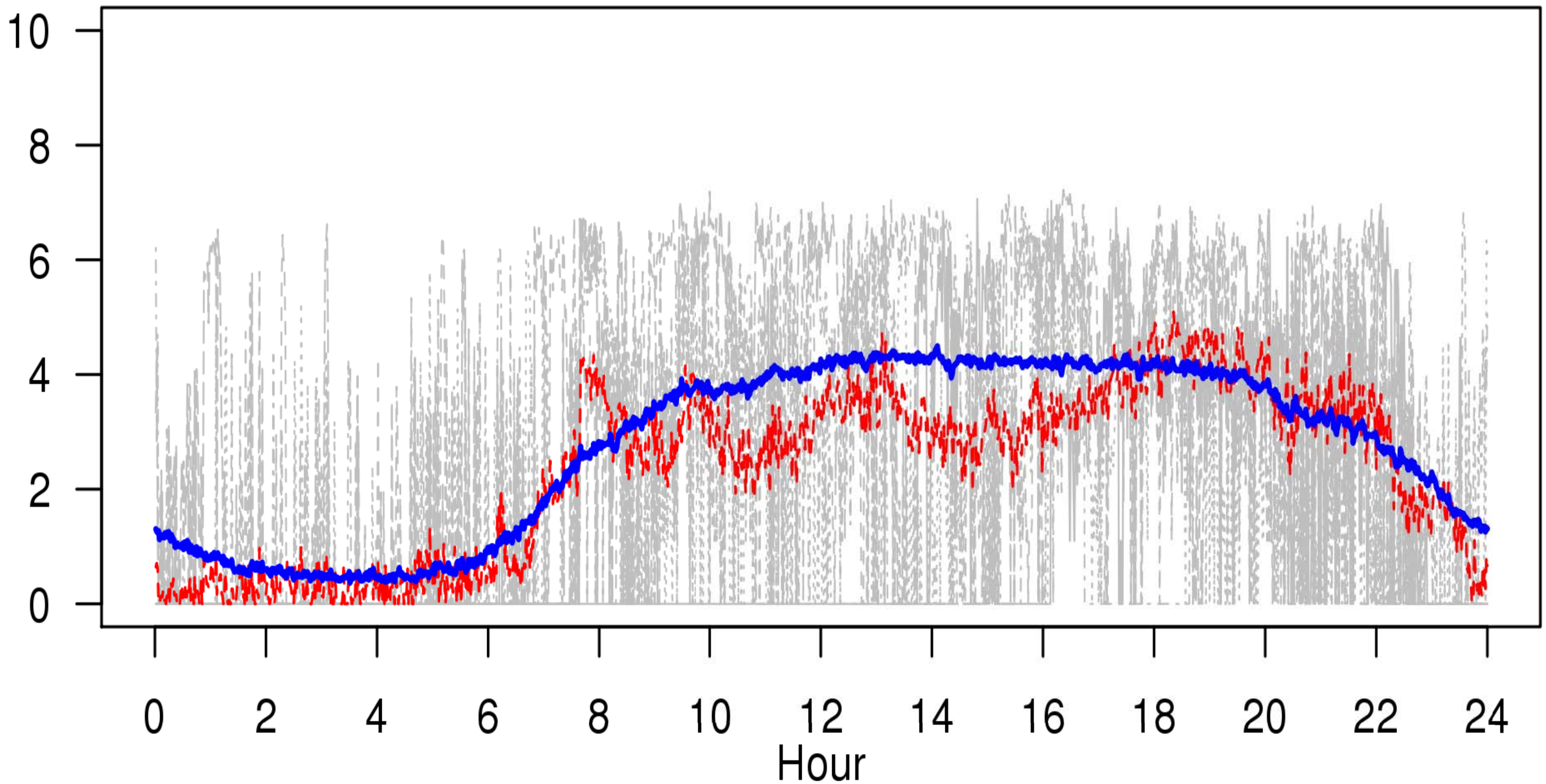
Activity intensity (counts, steps, vector magnitude)



Daily patterns of activity counts



Data: one subject + subject mean + group mean



Baltimore Longitudinal Study of Aging (BLSA)

WIT: organized the BLSA data to the 1440+ standard

- Subjects : 773 (394 females, 379 males): i
- Average number of days/subjects : 7 : j
- Daily profile : 1440 minutes : t
- Age : between 31 and 96 : x
- Data set : 5478 by 1440

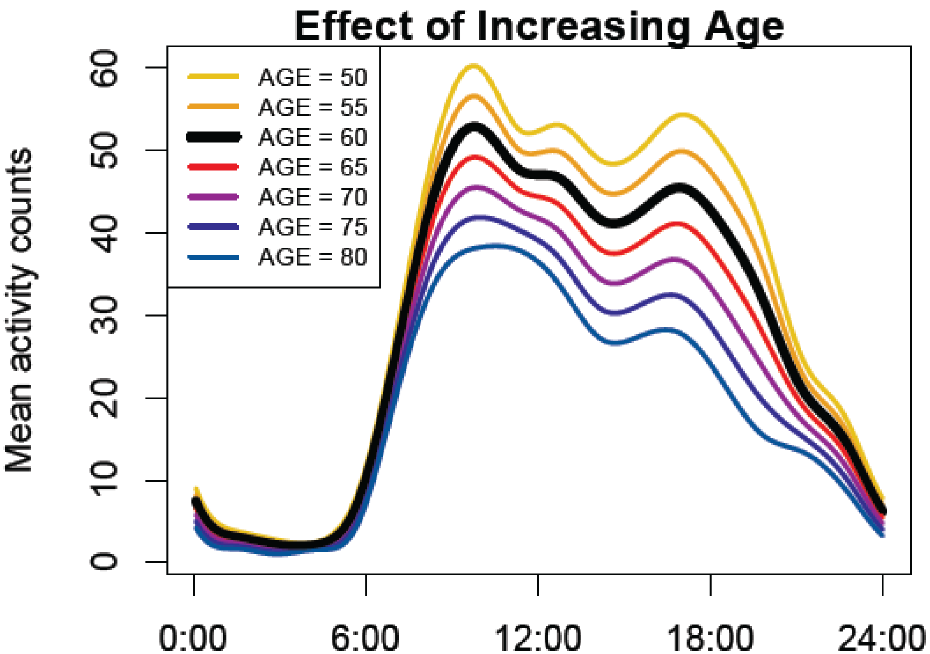
A macro level of the activity data

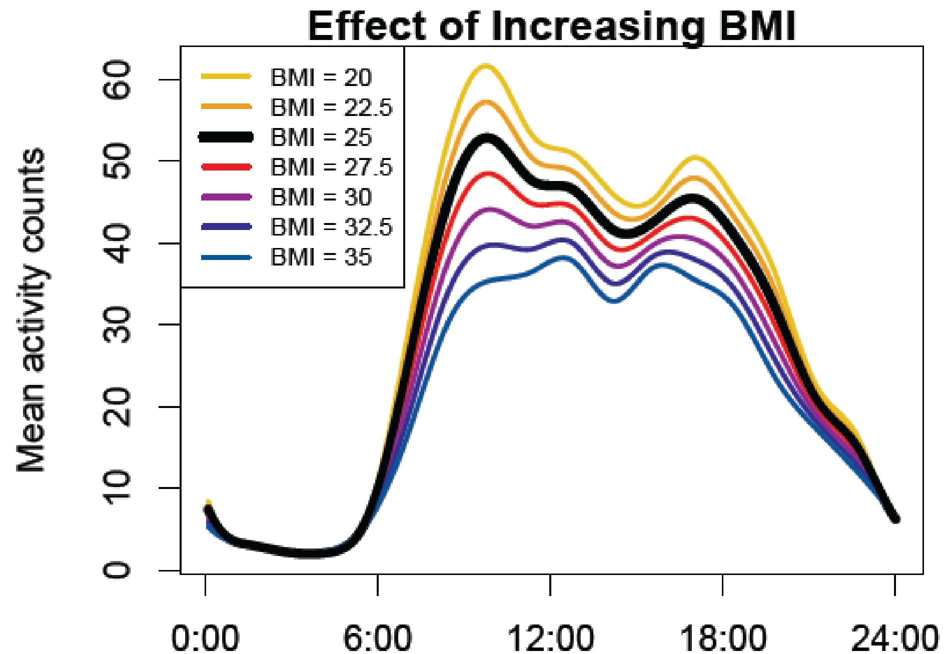
- $Y_{ij}(t)$ = "activity counts" for subject i, on day j, at minute t
- Interested in the time varying effect of age and BMI on activity

$$Y_{ij}(t) = \text{age}_i\, \beta(t) + \text{BMI}_i\, \gamma(t) + W_{ij}(t)$$

- Use penalized splines to fit $\beta(t)$, $\gamma(t)$
- Account for functional correlation within subjects
- For inference
  - bootstrap of subjects
  - structured functional decompositions (e.g. MFPCA, SFPCA)

Structured-function-on-scalar regression





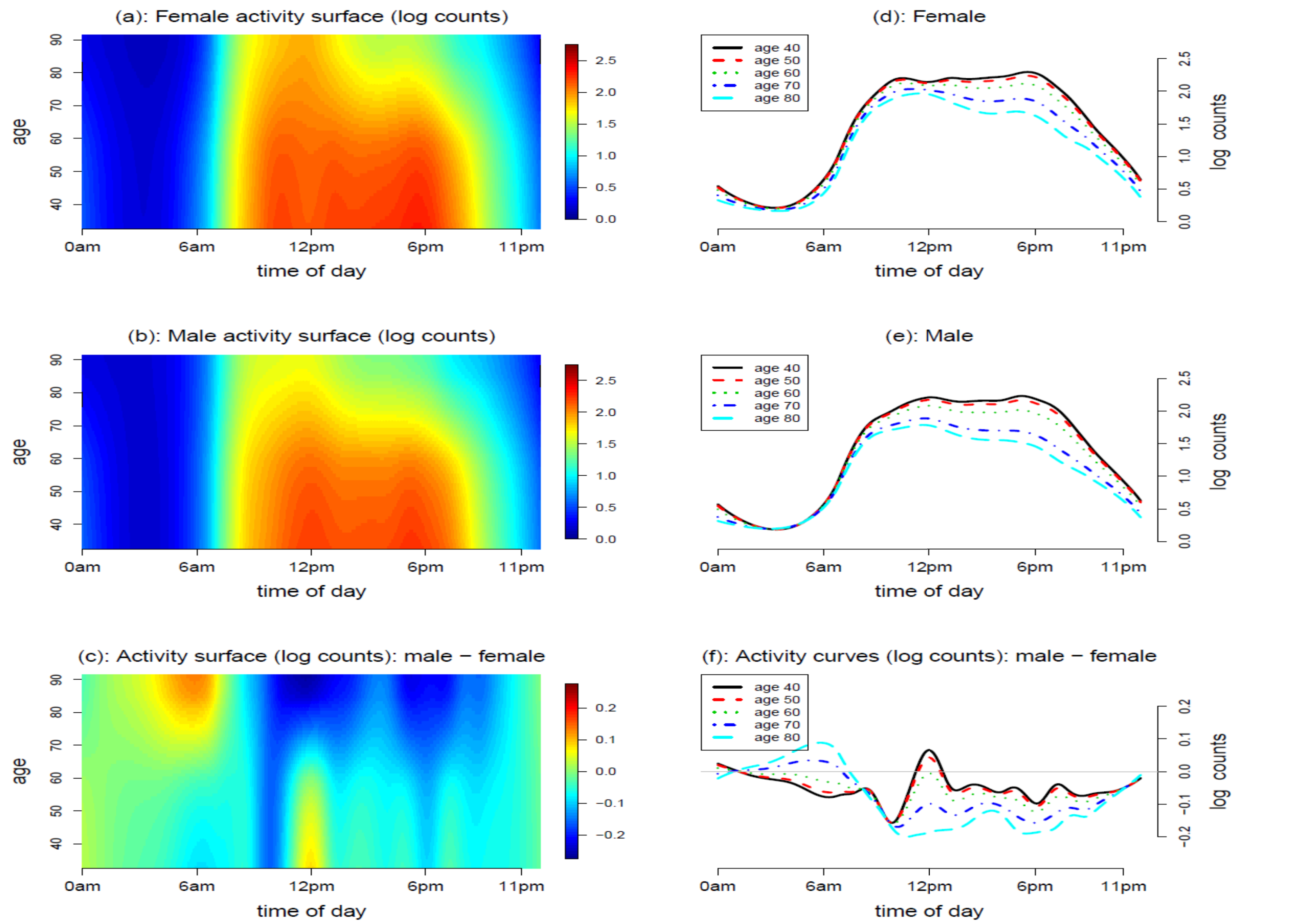
Generalized Multilevel Function-on-Scalar Regression and Principal Component Analysis (2014), Goldsmith, Zipunnikov, Schrack, Biometrics

High dimensional bi/tri-variate smoothing (BLSA)

$$Y_{ij}(t)=m(t,x_i)+U_i(t,x_i)+V_{ij}(t,x_i)+\varepsilon_{ij}(t)$$

- Requires:
  - fast new smoothers (Luo Xiao's penalty)
  - leave-one-subject-out CV (one-time data pass)

BLSA



(a): Female activity surface (log counts)
(b): Male activity surface (log counts)
(c): Activity surface (log counts): male − female
(d): Female
(e): Male
(f): Activity curves (log counts): male − female
age 40
age 50
age 60
age 70
age 80
age
log counts
time of day
0am
6am
12pm
6pm
11pm

Some thoughts on wearable devices for COVID-19

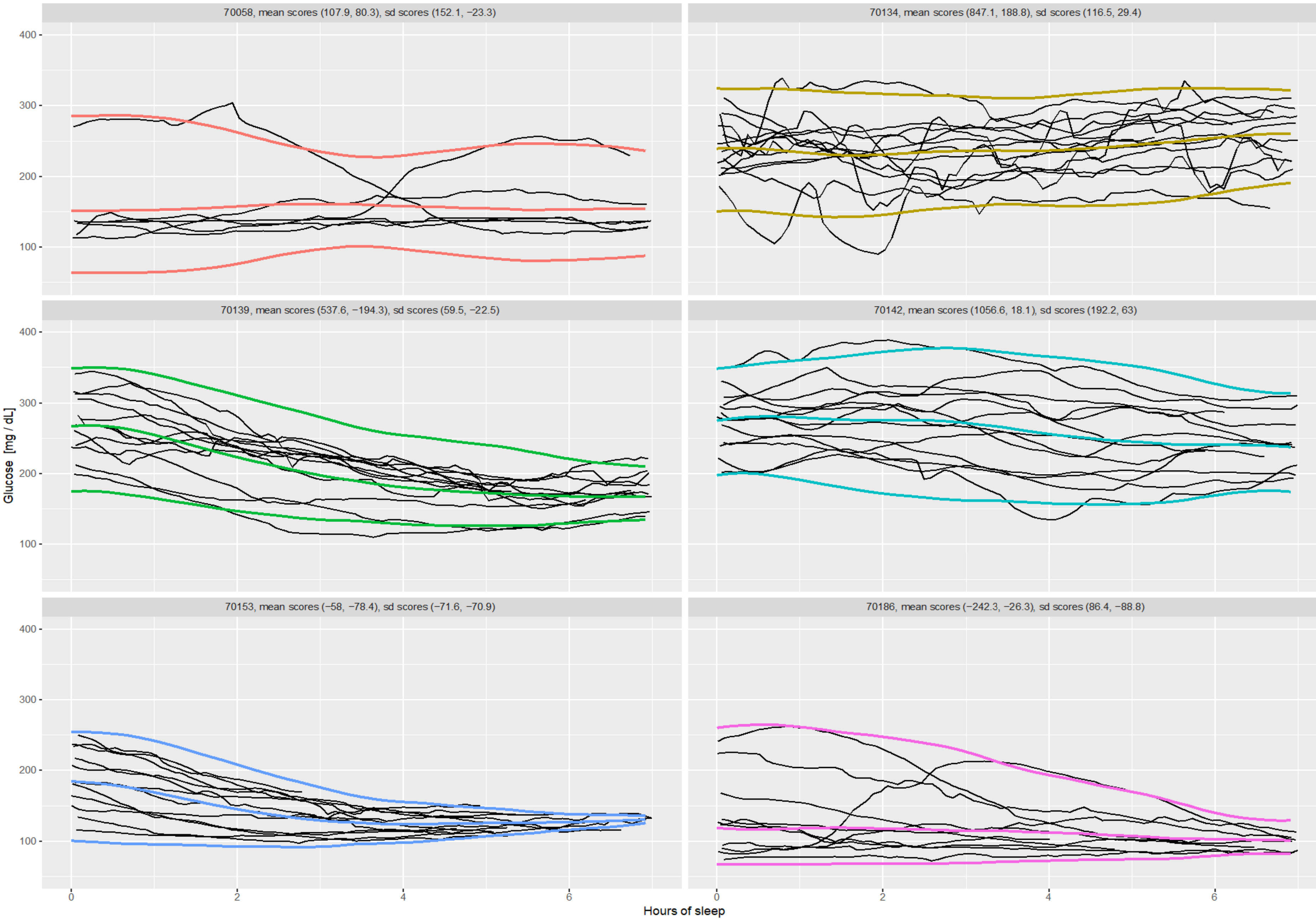
- Part of the solution
- Contact tracing in combination with testing
- Sensor-to-sensor communication (signal test-negative, record person, time, and duration of contact)
- Understand and improve in-hospital patient and hospital staff interactions to reduce transmission rates
- Use EMA (apps) to quantify contextual information on physical and mental effects of isolation, number, type, length of contact
- Pair with activity, temperature sensors for earlier detection of potential cases

Glucose profiles in Type II Diabetes during actigraphy-estimated sleep

Johns Hopkins study (PI Naresh Punjabi)

- 124 study participants with Type II DM
  - Not using insulin therapy
  - $HbA_{1c} \geq 6.5\%$
  - Oxygen desaturation index (ODI) ≥ 15 events/hour
- Two monitors (CGM, Actiwatch) worn continuously for 7 days
- CGM every 5 minutes using Dexcom G4
- Actigraphy using Philips Actiwatch
  - estimator of sleep period
  - estimator of activity intensity
  - 1307 estimated sleep periods, from 4 to 15 per person

Data and model fits for six study participants



A functional Beta model for CGM

$$Z_{ij}(t) \leftarrow \frac{Y_{ij}(t) - m_i}{M_i - m_i}$$

Rescaling CGM data to [0,1]

$$Z_{ij}(t) \sim Beta\left\{\mu_i(t), \sigma_i(t)\right\}$$

Multilevel functional model

$$\mu_i(t) = \sum_{k=1}^{K_\mu} \xi_{ik} \varphi_k(t) + \varepsilon_{it}$$

$$\sigma_i(t) = \sum_{k=1}^{K_\mu} \zeta_{ik} \psi_k(t) + e_{it}$$

FPCA decomposition of the subject-specific mean and standard deviation processes

PC scores versus HbA_{1c}

- R^2 for regression with HbA_{1c} as outcome
  - mean PC1, PC2 and SD PC1 = 0.70
  - mean PC1 and SD PC1 = 0.64

- Correlation
  - mean PC1 and HbA_{1c} = 0.79
  - SD PC1 and HbA_{1c} = 0.60
  - other scores and $HbA_{1c} \leq 0.21$

Importance of results

- Scores strongly correlate with HbA_{1c}
- Scores visually quantify part of the observed variability
- Simple decomposition of the mean and SD processes
- CGM is not currently used for diabetes diagnosis
- CGM is used for disease monitoring and management
  - During sleep the person cannot typically monitor their CGM
  - Need for automatic and accurate approaches

Literature

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