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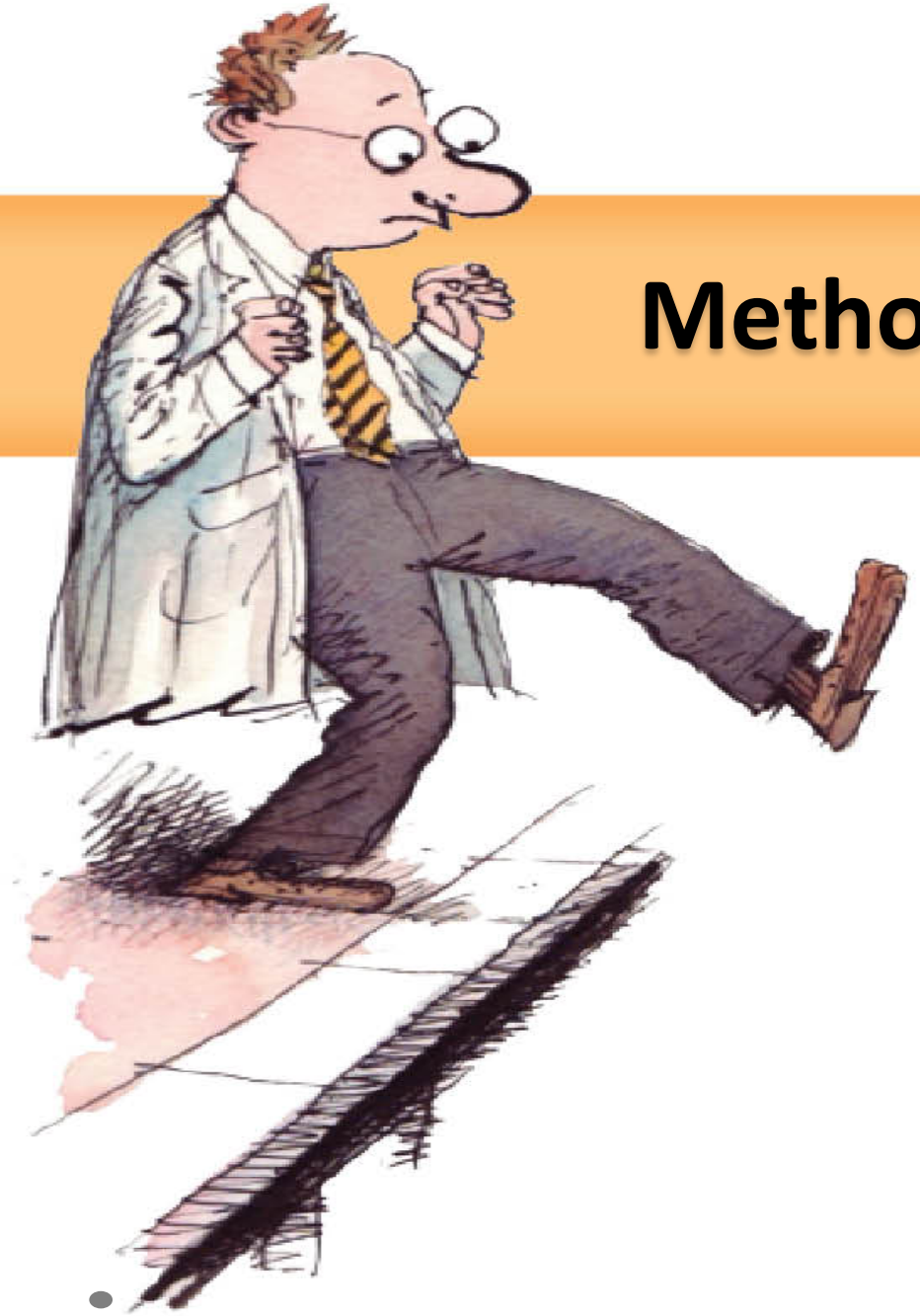


Methods: Mind the Gap Webinar Series

Joint Models of Longitudinal and Time-to-Event Data for Informing Multi-Stage Decision Making in mHealth

Presented by

Walter Dempsey, Ph.D.

University of Michigan

Outline

- Mobile health: an introduction
- Joint models: an introduction
- Assessing association (Decision making, stage 1)
- Defining risk strata (Decision making, stage 2)
- Assessing time-varying treatment effects (Decision making, stage 3)
- Conclusions: towards incorporating joint models in mHealth decision making

Mobile Health

"The delivery of healthcare services via mobile communication devices" – Foundation for the National Institutes of Health (FNIH)

Active data

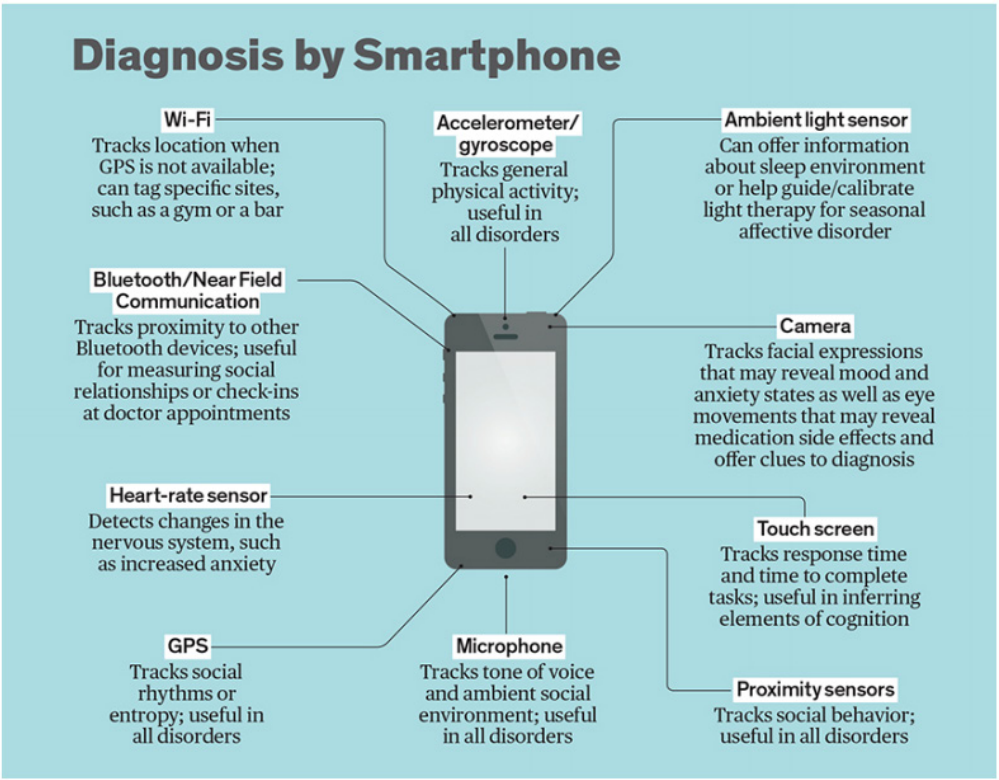
- Active data involves explicitly asking participants for information, preferences, and/or opinions

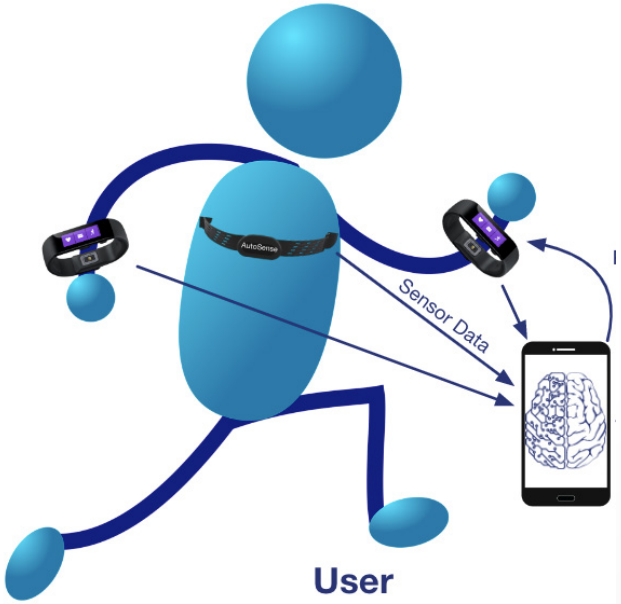
- **Ecological Momentary Assessments (EMAs)**
  - Administrative: fixed self-report times
    - E.g., Daily dairy
  - Random:
    - 1 EMA uniformly sent in 4-hour time blocks
    - Can depend on observed history
  - Event-contingent: Participant initiated
    - Engages in NSSI
    - Engages in smoking

- How many questions and how often you ask depends on
  - Attendant burden and intrusiveness
  - Behavioral constructs of interest
    - E.g., subset of a baseline battery assessment asked multiple times per day

Passive data

- Passive data, participant has little awareness of the data collection effort
- How many sensors and data depends on
  - Attendant burden and intrusiveness
  - Behavioral constructs of interest





Why are we collecting data?

- Example: Sense2Stop
- To…
  - Monitor stress continuously
  - Decide whether/how to intervene based on level of stress
  - Deliver the intervention as soon as stress occurs
    - In the person's natural environment
- And…
  - Monitor Context
  - Ensure that the context enables the person to receive and employ the intervention

Why are we collecting so **much** data?

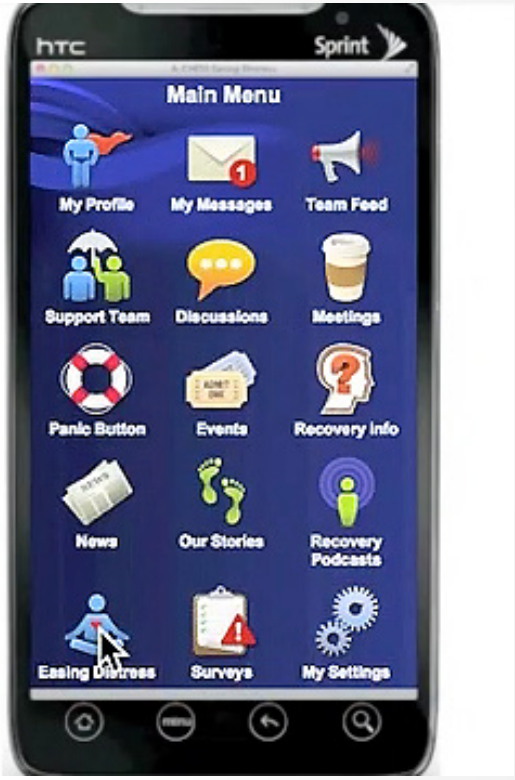
- Goal is delivery of the right type of support at the right time (JITAIs) while minimizing disruptions
  - Data-driven decision making
    - Both using collected data and in experimental design for intervention development
  - Recall mHealth most useful when we minimize attendant burden and maximize therapeutic effects of JITAIs

- Research Questions:
  - How strong is association between behavioral biomarker and event outcome of interest?
    - How strong is the association between stress and the risk of lapse?
  - Can we use passive and active data to discriminate between patients of low and high risk?
  - Are the digital phenotyping biomarkers good?
    - E.g., is stress a good biomarker?
    - If treatment improves stress, does it also lower risk of lapse?

Example: A-CHESS

- Smartphone application to support recovery from alcoholism (A-CHESS)
  - Mobile phone administered
- A-CHESS had both static content (e.g., audio-guided relaxation) and interactive features
- If an individual is near a high-risk location (e.g., a bar she used to frequent), GPS initiated alert will ask if patient wants to be there.
- ***Event can be passively-detected via GPS.***

(Gustafson et al., 2011 & 2014)



Joint models for longitudinal and survival data

Methods overview for mHealth

Research questions: Multiple outcomes

- **Association:** How strong is the association between behavioral biomarker and instantaneous risk rate of event?
  - Does the association vary over time?
  - How are behavioral biomarkers related to each other?

- **Prediction**: Can we improve predictions of event risk by considering behavioral biomarkers?

- **Treatment effect**: Does treatment improve the behavioral biomarker?
  - What is the direct and indirect effect of treatment on hazard rate of event?

Linear Mixed Model

- Repeated measurements on the same individual are expected to be (positively) correlated

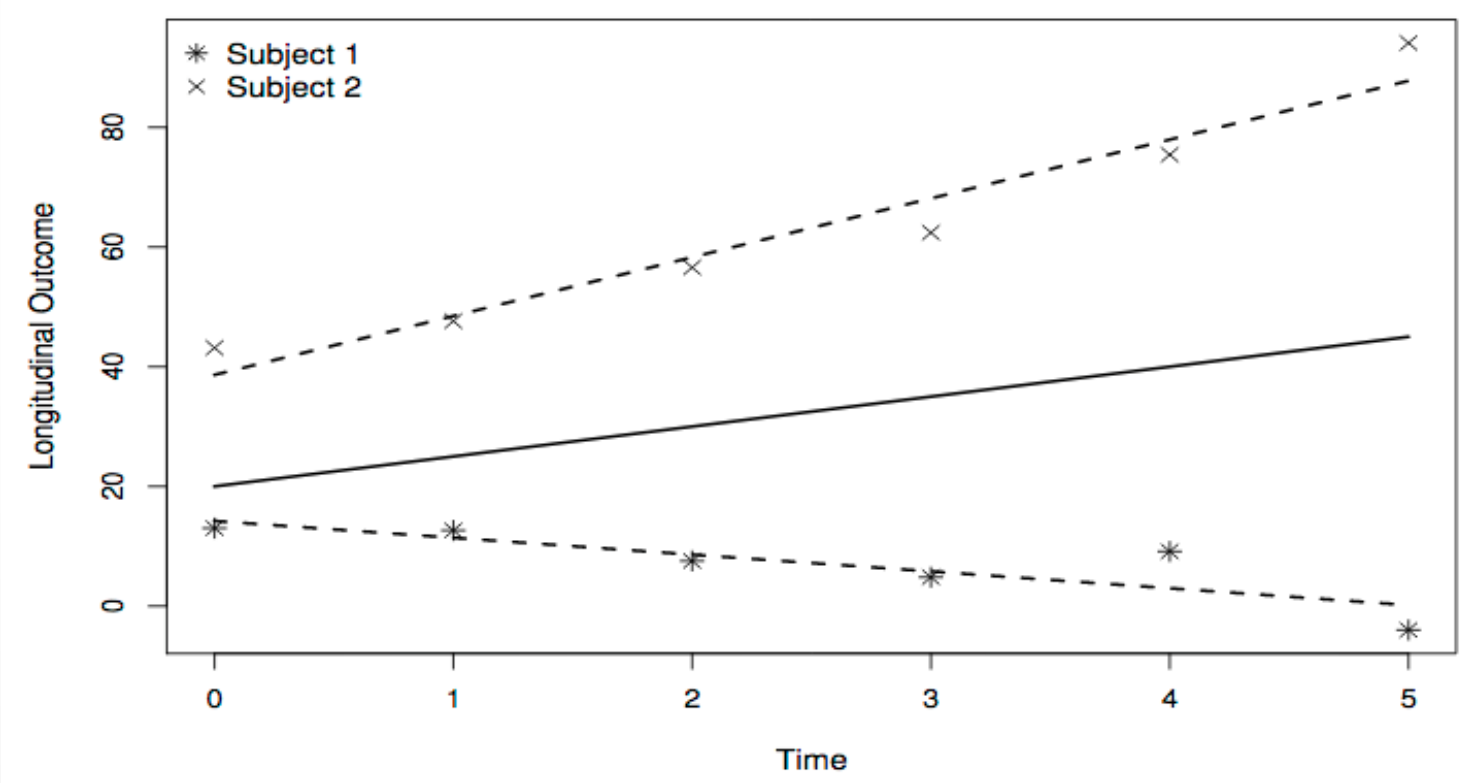
$$y_i = X\beta + Z_i b_i + \epsilon_i,$$

$$b_i \sim N(0, D) \text{ and } \epsilon_i \sim N(0, \sigma^2 I_{n_i})$$

- Where
  - y_i is the outcome
  - X is the design matrix for fixed effects
  - Z is the design matrix for random effects
  - $b_i \perp \epsilon_i$

Linear Mixed Model

- Assume there exists subject-specific coefficients: $\beta_i \sim N(\beta, D)$



Rizopolous (2016), Tutorial: Joint model for Longitudinal and Survival Data

Time-to-event data

- Notation:
  - $T_i^\star$: "true" time-to-event
  - C_i: censoring time
- Observable data
  - $T_i = \min(T_i^\star, C_i)$: observed event time
  - $\Delta_i = 1[T_i = T_i^\star]$: censoring indicator
- Goal:

Valid inference for $T_i^\star$ using observed data

Time-to-event analysis

- Distribution functions

$$F(t) = P(T^\star < t); f(t) = \frac{d}{dt}F(t)$$

- Survival function

$$S(t) = P(T^\star \geq t)$$

- Hazard function

$$h(t) = \lim_{\delta \to 0} \frac{P(t \leq T^\star < t + \delta \mid T \geq t)}{\delta}$$

$$\Rightarrow S(t) = \exp\left(-\int_0^t h(u)du\right)$$

Time-to-event analysis

- **Relative risk model**

$$h_i(t) = h_0(t)\exp\left(\gamma_1 w_{i1} + \cdots + \gamma_p w_{ip}\right)$$

$$\log h_i(t) = \log h_0(t) + \gamma_1 w_{i1} + \cdots + \gamma_p w_{ip}$$

- Where
  - $h_i(t)$ denotes the hazard for patient i at time t
  - $h_0(t)$ denotes the baseline hazard
  - $w_{i1}, \ldots, w_{ip}$ a set of covariates

Cox model: baseline covariates

- **Cox model:** no assumptions for baseline hazard

$$pl(\gamma) = \sum_{i=1}^{n} \delta_i \left[\gamma^\top w - \log \left\{ \sum_{j:T_j \geq T_i} \exp(\gamma^\top w_j) \right\} \right]$$

- Example: PBC dataset

$$h_i(t) = h_0(t) \exp(\gamma_1 Treatment_i + \gamma_2 Female_i + \gamma_3 Age_i)$$

Variable	Value	HR	Std. Err.	Z-value	P-value
γ_1	-0.138	0.871	0.156	-0.882	0.378
γ_2	-0.493	0.611	0.207	-2.379	0.017
γ_3	0.021	1.022	0.008	2.784	0.005

- Rizopolous (2016), Tutorial: Joint model for Longitudinal and Survival Data

Time dependent covariates

- We often wish to answer questions related to time-dependent biomarker measures
- There are two types of time-dependent covariates (Kalbfleisch and Prentice, 2002):
  - Exogenous/External: Future trajectory of the variable is not affected by occurrence of an event:

$$P(Y_i(t)|\, Y_i(s), T_i^\star \geq s) = P(Y_i(t)|\, Y_i(s), T_i^\star = s)$$

  - Endogenous: not external
    - **Biomarkers are almost ALWAYS endogenous**

Extended Cox Model

- Extend the Cox model to handle time-dependent covariates

$$h_i(t \mid Y_i(t), w_i) = h_0(t) R_i(t) \exp(\gamma^\top w_i + \alpha y_i(t))$$

- Where
  - $R_i(t)$ is the at-risk indicator
  - $\exp(\alpha)$ is relative risk translating a one unit increase in $y_i(t)$ at the same time point
- Parameters can be estimated based on partial likelihood
  - Assumes no measurement error
  - Step-function path
  - Existence of covariate not related to failure status
- Extended Cox model valid ONLY for exogenous variables
  - Treating endogenous variables as exogenous may produce spurious results

Joint modeling framework

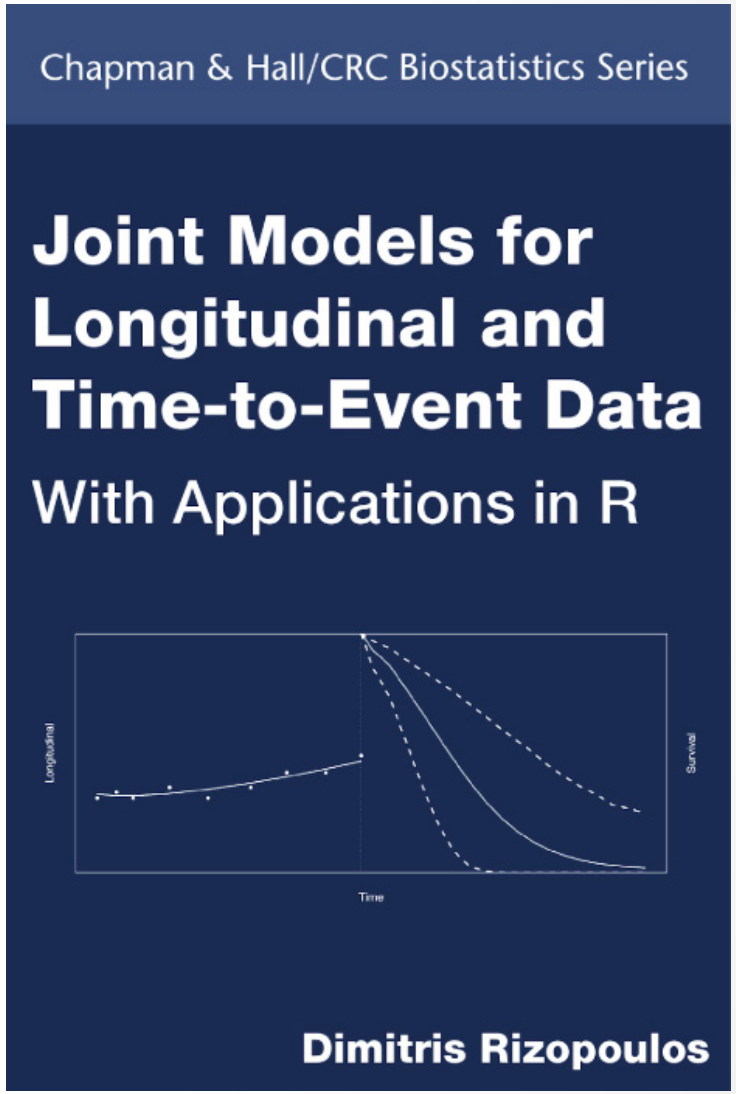
- Special feature of endogenous covariates leads to a new class of models

Joint models for longitudinal and time-to-event data

- Intuitive idea behind the standard joint model
  - Use an appropriate model to describe the evolution of the marker in time in each patient
  - The estimated evolutions are then used in a Cox model

Method 1: Shared Random Effect Model

- Assume a latent trajectory (typically referred to as "true biomarker trajectory")
- Build longitudinal model for biomarkers given true trajectory
- Build survival model depends on true trajectory
- Conditional independent processes given the true trajectory
- Requires knowledge of trajectory and association
- Typically flexible parametric modeling assumptions



Method 1: Shared Random Effect Model

- Assume a true and unobserved biomarker trajectory:

$$M_i(t) = \{m_i(s), 0 \leq s < t\} \text{ longitudinal history}$$

- Define relative risk model

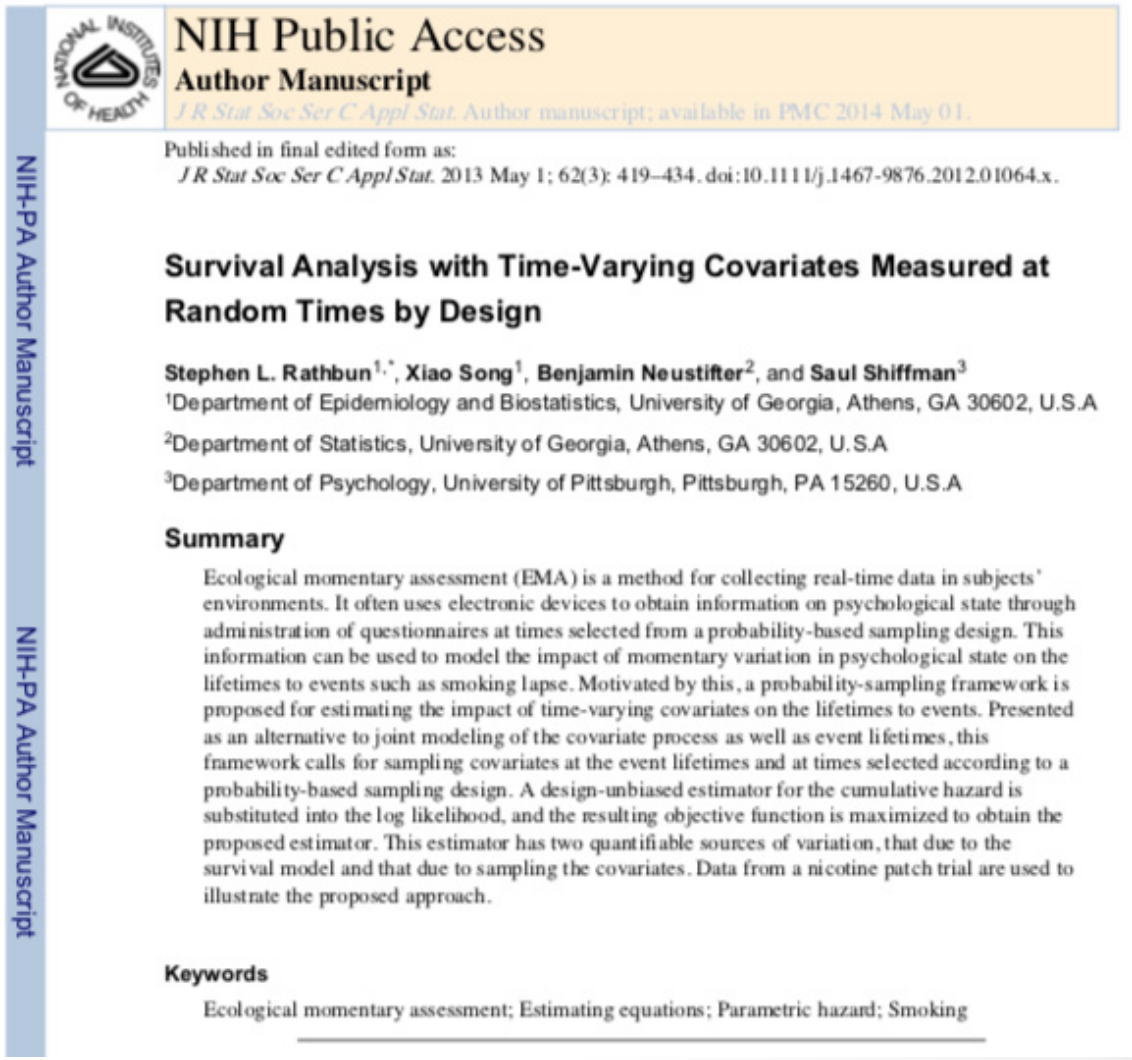
$$h_i\big(t \mid M_i(t)\big) = h_0(t)\exp(\gamma^\top w_i + \alpha m_i(t))$$

- Define mixed effects model

$$y_i(t) = m_i(t) + \epsilon_i(t) = x_i(t)^\top \beta + z_i(t)^\top b_i + \epsilon_i(t)$$

Method 2: Random Sampling Method

- Use random EMA design instead of modeling assumptions
- Construct a design-unbiased estimator of the cumulative hazard
- Requires knowledge of the EMA design
- Parametric modeling assumptions
- Quantifiable sources of variance



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Survival Analysis with Time-Varying Covariates Measured at Random Times by Design

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Summary

Ecological momentary assessment (EMA) is a method for collecting real-time data in subjects' environments. It often uses electronic devices to obtain information on psychological state through administration of questionnaires at times selected from a probability-based sampling design. This information can be used to model the impact of momentary variation in psychological state on the lifetimes to events such as smoking lapse. Motivated by this, a probability-sampling framework is proposed for estimating the impact of time-varying covariates on the lifetimes to events. Presented as an alternative to joint modeling of the covariate process as well as event lifetimes, this framework calls for sampling covariates at the event lifetimes and at times selected according to a probability-based sampling design. A design-unbiased estimator for the cumulative hazard is substituted into the log likelihood, and the resulting objective function is maximized to obtain the proposed estimator. This estimator has two quantifiable sources of variation, that due to the survival model and that due to sampling the covariates. Data from a nicotine patch trial are used to illustrate the proposed approach.

Keywords

Ecological momentary assessment; Estimating equations; Parametric hazard; Smoking

Simulation comparison

- Assume incorrectly specified biomarker model (linear when truth is quadratic)

		Randomization-based			Joint Modeling		
n	**π**	**Bias**	**SD**	**CR**	**Bias**	**SD**	**CR**
300	16	0.009	0.062	95.5	0.092	0.065	71.4
	8	0.011	0.068	95.3	0.099	0.067	68.9
	4	0.011	0.072	94.4	0.102	0.068	71.0
100	16	0.024	0.110	93.7	0.104	0.117	89.0
	8	0.033	0.119	94.3	0.112	0.119	88.2
	4	0.033	0.134	91.1	0.109	0.122	89.7

Assessing association

Decision making, stage 1

Research Question: Assessing association

- Claim: Biomarker is strongly associated with a particular negative behavioral event outcome
  - Craving ↦ Drug Lapse
  - Stress ↦ Smoking Lapse
  - Suicidal ideation ↦ Distress, Attempts
- In support of: interventions aimed at biomarker
  - Coping with Craving and Urges module ↦ reduce craving ↦ reduce risk of substance use
  - Reminder to practice mindfulness ↦ reduce stress ↦ reduce risk of lapse
  - Automated call to increase social support ↦ reduce loneliness ↦ reduce risk of STBs

Case Study: Smoking Cessation Study

Covariates	Estimate	S.E.	Z	P-value
Treatment (0,1)	0.2129	0.1706	1.25	0.2120
Craving (1-11)	0.4234	0.0273	15.51	<0.0001
Negative Affect (-2.31, 5.85)	0.4941	0.0714	6.92	<0.0001
Restlessness (1-11)	0.0631	0.0285	2.21	0.0268
Attention Disturbance (1-11)	-0.0573	0.0410	1.40	0.1602
Positive Affect (-3.43, 2.84)	0.0856	0.0872	0.98	0.3266

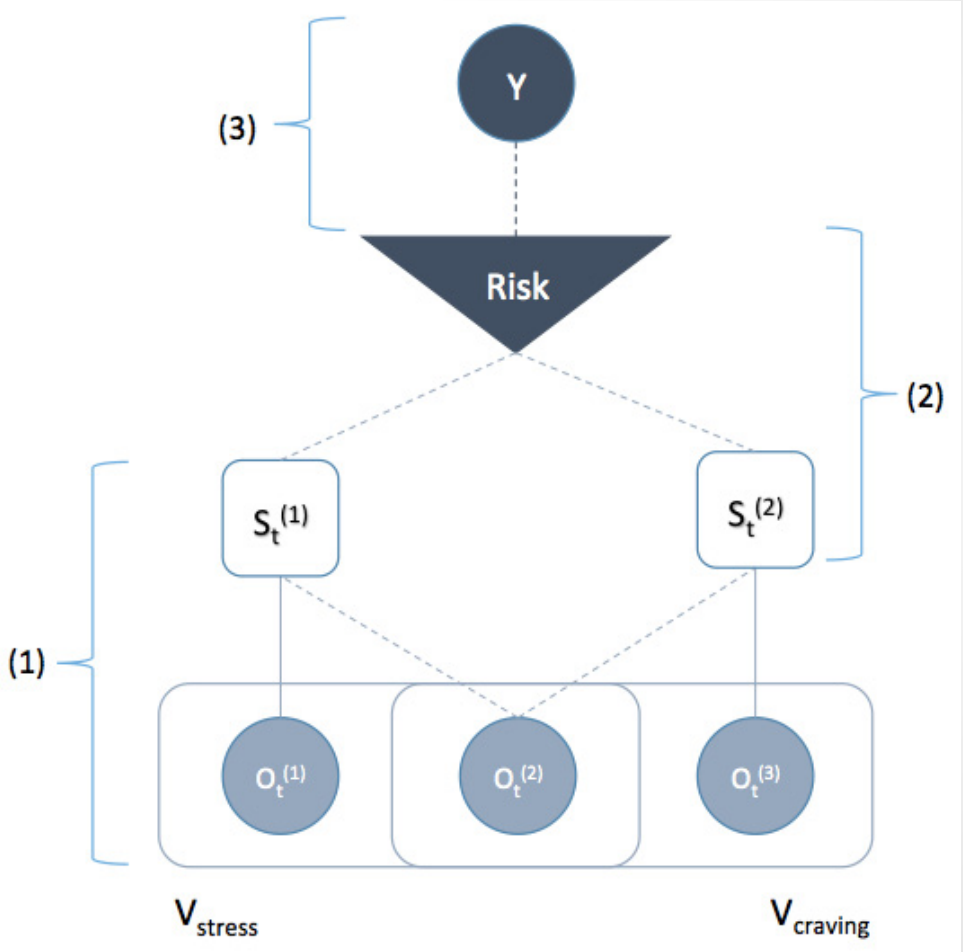
- Rathbun et al. (2014), J. Royal Stat Soc., Series C

Building predictions/classifications

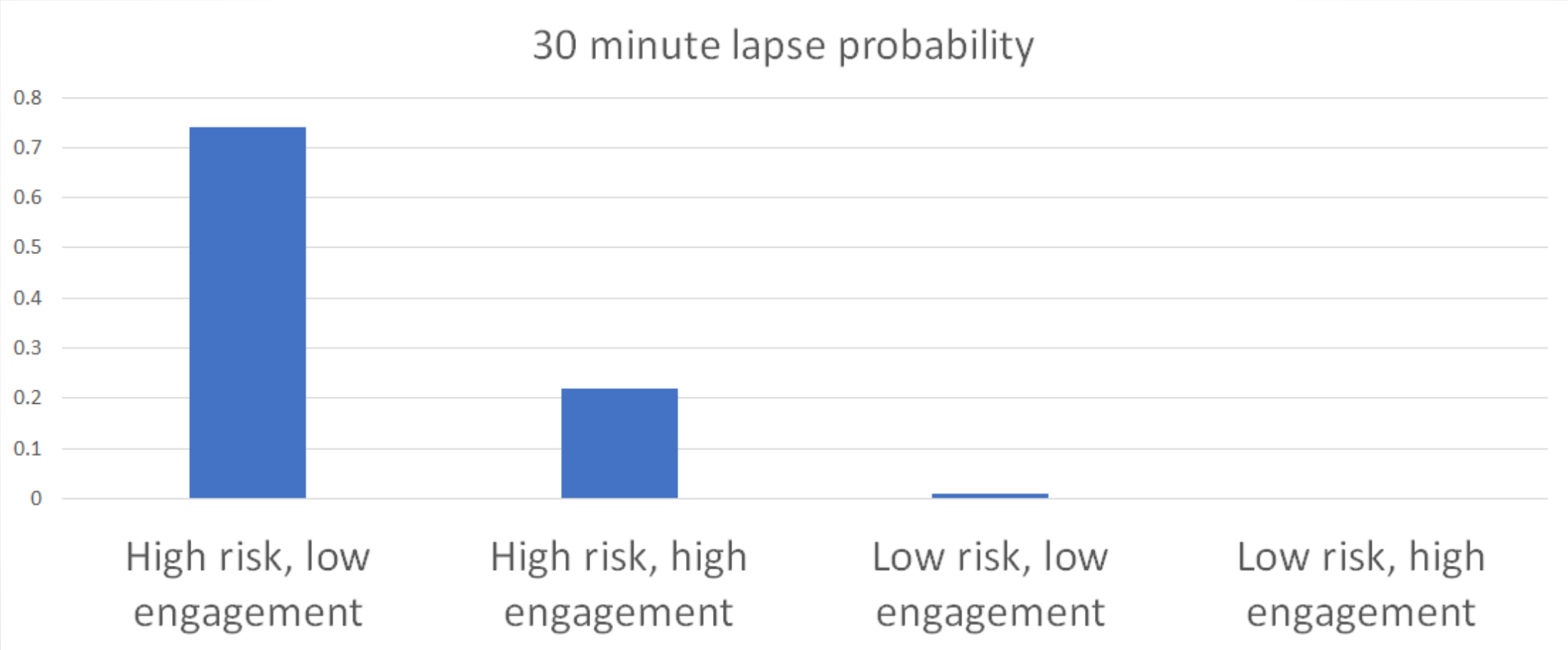
Decision making, stage 2

Method 3: Leveraging behavioral latent constructs

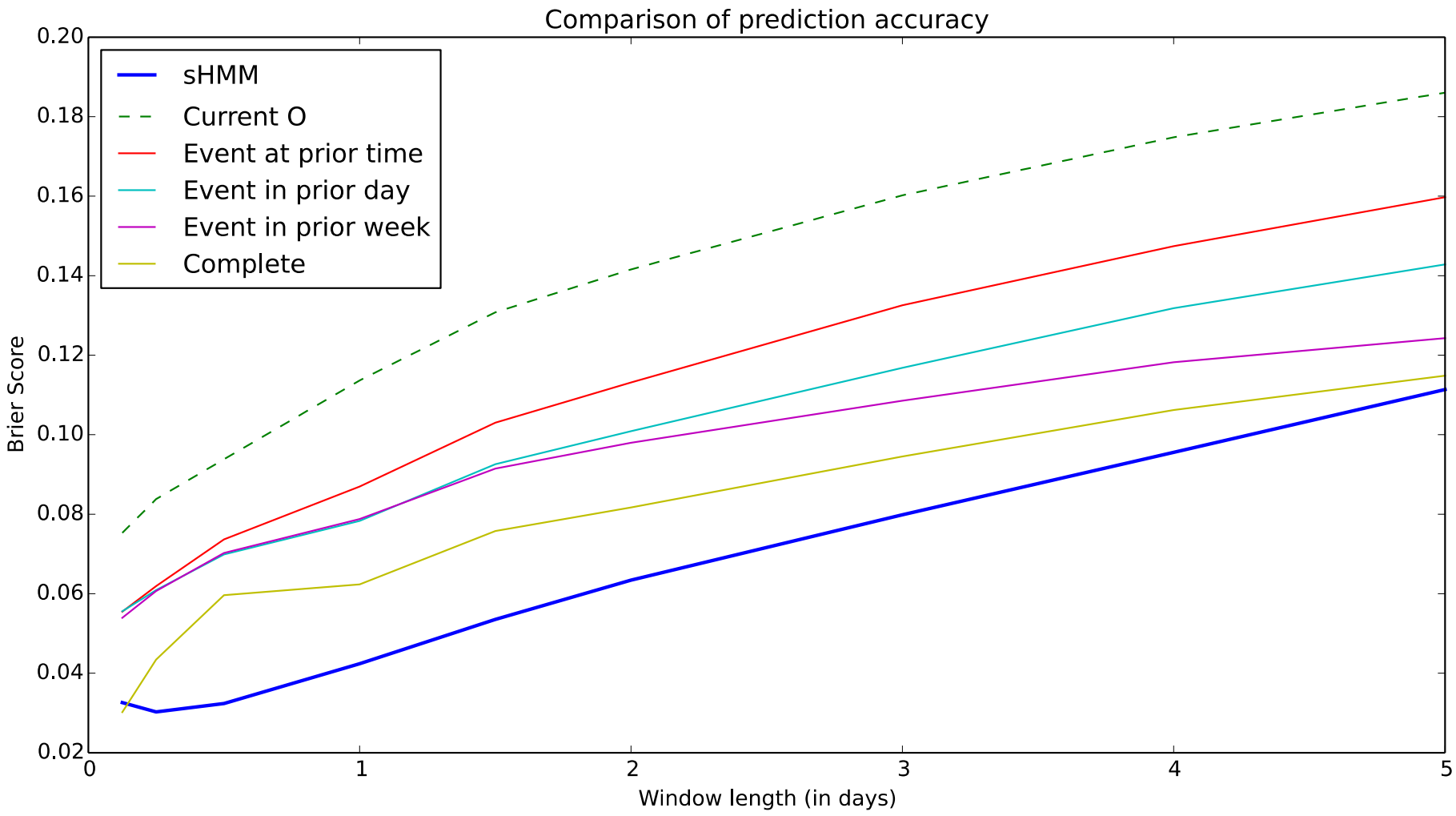
1. **Latent behavioral constructs**
   - Measurement-error models to connect observables to the latent states
   - GLM: $\mathrm{E}\left[O_t^{(j)}\right] = g(S_t'\beta) = g\left(S_t^{(1)}\beta_1 + S_t^{(2)}\beta_2\right)$
   - Use anchor measurements to make latent constructs identifiable
2. **Latent risk model**
   - $\mathrm{R_t} = S_t^{(1)}\tilde{\beta}_1 + S_t^{(2)}\tilde{\beta}_2$
3. **Latent risk connects to observed event outcome of interest**
   - Probability of reporting drug use = $expit\ (R_t)$



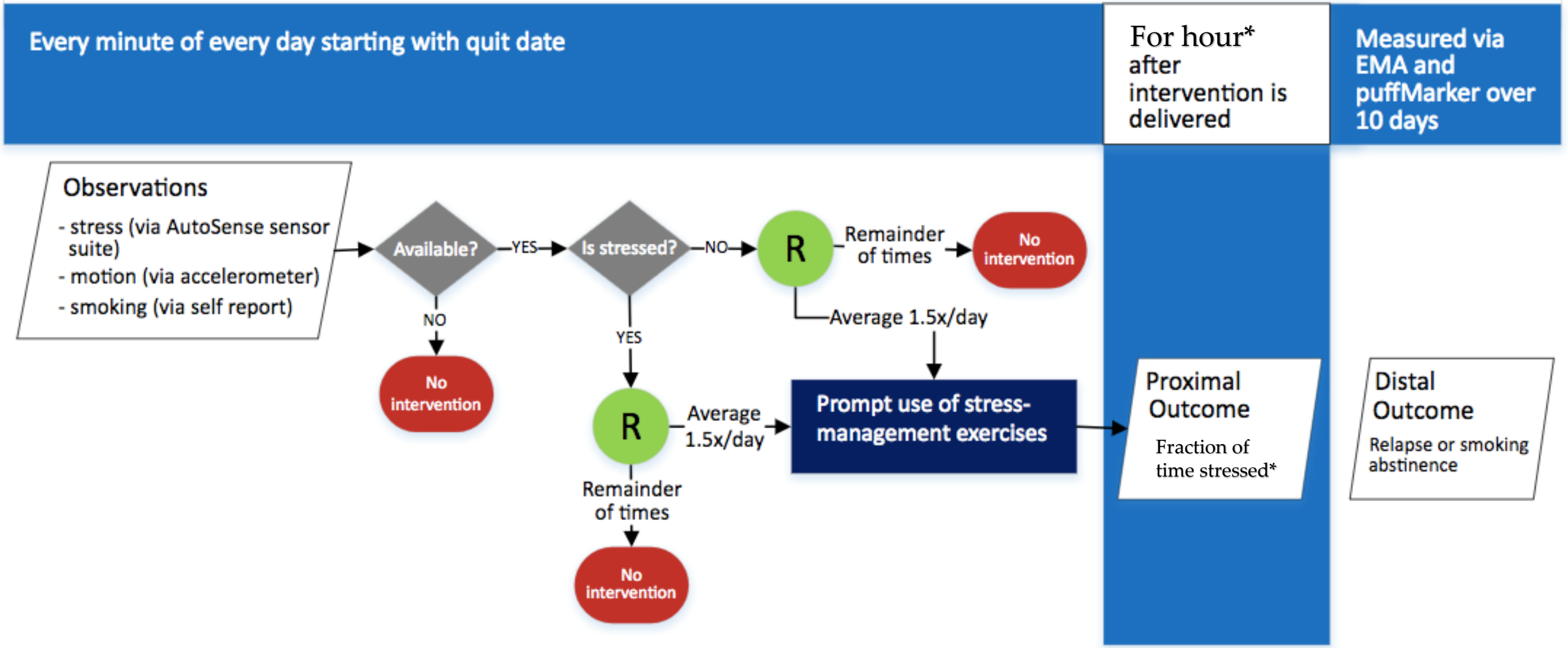
Case Study 2: Recovery Support Services



Comparison of prediction accurary



Sense²Stop MRT for Stress Management in Newly Abstinent Smokers



*Adjusted for current talk

Assessing treatment effects

Decision making, stage 3

Case Study 1: Smoking Cessation Study

Covariates	Estimate	S.E.	Z	P-value
Treatment (0,1)	0.2129	0.1706	1.25	0.2120
Craving (1-11)	0.4234	0.0273	15.51	<0.0001
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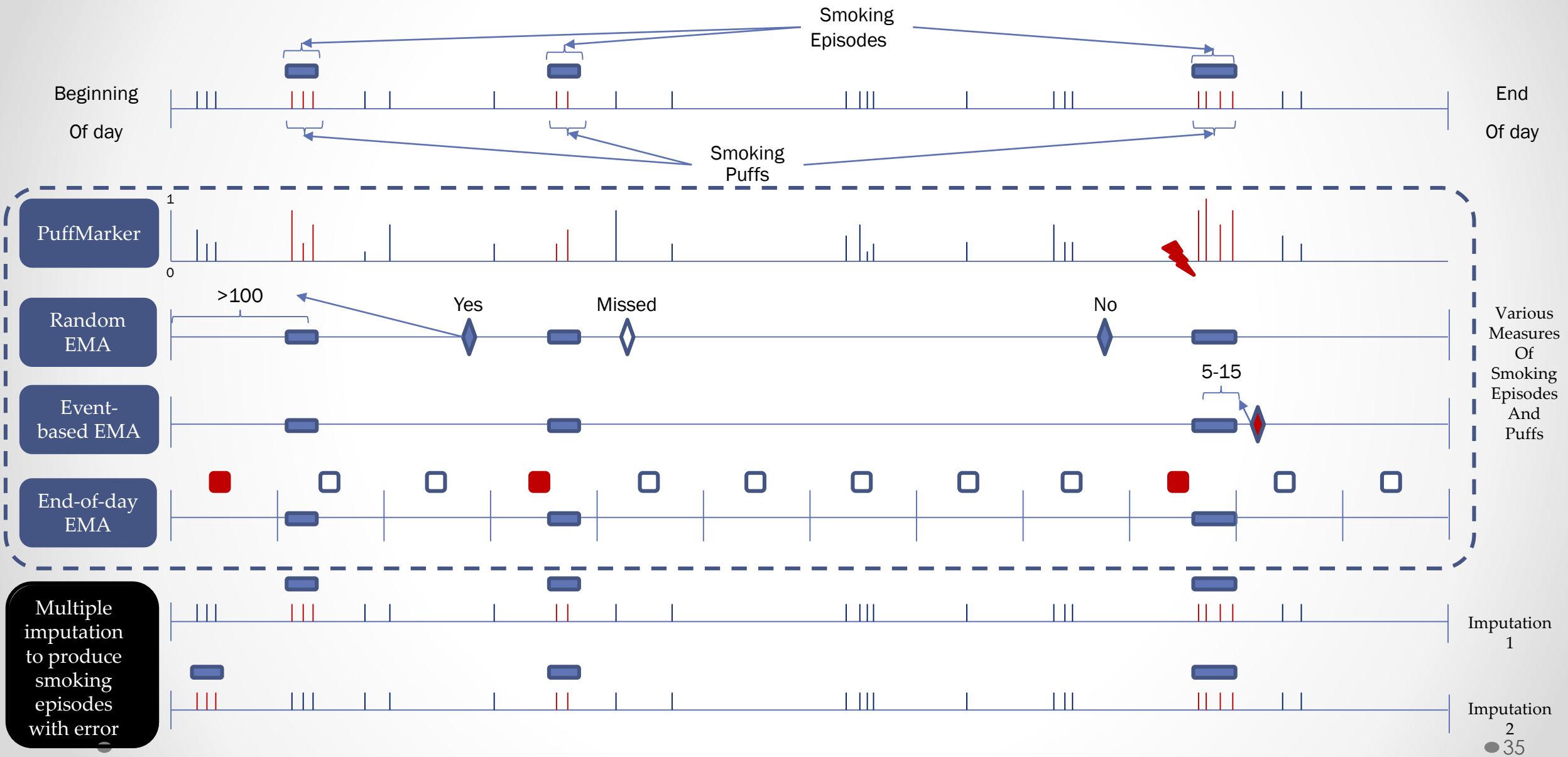
Positive Affect (-3.43, 2.84)	0.0856	0.0872	0.98	0.3266

- Rathbun et al. (2014), J. Royal Stat Soc., Series C

Current issues in JMs in mHealth

Translating JMs into mHealth research

Topic 1: Multiple noisy measurements

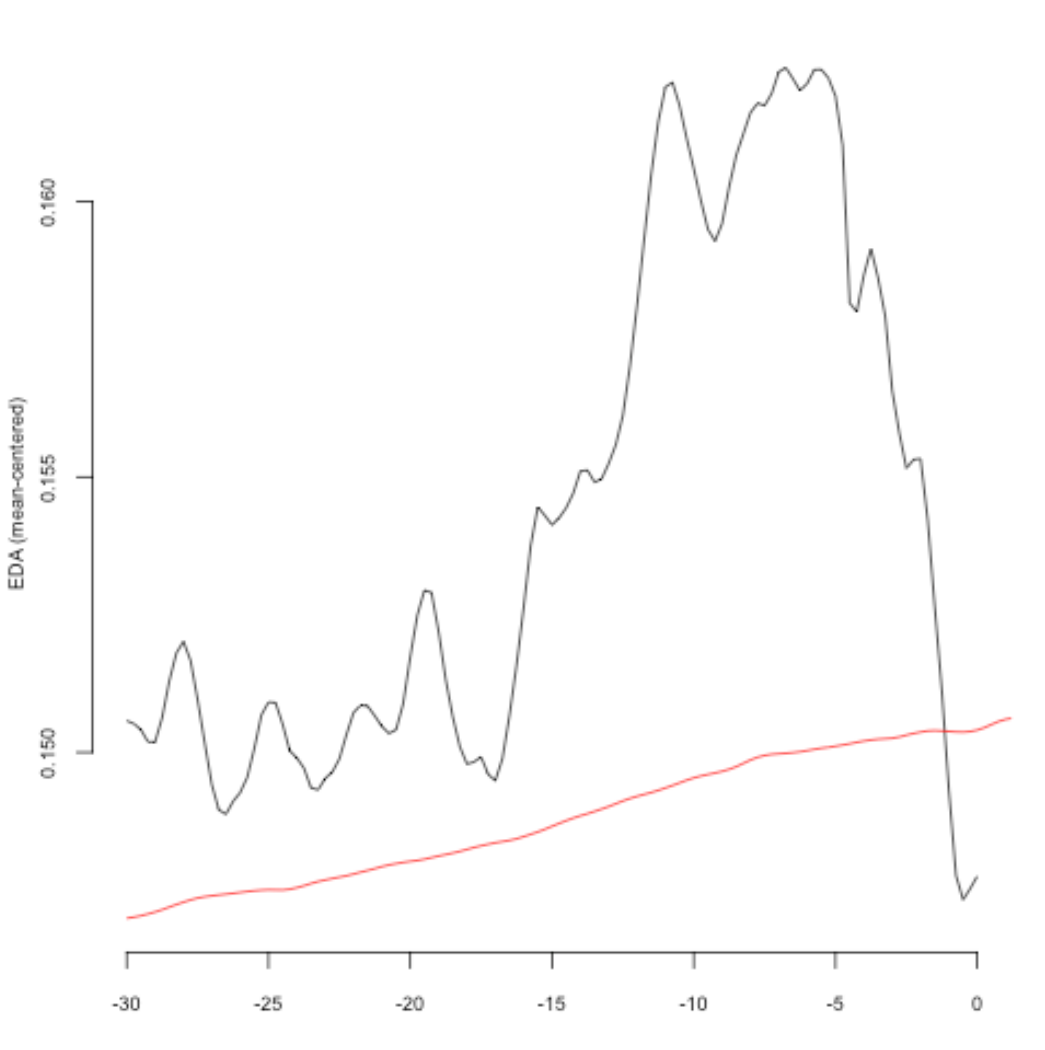


Topic 2: Sensors + Event outcomes

- Participant wears Empatic E4 bracelets
- Measure various physiological responses (including EDA)
- Self-report via button press moments of distress
- Research question: how can we map these high-frequency sensor curves onto instantaneous risk?

$$h_i(t \mid M_i(\ ))$$

$$= h_0(t)\exp\left(\gamma^\top w_i + \int_{t-\Delta}^{t} m_i(u)\alpha(u)du\right)$$



Conclusion

- Focused on mHealth (mobile health) studies in which both longitudinal and time-to-event data are recorded per participant
- Discussed how joint models enter into various stages of the intervention development process
  - Assessing levels of biomarker association with event risk,
  - Defining risk strata for a stratified micro-randomized trial,
  - Post-study analysis of the treatment effect on event risk
- Discussed how mHealth studies present novel methodological challenges for joint modeling and solutions in several case studies
- Data collection and analysis geared toward informing multi-stage decision making in mHealth

The End

Email me with questions:

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Data science for dynamic decision making (d3-) lab
University of Michigan

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Danny Almirall
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Method 2: Random Sampling Method

- Assuming EMAs are sent at random times; that is,

$$\pi_\theta(t) = \lim_{\delta \to 0} \delta^{-1} \mathrm{P}(N_i^c[0, t+\delta) - N_i^c[0, t) \mid H_t)$$

  is a known intensity function for sending EMAs.

- Random EMAs then $\pi_\theta(t) \propto 1$

- Self-correcting point process (Isham and Wescott, 1970):

$$\pi_\theta(t) = \exp(\alpha + \beta(t - \rho N_i^c[0, t)))$$

  corrects when far from target $= t/\rho$.

Method 2: Random Sampling Method

- Recall the likelihood

$$l_n(\theta) = \sum_{i=1}^{n} \Delta_i \log h_i(T_i;\theta) - H_i(T_i;\theta)$$

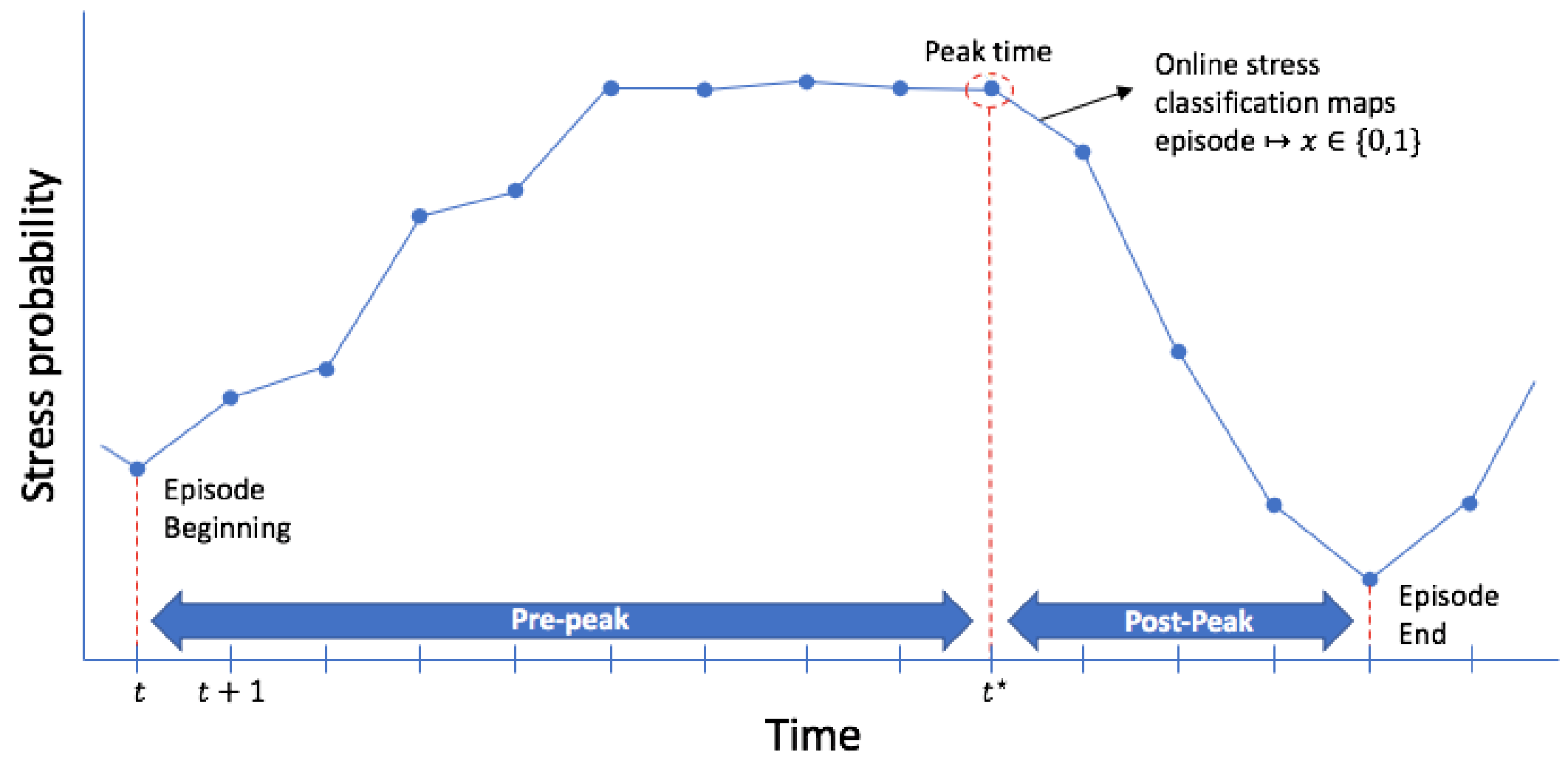
- Where

$$H_i(T_i;\theta) = \int_0^{T_i} h_i(u;\theta)du$$

- **Key idea**: approximate cumulative hazard using random-design:

$$\widehat{H}_i(T_i;\theta) = \sum_{j=1}^{N_i^c(T_i)} h_i(u_{ij};\theta)\pi_i(u_{ij})^{-1}$$

Case Study 3: Sense2Stop



Motivating studies

- Recovery Support Services (RSS) Studies of individuals with Substance Use Disorders (SUDs) (PI: Scott)
  - 2 pilot RSS studies on individuals who have been discharged from outpatient, intensive outpatient, or residential treatment
  - EMA + EMI usage data
- Smoking cessation study (PI: Shiffman)
  - N=412 volunteer smokers
  - Randomized at quit date N=188 to nicotine patch, N=136 to placebo
  - Random EMAs, no passive data
- Sense2Stop (PI: Spring)
  - Stratified micro-randomized trial
  - N=75 (expected)
  - Various EMA + sensor data;
  - Sequential randomization to reminder to practice mindfulness
- Suicidal Inpatient study (PI: Nock)
  - N=91
  - Wrist sensor (measures EDA and accelerometer)
  - User-initiated button press to denote times of distress (i.e., recurrent event outcome)

What can digital phenotyping tell us?

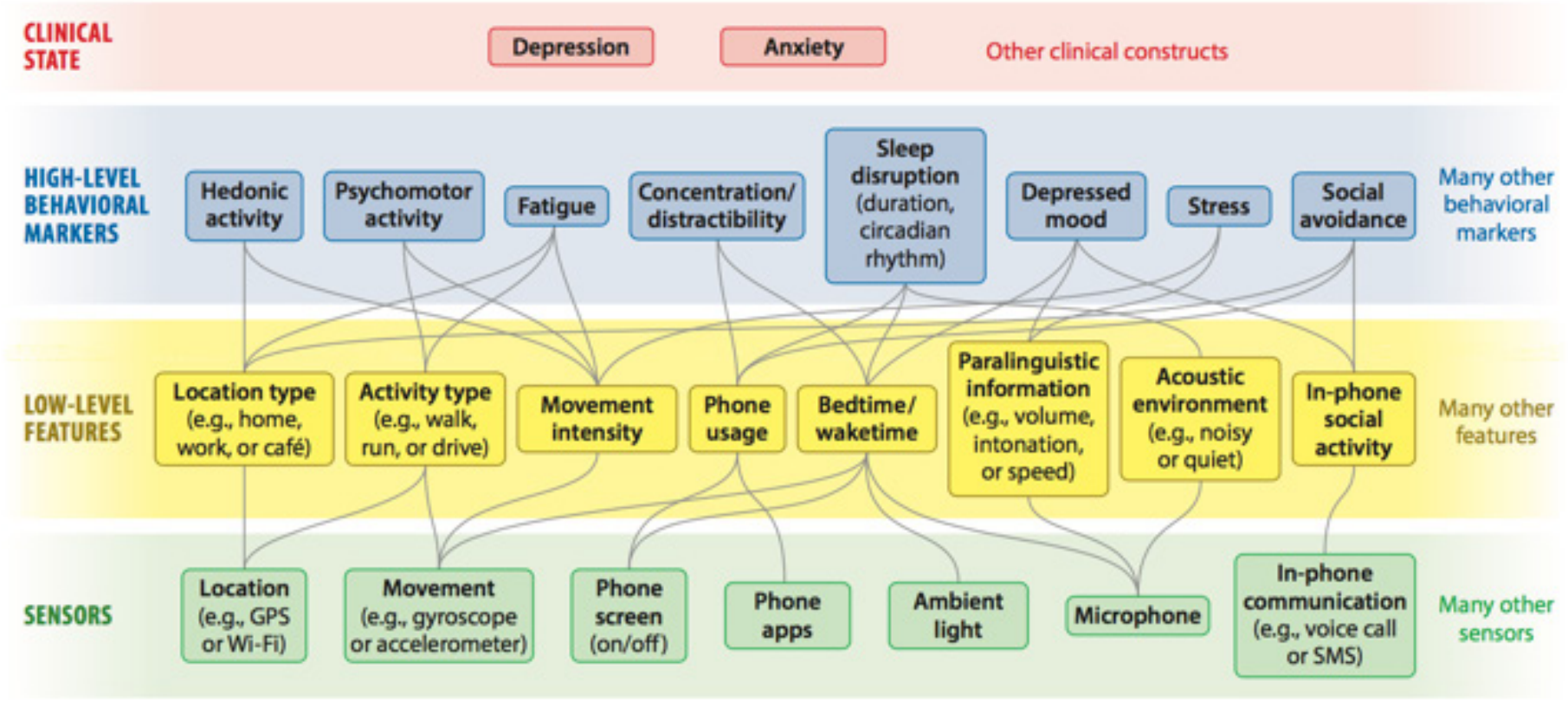


Figure 1

Example of a layered, hierarchical sensemaking framework. Green boxes at the bottom of the figure represent inputs to the sensing platform. Yellow boxes represent features. Blue boxes represent high-level behavioral markers. Abbreviations: GPS, global positioning system; SMS, short message service.

- Mohr et al. (2017), Annual Reviews of Clinical Psychology

Topic 3: Missing data assumptions

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DOI: 10.1002/sim.7989

RESEARCH ARTICLE

Latent trait shared-parameter mi ecological momentary assessmen

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ecological momentary assessme
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Health Serv Outcomes Res Method (2018) 18:227–243
https://doi.org/10.1007/s10742-018-0184-5

CrossMark

A shared parameter location scale mixed e for EMA data subject to informative missi

Xiaolei Lin[1] · Robin Mermelstein[2] · Donald Hedeker[1]

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Abstract In this paper, we address the problem of accounti the context of ecological momentary assessment studies (so sive longitudinal studies), where each study unit gets measu intermittent missing is usually present. We present a shared that links the primary longitudinal outcome with potentially common set of random effects that summarize a subjects' s mean (location) and variability (scale). The primary outcom effects, are allowed to exhibit heterogeneity in terms of both variance. Unlike previous methods which largely rely on nun mation, we estimate the model by a full Bayesian approach Carlo. An adolescent mood study example is illustrated togetl studies. Results in comparison to more conventional appro for the common but unobserved random subject mean and va the primary outcome and missingness models, can significan also provide the benefit of understanding how missingness c primary outcome.

Keywords Ecological momentary assessments · Informative missing · Mixed effects · Shared parameter model

Statistics in Medicine

Research Article

Received 5 July 2013, Accepted 16 February 2014 Published online 17 March 2014 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/sim.6137

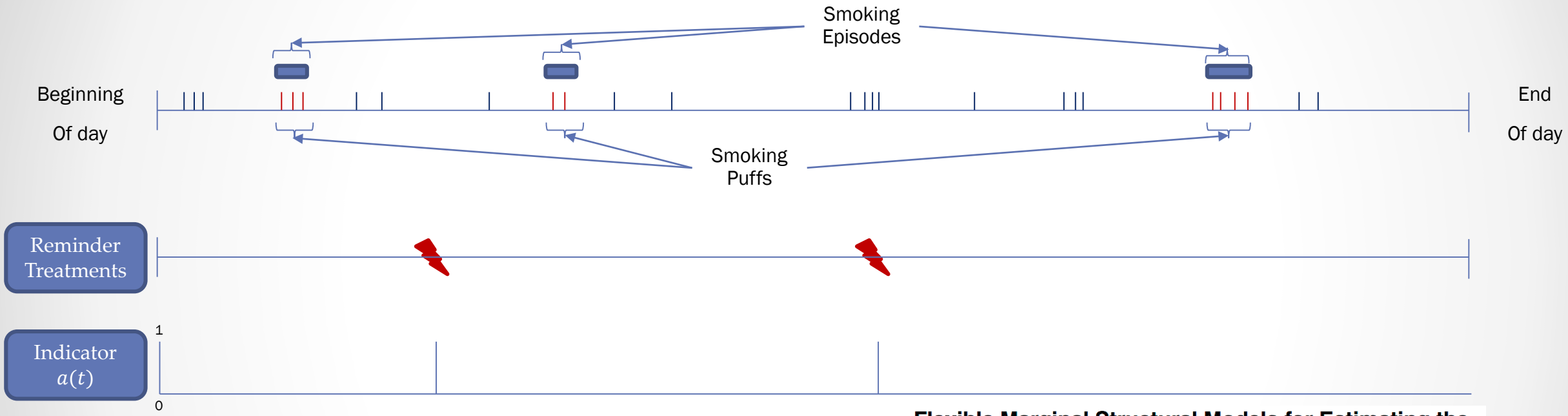
Binary variable multiple-model multiple imputation to address missing data mechanism uncertainty: application to a smoking cessation trial

Juned Siddique,[a*†] Ofer Harel,[b] Catherine M. Crespi[c] and Donald Hedeker[d]

The true missing data mechanism is never known in practice. We present a method for generating multiple imputations for binary variables, which formally incorporates missing data mechanism uncertainty. Imputations are generated from a distribution of imputation models rather than a single model, with the distribution reflecting subjective notions of missing data mechanism uncertainty. Parameter estimates and standard errors are obtained using rules for nested multiple imputation. Using simulation, we investigate the impact of missing data mechanism uncertainty on post-imputation inferences and show that incorporating this uncertainty can increase the coverage of parameter estimates. We apply our method to a longitudinal smoking cessation trial where nonignorably missing data were a concern. Our method provides a simple approach for formalizing subjective notions regarding nonresponse and can be implemented using existing imputation software. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: binary data; NMAR; nonignorable; not missing at random

Topic 4: Multiple treatment effects



$$\log h_i(u;\theta) = \beta_0 + \int_{u-c}^{u} a_i(t) w(u-t)\,dt + \cdots$$

Flexible Marginal Structural Models for Estimating the Cumulative Effect of a Time-Dependent Treatment on the Hazard: Reassessing the Cardiovascular Risks of Didanosine Treatment in the Swiss HIV Cohort Study

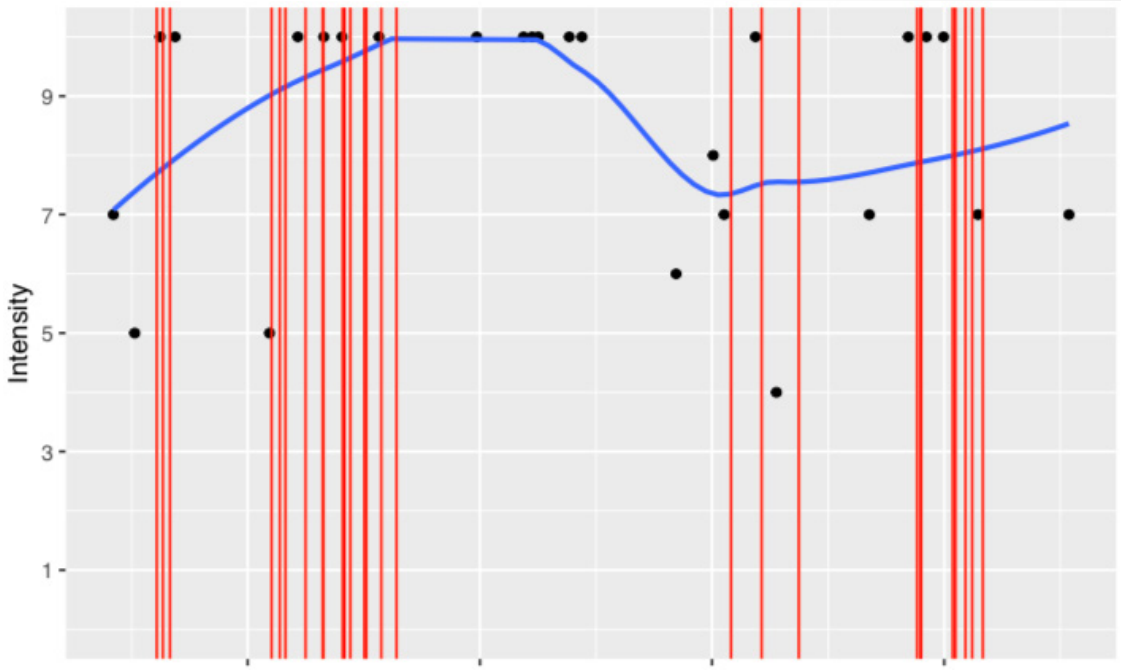
Yongling Xiao, Michal Abrahamowicz, Erica E. M. Moodie, Rainer Weber, and James Young

The association between antiretroviral treatment and cardiovascular disease (CVD) risk in HIV-positive persons has been the subject of much debate since the Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study reported that recent use of two antiretroviral drugs, abacavir (ABC) and didanosine (DDI), was associated with increased risk. We focus on the potential impact of DDI use, as this drug has not been as studied intensively as ABC. We propose a flexible marginal structural Cox model with weighted cumulative exposure modeling (Cox WCE MSM) to address two key challenges encountered when using observational longitudinal data to assess the adverse effects of medication: (1) the need to model the cumulative effect of a time-dependent treatment and (2) the need to control for time-dependent confounders that also act as mediators of the effect of past treatment. Simulations confirm that the Cox WCE MSM yields accurate estimates of the causal treatment effect given complex exposure effects and time-dependent confounding. We then use the new flexible Cox WCE MSM to assess the association between DDI use and CVD risk in the Swiss HIV Cohort Study. In contrast to the nonsignificant results obtained with conventional parametric Cox MSMs, our new Cox WCE MSM identifies a significant short-term risk increase due to DDI use in the previous year. Supplementary materials for this article are available online.

KEY WORDS: Antiretroviral treatment; Cardiovascular disease; Regression splines; Survival analysis.

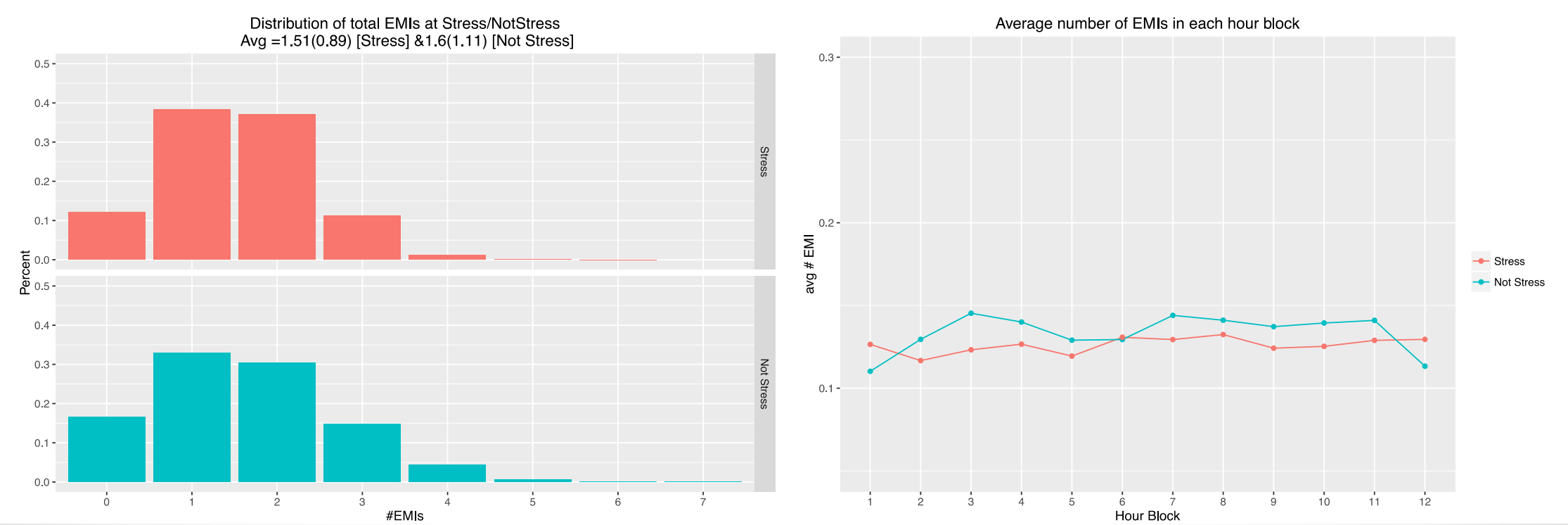
Topic 5: EMA + Event outcomes

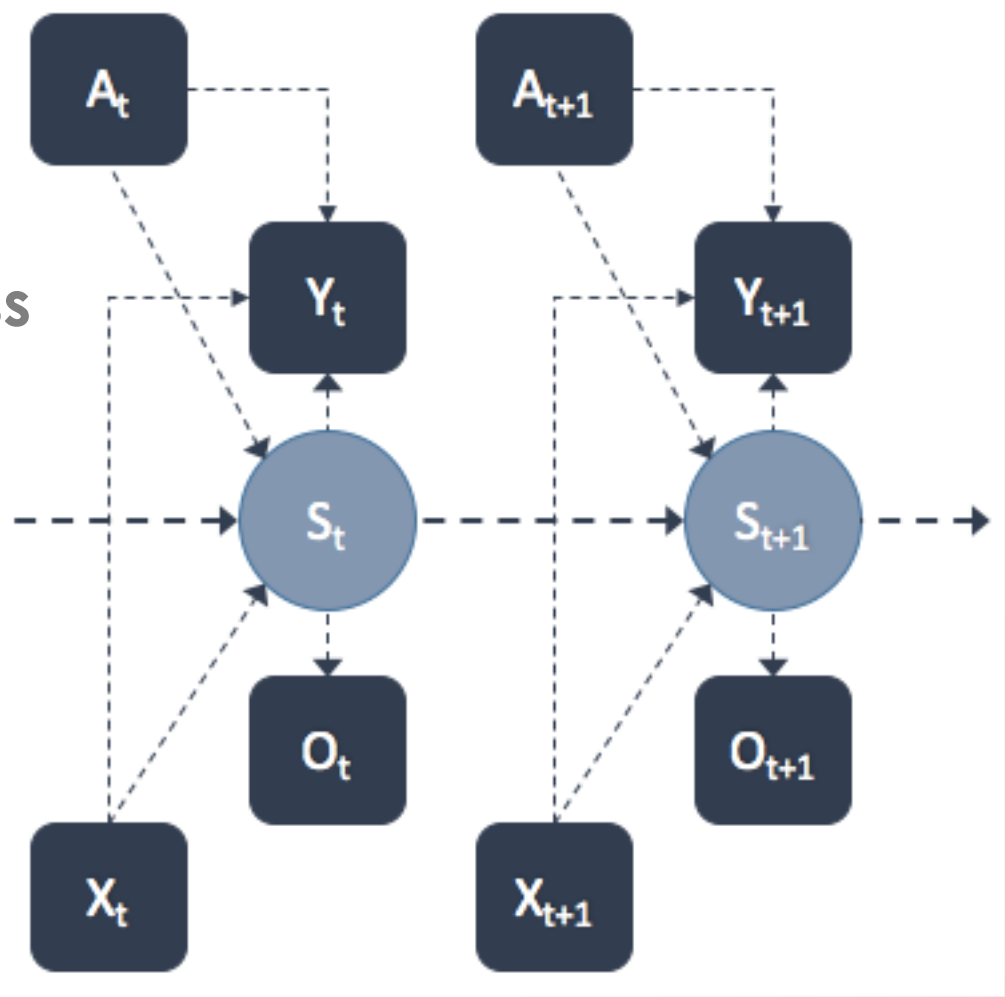
- Participant wears Empatic E4 bracelets
- EMA question on suicidal ideation also asked 5-times per day
- Research question: can we disentangle "actual risk" from the risk due to reminder based on EMA and study fatigue?



Randomization formula with soft-budget constraint

- Assume the randomization probability formula, $\mathrm{P}(A_t = 1 \mid H_t) = \mathrm{p_t}(H_t)$, is known



Markov dynamics for latent constructs

1. Partially **observable** Markov decision process
2. Time-varying exogenous process affects risk (e.g., weather)
3. Actions can impact outcome directly and indirectly
4. Latent state can account for impact of continuing impact of actions on risk