# Micro-randomized Trials in Mobile Health

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# mHealth

MD2K Smoking Cessation Coach

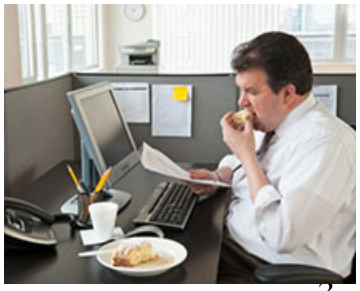
- Wearable wrist/chest bands measure activity, stress, cigarette smoking…; phone records location, burden,…..
- Supportive stress-regulation interventions available on smartphone 24/7
- In which contexts should the wrist band provide supportive “cue” and smartphone activate to highlight associated support?

# mHealth

HeartSteps Activity Coach

- Wearable bands measure activity and sleep quality; phone sensors measure busyness of calendar, location, weather, .....

- In which contexts should smartphone ping and deliver activity ideas?



# Data from wearable devices that sense and provide treatments

On each individual:

$$O_1, A_1, Y_2, \ldots, O_t, A_t, Y_{t+1}, \ldots$$

$O_t$: Observations at t[th] decision time (high dimensional)

$A_t$ : Action at t[th] decision time (treatment)

$Y_{t+1}$ : Proximal Response (aka: Reward, Utility, Cost)

# Examples

1) Decision Times (Times at which a treatment can be provided.)
    1) Regular intervals in time (e.g. every 10 minutes)
    2) At user demand

HeartSteps: Approximately every 2-2.5 hours

Smoking Cessation: Every 1 minute during 10 hour day.

# Examples

2) Observations $O_t$
   1) Passively collected (via sensors)
   2) Actively collected (via self-report)

HeartSteps: activity recognition, location, step count, busyness of calendar, usefulness ratings, adherence…….

Smoking Cessation: stress, smoking detection, mood, driving,….

# Examples

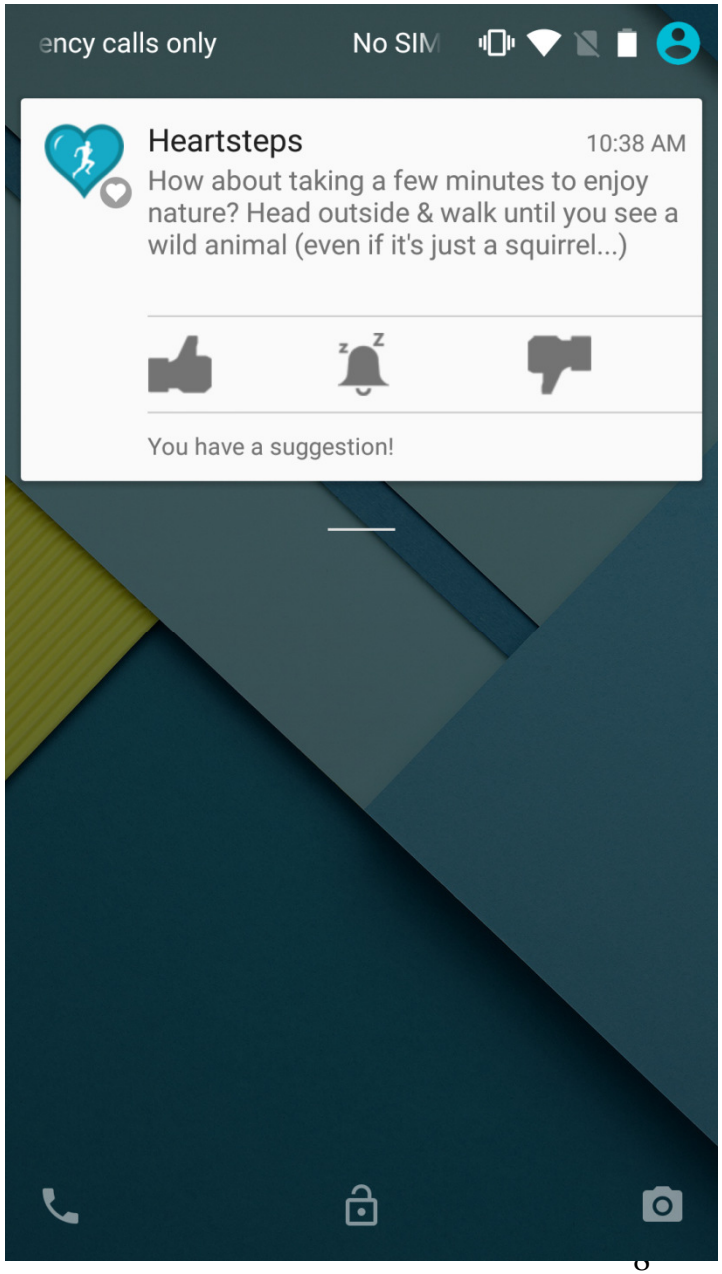
3) Actions $A_t$
    1) Treatments that can be provided at a decision time
    2) Whether to provide a treatment

HeartSteps: Activity recommendation on phone

Smoking Cessation: Cue on wrist band

# Activity Recommendation

No Message or



# Examples

4) Proximal Response (reward) $Y_{t+1}$

HeartSteps: Activity (step count) over next 60 minutes.

Smoking Cessation: Stress level over next x minutes

# Continually Learning Mobile Health Intervention

1) Trial Designs: Are there effects of the actions on the proximal response? *experimental design*

2) Data Analysis Methods for use with trial data: Are there delayed effects of the actions? Do effects vary by context, observations; predict treatment burden? *causal inference*

3) Learning algorithms for use with trial data: Construct a "warm-start" treatment policy. *batch RL*

4) Online training algorithms that will result in a Personalized Continually Learning mHealth Intervention. *online RL*

# Experimental Design: "Micro-Randomized Trial"

Randomize between actions at decision times → Each person may be randomized 100's or 1000's of times.

- These are sequential, "full factorial," designs.
- Design trial to detect main effects.

# Why Micro-Randomization?

- Treatment actions are often designed to have a near-time, proximal effect.
  - Randomization is the gold standard for providing data to assess the causal effect of a treatment

- Sequential randomization will enhance quality of many interesting subsequent data analyses.

# Micro-Randomized Trial Elements

1. Record outcomes
   - Distal (scientific/clinical goal) & Proximal Response
2. Record context (sensor & self-report data)
3. Randomize among treatment actions at decision points
4. Use data after study ends to assess treatment effects, learn warm-start treatment policy

# Micro-Randomized Trial

How to justify the trial costs?

- Address a question that can be stated clearly across disciplinary boundaries and be able to provide guarantees.
- Design trial so that a variety of further interesting questions can be addressed.

First Question to Address: Do the treatment actions impact the proximal response? (aka, is there a *main effect*?)

# Micro-Randomized Trial for HeartSteps

- 42 day trial
- Whether to provide an Activity recommendation? $A_t \in \{0, 1\}$
- Test for main effects on proximal response
- Randomization in HeartSteps

$$P[A_t = 1] = .4 \quad t = 1, \ldots, T$$

# Time-varying Main Effects

Time varying potentially intensive/intrusive treatment actions $\rightarrow$ potential for accumulating habituation and burden

$\rightarrow$

In the test statistic allow the main effect of the treatment actions on proximal response to vary with time

# Availability & the Treatment Effect

- Treatment actions can only be delivered at a decision time if an individual is *available*.

- The effect of treatment at a decision time is the difference in proximal response between *available* individuals assigned an activity recommendation and *available* individuals who are not assigned an activity recommendation.

# Availability

- Treatment actions can only be delivered at a decision time if an individual is *available*

- Set $I_t = 1$ if the individual is available at decision time $t$, otherwise, $I_t = 0$

# Potential Outcomes

- Define

$$\bar{A}_t = \{A_1, A_2, \ldots, A_t\}, \bar{a}_t = \{a_1, a_2, \ldots, a_t\}$$

- Define $Y_{t+1}(\bar{a}_t)$ to be the observed response, $Y_{t+1}$ if $\bar{A}_t = \bar{a}_t$, e.g., $Y_{t+1} = Y_{t+1}(\bar{A}_t)$

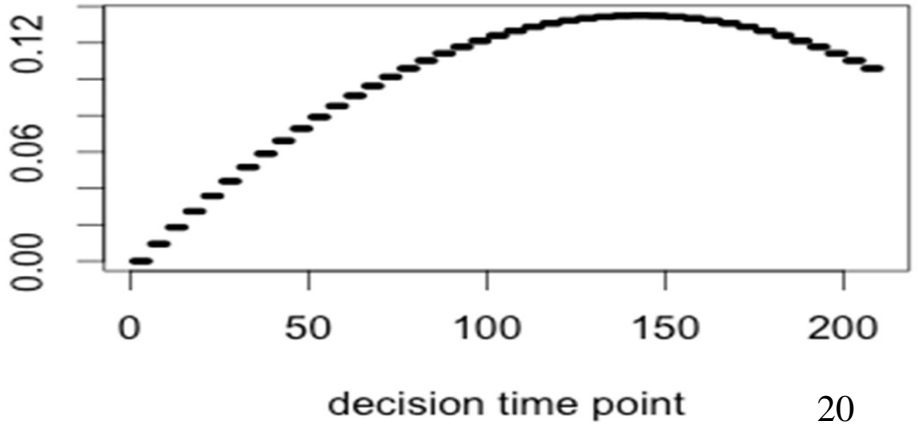
- Define $I_t(\bar{a}_{t-1})$ to be the observed "available for treatment" indicator if $\bar{A}_{t-1} = \bar{a}_{t-1}$

# Main Effect

- Define the Main Effect at time $t$ as

$$E\left[Y_{t+1}(\bar{A}_{t-1}, 1) - Y_{t+1}(\bar{A}_{t-1}, 0) \middle| I_t(\bar{A}_{t-1}) = 1\right]$$

- What does this estimand mean?



# Main Effect

- The randomization implies that

$$E\left[Y_{t+1}(\bar{A}_{t-1},1) - Y_{t+1}(\bar{A}_{t-1},0)\middle| I_t(\bar{A}_{t-1}) = 1\right] =$$
$$E\left[Y_{t+1}|I_t = 1, A_t = 1\right] - E\left[Y_{t+1}|I_t = 1, A_t = 0\right]$$

- Put

$$\beta(t) = E\left[Y_{t+1}|I_t = 1, A_t = 1\right] - E\left[Y_{t+1}|I_t = 1, A_t = 0\right]$$

# Proposal

*Design and size micro-randomized trial to detect main effect of treatment on proximal response*

The main effect is a time-varying main effect $\beta(t)$, $t=1,\ldots,T$

The main effect is a causal effect!

# Sample Size Calculation

- We calculate the number of subjects to test $H_0$: no effect of the action, i.e.,

$$H_0 : \beta(t) = 0, t = 1, 2, ....T$$

- Size to detect a low dimensional, smooth alternate $H_1$.
  - Example: $H_1$: $\beta(t)$ quadratic with intercept, $\beta_0$, linear term, $\beta_1$, and quadratic term $\beta_2$ and test

$$\beta_0 = \beta_1 = \beta_2 = 0$$

# Overview

- Our test statistic uses estimators from a "generalization" of linear regression.
- The test statistic is quadratic in the estimators of the $\beta$ terms.
- Given a specified power to detect the smooth alternative, $H_1$, a false-positive error prob., and the desired detectable signal to noise ratio, we use standard statistics to derive the sample size.

# Sample Size Calculation

Alternative hypothesis is low dimensional

$\longrightarrow$ assessment of the effect of the activity recommendation uses contrasts of *between subject responses* **+** contrasts of *within subject responses.*

--The required number of subjects will be small.

# Test Statistic for Sample Size Calculation

- Test statistic based on fit of model:

$$E[Y_{t+1}|I_t = 1, A_t] = \gamma(t) + \beta(t)(A_t - q_t)$$

where $q_t$ is the randomization probability

- $q_t$ =.*4* in HeartSteps

# Test Statistic for Sample Size Calculation

- Test statistic is based on least squares fit of

$$E[Y_{t+1}|I_t = 1, A_t] = \gamma(t) + \beta(t)(A_t - q_t)$$

HeartSteps:

$$\beta(t) = \beta_0 + \beta_1 \lfloor \frac{t-1}{5} \rfloor + \beta_2 \lfloor \frac{t-1}{5} \rfloor^2$$

- You select parameterization of $\gamma(t)$

# Alternative for Sample Size Calculation

- One calculates a sample size to detect a given alternative with a given power.

- Alternative:

$$H_1 : \beta_i = d_i \bar{\sigma}, i = 0, 1, 2$$

where $\bar{\sigma}^2$ is the average conditional variance.

# Alternative for Sample Size Calculation

- Average conditional variance is

$$\bar{\sigma}^2 = (1/T)\sum_{t=1}^{T} E\left[VAR\left(Y_{t+1}\middle|I_t = 1, A_t\right)\right]$$

# Specify Alternative for Sample Size Calculation

- Scientist indirectly specifies standardized $d_i$'s
  - initial proximal treatment effect: $d_0$,
  - average proximal effect over trial duration:

$$\frac{1}{T}\sum_{t=1}^{T}\left(d_0 + d_1\lfloor\tfrac{t-1}{5}\rfloor + d_2\lfloor\tfrac{t-1}{5}\rfloor^2\right),$$

  - and day of maximal proximal effect: $-\frac{d_1}{2d_2}$
- We solve for $d_0$, $d_1$, $d_2$

# Test Statistic for Sample Size Calculation

- Put $Y_i = (Y_{i2}, \ldots, Y_{iT+1})^T$ for $i^{th}$ subject

$p$ is the total number of parameters ($p > 3$);

$X_i$ is the associated design matrix ($T$ by $p$)

N is sample size

Last 3 columns of $X_i$ contain row entries:

$$I_{it}(A_{it} - q_t), I_{it}(A_{it} - q_t)\lfloor \tfrac{t-1}{5} \rfloor,$$
$$I_{it}(A_{it} - q_t)\lfloor \tfrac{t-1}{5} \rfloor^2$$

# Test Statistic for Sample Size Calculation

- "GEE" test statistic is

$$N\hat{\beta}^T(K\hat{\Sigma}K^T)^{-1}\hat{\beta} = N\hat{\beta}^T(\hat{\Sigma}_\beta)^{-1}\hat{\beta}$$

where $\hat{\Sigma}$ is the usual sandwich estimator of the variance-covariance and $K$ is 3 by $3+q$ matrix picking out columns associated with coefficients $\beta$

# Working Assumptions for Sample Size Calculation

1) $E(\epsilon_{it}\epsilon_{it'} \mid I_{it} = 1, I_{it'} = 1, A_{it}, A_{it'})$ is constant.

2) $E(\epsilon_{it} \mid I_{it} = 1, A_{it}) = 0$

3) $Var(\epsilon_{i,t} \mid I_{it} = 1, A_{it})$ is constant.

$$\epsilon_{it} = Y_{i,t+1} - \Big(\gamma(t) + \beta(t)(A_{it} - q_t)\Big),$$

# Sample Size Calculation

- Under the working assumptions, $\Sigma_\beta$ only depends on polynomials in $\lfloor \frac{t-1}{5} \rfloor$, the marginal distribution of $I_t$ and on the randomization probabilities.

- $\Sigma_\beta$ does not depend on the form of $\gamma(t)$

# Sample Size Calculation

- Under standard moment assumptions, the asymptotic distribution of the "GEE test statistic" is a Chi-Squared on 3 degrees of freedom with non-centrality parameter:

$$N d^T (\Sigma_\beta)^{-1} d$$

- Instead of a Chi-Squared on 3 degrees we use $\frac{3(N-q-1)}{N-q-3} F_{3,N-q-3}$ with the same non-centrality parameter.

# HeartSteps Example

- Standardized $d_i$'s
  - initial proximal effect: $d_0$=0
  - output average proximal effect
  - day of maximal proximal effect: $-\frac{d_1}{2d_2} = 28$
- Model for test statistic:

$$\gamma(t) + \beta(t)(A_{it} - .4), \ t = 1, \ldots, 210$$

where

$$\gamma(t) = \gamma_0 + \gamma_1 \lfloor \tfrac{t-1}{5} \rfloor + \gamma_2 \lfloor \tfrac{t-1}{5} \rfloor^2$$

# HeartSteps Sample Sizes
# Power=.80, False-positive error=.05

| Standardized Average Main Effect over 42 Days | Sample Size For 70% availability or 50% availability |
|---|---|
| 0.06 standard deviations | 81 or 112 |
| 0.08 standard deviations | 48 or 65 |
| 0.10 standard deviations | 33 or 43 |

# Same Test Statistic for Analysis

- "GEE" test statistic is

$$N\hat{\beta}^T(K\hat{\Sigma}K^T)^{-1}\hat{\beta}$$

where $K$ is 3 by $3+q$ matrix picking out columns associated with $\beta$ coefficients

- No working assumptions

# Small Sample Adjustment

- $\hat{e}_{it}$ is the $i^{th}$ subject, $t^{th}$ time point residual and $\hat{e}_i = (\hat{e}_{i1}, \ldots, \hat{e}_{iT})^T$

- Adjusted sandwich estimator:

$$\hat{\Sigma} = \hat{\sigma}^2 N \Big( \sum_{i=1}^{N} X_i^T X_i \Big)^{-1} \Big\{ \sum_{i=1}^{N} X_i^T B_i \hat{e}_i \hat{e}_i^T B_i X_i \Big\} \Big( \sum_{i=1}^{N} X_i^T X_i \Big)^{-1}$$

$$B_i = (I - H_{ii})^{-1}$$

# Simulation Results
# Type 2 Error Rate (2000 data sets)

| Average Proximal Effect (Sample Size) | Power |
|---|---|
| 0.05(115) | 0.790 |
| 0.06(81) | 0.794 |
| 0.07(61) | 0.800 |
| 0.08(48) | 0.801 |
| 0.09(39) | 0.798 |
| 0.10(33) | 0.803 |

# Discussion

The micro-randomized trial is a sequential factorial trial with multiple factors, e.g. in HeartSteps:

Factor 1: Activity recommendation is randomized 5 times per day (yes/no)

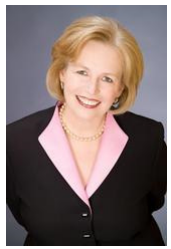
Factor 2: Daily activity planning is randomized each evening (yes/no)

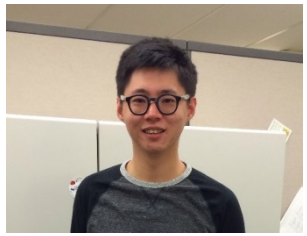
# Experimental Design Challenges

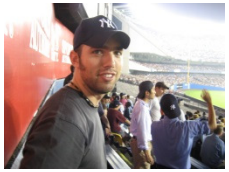
Micro-randomized trials are a new type of factorial design

i. Time varying factors→ time varying main effects, time-varying two-way interactions, different delayed effects
ii. Better trial designs?
iii. Design studies specifically to detect interactions between factors or delayed effects.

# Collaborators!







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