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

- 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

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

• What does this estimand mean?
Main Effect

• The randomization implies that

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

• Put

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

\[ H_0 : \beta(t) = 0, \ t = 1, 2, \ldots, T \]

• 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 → 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

• \( q_t = 0.4 \) 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:

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

• 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

\[
\bar{\sigma}^2 = \frac{1}{T} \sum_{t=1}^{T} E[VAR(Y_{t+1}|I_t = 1, A_t)]
\]
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:
    $\frac{1}{T} \sum_{t=1}^{T} \left( d_0 + d_1 \left\lfloor \frac{t-1}{5} \right\rfloor + d_2 \left\lfloor \frac{t-1}{5} \right\rfloor^2 \right)$,
  – 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:

$$I_{it}(A_{it} - q_t), I_{it}(A_{it} - q_t)\left[\frac{t-1}{5}\right], I_{it}(A_{it} - q_t)\left[\frac{t-1}{5}\right]^2$$
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) $\mathbb{E}(\epsilon_{it}\epsilon_{it'} \mid I_{it} = 1, I_{it'} = 1, A_{it}, A_{it'})$ is constant.

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

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

$$\epsilon_{it} = Y_{i,t+1} - \left( \gamma(t) + \beta(t)(A_{it} - q_t) \right)$$
Sample Size Calculation

- Under the working assumptions, $\Sigma_\beta$ only depends on polynomials in $\left\lfloor \frac{t-1}{5} \right\rfloor$, 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:

\[ Nd^T (\Sigma \beta)^{-1} d \]

• 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

$$\gamma(t) = \gamma_0 + \gamma_1 \left\lfloor \frac{t-1}{5} \right\rfloor + \gamma_2 \left\lfloor \frac{t-1}{5} \right\rfloor^2$$
### HeartSteps Sample Sizes

**Power= .80, False-positive error= .05**

<table>
<thead>
<tr>
<th>Standardized Average Main Effect over 42 Days</th>
<th>Sample Size For 70% availability or 50% availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06 standard deviations</td>
<td>81 or 112</td>
</tr>
<tr>
<td>0.08 standard deviations</td>
<td>48 or 65</td>
</tr>
<tr>
<td>0.10 standard deviations</td>
<td>33 or 43</td>
</tr>
</tbody>
</table>
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:
  $\hat{\Sigma} = \hat{\sigma}^2 N \left( \sum_{i=1}^{N} X_i^T X_i \right)^{-1} \left\{ \sum_{i=1}^{N} X_i^T B_i \hat{e}_i \hat{e}_i^T B_i X_i \right\} \left( \sum_{i=1}^{N} X_i^T X_i \right)^{-1}$
  $B_i = (I - H_{ii})^{-1}$
### Simulation Results

**Type 2 Error Rate (2000 data sets)**

<table>
<thead>
<tr>
<th>Average Proximal Effect (Sample Size)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05(115)</td>
<td>0.790</td>
</tr>
<tr>
<td>0.06(81)</td>
<td>0.794</td>
</tr>
<tr>
<td>0.07(61)</td>
<td>0.800</td>
</tr>
<tr>
<td>0.08(48)</td>
<td>0.801</td>
</tr>
<tr>
<td>0.09(39)</td>
<td>0.798</td>
</tr>
<tr>
<td>0.10(33)</td>
<td>0.803</td>
</tr>
</tbody>
</table>
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 $\rightarrow$ 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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