Title: Micro-randomized Trials for Just-In-Time Adaptive Intervention Development

Summary: Micro-randomized trials are trials in which individuals are randomized 100's or 1000's of times over the course of the study. The goal of these trials is to assess the impact of momentary interventions, e.g. interventions that are intended to impact behavior over small time intervals. We discuss the design and analysis of these types of trials with a focus on their use in developing JITAI's in mobile health.
Outline

• Adaptive Interventions and Just-in-Time Adaptive Interventions

• HeartSteps

• Micro-Randomized Trial

• Sample Size Considerations
The idea is that the same treatment is not good for everyone, and each person may need different things at different time points.

Adaptive Interventions in Drug Court: A Pilot Experiment. Criminal Justice Review 2008; 33; 343 Douglas B. Marlowe, David S. Festinger, Patricia L. Arabia, Karen L. Dugosh, Kathleen M. Benasutti, Jason R. Croft and James R. McKay


Adaptive Programming Improves Outcomes in Drug Court : An Experimental Trial Criminal Justice and Behavior 2012 39: 514 Douglas B. Marlowe, David S. Festinger, Karen L. Dugosh, Kathleen M. Benasutti, Gloria Fox and Jason R. Croft
Douglas B. Marlowe: developed and implemented an adaptive intervention for drug offenders

Following their initial court hearing, risk was assessed.

High risk: ASPD (Antisocial Personality Disorder, based on Diagnostic Interview: APD-DI) or history of formal drug abuse treatment otherwise low risk.

These are assessed monthly:
Noncompliance: is (1) falls below threshold for attendance in counseling sessions or (2) fails to provide 2 or more scheduled urine specimens

Nonresponsive = (1) is attending sessions and completing program requirements, and (2) is not committing new infractions, but (3) provides 2 or more drug-positive urine specimens.

If non compliance, contact with the judge is increased.
ICM– intensive clinical case management: Participants are required to meet twice weekly with an intensive clinical case manager who provides individual substance abuse counseling with an emphasis on motivational enhancement, relapse prevention, and cognitive restructuring (“criminal thinking”) techniques.

Jeopardy contract: involves “zero tolerance” for further violations of the rules of the program. Any further violation leads to a termination hearing, also known as a show-cause hearing. At the termination hearing, the individual is terminated from the program and sentenced on the original charge or charges unless he or she can provide a good reason to be given another chance. The decision of whether or not to grant another chance is within the discretion of the judge.

To graduate offender must attend 12 counseling sessions; provide 14 consecutive weekly negative drug urine specimens; remain arrest-free; obey program rules and procedures; pay 200 dollar court fee.
Adaptive Intervention: 5 Elements

The adaptation is guided by consideration of
(1) Distal Outcome and Proximal Response

The adaptation process is composed of
(2) Tailoring Variables,
(3) Decision Rules and
(4) Intervention Options

The adaptation is triggered at
(5) Decision Points

Monitoring, individualizing, delivering
The same elements that we used to describe an adaptive intervention can be used to describe JITAISs, only that now all these elements are in-the-moment.

Dynamic Models of Behavior for Just-in-Time Adaptive Interventions

Donna Spruijt-Metz, University of Southern California
Wendy Nilsen, National Institutes of Health

PERVASIVE computing, 1536-1268/14/2014 IEEE


Different terms have been used in various fields to describe a JITAI, including dynamic tailoring, intelligent real-time therapy, and dynamically and individually tailored EMI.
Development and evaluation of a mobile intervention for heavy drinking and smoking among college students.

Witkiewitz, Katie; Desai, Sruti A.; Bowen, Sarah; Leigh, Barbara C.; Kirouac, Megan; Larimer, Mary E.

Psychology of Addictive Behaviors, Vol 28(3), Sep 2014, 639-650
Quote from paper: whenever 30 min of nearly uninterrupted computer activity was recorded, a short text message (SMS) containing a hyperlink was sent to the participant’s smartphone. When participants clicked on this hyperlink, they were shown a message persuading them to be more active. Although all messages contained the same general advice, this advice was phrased in various ways, using four different persuasive strategies. The four strategies are a subset of the six social influence strategies defined by Cialdini [22].

The same elements that compose an adaptive intervention, also compose a JITAI. However, in a JITAI these elements are in-the-moment – they can occur at any moment.
Just-in-Time Adaptive Intervention
5 Elements

The adaptation is guided by consideration of
(1) Proximal Response and Distal Outcome

The adaptation process is composed of
(2) Tailoring Variables,
(3) Decision Rules and
(4) Intervention Options

The adaptation is triggered at
(5) Decision Points

In-the-Moment Impact

Real-Time
Distal Outcomes

The goal is to improve a longer-term, distal, outcome
- Substance use cessation; maintain increased activity level; maintain adherence to meds

To improve the distal outcome, the intervention options are formulated to target proximal responses

In MD2K smoking study the distal outcome might be smoking rate.
Likely multiple proximal responses

In MD2k study the proximal response might be stress over next x minutes.
In MD2K study the intervention option might be a recommendation to access one of the four stress-regulation apps (headspace; mood-surfing; thought distancing; and cognitive restructuring) residing on the smartphone vs. no recommendation.

Intervention options in JITAs include types of support, sources of support (e.g., automated sources, social sources); and modes of support delivery.

**Recommendations**

Reach out recommendation (contact a friend)

Behavioral strategies (exercise; stay in locations)
that are supportive of change)

Cognitive strategies (relaxation; reframing)

Motivational messages (reasons for behavior change; barriers for change);

Setting goals; modifying goals

Feedback (often with visualization: fish; flower; garden)

Distractions (game, music, etc.)

Michel Klein et al. have a nice review of all the health behavior change theories used to inform EMI.


Kennedy et al., (2012) conceptualize the EMI as active assistance.

In MD2K smoking study tailoring variables might be current level of stress (low, moderate, high) and location (home, work), time of day (before work, during work, after work) indicate risk or vulnerability. --internal risk factors, external risk factors: behaviors, social context, geographical location.

When user ignores assessment requests or ignores intervention.
In the MD2K smoking study, decision points might be every 2 min or even more frequent depending on how variable we think stress may be.

Recall that a decision point is the time in which we need to make critical decisions about the intervention options based on patient information.

decision points can result in the “do nothing intervention option,” hence a decision point every 3 minutes does not imply an intervention every 3 minutes.
Decision Rules

Link patient information to intervention options at decision points

- A decision rule is implemented at each decision point
- A JITAI often includes many different decision rules
- Development of decision rules is guided by an integration of empirical evidence, theory and clinical experience.

The decision rules are constructed with the aim to impact a proximal/short term response.

We can use the data from the micro-randomized study along with behavioral science to construct decision rules.
Summary of JITAI elements

1. Outcomes
   - Distal (scientific/clinical goal) & Proximal Response
     (guided by mediational theories pinpointing the necessary processes needed to achieve the distal outcome)

2. Intervention options
   - Guided by the proximal responses

3. Tailoring variables
   - Guided by theory concerning moderation.

4. Decision points
   - Guided by the dynamics of tailoring variable and in-the-moment nature of the effect of the intervention option.

5. Decision rules
Outline

• Adaptive Interventions and Just-in-Time Adaptive Interventions

• HeartSteps

• Micro-Randomized Trial

• Sample Size Considerations
HeartSteps

- Goal: Develop a Just-in-Time Adaptive Intervention for Encouraging and Maintaining Physical Activity

Collaborators:
MD collaborator is Lisa Jackson
Pedja Klasnja
Ambuj Tewari
Eric Heckler
HeartSteps

**Distal Outcome:**
Activity over the 42 day study.

**Proximal Response:**
Proximal activity (step count) over next hour.
Two types of activity recommendations: reduce sedentary behavior or physical activity
Two types of daily activity planning: structured vs unstructured.
HeartSteps

**Decision times:**
1) **Momentary**: Approximately every 2-2.5 hours
2) **Daily**: Each evening at user specified time.

**Potential Tailoring Variables:**
activity recognition (walking, driving, standing/sitting), weather, location, busyness of calendar, adherence, step count, availability for momentary intervention, self-report: usefulness, burden

The momentary times were selected because these times are the times at which most people are able to be active
Pre-morning commute, mid-day, mid-afternoon, evening commute, after dinner.
The location of the thumbs up button biases against the person hitting like.
The snozz button turns off the momentary lock screen recommendations for 4 or 8 hours.

Occurs up to 5 times per day

the suggestion, "Need a coffee or tea break? Instead of using the office coffeemaker, why not walk to a nearby cafe and order a to-go cup?" has the following tags:

Location : work
Activity Type : sedentary, active
Time Slot : morning, lunch, afternoon, evening
Weather : outdoor
Day Type : weekday
Outline

- Adaptive Interventions and Just-in-Time Adaptive Interventions
- HeartSteps
- Micro-Randomized Trial
- Sample Size Considerations
42*5=210 times in pilot planned study 2160 decision times.
In MD2K smoking cessation study, with 1 minute intervals between decision times and wearing autosense 10 hours per day for 14 days, we have $60*10*14$ decision points at which a person may be randomized.
Micro-Randomized Trial Elements

1. Record outcomes
   – Distal (scientific/clinical goal) & Proximal Response
2. Record potential tailoring variables
3. Randomize among Intervention Options at decision points
4. At End of Trial use Resulting Data to assess moderation, construct decision rules
Why Micro-Randomization?

- Randomization (+ representative sample) is a gold standard in providing data to assess the causal effect of an intervention option.

- Sequential randomizations will enhance replicability and effectiveness of data-based decision rules.
HeartSteps (42 day study)

- Focus on whether to provide a Momentary Lock Screen Recommendation at the decision times.
- 210 decision times for the lock-screen activity recommendations.

<table>
<thead>
<tr>
<th>Randomization Probability</th>
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<tbody>
<tr>
<td>Lock-screen activity</td>
</tr>
<tr>
<td>Recommendation?</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

So on average 2 times per day
First Question to Address: Do the intervention options have an effect on the proximal response?

--Test for proximal *main effects* of the intervention

42*5=210 times in pilot planned study 2160 decision times.
Micro-Randomized Trial

A JITAI involves time varying potentially intensive intervention delivery → potential for accumulating habituation and burden

→

Allow proximal main effects of the intervention components to vary with time

42*5=210 times in pilot planned study 2160 decision times.
Sample Size for a Micro-Randomized Trial

Determine sample size to detect a *time-varying proximal main effect* of the Lock Screen Recommendation on Activity
The momentary intervention can be turned off for 1-8 hours by the participant. The intervention is also off if the participant is currently active (e.g. walking) or if the participant may be driving a car.

In the MD2K smoking study we might tentatively define availability as:
A person is available if he/she (1) is wearing autosense (our understanding is that autosense will be worn up to 16 hours a day, participants will not wear it when they sleep or when in the shower); if the person is not wearing Autosense, no data will be collected and recommendations will not be pushed); (2) did not receive a message in the past 120 minutes; and (3) is not driving a car.

Adherence (i.e. compliance) is very different from availability. Suppose a person is available at a decision point. However the phone is in their purse across the room. So they don’t hear whether the phone pings/ see the lockscreen light up. This person is non-adherent at this decision point. Primary analyses will be intention-to-treat and thus will average over non-compliance.
Main effects are marginal effects!

Why would the main effect vary with time? Proximal effect varies with time (maybe diminishes due to habituation and/or non-adherence). Population of available individuals varies with time. The individuals who are available near the end of the study may be the least sensitive to the influence of the activity message.

Delayed effects which are akin to higher order interactions would be investigated in secondary analyses.
Since the model for the proximal effect of Aj on Yj does not depend on time of day, we are averaging any variation in proximal effect across the occasions during the day (recall we are sizing the study; a primary analysis might be a little more complex and in secondary data analyses one would likely estimate and test if the proximal effect varies by time of day and/or varies by j, since j denotes duration in study).

Sample Size Calculation

- We calculate a sample size to test:

\[ H_0 : \beta(j) = 0, j = 1, 2, \ldots, 210 \]

- A simple approach is to consider \( \beta(j) \) as a quadratic with intercept, \( \beta_0 \), linear term, \( \beta_1 \), and quadratic term \( \beta_2 \)

and test \( \beta_0 = \beta_1 = \beta_2 = 0 \).
Sample Size Calculation

Because we assume the proximal main effect is approximately quadratic, assessment of the effect of the lock-screen message uses not only contrasts of *between person responses* but also contrasts of *within person responses*.

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We can expect that the required sample size (number of subjects) will be small.

The contrasts become within person contrasts due to the assumption of smoothness over time. If the proximal effect at each time point were to be estimated separately then it would be like a two arm study at each time j.
Sample Size Calculation

- Our test is based on GEE regression.

- To calculate a sample size we need to specify a clinically/scientifically important effect to detect.
Specify Alternative for Sample Size Calculation

SPECIFY:

- Standardized main effects:
  - proximal effect on first day,
  - average proximal effect over trial duration
- Day of maximal proximal effect.
HeartSteps (42 day study)

Standardized effects:

- initial proximal effect: 0
- average standardized proximal effect over trial duration:
- day of maximal proximal effect: 28

Meaningful increase in stepcount is 1000/day
Usual std is 2000/day
Roughly a standardized treatment effect of $\frac{200}{666} = .3$
Average proximal effect is standardized.

#parameters=6

<table>
<thead>
<tr>
<th>Standardized Average Proximal Effect over 42 Days</th>
<th>Sample Size For 70% availability or 50% availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.06</td>
<td>81 or 112</td>
</tr>
<tr>
<td>0.08</td>
<td>48 or 65</td>
</tr>
<tr>
<td>0.10</td>
<td>33 or 43</td>
</tr>
</tbody>
</table>
Average availability is 70%

Simulations indicate:
Method is sensitive to
Guess of average amount of time intervention is on: \( \frac{1}{J} \sum_{j=1}^{J} \mathbb{E}[I_j] \).
Choose on the low side to be safe

Guess of average proximal txt effect. Choose on the low side to be safe.

Heteroscedasticity of errors: variance of \( Y \) when \( A=1 \) is larger than variance of \( Y \) when \( A=0 \) is problematic

Simulations indicate robustness to
\( I_{j+1} \) a function of past \( A_j \)'s

Guess at day of maximal proximal effect (we use different function from quadratic when this day is less than \( \frac{1}{2} \) of the way through the study—this is not presented here)

Non-symmetry or skewness to residual error distribution.
Positive correlated across time residual errors
Mixture of people, some of whom have the intervention turned off x% of time and some who have their intervention turned off y% of the time where overall % time turned off is .7 or .5
A Micro-Randomized Trial

1) We also micro-randomize other components (e.g. Daily Activity Planning) to obtain a sequential, factorial design.

2) Be conservative in planning the trial!
   1) Under-estimate the amount of time participants are available for the intervention component.
   2) Under-estimate the average proximal effect.
A Micro-Randomized Trial

3) Power to detect proximal main effect is robust to interactions and to delayed effects (e.g., burden)

4) Secondary data analyses concern time varying effect moderation and data analyses to construct data-driven decision rules for the JITAI
HeartSteps Collaborators: P. Liao, A. Lee, C. Anderson, P. Klasnja, A. Tewari & Inbal Nahum-Shani

Email if you have questions!

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