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. A fast growing area of mHealth concerns the use of mobile devices for both collecting real-time data, for processing this data and for providing momentary interventions. We discuss the design and analysis of these types of trials.
Outline

- Adaptive Interventions and Just-in-Time Adaptive Interventions
- HeartSteps
- Micro-Randomized Trial
- Sample Size Considerations
Adaptive Interventions

- Intervention design that takes advantage of response heterogeneity by individualizing intervention options to the specific and changing needs of individuals

- Example: Adaptive drug court program for drug abusing offenders

Marlowe et al., 2008; 2009; 2012

The idea is that the same treatment is not good for everyone, and different people need different things at different time point.

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 noncompliance, 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
Examples:

Intervention to reduce heavy drinking and smoking by young adults
- Participants prompted 3/day by mobile device for assessments
  - Smoking urge, self-regulation demands, drinking behaviors
- Urge-management interventions delivered by the mobile device only if participant reports an urge to smoke at an assessment.

(Witkiewitz et al., 2014)

Complete assessments such as smoking urge, drinking and affective state

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
The proximal response can occur at any time, and is more immediate than the primary long-term outcome. The decision rules are constructed with the aim to manipulate a more proximal/short term response.

The term momentary outcome was used by Schwartz & Stone (2007).

Recall that the outcome of interest, is the outcome that guides you when constructing the decision rules.

In a typical adaptive intervention that is not a JITAI (e.g., the drug court program) the outcome is long-term – program graduation at the end of study. This outcome guided the investigators when constructing the decision rule. JITAI's are also guided by a long-term outcome, because the overall purpose is to make some long-term distal impact (e.g., smoking cessation; relapse prevention; promoting a healthier lifestyle etc.). However, the decision rules in a JITAI are also guided by a momentary outcome.

This is because the aim of JITAI's is to generate some immediate impact (otherwise why would you intervene in real-time). The idea is that in real-time the participants needs something, and by providing an intervention, these momentary needs will be met.

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**Proximal Responses**

*Mediators* that may be critical to achieving the long-term goal

1) Short term targeted behavior
   - Substance use over x hours
   - Physical activity over x minutes
   - Social interactions over next hour
2) Short term risk
   - Momentary craving, stress
3) Engagement in intervention
Intervention options in JITAls include types of support (e.g., instrumental, emotional), sources of support (e.g., automated sources, social sources); and modes of support delivery (e.g., support provision and/or support availability).

**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.
Tailoring variables

Tailoring variables are moderators that inform which intervention option is best when, where and for whom.

- Often past proximal responses: craving, activity
- Risk & protective factors: busyness of calendar, momentary mood or stress, location, social context
- Adherence & burden

indicate risk or vulnerability. --internal risk factors, external risk factors: behaviors, social context, geographical location,
When user ignores assessment requests or ignores intervention

Overall, a JITAI might include multiple tailoring variables and their selection should be guided by the various proximal outcomes the JITAI is intended to achieve.
Recall that a decision point is the time in which we need to make critical decisions about the intervention options based on patient information. The selection should be guided by what is known about the extent to which the tailoring variables are expected to change systematically over time, and whether and how change in proximal outcome can be influenced by the intervention options. If the tailoring variable is likely to change in a meaningful manner every (e.g., location), and the intervention options are thought to impact the proximal outcome in 1-2 minutes (e.g., send a warning to the participant), then there should be a decision point every minute. Recall that 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.
for every decision point, the investigator should be able to articulate the proximal outcomes and the distal outcome that is reasonable to expect if an individual with a specific value of the tailoring variable receives each of the intervention options under consideration. This has to be expressed for all values of the tailoring variable, and for each one of the proximal outcomes. This is necessary in order to identify the most effective intervention option, for a given value of the tailoring variable, in order to maximally impact the proximal outcome.

**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.
Decision Rules: Example 1

What to do when composite risk assessment at random prompt indicates risk

At self-report assessment

If composite substance abuse risk $\geq R_0$

*Then*, $IO = \{\text{reminder to access intervention}\}$

Else if composite substance abuse risk $< R_0$

*Then*, $IO = \{\text{do nothing}\}$

Tailoring Variable

Proximal Response: Craving

Intervention options

Decision Point
Decision Rules: Example 2

At 5 minute intervals

\textit{If} current accumulated computer activity > P_0

\textit{Then}, \text{IO} = \{\text{recommend movement}\}

\textit{Else if} current accumulated computer activity \leq P_0

\textit{Then}, \text{IO} = \{\text{do nothing}\}
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

health domains
Behavior change and maintenance of this change (exercise, healthy eating, sedentary behavior)
Self-management of a chronic disorder (Adherence to meds, adherence to self-care behaviors, mental illness, cognitive support, substance abuse)

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.
HeartSteps

Intervention Options:
1) Whether to provide an intervention
   1) Provide Momentary Lock Screen Activity Recommendation?
   2) Provide Daily Activity Planning?

2) Type of Daily Activity Planning to provide if provided
   1) Structured versus unstructured daily activity planning
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, 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 like 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
Micro-Randomized Trial

Randomize between appropriate intervention options at decision times → Each person may be randomized 100’s or 1000’s of times.

42*5=210 times in pilot planned study 2160 decision times.
Why Micro-Randomization?

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

- Sequential micro-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>Lock-screen activity Recommendation?</th>
<th>Randomization Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2/5</td>
</tr>
<tr>
<td>No</td>
<td>3/5</td>
</tr>
</tbody>
</table>
Micro-Randomized Trial

A JITAI is a multi-component intervention

First Question to Address: Do the intervention components have an effect on the proximal response?

--Test for proximal main effects of the intervention components

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

A JITAI is composed of sequences of intervention components with the 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

- Size to detect a *proximal main effect* of the Lock Screen Recommendation on Activity

- Permit proximal main effect to vary with time
Availability & The Main Effect

- Just in time interventions can only be delivered at a decision time if an individual is available.

- The proximal main effect of treatment at a decision time is the difference in proximal response between available individuals assigned a lock-screen message and available individuals who are not assigned a lock-screen message.

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.
Main effects are marginal effects!
Why would the main effect vary with time? Proximal effect varies with time
(maybe diminishes due to habituation). 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

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*.

--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 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 standard regression.

- To calculate a sample size we need to specify a clinically/scientically 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.
Meaningful increase in stepcount is 1000/day
Usual std is 2000/day
Roughly a standardized treatment effect of $\frac{200}{666} = .3$
### HeartSteps Sample Sizes
Power=.8, α=.05

<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 proximal effect is standardized.
#parameters=6
$E[R]=.7$
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 for use in constructing data-driven decision rules for the JITAI
Collaborators: P. Liao, A. Lee, C. Anderson, P. Klasnja, A. Tewari & Inbal Nahum-Shani

Email if you have questions!

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