85 min.
What is a JITAI -- how it relates to multi-component interventions and to AIs
Motivation for JITAI
What is MRT (basic features)
The connection between MRT and MOST, Factorial designs and SMART
three available stress-regulation apps (headspace; mood-surfing; thought distancing; and cognitive restructuring).

- Wearable wrist/chest bands provide multiple physiological sensor streams…;
  Self-report provides craving, burden,…..
- Stress-management exercises available on smartphone 24/7
- In which contexts should the smartphone remind the user to access the stress-management apps and practice the exercises?
HeartSteps Activity Coach

- Wearable band senses activity and sleep quality; phone sensors measure busyness of calendar, location, weather; self-report provide burden, utility ..... 

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

Sedentary adults
Next study will be with adults who are at high risk for heart attack
Outline

Just-in-Time Adaptive Intervention (JITAIIs)
- What are they, Components, Motivation

Micro-Randomized Trials (MRTs)
- Using data to inform the development of JITAIIs
- Key features
- Sample size considerations
- MRTs vs. other designs
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Adaptive Intervention: 5 Elements

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

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 JITAISSs, 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
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.
Motivation for JITAIs

1. Individuals may need support when it is difficult or expensive to provide
2. Individuals are not always aware of when they need support
3. Intervention options may have negative effects (burden, habituation)
Just-in-Time Adaptive Intervention
5 Elements

The adaptation is guided by consideration of
(1) Proximal 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
Distal Outcomes

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

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

In MD2K smoking study the distal outcome might be time to relapse.
**Proximal Outcomes**

*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
   - Adherence over next hour
2. Short term risk
   - Current craving, stress
3. Engagement with mobile app/intervention burden

Likely multiple proximal outcomes

In MD2k study the proximal outcome might be stress over next x minutes.
Intervention options

- Intervention options:
  - Behavioral strategies, cognitive strategies, self-monitoring, social linkages, motivational, engagement strategies…
  - Whether to provide an intervention or whether to prompt self-monitoring
  - How to provide an intervention option
  - “Provide nothing” option

- Theoretically/scientifically driven (Klein et al., 2011; West & Michie, 2016)

Intervention options are typically designed to impact distal outcome via the proximal outcome.

In MD2K study the intervention option might be a recommendation to access one of the three stress-regulation apps (headspace; mood-surfing; and ?) residing on the smartphone vs. no recommendation.

Intervention options in JITAls 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 health behavior change theories used to inform EMI.


In MD2K smoking study tailoring variables might be current classification of stressed or not and location (home, work), time of day (before work, during work, after work). Also weather.

indicate risk or vulnerability. --internal risk factors, external risk factors: behaviors, social context, geographical location,
When user ignores assessment requests or ignores intervention
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.
The decision rules are constructed with the aim to impact a proximal outcome.

We can use the data from the micro-randomized study along with behavioral science to construct decision rules.
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 ≥ R₀
Then, IO = \{reminder to access intervention\}

Else if composite substance abuse risk < R₀
Then, IO = \{do nothing\}

Tailoring Variable
Proximal Outcome: Craving

Intervention options
Decision Point
Decision Rules: Example 2

At 1 minute intervals

*If* current accumulated computer activity $> P_0$

*Then*, IO = \{recommend movement\}

*Else if* current accumulated computer activity $\leq P_0$

*Then*, IO = \{do nothing\}
Summary of JITAI elements

1. Outcomes
   - Distal (scientific/clinical goal) & Proximal Outcome (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 the tailoring variable and in-the-moment nature of the effect of the intervention option.

5. Decision rules
Outline

Just-in-Time Adaptive Intervention (JITAI<sub>s</sub>)
- What are they, Components, Motivation

Micro-Randomized Trials (MRTs)
- Using data to inform the development of JITAI<sub>s</sub>
- Key features
- Sample size considerations
- MRTs vs. other designs

Make a break –everyone stretches!
Sedentary adults
Next study will be with adults who are at high risk of an adverse cardiac event
Currently, AutoSense consists of an arm band with four wireless sensors and a chestband with six wireless sensors. All the ten sensors are integrated onto an embedded platform called “mote,” a tiny self-contained, battery-powered computer with a wireless radio that can host multiple sensors, collect and process data from them using customized algorithms, and communicate on secure wireless channels.

The chestband consists of 2-lead Electrocardiogram (ECG), galvanic skin response (GSR), respiratory inductive plethysmograph (RIP) band for robust measurement of respiration, skin temperature, ambient temperature, and a 3-axis accelerometer. Accelerometers help classify physical activities, estimate their intensities, and help remove motion artifacts from the measurements of ECG, RIP, and GSR. The armband consists of WrisTAS alcohol sensor from Giner Inc., accelerometers, GSR, and temperature sensors. All sensors communicate wirelessly with a smart phone. Sensors on the phone (e.g., GPS, microphone) complement those on the body. The phone also acts as a local server for heavier computation and storage.

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 x minutes; and (3) is not driving a car.
Data from wearable devices that sense and provide treatments

- On each individual: $O_1, A_1, Y_2, \ldots, O_t, A_t, Y_{t+1}, \ldots$

- $t$: Decision point
- $O_t$: Observations at $t^{th}$ decision point
- $A_t$: Intervention option at $t^{th}$ decision point
- $Y_{t+1}$: Proximal outcome (e.g., reward, utility, cost)
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.

Another example: The phone software monitors a risk measure at regular time intervals and if the risk measures hits a criterion then a treatment is provided.

Examples

1) Decision Points, $t$ (Times at which interventions can be provided.)
   1) Regular intervals in time (e.g. every 10 minutes)
   2) At user demand

HeartSteps: Approximately every 2-2.5 hours

Sense2Stop : Every 1 minute during 10 hour day.
Examples

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

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

Sense$^2$Stop: classifications of stress, smoking detection, mood, driving, prior app use ....

Can include time of day or day of week and present weather.
Examples

3) Intervention options $A_t$
   1) Intervention options that can be provided at a decision time
   2) Whether to provide an intervention

HeartSteps: Tailored activity recommendation notification by phone
Sense$^2$Stop: Reminder to access app so as to practice stress-management exercises
Tailored Activity Recommendation

No Message or

Tailored to time of day, location, weather outside, weekday

The location of the like button biases against the person hitting like.
The snoozz button turns off the momentary lock screen recommendations for x hours.

Occurs up to 5 times per day
Frequently the actions are primarily designed to have a near-term effect on the individual. E.g. Help them manage current craving/stress, help them manage or be aware of the impact of their social setting on their craving/stress.

Examples

4) Proximal Outcome $Y_{t+1}$

**HeartSteps:** Activity (step count) over next 30 minutes.

**Sense²Stop:** Stress over next 120 minutes
Micro-Randomized Trial

Randomize between intervention options at decision points → 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?

- Randomization (+ representative sample) is a gold standard in providing data to assess causal effects.

- Sequential randomizations (+ representative sample) will enhance replicability of data analyses (moderation, decision rule development).
Micro-Randomized Trial Elements

1. **Record** outcomes
   - Distal (scientific/clinical goal) & Proximal Outcome
2. **Record** context (sensor & self-report data)
3. **Randomize among intervention options at decision points**
4. **Use data after study ends to assess treatment effects, develop warm-start JITAI**
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 intervention options differentially impact the proximal outcome? (aka, is there a main effect?)
Micro-Randomized Trial for HeartSteps

- 42 day trial
- Whether to provide a tailored activity recommendation? $A_t \in \{0, 1\}$
- Test for main effects on proximal outcome
- Randomization in HeartSteps
  \[ P[A_t = 1] = .4 \quad t = 1, \ldots, T = 210 \]

$J=42*5=210$ momentary randomizations
Time-varying Main Effects

Time varying potentially intensive/intrusive intervention options → potential for accumulating habituation and burden

In the test statistic allow the main effect of the intervention options on proximal outcome to vary with time
Availability

- Intervention options can only be delivered at a decision point if an individual is available.
- In HeartSteps an individual is unavailable if:
  - Might be driving a vehicle
  - Is currently walking
  - Has turned off the intervention

- Availability is not the same as adherence

Availability is measured prior to randomization. Adherence is measured after randomization.

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-adherence.
Marginal over randomization (and effects thereof), conditional on those who are available.

The group who are available is a selected group of people likely depending on the intervention dose they experienced up to time $j$. This intervention dose may have caused burden, may have caused learning.
Design of MRT

Determine the number of participants so that micro-randomized trial can detect a main effect on proximal outcome

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

The main effect is a causal effect.

In heartsteps beta(t) is the effect of tailored activity suggestion on next 30min step count.

Delayed effects which are akin to higher order interactions would be investigated in secondary analyses.
### Sample Size Calculation

- We calculate the number of subjects to test $H_0$: no effect of the intervention option, 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 $\beta_0 = \beta_1 = \beta_2 = 0$

Instead of a sparsity bet, we place a smoothness bet. We are not assuming that the main effect has a quadratic form.

Since the test statistic for the main effect does not depend on time of day, we are averaging any variation in main 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 effect varies by time of day and/or varies by day in study).
Sample Size Calculation

- 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.

The contrasts become within person contrasts due to smoothness over time in the targeted quadratic alternative. If the main effect at each time point were to be estimated separately then it would be like a two arm study at each time j.
Specify Alternative for Sample Size Calculation

SPECIFY:

• Standardized main effects:
  – main effect on first day,
  – average main effect over trial duration
• Day of maximal main effect.
• Average availability over trial duration
Meaningful increase in stepcount is 1000/day
Usual std is 2000/day
Roughly a standardized treatment effect of 200/666 = .3

Sample size calculators
https://pengliao.shinyapps.io/mrt-calculator/
R package
https://cran.r-project.org/web/packages/MRTSampleSize/index.html
<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>
Planning a Micro-Randomized Trial?

1) Be conservative in planning the trial:

   1) Under-estimate the amount of time participants are available for the intervention.
   2) Under-estimate the average standardized effect
Micro-Randomized Trial

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

3) Secondary data analyses concern time varying effect moderation and data analyses to construct data-driven decision rules for the JITAI
Micro-Randomized Trials: When are they (not) useful?

- NOT USEFUL: When malleable circumstances are rare: Want to learn the best type of alert to prevent suicide attempt
- USEFUL: When malleable circumstances change rapidly: Stress, urges to smoke, adherence, physical activity, eating
- NOT USEFUL: Proximal outcome cannot be feasibly assessed.
- USEFUL: Proximal outcome can be unobtrusively sensed or unobtrusively self-reported.
MRTs
vs
Other designs

• RCT
• N-of-1 Trials (& Crossover Trials)
• Factorial Designs

Single-patient trials or individual-patient trials or single-case experiments
MRT vs. Randomized Control trial (RCT)

A randomized control trial (RCT) evaluating a JITAI compared to a suitable control.

– Assumes evidence exists to develop a high-quality JITAI including the
  • choice of tailoring variables & decision rules
– The primary aim of an RCT is to confirm the JITAI’s effectiveness compared to an alternative
  • Is not well suited to constructing or optimizing a JITAI
– RCT is optimal for evaluation
MRT vs. N-of-1 Trial

N-of-1 Trials are usually multiple cross-over trials in which the order of the treatments are randomized within a person.

- RCT is too expensive or not feasible
  - Test: Is one-time treatment A better than one-time treatment B?
  - Ideally the treatments should have minimal delayed effects (minimal carryover effects) or N-of-1 design should incorporate a suitable washout period


ABBA trials, single case designs, quasi-experimental

Design and Implementation of N-of-1 Trials: A users’ guide

MRTs vs Factorial Experiments

A factorial design

- is an experimental design involving more than one components (e.g., factors); the levels of the components can be meaningfully crossed.

A MRT

- is a special form of a factorial; components are employed sequentially in time within a person.
- components can operate at different time scales
- randomization to subsequent components in a MRT may depend on outcomes of prior components

No notion of availability
MRTs vs Factorial Experiments

Components can be randomized at different time scales, e.g. in HeartSteps:

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

Factor 2: Daily activity planning is randomized each evening (yes/no)
This project tests the feasibility and effectiveness of providing, via a smartphone, just-in-time tailored physical activity suggestions as well as evening prompts to plan the following day's physical activity so as to help sedentary individuals increase their activity. The resulting data will be used to inform the development of a JITAI for increasing physical activity.

PI: Predrag Klasnja

Location: University of Michigan

Funding: NHLBI/NIA R01HL125440

heartsteps MRT

https://www.clinicaltrials.gov/ct2/show/NCT03225521?titles=HeartSteps&rank=1
MRTs vs Factorial Experiments

Randomization to subsequent components in a MRT may depend on outcomes of prior components, e.g. in Sense2Stop:

- Randomization probabilities aim to result in an average of 1.5 reminders per day when the person is currently stressed
- Randomization probabilities aim to result in an average of 1.5 reminders per day when the person is not currently stressed.
This project tests the feasibility of conducting an MRT aiming to investigate whether real-time sensor-based assessments of stress are useful in optimizing the provision of just-in-time prompts to support stress-management in chronic smokers attempting to quit. The resulting data will be used to inform the development of a JITAI for smoking cessation.

**PI:** Santosh Kumar, Center of Excellence for Mobile Sensor Data-to-Knowledge (MD2K, [https://md2k.org](https://md2k.org))

**Location:** Northwestern University, Bonnie Spring, (site P.I.)

**Funding:** NIBIB through funds provided by the trans-NIH Big Data to Knowledge (BD2K) initiative ([www.bd2k.nih.gov](http://www.bd2k.nih.gov)). [U54EB020404](https://www.clinicaltrials.gov/ct2/show/study/NCT03184389?recrs=a&lead=Northwestern+University&ctrid=NA%3AUS&state1=NA%3AUS%3AIL&draw=1)

MD2K smoking cessation study
[https://www.clinicaltrials.gov/ct2/show/study/NCT03184389?recrs=a&lead=Northwestern+University&ctrid=NA%3AUS&state1=NA%3AUS%3AIL&draw=1](https://www.clinicaltrials.gov/ct2/show/study/NCT03184389?recrs=a&lead=Northwestern+University&ctrid=NA%3AUS&state1=NA%3AUS%3AIL&draw=1)
Micro-randomized Trials

A new type of factorial design

i. Time varying factors $\rightarrow$ time varying main effects, time-varying two-way interactions, different delayed effects

ii. Design studies specifically to detect interactions between factors.

iii. Calculator:

https://sites.google.com/a/umich.edu/pengliao/
MRTs and MOST

The Multiphase Optimization Strategy (MOST)

Preparation
- Derive/review conceptual model
- Identify set of candidate components
- Identify optimization criterion

Optimization
- Optimization trial(s)
  - Functional requirement
  - Technical/managerial feasibility
  - System/technological fit
  - Operational characteristics
  - Cost
- Continual improvement process
  - Based on results, identify intervention that meets optimization criterion

Evaluation
- Confirm effectiveness of optimized intervention via MCT

Continual optimization principle

Resource management principle
Researchers are conducting this quality-improvement MRT aiming to promote weight maintenance through increased activity and improved diet among people who received bariatric surgery. At the time it was developed, this project was novel in that it implemented separate randomizations at the start of the study, on a daily basis, and five times throughout the day.

**PI:** Pedja Klasna  
**Location & Funding:** Kaiser Permanente

**50 participants in a 4-month Micro-randomized trial.**

**Before the study:** There is a 7-day baseline data collection prior to randomization. Participants will be wearing a screen-less accelerometer for a week before they start the study, to capture step count data that will be used to generate adaptive step goals (percentile values).
Concluding Remarks

- We should not only register our MRTs with clinicaltrials.gov but also preregister with Open Science!
  - Non-trivial and slightly stressful!
  - See our Open Science preregistration for MRT on SARA
    - an OK but not great start!


Go to the files section.
The Substance Abuse Research Assistance (SARA) is an app for gathering data about substance use in high-risk populations. App developers are using an MRT to improve engagement with completion of the self-report data collection measures. At the time this summary was written, this MRT is unique in that it has an engagement component, but not a treatment one.

**PIs:** Maureen Walton, Susan Murphy, and Mashfiqui Rabbi Shuvo  
**Location:** University of Michigan  
**Funding:** Michigan Institute for Data Science (PI S. Murphy), University of Michigan Injury Center (PI M. Walton), NIDA P50 DA039838 (PI Linda Collins), NIAAA R01 AA023187 (PI S. Murphy), CDC R49 CE002099 (PI: M. Walton)

[https://clinicaltrials.gov/ct2/show/NCT03255317](https://clinicaltrials.gov/ct2/show/NCT03255317)  
And  
[https://osf.io/whgfp/](https://osf.io/whgfp/)
JOOL is a behavioral health and well-being app that is designed to help people monitor and improve their sleep, presence, activity, creativity, and eating, with the ultimate goal of helping people move closer to fulfilling their life’s purpose. This MRT aims to understand whether push notifications of tailored health messages are useful in promoting engagement with the JOOL app; and, if so, when and under what circumstances they are most effective.

**PI:** Victor Strecher, PhD, MPH, CEO of JOOL Health

**Location & Funding:** Ann Arbor, MI

**URL:** [https://www.joolhealth.com](https://www.joolhealth.com)