

# Stratified Micro-Randomized Trials



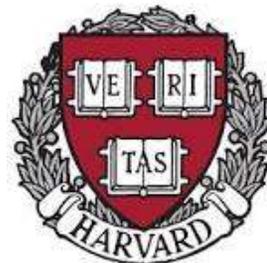
JOOHEALTH

with applications to mobile health



BariFit

Susan A Murphy  
ISCB-ASC-2018



The Methodology Center  
advancing methods, improving health

# Experimentation, Continual Optimization

- “Iterative nature of experimentation” (RA Fisher & G. Box)
- “At Google, experimentation is practically a mantra; we evaluate almost every change that potentially affects what our users experience.” (4 Google scientists)
- “Online experiments are widely used to compare specific design alternatives, but they can also be used to produce generalizable knowledge and inform strategic decision making. Doing so often requires sophisticated experimental designs, iterative refinement, and careful logging and analysis.” (3 Facebook scientists)

# Outline

- Introduction to Mobile Health
- Sense<sup>2</sup>STOP
- Stratified Micro-Randomized Trials
- The Causal Treatment Effect (a.k.a, causal excursions)
- Test Statistic for Primary Hypothesis
- Discussion

**Smart wt loss**



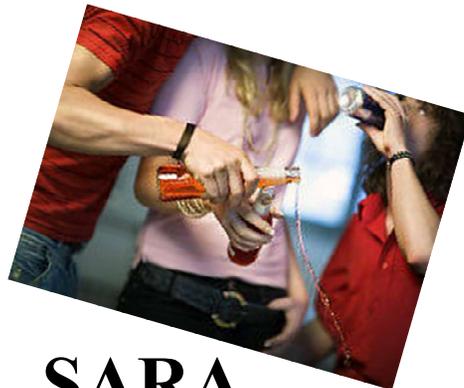
**JOOLHEALTH**



**BariFit**



**HeartSteps**



**SARA**



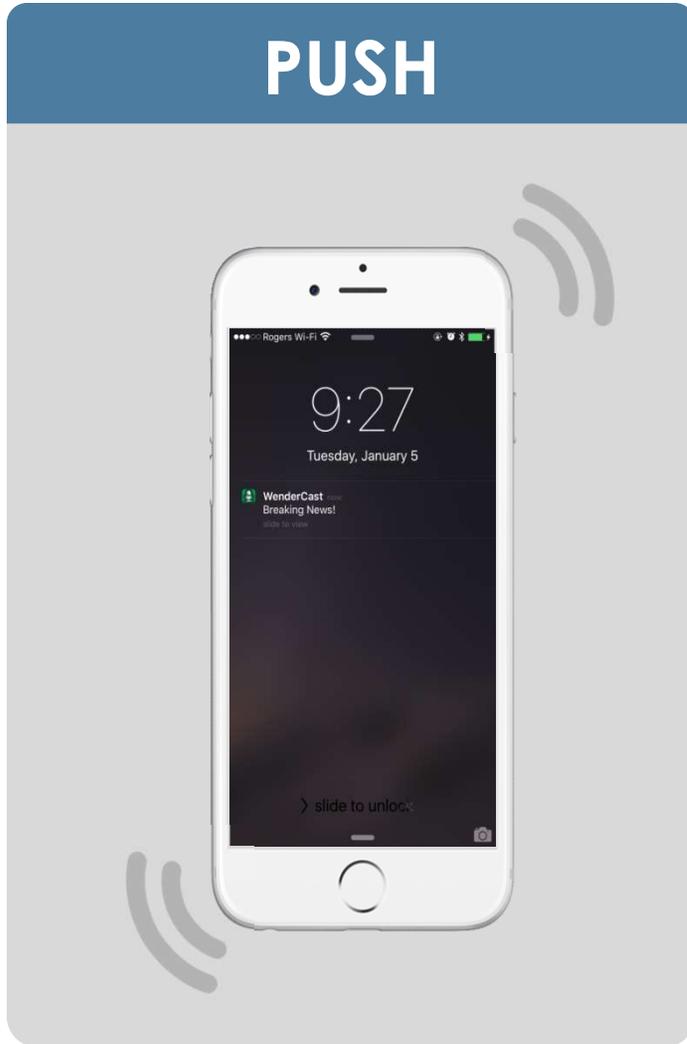
**Sense<sup>2</sup>STOP**

<https://methodology.psu.edu/ra/adap-inter/mrt-projects#proj>

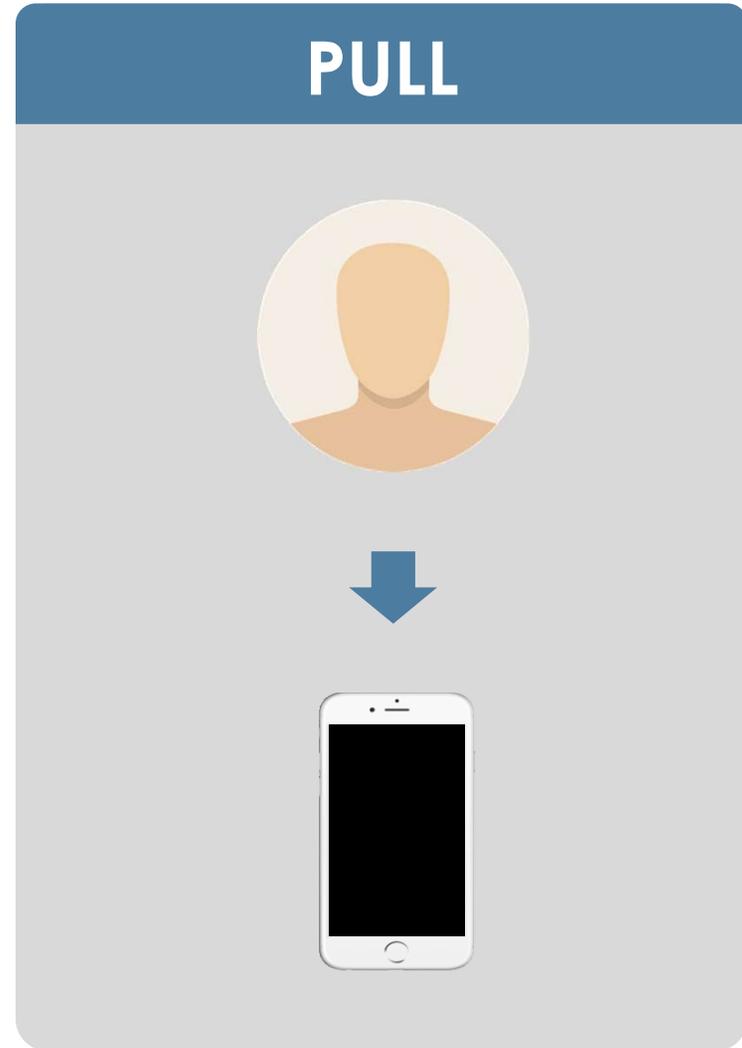


# Mobile Intervention Treatments

**PUSH**



**PULL**



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PI: S. Kumar

Most (93%) unaided smoking cessation attempts fail in 1st week

- 95% of **lapses** (few puffs) followed by **relapse**
- Patients are encouraged to call when tempted to smoke.  
...but they rarely do

**Stress** predicts lapse/relapse=> increasing state of risk

- Performing brief relaxation exercises can buffer/blunt real-life life stress
- \*\*\*But people fail to use them\*\*\*
- Should the phone push reminders to individuals at times of stress to access exercises on smartphone?



# Using sensors to detect “stress”

- Participant wears Autosense chestband + sensors on each wrist
- Measure various physiological responses and body movements to robustly assess physiological stress.
- Pattern-mining algorithm uses the sensor data to construct a binary time-varying stress classification
- Participant is then classified at each minute as either “Stressed” or “Does not qualify as Stressed” or “UK”





- In the near term the reminder push notification should reduce:
  - Near time, proximal, stress
- Primary: Should the smartphone push a reminder to utilize app directed stress-management exercises when the user is stressed?
  - Does the effect vary with time or with current context?

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# Stratified Micro-Randomized Trial

- On each participant:  $O_1, A_1, \dots, O_t, A_t, \dots$
- $t$  : Times at which a treatment might be provided
- $O_t$ : Observations after time  $t - 1$  and up to and including time  $t$ 
  - $X_t \subset O_t$  : time-varying stratification variable

# Stratified Micro-Randomized Trial

- On each participant:  $O_1, A_1, \dots, O_t, A_t, \dots$
- $t$  : Times at which a treatment might be provided
  - Sense<sup>2</sup>STOP: each minute
- $O_t$ : Observations after time  $t - 1$  and up to and including time  $t$ 
  - $X_t \subset O_t$  : time-varying stratification variable
  - Sense<sup>2</sup>STOP:  $X_t = 1$  each minute if classified as stressed and  $=0$ , otherwise

# Stratified Micro-Randomized Trial

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- $I_t \subset O_t$  : availability indicator
- Sense<sup>2</sup>STOP:  $I_t = 1$  if not treated in prior hour and if online classification is possible; =0 otherwise

# Stratified Micro-Randomized Trial

- $O_t$ : observations after time  $t - 1$  and up to and including time  $t$ 
  - $I_t \subset O_t$  : availability indicator
  - Sense<sup>2</sup>STOP:  $I_t = 1$  if not treated in prior hour and if online classification is possible; =0 otherwise

Randomization occurs only if  $I_t=1$

- $A_t$ : Randomized treatment at time  $t$ 
  - Sense<sup>2</sup>STOP:  $A_t = 1$  if reminder is pushed to participant; =0 otherwise

# Stratified Micro-Randomized Trial

- $A_t$ : Randomized treatment at time  $t$ 
  - Sense<sup>2</sup>STOP:  $A_t = 1$  if reminder is pushed to participant; =0 otherwise
- $Y_{t,\Delta}$ : “Proximal” response is a known function of participant’s data within subsequent window of length  $\Delta$  times
  - Sense<sup>2</sup>STOP: fraction of time stressed in  $\Delta=60$  minutes

$$Y_{t,\Delta} = \Delta^{-1} \sum_{s=1}^{\Delta} 1[X_{t+s} = 1]$$

# Why Micro-Randomize?

- In  randomization ensures that we can assess causal effects of the reminder.
- Sequential randomization facilitates investigating:
  - Does the reminder vs. no reminder impact stress management in the near term?
  - Does this effect vary with time and/or current context?

# Why Stratify?

- Fraction of time points in one strata is low compared to other strata
  - Stratify the randomization to ensure sufficient treatment/no treatment in each strata.
- Sense<sup>2</sup>STOP:
  - On average 1 minute stressed for each 6 minutes not stressed

# Stratified Micro-Randomized Trial

- Generally there is a “soft” budget,  $\tilde{N}_x$ , for the number of treatments that can be provided over T times for each strata.
  - $E\left[\sum_{t=1}^T A_t 1_{X_t=x} I_t\right] \cong \tilde{N}_x$
  - Budget is usually due to participant burden concerns
- In  Sense<sup>2</sup> STOP
  - the budget is  $E\left[\sum_{t \in \text{day}} A_t 1_{X_t=x} I_t\right] \cong 1.5$ , for  $x=0,1$

# Optimization Criterion for Randomization Probabilities

Subject to the budget constraint

$$E \left[ \sum_{t \in \text{day}} A_t 1_{X_t=1} I_t \right] \cong 1.5$$

Minimize deviance from uniform randomization across all person-time points at which  $X_t = 1$ ,  $I_t = 1$ ,

- Minimize Kullback-Leibler divergence of randomization probabilities from uniform distribution.

# Randomization probabilities

- Given  $H_t = \{O_1, A_1, \dots, O_t\}$ ,  $X_t = x$  and  $I_t = 1$ , we deliver the treatment at time  $t$  with probability

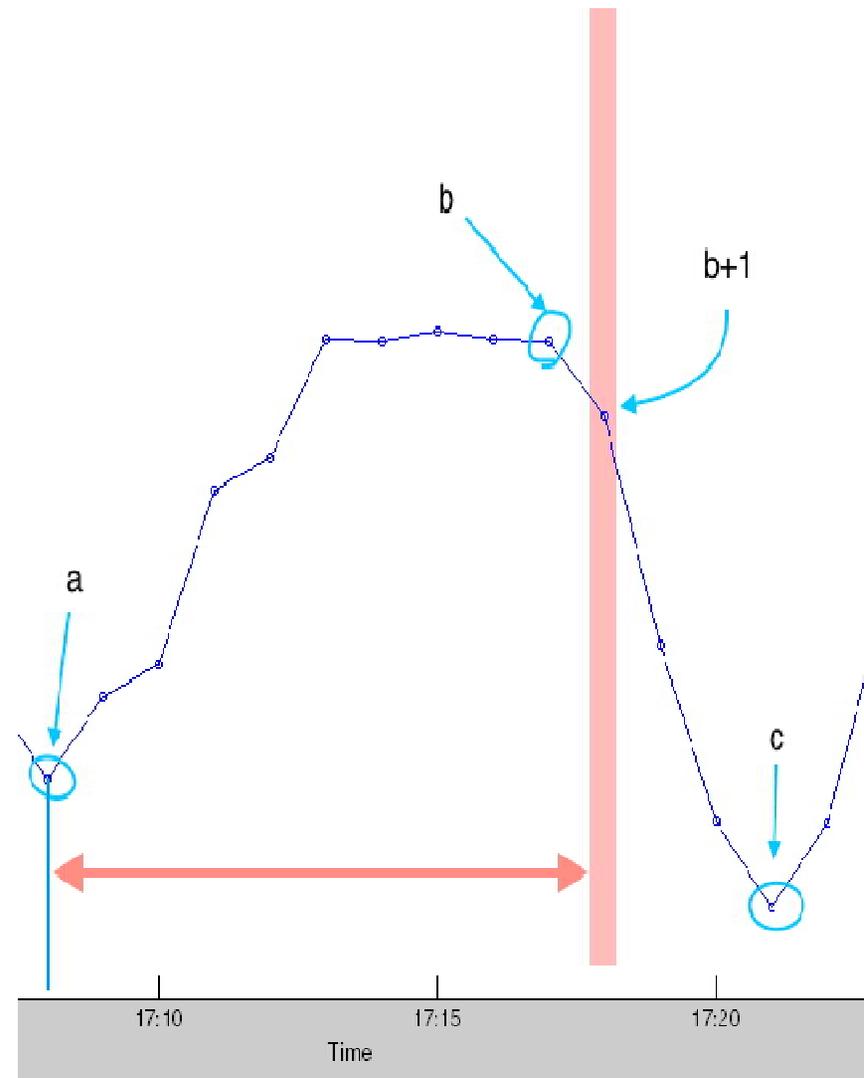
$$p_t(H_t) = \frac{\tilde{N}_x - C_{t,\lambda}(x)}{1 + g(x | H_t)}$$

- $\tilde{N}_x$  is desired average no. of treatments per day
- $C_{t,\lambda}(x)$  : soft version of the number of treatments that have already been delivered that day
- $g(x | H_t)$  : forecast of number of available decision points at level  $x$  remaining during day given data  $H_t$

# Forecast is based on a no-treatment-effect model

Forecast based on data collected in an observational, no treatment, smoking cessation study of 45 cigarette smokers wearing the same sensor suite

- For each episode type (i.e.,  $x \in \{0,1\}$ ), estimate the probability that the next episode will be a stress episode to form Markovian transition matrix
- For each episode type (i.e.,  $x \in \{0,1\}$ ), use a parametric model for the episode length





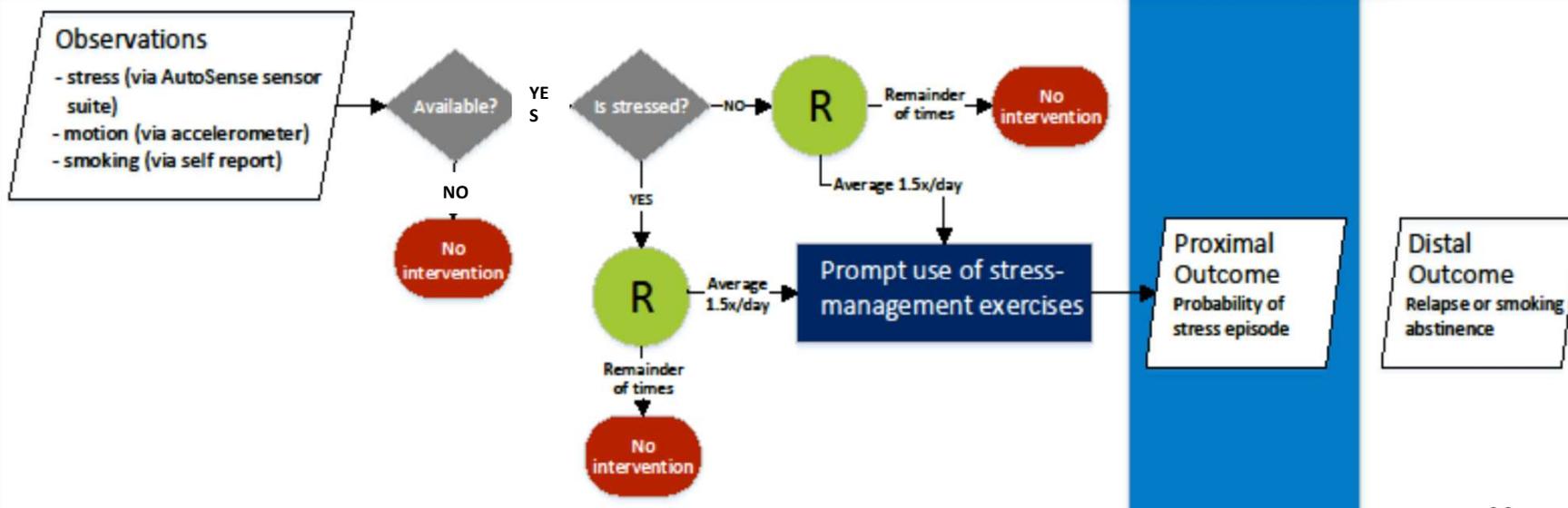
10 day study  
from  
Quit Date

## MRT for Stress Management in Newly Abstinent Smokers

Every minute of every day starting with quit date

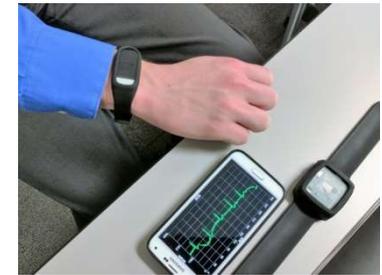
For two hours  
after  
intervention is  
delivered

Measured via  
EMA and  
puffMarker over  
10 days



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- Primary: Should the smartphone push a reminder to utilize app directed stress-management exercises when the user is stressed?
  - The reminder push notification should reduce near time stress compared to no reminder.
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View through the lens of Continual  
Learning/Experimentation

# To make English precise use potential outcomes

- $\bar{A}_t = \{A_1, \dots, A_t\}$  (random treatments);
- $\bar{a}_t = \{a_1, \dots, a_t\}$  (realizations of treatments)
- $Y_{t,\Delta}(\bar{a}_{t+\Delta-1})$  (one potential proximal response)  
Recall  $Y_{t,\Delta} = \Delta^{-1} \sum_{s=1}^{\Delta} 1[X_{t+s} = 1]$
- $I_t(\bar{a}_{t-1})$  (one potential availability indicator)
- $H_t(\bar{a}_{t-1})$  (one potential history vector)

# Treatment effect

Define the individual level effect as a contrast between **two excursions**:

$$Y_{t,\Delta}(\bar{A}_{t-1}, a_t = 1, a_{t+1} = 0, \dots, a_{t+\Delta-1} = 0) \\ - Y_{t,\Delta}(\bar{A}_{t-1}, a_t = 0, a_{t+1} = 0, \dots, a_{t+\Delta-1} = 0)$$

Causal

# Treatment effect

The individual level effect is a contrast between two excursions from the present course,  $\bar{A}_{t-1}$ :

$$Y_{t,\Delta}(\bar{A}_{t-1}, a_t = 1, a_{t+1} = 0, \dots, a_{t+\Delta-1} = 0) \\ - Y_{t,\Delta}(\bar{A}_{t-1}, a_t = 0, a_{t+1} = 0, \dots, a_{t+\Delta-1} = 0)$$

# Treatment effect

The individual level effect is a contrast between two excursions:

$$Y_{t,\Delta}(\bar{A}_{t-1}, 1, \bar{0}_{t+1:t+\Delta-1}) - Y_{t,\Delta}(\bar{A}_{t-1}, 0, \bar{0}_{t+1:t+\Delta-1})$$

Absent assumptions, individual level effect is not estimable

# Treatment effect

Absent strong assumptions, individual level effect is not estimable.....

Define  $\beta(t; x) =$

$$E \left[ \left( Y_{t,\Delta}(\bar{A}_{t-1}, 1, \bar{0}) - Y_{t,\Delta}(\bar{A}_{t-1}, 0, \bar{0}) \right) \mid I(\bar{A}_{t-1}) = 1, X_t(\bar{A}_{t-1}) = x \right]$$

$\beta(t; x)$ : causal, excursion effect at time  $t$  beginning in strata  $x$

# Marginal, Conditional & Causal

$\beta(t; x)$ : excursion effect at time  $t$  in strata  $x$

$$E \left[ \left( Y_{t,\Delta}(\bar{A}_{t-1}, 1, \bar{0}) - Y_{t,\Delta}(\bar{A}_{t-1}, 0, \bar{0}) \right) \mid I_t(\bar{A}_{t-1}) = 1, X_t(\bar{A}_{t-1}) = x \right]$$

- Effect is conditional on availability and in strata  $x$  at time  $t$ :  $I_t = 1, X_t = x$
- Effect is marginal over past data,  $H_t$
- Why are we focusing on contrasts between excursions?

# Expression for Treatment Effect

## $\beta(t; x)$

- The sequential randomization + randomization probabilities bounded away from 0, 1 imply that  $\beta(t; x)$  can be expressed in terms of the data distribution:

$$\begin{aligned} & E \left[ E \left[ \left( \prod_{j=t+1}^{t+\Delta-1} \frac{\mathbf{1}[A_j = 0]}{p_j(H_j)^{A_j} (1 - p_j(H_j))^{1-A_j}} \right) Y_{t,\Delta} \mid A_t = 1, H_t \right] \mid I_t = 1, X_t = x \right] \\ & - E \left[ E \left[ \left( \prod_{j=t+1}^{t+\Delta-1} \frac{\mathbf{1}[A_j = 0]}{p_j(H_j)^{A_j} (1 - p_j(H_j))^{1-A_j}} \right) Y_{t,\Delta} \mid A_t = 0, H_t \right] \mid I_t = 1, X_t = x \right] \end{aligned}$$

- $p_j(H_j)$  is randomization probability

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# Primary Hypothesis



- Consider decision points at which the individual is classified as stressed.
- We aim to contrast two treatment “excursions:”
  - (A) treatment now, no further treatment over subsequent 1 hour versus
  - (B) no treatment now, no further treatment over subsequent 1 hour
- Proximal response is fraction of time stressed over subsequent 1 hour.

# Test Statistic

- Primary Hypothesis Test:

$$H_0: \{\beta(t; x)\}_{t=1, \dots, T, x=0,1} = 0$$

(e.g. is there anything going on here?!) )

- Construct test statistic to target particular alternatives; consider alternatives of the form:
  - $\beta(t; x) = f_t(x)' \beta$  where  $f_t(x) \in R^q$  is feature vector depending on  $t$  and  $x$

# Test Statistic

Primary Hypothesis

$$H_0: \{\beta(t; x)\}_{t=1, \dots, T, x=0,1} = 0$$

Trade off bias and power via low dimensional alternatives.

--- capture a decreasing effect with day in study in a coarse manner:

$$H_1: \beta(t; x) = f_t(x)' \beta$$

- $f_t(x)' = (x, xd_t, xd_t^2, (1-x), (1-x)d_t, (1-x)d_t^2)$   
or
- $f_t(x)' = (x, xd_t, (1-x), (1-x)d_t)$

$d_t$  is day in study at decision point  $t$

# Control variables

Used to reduce the variance/increase power

- Control variables will be used in a working model for the average proximal response:

$$E(.5Y_{t,\Delta}(\bar{A}_{t-1}, 1, \bar{0}) + .5Y_{t,\Delta}(\bar{A}_{t-1}, 0, \bar{0}) | H_t, I_t = 1) = g_t(H_t)' \alpha$$

for  $g_t(H_t)$ , a vector of summaries of prior data.

- The test statistic/Type 1 error rate will be robust to the mis-specification of this working model.

# Weighted-centered least squares criteria

To construct the test statistic calculate

$$\arg \min_{\alpha, \beta} P_n \left[ \sum_{t=1}^T I_t w_t(H_{t+\Delta-1}) (Y_{t,\Delta} - g_t(H_t)' \alpha - (A_t - .5) f_t(X_t)' \beta)^2 \right]$$

- $P_n$  means average over  $n$  participants' data

- $w_t(H_{t+\Delta-1}) = \frac{\prod_{s=1}^{\Delta-1} \mathbf{1}[A_{t+s}=0]}{\prod_{s=0}^{\Delta-1} p_{t+s}^{A_{t+s}} (1-p_{t+s})^{1-A_{t+s}}}$

- $p_{t+s} = p_{t+s}(H_{t+s})$  is the randomization probability used in the study

# Estimand for Test Statistic

$\hat{\beta}$  is an estimator of

$$\beta^* = \arg \min_{\beta} E \left[ \sum_{t=1}^T I_t (\beta(t; X_t) - f_t(X_t)' \beta)^2 \right]$$

$\beta(t; x)$  is time varying causal excursion effect.

$f_t(x) \in R^q$  is feature vector depending on  $t$  and  $x$

# Test Statistic

To construct the test statistic calculate

$$\arg \min_{\alpha, \beta} P_n \left[ \sum_{t=1}^T I_t w_{ct}(H_{t+\Delta-1}) (Y_{t,\Delta} - g_t(H_t)' \alpha - (A_t - .5) f_t(X_t)' \beta)^2 \right]$$

This results in  $\hat{\beta}$ .

We also construct an estimator of the standard error of  $\sqrt{n} \hat{\beta}$  ( $n$  is the sample size):  $\hat{\Sigma}$  using small sample corrections

This standard error must allow for unspecified correlation across time in the  $Y_{t,\Delta}$

# Hypothesis test

The rejection region for the test

$$H_0: \{\beta(t; x)\}_{t=1, \dots, T, x=0,1} = 0$$

is:

$$\left\{ n\hat{\beta}'\hat{\Sigma}^{-1}\hat{\beta} > \frac{q(n - (q' + 1))}{n - (q' + q)} F_{q, n - (q' + q); 0}^{-1}(1 - \alpha_0) \right\}$$

where  $\alpha_0$  is the Type I error rate,  $q$  is the size of  $f_t(x)$  and  $q'$  is the size of the controls,  $g_t(H_t)$

Stand on the shoulders of the scientists who came before you!

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# Comments on Sample Size



- Type I error = 0.05; Power = 0.80
- Targeted Alternative:  $\beta(t; x) = f_t(x)' \beta$
- Working model for average proximal response  $g_t(H_t)' \alpha$ 
  - where  $f_t(x)' = g_t(x)' = (x, x d_t, x d_t^2, (1 - x), (1 - x) d_t, (1 - x) d_t^2)$

## Results:

Table 1: Estimated sample size,  $n$ , and achieved power.

	Sample size	Power
$\beta = 0.030$	50	80.6
$\bar{\beta} = 0.025$	67	80.7
$\bar{\beta} = 0.020$	127	80.6

# Intuition Behind the Sample Sizes

- Low dimensional alternative:  $\uparrow$  power and  $\downarrow$  sample size--test is able to use within participant contrasts
- Small effect sizes:  $\downarrow$  power and  $\uparrow$  sample size
- Short study with small no of treatments per day:  $\downarrow$  power and  $\uparrow$  sample size

# Continual Learning/Experimentation

- Where is all of this going?  
A mobile health intervention that incorporates continual optimization via sequential experimentation.
- Treatment design and experimental design are intertwined when the goal is to continually learn and optimize.
- Algorithms are not only *\*\*part\*\** of the experimental design they are treatment components in the mobile health intervention.

# Cole Porter's "Experiment"

## (Verse)

Before you leave these portals  
To meet less fortunate mortals  
There's just one final message  
I would give to you

You all have learned reliance  
On the sacred teachings of  
science  
So I hope, through life, you  
never will decline  
In spite of Philistine defiance  
To do what all good scientists  
do

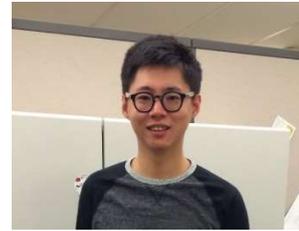
## (Chorus)

Experiment, make it your motto day  
and night  
Experiment and it will lead you to  
the light  
The apple on the top of the tree is  
never too high to achieve  
So take an example from Eve  
Experiment

Be curious  
Though interfering friends may  
frown  
Get furious  
At each attempt to hold you down

If this advice you always employ  
The future can offer you infinite joy  
And merriment  
Experiment  
And you'll see

# Collaborators!



# Continual Mobile Intervention Optimization

Is not mundane!!

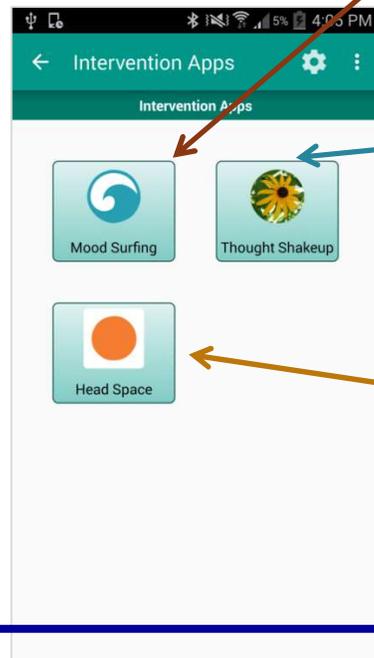
Exploration produces variation

- used by us to learn and optimize
- within person exploration → within person variation
  - can reduce user habituation, boredom
  - can increase user novelty, positive arousal
  - can provide variable reinforcement
  - enables dynamic, within person, learning

# Intervention Push is a Reminder to Access Stress Management Apps:

## Apps employ

- Evidence-based exercises to manage stress
- Take about 3-5 minutes to practice
- Developed and refined based on input from experts and users



### Mood Surfing:

- 3 exercises
- Grounded in ACT
- Target cognitive defusion
- Experts: K. Witkiewitz, I. Yovel.
- Literacy level editor: A. Applegate
- HCI: M. Sharmin; Programmer: M. Hossain

### Thought Shakeup

- Grounded in CBT
- Target cognitive restructuring
- Expert: I. Yovel.
- Literacy level editor: A. Applegate
- HCI: M. Sharmin; Programmer: M. Hossain

### Head Space

- Grounded in ACT
- Mediation / Mindfulness
- Consistently rated as one of the best 5 commercial mediation apps
- Permission for free use in the trial