Matched Learning with Electronic Health Records for Personalized Medicine

Yuanjia Wang, Ph.D.

Department of Biostatistics, Mailman School of Public Health
Columbia University
& Division of Biostatistics, New York State Psychiatric Institute
President’s Council of Advisors on Science and Technology (PCAST) defines personalized medicine as: “the tailoring of medical treatment to the individual characteristics of each patient”.

Why personalized medicine?

- Patient response rate is inadequate (e.g., MDD 30-35%, Murphy 2007; relapse rate 50%, APA 2000)
- Presence of substantial patient heterogeneity (Trivedi 2006)

**Individualized treatment rules (ITRs):** decision rules mapping patient’s pre-treatment state variables (e.g., intermediate outcomes, biomarker, clinical measure) into the space of possible treatment decisions (e.g., switch to an alternative treatment).
Example 1: Healing Emotion After Loss (HEAL) trial for complicated grief

**ITR:** Administer clinical management as the initial treatment; if a patient does not respond within 8 weeks then offer an anti-depressant (Citalopram).

**Standard:** Treating all patients with clinical management
Tailoring Treatments Using ITR

Example 2: SBP management strategy tailored to individual patient physiology

**ITR:** Patients with high risk of postoperative kidney injury, SBP targeted to remain within 10% of the reference using a continuous infusion of norepinephrine.

**Standard:** Treating SBP less than 80 mm Hg
Constructing ITRs

**Goal**: maximize the value function in a target population when implementing ITRs.

Data available to construct ITRs

- biological measures (e.g., neuroimaging biomarkers), clinical and behavioral measures

*Original Investigation*

**Toward a Neuroimaging Treatment Selection Biomarker for Major Depressive Disorder**

Callie L. McGrath, BA; Mary E. Kelley, PhD; Paul E. Holtzheimer III, MD; Boadie W. Dunlop, MD; W. Edward Craighead, PhD; Alexandre R. Franco, PhD; R. Cameron Craddock, PhD; Helen S. Mayberg, MD

- genomic measures, electronic health records (EHRs)

*Defining a comprehensive verotype using electronic health records for personalized medicine*

Mary Regina Boland, George Hripcsak, Yufeng Shen, Wendy K Chung, Chunhua Weng

*Journal of the American Medical Informatics Association*, Volume 20, Issue e2, 1 December 2013, Pages e232–
Challenges: tailoring variables unknown, a large number of (structured) candidate variables, each may have a small effect

- In clinical psychiatry, machine learning largely is restricted to neuroimaging research (e.g., classifying diagnosis of mental disorders) until recently:

  Cross-trial prediction of treatment outcome in depression: a machine learning approach

  Adam Mourad Chekroud, Ryan Joseph Zotti, Zarrar Shehzad, Ralitza Gueorgieva, Marcia K Johnson, Madhukar H Trivedi, Tyrone D Cannon, John Harrison Krystal, Philip Robert Corlett

  Summary
  Background Antidepressant treatment efficacy is low, but might be improved by matching patients to interventions. At present, clinicians have no empirically validated mechanisms to assess whether a patient with depression will respond to a specific antidepressant. We aimed to develop an algorithm to assess whether patients will achieve symptomatic remission from a 12-week course of citalopram.

  For learning ITR, the goal of optimizing the value function of an ITR coincides with the task-driven/prediction-driven nature of machine learning tools.
Existing Methods for Personalized Medicine and Optimizing ITR

- Q-Learning (Qian and Murphy 2011; Nahum-Shani et al. 2012)
- O-Learning (Zhao et al. 2012, 2015; Liu et al. 2018)
- Virtue Twins (Foster et al. 2011)
- Interaction Trees (Su et al. 2009)
- Qualitative interaction trees (Dusseldorp and Van Mechelen 2014)
- Benefit-risk learning (Wang et al. 2018): identifies ITRs for type 2 diabetes (T2D) patients to maximize glycemic control while considering the risk outcomes.

Most of the existing work aims at randomized controlled trials (RCTs).
RCT versus Real World Clinical Practices

RCT characteristics:

▶ Stringent inclusion/exclusion criteria (e.g., excluding comorbidities): 80% of MDD patients excluded due to failure to meet one or more inclusion criteria (Zimmerman et al. 2002)

▶ Strict standardization of treatment procedures (e.g., treatment protocols based on manuals)

▶ Broad range of real-world medication use patterns not captured by RCTs were observed in EHRs (Hripcsak et al., 2016)

▶ Lack of long term outcomes or adverse events

▶ High internal validity but may lack generalizability

EHR characteristics:

▶ Greater variance in outcomes in naturalistic settings

▶ More modest treatment effect sizes (Gibbons et al. 2010)
Shifting Towards Real World Data
Real World Setting: Electronic Health Records (EHRs)

Figure: Comparing 1,761 T2D clinical trials and the EHRs of 26,120 patients with T2D who visited CUMC/NYP (Weng et al. 2011).

Columbia University Medical Center/New-York Presbyterian Hospital contains 20 years health information on 4.5 million patients; Provides infrastructure for the 1-million volunteer Precision Medicine Initiative Cohort Program.
Challenges with Analyzing EHRs

Studies of CUMC EHR data quality assessed completeness, correctness, concordance, plausibility and timelyness (Weiskopf et al. 2013).

Need to address statistical challenges (e.g., confounding bias, selection bias; Hripcsak and Albers 2013).
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**Goal**: learn $\mathcal{D}(H)$ that maximizes the value function

$$V(\mathcal{D}) = E_{\mathcal{D}}(Y) = E \left( \frac{Y \mathbb{1}(A = \mathcal{D}(H))}{P(A|H)} \right)$$

$Y$: post-treatment outcome (e.g., symptom reduction; change in HbA1c); $A \in \{-1, 1\}$: two treatment options; $H$: patient’s pre-treatment feature variables; ITR $\mathcal{D}(H)$: mapping from $H$ to $\{-1, 1\}$.

Use inverse probability weighting (IPW) of propensity scores (PS) to handle confounding bias.

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Heuristics of the value function:

Maximize the value  
\[ E \left[ I(A = D(X)) \frac{R}{P(A|X)} \right] \]

Minimize the risk  
\[ E \left[ I(A \neq D(X)) \frac{R}{P(A|X)} \right] \]

- Subjects with large response: more likely \( D(X) \) would be the same as the assigned treatment.
- Subjects with little response: more likely \( D(X) \) would be the opposite of the assigned treatment.

Optimization reduces to a weighted classification problem with outcome as weights and minimizes an empirical risk function.

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Inverse Weighting and Matching

Existing work expresses the value function through IPW of PS.

- IPW needs a model for PS, unstable with small weights
- IPW ensures similar distribution of confounders at the treatment group level.

Alternatively, matching is often used:

- Direct control over achieving covariates balance, useful for EHR applications.
- Matching at subgroup level, useful for learning ITRs.
- Matching approaches require less model specification and can be nonparametric.
- Matching by prognostic scores can improve efficiency.
Matched Learning (M-Learning)

Matching-based value function:

\[ V_n(D; g) = \sum_{i=1}^{n} |M_i|^{-1} \sum_{j \in M_i} \left\{ I(Y_j \geq Y_i, D(H_i) = -A_i) + I(Y_j \leq Y_i, D(H_i) = A_i) \right\} g(|Y_j - Y_i|) \]

\( M_i \): matching set; \( g(\cdot) \): monotone increasing function to weight different matched pairs.

Heuristics of M-learning value function:

- Two subjects who are matched on confounders and receive different treatments, the treatment with a larger clinical outcome more likely to be optimal.

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Matched Learning (M-learning)

Matching-based value function:

\[
V_n(D; g) = \sum_{i=1}^{n} |\mathcal{M}_i|^{-1} \sum_{j \in \mathcal{M}_i} \left\{ I(Y_j \geq Y_i, D(H_i) = -A_i) + I(Y_j \leq Y_i, D(H_i) = A_i) \right\} g(|Y_j - Y_i|)
\]

Heuristics of M-learning value function (continued):

- Allow subjects to be matched with themselves, replace \(Y_j\) by predicted average outcome across treatments and use \(1/PS\) as weights, M-learning reduces to (augmented) O-learning.

- M-learning compares individual outcomes when treatment assignment is approximately “random” given \(H_i\) but received treatments are opposite.

- Accommodates discrete, ordinal, and continuous outcomes.

- More robust to error in outcomes due to using the relative ranking. Useful for EHR applications.
Maximizing matching-based value function is equivalent to minimizing empirical risk function

\[ V_n(f; g) = n^{-1} \sum_{i=1}^{n} |\mathcal{M}_i|^{-1} \sum_{j \in \mathcal{M}_i} I(f(H_i)A_i \text{sign}(R_i - R_j) \leq 0)g(|R_i - R_j|) \]

where \( \mathcal{D}(H) = \text{sign}(f(H)) \).

Learning ITR:

- Replacing zero-one loss in the empirical risk function by a surrogate loss
- Computational algorithm: under hinge-loss implemented by weighted SVM with paired observations
- Other classification tools can be used
Fisher consistency can be established

\[ V_n(f, g) \rightarrow V(f, g), \]

where the minimizer of \( V(f, g) \), denoted by \( f^* \), satisfies

\[ \text{sign}(f^*(h)) = E(Y|A = 1, H = h) - E(Y|A = -1, H = h). \]

Residualized M-learning (replace \( Y_i \) by \( Y_i - s(H_i) \)) improves efficiency.

Additional matching by prognostic scores further improves efficiency (Antonelli et al. 2016).
Simulation Results
Simulation Designs

We considered 3 simulation designs:

1. Propensity score model is correctly specified
2. Propensity score model is misspecified
3. Presence of unmeasured confounder (treatment assignment depends on potential outcomes and latent tailoring variable).

Considered 1:1 nearest neighbor matching (NNM) with replacement using Euclidean distance. The procedures repeated 100 times using 3-fold CV tuning and tested on a large independent testing set.
Simulation Designs

Outcome model:

- $S_1: R = 2H_3 - H_4 + A(H_1 - H_2) + 6\text{sign}(H_1) + N(0, 1)$;
- $S_2: R = 2H_3 - H_4 + A(H_1 - H_2 + X) + 6\text{sign}(H_1) + N(0, 1)$;
- $S_3: R = 1 + 2H_1 + H_2 + 0.5H_3 + A(H_2 + H_1^2 + X - 1) + 6\text{sign}(H_1) + N(0, 1)$;

Treatment assignment model:

- Setting a: $P(A = 1|H) = \text{expit}(1 + 2H_1 + H_2)$
- Setting b: $P(A = 1|H) = \text{expit}(1 + \exp(H_2))$.
- Setting c: $P(A = 1|H, X) = \text{expit}(1 + R^{(-1)} - R^{(1)} + 2X + H_1)$ and $X$ is an unmeasured confounder and $R^{(-1)}, R^{(1)}$ are potential outcomes under each treatment.
Simulations: PS Correctly Specified or Misspecified

Figure: PS model correct (a) and PS model incorrect (b) (outcome S1, optimal value= 1.2)

M-learning not affected by PS. Matching by prognostic scores enhances the performance of M-learning.

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Presence of Unmeasured Confounders

Figure: Treatment model depends on potential outcomes (linear boundary, S2, optimal value=1.37) and setting 3 (nonlinear boundary, S3, optimal value=2.61)

None of methods can recover optimal value; M-learning closest to optimal in nonlinear setting.

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Applications to EHRs
Recommended first-line treatment: metformin (MET) (Group et al. 2008; NEJM).

Most patients with T2D cannot maintain adequate long-term glycemic control using MET and will need to progress to a second-line agent.

No consensus on the best second-line treatment (American Diabetes Association recommends sulfonylureas [SFU], basal insulin, or meglitinide).

Estimate ITR for second-line therapy: MET + insulin vs MET + SFU.
EHRs: CUMC CDW adults age 18 or older, with at least one T2D ICD-9 diagnosis code between 1/1/2008 and 12/31/2012

Figure: New User Design of Ascertaining T2D Patient EHRs

First-line treatment initiation (Metformin) <= 12 months post-index HbA1c outcomes

Baseline period

Before 1st line treatment initiation

Index Date: exposure to Second-line treatments (insulin or 2nd line OHA),

Matches time-varying confounding variables and captures early outcomes.

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Met + insulin: $n = 292$; Met + SFU: $n = 448$; about 8,000 features
Detailed Information Captured in CDW EHRs

Figure: Medication prescription events of T2D patients*

Figure: Sunburst plot of treatment sequences of T2D patients*

*: Layer corresponds to stage of treatment, patients with 2-3 stages were shown

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Figure: HbA1c and Glucose Measurement Patterns

Metformin -> Insulin

Metformin -> Glipizide

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Group 1: moderately ill; regular, frequent documentation pattern; more co-morbidity and non-diabetic medications; (2) moderately ill, less-frequent measurements, less co-morbidity and medications; (3) more severe, faster progression; less measurements, lower HDL, higher LDL.
Address Statistical Challenges

- Confounding bias: matching based on measurement patterns, ICD counts, and lab tests with Mahalanobis distance as similarity measure.
- Selection bias: inverse probability weighting (logistic regression model to estimate probability of a subject having any post index date measure)
- Prognostic scores included to improve efficiency
- Features for learning ITRs from five domains
- Outcome: HbA1c at 6 month post second-line treatment
Construct ITRs to Optimize Glycemic Control

Figure: Empirical Value Function of HbA1c in Low (baseline HbA1c < 8.5%) and High (≥8.5%) Group With 100 2-fold CVs

- Top features: rate of change of BMI, baseline glucose and LDL, co-medication count, patient cluster membership.
- In high group, 81% of those received MET+SFU predicted to be optimal vs 16% of those MET+insulin.
- In low group, 66% of those received MET+SFU predicted to be optimal vs 26% in MET+insulin.
Construct ITRs to Minimize Co-morbidity

Figure: Empirical Value Function of Co-morbidity Counts (essential hypertension, hyperlipidemia, hypercholesterolemia) in Low (baseline HbA1c < 8.5%) and High (≥8.5%) Group

- Top features: baseline HbA1c and glucose, rate of change of glucose, cluster membership.
- In high baseline group, 38% received MET+SFU predicted to be optimal vs 70% received MET+insulin.
- In low baseline group, 73% received MET+SFU predicted to be optimal vs 29% received MET+insulin.
Final Remarks
Conclusions

Propose matching-based M-learning as a machine learning technique to optimize ITRs using EHRs:

- Feasible to use EHRs for personalized medicine research.
- Real world treatment decision is a complex process.

Future directions:

- Better feature extraction (e.g., jointly model lab measurement patterns) to adjust for confounding and selection bias
- Dynamic multi-stage decisions
- Integrate information from multiple sources (e.g., other EHR databases; RCT and EHRs)
- Precision medicine: incorporates EHRs and genomic data, environmental risk factors, social and behavioral measures.
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