Machine Learning Foundations & Methods for Precision (Medicine and Healthcare)

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Introduction

A $3 Trillion Challenge to Computational Scientists: Transforming Healthcare Delivery

Suchi Saria, Johns Hopkins University

Healthcare spending in the US is nearing $3 trillion per year, but in spite of this expenditure, the US is outpaced by most developed countries in terms of health and quality of life outcomes—for example, it ranks 36th internationally in life expectancy. The share of health spending in its gross domestic product has increased sharply, from 5 percent of GDP in 1960 to more than 17 percent today, a rate of increase that’s widely believed to be unsustainable.

Policy and regulatory reform have important roles to play in addressing these challenges. Yet one of the largest underexplored avenues is the better use of information derived from the vast amount of health data now being collected in digital format. I believe that one of the most significant gaps from paper records that weren’t amenable to retrospective, automated analyses. The Health Information Technology for Economic and Clinical Health (HITECH) Act, a program that was part of the American Recovery and Reinvestment Act of 2009, incentivized the adoption of Electronic Health Records (EHRs) to encourage the shift from paper to digital records. That program has made more than $15.5 billion available to hospitals and healthcare professionals conditioned on their meeting certain EHR benchmarks for so-called “meaningful use.” It’s one of the largest investments in healthcare infrastructure ever made by the federal government.

A survey by the American Hospital Association showed that adoption of EHRs has doubled from 2009 to 2011. Today, much of an individual’s health data—demographic, clinical, laboratory, and imaging information—is stored in digital formats.
Electronic Health Records

- **Genomic data**
- **Sensors & Devices**
- **Administrative Claims**
- **Continuous physiologic measurements**
- **Progress notes**
- **Imaging Data**
- **Discrete Events: Laboratory**
- **Interventions: Medicines, Procedures**

Related images and graphs illustrating various aspects of electronic health records.
Scope

• Focus of this talk is on **Precision and Personalized Medicine**

• Intended audience: Machine learners
  • Relevant to anyone with interest in personalization
  • Domains: education, recommender systems, retail
Based on a *coarse* set of characteristics, define a population $P$.

- Conduct trials to determine Intervention A vs B.
- Define guideline to assign intervention to $P$.

*Often referred to as population models. Does not adequately account for individual-specific variability.*
• **Example**: managing high blood pressure in adults

> James, Oparil, Carter, et al. 2014

• “Recommendation 8”:
  • In population ≥18 with chronic kidney disease (CKD)
  • Initial anti-hypertensive treatment should include:
    • (1) ACEI or (2) ARB
  • Use for all CKD patients regardless of race or diabetes status

(1) **Indications are coarse.**

(2) **Not relevant to many** in the population — people with multiple diseases or allergies.
Systemic autoimmune disease
Main symptom: skin fibrosis
Affects many visceral organs—lungs, heart, GI tract, kidney, vasculature, and muscles

Affects 300K individuals; 80 other autoimmune diseases — lupus, multiple sclerosis, diabetes, Crohn’s — many of which are systemic & highly multiphenotypic.
• Will this individual continue to decline?
• Should we administer immunosuppressants, which can be toxic?
The need for “precision”/“personalization”

Sources of variation:
- The profile of symptoms over time can vary
- Response to treatments can vary

(1) Characterize diseases more precisely? Is diabetes one disease or many diseases?
(2) Moving away from coarse rules to algorithms for generating targeted treatment plans.
Problem Setting

Sequential Data: No Control over Data Collection Process

• (1) Off-line learning:
  • Learn from data about other individuals to generalize to a given individual

• (2) Online learning:
  • Learn as we collect new data about a given individual from repeated measurements

Learning with Control over Data Collection

• (3) Reinforcement Learning:
  • Explore to improve model learning
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• Key takeaways:
  • Provide computational strategies for personalization
  • Describe example data
  • Introduce concrete applications
  • Give intuition into why approach it one way vs another
  • Throughout make connections to literature in sub-areas of machine learning, reinforcement learning, causal inference, and informatics
Overview

• Part 1—Setting up the problem of Individualization
  • Example using a chronic disease
  • Simple setting: No Treatment Effects
  • Bayesian Hierarchical Framework for Individualizing Predictions
  • Key ideas: Transfer learning, Multilevel modeling

• Part 2—Estimating Treatment Effects & Individualized Treatment Effects
  • Example using inpatient data
  • Learning from observational data
  • Key ideas: Potential Outcomes, Causal Inference for Bias Adjustment, BNP

• Part 3—Causal Predictions
  • Relax assumption from Part 1 about no treatment effects
  • Discuss predictions that are robust to changes in physician practice behavior

• Part 4—From Predictions to Treatment Rules
  • Key ideas: Q-learning, Dynamic Treatment Regimes
  • Connections to Reinforcement Learning
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Individualization and why do we need it?

Develop a predictive model by using regression on the observed risk factors

\[ y = f (\text{age, gender, baseline test values}) \]
Population Precision medicine

Develop a predictive model by using regression on the observed risk factors

\[ y = f(\text{age}, \text{gender}, \text{baseline test values}, \ldots) \]

Expand the set of covariates to include high-dimensional molecular measurements

- Collins and Varmus, 2015
- Ziegler et al. 2012
- Shipp et al. 2002
Population Precision medicine

Develop a predictive model by using regression on the observed risk factors

\[ y = f (\text{age, gender, baseline test values, ...}) \]

Expand the set of covariates to include high-dimensional molecular measurements

Is there any other structure we can capture?

- Shipp et al. 2002
- Ziegler et al. 2012
- Collins and Varmus, 2015
**Data & Problem Motivation**

- **Functional markers collected to track organ health**

<table>
<thead>
<tr>
<th>Years Since Diagnosis</th>
<th>tss</th>
<th>pfvc</th>
<th>pdlco</th>
<th>rvsp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td><img src="chart1" alt="" /></td>
<td><img src="chart2" alt="" /></td>
<td><img src="chart3" alt="" /></td>
<td><img src="chart4" alt="" /></td>
</tr>
<tr>
<td>Lung</td>
<td><img src="chart1" alt="" /></td>
<td><img src="chart2" alt="" /></td>
<td><img src="chart3" alt="" /></td>
<td><img src="chart4" alt="" /></td>
</tr>
<tr>
<td>Pulmonary Vasculature</td>
<td><img src="chart1" alt="" /></td>
<td><img src="chart2" alt="" /></td>
<td><img src="chart3" alt="" /></td>
<td><img src="chart4" alt="" /></td>
</tr>
<tr>
<td>Heart</td>
<td><img src="chart1" alt="" /></td>
<td><img src="chart2" alt="" /></td>
<td><img src="chart3" alt="" /></td>
<td><img src="chart4" alt="" /></td>
</tr>
</tbody>
</table>

**Medication**
- Prednisone
- Methotrex
- Cyclophosphamide Cytoxan
Data & Problem Motivation

- Functional markers collected to track organ health
Predicting Disease Trajectories

Function valued-regression
\[ y = f (\text{age, gender, baseline test values, } [\phi_1(t), \ldots, \phi_d(t)]) \]

Expand the set of covariates to include non-linear functions of time
Predicting Disease Trajectories

Function valued-regression
\[ y = f(\text{age, gender, baseline test values, ...}) \]

**BUT**
this assumes that sources of heterogeneity across individuals entirely explained away by observed factors.

Many factors leading to differences in trajectory may be **unobserved** (e.g., difference in genetic mutations, athleticism, lifestyle)

- Account for heterogeneity in disease course due to both observed and latent factors
Transfer information from others to refine estimates for a given individual.

- #1 Specify Latent Variable Models to make inferences about latent (individual-specific) sources of heterogeneity
- #2 Learn the transfer hierarchy — i.e. whom to transfer from and what to transfer?
- #3 Bayesian formulation to prevent overfitting and learn as new data are collected on the individual
A Gaussian process (GP) is a collection of random variables, any finite number of which have a joint Gaussian distribution.

\[
\begin{align*}
  f(x) &\sim \mathcal{GP}(m(x), k(x, x')) \\
  m(x) &= \mathbb{E}[f(x)] \\
  k(x, x') &= \mathbb{E}[(f(x) - m(x))(f(x') - m(x'))]
\end{align*}
\]

\[
\begin{align*}
f_*|X_*, X, f &\sim \mathcal{N}(K(X_*, X)K(X, X)^{-1}f, \\
K(X_*, X_*) - K(X_*, X)K(X, X)^{-1}K(X, X_*) )
\end{align*}
\]
A Gaussian process (GP) is a collection of random variables, any finite number of which have a joint Gaussian distribution.

\[ f(x) \sim \mathcal{GP}(m(x), k(x, x')) , \]
\[ m(x) = \mathbb{E}[f(x)] , \]
\[ k(x, x') = \mathbb{E}[(f(x) - m(x))(f(x') - m(x'))] \]

\[ f_\ast|X_\ast, X, f \sim \mathcal{N}(K(X_\ast, X)K(X, X)^{-1}f, \]
\[ K(X_\ast, X_\ast) - K(X_\ast, X)K(X, X)^{-1}K(X, X_\ast)) \]

Rasmussen and Williams, 2006

http://www.slideshare.net/maushard/skin-manifestations-of-scleroderma-by-dr-lorinda-chung-md

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**Subtyping research in other diseases:**

**Autism:** [State and Sestan, 2012](#)  **Doshi-Velez et al., 2014**  **Parkinson’s:** [Lewis et al. 2005](#)

**Cardiovascular disease:** [De Keulenaer and Brutsaert, 2009](#)  **Asthma:** [Anderson 2008](#)
Latent Subpopulation Structure

- Two different subpopulations:
  - Subtype 1: Decliners who stabilize
  - Subtype 2: Those who improve over time

- Can we learn or make inferences about this systematic deviation as we observe more data about this individual?
Can we learn or make inferences about this systematic deviation as we observe more data about this individual?
Bayesian Formulation for Disease Trajectories

Function valued-regression
\( f(\text{age}, \text{gender}, \text{baseline test values}, \ldots) \)

\[ y_{ij}, z_i, b_i, f_i \sim \mathcal{N} \left( \Phi_p(t_{ij})^\top \Lambda \bar{x}_i, \sigma^2 \right) \]

Ramsay and Silverman 2005
Accounting for Latent Sources of Heterogeneity

Sub-pop structure

\[ y_{ij} | z_i, b_i, f_i \sim N \left( \Phi_p(t_{ij})^\top \Lambda \bar{x}_i + \Phi_z(t_{ij})^\top \beta z_i, \sigma^2 \right) \]

\( z_i \) indexes a given subpopulation
Accounting for Latent Sources of Heterogeneity

Sub-type 1

Sub-type 2

Sub-pop structure

Individual-specific adjustments

\[
\begin{align*}
&y_{ij}, z_i, b_i, f_i \sim \mathcal{N}_n \left( \Phi_p(t_{ij})^\top \Lambda \bar{x}_i + \Phi_z(t_{ij})^\top \beta z_i + \Phi_\ell(t_{ij})^\top b_i, \sigma^2 \right) \\
&\quad \text{(A) population} \quad \text{(B) subpopulation} \quad \text{(C) ind. long-term}
\end{align*}
\]

\( b_i \) parameters specifying individual-specific adjustments
Treated as random effects
Accounting for Latent Sources of Heterogeneity

Sub-type 1

Sub-type 2

Sub-pop structure

Individual-specific adjustments

$pFVC$

explains remaining noise sources

\[ y_{ij} \mid \bar{x}_{ip}, z_i, b_i \sim \mathcal{N} \left( \Phi_p(t_{ij})^\top \Lambda \bar{x}_{ip} + \Phi_z(t_{ij})^\top \beta_{z_i} + \Phi_\ell(t_{ij})^\top \beta_i + f_i(t_{ij}), \sigma^2 \right) \]

Schulam, Saria, 2015
Accounting for Latent Sources of Heterogeneity

Subtype 1

Subtype 2

Sub-pop structure

Individual-specific adjustments

Reminder: Only means are shown. Uncertainty bands not shown

\[ y_{ij} | \tilde{x}_{ip}, z_i, b_i \sim \mathcal{N} \left( \begin{array}{c} \Phi_p(t_{ij})^\top \Lambda \tilde{x}_{ip} \\ \Phi_z(t_{ij})^\top \beta_{z_i} \\ \Phi_\ell(t_{ij})^\top b_i \\ f_i(t_{ij}) \end{array} \right), \sigma^2 \]

(A) population (B) subpopulation (C) individual (D) structured noise

Lawrence, 2004

Schulam, Saria, 2015
Use hierarchical Bayes to allow transfer at multiple resolutions. Parameters use different subsets of the data:

- **Population trajectory**: data from all individuals
- **Subtype mean trajectories**: data from subgroups of similar individuals
- **Individual adjustments**: repeated measurements on the given individual
- **Transient adjustments**: trends over short periods of time

\[
y_{ij}|\bar{x}_{ip}, z_i, b_i \sim N \left( \begin{array}{c} \Phi_p(t_{ij})^T \Lambda \bar{x}_{ip} + \Phi_z(t_{ij})^T \beta_{zi} + \Phi_\ell(t_{ij})^T b_i + f_i(t_{ij}) \\ \end{array} \right), \sigma^2 \]

(A) population   (B) subpopulation   (C) individual   (D) structured noise
• Use the posterior predictive for *online* predictions as new data are collected.

• Mean of posterior predictive has an intuitive form: replace unobserved individual-specific parameters with their expectations given the clinical history.
Qualitative Analysis

(a) Pr(•) = 0.43
Pr(○) = 0.22

(b) Pr(•) = 0.76
Pr(○) = 0.19

Pr(•) = 0.30
Pr(○) = 0.29

Pr(•) = 0.39
Pr(○) = 0.32

Pr(•) = 0.51
Pr(○) = 0.30

Pr(•) = 0.74
Pr(○) = 0.14

Schulam, Saria, 2015
Missing Data

• We observe the trajectory at a finite number of times

• Do we need to worry about bias due to when the measurements were made?

• When we want to model a trajectory there is always going to be missing data

• Is there bias due to when the data are missing?

• When can we use likelihood-based learning?

Little and Rubin, 2014
• Consider the three-observation example

$$T_1 \rightarrow T_2 \rightarrow T_3 \rightarrow Y_1 \rightarrow Y_2 \rightarrow Y_3$$

Unobserved trajectory

Noisy observation of trajectory at time $T$

Random observation time
For an arbitrary number of observations, the probability of the observed data can be factored

\[
\int p(F = f)p(T_{1:n}, Y_{1:n} \mid F = f) df
\]

\[
= \int p(F = f) \prod_{i=1}^{n} p(T_i \mid \bar{t}_i, \bar{y}_i)p(Y_i \mid t_i, f) df
\]

\[
= \left[ \prod_{i=1}^{n} p(T_i \mid \bar{t}_i, \bar{y}_i) \right] \left[ \int p(F = f) \prod_{i=1}^{n} p(Y_i \mid t_i, f) df \right]
\]

- Allows fitting of likelihood without modeling measurement times

Schulam, Saria, 2016
Missing Data Assumptions

• Note: this is **Missing at Random (MAR)** \cite{LittleRubin2014}
  
  - The choice of when to measure is based on observed data only.
  
  - Common to decide when to measure based on past observed data
  
  - For example:
    
    - If there are no recent tests, then clinician is more likely to order a new test.
    
    - If the past few tests suggest results getting worse, clinician may increase frequency of measurement.
  
- **More explicitly, we made the following assumption**
  
  - The times at which the trajectory is observed depend on (a) observed baseline covariates, and (b) the previous measurement times and values of observed time-dependent variables
Missing Not at Random (MNAR)

• These assumptions do not always hold

• When the observation times depend on unobserved variables, the missing data is **Missing Not at Random**

Little and Rubin, 2014

• For example:
  
  • If individuals schedule their own visits, they may only have measurements when they feel sick
  
  • If observation times are determined by other time-dependent variables (e.g. other lab tests) that are **not** in the data
General Ideas vs. Domain Specific

What to take away to new problems?

- #1 Latent Variable model to account for latent sources of heterogeneity
- #2 Posterior Predictive distribution to prevent overfitting and learn as new data are collected on the individual
- #3 Transfer at multiple resolutions

- Choice of hierarchy potentially introduces bias. Generates intermediate quantities that are interpretable by clinicians.

Two useful by-products: (1) Couple models, (2) Subtyping

Which modeling decisions were specific to this app?

- #1 No treatment effects
- #2 Choice of basis for the trajectories and noise models should reflect properties of the disease data.
Another example: Chronic Kidney Disease Prediction

- Use clinical markers measured over time (eGFR) to dynamically predict the probability of stroke
Motivation:

- Lung subtypes likely related to skin subtype.
- In **systemic** diseases, many clinical markers are measured to monitor different organ systems.

Challenges:

- Measurement times are not aligned.
- Some measurements may never be made on an individual.
- Rate of measurement varies across individuals.
• Need joint models that can flexibly encode complex dependencies across markers

• Classic assumption of Naive Bayes structure is incorrect. In general, hard to specify generative model.
Coupled Latent Variable Models

Conditional random field (CRF) to model pairwise dependencies

Model target marker conditioned on auxiliary markers.

\[
\hat{y}(t^*) = \sum_{z_i = 1}^{G} \int_{R^{d_i}} \int_{R^{N_i}} \mathbb{E} [y^*_i | z_i, b_i, f_i] \ P \left( z_i, b_i, f_i \mid y_{1:t}, \bar{y}_{1:C, i, \leq t}, x_{ip}, \Theta \right) \ df_i, \ db_i
\]
- Allows what-if reasoning.
- Ways to incorporate domain knowledge into individual marker-level sub-models.
- Plug-in / replace better models as they become available.
- Open question: Calibrated posteriors for specific clinical tasks
Subtypes and Precision Medicine

- **Desired**: Identify subgroups with distinct underlying biological mechanism driving disease.

- **Current Approach**: Identify candidate subtypes via clustering and associate with molecular determinants. See brief introductory review: [Saria, Goldenberg 2015](#)

- Open question: How do we increase the efficiency of subtype discovery experiments?
  - Combine high-dimensional multivariate data to identify subtypes?
  - Current approaches (e.g., k-means with a pre-specified distance metric).

**Eg: Subtypes based on disease trajectories**  [Schulam et al., 2015](#)

**Other e.g. of sub-grouping patients:**

[Doshi-Velez et al., 2014](#)  [Yuen et al., 2002](#)  [Wang et al., 2012](#)
Related Ideas

- Functional Data Analysis
  
  Ramsay and Silverman 2005  Bahadori et al. 2015  Schulam, Arora 2016

- Modeling Disease Trajectories
  
  Ross and Dy, 2013  Wang et al., 2014  Ghassemi et al. 2014

  Rizopoulos et al. 2015  Liu and Hauskrecht, 2016  Elibol et al. 2016  Wang et al., 2015

- Dynamical Prediction:
  

- Personalization
  
  Berkovsky et al. 2008  Salakhutdinov and Mnih 2008  Adomavicius and Tuzhilin 2010

- Multi-resolution/hierarchical models
  
  Gelman and Hill, 2006

- Multivariate time-to-event
  
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Example: Exercise and Blood Pressure

• Hypothesis: exercise lowers blood pressure

• In this example, we have:
  
  • (a) A treatment (exercise)
  
  • (b) An outcome (blood pressure)

• How can we use data to estimate whether exercise will lower blood pressure?
• Grab an existing dataset containing people who did and did not exercise and have measurements of blood pressure
  
  • Average the change in blood pressure among people who exercise and among those who don’t
  
  • Will this work?
Randomized Controlled Trial (RCT)

- Dataset generative model:

\[ x_{\text{BMI}} \sim \mathcal{N}(0, 1) \]

\[ y_{\text{BP}} \sim \mathcal{N}(x_{\text{BMI}}, 0.4) - 0.8 \cdot \text{Exerc} \]

![Graph showing BMI vs BP for Exercise outcomes](image.png)
Randomized Controlled Trial (RCT)

- Dataset generative model:

\[ x_{\text{BMI}} \sim \mathcal{N}(0, 1) \]
\[ x_{\text{BMI}} \rightarrow y_{\text{BP}} \]
\[ y_{\text{BP}} \sim \mathcal{N}(x_{\text{BMI}}, 0.4) - 0.8 \cdot \text{Exerc} \]

- Comparing averages will work!

Effect Estimate: -0.79
• Instead of running an expensive trial, suppose we simply collect information on 1000 individuals from general clinics around the country

• In the observational data, exercise is assigned by the clinicians caring for the individuals

• In particular, we assume that a higher BMI makes prescription of exercise more likely:

\[ \text{Exerc} \sim \text{Bern} \left( \frac{1}{1 + e^{-2x_{\text{BMI}}}} \right) \]

\[ x_{\text{BMI}} \sim \mathcal{N}(0, 1) \quad y_{\text{BP}} \sim \mathcal{N}(x_{\text{BMI}}, 0.4) - 0.8 \cdot \text{Exerc} \]
Observational Data

- Simply comparing averages no longer works!
- What’s going on? How can we adjust for this bias?

Effect Estimate: 0.29
Approach 1: Weighting

• If we know (or can estimate) a model of treatment assignment, then a common approach is to use inverse probability of treatment weights

• Intuitive idea: when computing averages, count an individual more if she was unlikely to receive treatment (probability is low —> weight is high) and vice versa

Horvitz and Thompson, 1952
Robins et al. 2000
Approach 1: Weighting

• For each individual, compute weight:

\[ w_i = \frac{1}{p(A_i = a_i \mid X_i = x_i)} \]

• Compute weighted averages among treated/not treated

\[
\bar{y}_{\text{Exerc}} = \frac{\sum_{i=1}^{n} w_i \cdot y_i \cdot \mathbb{1}[\text{Exerc} = 1]}{\sum_{i=1}^{n} w_i \cdot \mathbb{1}[\text{Exerc} = 1]}
\]

\[
\bar{y}_{\text{No Exerc}} = \frac{\sum_{i=1}^{n} w_i \cdot y_i \cdot \mathbb{1}[\text{Exerc} = 0]}{\sum_{i=1}^{n} w_i \cdot \mathbb{1}[\text{Exerc} = 0]}
\]

• Other approaches: matching, propensity scores

Rosenbaum and Rubin, 1983  Shalit and Sontag Tutorial, ICML 2016
Hernán and Robins, Forthcoming Textbook

• Off-policy evaluation:

Dudik et al., 2011  Jiang and Li, 2016  Paduraru et al. 2013
Alternative Framework: Potential Outcomes

- We will approach this problem using the framework of potential outcomes

  - Rubin, 1974
  - Neyman et al., 1990
  - Rubin, 2005

- For an individual, conceptualize two “alternate realities”
  - (1) They exercise
  - (2) They do not exercise

- In each reality, we can measure blood pressure and measure the potential outcome

- If we know both potential outcomes, we can answer the question of whether exercise lowers blood pressure
Potential Outcomes

- To formalize, define two distinct random variables:
  - $Y(a)$: blood pressure with exercise
  - $Y(b)$: blood pressure without exercise

- More generally, we can index a set of random variables using a set of actions/treatments:
  \[
  \{Y(a) : a \in A\}
  \]

- Offers a way to reason about counterfactuals.

- **Goal**: learn statistical models to estimate potential outcomes
Critical Assumptions

• To learn the potential outcome models, we will use three important assumptions:

• (1) Consistency
  • Links observed outcomes to potential outcomes

• (2) Treatment Positivity
  • Ensures that we can learn potential outcome models

• (3) No unmeasured confounders (NUC)
  • Ensures that we do not learn biased models
(1) Consistency

- Consider a dataset containing observed outcomes, observed treatments, and covariates:

\[
\{y_i, a_i, x_i\}_{i=1}^n
\]

- E.g.: blood pressure, exercise, BMI

- Consistency allows us to replace the observed response with the potential outcome of the observed treatment

\[
Y \triangleq Y(a) \mid A = a
\]

- Under consistency our dataset satisfies

\[
\{y_i, a_i, x_i\}_{i=1}^n \triangleq \{y_i(a_i), a_i, x_i\}_{i=1}^n
\]
(2) Positivity

- When working with observational data, for any set of covariates \( \mathbf{x} \) we need to **assume a non-zero probability of seeing each treatment**

- Otherwise, in general, cannot learn a conditional model of the potential outcomes given those covariates

- Formally, we assume that

\[
P_{\text{Obs}}(A = a \mid \mathbf{X} = \mathbf{x}) > 0 \quad \forall a \in \mathcal{A}, \forall \mathbf{x} \in \mathcal{X}
\]
(3) No Unmeasured Confounders (NUC)

- In our exercise example, BMI is a *confounder*

- It induces a statistical dependency between the observed treatment and observed outcome

- In general, unless we observe all confounders, we cannot learn unbiased models of potential outcomes from observational data

- Formally, NUC is an statistical independence assertion:

\[
Y(a) \perp A \mid X = x : \forall a \in \mathcal{A}, \forall x \in \mathcal{X}
\]

To explain NUC graphically, we introduce the graphical notation of SWIGs.
Single-World Intervention Graphs

- SWIGs extend graphical models to explicitly represent potential outcomes
- To obtain a SWIG, we define a causal graphical model and specify the set of treatment variables
- We apply *node-splitting* operations to treatment variables to represent interventions
Example SWIG

- We apply *node-splitting* operations to treatment variables to represent interventions.
- A simple “a” vs “b” example:

\[
\begin{align*}
Y_a & \xrightarrow{\mathcal{G}} Y \\

Y_b & \xrightarrow{\mathcal{G}} Y \\
\end{align*}
\]

Richardson and Robins, 2014
Interpreting SWIGs

- Treat SWIGs as standard causal graphs
  - Semi-circle nodes are just reminders that we have applied a node-splitting operation
  - From this graph, can read that $Y(a)$ is independent of the observed treatment $A$

Richardson and Robins, 2014

Richardson, 2014
NUC in SWIG Language

- SWIGs make NUC assumption easy to express
  \[ Y(a) \perp A \mid X = x : \forall a \in A, \forall x \in X \]

- Confounders X d-separate potential outcomes from observed treatment random variable when intervening on treatment

\[ G \]

\[ G(a) \]

Richardson and Robins, 2014

Richardson, 2014
Using Models to Adjust for Bias

- Assume models of potential outcomes given covariates
  \[ \{ P(Y(a) \mid X = x) : a \in A \} \]
- We can use them to adjust for bias in observational data
- Key idea: use models to “simulate” an RCT

Rubin 1977  Robins 1986
Using Potential Outcomes Framework to Simulate RCT

- Our observational data is drawn from

\[ Q \triangleq P(X)P_{\text{Obs}}(A \mid x)P(Y \mid a, x) = P(X)P_{\text{Obs}}(A \mid x)P(Y(a) \mid x) \]

- We want experimental data drawn from

\[ P \triangleq P(X)P_{\text{Exp}}(A)P(Y \mid a, x) = P(X)P_{\text{Exp}}(A)P(Y(a) \mid x) \]

- If we know potential outcome models:
  - Draw from empirical covariate distribution: \( X \sim \{x_i\}_{i=1}^n \)
  - Flip fair coin to assign treatment: \( A \sim \text{Bern}(0.5) \)
  - Simulate outcome from model: \( P(Y(a) \mid X = x) \)
Learning Potential Outcome Models

• To simulate data from a new policy, we need to learn the potential outcome models

• If we have an observational dataset where assumptions 1-3 hold, then this is possible!

• Assumptions allow estimation of potential outcomes from (observational) data:

\[
P(Y(a) \mid X = x) = P(Y(a) \mid X = x, A = a) \quad \text{(A3)}
\]
\[
= P(Y \mid X = x, A = a) \quad \text{(A1)}
\]
Exercise and Blood Pressure

- Returning to our exercise and blood pressure example

- We fit a model for blood pressure given exercise and BMI

- With estimated models, treatment effects are estimated as:

\[
\mathbb{E}[Y(1) - Y(0)] = \frac{1}{N} \sum_{n=1}^{N} (Y_n(1) - Y_n(0))
\]

Effect Estimate: 0.29

Simulated Effect Estimate: -0.87
Going beyond PATE

**PATE**: Population Average Treatment Effect:

\[ \mathbb{E}[Y(1) - Y(0)] = \frac{1}{N} \sum_{n=1}^{N} (Y_n(1) - Y_n(0)) \]

To account for the heterogeneous treatment effect among patients, it is more of interest to look at **CATE**, the conditional average treatment effect:

\[ \mathbb{E}[Y(1) - Y(0) | C_1 = c_1] \]

See e.g.:  
Foster et al., 2011  Imai et al., 2013  Tian et al., 2014  
Athey and Imbens, 2016
Sequential Treatment Assignment and Time-Varying Confounding

- Interventions and observations are interleaved
  - Intervention effects future observations
    Those observations affect future interventions
    And so on…

- When can we disentangle to learn unbiased models of potential outcomes?

- Also called time-varying confounding.

Robins 1986
Sequential Treatment Assignment and Time-Varying Confounding

- Interventions and observations are interleaved
  - Intervention effects future observations
    Those observations affect future interventions
    And so on...

- As in single-treatment, single-outcome examples, we need assumptions that allow us to link conditional distributions to the target potential outcome models

Robins 1986
For many diseases, response to therapy varies greatly across individuals. To personalize therapy, we need to estimate at the individual level their likely response to treatment.
We wish to obtain **uncertainty** estimate over an **individual’s treatment response over time**. And we want to estimate this from routinely collected data

- sparse, irregularly sampled clinical time series

- **Population averages vs. Individualized Estimates**
  - Refined as new measurements are collected on the individual

- **Point-in-time vs. Treatment Response Curve**
• The SWIG is:

\[
P(Y_1 = y_1)P(Y_2(a_1) = y_2 \mid Y_1 = y_1)P(Y_3(a_1, a_2) = y_3 \mid Y_1 = y_1, Y_2(a_1) = y_2) \\
= P(Y_1 = y_1)P(Y_2 = y_2 \mid Y_1 = y_1, A_1 = a_1)P(Y_3 = y_3 \mid Y_1 = y_1, Y_2 = y_2, A_1 = a_1, A_2 = a_2)
\]

• The SWIG shows us that for each outcome, conditioning on previous outcomes d-separates from observed treatments.
Approach: g-formula

For patient i:
Observations $Y_i = \{Y_{i1}, ..., Y_{iJ_i}\}$ measured at times $t_i = \{t_{i1}, ..., t_{iJ_i}\}$
Treatments $A_i = \{A_{i1}, ..., A_{iL_i}\}$ prescribed at times $\tau_i = \{\tau_{i1}, ..., \tau_{iL_i}\}$
A set of covariates $C_{ij} \in \mathbb{R}^p$

Estimation requires a statistical model for estimating conditionals:

$$P(Y_{ij} | a_{i,j}, a_i, \leq j-1, y_{i,\leq j-1}, C_{ij})$$

- Likelihood based approach; use flexible BNP to reduce error due to model mis-specification
  - Ferguson, 1973
  - Müller and Mitra, 2013
  - Müller and Rodriguez, 2013

- Other estimation techniques can be used.
  - Xu et al., 2016
$y_i | a_i, c_i = u_i(c_i) + f_i(a_i) + \epsilon_i$,  

baseline progression               treatment responses               noise

Parametrization for the treatment response curve:

$$g_{id}(t) = \begin{cases} 
    b_0 + \frac{\alpha_1}{1 + \exp(-\alpha_2(t - \gamma_{id}/2))}, & 0 \leq t < \gamma_{id}, \\
    b \cdot g_{\gamma_{id}} + \frac{\alpha_0}{1 + \exp(\alpha_3(t - 3\gamma_{id}/2))}, & t \geq \gamma_{id},
\end{cases}$$

Key parameters:
- $a_1$: peak effect
- $a_2$: how quickly the effect reaches the peak
- $a_3$: how quickly the effect diminish
- $r$: change point
- $b$: the ratio of the final effect to the peak effect

(a) A simulated trajectory with one treatment
(b) A simulated trajectory with multiple treatments
Choices to reduce error due to model misspecification

\[ y_i \mid a_i, c_i = u_i(c_i) + f_i(a_i) + \epsilon_i, \]

- **Gaussian Process to flexible model longitudinal traces**
- **Dirichlet Process mixture prior to cluster treatment response and baseline progression parameters**
  - Each individual samples its parameters from a cluster mean
  - No bias due to assuming that clusters are of equal size or a fixed number of clusters
  - Posterior Predictive: Estimates refined with new data

Ferguson, 1973

Xu et al., 2016
Heterogeneous Treatment Response

Data: EHR collected over two years at Howard County General Hospital from 2013-2015. 300 ICU patients who were prescribed at least one of the treatments.

Vasopressor:

Beta-blocker:

Fluid_bolus:

Xu et al., 2016
Overview

• Part 1—Setting up the problem of Individualization
  • Example using a chronic disease
  • Simple setting: No Treatment Effects
  • Bayesian Hierarchical Framework for Individualizing Predictions
  • Key ideas: Transfer learning, Multilevel modeling

• Part 2—Estimating Treatment Effects & Individualized Treatment Effects
  • Example using inpatient data
  • Learning from observational data
  • Key ideas: Potential Outcomes, Causal Inference for Bias Adjustment, BNP

• Part 3—Causal Predictions
  • Relax assumption from Part 1 about no treatment effects
  • Discuss predictions that are robust to changes in physician practice behavior

• Part 4—From Predictions to Treatment Rules
  • Key ideas: Q-learning, Dynamic Treatment Regimes
  • Connections to Reinforcement Learning

No Control over Data Collection Process

Control over Data Collection Process
Continuous Monitoring
Continuous Monitoring

Predictive Model for Forecasting Downstream Adverse Event

Severity Score

Adverse Event Onset
Use supervised learning for distinguishing patients with AE from those without.

Using Presence of AE as annotation.

Adverse Event Onset.
Pneumonia Severity Index: Risk of Mortality

- Identify candidate risk factors
- Learn score and relative weights by regressing against observed mortality

---

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Co-morbidities</th>
<th>Physical exam / vital signs</th>
<th>Laboratory / imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (1 point per year) Male Yr Female Yr -10 Nursing home residency +10</td>
<td>Neoplasia +30 Liver disease +20 CHF +10 Cerebrovascular disease +10 Renal disease +10</td>
<td>Mental confusion +20 Respiratory rate +20 SBP +20 Temperature +15 Tachycardia +15</td>
<td>Arterial pH +30 BUN +20 Sodium +20 Glucose +10 Hematocrit +10 Pleural effusion +10 Oxygenation +10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk class (Points)</th>
<th>Mortality (%)</th>
<th>Recommended site of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&lt;50)</td>
<td>0.1</td>
<td>Outpatient</td>
</tr>
<tr>
<td>II (51–70)</td>
<td>0.6</td>
<td>Outpatient</td>
</tr>
<tr>
<td>III (71–90)</td>
<td>2.8</td>
<td>Outpatient or brief inpatient</td>
</tr>
<tr>
<td>IV (91–130)</td>
<td>8.2</td>
<td>Inpatient</td>
</tr>
<tr>
<td>V (&gt;130)</td>
<td>29.2</td>
<td>Inpatient</td>
</tr>
</tbody>
</table>

But, interventions censor the true label.

Using Presence of AE as annotation

Adverse Event Onset

fluid bolus 500 ml fluid bolus 1200 ml

antibiotic pressors

Paxton et al., 2013 Dyagilev et al., 2016
But, interventions censor the true label.

Using Presence of AE as annotation

(!) Learnt Risk Estimates are Highly Sensitive to Provider Practice Pattern

Adverse Event Onset

Paxton et al., 2013
Dyagilev et al., 2016
Challenge: Learnt Risk Estimates Sensitive to Provider Practice Pattern

- Simple example (Flu)
  - Measure temperature
  - Measure WBC

- Increase in temperature or WBC increases risk of death
Key idea:

- Consider a unit where patients get treated as temperature increases above say, 102 degrees

- Therefore, *fewer deaths due to rising temperature*

- As fewer individuals experience death, the *algorithm no longer associates rise in temperature with risk.*
Bias Due to Interventional Confounds

- Model flu severity; temperature is observed
- Example: Synthetic-Pneumonia
  - If flu, temperature increases unless medicated
  - When medicated, temperature returns to normal
  - At 108 deg F, subject dies
- Consider hospitals with different practice patterns: $P(\text{med} \mid \text{temperature})$

Treatment practice:
(1) no antibiotics for $T < 102$ deg F;
(2) administer antibiotics with probability $\rho$ for $T \geq 102$ deg F
Bias Due to Interventional Confounds

- Model flu severity; temperature is observed
- Simulate using Synthetic-Pneumonia model:
  - If flu, temperature increases unless medicated
  - When medicated, temperature returns to normal
  - At 108 deg F, subject dies
- Consider hospitals with different practice patterns: $P(\text{med} \mid \text{temperature})$

Dyagilev et al., 2016
Bias Due to Interventional Confounds

Vary provider practice patterns between train and test:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>$\rho^{\text{train}}_T$</th>
<th>$\rho^{\text{train}}_{\text{WBC}}$</th>
<th>$\rho^{\text{test}}_T$</th>
<th>$\rho^{\text{test}}_{\text{WBC}}$</th>
<th>Logistic Regression</th>
<th>L-DSS</th>
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</thead>
<tbody>
<tr>
<td>#1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.974</td>
<td>0.973</td>
</tr>
<tr>
<td>#2</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.978</td>
<td>0.990</td>
</tr>
<tr>
<td>#3</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.963</td>
<td>0.974</td>
</tr>
<tr>
<td>#4</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.769</td>
<td>0.973</td>
</tr>
<tr>
<td>#5</td>
<td>0.3</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.510</td>
<td>0.978</td>
</tr>
</tbody>
</table>

Increase probability of treating for rising temperature

Increasing discrepancy in physician prescription behavior in train vs. test environment

Learned risk scores are high sensitive to changes in provider practice patterns:
- Resulting risk scores are also less interpretable
- They violate *construct validity* [Medsger et al., 2003]
Alternate forms of training and supervision?

Instead:

Regression

Often not practical because getting these annotations are challenging.
Alternate forms of training and supervision?

Instead:

- get severity annotation directly?

Regression

Today: Joint modeling of states and actions

Comparison Pairs: Dyagilev et al., 2016

Transportability not always possible: Bareinboim and Pearl, 2013
Causal Predictions

- Learnt risk is **conditional** on prescription patterns.

- Statistical model’s predictions may capture correlations that depend on **provider practice**

- E.g. “treat when temperature rises above 100”

- What we observe is “**what happens if they receive the treatments they did receive**”

- The desired target is: “what is likely to happen to this patient given their history if we **do not treat vs treat**” We will refer to this idea as estimating the causal risk.

Bottou et al., 2012
Personalization and Potential Outcomes

- Recall example application from Section 1
- Potential outcomes allow “what if?” reasoning
- To select best treatment for an individual, we can examine expected outcomes under each choice
• What is the future trajectory under different sequences of interventions?
Personalization and Potential Outcomes

- What if we administer another dose of Drug B?

![Graph showing lung capacity over years since first symptom with two drug regimens, Drug A and Drug B, and the expected value of $Y$ given $H = h$.]

Schulam and Saria, 2017
What about another dose of Drug A?

Personalization and Potential Outcomes

- History $H = h$

Drug A

Drug B

$Lung Capacity$

$Years Since First Symptom$

$E[Y(\mathbf{1}) | H = h]$

$E[Y(\mathbf{1}) | H = h]$

Schulam and Saria, 2017
What about two sequential doses of Drug A?
In the single-treatment, single-outcome case we learned models of the potential outcomes and used them to simulate experimental results.

We want to transplant this idea to the individual level:

- Can we learn personalized trajectory-valued potential outcome models?

- If so, can we use those models to simulate experiments that investigate the effect of different treatment decisions for this person?
Recall: Sequential Treatment Assignment and Time-Varying Confounding

- Interventions and observations are interleaved
  - Intervention effects future observations
    Those observations affect future interventions
    And so on...
- When can we disentangle to learn unbiased models of potential outcomes?
- Also called time-varying confounding.

Robins 1986
Recall: SWIG for Sequential Setting

- Assumptions: (1) Consistency, (2) Sequential Ignorability (NUC)

- The SWIG shows us that for each outcome, conditioning on previous outcomes d-separates from observed treatments

\[
P(Y_1 = y_1)P(Y_2(a_1) = y_2 \mid Y_1 = y_1)P(Y_3(a_1, a_2) = y_3 \mid Y_1 = y_1, Y_2(a_1) = y_2) = P(Y_1 = y_1)P(Y_2 = y_2 \mid Y_1 = y_1, A_1 = a_1)P(Y_3 = y_3 \mid Y_1 = y_1, Y_2 = y_2, A_1 = a_1, A_2 = a_2)
\]
Handling Irregularity

• In an irregular trace (i.e. sequence of interleaved actions and observations), there can be multiple observations between actions:

\[ h_i = [(y_{i1}, t_{i1}), (a_{i1}, \tau_{i1}), (y_{i2}, t_{i2}), (y_{i3}, t_{i3})]. \]

• We can handle irregularly sampled observations and treatments in a similar way [Part 1 and Part 2]

• We assume measurements are **missing at random** i.e. the choice of when to measure depends on the past observed data [Recall from Part 1]
Factoring Irregular Traces

• We can still factor these traces as we would regularly sampled traces (see paper for details)

• Define:
  
  • $\bar{y}_k$ to be the observations prior to action $k$
  
  • $\bar{a}_k$ to be the actions taken prior to action $k$
  
  • $y_k$ to be observations after action $k$, but before $k+1$
  
• Then we can factor an arbitrary trace:

$$p(h \mid x) = p(y_0 \mid x) \prod_{k=1}^{m} p(a_k, \tau_k \mid \bar{y}_k, \bar{a}_k, x)p(y_k \mid \bar{y}_k, a_k, \tau_k, \bar{a}_k, x),$$

Schulam and Saria, 2017
Irregular Traces and Functional Potential Outcomes

- Assuming Consistency and Sequential NUC (see paper for details)

\[
p(y_k \mid \bar{y}_k, a_k, \tau_k, \bar{a}_k, x) = p(y_k(a_k, \tau_k) \mid \bar{y}_k, \bar{a}_k, x)
\]

- Therefore can maximize probability of irregular trace:

\[
p(h \mid x) = p(y_0 \mid x) \prod_{k=1}^{m} p(a_k, \tau_k \mid \bar{y}_k, \bar{a}_k, x)p(y_k \mid \bar{y}_k, a_k, \tau_k, \bar{a}_k, x),
\]

- Policy is unknown, but assumed to be distinct so we can ignore the treatment policy terms when learning functional potential outcome models

Recall:

- Our observational data is drawn from

\[
Q \triangleq P(X)P_{\text{Obs}}(A \mid x)P(Y \mid a, x) = P(X)P_{\text{Obs}}(A \mid x)P(Y(a) \mid x)
\]

- We want experimental data drawn from

\[
P \triangleq P(X)P_{\text{Exp}}(A)P(Y \mid a, x) = P(X)P_{\text{Exp}}(A)P(Y(a) \mid x)
\]

Schulam and Saria, 2017
Many different ways to model conditional distributions over markers (green component in last slide)

One example: Gaussian process

\[
\text{GP}(m(\cdot ; a, x), k(\cdot , \cdot ))
\]

Mean function depending on covariates and sequence of treatments

Covariance function independent of treatments

Schulam and Saria, 2017
Many different ways to model conditional distributions over markers (green component in last slide)

One example: Gaussian process

\[ \text{GP}(m_i(\cdot; \mathbf{a}, \mathbf{x}), k_i(\cdot, \cdot)) \]

Recall individualization approach from Part 1:

\[ y_{ij}|\tilde{x}_{ip}, z_i, b_i \sim \mathcal{N}\left( \begin{array}{c} \Phi_p(t_{ij})^T \Lambda \tilde{x}_{ip} + \Phi_z(t_{ij})^T \beta_{z_i} + \Phi_{\ell}(t_{ij})^T \tilde{b}_i + f_i(t_{ij}) \end{array} \right), \sigma^2 \]

Schulam and Saria, 2017
Using previous lung disease progression patterns and learning from response to treatment, we can predict how individuals will respond to treatment and how they will progress when treatment is no longer given.

Example: Lung Disease Trajectories

- Example 1
- Example 2
- Example 3

**% Forced Vital Capacity**

<table>
<thead>
<tr>
<th>Years Seen</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
- Prednisone
- Hydroxychloroquine
- Methotrexate
- Cytoxan
Predicting trajectories for Targeting Treatments in Critically Ill Patients

(a) Example Trajectory of MAP and Treatment Response Curve of Fluid (FL)

(b) Example Trajectory of MAP and Treatment Response Curves of Vasopressor (VP) and Fluid (FL)

Patient ID 116053

Patient ID 120794

Xu et al., 2016

Liu et al., 2016
Caveats in Practice and Discussion

- Estimates of the individual components within the statistical model may not be good enough based on available data
  - Not enough data to train from.
  - Available measurements are not predictive.

- Inferences are correct assuming **no model mis-specification**.
  - Important aspect of causal modeling is getting your causal assumptions right.
    - Think hard about the problem—> avoids the chance of model mis-specification or making incorrect assumptions.
  - Semi-parametric or flexible nonparametric strategies are helpful here.
  - Methods to check sensitivity to assumption (e.g., posterior predictive checks)

- Driving modeling decisions based on practical utility
  - Decisions are made with a human in the loop.
    - Transparency does not have to be interpreted as the use of a linear model or a decision tree.
    - Estimating intermediate quantities that are interpretable or can serve as validation can be useful (e.g., subpopulation, individual-specific deviations)

- Need ways to monitor performance over time.
Overview

- Part 1—Setting up the problem of Individualization
  - Example using a chronic disease
  - Simple setting: No Treatment Effects
  - Bayesian Hierarchical Framework for Individualizing Predictions
  - Key ideas: Transfer learning, Multilevel modeling

- Part 2—Estimating Treatment Effects & Individualized Treatment Effects
  - Example using inpatient data
  - Learning from observational data
  - Key ideas: Potential Outcomes, Causal Inference for Bias Adjustment, BNP

- Part 3—Causal Predictions
  - Relax assumption from Part 1 about no treatment effects
  - Discuss predictions that are robust to changes in physician practice behavior

- Part 4—From Predictions to Treatment Rules
  - Key ideas: Q-learning, Dynamic Treatment Regimes
  - Connections to Reinforcement Learning
• A mapping of states to actions
  • In reinforcement learning, this is called a *sequential policy*
  • In treatment planning, sequential policies called *dynamic treatment regime*
• States are functions of an individual’s clinical history, and the policy maps these histories to actions.

The nodes that an action node is dependent on provides the context upon which the decision depends.

Times at which decisions are made.
A mapping of states (context) to actions
- In reinforcement learning, this is called a *sequential policy*
- In statistics, it is called a *dynamic treatment regime*

To obtain such a policy,
- we can use *model based* or *model-free* methods
- we use learn by either *interacting with the world* or learn from *offline* data.

Loosely speaking,
- model-based learns a dynamical model of the system (e.g., an MDP) → as a by-product, also make predictions
- for model-free methods, you evaluate the policy directly using traces

**Review:** Paduraru et al., 2013
Basic Q-learning algorithm

Q-function or the action-value function

\[ Q(s, a) = r(s, a) + \gamma \max_{a'}(Q(s', a')) \]

- \( r(s, a) = \) Immediate reward
- \( \gamma = \) relative value of delayed vs. immediate rewards (0 to 1)
- \( s' = \) the new state after action \( a \)
- \( a, a' = \) actions in states \( s \) and \( s' \), respectively

Selected action:

\[ \pi(s) = \arg\max_a Q(s, a) \]

Initialize Q-functions and update as you explore.
Basic Q-learning algorithm

\[ Q(s, a) = r(s, a) + \gamma \max_a’(Q(s’, a’)) \]
\[ r(s, a) = \text{Immediate reward} \]
\[ \gamma = \text{relative value of delayed vs. immediate rewards (0 to 1)} \]
\[ s' = \text{the new state after action } a \]
\[ a, a' : \text{actions in states } s \text{ and } s', \text{ respectively} \]

Selected action:

\[ \pi(s) = \text{argmax}_a Q(s, a) \]

\[ P(a_i|s) = \frac{k \hat{Q}(s, a_i)}{\sum_j k \hat{Q}(s, a_j)} \]

Review:

Ghavamzadeh et al., 2015

Watkins 1989
Safe Reinforcement Learning

- Two broad approaches to safe RL
  - Modifying optimization criterion (notion of reward)
  - Penalize movement through “error states”
  - Modifying exploration strategies
  - Incorporate domain knowledge
  - Apprenticeship: seed MDP parameters using a teachers demonstration

Garciá and Fernández, 2015
Geibel and Wysotzki, 2005
Martín and Lope, 2009
Abbeel and Ng, 2005
Dynamic Treatment Regimes: Learning from Offline Data

Optimal decision at time 1

$\arg\max_{A_1} \max_{A_2} f(P(Y_3(A_1, A_2)|Y_1))$

Robins 2004; Blatt et al., 2004; Rothøj et al. 2006; Henderson et al. 2010; Almirall et al. 2010

Dudik et al., 2011
Jiang and Li, 2016

Murphy 2003
Dynamic Treatment Regimes: Learning from Offline Data

When tree-size is large, use dynamic programming.

\[
\text{argmax}_{A_1} \max_{A_2} f(P(Y_3(A_1, A_2)|Y_1))
\]

When tree-size is large, use dynamic programming.

Dudik et al., 2011
Jiang and Li, 2016
Robins 2004
Blatt et al., 2004
Rothøj et al., 2006
Henderson et al., 2010
Almirall et al., 2010

Murphy 2003
Rationale:

Naltrexone (NTX, an opiate antagonist) is efficacious but

• Around 1/3 of patients relapse while on NTX,
• Hence, need to develop rescue tactics for non-responders
• And long-term maintenance tactics for responders
• Because of various barriers: Physiological/social/psychological

- Trials for evaluating sequential treatment strategies.
- Assignment is adaptive
Conclusion & Discussion

• Need for individualization based on diverse data.

• Our practice of medicine will change radically in at least some areas in the next decade and there is an exciting opportunity for us to make a difference.

• **Bayesian Hierarchical Framework for Individualizing Predictions**
  • Motivated latent sources of variability that can be inferred to refine predictions
  • Discussed the problem of inferring disease trajectories

• **Estimating Treatment Effects & Individualized Treatment Effects**
  • Learning from observational data
  • Key ideas: Potential Outcomes, Causal Inference for Bias Adjustment, BNP

• **Causal Predictions**
  • Relax assumption from Part 1 about no treatment effects
  • Discuss predictions that are robust to changes in physician practice behavior

• **From Predictions to Treatment Rules**
  • Connections to Reinforcement Learning, Dynamic Treatment Regimes, SMART
Publicly available datasets

HealthData.gov

- Health
  - State (66)
  - Community (60)
  - National (50)
  - Medicare (49)
  - Hospital (42)
  - Quality (33)
  - Inpatient (29)
Thank you!
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