Implementing Personalized Medicine: Estimating Optimal Treatment Regimes

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Personalized medicine

Clinical practice: Clinicians make (a series of) treatment decision(s) over the course of a patient’s disease or disorder

• Fixed schedule
• Milestone in the disease process
• Event necessitating a decision

Personalized medicine: Make the “best” treatment decision(s) for a patient given all the available information on the patient up to the time of the decision

• Genetic/genomic, demographic, . . .
• Physiologic, clinical measures, medical history, . . .
Operationalizing personalized medicine: At any decision

- Need a rule that takes as input the accrued information on the patient to that point and dictates the next treatment from among the possible options
- Rule(s) must be developed based on evidence; i.e., data
- Ideally, rule(s) should lead to the “best” clinical outcome

Dynamic treatment regime: A set of formal such rules, each corresponding to a decision point
Single decision

**Simple example:** Which treatment to give to patients who present with primary operable *breast cancer*?

- **Treatment options:** L-phenylalanine mustard and 5-fluorouracil ($c_1$) or $c_1 +$ tamoxifen ($c_2$)
- **Information:** age, progesterone receptor level (PR)

**Example rule:** “If age < 50 years and PR < 10 fmol, give $c_1$ (coded as 1); otherwise, give $c_2$ (coded as 0)”

- **Mathematically,** the rule $d$ is

  \[ d(\text{age}, \text{PR}) = I(\text{age} < 50 \text{ and PR} < 10) \]

- **Alternatively:** Rules of form

  \[ d(\text{age}, \text{PR}) = I\{\text{age} > 60 - 8.7 \log(\text{PR})\} \]
Multiple decision points

Two decision points:

- **Decision 1**: Induction chemotherapy (options $c_1$, $c_2$)
- **Decision 2**:
  - Maintenance treatment for patients who *respond* (options $m_1$, $m_2$)
  - Salvage chemotherapy for those who *don’t* (options $s_1$, $s_2$)
Multiple decision points

- **At baseline:** Information $x_1$ (accrued information $h_1 = x_1$)
- **Decision 1:** Two options $\{c_1, c_2\}$; rule 1: $d_1(x_1) \Rightarrow x_1 \rightarrow \{c_1, c_2\}$
- **Between decisions 1 and 2:** Collect additional information $x_2$, including responder status
- **Accrued information** $h_2 = \{x_1, \text{chemotherapy at decision 1}, x_2\}$
- **Decision 2:** Four options $\{m_1, m_2, s_1, s_2\}$; rule 2: $d_2(h_2) \Rightarrow h_2 \rightarrow \{m_1, m_2\}$ (responder), $h_2 \rightarrow \{s_1, s_2\}$ (nonresponder)
- **Regime:** $d = (d_1, d_2)$
Summary

Single decision: 1 decision point

- **Baseline information** $x \in \mathcal{X}$
- Set of treatment options $a \in \mathcal{A}$
- Decision rule $d(x), d : \mathcal{X} \rightarrow \mathcal{A}$
- Treatment regime: $d$

Multiple decisions: $K$ decision points

- **Baseline information** $x_1$, intermediate information $x_k$ between decisions $k - 1$ and $k$, $k = 2, \ldots, K$
- Set of treatment options at each decision $k$: $a_k \in \mathcal{A}_k$
- Accrued information $h_1 = x_1 \in \mathcal{H}_1,$

$$h_k = \{x_1, a_1, x_2, a_2, \ldots, x_{k-1}, a_{k-1}, x_k\} \in \mathcal{H}_k, \quad k = 2, \ldots, K$$

- Decision rules $d_1(h_1), d_2(h_2), \ldots, d_K(h_K), d_k : \mathcal{H}_k \rightarrow \mathcal{A}_k$
- Treatment regime $d = (d_1, d_2, \ldots, d_K)$
Defining “best”

Outcome: There is a *clinical outcome* by which treatment benefit can be assessed

- Survival time, CD4 count, indicator of no myocardial infarction within 30 days, . . .
- *Larger outcomes are better*
Obviously: There is an *infinitude* of possible regimes $d$

An optimal regime $d^{opt}$: Should satisfy

- If all patients in the population were to receive treatment according to $d^{opt}$, the *expected (average) outcome* for the population would be *as large as possible*.
- If an individual patient were to receive treatment according to $d^{opt}$, his/her *expected outcome* would be *as large as possible given the information available on him/her*.
- Can we *formalize* this?
For simplicity: Consider regimes involving a *single decision* with *two* treatment options (0 and 1)

- $\mathcal{A} = \{0, 1\}$
- *Baseline covariate information* $x \in \mathcal{X}$

**Treatment regime:** A single *rule* $d(x)$

- $d : \mathcal{X} \rightarrow \{0, 1\}$
- $d \in \mathcal{D}$, the class of *all* regimes
Potential outcomes

Formalize: We can hypothesize potential outcomes
- $Y^*(1) = \text{outcome that would be achieved if a patient were to receive treatment } 1$; $Y^*(0)$ defined similarly
- $\Rightarrow E\{Y^*(1)\}$ is the average outcome if all patients in the population were to receive 1; and similarly for $E\{Y^*(0)\}$

Potential outcome for a regime: For any $d \in D$, define $Y^*(d)$ to be the potential outcome for a patient with baseline covariate information $X$ if s/he were to receive treatment in accordance with regime $d$; i.e.,

$$Y^*(d) = Y^*(1)d(X) + Y^*(0)(1 - d(X))$$
Potential outcomes

Thus:

- $E\{ Y^*(d) \} = E[ E\{ Y^*(d) | X \} ]$ is the **average outcome** in the population if all patients in the population were assigned treatment according to $d \in \mathcal{D}$
- $E\{ Y^*(d) | X = x \}$ is the **expected outcome** for a patient with baseline information $x$ if s/he were to receive treatment according to regime $d \in \mathcal{D}$

Optimal regime: $d^{opt}$ is a regime in $\mathcal{D}$ such that

- $E\{ Y^*(d) \} \leq E\{ Y^*(d^{opt}) \}$ for all $d \in \mathcal{D}$
- $E\{ Y^*(d) | X = x \} \leq E\{ Y^*(d^{opt}) | X = x \}$ for all $d \in \mathcal{D}$ and $x \in \mathcal{X}$
Important philosophical point

Distinguish between:

- The “best” treatment for a patient
- The “best” treatment decision for a patient given the information available on the patient

**Best treatment for a patient:** The option \( a^{\text{best}} \in A \) corresponding to the largest \( Y^*(a) \) for the patient

**Best treatment given the information available:**

- We cannot hope to determine \( a^{\text{best}} \) because we can never see all potential outcomes on a given patient
- We can hope to make the optimal decision given the information available, i.e., find \( d^{\text{opt}} \) that makes \( E\{ Y^*(d) \} \) and \( E\{ Y^*(d) | X = x \} \) as large as possible
Goal: Given data from a clinical trial or observational study, estimate the optimal regime \( d^{opt} \) satisfying this definition.

Observed data: \((X_i, A_i, Y_i), i = 1, \ldots, n, \text{iid}\)
- \(X\) baseline covariate information, \(A = 0, 1\) treatment received, \(Y\) outcome observed under \(A\)
- We observe \(Y = Y^*(1)A + Y^*(0)(1 - A)\)
Critical assumption

No unmeasured confounders: *Assume that*

\[ Y^*(0), Y^*(1) \perp \perp A|X \]

- \( X \) contains all information used to assign treatments
- Automatically satisfied for data from a *randomized trial*
- Standard but *unverifiable* assumption for *observational studies*
- Implies that

\[
E\{Y^*(1)\} = E[E\{Y^*(1)|X\}] \\
= E[E\{Y^*(1)|X, A = 1\}] \\
= E\{E(Y|X, A = 1)\}
\]

and similarly for \( E\{Y^*(0)\} \)
Optimal regime

Recall: \( Y^*(d) = Y^*(1)d(X) + Y^*(0)\{1 - d(X)\} \)

- This implies (using \textit{no unmeasured confounders})

\[
E\{ Y^*(d) \} = E[E\{ Y^*(d) | X \}]
= E \left[ E\{ Y^*(1) | X \}d(X) + E\{ Y^*(0) | X \}\{1 - d(X)\} \right]
= E \left[ E(Y | X, A = 1)d(X) + E(Y | X, A = 0)\{1 - d(X)\} \right]

- Thus it is clear that

\[
d^{opt}(x) = I[E\{ Y^*(1) | X = x \} > E\{ Y^*(0) | X = x \}]
= I\{ E(Y | X = x, A = 1) > E(Y | X = x, A = 0) \}

- \textbf{Result}: If \( E(Y | X, A) \) were \textit{known}, we could find \( d^{opt} \)
Estimating an optimal regime

Problem: \( E(Y|X,A) \) is not known

- **Posit a model** \( Q(X,A; \beta) \) for \( E(Y|X,A) \)
- **Estimate** \( \beta \) using observed data \( \Rightarrow \hat{\beta} \) (e.g., least squares)
- **Estimate** \( d^{opt} \) by the **regression estimator**

\[
\hat{d}_{reg}^{opt}(x) = I\{ Q(x,1;\hat{\beta}) > Q(x,0;\hat{\beta}) \}
\]

- Corresponding estimator for \( E\{ Y^*(d^{opt}) \} \)

\[
REG(\hat{\beta}) = n^{-1} \sum_{i=1}^{n} [ Q(X_i,1;\hat{\beta})\hat{d}_{reg}^{opt}(X_i) + Q(X_i,0;\hat{\beta})\{1-\hat{d}_{reg}^{opt}(X_i)\} ]
\]

- If correct, \( E(Y|X,A) = Q(X,A;\beta_0) \) for some \( \beta_0 \)

**Concern:** \( Q(X,A;\beta) \) may be **misspecified**, so \( \hat{d}_{reg}^{opt} \) could be far from the true \( d^{opt} \)
Estimating an optimal regime

**Alternative perspective:** \( Q(X, A; \beta) \) defines a *class* of regimes

\[
d(x, \beta) = I\{Q(x, 1; \beta) > Q(x, 0; \beta)\},
\]

indexed by \( \beta \), that *may or may not* contain \( d^{opt} \)

- **Posit** \( Q(X, A; \beta) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + A(\beta_3 + \beta_4 X_1 + \beta_5 X_2) \)
- Regimes \( d(x, \beta) \) lead to a *class* \( D_\eta \)

\[
l(x_2 \geq \eta_1 x_1 + \eta_0) \text{ or } l(x_2 \leq \eta_1 x_1 + \eta_0), \quad \eta_0 = -\beta_3 / \beta_5, \quad \eta_1 = -\beta_4 / \beta_5
\]

depending on the sign of \( \beta_5 \)

- If *in truth*

\[
E(Y|X, A) = \exp\{1 + X_1 + 2X_2 + 3X_1 X_2 + A(1 - 2X_1 + X_2)\}
\]

\[ \implies d^{opt}(x) = l(x_2 \geq 2x_1 - 1) \quad (\text{so } d^{opt} \in D_\eta \text{ in this case}) \]
Estimating an optimal regime

Result:

- The parameter $\eta$ is defined as a function of $\beta$
- If the *posited* model is *correct*, then the optimal regime is *contained in* $\mathcal{D}_\eta$.
- However, the estimated regime $I\{Q(x, 1; \hat{\beta}) > Q(x, 0; \hat{\beta})\}$ may or may not estimate the optimal regime within $\mathcal{D}_\eta$ if the posited model is *incorrect*.
- Even if the model is correct, if $X$ is *high-dimensional* and/or $Q(X, A; \beta)$ is complicated, the resulting regimes may be *too complex* for practice (*“black box”*).
Optimal restricted regime

**Suggests:** Consider *directly* a restricted set of regimes $\mathcal{D}_\eta$ of the form $d(x, \eta)$ *indexed* by $\eta$

- Write $d_\eta(x) = d(x, \eta)$
- Such regimes may be motivated by a regression model or based on *cost, feasibility* in practice, *interpretability*; e.g.,

  $$d(x, \eta) = I(x_1 < \eta_0, x_2 < \eta_1)$$

- $\mathcal{D}_\eta$ *may or may not* contain $d^{opt}$, but still of interest
- *Optimal restricted regime* $d^{opt}_\eta(x) = d(x, \eta^{opt})$,

  $$\eta^{opt} = \arg \max_\eta E\{ Y^*(d_\eta) \}$$

- Estimate the optimal restricted regime by *estimating* $\eta^{opt}$
Approach: Maximize a “good” estimator for $E\{Y^*(d_\eta)\}$ in $\eta$

- **Missing data** analogy: For fixed $\eta$, define

$$C_\eta = Ad(X, \eta) + (1 - A)\{1 - d(X, \eta)\}$$

- $C_\eta = 1$ if the treatment received is *consistent with* having following $d_\eta$ and $= 0$ otherwise
- “**Full data**” are $\{X, Y^*(d_\eta)\}$
- “**Observed data**” are $(X, C_\eta, C_\eta Y)$
- Only subjects with $C_\eta = 1$ have observed outcomes *consistent with following* $d_\eta$; for the rest, such outcomes are *missing*
Estimating an optimal restricted regime

**Propensity score**: *Propensity* for treatment 1

\[ \pi(X) = \text{pr}(A = 1|X) \]

- **Randomized trial**: \( \pi(X) \) is known
- **Observational study**: Posit a model \( \pi(X; \gamma) \) (e.g., logistic regression) and obtain \( \hat{\gamma} \) using \( (A_i, X_i), i = 1, \ldots, n \)
- **Propensity** of receiving treatment *consistent with* \( d_\eta \)

\[
\pi_c(X; \eta) = \text{pr}(C_\eta = 1|X) \\
= E[Ad(X, \eta) + (1 - A)\{1 - d(X, \eta)\}|X] \\
= \pi(X)d(X, \eta) + \{1 - \pi(X)\}\{1 - d(X, \eta)\}
\]

- Write \( \pi_c(X; \eta, \gamma) \) with \( \pi(X; \gamma) \)
Estimating an optimal restricted regime

Inverse probability weighted estimator for $E\{Y^*(d_\eta)\}$:

$$IPWE(\eta) = n^{-1} \sum_{i=1}^{n} \frac{C_{\eta,i}Y_i}{\pi_c(X_i; \eta, \hat{\gamma})}.$$

- **Consistent** for $E\{Y^*(d_\eta)\}$ if $\pi(X; \gamma)$ (hence $\pi_c(X; \eta, \gamma)$) is correctly specified
- But only uses data from subjects with $C_{\eta} = 1$
Estimating an optimal restricted regime

Doubly robust augmented inverse probability weighted estimator:

$$AIPWE(\eta) = n^{-1} \sum_{i=1}^{n} \left\{ \frac{C_{\eta,i} Y_i}{\pi_c(X_i; \eta, \hat{\gamma})} - \frac{C_{\eta,i} - \pi_c(X_i; \eta, \hat{\gamma})}{\pi_c(X_i; \eta, \hat{\gamma})} m(X_i; \eta, \hat{\beta}) \right\}$$

$$m(X; \eta, \beta) = E\{Y^*(d_\eta)|X\} = Q(X, 1; \beta)d(X, \eta) + Q(X, 0; \beta)\{1 - d(X, \eta)\}$$

- $Q(X, A; \beta)$ is a model for $E(Y|X, A)$
- **Consistent if either** $\pi(X, \gamma)$ or $Q(X, A; \beta)$ is correct (doubly robust)
- Attempts to gain **efficiency** by using data from all subjects
Estimating an optimal restricted regime

**Result:** Estimators $\hat{\eta}^{opt}$ for $\eta^{opt}$ obtained by *maximizing* $\text{IPWE}(\eta)$ or $\text{AIPWE}(\eta)$ in $\eta$

- Estimated optimal restricted regime $\hat{d}_{\eta}^{opt}(x) = d(x, \hat{\eta}^{opt})$
- *Non-smooth* in $\eta$; need suitable *optimization techniques*
- Estimators for $E\{ Y^*(d_\eta) \}$

\[
\text{IPWE}(\hat{\eta}_{\text{IPWE}}^{opt}) \text{ or } \text{AIPWE}(\hat{\eta}_{\text{AIPWE}}^{opt})
\]

Can calculate *standard errors*

- *Semiparametric theory*: $\text{AIPWE}(\eta)$ is *more efficient* than $\text{IPWE}(\eta)$ for estimating $E\{ Y^*(d_\eta) \}$
- Estimating regimes based on $\text{AIPWE}(\eta)$ should be “*better*”
- Zhang et al. (2012), *Biometrics*
Empirical studies

Extensive simulations: Qualitative conclusions

- Estimated optimal regime based on regression can achieve the true $E\{Y^*(d^{opt})\}$ if $Q(X, A; \beta)$ is correctly specified.
- But performs poorly if $Q(X, A; \beta)$ is misspecified.
- Estimated regimes based on IPWE($\eta$) are so-so even if the propensity model is correct.
- Estimated regimes based on AIPWE($\eta$) achieve the true $E\{Y^*(d^{opt})\}$ if $Q(X, A; \beta)$ is correctly specified even if the propensity model is misspecified.
- And are much better than the regression estimator when $Q(X, A; \beta)$ is misspecified.
Empirical studies

One representative scenario:

- **True** $E(Y|X, A)$ of form

  $$Q_t(X, A; \beta) = \exp\{\beta_0 + \beta_1 X_1^2 + \beta_2 X_2^2 + \beta_3 X_1 X_2 + A(\beta_4 + \beta_5 X_1 + \beta_6 X_2)\}$$

- **Misspecified** model for $E(Y|X, A)$

  $$Q_m(X, A; \beta) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + A(\beta_3 + \beta_4 X_1 + \beta_5 X_2)$$

- **True** propensity score

  $$\text{logit}\{\pi_t(X; \gamma)\} = \gamma_0 + \gamma_1 X_1^2 + \gamma_2 X_2^2$$

- **Misspecified** propensity score

  $$\text{logit}\{\pi_m(X; \gamma)\} = \gamma_0 + \gamma_1 X_1 + \gamma_2 X_2$$
Here: Both the *correct and misspecified* outcome regression models define a class of regimes

\[ \mathcal{D}_\eta = \{ I(\eta_0 + \eta_1 x_1 + \eta_2 x_2 > 0) \} \]

so that \( d^{opt} \in \mathcal{D}_\eta \)

- Other scenarios with \( d^{opt} \notin \mathcal{D}_\eta \)
Empirical studies

- **Truth:** $E\{ Y^*(d^{opt}) \} = 3.71$
- $V(\eta) = E\{ Y^*(d_{\eta}) \}$ (using $10^6$ Monte Carlo simulations)

<table>
<thead>
<tr>
<th>Method</th>
<th>$\hat{E}{ Y^*(d^{opt}) }$</th>
<th>SE</th>
<th>Cov</th>
<th>$V(\hat{\eta}^{opt})$</th>
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<tbody>
<tr>
<td>REG-$Q_t$</td>
<td>3.70 (0.14)</td>
<td></td>
<td></td>
<td>3.71 (0.00)</td>
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<tr>
<td>REG-$Q_m$</td>
<td>3.44 (0.18)</td>
<td></td>
<td></td>
<td>3.27 (0.19)</td>
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<td><strong>IPWE</strong></td>
<td>4.01 (0.26)</td>
<td>0.28</td>
<td>86.1</td>
<td>3.63 (0.07)</td>
</tr>
<tr>
<td><strong>AIPWE-$Q_t$</strong></td>
<td>3.72 (0.15)</td>
<td>0.15</td>
<td>94.7</td>
<td>3.70 (0.01)</td>
</tr>
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<td><strong>AIPWE-$Q_m$</strong></td>
<td>3.85 (0.21)</td>
<td>0.23</td>
<td>91.8</td>
<td>3.66 (0.07)</td>
</tr>
<tr>
<td><strong>PS correct</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>IPWE</strong></td>
<td>4.06 (0.22)</td>
<td>0.23</td>
<td>69.4</td>
<td>3.42 (0.20)</td>
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<td><strong>AIPWE-$Q_t$</strong></td>
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<td>0.15</td>
<td>95.2</td>
<td>3.70 (0.01)</td>
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<td><strong>AIPWE-$Q_m$</strong></td>
<td>3.81 (0.18)</td>
<td>0.19</td>
<td>94.1</td>
<td>3.57 (0.20)</td>
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<tr>
<td><strong>PS incorrect</strong></td>
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</tbody>
</table>
Multiple decisions

Same ideas, only more complicated…

- Find $d^{opt}$ so that a patient with baseline information $X_1 = x_1$ who receives all $K$ treatments according to $d^{opt}$ has expected outcome as large as possible

Potential outcomes under a regime $d \in D$:

- Initial information $X_1$, potential outcomes

$$X_2^*(d), \ldots, X_K^*(d), Y^*(d)$$

Optimal regime: $d^{opt}$ satisfies

- $E\{Y^*(d) | X_1 = x_1\} \leq E\{Y^*(d^{opt}) | X_1 = x_1\}$ for all $d \in D$ and values of $x_1$

- And thus $E\{Y^*(d)\} \leq E\{Y^*(d^{opt})\}$ for all $d \in D$
Complication:

- Can’t we just estimate the rules at each decision \textit{separately} using previous methods and “\textit{piece together}” the estimated regime from separate studies?
- \textit{Unfortunately not}
- \textit{Delayed effects}: E.g., $c_1$ may not appear best initially but may have enhanced effectiveness when followed by $m_1$
- $\implies$ Must use data from a \textit{single study} (same patients) reflecting the \textit{entire sequence of decisions} and use methods that \textit{acknowledge} this
Observed data

Data required:

\[(X_1i, A_1i, X_2i, A_2i, \ldots, X_{(K-1)i}, A_{(K-1)i}, X_Ki, A_Ki, Y_i), \ i = 1, \ldots, n, \ i.i.d\]

- \(X_1 = \text{Baseline covariate information}\)
- \(X_k, k = 2, \ldots, K = \text{intermediate information}\) observed between decisions \(k - 1\) and \(k\)
- \(A_k, k = 1, \ldots, K = \text{treatment received}\) at decision \(k\)
- \(Y = \text{observed outcome}\); can be \(\text{ascertained after}\) decision \(K\) or can be a \(\text{function}\) of \(X_2, \ldots, X_K\)

Studies:

- Longitudinal observational
- \(\text{Sequential, Multiple Assignment, Randomized Trial}\)
Cancer example: Randomization at $s$
Estimating an optimal regime

**Sequential regression:** Using *backward induction* – illustrate for $K = 2$ and 2 treatment options $\{0, 1\}$ at each decision

- **Posit and fit a model** for $Q_2(X_1, A_1, X_2, A_2) = E(Y|X_1, A_1, X_2, A_2)$ and substitute in

$$d_2^{\text{opt}}(x_1, a_1, x_2) = I\{Q_2(x_1, a_1, x_2, 1) > Q_2(x_1, a_1, x_2, 0)\}$$

- Move *backward*: **posit and fit a model** for expected outcome assuming $d_2^{\text{opt}}(x_1, a_1, x_2)$ is used to determine treatment at decision 2 *in the future*, i.e.

$$Q_1(X_1, A_1) = E[\max\{Q_2(X_1, A_1, X_2, 0), Q_2(X_1, A_1, X_2, 1)\}|X_1, A_1]$$

and substitute in

$$d_1^{\text{opt}}(x_1, a_1) = I\{Q_1(x_1, 1) > Q_1(x_1, 0)\}$$

- **Q-learning**, form of *dynamic programming, reinforcement learning* in computer science

- See Schulte et al. (2013), *Statistical Science*, for overview
Estimating an optimal regime

Inverse weighted methods: Analogy to methods for semiparametric estimation with monotone coarsening (like a dropout problem)

- Restricted class $\mathcal{D}_\eta$
- Generalization of $IPWE(\eta)$, $AIPWE(\eta)$
- Subjects are included as long as observed sequential treatments are consistent with following $d_\eta$
- See Zhang et al. (2013), Biometrika

In either case: Require a generalization of the no unmeasured confounders assumption
Future challenges

- Estimation of optimal treatment regimes is a *wide open* area of research
- *High-dimensional* covariate information? Regression *model selection*?
- “*Black box*” vs. *restricted class* of regimes?
- *Design considerations* for SMARTs?
- Alternative formulation as an *optimal classification problem*, e.g., Zhang et al. (2012), *Stat*
Recognition

2013 MacArthur Fellow Susan Murphy and Jamie Robins


Augmented inverse propensity weighted estimator

Under “MAR”: $Y^*(d_\eta) \perp C_\eta \mid X$

- If $\widehat{\gamma} \xrightarrow{p} \gamma^\ast$ and $\widehat{\beta} \xrightarrow{p} \beta^\ast$, this estimator $\xrightarrow{p}$

\[
E \left\{ \frac{C_\eta Y}{\pi_c(X; \eta, \gamma^\ast)} - \frac{C_\eta - \pi_c(X; \eta, \gamma^\ast)}{\pi_c(X; \eta, \gamma^\ast)} m(X; \eta, \beta^\ast) \right\}
\]
\[
= E \left[ Y^*(d_\eta) + \left\{ \frac{C_\eta - \pi_c(X; \eta, \gamma^\ast)}{\pi_c(X; \eta, \gamma^\ast)} \right\} \{ Y^*(d_\eta) - m(X; \eta, \beta^\ast) \} \right]
\]
\[
= E\{ Y^*(d_\eta) \} + E \left\{ \left\{ \frac{C_\eta - \pi_c(X; \eta, \gamma^\ast)}{\pi_c(X; \eta, \gamma^\ast)} \right\} \{ Y^*(d_\eta) - m(X; \eta, \beta^\ast) \} \right\}
\]

- Hence the estimator is consistent for $E\{ Y^*(d_\eta) \}$ if either
  - $\pi(X; \gamma^\ast) = \pi(X) \Rightarrow \pi_c(X; \eta, \gamma^\ast) = \pi_c(X; \eta)$ (propensity correct)
  - $Q(X, A; \beta^\ast) = Q(X, A) \Rightarrow m(X; \eta, \beta^\ast) = m(X; \eta)$ (regression correct)

- Double robustness