Finding a compromise between information and regret in clinical trials

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Luc Pronzato

I know Luc since 2014...

Sophia Antipolis, I3S, Algorithmes: Luc works in I3S since 1992...

Luc, Antibes, sea: leisure or work?
Optimal allocations in clinical studies
...an optimal design problem...

■ 1. Compromise between information and ethics
   - Clinical studies.
   - Objectives of adaptive allocation.
   - Information, ethics and compromise criterion.

■ 2. Allocation rules converging to the optimum
   - Equivalence theorem: characterization of optimal allocation.
   - Oracle allocation rule.
   - Randomized oracle rule.

■ 3. CARA and empirical process allocation
   - CARA type allocation.
   - Allocation based on empirical measures.
   - Compromise procedures proposed in literature.

■ 4. Conclusion and perspectives
Optimal designs

Design space $\mathcal{X}$

Parametric or non-parametric model(s): $f(x, \theta), x \in \mathcal{X}$

Criterion $G$ to maximize or minimize

- Choose measure $\xi = \begin{pmatrix} w_1 & \cdots & w_k \\ x_1 & \cdots & x_k \end{pmatrix}$ to optimize $G(\xi)$
- Generate a sequence $\{x_1, \ldots, x_n\}$ to (quasi-)optimize $G(x_1, \ldots, x_n)$
Clinical trials

n subjects. i-th subject:

\[ X_i, T_i, Y_i \]

covariates, allocation, outcome

Assumptions:

- \( \mathbb{E}(Y_i|X_i = x, T_i = k) = \eta_k(x, \theta_k), \ Y_i \in \mathcal{Y} \subset \mathbb{R}, \ k = 1, \ldots, K. \)
- \( X_i \) are i.i.d. \( \sim \mu, \ (X_i \in \mathcal{X} \subset \mathbb{R}^d, \mu(x) \geq 0, \int_{\mathcal{X}} \mu(dx) = 1) \)
- covariate-adaptive allocations

\[ \mathbb{P}(T_i = k|X_i = x) = \pi_k(x) \]

Example 1: Logistic regression.
\( \mathcal{Y} = \{0, 1\}, \mathcal{X} = [-1, 1], \ K = 2 \)

\[ \mathbb{P}(Y_i = 1|X_i = x, T_i = k) = \eta_k(x, \theta_k) \]

\[ \eta_k(x, \theta_k) = \frac{1}{1 + e^{-\theta_k x}} \]

\( \theta_1 = 5, \theta_2 = -5. \)
Clinical trials

n subjects. i-th subject:

\[ X_i, T_i, Y_i \]

covariates, allocation, outcome

Assumptions:
- \( \mathbb{E}(Y_i|X_i = x, T_i = k) = \eta_k(x, \theta_k), \)
- \( X_i \) are i.i.d. \( \sim \mu, \)
- covariate-adaptive allocations

\[ \mathbb{P}(T_i = k|X_i = x) = \pi_k(x) \]
Clinical trials

n subjects. i-th subject:

\[ X_i, T_i, Y_i \]

covariates, allocation, outcome

Assumptions:

- \( \mathbb{E}(Y_i|X_i = x, T_i = k) = \eta_k(x, \theta_k) \),
- \( X_i \) are i.i.d. \( \sim \mu \),
- covariate-adaptive allocations

\[ \mathbb{P}(T_i = k|X_i = x) = \pi_k(x) \]

10 subjects allocated
Clinical trials

n subjects. i-th subject:

\[ X_i, T_i, Y_i \]

covariates, allocation, outcome

Assumptions:

- \( \mathbb{E}(Y_i|X_i=x, T_i=k) = \eta_k(x, \theta_k) \),
- \( X_i \) are i.i.d. \( \sim \mu \),
- covariate-adaptive allocations

\[ \mathbb{P}(T_i = k|X_i = x) = \pi_k(x) \]

Example 2: Linear regression with i.i.d errors.
\( \mathcal{Y} = \mathbb{R}, \mathcal{X} = [0, 1], K = 2 \)
\( Y_i = \eta_k(X_i, \theta_k) + \epsilon_i \) if \( T_i = k \), \( \epsilon_i \perp X_i \)
\( \eta_k(x, \theta_k) = a_k + b_k x \)
\( a_1 = 0, b_1 = 10, a_2 = 5, b_2 = -4. \)
Clinical trials

n subjects. i-th subject:

\[ X_i, T_i, Y_i \]

covariates, allocation, outcome

Assumptions:

- \( \mathbb{E}(Y_i|X_i = x, T_i = k) = \eta_k(x, \theta_k) \),
- \( X_i \) are i.i.d. \( \sim \mu \),
- covariate-adaptive allocations

\[ \mathbb{P}(T_i = k|X_i = x) = \pi_k(x) \]
Objectives of clinical trial

Objectives:

- **Information**: to better estimate \( \theta = (\theta_1, \ldots, \theta_K) \)
- **Ethics**: to favor allocation to best treatment \( \eta^*(X_i) = \max_{k=1 \ldots K} \eta_k(X_i, \theta_k) \)

\[
Y_i | T_i = k \text{ are i.i.d with } \quad \mathbb{E}(Y_i | T_i = k) = \int_{\chi} \eta_k(x, \theta_k) \pi_k(x)\mu(dx) \]

\[
\eta_k^{\text{new}}(x, \theta_k) = \eta_k(x, \theta_k)\pi_k(x) \quad \text{or} \quad \xi = (\xi_1, \ldots, \xi_K) \in \Xi(\mu)
\]

\[
\Xi(\mu) = \{\xi = (\xi_1, \ldots, \xi_K) \mid \xi_k \text{ is } \mu - \text{a.c.}, \sum_{k=1}^K \xi_k = \mu, \xi_k \geq 0\}
\]

is a convex set.
Objectives:

**Information**: to better estimate \( \theta = (\theta_1, \ldots, \theta_K) \)

Maximize \( \Psi(M(\xi, \theta)) \):

- \( \Psi \) strictly concave, Lowener increasing, differentiable
- \( M(\xi, \theta) = \sum_{k=1}^{K} \int_X M_k(x, \theta_k) \xi_k \, dx \) Fisher information.

Example: \( \Psi(M) = \log \det(M), \quad \Psi(M) = -\text{tr}(M^{-q}), \quad q \in (0, +\infty) \).

Motivation:
*Asymptotic normality of ML estimator \( \hat{\theta}_n \),*

\[
\sqrt{n}(\hat{\theta}_n - \theta) \to \mathcal{N}(0, M(\xi, \theta)^{-1})
\]

*Unbiased estimators: Cramer-Rao bound for variance.*
Optimal Allocation

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Compromise between information and ethics

Allocation rules converging to the optimum

CARA and empirical process allocation

Information

Objectives:

- **Information**: to better estimate \( \theta = (\theta_1, \ldots, \theta_K) \) \( \Rightarrow \) \( \max_{\xi \in \Xi(\mu)} \psi(M(\xi, \theta)) \).

\( \psi \) concave, \( \Xi(\mu) \) convex set \( \Rightarrow \) \( \xi^*(x, \theta) = \arg \max_{\xi \in \Xi(\mu)} \psi(M(\xi, \theta)) \)

Example 1: logistic regression

\( Y \in \{0, 1\}, X = [-1, 1], \mu = \mathcal{U}([-1, 1]), \theta_k \in \mathbb{R}, \) no covariates in common.

\( \Rightarrow \) \( M(\xi, \theta) \) has a block structure:

\[
M(\xi, \theta) = \begin{pmatrix}
\int_0^1 \frac{x^2}{\eta(x, \theta_1)(1-\eta(x, \theta_1))} \xi_1(dx) & 0 \\
0 & \int_0^1 \frac{x^2}{\eta(x, \theta_2)(1-\eta(x, \theta_2))} \xi_2(dx)
\end{pmatrix}
\]

\( \psi(M(\xi, \theta)) = \log(\det(M(\xi, \theta))) = \sum_{k=1}^2 \log \left( \int_0^1 \frac{x^2 \pi_k(x)}{\eta_k(x, \theta_k)(1-\eta_k(x, \theta_k))} dx \right) \)
Information

Objectives:

- **Information**: to better estimate $\theta = (\theta_1, \ldots, \theta_K)$ \(\Rightarrow\) \(\max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta))\).

\(\Psi\) concave, \(\Xi(\mu)\) convex set \(\Rightarrow\) \(\xi^*(x, \theta) = \arg\max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta))\)

Example 2: linear regression with i.i.d. \(N(0, 1)\) errors.
\(\mu = \mathcal{U}([0, 1]). \) \(\eta_k(x, \theta_k) = a_k + b_k x,\) no common parameters.
\(\Rightarrow\) \(M(\xi, \theta)\) has a block structure:

\[
M(\xi) = \begin{pmatrix}
\int_0^1 \xi_1(dx) & \int_0^1 x \xi_1(dx) & 0 & 0 \\
0 & 0 & 0 & 0 \\
\int_0^1 x \xi_1(dx) & \int_0^1 x^2 \xi_1(dx) & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & \int_0^1 \xi_2(dx) & \int_0^1 x \xi_2(dx) \\
0 & 0 & \int_0^1 x \xi_2(dx) & \int_0^1 x^2 \xi_2(dx)
\end{pmatrix}
\]
Objectives:

- Information: to better estimate \( \theta = (\theta_1, \ldots, \theta_K) \) \( \Rightarrow \max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta)). \)

\( \Psi \) concave, \( \Xi(\mu) \) convex set \( \Rightarrow \xi^*(x, \theta) = \arg \max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta)) \)

Example 2: linear regression with i.i.d. \( N(0, 1) \) errors.
\( \mu = \mathcal{U}([0, 1]) \). \( \eta_k(x, \theta_k) = a_k + b_k x \), no common parameters.
\( \Rightarrow M(\xi, \theta) \) has a block structure:

\[
M(\xi) = \begin{pmatrix}
m_1 & m_2 & 0 & 0 \\
m_2 & m_3 & 0 & 0 \\
0 & 0 & 1 - m_1 & \frac{1}{2} - m_2 \\
0 & 0 & \frac{1}{2} - m_2 & \frac{1}{3} - m_3 \\
\end{pmatrix}
\]

\[
m_1 = \int \pi_1(x) dx, \quad m_2 = \int x \pi_1(x) dx, \quad m_3 = \int x^2 \pi_1(x) dx.
\]

\( \Psi(M(\xi)) = \log \det(M(\xi)) = \log \left( m_1 \cdot m_3 - m_2^2 \right) + \log \left( (1 - m_1)(\frac{1}{3} - m_3) - \left( \frac{1}{2} - m_2 \right)^2 \right) \)
Objectives:

- **Information**: to better estimate \( \theta = (\theta_1, \ldots, \theta_K) \) \( \Rightarrow \max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta)) \).

\( \Psi \) concave, \( \Xi(\mu) \) convex set \( \Rightarrow \xi^*(x, \theta) = \arg\max_{\xi \in \Xi(\mu)} \Psi(M(\xi, \theta)) \)

Example 3: linear regression with i.i.d. \( N(0, 1) \) errors.
\( \mu = \mathcal{U}([-1, 1]) \). \( \eta_k(x, \theta_k) = a + b_k x \), with one common parameter.

\[
M(\xi) = \begin{pmatrix}
1 & m_2 & -m_2 \\
m_2 & m_3 & 0 \\
-m_2 & 0 & \frac{1}{3} - m_3
\end{pmatrix}
\]

\( m_2 = \frac{1}{2} \int_{\mathbb{R}}^1 x \pi_1(x) dx \),
\( m_3 = \frac{1}{2} \int_0^1 x^2 \pi_1(x) dx \).
Regret and reward

Objectives:

- **Ethics**: to favor allocation to best treatment $\eta^*(X_i) = \max_{k=1,...,K} \eta_k(X_i, \theta_k)$

Minimize the regret

$$R(\xi, \theta) = \sum_{k=1}^{K} \int_{\mathcal{X}} (\eta^*(x, \theta) - \eta_k(x, \theta)) \xi_k(dx)$$

Maximize the reward

$$\Phi(\xi, \theta) = \sum_{k=1}^{K} \int_{\mathcal{X}} \eta_k(x, \theta) \xi_k(dx)$$

Best treatment allocation:

$$\frac{d\xi_k}{d\mu}(x, \theta) = \pi_k(x, \theta) = \begin{cases} 1, & \text{if } \eta_k(x, \theta_k) = \eta^*(x, \theta) \\ \frac{1}{m}, & \text{if } m \text{ ties} \\ 0, & \text{otherwise} \end{cases}$$
Information, ethics and compromise

Problem: information OR ethics? May be contradictory!

Example: \( Y_i \in \{0, 1\} \), \( \eta_i(x, \theta) = \theta_i \), no covariates

Information Neyman allocation: \( \mathbb{P}(T_i = 1) = \frac{\sqrt{\theta_1(1-\theta_1)}}{\sqrt{\theta_1(1-\theta_1)} + \sqrt{\theta_2(1-\theta_2)}} \):

- maximizes the power of Wald’s test \( (\text{with statistics } \frac{\hat{\theta}_n - \theta}{\sqrt{\theta_n}}) \).
- favors inferior treatment if \( \theta_1 + \theta_2 > 1 \).

Ethics Best treatment allocation: \( \mathbb{P}(T_i = 1) = \delta_{\theta_1 \geq \theta_2} \) no information about the worth treatment parameters.

Solution: Compromise criterion = convex combination of information and reward:

\[
\text{Maximize } (1 - \alpha) \cdot \Psi(M(\xi, \theta)) + \alpha \cdot \Phi(\xi, \theta), \quad \alpha \in (0, 1)
\]

Equivalent to \[
\begin{cases}
\max \Psi(M(\xi, \theta)) \\
\Phi(\xi, \theta) \geq \tau(\alpha, \theta).
\end{cases}
\]
**Optimal allocation measure**

\[ K = 2. \text{ Optimal allocation measure: } \xi^*_\alpha(\theta) = \arg \max_{\xi \in \Xi(\mu)} H_\alpha(\xi, \theta) \]

Asymptotic optimality criterion:

\[
H_\alpha(\xi, \theta) = (1 - \alpha) \psi \left( \sum_{k=1}^{2} \mathcal{M}_k(\xi_k, \theta) \right) + \alpha \sum_{k=1}^{2} \phi_k(\xi_k, \theta).
\]

\[
\mathcal{M}_k(\theta, \xi_k) = \int_X M_k(x, \theta) \xi_k(dx) \quad \text{and} \quad \phi_k(\theta, \xi_k) = \int_X \eta_k(x, \theta) \xi_k(dx).
\]

Convex set of allocation measures

\[
\Xi(\mu) = \{ \xi = (\xi_1, \xi_2) \in \mathcal{M}_X^2 \mid \xi_1 + \xi_2 = \mu, \xi_1 \geq 0, \xi_2 \geq 0, \xi_1, \xi_2 \text{ a.c. wrt } \mu \}.
\]

Maximize concave function \( H_\alpha(\xi, \theta) \) on a convex set \( \Xi(\mu) \Rightarrow \text{Equivalence Theorem} \)
**Equivalence Theorem**

Under differentiability conditions: 
\( \xi^*_\alpha(\theta) \) can be characterized through directional derivatives of \( H_\alpha \).

**Equivalence theorem**

\( \xi^*_\alpha = \arg \max_{\xi \in \Xi(\mu)} H_\alpha(\xi, \theta) \) is characterized by the function \( \Delta_{12}(\xi, x, \theta) \):

1. \( \Delta_{12}(\xi, x, \theta) \geq 0 \quad \xi_1^*-\text{a.s.}, \quad \Delta_{12}(\xi, x, \theta) \leq 0 \quad \xi_2^*-\text{a.s.} \)

2. There exist \( X_1, X_2 \subset X \) such that
   - \( \xi_1^* = \mu \) on \( X_1 \), \( \xi_2^* = \mu \) on \( X_2 \),
   - \( \inf_{x \in X_1} \Delta_{12}(\xi, x, \theta) \geq 0 \), \( \sup_{x \in X_2} \Delta_{12}(\xi, x, \theta) \leq 0 \)
   - \( \Delta_{12}(\xi, x, \theta) = 0 \), if \( x \in X \setminus (X_1 \cap X_2) \).

- Here \( \Delta_{12}(\xi, x, \theta) = G_1(\xi, x, \theta) - G_2(\xi, x, \theta) \).
- Directional derivatives (in direction of point mass at \( x \))

\[
G_1(\xi, x, \theta) = \lim_{\gamma \to 0^+} \gamma^{-1} [H_\alpha(\xi + \gamma(\delta_x, 0), \theta) - H_\alpha(\xi, \theta)]
\]

\[
G_2(\xi, x, \theta) = \lim_{\gamma \to 0^+} \gamma^{-1} [H_\alpha(\xi + \gamma(0, \delta_x), \theta) - H_\alpha(\xi, \theta)]
\]
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Logistic regression example

\[ X = [0, 1] \text{ and } \mu = \mathcal{U}([0, 1]). \quad \Psi(M) = \log \det(M). \]

Logistic regression \( \eta_k(x, \theta) = 0.25 + 0.5 \cdot \frac{1}{1 + \exp(-(\theta_{k1}-x)\theta_{k2})} \).

\[ \theta = (\theta_1, \theta_2), \quad \theta_k \in \mathbb{R}^2, \ k = 1, 2. \]

Figure: Left: Statistical model of response \( \eta_1(x, \theta_1) \) et \( \eta_2(x, \theta_2) \).
Middle: Function \( \Delta_{12}(\xi_2, x, \theta) \) from Equivalence Theorem for \( \alpha = 0.7 \).
Right: Ensembles \( X_1 \) (treatment 1) et \( X_2 \) (treatment 2) as function of \( \alpha \).
Rule 1. Oracle allocation rule

(necessitates the knowledge of $\mu$, $\theta$ and construction of $\xi^*_\alpha(\theta)$)

$$\mathbb{P}(T_{n+1} = 1|X_{n+1} = x) = \pi^*_\alpha(x, \theta)$$

with $\pi^*_\alpha(x, \xi, \theta) = \frac{d\xi^*_1,\alpha}{d\mu}(x, \theta)$.

Remark: $\pi^*_\alpha(x, \theta) = 1$ on a subset $x \in X_0 \subset X$ is possible.

Example:
$$\mathbb{P}(T_i = 2[X_i = x]) = 1 \text{ if } x \in [0, A] \cap (B, C),$$
$$\mathbb{P}(T_i = 1[X_i = x]) = 1 \text{ if } x \in (A, B) \cap (C, 1).$$
Empirical information and reward

Empirical compromise criterion:

\[(1 - \alpha) \cdot \Psi(M_n(\theta)) + \alpha \cdot (\Phi_n(\theta)), \; \alpha \in (0, 1)\]

Empirical reward:

\[\Phi_n(\theta) = \frac{1}{n} \sum_{k=1}^{2} \sum_{i=1, T_i = k}^{n} \eta_k(X_i, \theta)\]

Empirical information

\[\Psi(M_n(\theta)) \quad \text{with} \quad M_n(\theta) = \frac{1}{n} \sum_{k=1}^{2} \sum_{i=1, T_i = k}^{n} M_k(X_i, \theta)\]

- \(\delta_{T_i = 1} X_i\) are i.i.d. \(\sim \xi^*_1(\theta)\).
- Empirical allocations \(\hat{\xi}_{\alpha n} = \frac{1}{n} \sum_{i=1}^{n} (\delta_{T_i = 1}, \delta_{T_i = 2})\) are asymptotically optimal:

\[H_\alpha(\hat{\xi}_{\alpha n}, \theta) \rightarrow H_\alpha(\xi^*_\alpha(\theta), \theta) \; \text{a.s.}\]
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Randomized oracle randomization

\[ \pi^*_\alpha(x, \theta) = 1 \] for \( x \in X_0 \) with \( \mu(X_0) > 0 \) \( \Rightarrow \) prediction bias.

Optimal allocation measure under a constraint of randomization level \( \beta \in (0, 1) \):

\[ \xi^*_{\alpha, \beta}(\theta) = \beta \xi_{\mu} + \tilde{\xi}_{\alpha, \beta}(\theta) \quad \text{with} \]

\[ \xi_{\mu} = \left( \frac{\mu}{2}, \frac{\mu}{2} \right) \quad \text{and} \quad \tilde{\xi}_{\alpha, \beta}(\theta) = \arg \max_{\xi \in \Xi(\mu(1-\beta))} H_{\alpha}\left( \beta \xi_{\mu} + \xi, \theta \right). \]

Randomized Oracle Rule 1.

\[ \mathbb{P}( T_{n+1} = 1 | X_{n+1} = x ) = \frac{\beta}{2} + \pi^*_{\alpha, \beta}(x, \theta) \]

with \( \pi_{\alpha, \beta}(x, \theta) = \frac{d\tilde{\xi}_{1, \alpha, \beta}}{d\mu}(x, \theta). \)
Example of logistic regression

\[ \mathcal{X} = [0, 1]. \; \theta = (\theta_1, \theta_2), \; \theta_k \in \mathbb{R}^2, \; k = 1, 2. \]

Logistic regression \( \eta_k(x, \theta) = a_k + 0.5 \cdot \frac{1}{1 + \exp(-\theta_{k,1} - \theta_{k,2}x)} \).

\( a_1 = 0.1, \; a_2 = 0.25 \)

**Figure**: Left: Outcome models.
Right: Randomization level \( \beta = 0.2 \), deterministic part of allocation function \( \tilde{\xi}_{\alpha, \beta}(\theta) \) as function of \( \alpha \).
Randomized *oracle* rule

\( \alpha, \beta \in (0, 1) \). Asymptotic properties of:

- Empirical allocations \( \hat{\xi}_n = \frac{1}{n} \sum_{i=1}^{n} T_i X_i \) converge to \( \xi_{\alpha, \beta}^* \).
- Compromise criterion is asymptotically optimal: \( H(\hat{\xi}_n, \theta) \xrightarrow{n \to \infty} H(\xi_{\alpha, \beta}^*, \theta) \).
- Allocation proportions \( \rho_n = \frac{1}{n} \sum_{i=1}^{n} T_i \) are consistent and asymptotically normal:
  \[
  \rho_n \xrightarrow{n \to \infty} \rho_k^*(\theta) \quad \text{where} \quad \rho_k^*(\theta) := \xi_k^*(X, \theta).
  \]
  \[
  \sqrt{n} \left( \rho_n - \rho_k^*(\theta) \right) \xrightarrow{d} \mathcal{N}(0, \Sigma^*) \quad \Sigma^* = \text{diag}(\rho_k^*(\theta)) - \rho_k^*(\theta)\rho_k^*(\theta)^t
  \]
- Bounds on regret(reward) and information.
Adaptive sequential allocations:

Subjects arrive sequentially ⇒ can use past covariates, allocations, outcomes information.

Allocation functions:  \( P(T_n = k | X_n = x, \mathcal{F}_n) \)

where \( \mathcal{F}_n = \sigma(X_1, \ldots, X_{n-1}, T_1, \ldots, T_{n-1}, Y_1, \ldots, Y_{n-1}) \)

The sequence \( (T_1, \ldots, T_n) \) is a stochastic process.

Motivation:

\( K = 2, \mathcal{Y} = \{0, 1\}, \eta_k(x) = \theta_k, \theta_k \in [0, 1], N_{n,1} := \sum_{i=1}^{n} (T_i = 1). \)

Variance of \( (N_{n,1} - \frac{n}{2}) \) is of order \( n \) for  \( P(T_n = 1) = \frac{1}{2}, \)

bounded Biased Coin Design BCD\((p), \quad p \in (\frac{1}{2}, 1] \)

\[
P(T_{n+1} = 1 | \mathcal{F}_n) = \begin{cases} 
    p, & 2N_{n,1} < n \\
    \frac{1}{2}, & 2N_{n,1} = n \\
    (1 - p), & 2N_{n,1} > n 
\end{cases}
\]

[Efron1971],[Markaryan,Rosenberger 2010]
Covariate Adjusted Response Adaptive designs

\[ \mu \text{ known, } \theta \text{ unknown } \Rightarrow, \text{ use } \hat{\theta}_n \text{ (well defined } n > n_0, \beta > 0) \]  

[Zhang et al.'07]

- **Rule 2** Covariate-Adjusted Response Adaptive targeting \( \xi^*_\alpha(\theta) \):

\[ \mathbb{P}(T_{n+1} = 1 | X_{n+1} = x, \mathcal{F}^n) = \pi(x, \hat{\theta}_n) \]

here \( \pi \) is computed from \( \xi^*_{\alpha, \beta}(\hat{\theta}_n) \).

Asymptotic properties:

- Consistency and asymptotic normality of \( \hat{\theta}_n \):

- Asymptotic optimality of \( \hat{\xi}_{n} = \frac{1}{n} \sum_{n=1}^{n} (\delta_{T_i=1} \delta_{X_i}(.), \delta_{T_i=2} \delta_{X_i}(.)) \)

- Asymptotic properties of proportions.
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_allocation based on empirical process._

- \( \theta \) known, \( \mu \) unknown \( \Rightarrow \) replace \( \xi_\alpha^*(\theta) \) by \( \hat{\xi}_{n} \).

- **Rule 3.** Allocation based on empirical process

\[
\mathbb{P}(T_{n+1} = 1 | T^n, X^n, X_{n+1} = x) = \pi_n(x, \theta)
\]

with \( \pi(x, \xi, \theta) = \frac{d\xi_1}{d\mu}(x, \theta) \) et \( \hat{\xi}_{n} = \frac{1}{n} \sum_{1}^{n}(\delta_{T_i=1} \delta_{X_i}, \delta_{T_i=2} \delta_{X_i}) \).

- Asymptotic optimality: \( H_\alpha(\hat{\xi}_{n}, \theta) \rightarrow H_\alpha(\xi_\alpha^*, \beta(\theta), \theta) \) a.s.

- Simulations: \( \Rightarrow \) allocation proportions \( \rho_n \) very less that for rules 1 and 2.

- Randomization \( \beta > 0 \), \( \theta \) and \( \mu \) are unknown.

- **Rule 4.** Empirical procedure of CARA type use both \( \hat{\xi}_{n} \) and \( \hat{\theta}_n \)

\[
\mathbb{P}(T_{n+1} = 1 | \mathcal{F}^n, X_{n+1} = x) = \pi_n(x, \hat{\theta}_n).
\]
Logistic regression example

\[ \beta = 0, \ X = [0, 1]. \ \theta = (\theta_1, \theta_2), \ \theta_k \in \mathbb{R}^2, \ k = 1, 2. \]

Logistic regression \[ \eta_k(x, \theta) = \frac{1}{1 + \exp(-\theta_k,1 - \theta_k,2 x)}, \ \theta_k = (2, 10). \]

![Logistic regression example](image)

**Figure**: Variability of treatments proportions:
dotted = rule 3, red = rule 1, blue = limit law for rule 1.
Comparison with procedures proposed in literature

**Ad-hoc rules proposed in literature (logistic regression)**

- **Allocation based on covariates-adjusted odds ratio** [Rosenberger et al.’01]
  \[
P(T_{n+1} = 1 \mid F_n, X_{n+1} = x) = \frac{\eta_1(x, \hat{\theta}_n)(1 - \eta_2(x, \hat{\theta}_n))}{(1 - \eta_1(x, \hat{\theta}_n))\eta_2(x, \hat{\theta}_n)} \text{ odds ratio.}
\]

- **Modification of allocation rule from** [Hu&Zhu&Hu’15]
  \[
P(T_{n+1} = 1 \mid F_n, X_{n+1} = x) \frac{d_1^a \cdot e_1^b}{d_1^a \cdot e_1^b + d_2^a \cdot e_2^b}
\]
  with
  - \(a > 0, b > 0\).
  - **Information** \(d_k = d_k(\xi_n, x, \theta) = \text{tr}(M^{-1}(\xi_n, \theta)M_k(x, \theta))\)
  - **Inverse of reward** \(e_k = e_k(x, \theta) = 1/(1 - \eta_k(x, \theta))\).
Example: Logistic regression.

![Graph](image)

**Figure**: Red curve $\Psi(M(\xi^*_\alpha))$ vs. $R(\xi^*_\alpha)$ parametrized by $\alpha$.

- $\star$ = allocation based on odd rations [Rosenberger et al.'01].
- $\triangledown$ = modified procedure [Hu&Zhu&Hu'15] (from left to right $a = 1, b = 10, 6, 4, 3$.)

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**Optimal Allocation**

Asya Metelkina and Luc Pronzato

Compromise between information and ethics

Allocation rules converging to the optimum

CARA and empirical process allocation
Conclusion and perspectives

Fo more details see: [A. Metelkina, L. Pronzato “Information-regret compromise in covariate-adaptive treatment allocation” AoS’17]

Perspectives:

- Adaptation of efficient allocation procedure [Zhang&Hu AMJCU’09].
- Other forms of regret/reward, e.g. quadratic in \((\eta^* - \eta_k)\).
- Approximate computation of \(\theta \mapsto \Delta_{12}(x, \xi_\alpha^*(\theta), \theta)\).
- \(\alpha = \alpha(\tau') \) for \(R(\xi_\alpha^*) \leq \tau'\), so \(\Phi(\xi, \theta) \geq \tau(\tau', \theta)\).
- Sequence of \(\alpha_n\) tending to 0. At which speed?
- Bayesian approach (wrt to \(\theta\))