Sequential Design for Personalized Medicine

ICRA8

Mia Tackney[1], Prof. Dave Woods[1],
Dr. Kim May Lee[2], Dr. Ilya Shpitser[3], Prof. Peter Smith[1]

[1] University of Southampton [2] MRC Biostatistics Unit, Univeristy of Cambridge [3] Johns Hopkins University

Overview of talk

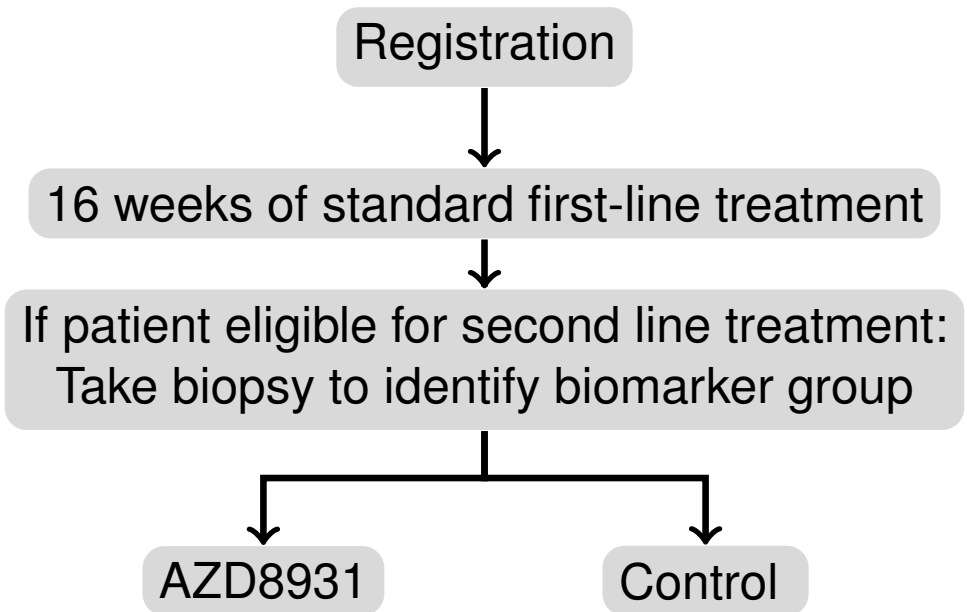
SC.DTP South Coast Doctoral Training Partnership

MOTIVATION

PERSONALIZED CLINICAL TRIALS

FOCUS4 (2004-present, UK) aims to find biomarker-targeted treatments for colon cancer.

Kaplan (2015)



PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

(0, 0) Neither Biomarker

PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

(0, 0) Neither Biomarker

(1, 0) First Biomarker

PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

(0, 0) Neither Biomarker

(1, 0) First Biomarker

(0, 1) Second Biomarker

PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

(0, 0) Neither Biomarker

(1, 0) First Biomarker

(0, 1) Second Biomarker

(1, 1) Both biomarkers

PERSONALIZED CLINICAL TRIALS

For example, if there are two binary biomarkers which may be linked to colon cancer, there are four biomarker subgroups of interest:

(0, 0) Neither Biomarker

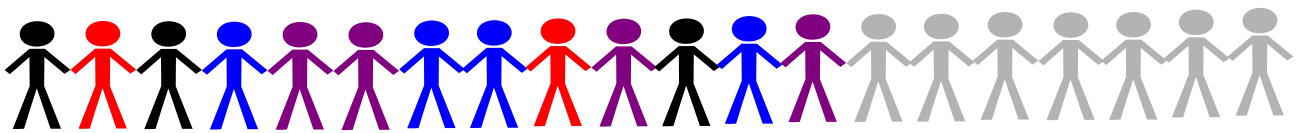
(1, 0) First Biomarker

(0, 1) Second Biomarker

(1, 1) Both biomarkers

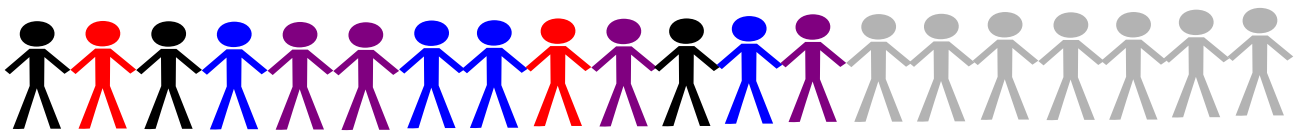
GIVEN THE BIOMARKER STATUS OF A PATIENT, HOW DO WE DECIDE WHETHER TO GIVE THEM THE TREATMENT OR THE CONTROL?

PERSONALIZED CLINICAL TRIALS



We need a method which allocates treatments to patients which is:

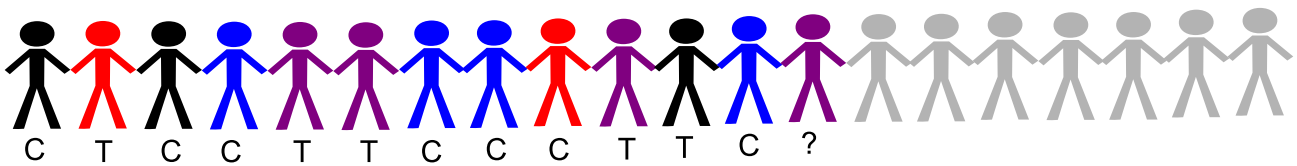
PERSONALIZED CLINICAL TRIALS



We need a method which allocates treatments to patients which is:

- Sequential.

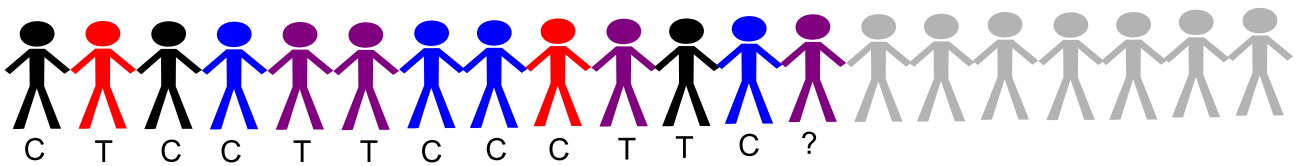
PERSONALIZED CLINICAL TRIALS



We need a method which allocates treatments to patients which is:

- Sequential.

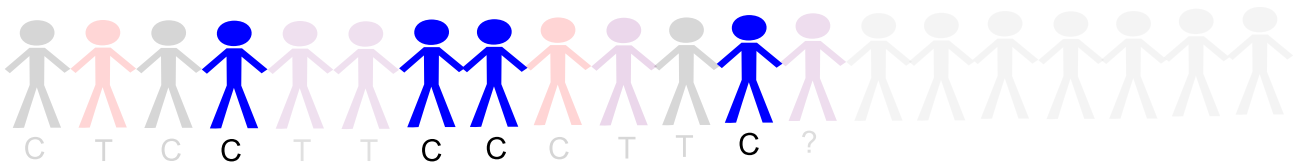
PERSONALIZED CLINICAL TRIALS



We need a method which allocates treatments to patients which is:

- Sequential.
- Able to estimate interactions between treatments and biomarkers with minimum possible variance.

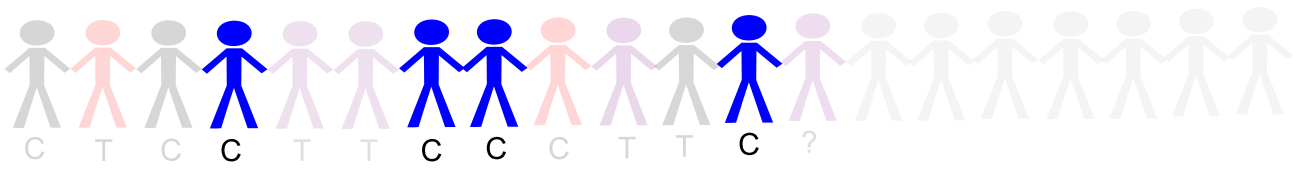
PERSONALIZED CLINICAL TRIALS



We need a method which allocates treatments to patients which is:

- Sequential.
- Able to estimate interactions between treatments and biomarkers with minimum possible variance.

PERSONALIZED CLINICAL TRIALS

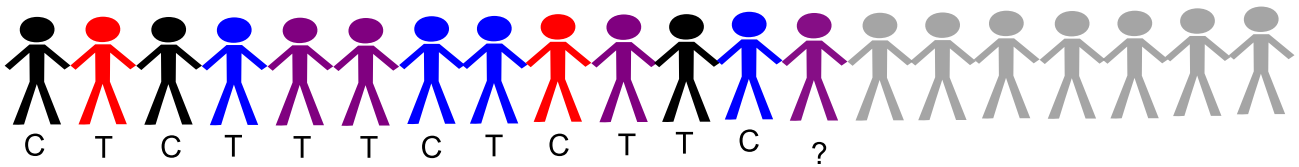


We need a method which allocates treatments to patients which is:

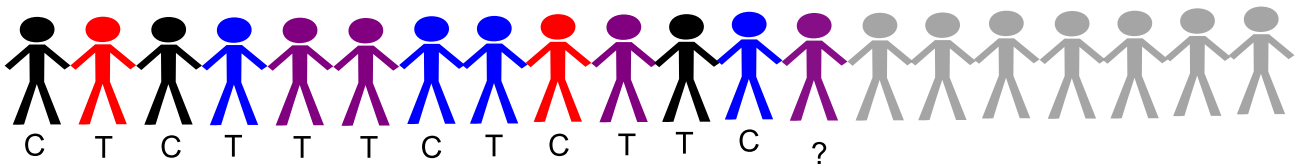
- Sequential.
- Able to estimate interactions between treatments and biomarkers with minimum possible variance.

  ... a random allocation can be unlucky.

Sequential Design with Covariates



Sequential Design with Covariates

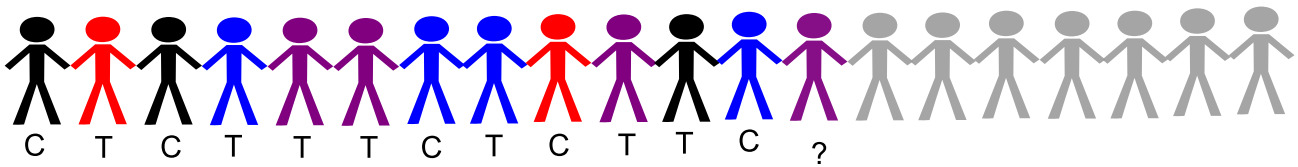


Myopic Approaches:

MINIMIZATION (POCOCK AND SIMON, 1975) Commonly used in clinical trials

ATKINSON (1982) Optimal design based approach

Sequential Design with Covariates

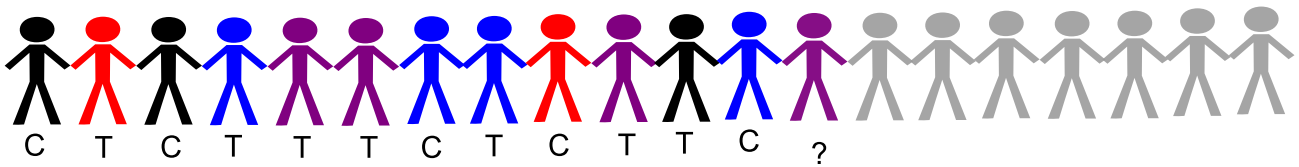


Myopic Approaches:

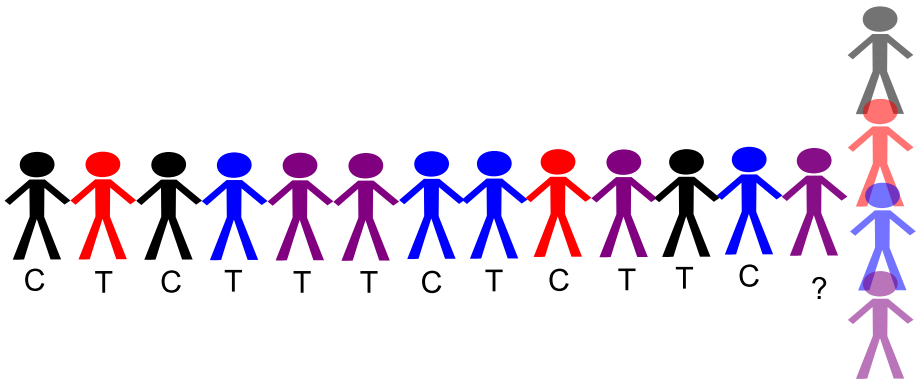
MINIMIZATION (POCOCK AND SIMON, 1975) Commonly used in clinical trials

ATKINSON (1982) Optimal design based approach

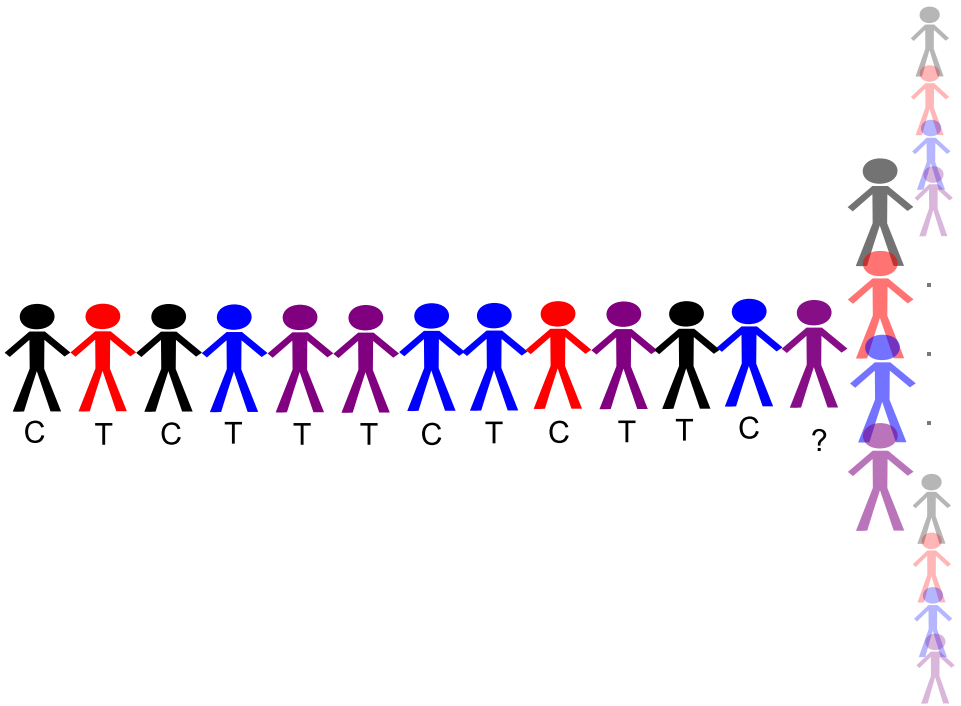
Sequential Design with Covariates



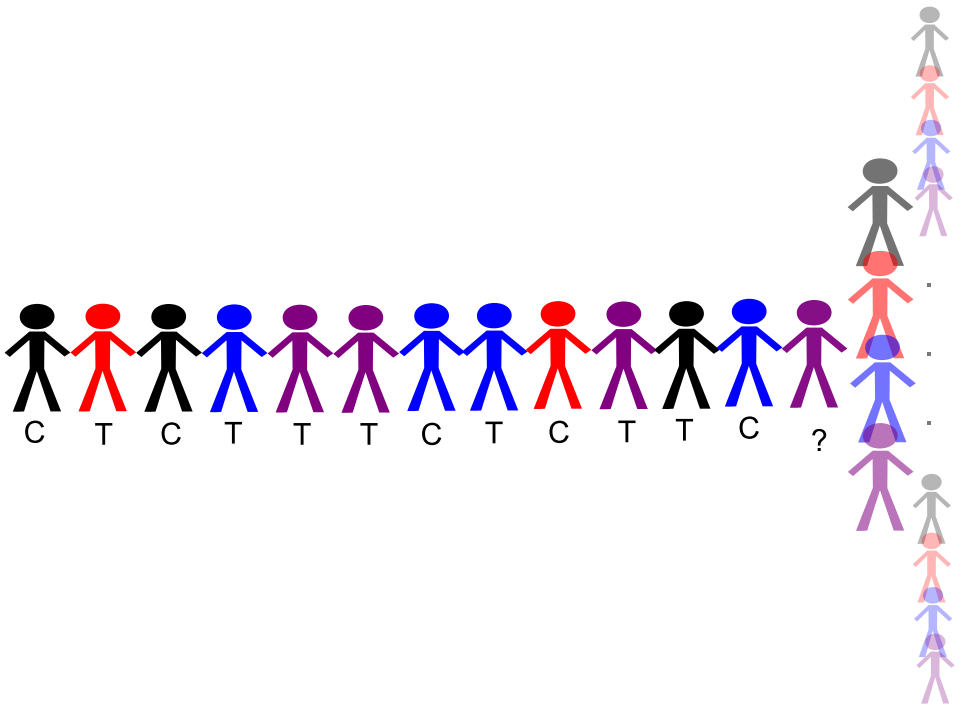
Sequential Design with Covariates



Sequential Design with Covariates



Sequential Design with Covariates

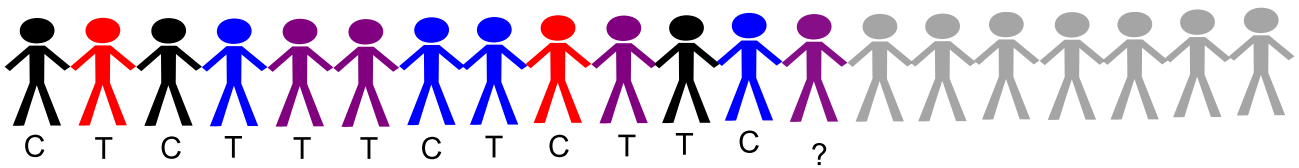


Nonmyopic Approaches:

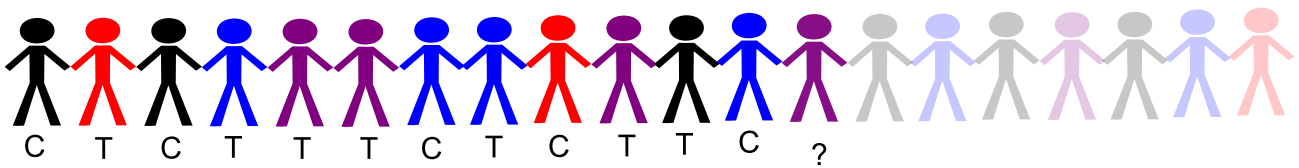
HUAN AND MARZOUK (2016) Dynamic Programming

CHENG AND BERRY (2007) Clinical trials for dose-finding

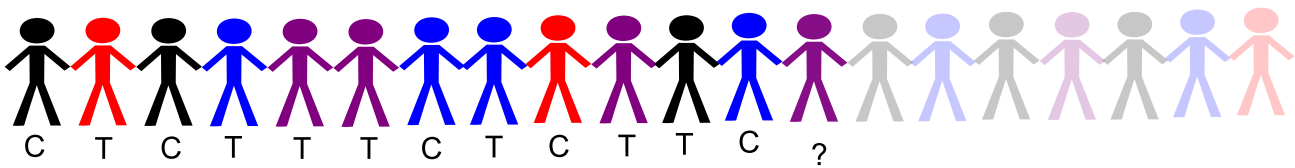
Sequential Design with Covariates



Sequential Design with Covariates



Sequential Design with Covariates



Pseudo-nonmyopic Approach

Approximation to the computationally expensive non-myopic approach

HOW DOES IT COMPARE TO THE MYOPIC APPROACH?

DESIGN FOR PERSONALIZED MEDICINE

NOTATION

- n patients become available sequentially.

NOTATION

- n patients become available sequentially.
- k binary biomarkers are observed for each patient:

NOTATION

- n patients become available sequentially.
- k binary biomarkers are observed for each patient:

  2^k biomarker subgroups.

NOTATION

- n patients become available sequentially.
- k binary biomarkers are observed for each patient:

  2^k biomarker subgroups.

$$b_{i,m} = \begin{cases} 1 & \text{if patient } i \text{ has biomarker } m \\ 0 & \text{otherwise} \end{cases}$$

NOTATION

- n patients become available sequentially.
- k binary biomarkers are observed for each patient:

  2^k biomarker subgroups.

$$b_{i,m} = \begin{cases} 1 & \text{if patient } i \text{ has biomarker } m \\ 0 & \text{otherwise} \end{cases}$$

- t new treatments are of interest.

NOTATION

- n patients become available sequentially.
- k binary biomarkers are observed for each patient:

  2^k biomarker subgroups.

$$b_{i,m} = \begin{cases} 1 & \text{if patient } i \text{ has biomarker } m \\ 0 & \text{otherwise} \end{cases}$$

- t new treatments are of interest.

$$t_{i,j} = \begin{cases} 1 & \text{if patient } i \text{ receives new treatment } j, \quad j \in \{1, ..., t\} \\ 0 & \text{otherwise} \end{cases}$$

  $t_{i,1} = ... = t_{i,j} = 0$ implies patient i receives standard treatment ($j = 0$)

THE MODEL

We assume a logistic model for the response:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

THE MODEL

We assume a logistic model for the response:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

- Model matrix $\boldsymbol{X}$ has ith row $\boldsymbol{x}_i = [1 \quad b_{i,1} \ \ldots \ b_{i,k} \quad t_{i,1} \ \ldots \ t_{i,t} \quad b_1 t_1 \ \ldots \ b_k t_t]$

THE MODEL

We assume a logistic model for the response:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta}.$$

- Model matrix $\boldsymbol{X}$ has ith row $\boldsymbol{x}_i = [1 \quad b_{i,1} \ \ldots \ b_{i,k} \quad t_{i,1} \ \ldots \ t_{i,t} \quad b_1 t_1 \ \ldots \ b_k t_t]$

There are $R = 2^k \times t$ hypotheses to consider:

$$H0 : \boldsymbol{c}_r^\top \boldsymbol{\beta} \geq \tau_r$$
$$H1 : \boldsymbol{c}_r^\top \boldsymbol{\beta} < \tau_r,$$

- $\boldsymbol{c}_r$ indicate subsets of parameters, for $r \in \{1, \ldots, R\}$.
- τ_r are thresholds for effective treatment difference.

A SIMPLE EXAMPLE

For the case with two biomarkers and one new treatment:

A SIMPLE EXAMPLE

For the case with two biomarkers and one new treatment:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$$

A SIMPLE EXAMPLE

For the case with two biomarkers and one new treatment:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \beta$$

- Model matrix has ith row given by $\boldsymbol{x}_i = [1 \quad b_{i,1} \quad b_{i,2} \quad t_i \quad b_{i,1}t_i \quad b_{i,2}t_i]$

A SIMPLE EXAMPLE

For the case with two biomarkers and one new treatment:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \beta$$

- Model matrix has ith row given by $\boldsymbol{x}_i = [1 \quad b_{i,1} \quad b_{i,2} \quad t_i \quad b_{i,1}t_i \quad b_{i,2}t_i]$
- Four hypotheses:

$$H0 : \boldsymbol{c}_r^\top \beta \geq \tau_r$$
$$H1 : \boldsymbol{c}_r^\top \beta < \tau_r,$$

A SIMPLE EXAMPLE

For the case with two biomarkers and one new treatment:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \beta$$

- Model matrix has ith row given by $\boldsymbol{x}_i = [1 \quad b_{i,1} \quad b_{i,2} \quad t_i \quad b_{i,1}t_i \quad b_{i,2}t_i]$
- Four hypotheses:

$$H0 : \boldsymbol{c}_r^\top \beta \geq \tau_r$$
$$H1 : \boldsymbol{c}_r^\top \beta < \tau_r,$$

with vectors $\boldsymbol{c}_r$ given by:

$$\boldsymbol{c}_1^\top = (0,0,0,1,0,0)$$
$$\boldsymbol{c}_2^\top = (0,0,0,1,1,0)$$
$$\boldsymbol{c}_3^\top = (0,0,0,1,0,1)$$
$$\boldsymbol{c}_4^\top = (0,0,0,1,1,1)$$

OPTIMALITY

HOW TO CHOOSE $t_i, \ldots, t_t$ TO MINIMIZE VARIANCE OF SUCCESSFUL $\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}$?

OPTIMALITY

HOW TO CHOOSE $t_i, \ldots, t_t$ TO MINIMIZE VARIANCE OF SUCCESSFUL $\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}$?

Variance is given by:

$$\mathbb{V}\text{ar}\left(\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}\right) = \boldsymbol{c}_r^\top (\boldsymbol{X}^\top \boldsymbol{W}\boldsymbol{X})^{-1} \boldsymbol{c}_r,$$

where $\boldsymbol{W}$ is a diagonal matrix with ith entry given by $\hat{\pi}_i (1 - \hat{\pi}_i)$.

OPTIMALITY

HOW TO CHOOSE $t_i, \ldots, t_t$ TO MINIMIZE VARIANCE OF SUCCESSFUL $\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}$?

Variance is given by:

$$\mathbb{V}\text{ar}\left(\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}\right) = \boldsymbol{c}_r^\top (\boldsymbol{X}^\top \boldsymbol{W}\boldsymbol{X})^{-1} \boldsymbol{c}_r,$$

where $\boldsymbol{W}$ is a diagonal matrix with ith entry given by $\hat{\pi}_i (1 - \hat{\pi}_i)$.

Define weights:

$$w_r = P(\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}} < \tau_r).$$

OPTIMALITY

HOW TO CHOOSE $t_i, \ldots, t_t$ TO MINIMIZE VARIANCE OF SUCCESSFUL $\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}$?

Variance is given by:

$$\mathbb{V}\text{ar}\left(\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}}\right) = \boldsymbol{c}_r^\top (\boldsymbol{X}^\top \boldsymbol{W}\boldsymbol{X})^{-1} \boldsymbol{c}_r,$$

where $\boldsymbol{W}$ is a diagonal matrix with ith entry given by $\hat{\pi}_i\,(1 - \hat{\pi}_i)$.

Define weights:

$$w_r = P(\boldsymbol{c}_r^\top \hat{\boldsymbol{\beta}} < \tau_r).$$

Lee and Wason (2019) propose a **weighted L-optimal objective function**, which seeks to minimize the variance of a linear combination of parameters in $\boldsymbol{\beta}$, weighted by their probabilities of success:

$$\Psi_L(\boldsymbol{X}) = \sum_{r=1}^{R} w_r \boldsymbol{c}_r^\top (\boldsymbol{X}^\top \boldsymbol{W}\boldsymbol{X})^{-1} \boldsymbol{c}_r.$$

ALGORITHM

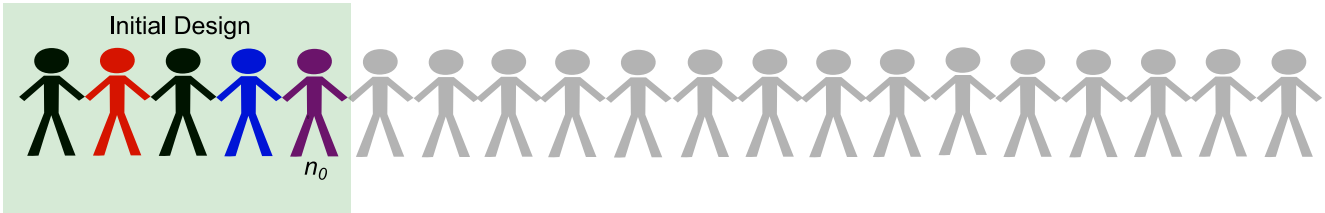
INITIALIZATION

INITIALIZATION

INITIALIZE

1. Construct an **initial** design with n_0 patients.

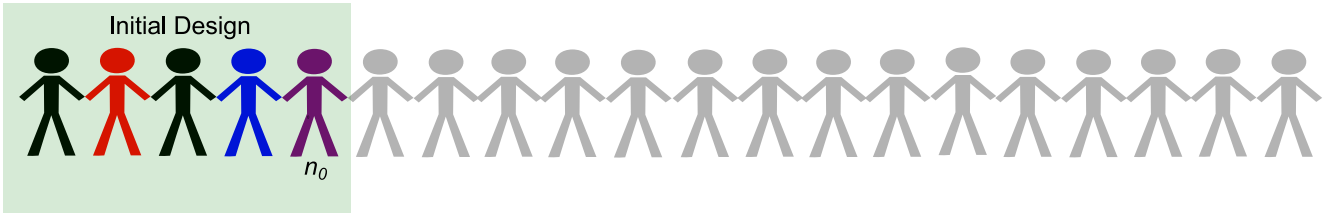
INITIALIZATION



INITIALIZE

1. Construct an **initial** design with n_0 patients.

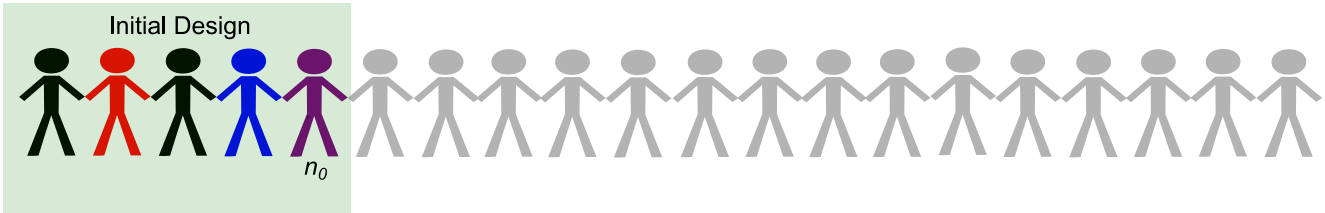
INITIALIZATION



INITIALIZE

1. Construct an **initial** design with n_0 patients.
2. Observe the **initial responses** $y_1, ..., y_{n_0}$.

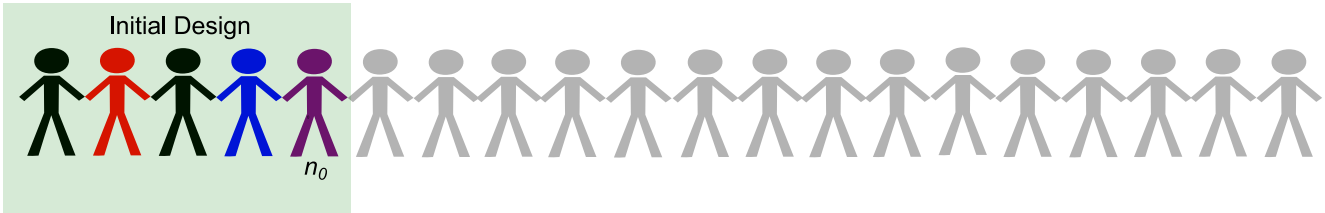
INITIALIZATION



INITIALIZE

1. Construct an **initial** design with n_0 patients.
2. Observe the **initial responses** $y_1, ..., y_{n_0}$.
3. Fit the model to obtain the **initial parameter estimates** $\hat{\beta}_0$.

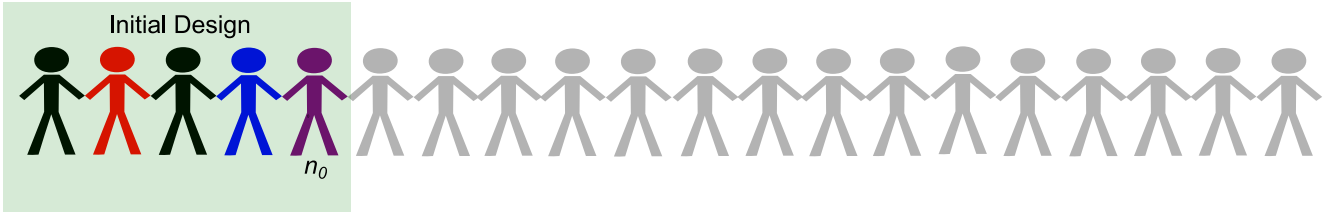
INITIALIZATION



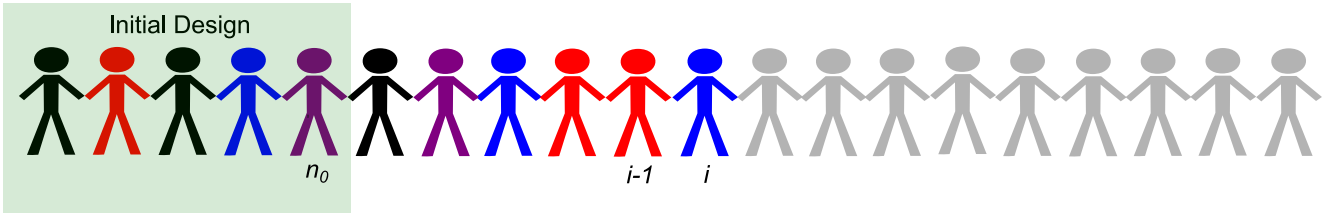
INITIALIZE

1. Construct an **initial** design with n_0 patients.
2. Observe the **initial responses** $y_1, ..., y_{n_0}$.
3. Fit the model to obtain the **initial parameter estimates** $\hat{\beta}_0$.
4. Calculate **initial weights** $w_{r_0} = P(\boldsymbol{c}_r^\top \hat{\beta}_0 < \tau_r)$ for all r.

MYOPIC DECISION FOR *i*TH PATIENT



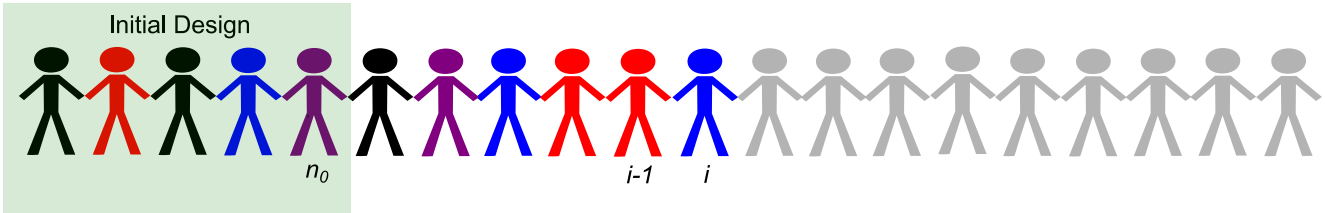
MYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

MYOPIC DECISION FOR iTH PATIENT



ITERATE

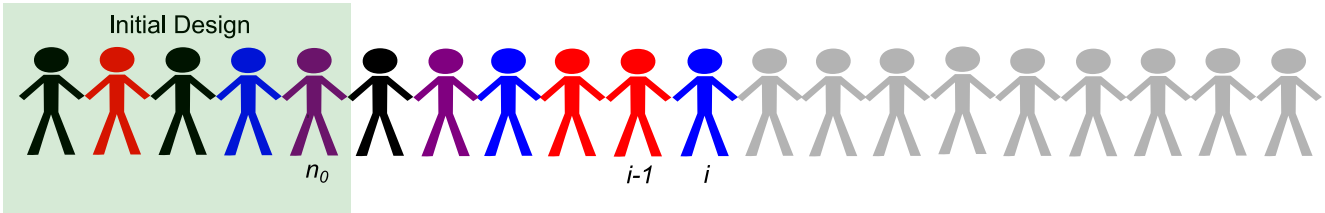
For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. Calculate the **weighted L-optimal criterion** for $t \in \{0, 1\}$:

$$\Psi_L(\boldsymbol{X}_{i,t}) = \sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^\top (\boldsymbol{X}_{i,t}^\top \boldsymbol{W}_{i-1} \boldsymbol{X}_{i,t})^{-1} \boldsymbol{c}_r,$$

where $\boldsymbol{X}_{i,j}$ is the design matrix where patient i receives treatment t.

MYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

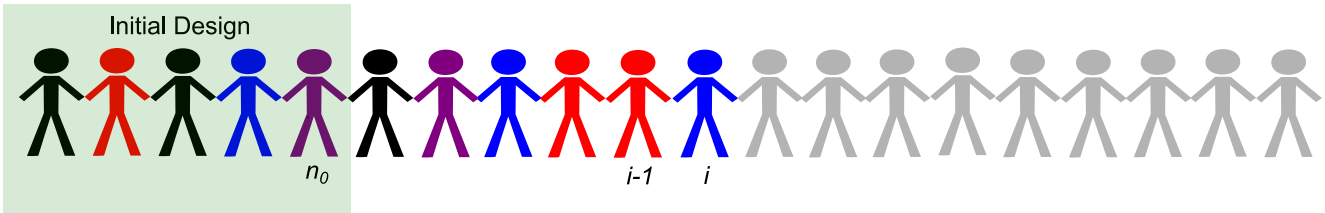
1. Calculate the **weighted L-optimal criterion** for $t \in \{0, 1\}$:

$$\Psi_L(\boldsymbol{X}_{i,t}) = \sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^\top (\boldsymbol{X}_{i,t}^\top \boldsymbol{W}_{i-1} \boldsymbol{X}_{i,t})^{-1} \boldsymbol{c}_r,$$

where $\boldsymbol{X}_{i,j}$ is the design matrix where patient i receives treatment t.

2. Assign the treatment t which minimizes $\Psi_L(\boldsymbol{X}_{i,t})$

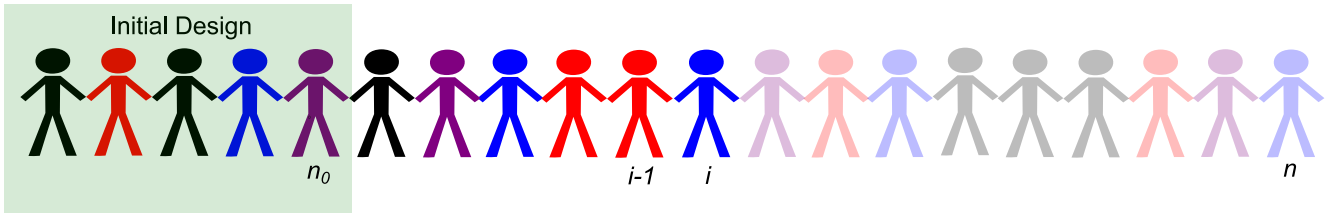
PSEUDONONMYOPIC DECISION FOR *i*TH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

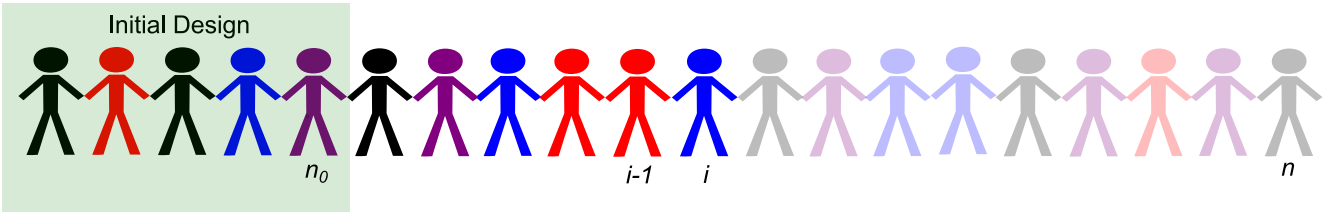
PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

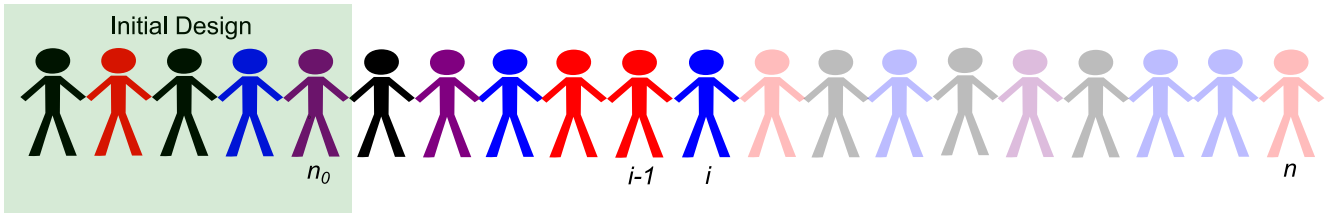
PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

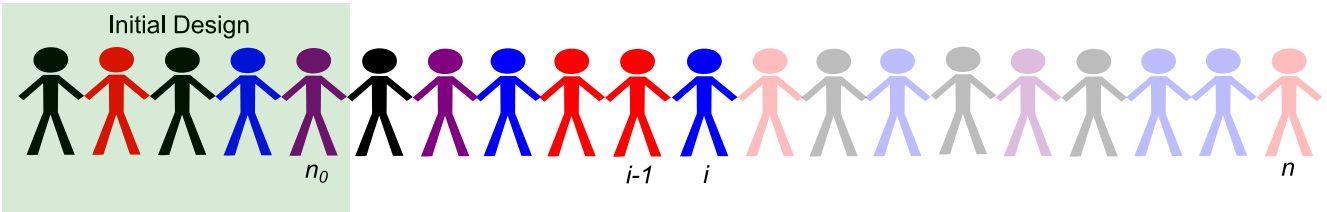
PSEUDONONMYOPIC DECISION FOR *i*TH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

PSEUDONONMYOPIC DECISION FOR *i*TH PATIENT



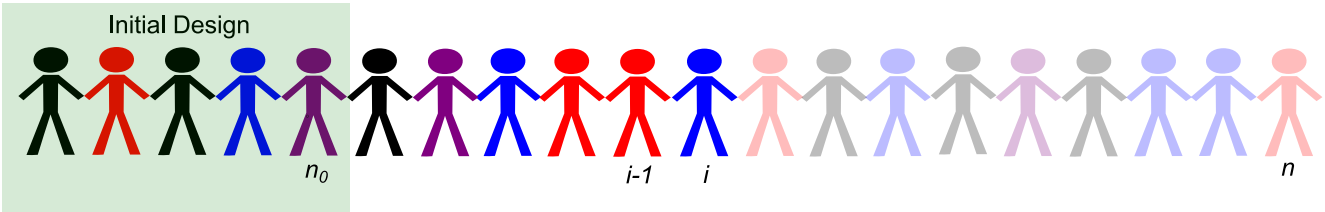
ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. For m in 1 to M:

a. **Generate biomarkers** for patients $i + 1$ to n.

PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

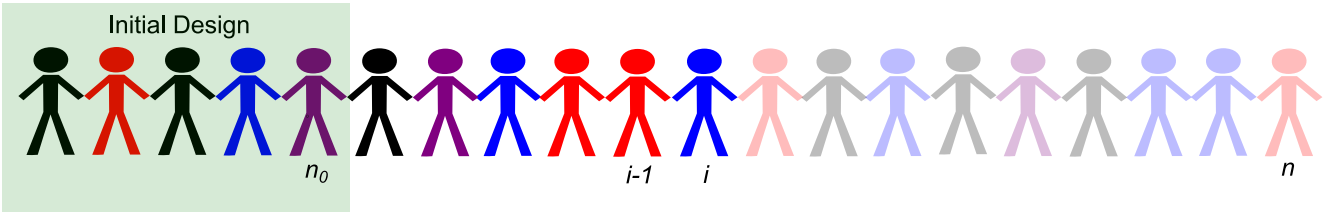
For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. For m in 1 to M:

a. **Generate biomarkers** for patients $i + 1$ to n.

b. Assuming patient i gets treatment $t \in \{0, 1\}$, select treatments $t_{i+1}, \ldots, t_n$ to minimize the weighted L-optimality criterion. Denote the resulting design matrix by $\boldsymbol{X}^t_{i,t}$.

PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. For m in 1 to M:

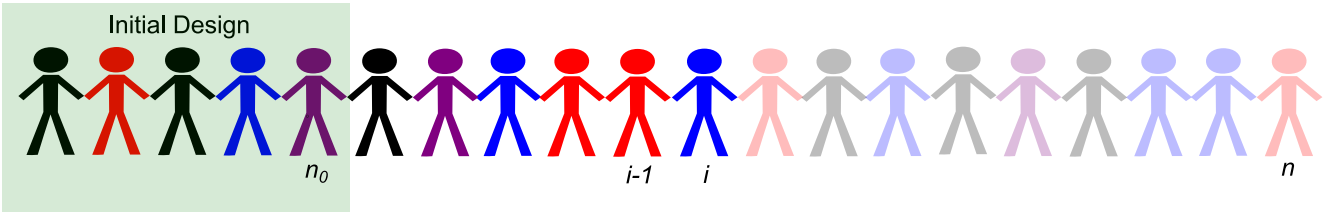
a. **Generate biomarkers** for patients $i + 1$ to n.

b. Assuming patient i gets treatment $t \in \{0, 1\}$, select treatments $t_{i+1}, \ldots, t_n$ to minimize the weighted L-optimality criterion. Denote the resulting design matrix by $\boldsymbol{X}_{i,t}^{t}$.

c. Compute the objective function **at the end of the trial**:

$$\Psi_L(\boldsymbol{X}_{i,t}^{m}) = \sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^{\top} (\boldsymbol{X}_{i,t}^{m\top} \boldsymbol{W}_{i-1} \boldsymbol{X}_{i,t}^{m})^{-1} \boldsymbol{c}_r .$$

PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. For m in 1 to M:

a. **Generate biomarkers** for patients $i + 1$ to n.

b. Assuming patient i gets treatment $t \in \{0, 1\}$, select treatments $t_{i+1}, \ldots, t_n$ to minimize the weighted L-optimality criterion. Denote the resulting design matrix by $\boldsymbol{X}_{i,t}^{t}$.

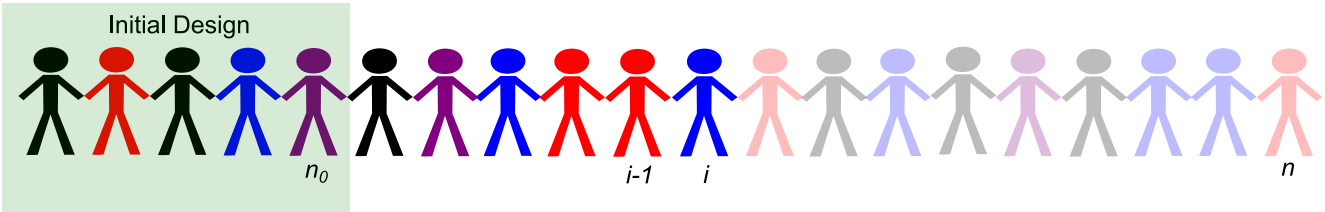
c. Compute the objective function **at the end of the trial**:

$$\Psi_L(\boldsymbol{X}_{i,t}^{m}) = \sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^{\top} (\boldsymbol{X}_{i,t}^{m\top} \boldsymbol{W}_{i-1} \boldsymbol{X}_{i,t}^{m})^{-1} \boldsymbol{c}_r .$$

2. Compute the **average objective function** for $t \in \{0, 1\}$:

$$\overline{\Psi}_L(t_i = t) = \frac{1}{M} \sum_{m=1}^{M} \Psi_L \left(\boldsymbol{X}_{i,t}^{m} \right) .$$

PSEUDONONMYOPIC DECISION FOR iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

1. For m in 1 to M:

a. **Generate biomarkers** for patients $i + 1$ to n.

b. Assuming patient i gets treatment $t \in \{0, 1\}$, select treatments $t_{i+1}, \ldots, t_n$ to minimize the weighted L-optimality criterion. Denote the resulting design matrix by $\boldsymbol{X}_{i,t}^t$.

c. Compute the objective function **at the end of the trial**:

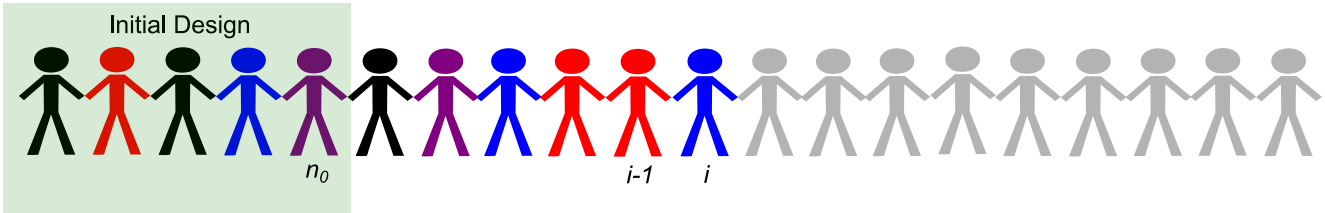
$$\Psi_L(\boldsymbol{X}_{i,t}^m) = \sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^\top (\boldsymbol{X}_{i,t}^{m\top} \boldsymbol{W}_{i-1} \boldsymbol{X}_{i,t}^m)^{-1} \boldsymbol{c}_r .$$

2. Compute the **average objective function** for $t \in \{0, 1\}$:

$$\overline{\Psi}_L(t_i = t) = \frac{1}{M} \sum_{m=1}^{M} \Psi_L \left(\boldsymbol{X}_{i,t}^m \right) .$$

Assign the treatment t which minimizes $\overline{\Psi}_L(t)$.

UPDATE TO INCLUDE iTH PATIENT

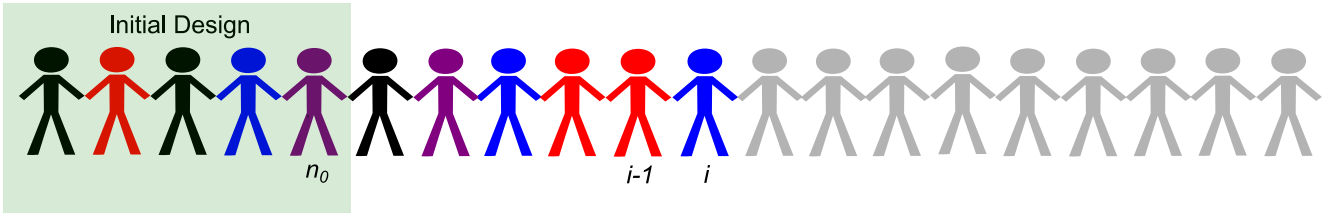


ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

3. Observe **response** y_i.

UPDATE TO INCLUDE iTH PATIENT



ITERATE

For $i = n_0 + 1, \ldots, n$, given biomarker profile of patient i:

3. Observe **response** y_i.
4. Refit model and update **parameter estimates** $\hat{\beta}_i$.
5. Update **weights** w_{r_i} for all r.

RESULTS FROM SIMULATIONS

Set-Up

A simple case with two biomarkers and one treatment:

$$y_i = \text{Bernoulli}(\pi_i), \text{where logit}\left(\frac{\pi_i}{1-\pi_i}\right) = \boldsymbol{x}_i^\top \boldsymbol{\beta}$$

- Design matrix has ith row given by $\boldsymbol{x}_i = \begin{bmatrix} 1 & b_{i,1} & b_{i,2} & t_i & b_{i,1}t_i & b_{i,2}t_i \end{bmatrix}$
- Linear combinations of interest given by these contrast vectors:

$$\boldsymbol{c}_1^\top = (0,0,0,1,0,0)$$
$$\boldsymbol{c}_2^\top = (0,0,0,1,1,0)$$
$$\boldsymbol{c}_3^\top = (0,0,0,1,0,1)$$
$$\boldsymbol{c}_4^\top = (0,0,0,1,1,1)$$

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

- True parameters such that treatment effective only when $b_{1,i} = 1$.

$$\beta = (0, 0, 0, 0, -2, 0)$$

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

- True parameters such that treatment effective only when $b_{1,i} = 1$.

$$\beta = (0, 0, 0, 0, -2, 0)$$

- Threshold for effective treatment difference $\tau_r = -1$ for all r.

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

- True parameters such that treatment effective only when $b_{1,i} = 1$.

$$\beta = (0, 0, 0, 0, -2, 0)$$

- Threshold for effective treatment difference $\tau_r = -1$ for all r.
- Initial sample is 5.

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

- True parameters such that treatment effective only when $b_{1,i} = 1$.

$$\beta = (0, 0, 0, 0, -2, 0)$$

- Threshold for effective treatment difference $\tau_r = -1$ for all r.
- Initial sample is 5.
- Design constructed with myopic and pseudononmyopic ($M = 100$) algorithms.

Set-Up

- Biomarkers generated independently. For $i \in \{1, ..., 100\}$,

$$b_{i,1} \sim \text{Bernoulli}(0.5)$$
$$b_{i,2} \sim \text{Bernoulli}(0.7)$$

True distributions assumed to be known for the pseudononmyopic approach.

- True parameters such that treatment effective only when $b_{1,i} = 1$.

$$\beta = (0, 0, 0, 0, -2, 0)$$

- Threshold for effective treatment difference $\tau_r = -1$ for all r.
- Initial sample is 5.
- Design constructed with myopic and pseudononmyopic ($M = 100$) algorithms.
- Simulation repeated 100 times.

Results: Parameter Estimates

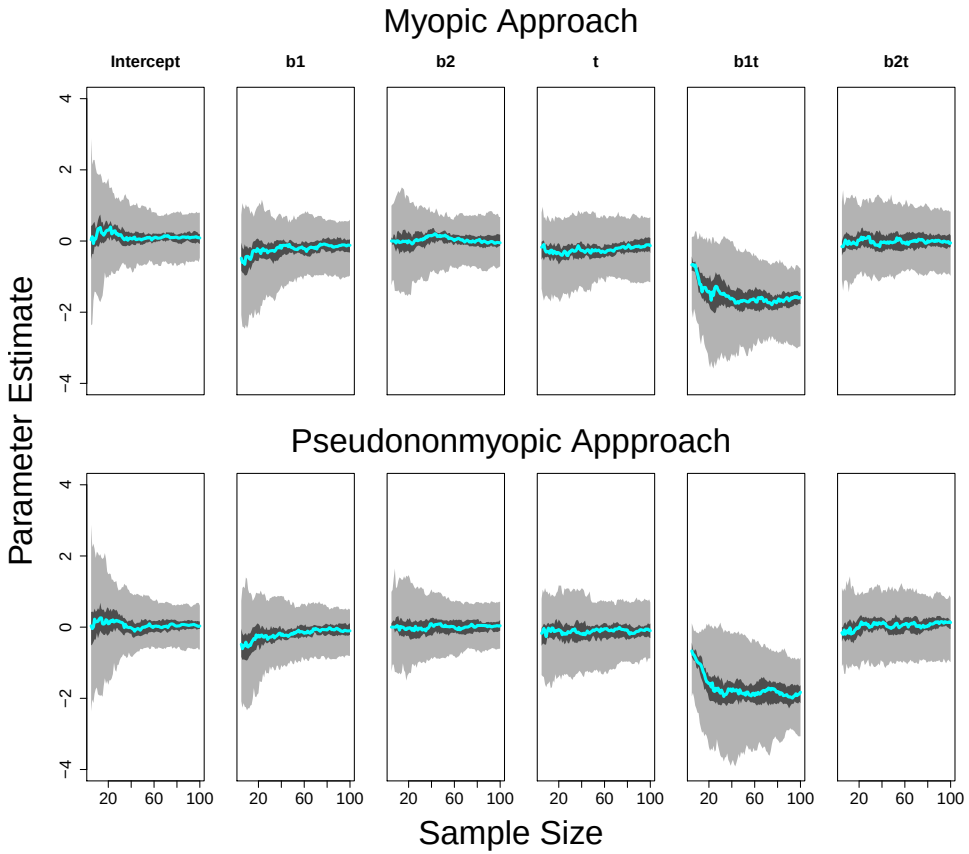


Figure 1: Distribution of $\hat{\beta}$ vs sample size, $\boldsymbol{\beta} = (0, 0, 0, 0, -2, 0)$
median $40 - 60\%$ $10 - 90\%$

Results: Weights

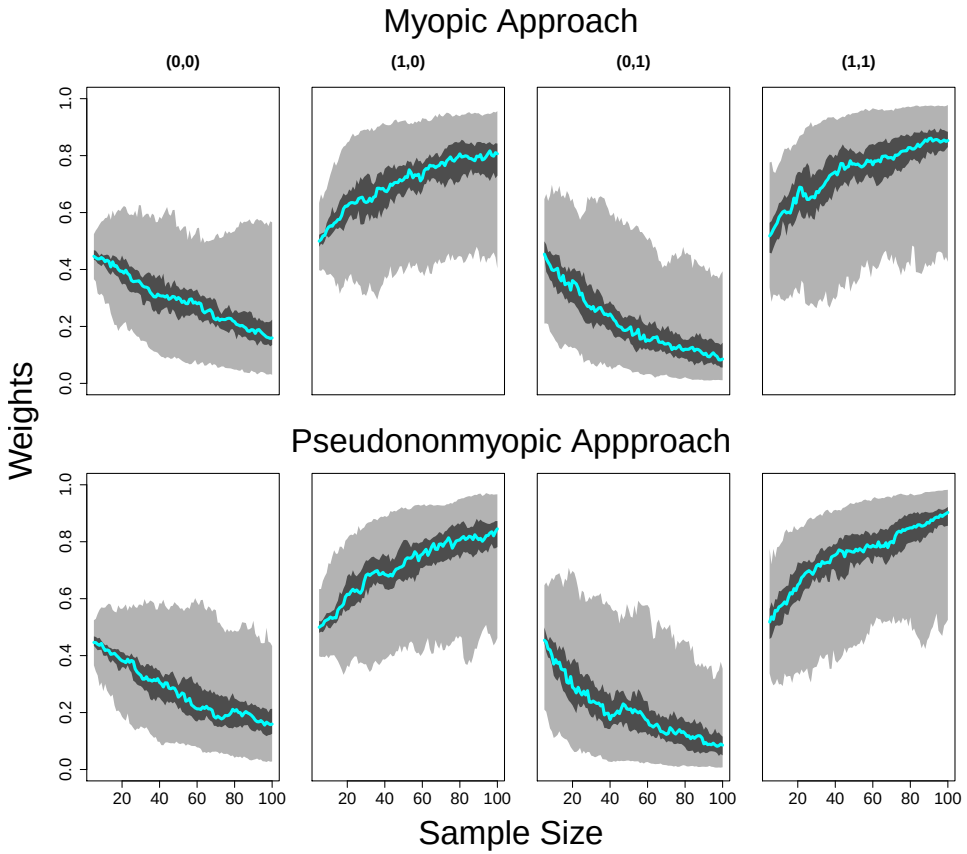


Figure 2: Distribution of w_r vs sample size
median $40-60\%$ $10-90\%$

Results: *L*-Optimality

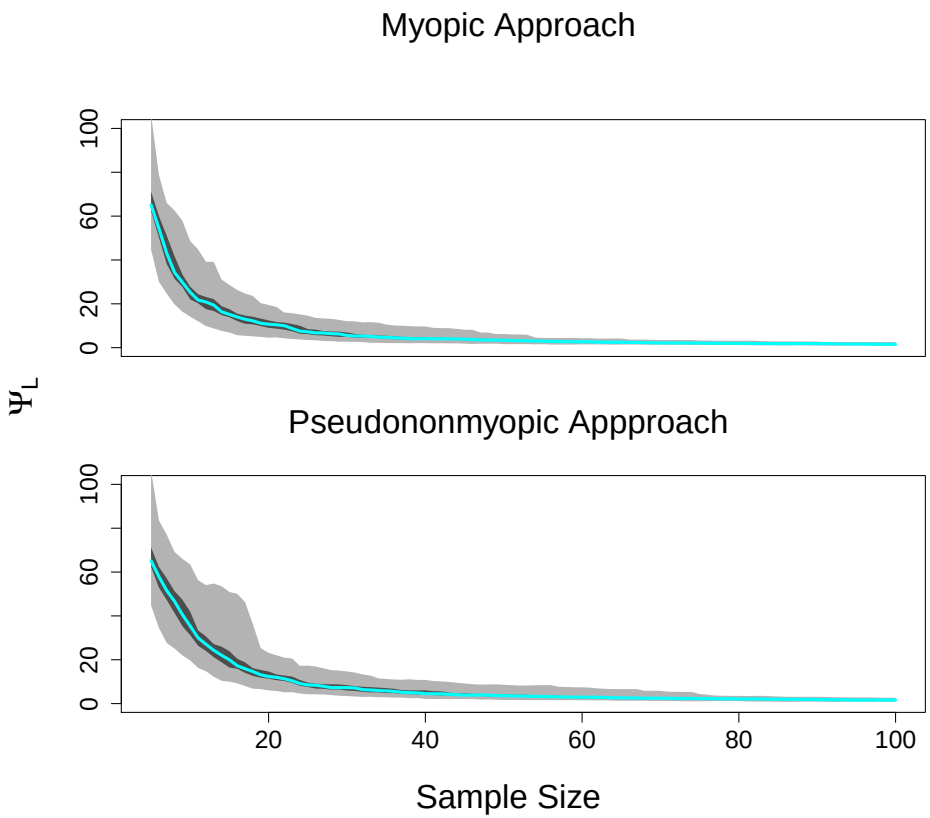


Figure 3: Distribution of Ψ_L vs sample size
median $40-60\%$ $10-90\%$

DISCUSSION

Discussion

It is more efficient to be myopic rather than pseudo-nonmyopic

Discussion

It is more efficient to be myopic rather than pseudo-nonmyopic
... even when the true future biomarker distributions are known.

Discussion

It is more efficient to be myopic rather than pseudo-nonmyopic
... even when the true future biomarker distributions are known.

Also true for examples with:

- linear models
- $D-$, D_A- and $A-$ optimality
- time-varying biomarkers

Discussion

It is more efficient to be myopic rather than pseudo-nonmyopic
... even when the true future biomarker distributions are known.

Also true for examples with:

- linear models
- $D-$, D_A- and $A-$ optimality
- time-varying biomarkers

WHAT ABOUT FOR (MULTIPLE) CONTINUOUS TREATMENT(S)?

Thank you

M.S.Tackney@soton.ac.uk

Slides and R code provided here:
https://github.com/mst1g15/biasedcoin

References

Atkinson, A. C. (1982) Optimum biased coin designs for sequential clinical trials with prognostic factors. *Biometrika* **69**, 61-67.

Atkinson, A. C. (1999) Optimum biased-coin designs for sequential treatment allocation with covariate information. *Statistics in Medicine* **18**, 1741-1752.

Cheng, Y. and Berry, D. A. (2007) Optimal adaptive randomized designs for clinical trials. *Biometrika* **94**, 673-687.

Huan, X and Marzouk, Y. M. (2016) Sequential Bayesian optimal experimental design via approximate dynamic programming. *SIAM/ASA Journal on Uncertainty Quantification*, 1-34.

Kaplan, R. (2015) The FOCUS4 design for biomarker stratified trials. *Chinese Clinical Oncology*, **4**(3).

Lee, K.M and Wason, J. (2019) Design of experiments for a confirmatory trial of precision medicine. *Journal of Statistical Planning and Inference* **199**, 179-187.

Pocock, S.J. and Simon, R. (1975) Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* **31**, 103-115.