SEQUENTIAL DESIGN OF EXPERIMENTS FOR PERSONALIZED MEDICINE

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

[1]University of Southampton   [2]Medical Research Council, University of Cambridge   [3]Johns Hopkins University

PERSONALIZED MEDICINE

Advances in genomics are making it possible to tailor treatment recommendations to individuals' genetic characteristics. In a personalized clinical trial, patients go through a genetic screening to identify their **biomarker** group. We wish to identify **effective treatment-biomarker combinations**.
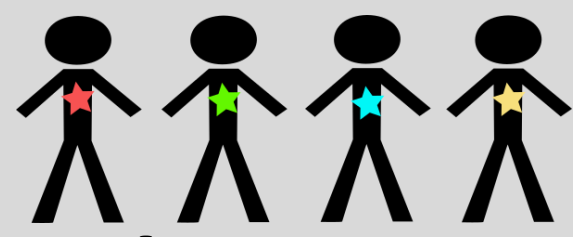
Assume that there are n patients arriving sequentially for the trial, k binary biomarkers and a binary treatment factor. We need a way of allocating treatments to patients which is:

1. Sequential.
2. Able to test for effective treatment-biomarker combinations.
3. Able to estimate treatment effects with minimum variance.

Treatment Control Treatment Control Control ?
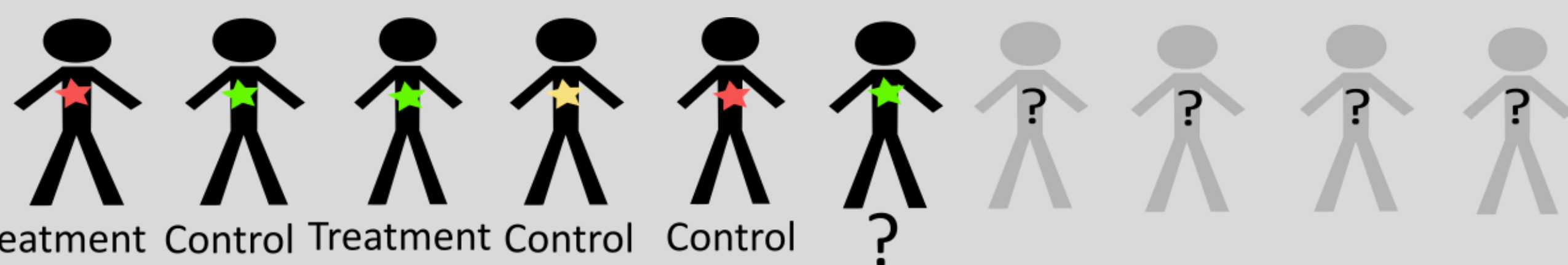
We compare myopic and non-myopic approaches.

OPTIMAL DESIGN OF EXPERIMENTS

We use a logistic model for the response:

$$y_i \sim \text{Bernoulli}(\pi_i), \text{ where } \text{logit}\left(\frac{\pi_i}{1-\pi_i}\right) = x_i^T \boldsymbol{\beta},$$

where x_i is the ith row of the design matrix X which effects for all biomarkers, treatments and biomarker-treatment interactions. We wish to test $R = 2^k$ hypotheses:

$$H_0: c_r^T \boldsymbol{\beta} \geq \tau_r$$
$$H_1: c_r^T \boldsymbol{\beta} < \tau_r,$$

where c_r are vectors in $\{0,1\}^p$ to indicate **linear combinations of interest**, and τ_r is a threshold for the minimum interesting treatment difference, for $r \in \{1, \dots, R\}$. We define weights:

$$w_r = P(c_r^T \hat{\boldsymbol{\beta}} < \tau_r).$$

We use a **weighted L-optimal objective function** proposed by Lee and Wason (2017) to minimize the variance of successful $c_r^T \hat{\boldsymbol{\beta}}$:

$$\Psi_L(X) = \left(\sum_{r=1}^R w_r c_r^T (X^T W X)^{-1} c_r\right)^{-1},$$

where W is a diagonal matrix with ith entry equal to $\hat{\pi}_i(1-\hat{\pi}_i)$ where $\hat{\pi}_i = \frac{\hat{\beta} x_i}{1+\hat{\beta} x_i}$.

A MYOPIC ALGORITHM FOR SEQUENTIAL L-OPTIMAL DESIGN

- Construct an initial design with n_0 patients with co-ordinate exchange algorithm, assume $\boldsymbol{\beta} = 0$.
- Observe initial responses $y_1, \dots, y_{n_0}$.
- Fit the model to obtain $\hat{\boldsymbol{\beta}}_0$.
- Compute weights $w_{r_0} = P(c_r^T \hat{\boldsymbol{\beta}}_0 < \tau_r)$.
- For i in $n_0 + 1$ to n:
  1. Observe biomarkers for patient i.
  2. Calculate the weighted L-optimal criterion for the design $X_{i,t}$ with i patients where patient i gets treatment t, for $t \in \{0,1\}$, using $\hat{\boldsymbol{\beta}}_{i-1}$ to compute W_i:
  $$\Psi_L(X_{i,t}) = \left(\sum_{r=1}^R w_{r_{i-1}} c_r^T (X_{i,t}^T W_{i-1} X_{i,t})^{-1} c_r\right)^{-1}.$$
  3. Sample the treatment for patient i, where the probability of selecting treatment 1 is: $\frac{\Psi_L(X_{i,t=1})}{\Psi_L(X_{i,t=0})+\Psi_L(X_{i,t=1})}$.
  4. Observe response y_i and refit the model to obtain $\hat{\boldsymbol{\beta}}_i$.

A NON-MYOPIC APPROACH

A non-myopic approach to designing sequential experiments considers the impact of the choice of treatment for patient i on **future possible patients**. Our non-myopic algorithm generates M possible **trajectories** of biomarker values for patient $i+1$ up to patient n from an assumed distribution of the biomarkers. We select treatments for the future possible patients in the trajectory and choose a treatment based on the optimality of the M designs each containing i real patients and $n - i$ simulated patients.

T C T C C ?

T C T C
$\vdots$ M possible trajectories
C C T M
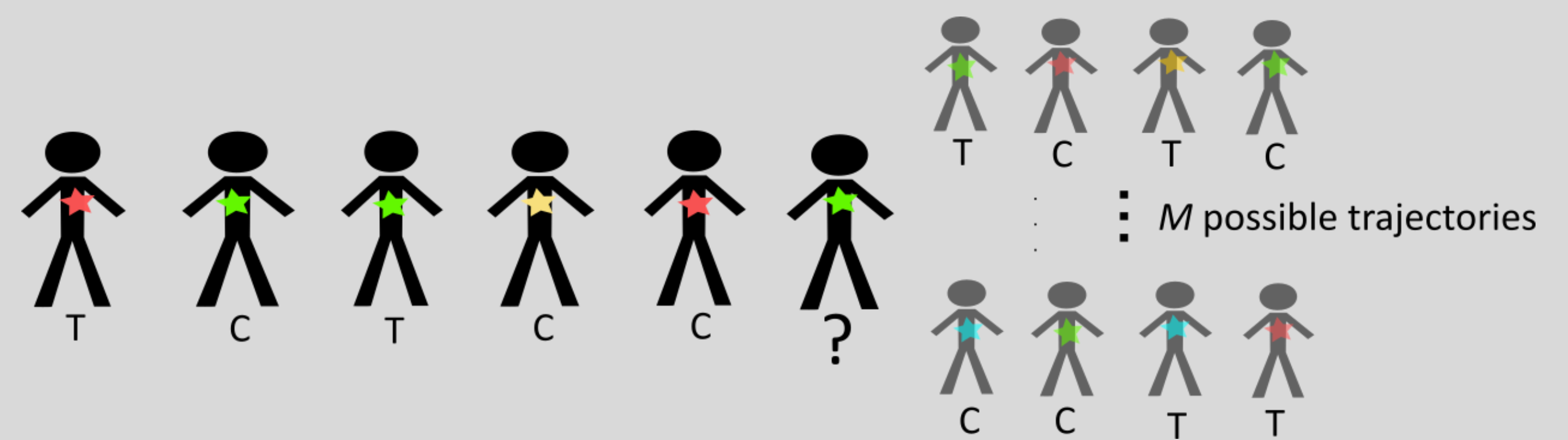
CHANGE STEPS 2 AND 3 THE ALGORITHM:

2. For m in 1 to M:
   a. From the assumed biomarker distribution, generate biomarkers for patient $i - 1$ to n.
   b. Assuming that patient i gets treatment t, for $t \in \{0,1\}$, sequentially select the treatment which minimizes the L-optimality criterion for the future patients. Denote the resulting design matrix by $X_{i,t}^m$. Compute
   $$\Psi_L(X_{i,t}^m) = \left(\sum_{r=1}^R w_{r_i} c_r^T (X_{i,t}^{mT} W_{i-1} X_{i,t}^m)^{-1} c_r\right)^{-1}.$$
   c. For $t \in \{0,1\}$, compute $\overline{\Psi_L}(t_i = t) = \frac{1}{M}\sum_{m=1}^M \Psi_L(X_{i,t}^m)$
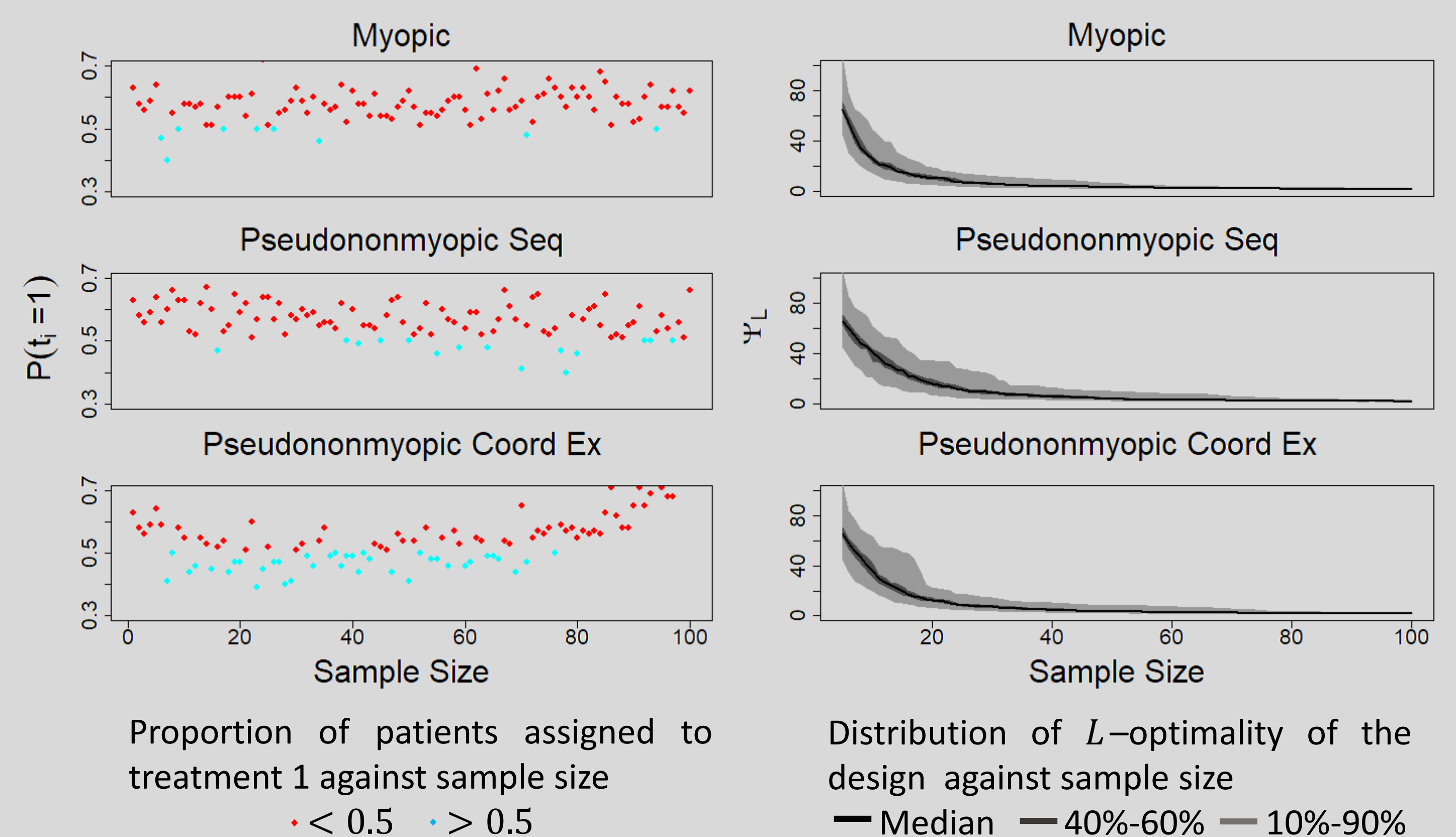3. Sample the treatment for patient i, where the probability of selecting treatment is: $\frac{\overline{\Psi_L}(t_i=1)}{\overline{\Psi_L}(t_i=1)+\overline{\Psi_L}(t_i=0)}$.

Note: Step (b) can be done with a coordinate exchange algorithm instead of sequentially.

RESULTS

SURPRISINGLY, WE FIND THAT THE MYOPIC APPROACH IS MORE EFFICIENT THAN THE NON-MYOPIC APPROACH.

EXAMPLE:
- Two biomarkers with distributions Bernoulli(0.5) and Bernoulli(0.7)
- 100 patients ▶ initial sample size 15 ▶ 100 simulations

Proportion of patients assigned to treatment 1 against sample size
· < 0.5   · > 0.5

Distribution of L−optimality of the design against sample size
— Median — 40%-60% — 10%-90%

We also found this result to be true for the linear and logistic model case, for D- and L- optimality, for time-varying and static biomarkers, and for binary and continuous treatment factors.

REFERENCES
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