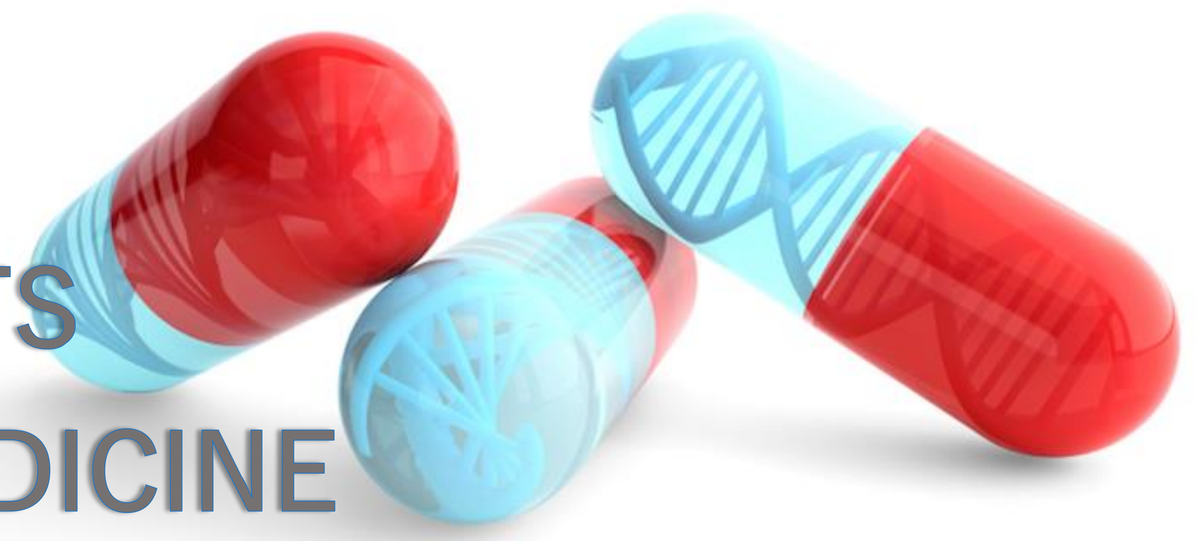
Sequential Design of Experiments for Personalized Medicine



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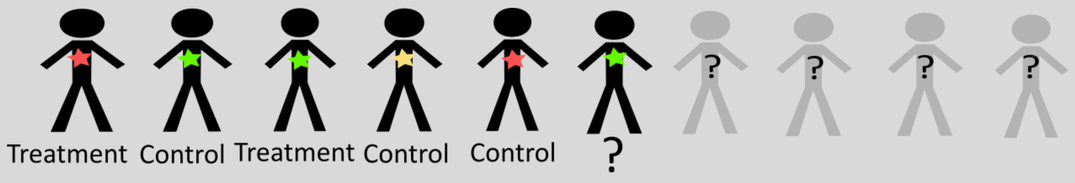
Personalized Medicine

Advances in genomics are making it possible to tailor treatment recommendations based on individual patient characteristics. In a personalized clinical trial, patients are stratified into subgroups based on their **biomarker** profile. 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 estimate interaction effects corresponding to effective treatment-biomarker combinations as efficiently as possible.



We compare myopic and non-myopic approaches. **Does taking into account future possible patients improve efficiency?**

Optimal Design of Experiments

We use a logistic model for the response:

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

where $\boldsymbol{x}_i$ is the ith row of design matrix $\boldsymbol{X}$ with includes columns corresponding to effects for all biomarkers, treatments and biomarker-treatment interactions. We aim to test $R = 2^k$ hypotheses:

$$H_0: \boldsymbol{c}_r^T\boldsymbol{\beta} \geq \tau_r \quad \text{vs} \quad H_1: \boldsymbol{c}_r^T\boldsymbol{\beta} < \tau_r,$$

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:

$$w_r = P\left(\boldsymbol{c}_r^{\mathrm{T}}\widehat{\boldsymbol{\beta}} < \tau_r\right).$$

We use a **weighted *L*-optimal objective function** proposed by Lee and Wason (2019) to minimize the variance of successful $\boldsymbol{c}_r^{\mathrm{T}}\widehat{\boldsymbol{\beta}}$:

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

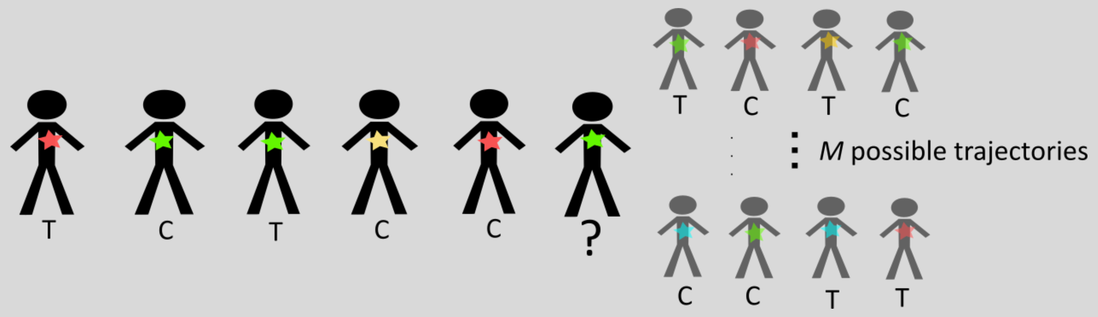
where $\boldsymbol{W}$ is a diagonal matrix with ith entry equal to $\hat{\pi}_i(1-\hat{\pi}_i)$ where $\hat{\pi}_i = \frac{\widehat{\beta}x_i}{1+\widehat{\beta}x_i}$.

A Myopic Algorithm for Sequential *L*-Optimal Design

- Construct an initial design with n_0 patients which minimizes Ψ_L, assuming equal weights.
- Observe initial responses $y_1, \dots, y_{n_0}$.
- Fit the model to obtain $\widehat{\boldsymbol{\beta}}_{\boldsymbol{0}}$.
- Compute weights $w_{r_0} = P(\boldsymbol{c}_r^{\mathrm{T}}\widehat{\boldsymbol{\beta}}_{\boldsymbol{0}} < \tau_r)$.
- For i in $n_0 + 1$ to n, given biomarker profile of patient i:
  1. Calculate the weighted *L*-optimal objective function for the design $\boldsymbol{X}_{i,t}$ with i patients where patient i gets treatment t, for $t \in \{0,1\}$, using $\widehat{\boldsymbol{\beta}}_{i-1}$ to compute $\boldsymbol{W}_i$:
     $\Psi_L(\boldsymbol{X}_{i,t}) = \left(\sum_{r=1}^{R} w_{r_{i-1}} \boldsymbol{c}_r^T(\boldsymbol{X}_{i,t}^T\boldsymbol{W}_{i-1}\boldsymbol{X}_{i,t})^{-1}\boldsymbol{c}_r\right)^{-1}$.
  2. Sample the treatment for patient i, where the probability of selecting treatment 1 is: $\frac{\Psi_L(\boldsymbol{X}_{i,t=1})}{\Psi_L(\boldsymbol{X}_{i,t=0})+\Psi_L(\boldsymbol{X}_{i,t=1})}$.
  3. Observe response y_i and refit the model to obtain $\widehat{\boldsymbol{\beta}}_i$.

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 efficiency of the M designs each containing i real patients and $n-i$ simulated patients.



Change steps 2 and 3 the Algorithm:

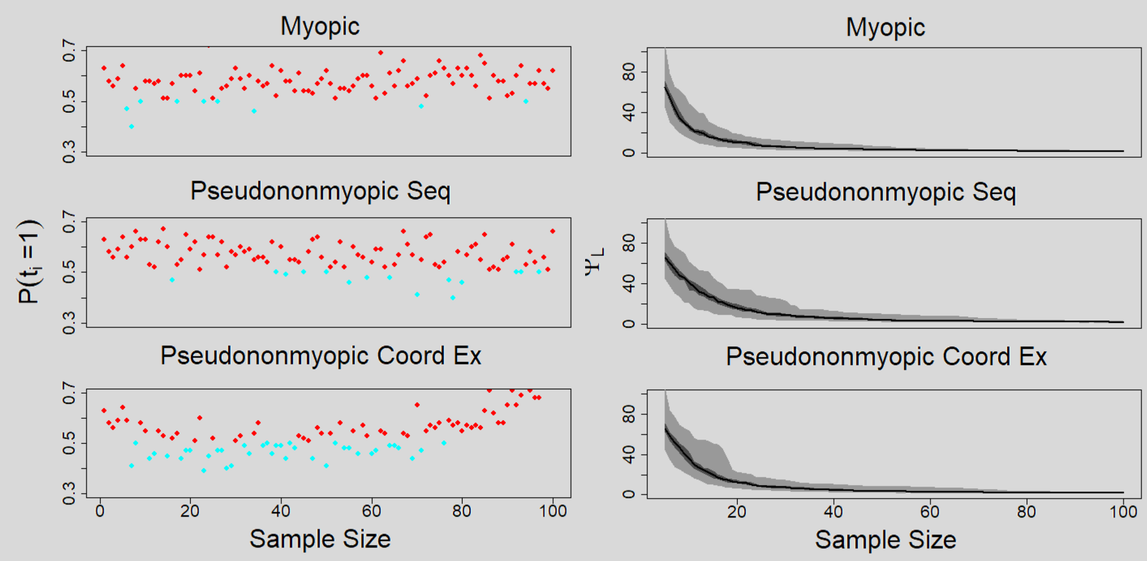
2. For m in 1 to M:
   a. From the assumed biomarker distribution, generate biomarkers for patients $i-1$ to n.
   b. Assuming that patient i gets treatment t, for $t \in \{0,1\}$, sequentially select the treatment which minimizes the *L*-optimality criterion for the future patients. Denote the resulting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

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

Results

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)
- New treatment better than control, especially in second biomarker group
- 100 patients
- initial sample size 15
- 100 simulations



Proportion of patients assigned to treatment 1 against sample size

$\cdot < 0.5$ $\cdot > 0.5$

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

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

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