Unbiased Estimation After Phase II Clinical Trials Involving Multiple Endpoints

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Outline

- Introduction
- A motivating example
- Overview of the Simon 2-Stage Design Combined with Continuous Toxicity Monitoring
- Unbiased Estimation
- Conclusion

Introduction - Phase II Clinical Trial

Phase II Clinical Trials in Oncology

- Single Arm trials
- Use binary endpoint to test response
  - Partial Response (PR)
  - Complete Response (CR)
  - Stable Disease (SD)
  - Progressive Disease (PD)
- Include some sort of ad hoc rule to monitor toxic events (Ivanova *et al.*, *Biometrics*, 2005).

Introduction - Patient Safety

The phase II designs

- Are designed to evaluate the primary endpoint
- An ad hoc toxicity monitoring rule is added
  - If 13 or more patients experience a toxic event out of the first 20 patients then stop the trial
  - $P\{\#\text{ of Toxicities } \geq 13 | P_{T0} = 0.40, n_t = 20\} \leq 0.05$

Introduction - Patient Safety

Ivanova *et al.* (*Biometrics*, 2005) suggest monitoring toxicity in an ad hoc manner using Continuous Toxicity Monitoring

- Relies on group sequential theory to create boundary values
  - Compare the cumulative number of toxic events after each patient is treated to the computed boundary
  - Can stop the trial for safety considerations at almost any point
  - Reassures investigator if there appears to be a large number of toxic events early
- We combined the concept with Simon 2-Stage in the motivating example (Ray and Rai, *Contemp Clin Trials*, 2011)

Motivating Example

- The population - Patients with Relapsed/Refractory Multiple Myeloma
- The treatment - Combined Simvastatin with two cytotoxic agents Bortezomib and Bendamustine
- The response - Stable Disease, Partial Response, or Complete Response
- The concern - Combination of drugs may cause severe toxic events very quickly

Motivating Example - Toxicity Monitoring with Simon 2-Stage

Response Considerations

- Design the trial based on the response criteria
  - P_{R_0}, P_{R_A}, α_R, and β_R

Toxicity Considerations

- Select Boundary Type - Pocock (*Biometrika*, 1977), O'Brien-Flemming (*Biometrics*, 1979), or others.
- Determine the maximum tolerated toxicity rate
- Set α_T
- Calculate usual Group Sequential boundaries
- Transform into discrete, integer boundaries

Ivanova *et al.*, *Biometrics*, 2005.

Motivating Example - The Clinical Trial Design

Response

- Simon 2-stage Design (1989)
  $P_{R_0} = 0.48$, $P_{R_A} = 0.68$ (Richardson *et al. NEJM* 2003),
  $\alpha_R = 0.05$, $\beta_R = 0.2$
  - Stage 1: $r_1 = 10$, $n_1 = 20$
  - Stage 2: $r = 24$, $n = 40$

Toxicity Monitoring

- Maximum Tolerated Toxicity Rate of 33%, α_T = 0.05
- Boundary Value Functions
  - Selected the Pocock (1977) type

Motivating Example - The Toxicity Boundary Values

Table: Toxicity Boundary Values

Min # of Obs.	4	5	7	8	10	12	15	17	19	20	23	24	28	...	36
Max # of Obs.	4	6	7	9	11	14	16	18	19	22	23	27	28	...	40
# of Toxicities	4	5	6	7	8	9	10	11	12	13	14	15	16	...	21
Response Boundaries										10					24

Notation

X_{rti} is the response vector
- r is the indicator for response
- t is the indicator for toxicity
- i indicates the patient number

Then $X_{rti} = (X_{00i}, X_{01i}, X_{10i}, X_{11i})$ follows a multinomial distribution with parameters $P_{00}, P_{01}, P_{10},$ and P_{11}.

Response is $X_{Ri} = X_{10i} + X_{11i}$ where $X_{Ri} \in \{0, 1\}$

Toxic Event is $X_{Ti} = X_{01i} + X_{11i}$ where $X_{Ti} \in \{0, 1\}$

Notation

Table: Contingency Table for Response and Toxicity of the *ith* Subject

		Toxicity		
		No	Yes	
Response	No	X_{00i}	X_{01i}	
	Yes	X_{10i}	X_{11i}	X_{Ri}
			X_{Ti}	

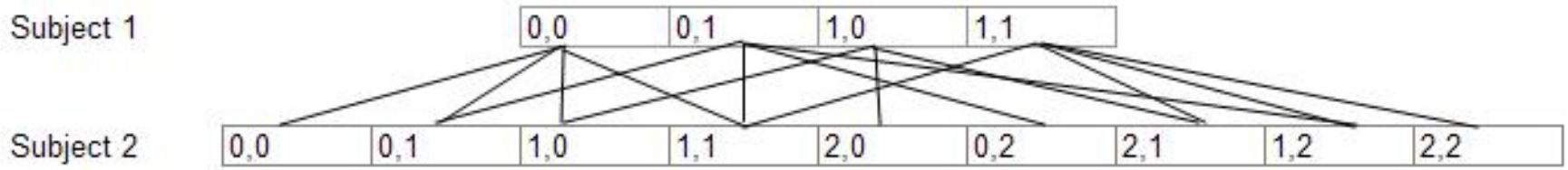
Notation

Total Number of responses $Y_{Rm} = \sum_{i=1}^{m} \sum_{t=0}^{1} X_{1ti} = \sum_{i=1}^{m} X_{Ri}$

Total Number of Toxicities $Y_{Tm} = \sum_{i=1}^{m} \sum_{r=0}^{1} X_{r1i} = \sum_{i=1}^{m} X_{Ti}$

$C_m(Y_{Rm}, Y_{Tm}|P_{00}, P_{01}, P_{10}, P_{11})$ is the probability of enrolling m patients with Y_{Rm} responses and Y_{Tm} toxicities

Example Sample Path



Summary of the Combined Procedure

- The ad hoc design assumes response and toxicity are independent
- The design becomes more conservative as the joint probability of experiencing both events increases
- There is very little reduction in power due to the joint probability
- The continuous toxicity monitoring may be too burdensome in some instances

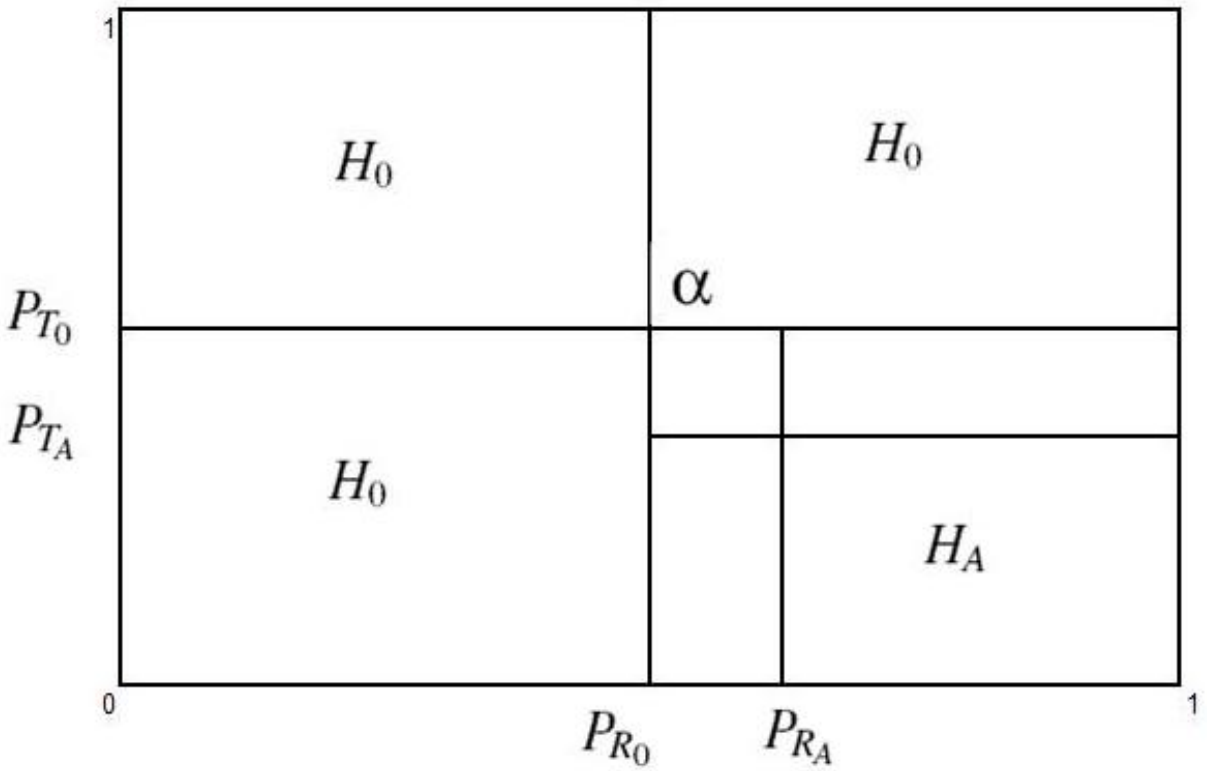
Flexible Phase II Bivariate Clinical Trial Design

$$H_0 : P_R \leq P_{R_0} \quad \text{or } P_T \geq P_{T_0}$$
$$\text{versus}$$
$$H_1 : P_R > P_{R_A} \quad \text{and } P_T < P_{T_A}.$$

- P_{R_0} is maximum response that is not clinically interesting
- P_{R_A} is the minimum response rate that is clinically interesting
- P_{T_0} is the maximum tolerated toxicity rate
- P_{T_A} is the minimum toxicity that is unacceptable

Flexible Phase II Bivariate Clinical Trial Design

Figure: The Hypothesis Space Associated with Phase II 2-Stage Bivariate Design



The Conaway and Petroni Design

$$CR = \{(Y_{Tn_k}, Y_{Rn_k}) : Y_{Tn_k} < T_k, Y_{Rn_k} > R_k\}$$

$$\begin{aligned} P\{(Y_{Tn_1}, Y_{Rn_1}), \ldots, (Y_{Tn_K}, Y_{Rn_K}) \in CR | (P_{R_0}, P_{T_0}), \rho\} &\leq \alpha \\ \sup_{H_0} P\{(Y_{Tn_1}, Y_{Rn_1}), \ldots, (Y_{Tn_K}, Y_{Rn_K}) \in CR | (P_R, P_T), \rho\} &\leq \gamma \\ P\{(Tn_1, Y_{Rn_1}), \ldots, (Y_{Tn_K}, Y_{Rn_K}) \in CR | (P_{R_A}, P_{T_A}), \rho\} &\geq 1 - \beta \end{aligned}$$

Flexible Phase II Bivariate Clinical Trial Design

The Simon 2-Stage design combined with Continuous Toxicity Monitoring

$$\begin{aligned} CR_{ctm} = \quad & \{(Y_{Tn_k}, Y_{Rn_k}) : Y_{Tn_k} < T_k, Y_{Rn_k} > R_k, k = 1 \text{ or } 2\} \bigcup \\ & \{Y_{Ti} : Y_{Ti} < T_i, i = 1, \ldots, n_1 - 1, n_1 + 1, \ldots, n_2 - 1\} \end{aligned}$$

$$\begin{aligned} P\{Y_{Rn_1} > R_1, Y_{Rn_2} > R_2 | P_{R_0}\} &\leq \alpha_R \\ P\{Y_{Rn_1} > R_1, Y_{Rn_2} > R_2 | P_{R_A}\} &\geq 1 - \beta_R \\ \sum_{i=1}^{n} \alpha_{T_i} &\leq \alpha_T \end{aligned}$$

Flexible Phase II Bivariate Clinical Trial Design

Where the toxicity boundary values are determined as

$$\begin{aligned} P\{Z_{b1} \geq b_1 | P_{T0}\} &= \alpha_{b_1} \\ P\{Z_{b2} \geq b_2, Z_{b1} < b_1 | P_{T0}\} &= \alpha_{b_2} - \alpha_{b_1} \\ &\vdots \\ P\{Z_{bn} \geq b_I, Z_{b1} < b_1, Z_{b2} < b_2, \ldots, Z_{b(n-1)} < b_{n-1}, | P_{T0}\} &= \alpha_{b_n} - \alpha_{b_{n-1}} \end{aligned}$$

$$T_i = \left\lceil \left\{ b_i \sqrt{\frac{P_{T_0}(1 - P_{T_0})}{n_i}} + P_{t_0} \right\} n_i \right\rceil$$

Flexible Phase II Bivariate Clinical Trial Design

The Ray and Rai design

$$
\begin{aligned}
CR_{RR} = \quad & \{(Y_{Tn_i}, Y_{Rn_k}) : \quad Y_{Tn_i} < T_i, Y_{Rn_k} > R_k, n_i = n_k\} \bigcup \\
& \{Y_{Tn_i} : \qquad Y_{Tn_i} < T_i, n_i < n_k\} \bigcup \\
& \{Y_{Rn_k} : \qquad Y_{Rn_k} > R_k\}, n_k < n_i\}
\end{aligned}
$$

The test statistic is defined similar to Conaway and Petroni

$$
A_{ik} = \begin{cases} (Y_{Tn_i}, Y_{Rn_k}) & \text{if } n_i = n_k \\ Y_{Tn_i} & \text{if } n_i < n_k \\ Y_{Rn_k} & \text{if } n_k < n_i \end{cases}
$$

Flexible Phase II Bivariate Clinical Trial Design

The constraints are

$$
\begin{aligned}
P\{A_{11}, \ldots, A_{i1}, \ldots, A_{ik}, \ldots, A_{IK} \in CR_{RR} | (P_{R_0}, P_{T_0}), \rho\} &\leq \alpha \\
P\{A_{11}, \ldots, A_{i1}, \ldots, A_{ik}, \ldots, A_{IK} \in CR_{RR} | (P_{R_A}, P_{T_A}), \rho\} &\geq 1 - \beta \\
\sum_{i=1}^{I} \alpha_{T_i} &\leq \alpha_T
\end{aligned}
$$

Flexible Phase II Bivariate Clinical Trial Design

Historical Designs

- Conaway and Petroni Design (*Biometrics*, 1995)
  - Multiple-stage bivariate clinical trial design
  - Relies on the multinomial distribution and the odds-ratio
  - No supporting software - computationally intense search algorithm
  - Does not appear to be used very often
- Bryant and Day Design (*Biometrics*, 1995)
  - Only a two-stage design
  - Web-based software
  - Still does not seem to be used very often

Ray and Rai, (*Stats in Medicine*, 2013)

The Bivariate Distribution

The probability X_{Rk}, X_{Tk} and X_{11k} responses is

$$f(x_{Rk}, x_{Tk}, x_{11k}|\mathbf{P}, k)$$
$$= \frac{n_k! P_{00}^{(n_k - X_{Rk} - X_{Tk} - X_{11k})} P_{10}^{(X_{Rk} - X_{11k})} P_{01}^{(X_{Tk} - X_{11k})} P_{11}^{X_{11k}}}{(n_k - X_{Rk} - X_{Tk} - X_{11k})!(X_{Rk} - X_{11k})!(X_{Tk} - X_{11k})!(X_{11k})!}$$

The full joint distribution

$$
\begin{aligned}
& f(y_{Rk}, y_{Tk}, y_{11k} | \mathbf{P}, k) \\
& = Pr\{Y_{Rk} = y_{Rk}, Y_{Tk} = y_{Tk}, Y_{11k} = y_{11k}, K = k | \mathbf{P}\} \\
& = Pr\{Y_{Rk} = y_{Rk}, Y_{Tk} = y_{Tk}, Y_{11k} = y_{11k}, A_i \in \mathbf{TCR}_i \text{ for } i = 1 \cdots (k-1) | \mathbf{P}\} \\
& = \sum_{R(y_{Rk}, y_{Tk}, y_{11k})} Pr\{X_{Rk} = x_{Rk}, X_{Tk} = x_{Tk}, X_{R1} = x_{R1}, ..., X_{Rk-1} = x_{Rk-1} \\
& X_{T1} = x_{T1}, \cdots, X_{Tk-1} = x_{Tk-1}, X_{111} = x_{111}, \cdots, X_{11k-1} = x_{11k-1} | \mathbf{P}\}
\end{aligned}
$$

The full joint distribution

$$f(y_{Rk}, y_{Tk}, y_{11k}|\mathbf{P}, k)$$

$$\sum_{R(y_{Rk}, y_{Tk}, y_{11k})} \frac{n_1! P_{00}^{(n_1 - X_{R1} - X_{T1} - X_{111})} P_{10}^{(X_{R1} - X_{111})} P_{01}^{(X_{T1} - X_{111})} P_{11}^{X_{111}}}{(n_1 - X_{R1} - X_{T1} - X_{111})!(X_{R1} - X_{111})!(X_{T1} - X_{111})!(X_{111})!} \cdots$$

$$\frac{n_k! P_{00}^{(n_k - X_{Rk} - X_{Tk} - X_{11k})} P_{10}^{(X_{Rk} - X_{11k})} P_{01}^{(X_{Tk} - X_{11k})} P_{11}^{X_{11k}}}{(n_1 - X_{Rk} - X_{Tk} - X_{11k})!(X_{Rk} - X_{11k})!(X_{Tk} - X_{11k})!(X_{11k})!}$$

The full distribution

To simplify the notation, let

$$a_k = n_k - x_{rk} - x_{tk} + x_{11k}$$
$$b_k = x_{rk} - x_{11k}$$
$$c_k = x_{tk} - x_{11k}$$
$$d_k = x_{11k}$$

Also,

$$A_k = N - y_{rk} - y_{tk} + y_{11k}$$
$$B_k = y_{rk} - y_{11k}$$
$$C_k = y_{tk} - y_{11k}$$
$$D_k = y_{11k}$$

The full distribution

Then we will have

$$P_{00}^{(A_K)} P_{10}^{(B_K)} P_{01}^{(C_K)} P_{11}^{D_K}$$

$$\sum_{x_{r1}} \cdots \sum_{x_{rk}} \sum_{x_{t1}} \cdots \sum_{x_{tk}} \sum_{x_{111}} \cdots \sum_{x_{11k}} \frac{n_1 n_2 \cdots n_k}{a_1! \cdots a_k! b_1! \cdots b_k! c_1! \cdots c_k! d_1! \cdots d_k!}$$

The full distribution

The sufficient statistic is Y_{rk}, Y_{tk}, Y_{11k} since n_k is fixed. The proof that is the complete and sufficient sufficient is in the paper to be submitted. We need to find $E(X_{r1}/n_1 | Y_{rk}, Y_{tk}, Y_{11k})$ which is also in the paper.

Simulation Study

- Bryant and Day Design
- Three different levels of correlation
- Varied Response
- Fixed toxicity

- Design I - $(P_{R0}, P_{RA}) = (0.10, 0.30)$
- Design II - $(P_{R0}, P_{RA}) = (0.20, 0.40)$
- Design III - $(P_{R0}, P_{RA}) = (0.30, 0.50)$.

Figure: Bias of MLE

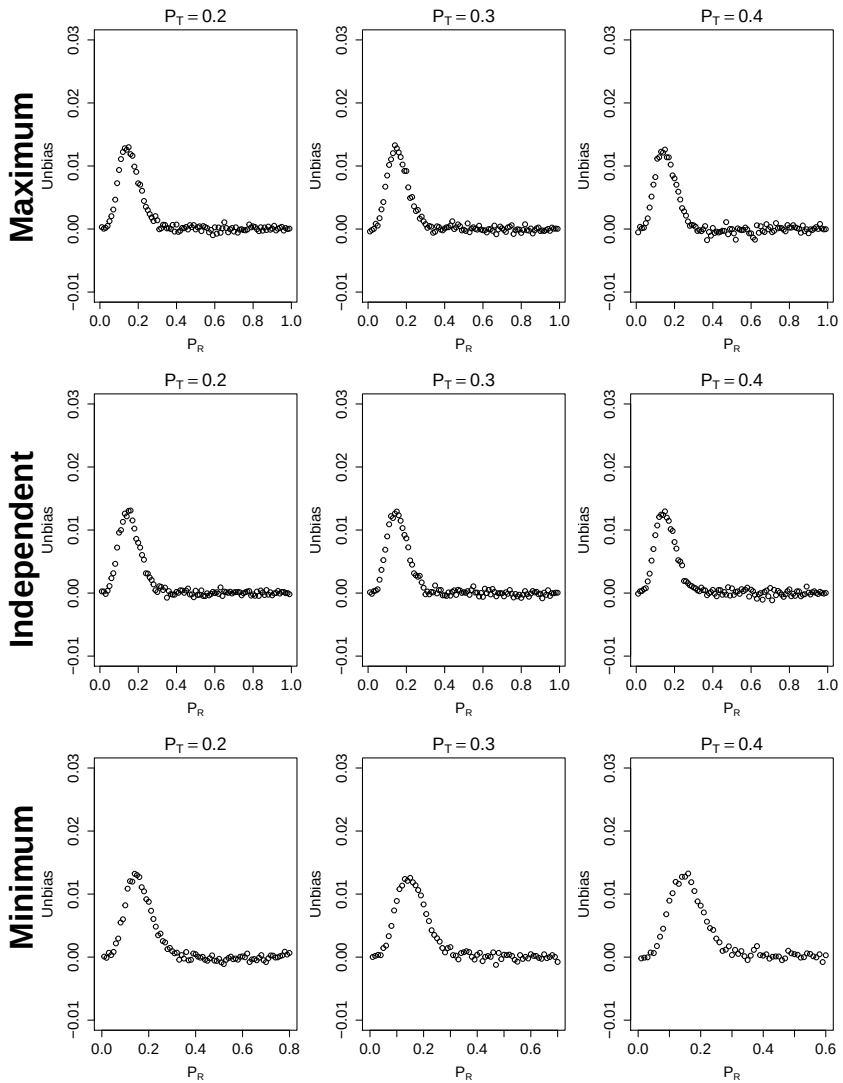


Figure: Bias of UMVUE

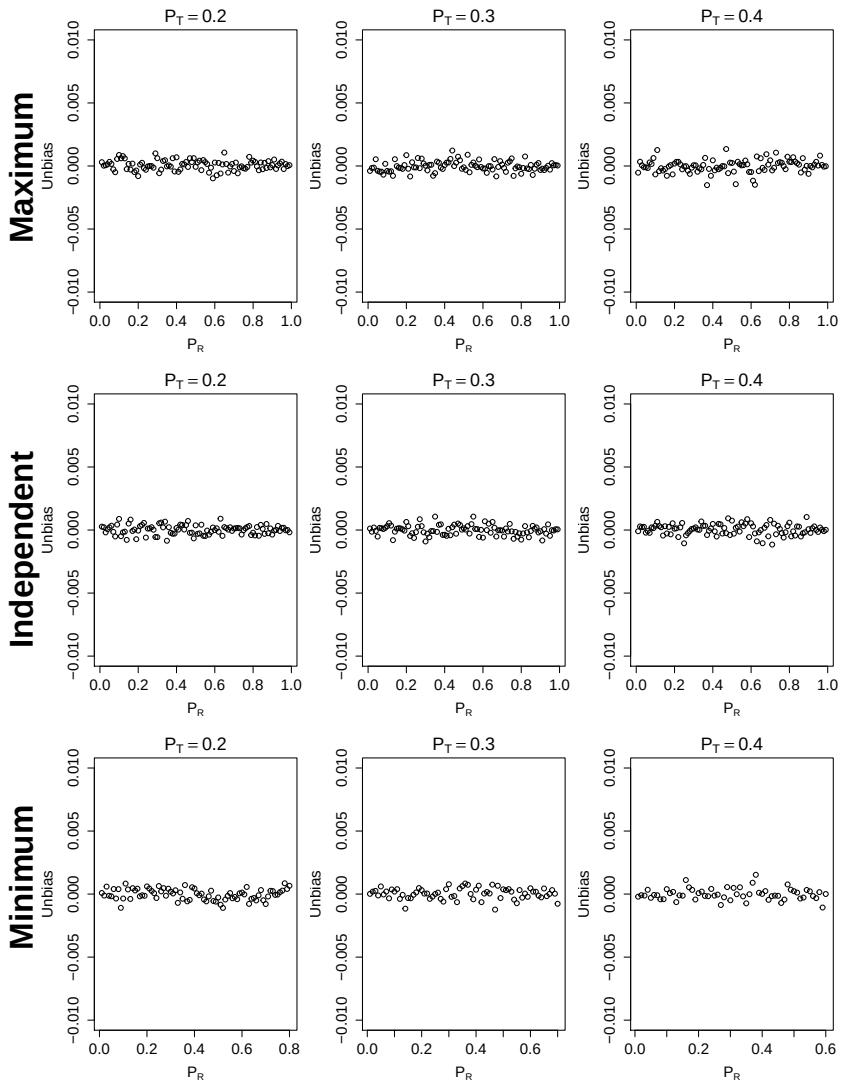
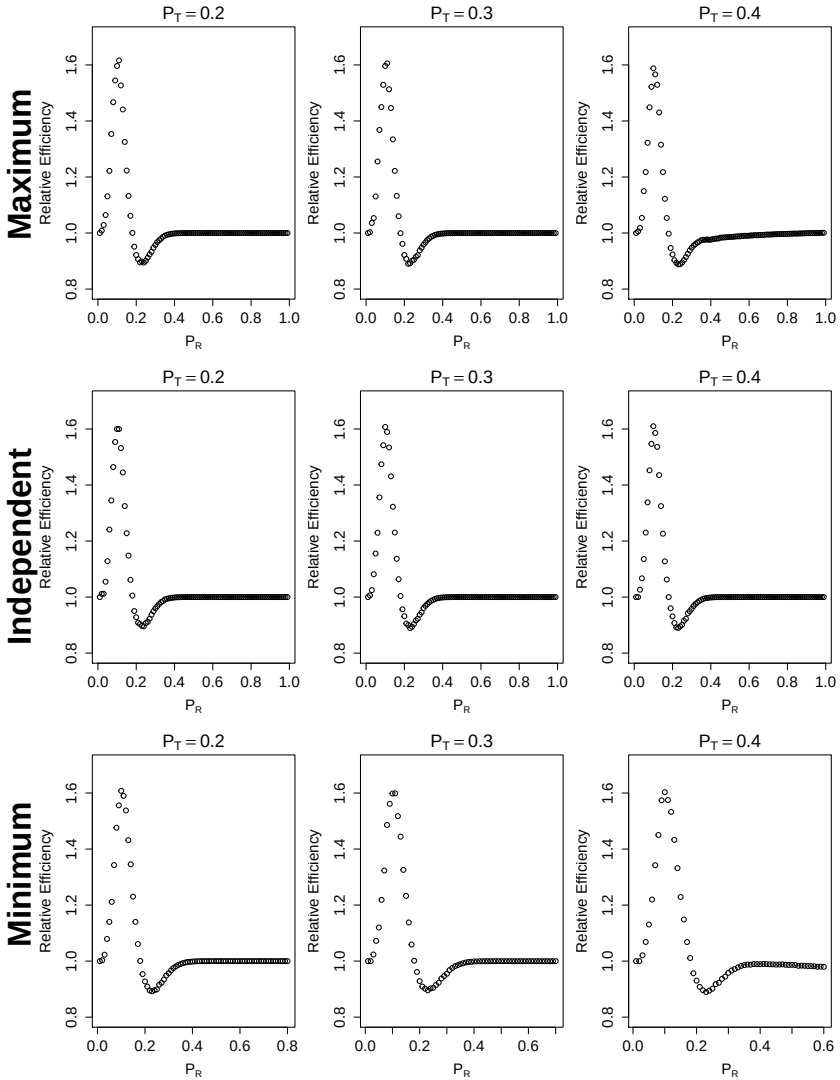


Figure: Relative Effeciency



Conclusions

- Proposed an UMVUE
- Examined the bias of the MLE
- Examined the bias of the proposed UMVUE
- Examined the relative efficiency of the proposed estimator

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Acknowledgments

Dr. Shesh N. Rai,
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Thank you!

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