A Rigorous Framework for Automated Design Assessment and Type I Error Control

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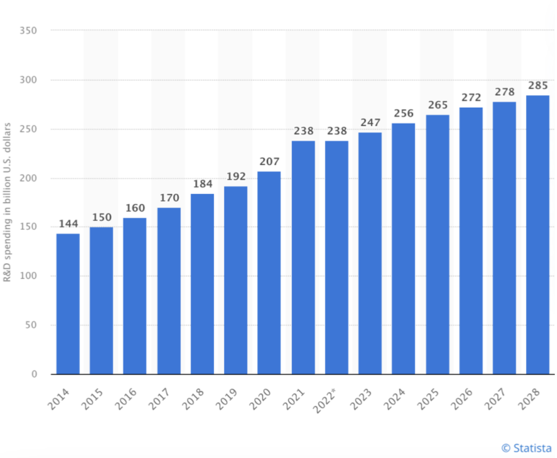
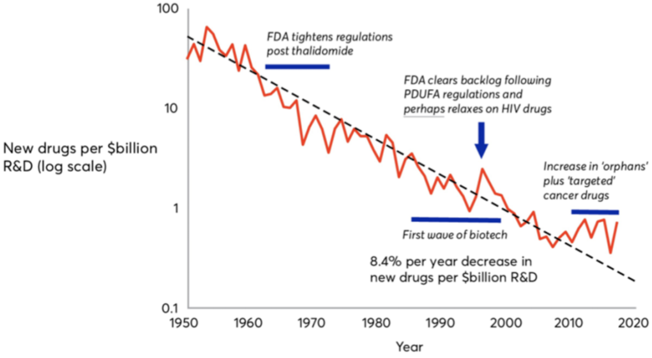
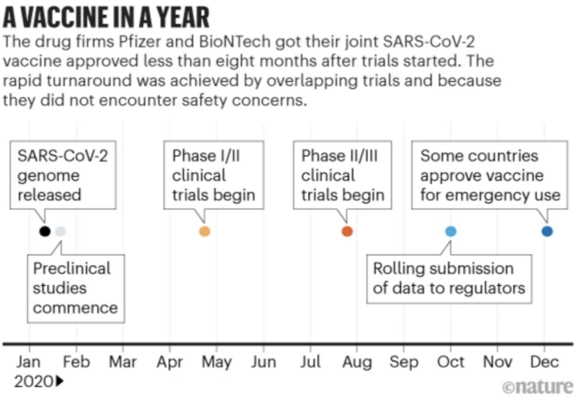
Pharma R&D is Growing



Eroom's Law: Efficiency Down

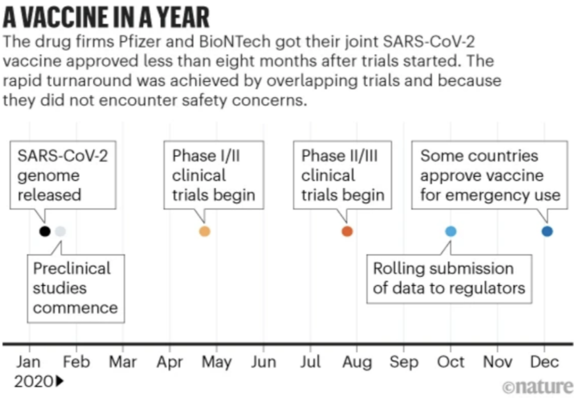


Covid Put a Focus on Shortening Clinical Trials



Sources: BioNTech/Pfizer; *Nature* analysis

Covid Put a Focus on Shortening Clinical Trials



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How can statisticians speed up the clinical trials system?

Add Features to Improve Trial Efficiency

- Smoothly combine studies (e.g. Phase I/II, or II/III).
- Stop early for success (efficacy), or failure (futility).
- Compare multiple treatments or doses to select the best.
- Adaptive sample sizing.
- Use of outside data.

Problem: Analytic Control goes Out the Window!

Adaptive T-Test:

- $X_i \sim \mathcal{N}(\mu, \sigma^2)$ (unknown μ, σ).
- $H_0 : \mu = 0$.
- Total of 6 analyses.
- Before each analysis, add 10 i.i.d. samples.
- At each analysis i, reject if

$$T_i := \frac{\sqrt{N_i}\bar{X}_i}{\hat{\sigma}_i} > 2 \quad \text{and} \quad \bar{X}_i > 0.1$$

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What is the Type I Error?

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What is the Type I Error?

Classical toolkit breaks even with Gaussian data.

Adaptive T-Test Non-Trivial Null Distribution

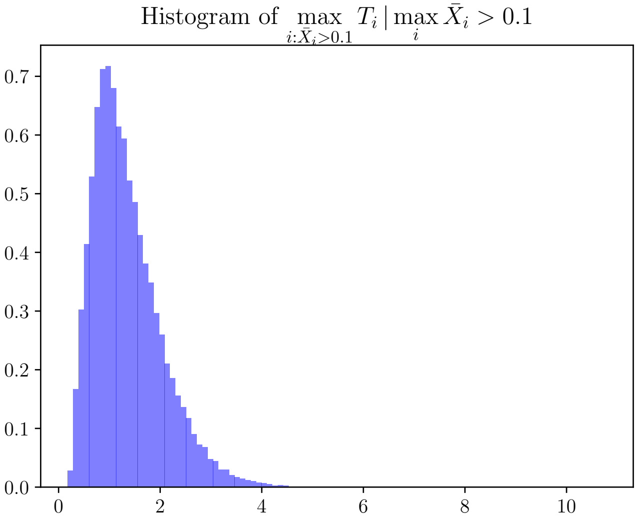
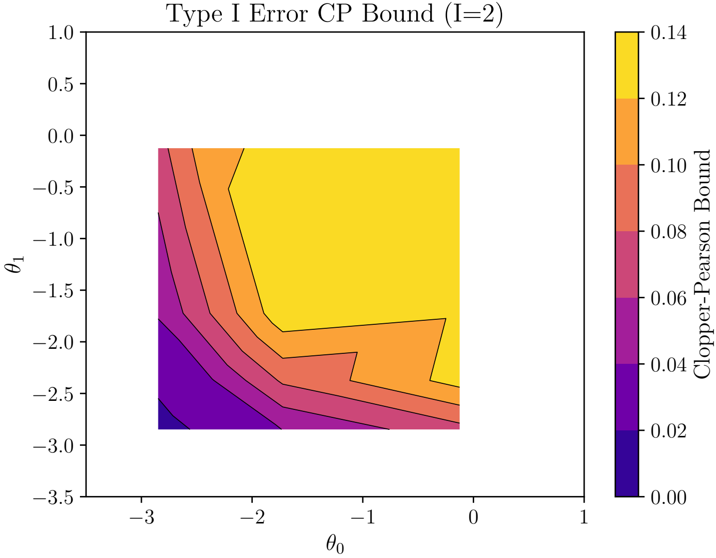


Figure: Adaptive T-Test test statistic distribution for $\sigma \equiv 1$.

Intermediate Techniques Fail

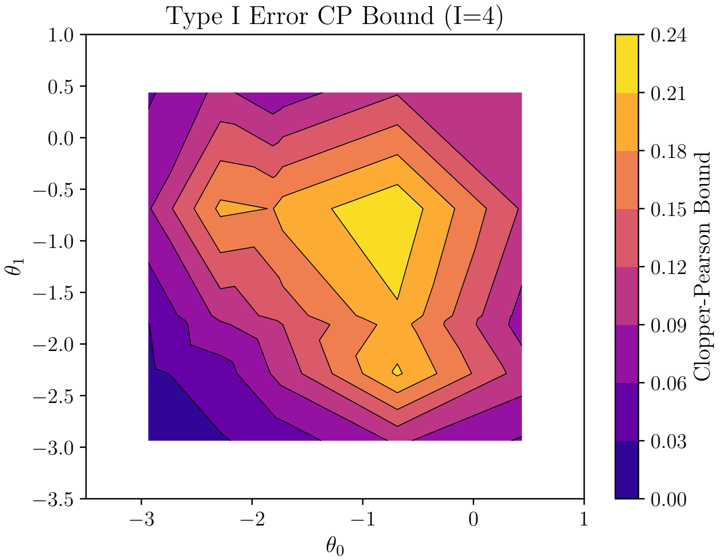
- Composite null with nuisance parameters (noise levels).
  Simulating on single null point $\not\Longrightarrow$ Type I Error control.
- Sharp null hypothesis (exact zero causal effect) is usually false ("null" treatments often increase the variability of outcomes).
  Breaks permutation methods.
- Adaptive sampling renders the test statistic to be non-pivotal.
  Breaks the bootstrap.

Simulation to the Rescue?



To accept or not to accept?

Simulation to the Rescue?



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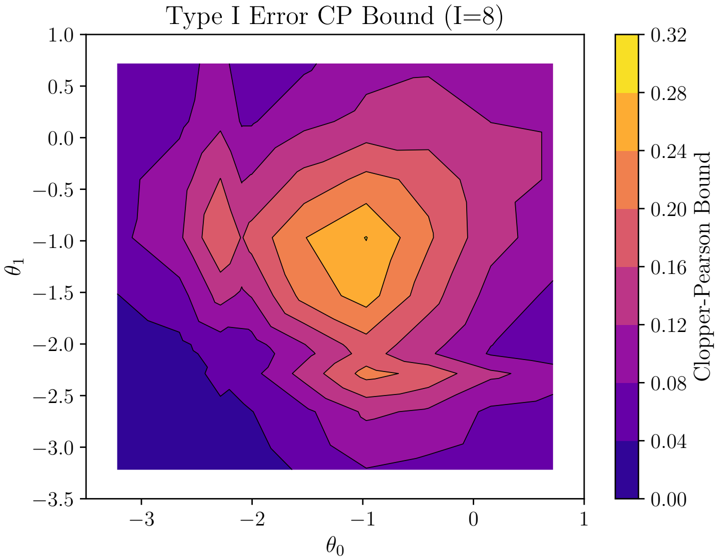

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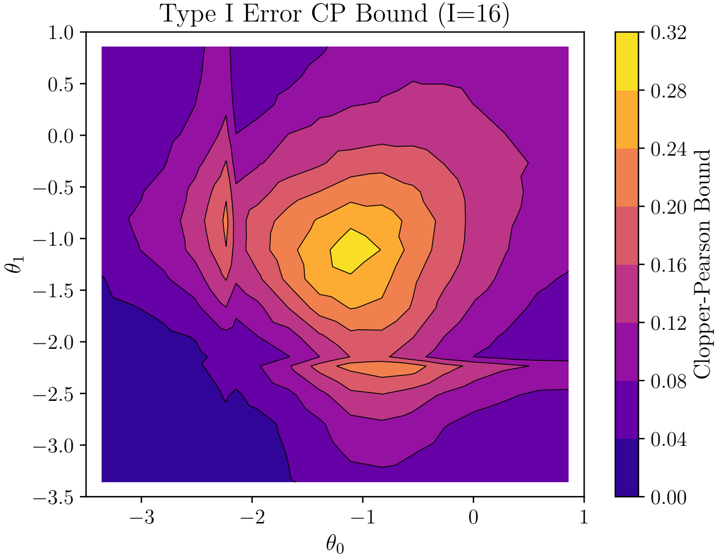

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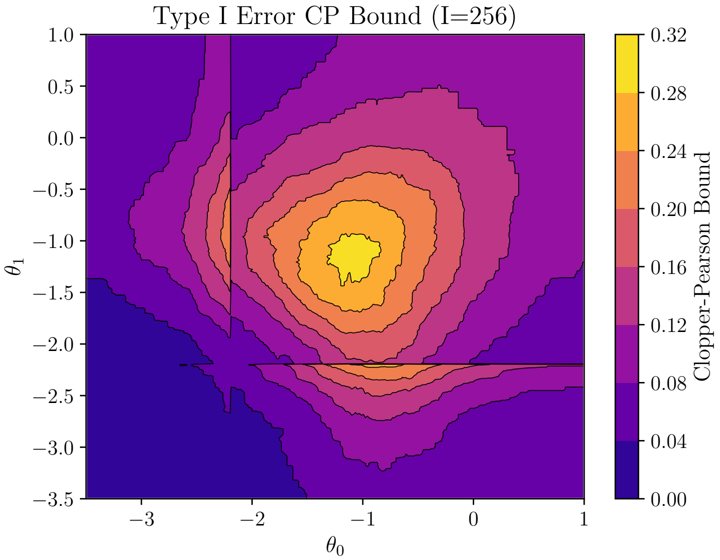
Simulation to the Rescue?



To accept or not to accept?

Simulation Raises New Challenges

- Simulation constrained to **finite** number of null points.

  How do we deal with composite nulls?
- Simulation has Monte Carlo error.

  How do we deal with Monte Carlo error?
- Bounded computing power.

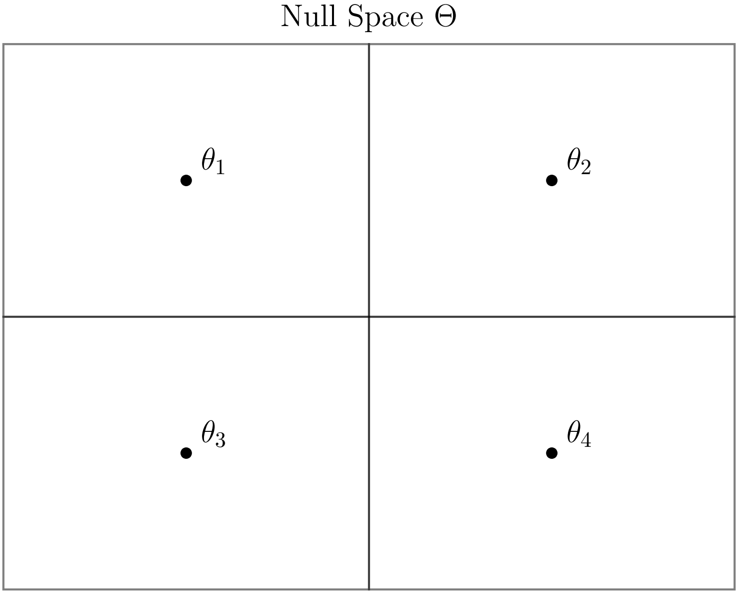
  How many points in the null space to simulate?

  Are the simulations even tractable?

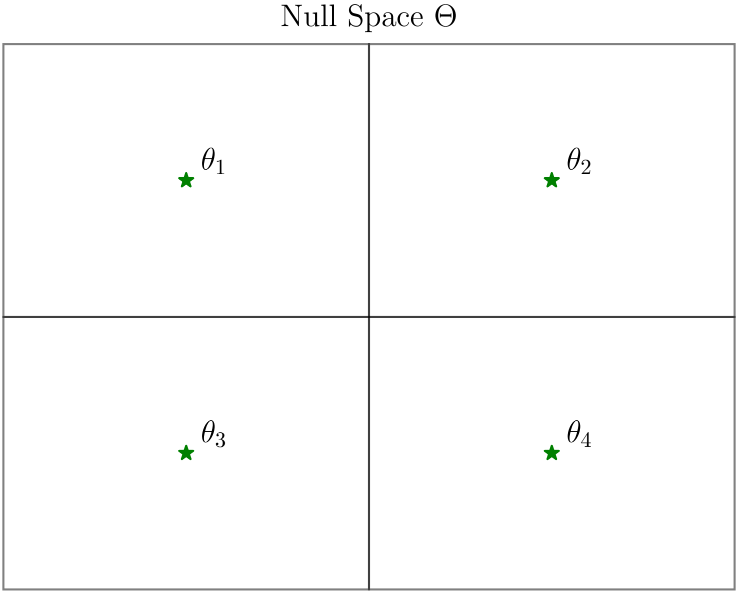
Intuition of Our Approach

Null Space Θ

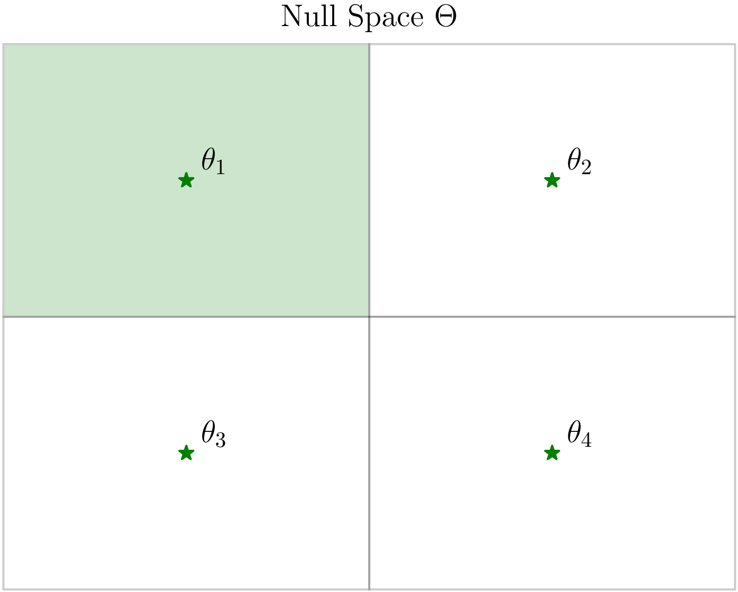
Partition Θ into Tiles with Representatives



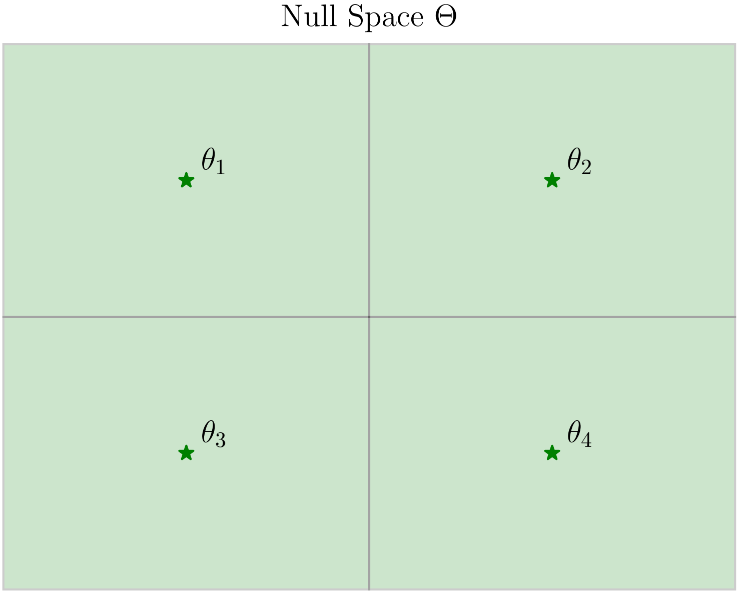
Simulate on each Representative



Extend Simulation Information to Tile



Divide-and-Conquer for Guarantees on All of Θ

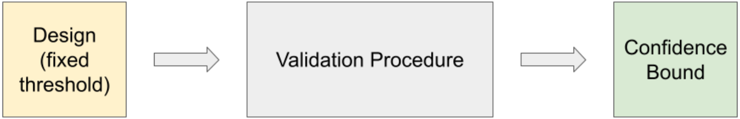


Our Approach: Proof-by-Simulation

General Workflow:

- Let Θ be a (bounded) null hypothesis space.
- Partition Θ into tiles $\{\Theta_i\}_{i=1}^{I}$ with representatives $\{\theta_i\}_{i=1}^{I}$.
- Simulate the design on each θ_i and output test statistics.
- Use our method **Continuous Simulation Extension** (CSE) to *extend* information at each θ_i to any other point in Θ_i.
- Divide-and-conquer to get guarantees on *all of* Θ.

Method 1: Validation for Point-wise Confidence



Method 1: Validation for Point-wise Confidence

- **Validation**: Construct bounds $(\hat{l}(\cdot), \hat{u}(\cdot))$ for the true Type I Error, $f(\cdot)$, with confidence $1-\delta$:

$$\forall \theta \in \Theta, \mathbb{P}\left(\hat{l}(\theta) \leq f(\theta)\right) \geq 1-\delta \text{ and}$$
$$\mathbb{P}\left(\hat{u}(\theta) \geq f(\theta)\right) \geq 1-\delta$$

- Point-wise guarantee is appropriate since there is only one *true* value of θ.

Method 2: Calibration for Type I Error Proof

Method 2: Calibration for Type I Error Proof

- **Calibration**: Select a (random) critical threshold, $\hat{\lambda}^*$, such that

$$\forall \theta \in \Theta, \mathbb{E}\left[f_{\hat{\lambda}^*}(\theta)\right] \leq \alpha$$

where $f_\lambda(\theta)$ is the Type I Error at θ using threshold λ.

Random $\hat{\lambda}^*$ is acceptable

- Guarantee is **overall** valid (regulators want this!).
- Practitioners **already use** simulations to evaluate designs.
- Our approach is **strictly stronger** because we can give guarantees.

Main Task: Find Type I Error at θ

- $X \sim P_\theta$ (known distribution), null space Θ.
- Any arbitrary design $\mathcal{D}$.
- $f(\theta) := \mathbb{P}_\theta(\mathcal{D} \text{ rejects})$.

Main Task: Find **Upper Bound** of Type I Error at θ

- $X \sim P_\theta$ (known distribution), null space Θ.
- Any arbitrary design $\mathcal{D}$.
- $f(\theta) := \mathbb{P}_\theta(\mathcal{D} \text{ rejects})$.

Main Task: Find **Upper Bound** of Type I Error at θ

- Assume further that P_θ is an **exponential family**.
- Does this help?

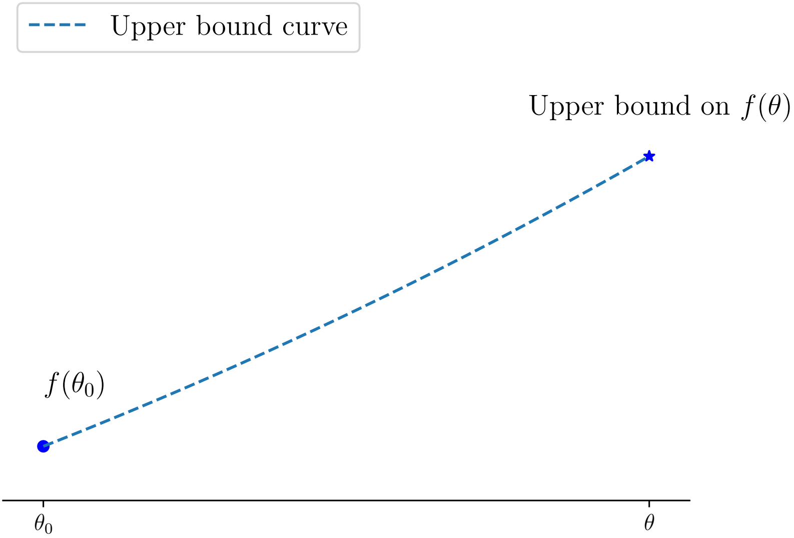
Main Task: Find **Upper Bound** of Type I Error at θ

- Assume further that P_θ is **Gaussian**.
- Does this help?

Intuition for Upper Bounding the Type I Error

- **Morally**, distribution assumptions *should* help!
- Use **“curvature”** information in distribution.
- **Restrict** the possible values for $f(\theta)$.

Claim: Upper Bound on the Type I Error



Derivation: Begin with a Change of Measure

Let $A := \{x : \mathcal{D}(x) \text{ rejects}\}$.
Then,

$$f(\theta) = \mathbb{E}_\theta \left[\mathbb{1}_{X \in A} \right] = \mathbb{E}_{\theta_0} \left[\mathbb{1}_{X \in A} \frac{p_\theta(X)}{p_{\theta_0}(X)} \right]$$

Use Hölder's Inequality!

For any $p, q \geq 1$ such that $\frac{1}{p} + \frac{1}{q} = 1$,

$$
\begin{aligned}
f(\theta) &\leq \|\mathbb{1}_{X \in A}\|_{L^p(P_{\theta_0})} \left\| \frac{p_\theta(X)}{p_{\theta_0}(X)} \right\|_{L^q(P_{\theta_0})} \\
&= f(\theta_0)^{1-\frac{1}{q}} \left\| \frac{p_\theta(X)}{p_{\theta_0}(X)} \right\|_{L^q(P_{\theta_0})}
\end{aligned}
$$

Introduce Distributional Assumptions

Let P_θ have a density of the form:

$$p_\theta(x) = \exp\{g_\theta(x) - A(\theta)\}$$

By a simple calculation, one can show that

$$\left\| \frac{p_\theta(X)}{p_{\theta_0}(X)} \right\|_{L^q(P_{\theta_0})} = \exp\left\{ \frac{\psi(\theta_0, \theta - \theta_0, q)}{q} - \psi(\theta_0, \theta - \theta_0, 1) \right\}$$

$$\psi(\theta_0, v, q) := \log \mathbb{E}_{\theta_0}\left[\exp\left\{q\left(g_{\theta_0+v}(X) - g_{\theta_0}(X)\right)\right\}\right]$$

We did it!

For any $q \geq 1$,

$$f(\theta) \leq f(\theta_0)^{1-\frac{1}{q}} \exp\left\{ \frac{\psi(\theta_0, \theta - \theta_0, q)}{q} - \psi(\theta_0, \theta - \theta_0, 1) \right\}$$

Tilt-Bound and Special Cases

Tilt-Bound ($q \geq 1$):

$$U(\theta_0, v, q, f(\theta_0)) := \underbrace{f(\theta_0)^{1-\frac{1}{q}}}_{\theta_0 \textbf{ info}} \underbrace{\exp\left\{\frac{\psi(\theta_0, v, q)}{q} - \psi(\theta_0, v, 1)\right\}}_{\textbf{Curvature info}}$$

Exponential family:

$$\psi(\theta_0, v, q) := A(\theta_0 + qv) - A(\theta_0)$$

Normal family $\{\mathcal{N}(\theta, 1) : \theta \in \Theta\}$:

$$U(\theta_0, v, q, f(\theta_0)) := f(\theta_0)^{1-\frac{1}{q}} \exp\left\{\frac{(q-1)v^2}{2}\right\}$$

Optimize over q!

$$f(\theta_0 + v) \leq U(\theta_0, v, q, f(\theta_0)) \quad \forall q \geq 1$$

$$\implies f(\theta_0 + v) \leq \underbrace{\inf_{q \geq 1} U(\theta_0, v, q, f(\theta_0))}_{\textbf{Optimized Tilt-Bound}}$$

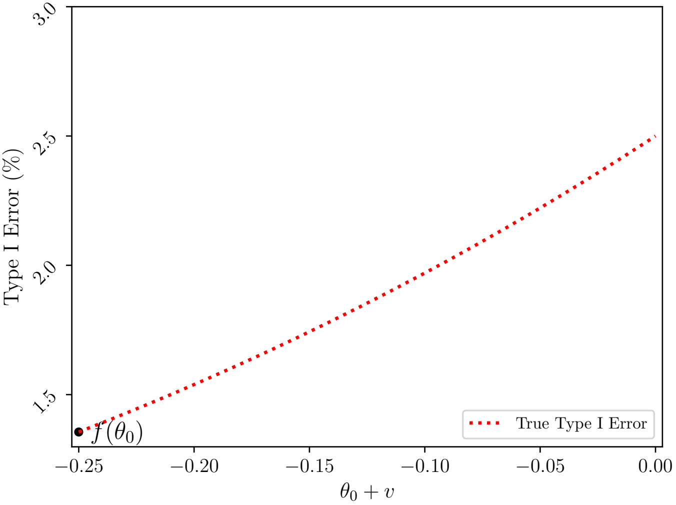
How to optimize over q?

- Tilt-Bound is **quasi-convex** in q!
- Very **simple, fast** $O(\log(\epsilon^{-1}))$ algorithm with **guaranteed convergence**.

Theorem (Quasi-convex in q)

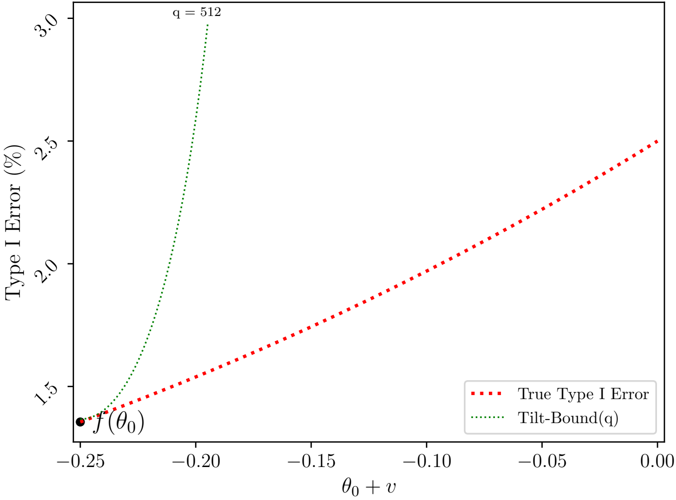
Fix any $\theta_0 \in \Theta \subseteq \mathbb{R}^d$, a set $S \subseteq \mathbb{R}^d$, and $a \geq 0$. Assume that for all $v \in S$, $\Delta(v, X) := g_{\theta_0+v}(X) - g_{\theta_0}(X)$ is not constant P_{θ_0}-a.s.. Then, $q \mapsto \sup_{v \in S} U(\theta_0, v, q, a)$ is quasi-convex. Moreover, it is strict if $a > 0$, S is finite, and not identically infinite, respectively.

Demonstrating the Tilt-Bound on the One-Sided Z-Test



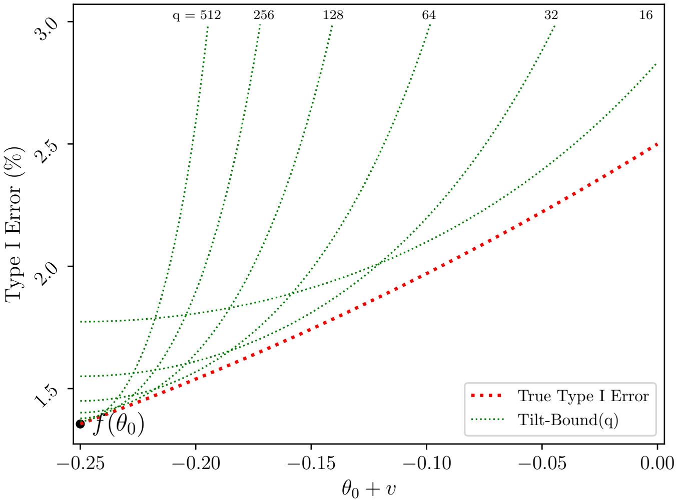
- $X \sim \mathcal{N}(\theta, 1)$, $\Theta = [-0.25, 0]$.
- $\mathcal{D}(X)$: reject if $X > z_{1-\alpha}$.

The Tilt-Bound for a Particular q



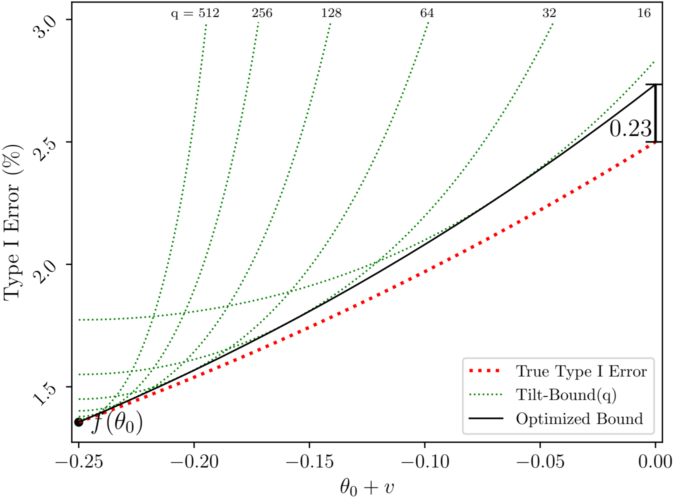
$$U(\theta_0, v, q, f(\theta_0)) = f(\theta_0)^{1-\frac{1}{q}} \exp\left\{\frac{(q-1)v^2}{2}\right\}$$

The Tilt-Bound for Many qs



$$U(\theta_0, v, q, f(\theta_0)) = f(\theta_0)^{1-\frac{1}{q}} \exp\left\{\frac{(q-1)v^2}{2}\right\}$$

The Optimized Tilt-Bound is Tight



$$\inf_{q \geq 1} U(\theta_0, v, q, f(\theta_0))$$

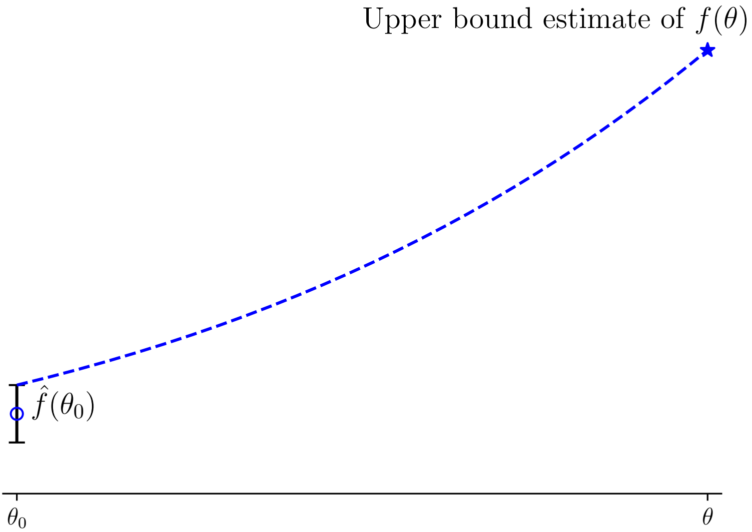
Tilt-Bound Summary

- Tilt-Bound is a **deterministic** bound.
- Tight over small to medium distances.
- Valid for **any rejection set**.
- Depends on Type I Error at the **initial point** θ_0 and the **distributional family** P_θ (which implicitly accounts for the sample size).

Main Task: Point-wise Valid Upper Bound on Type I Error

- $X \sim P_\theta$ (known distribution), null space Θ.
- Any arbitrary design $\mathcal{D}$.
- Clopper-Pearson bound using Monte Carlo estimate $\hat{f}(\theta_0)$.

Claim: Valid Upper Bound on the Type I Error



Use Tilt-Bound on Upper Bound Estimate!

Monotone Property:

- $a \mapsto U(\theta_0, v, q, a)$ is **non-decreasing**.

Validation Proof:

- $\hat{\eta}$ be a $1 - \delta$ upper bound of $f(\theta_0)$.
- $\hat{u} := U(\theta_0, v, q, \hat{\eta})$ for any $q \geq 1$.

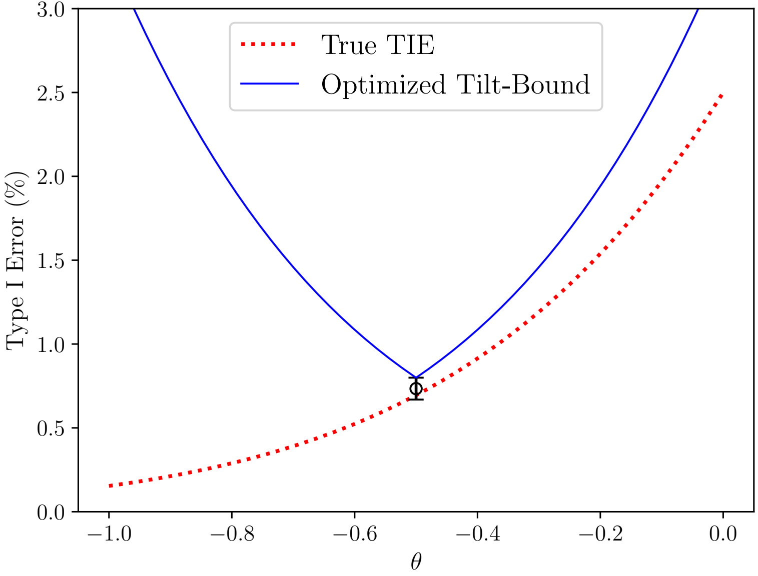
Recall,

$$f(\theta_0 + v) \leq U(\theta_0, v, q, f(\theta_0))$$

Then,

$$\mathbb{P}\left(f(\theta_0 + v) \leq \hat{u}\right) \geq \mathbb{P}\left(f(\theta_0) \leq \hat{\eta}\right) \geq 1 - \delta$$

Use Tilt-Bound on a Grid for the Z-Test



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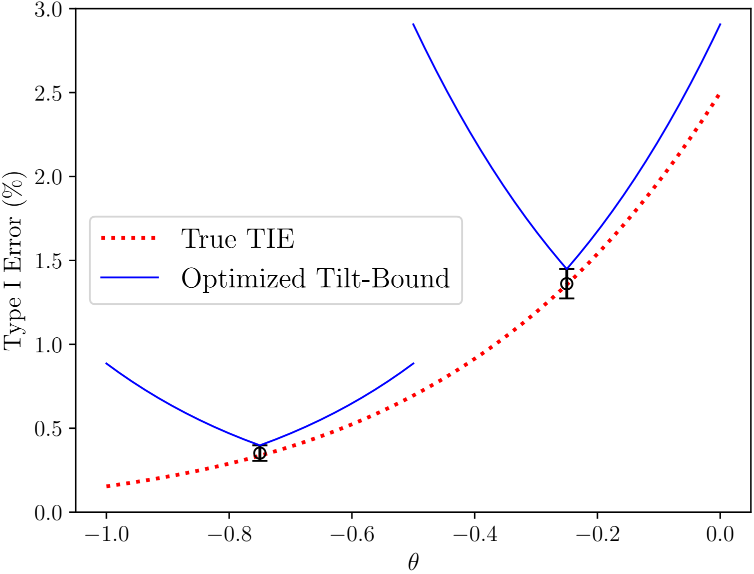
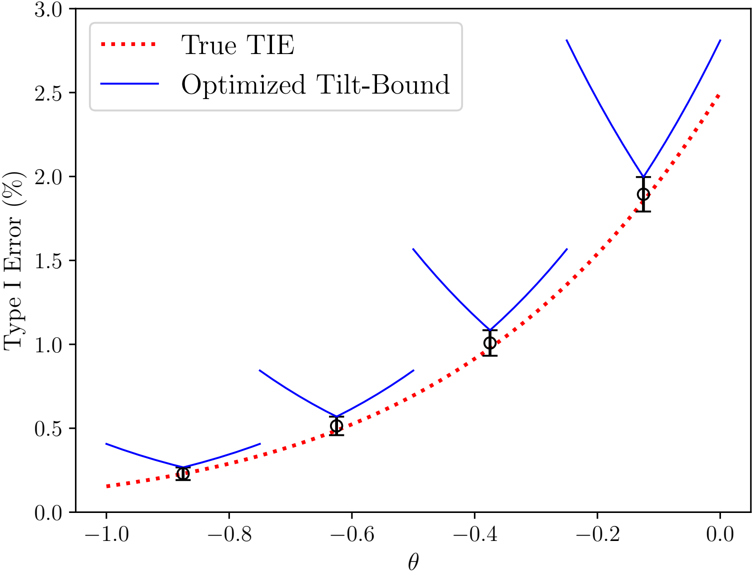


Use Tilt-Bound on a Grid for the Z-Test



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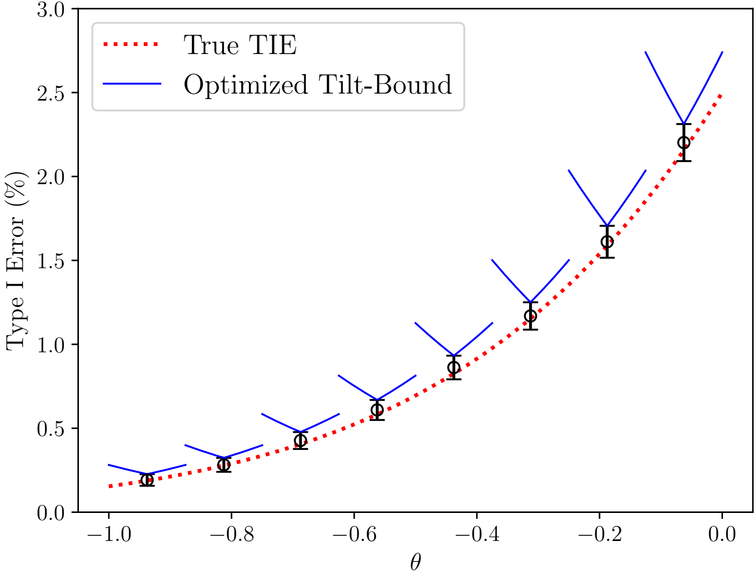

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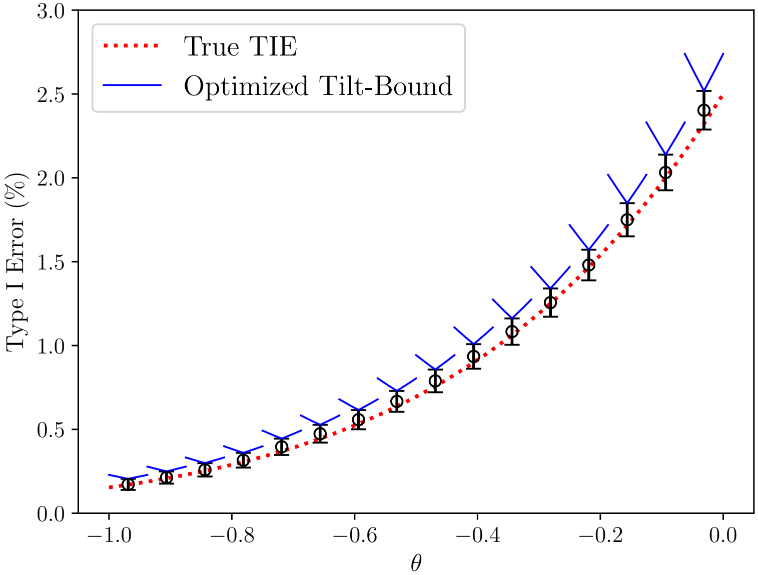

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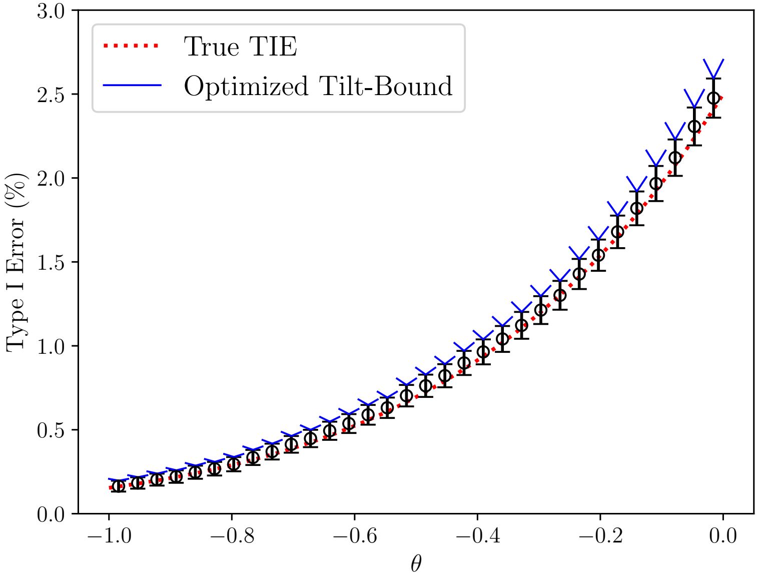

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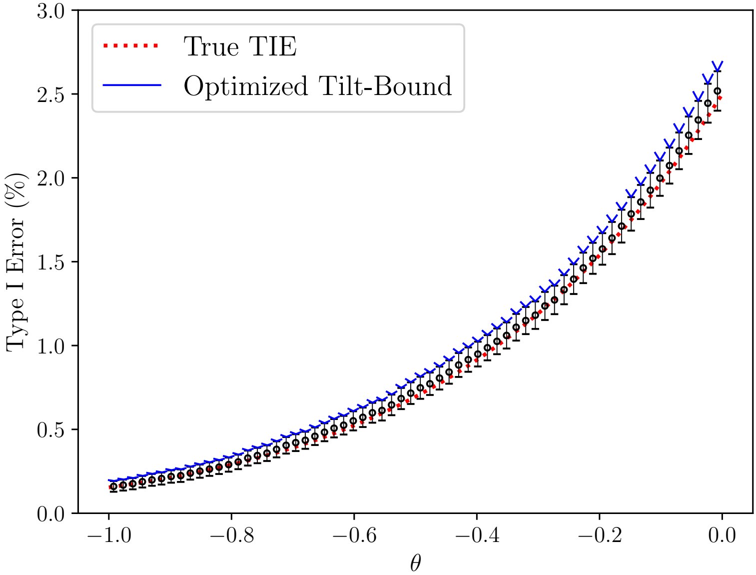
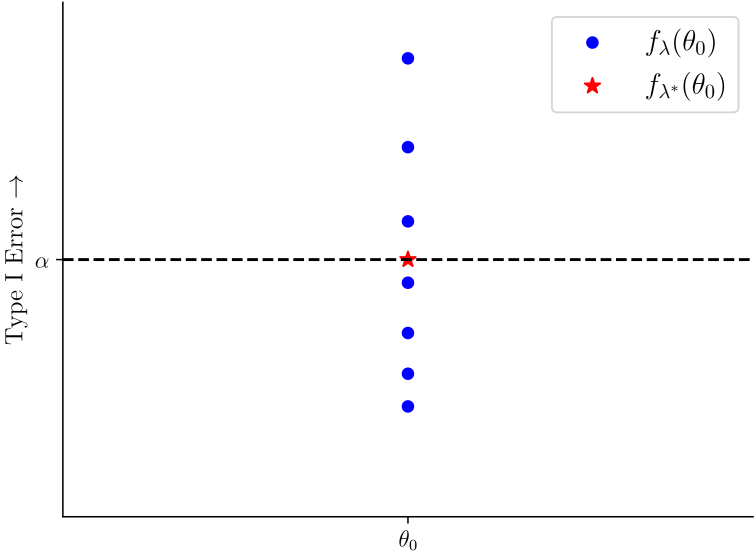


Main Task: Find Critical Threshold with Level α at θ_0



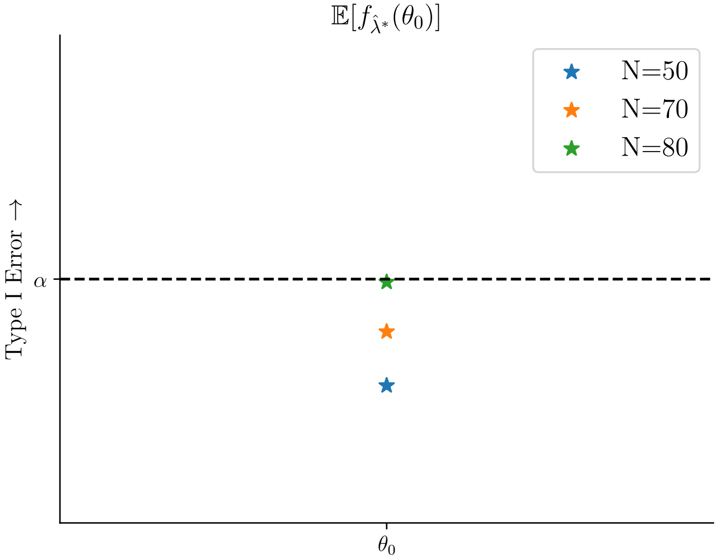
Straightforward for a Single Point

- Let $S(X)$ be the test statistic with data X.
- Design $\mathcal{D}$: rejects if $S(X) < \lambda$.
- Given $S_1, \ldots, S_N$ i.i.d. test statistics,

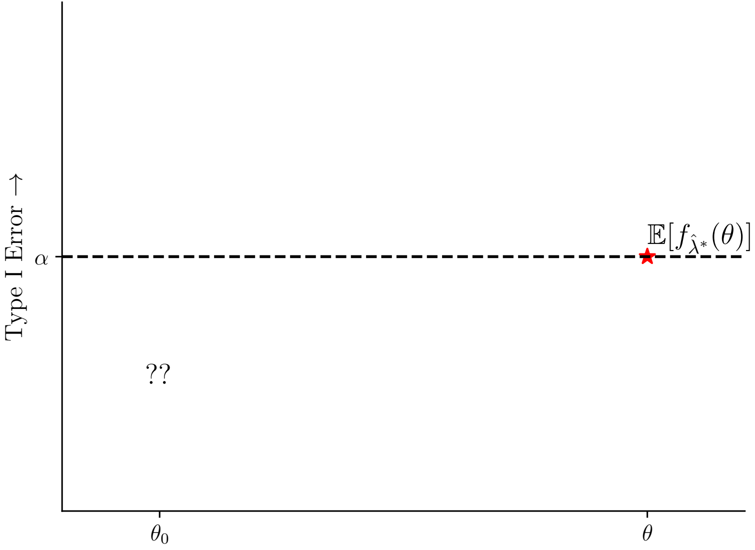
$$\hat{\lambda}^* := S_{\lfloor (N+1)\alpha \rfloor} \implies \mathbb{E}\left[f_{\hat{\lambda}^*}(\theta_0)\right] \leq \alpha$$

- Easy to show using Beta distribution.

Calibration Results for a Single Point

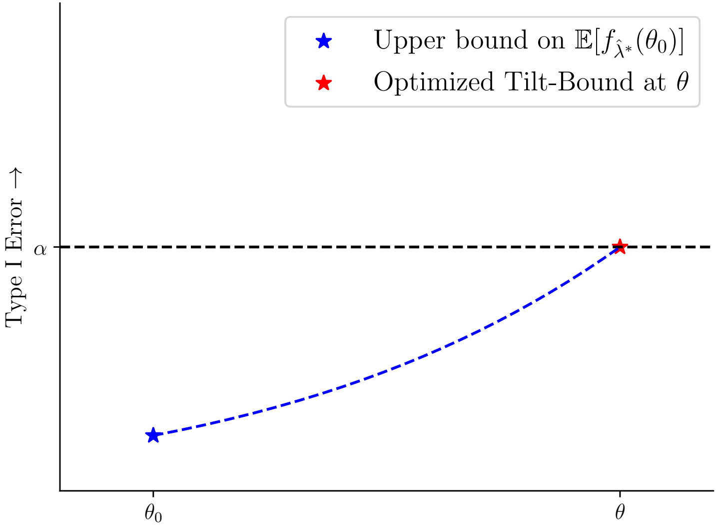


Main Task: Find Critical Threshold with Level α at θ



Inverted Tilt-Bound

Claim: Calibrate at θ_0 to Control Tilt-Bound at θ



Use CSE to Control Type I Error at θ

$$\mathbb{E}\left[f_\lambda(\theta_0 + v)\right] \leq U(\theta_0, v, q, \mathbb{E}\left[f_\lambda(\theta_0)\right])$$

- Back-solve to hit level α:

$$U(\theta_0, v, q, \mathbb{E}\left[f_\lambda(\theta_0)\right]) \leq \alpha \iff \mathbb{E}\left[f_\lambda(\theta_0)\right] \leq U^{-1}(\theta_0, v, q, \alpha)$$

Inverted Tilt-Bound:

$$U^{-1}(\theta_0, v, q, \alpha) := \left(\alpha \exp\left[-\frac{\psi(\theta_0, v, q)}{q} + \psi(\theta_0, v, 1)\right]\right)^{\frac{q}{q-1}}$$

Use Point-Null Case to Find Critical Threshold

- Let $\alpha' := U^{-1}(\theta_0, v, q, \alpha)$.
- Find $\hat{\lambda}^*$ such that

$$\mathbb{E}\left[f_{\hat{\lambda}^*}(\theta_0)\right] \leq \alpha'$$

- Maximize α' over $q \geq 1$ for free to get least-conservative threshold.

Then,

$$\mathbb{E}\left[f_{\hat{\lambda}^*}(\theta_0 + v)\right] \leq U(\theta_0, v, q, \mathbb{E}\left[f_{\hat{\lambda}^*}(\theta_0)\right]) \leq \alpha$$

Control Type I Error in a Region

- Back-solve with **worst-case** Tilt-Bound:

$$\begin{aligned} &\sup_{v \in \Theta - \theta_0} U(\theta_0, v, q, \mathbb{E}[f_\lambda(\theta_0)]) \leq \alpha \\ \iff \quad &\mathbb{E}[f_\lambda(\theta_0)] \leq \inf_{v \in \Theta - \theta_0} U^{-1}(\theta_0, v, q, \alpha) \end{aligned}$$

- Let $\alpha' := \inf_{v \in \Theta - \theta_0} U^{-1}(\theta_0, v, q, \alpha)$.
- Maximize α' over $q \geq 1$.
- Find $\hat{\lambda}^*$ such that

$$\mathbb{E}\left[f_{\hat{\lambda}^*}(\theta_0)\right] \leq \alpha'$$

How to optimize over v?

$$\inf_{v \in \Theta - \theta_0} U^{-1}(\theta_0, v, q, \alpha)$$

- **Assume a linearity condition**!
- Inverted Tilt-Bound is **quasi-concave** in v, respectively!
- If Θ is a polytope, suffices to compute only at the vertices!

How to optimize over v?

Theorem (Quasi-convex in v)

Let $\{P_\theta : \theta \in \Theta \subseteq \mathbb{R}^d\}$ *be a family of distributions:*

$$dP_\theta(x) = \exp\{g_\theta(x) - A(\theta)\}\, d\mu(x)$$

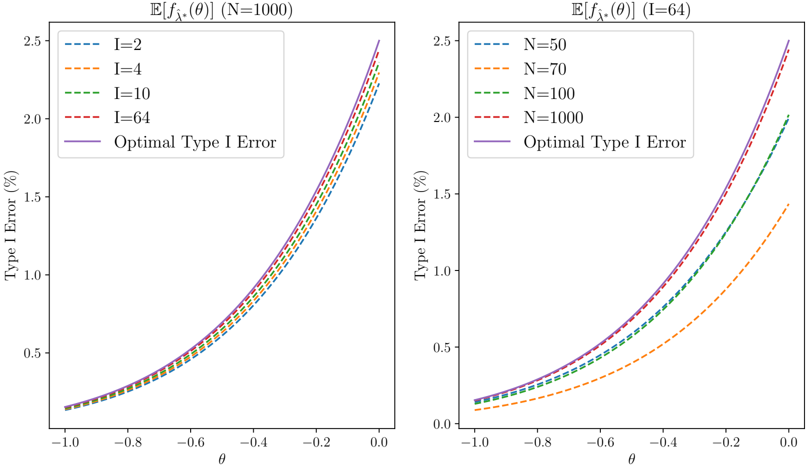
Fix any $\theta_0 \in \Theta$*. Suppose that* $\Delta(v, x) \equiv g_{\theta_0+v}(x) - g_{\theta_0}(x)$ *is linear in* v*, i.e.* $\Delta(v, x) = W(x)^\top v$ *for some* $W(x) \in \mathbb{R}^d$*. Then, the Inverted Tilt-Bound is quasi-concave as a function of* v*.*

Divide-and-Conquer yields a Global Guarantee

- Assume Θ any bounded space.
- Partition Θ into tiles $\{\Theta_i\}_{i=1}^{I}$ with representatives $\{\theta_i\}_{i=1}^{I}$.
- Calibrate to get $\hat{\lambda}_i^*$ for each tile Θ_i.
- Take the most conservative, $\hat{\lambda}^* := \min\limits_{i=1,\ldots,I} \hat{\lambda}_i^*$.
- Then,

$$\begin{aligned}
\sup_{\theta\in\Theta} \mathbb{E}\left[f_{\hat{\lambda}^*}(\theta)\right] &= \max_{i=1,\ldots,I} \sup_{\theta\in\Theta_i} \mathbb{E}\left[f_{\hat{\lambda}^*}(\theta)\right] \\
&\leq \max_{i=1,\ldots,I} \sup_{\theta\in\Theta_i} \mathbb{E}\left[f_{\hat{\lambda}_i^*}(\theta)\right] \\
&\leq \alpha
\end{aligned}$$

Type I Error Tightens with More Simulations and Tiles

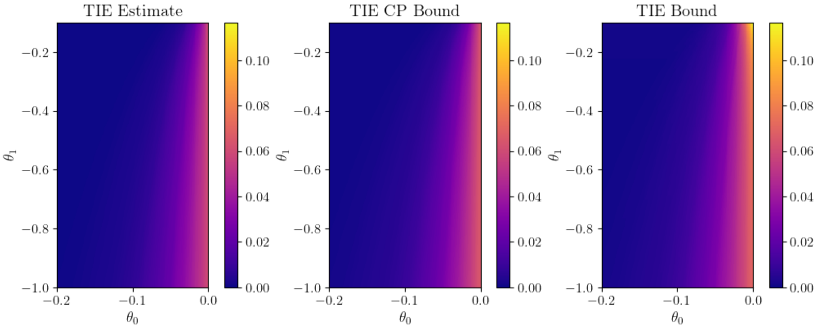


Revisiting the Adaptive T-Test

- Data $X_i \sim \mathcal{N}\left(\mu, \sigma^2\right)$ with unknown μ, σ^2.
- $H_0 : \mu \leq \mu_0$.
- Initial sample size of n_0.
- K interims where each interim stops if the t-statistic given observed data up to now is above the threshold t^*.
- If continue, add n_i more data.
- Final analysis: reject if t-statistic is above t^*.

$$\theta_0 := \frac{\mu}{\sigma^2} \quad \theta_1 := -\frac{1}{2\sigma^2}$$

Tight Analysis Despite Lack of Exact Theory



Adaptive T-Test Computation and Configuration

- **Computation:**
  - 327 million simulations.
  - Runtime: 2s.
  - M1 Macbook Pro.
- **Configuration:**
  - $K = 3$ interims.
  - $n_0 = 100$.
  - $n_i = 50$ for $1 \leq i \leq K$.
  - $\mu_0 = 0$.
  - $\alpha = 0.025$.

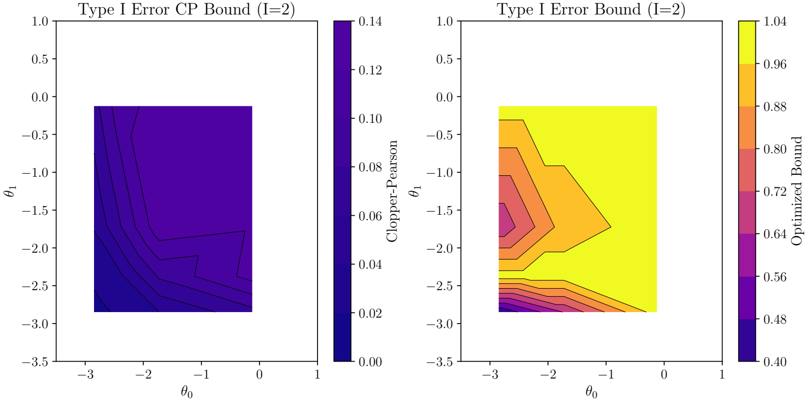
Bayesian Basket Trial from Berry et al. [2013]

- Design:

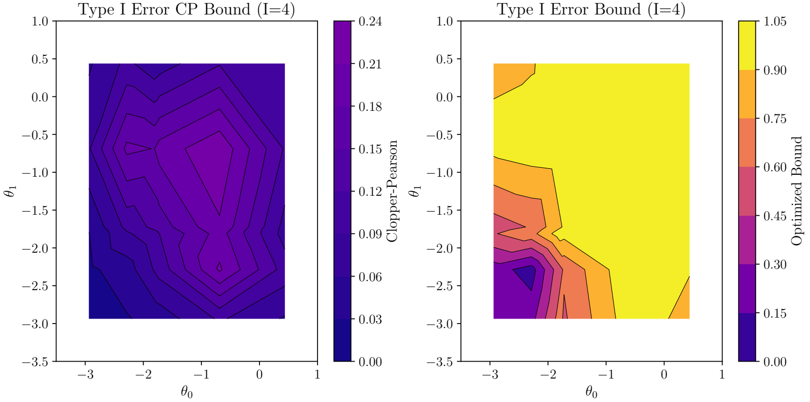
$$
\begin{aligned}
Y_j &\sim \text{Binom}(n_j, p_j) \quad j = 1, \ldots, d \\
\theta_j &= \theta_{0j} + \text{logit}(p_j) \\
\theta_j &\sim \mathcal{N}\left(\mu, \sigma^2\right) \\
\mu &\sim \mathcal{N}\left(\mu_0, \sigma_0^2\right) \\
\sigma^2 &\sim \Gamma^{-1}\left(\alpha_0, \beta_0\right)
\end{aligned}
$$

- Let $c \in [0,1]^{d-1}$ be a vector of fixed thresholds and $d \equiv 4$.
- Reject if $\mathbb{P}\left[p_i > p_0 | Y\right] > c_i$ for some null (treatment) arm i.

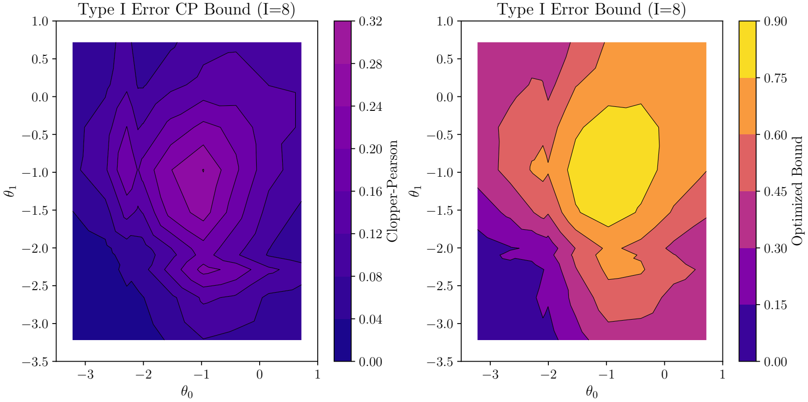
Validation shows Type I Error Surface for Bayesian Design



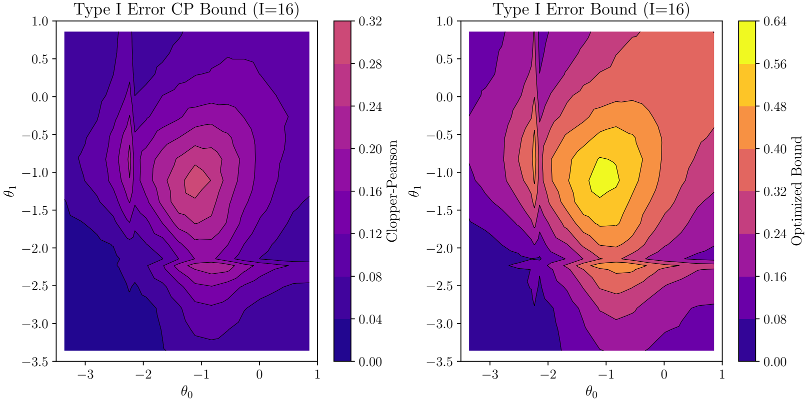
Validation shows Type I Error Surface for Bayesian Design



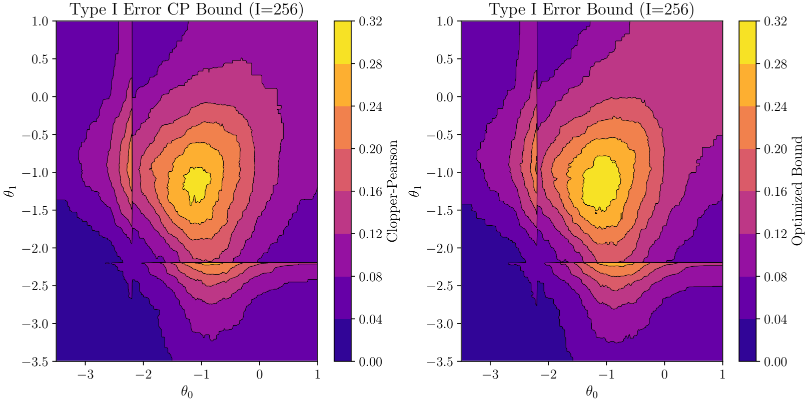
Validation shows Type I Error Surface for Bayesian Design



Validation shows Type I Error Surface for Bayesian Design



Validation shows Type I Error Surface for Bayesian Design



Berry et al. [2013] Computation and Configuration

- **Computation**:
  - 7.34 trillion simulations.
  - Runtime: 4 hours.
  - Nvidia V100 GPU.
- **Configuration:**
  - $n_i = 35$ for all $i = 1, \ldots, d$.
  - $\mu_0 = -1.34$, $\sigma_0 = 10$, $\alpha_0 = 0.0005$, $\beta_0 = 0.000005$.
  - $c_i = 0.85$ for all $i = 1, \ldots, d$.

A Complicated Phase II/III Selection Design

- 3 treatment and 1 control arm with binary outcomes.
- Trial decisions using the Bayesian hierarchical model as in Berry et al. [2013].
- Stage 1: select the "best" treatment arm against control with interim analyses.
- Each of 3 interim analyses can stop for futility, drop one or more poorly performing treatments, or accelerate an arm to move to stage 2.
- Stage 2: one interim and one final analysis.
- The total number of patients across all arms and stages is at most 800 with at most 350 in any single arm.

Phase II/III Selection Design Calibrated Successfully

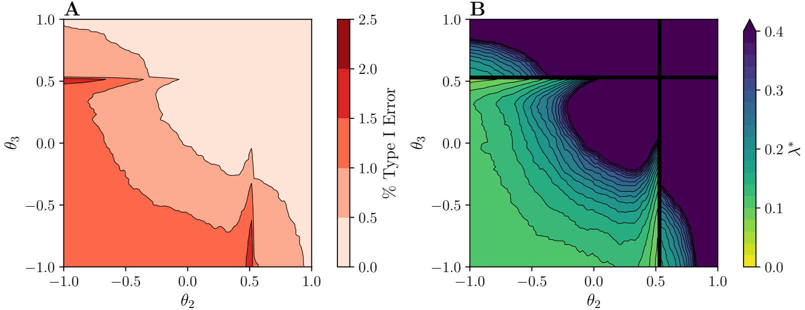


Figure: Both plots slice the domain by fixing 2 parameters, $\theta_0 = \theta_1 = 0.533$. Figure **A** shows the Tilt-Bound profile for the selected threshold $\hat{\lambda}^* = 0.06253$. Figure **B** shows the critical value $\hat{\lambda}_i^*$ separately for each tile such that its Tilt-Bound is 2.5%.

Phase II/III Selection Design Computation and Configuration

- **Computation:**
  - 960 billion simulations.
  - Runtime: 5 days.
  - Nvidia V100 GPU.
- **Configuration:**
  - $H_0 : \theta_i \leq \theta_0$ for all $i = 1, \ldots, d-1$.
  - Restrict to $\theta_i \in [-1, 1]$ for all i.

Phase II/III Selection Design Remarks (Optional)

- Max Tilt-Bound occurs at the tile with center $\theta_0 = (0.4925, 0.4925, 0.4925, -1.0)$.
- Paradox: worst Type I Error **does not** occur at the global null (where all treatments perform equally to control), but when **one** treatment performs poorly.

Further Results of CSE

- Can study **power, False Discovery Rate (FDR)**, and **bias of bounded estimators**.
- Theory also holds for **Generalized Linear Models (GLMs)** after conditioning on covariates.
  - E.g. logistic regression.
- **Quasi-convexity** results for the Tilt-Bound/Inverted Tilt-Bound simplify computations to checking vertices.
- See pre-print for details.

Computational Tricks

- Adaptive simulation/grid sizing (dramatic overall cost reduction!).
- Correlated simulations (dramatic sampling reduction!).
  - **BoTorch** uses a similar (more advanced) trick.
  - Thanks to **Prof. Art Owen** for the idea!
- How to perform **1 trillion simulations** of a complex Bayesian design?
  - **Integrated Nested Laplace Approximation (INLA)**.
  - Our INLA code is **1 million times faster** than standard MCMC packages.
  - Similar accuracy in most cases.

Remarks

- Proof-by-simulation is **general, powerful, and robust**.
- Continuous Simulation Extension converts simulations at finite points into guarantees over **regions**.
- Practical advantage: CSE analyzes the design **as represented in code**. Robust to:
  - Approximations.
  - Theoretical uncertainties with convergence of algorithms
- With the right software, method is **tractable**!

End Goals

- Streamline innovation in trial design.
- Improve regulatory consistency with objective proofs.
- Reduce time and human capital cost of validating new procedures.
- Speculatively: enable new “black-box” statistical procedures.

References I

Scott M. Berry, Kristine R. Broglio, Susan Groshen, and Donald A. Berry. Bayesian hierarchical modeling of patient subpopulations: efficient designs of phase ii oncology clinical trials. *Clinical Trials*, 10(5):720–734, 2013.