A New U-statistic with Superior Design Sensitivity in Observational Studies

Paul R. Rosenbaum

Wharton School, University of Pennsylvania

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Basis for this talk

- Rosenbaum, P. R. (2011), "A new U-statistic with superior design sensitivity in matched observational studies," *Biometrics*, 67, 1017-1027.
- Rosenbaum, P. R. (2010), "Design sensitivity and efficiency in observational studies," *JASA*, 105, 692-702.
- Rosenbaum, P. R. (2004), "Design sensitivity in observational studies," *Biometrika*, 91, 153-64.
- Rosenbaum, P. R. (2010), *Design of Observational Studies*, NY: Springer.

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- **Issue**: Without randomization, treated and control groups may not be comparable. Adjust for observed covariates, perhaps by matching.
- **Problem**: Adjusting for observed covariates does not typically control unobserved covariates.
- **Sensitivity analysis**: Asks what an unobserved covariate would have to be like to alter the conclusions of a naïve analysis that presumes adjustments for observed covariates suffice. Cornfield et al. (1959).

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- **Design sensitivity is**: a number, $\widetilde{\Gamma}$, such that, as the sample size increases, the study will eventually be insensitive to biases smaller than $\widetilde{\Gamma}$ and sensitive to biases larger than $\widetilde{\Gamma}$.
- **In particular**: in large samples, the limiting power of a sensitivity analysis is determined by the design sensitivity.

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- That is, the best procedure assuming that an observational study is effectively a randomized experiment need not be the best procedure under more realistic assumptions
- Will present a family of U-statistics for matched pairs that includes Wilcoxon's signed rank statistic, but other members of this family have much higher power in a sensitivity analysis and higher design sensitivity $\widetilde{\Gamma}$.

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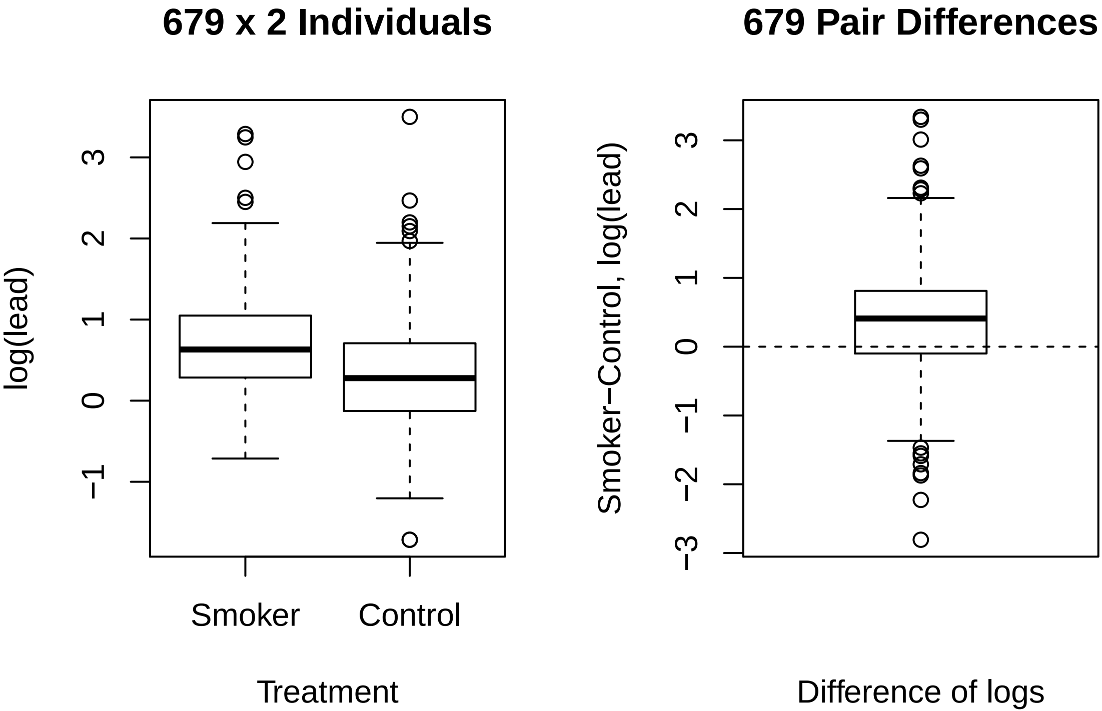
- **Sensitivity to**: an unobserved covariate u_{ij}, possibly with $u_{i1} \neq u_{i2}$.


679 x 2 Individuals
log(lead)
3
2
1
0
−1
Smoker
Control
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679 Pair Differences
Smoker−Control, log(lead)
3
2
1
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Difference of logs

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- Naïve analysis of an observational study assumes adjustments for $\mathbf{x}$ suffice to remove bias.
- Sensitivity analysis asks: What u would have to be like to alter the conclusions of the naïve analysis?

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- Write $\mathcal{F} = \{(r_{Tij}, r_{Cij}, \mathbf{x}_{ij}, u_{ij}),\ i = 1, \ldots, I,\ j = 1, 2\}$.
- H_0 is false if the treatment has an additive effect, $r_{Tij} - r_{Cij} = \tau$ for all ij, $\tau \neq 0$. (Easily replaced by treatment typically has an additive effect, $r_{Tij} - r_{Cij} = \tau + \xi_{ij}$ where the ξ_{ij} are mutually independent, independent of everything else, symmetric about 0.)

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- Looking ahead: A sensitivity analysis is an analysis of $Y_1, \ldots, Y_I$. Efficiency, the power of a sensitivity analysis, the design sensitivity refer to a stochastic model that generated the Y_i, such as $Y_i \sim_{iid} N(\tau, 1)$.

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- The sign test has $q_i = 1$ whenever $|Y_i| > 0$. Wilcoxon's signed rank test has $q_i = \text{rank}(|Y_i|)$ if $|Y_i| > 0$.
- Randomization creates the null distribution $\Pr(T \mid \mathcal{F}, \mathcal{Z})$ of T under Fisher's H_0 as the distribution of the sum of I independent random variables taking the values q_i or 0 each with probability $\frac{1}{2}$ if $q_i > 0$ or the value 0 with probability 1 if $q_i = 0$. E.g., the binomial distribution for the sign test or the usual reference distribution for Wilcoxon's test.

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- A simple model: In the population prior to matching, subjects have independent treatment assignments with unknown probabilities, $\pi_{ij}=\Pr\left(Z_{ij}=1 \mid \mathcal{F}\right)$, such that two subjects, say ij and ij', with the same observed covariates, $\mathbf{x}_{ij}=\mathbf{x}_{ij'}$, may differ in their odds of treatment by at most a factor of $\Gamma \geq 1$,

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  then condition on $Z_{i1} + Z_{i2} = 1$.
- For each $\Gamma \geq 1$, obtain a range of possible inference quantities, point estimates, p-values, etc.

Sensitivity analysis for a general signed rank statistic

- Let $\overline{\overline{T}}$ be the sum of I independent random variables taking the value q_i with probability $\Gamma / (1+\Gamma)$ or 0 with probability $1/(1+\Gamma)$. Define $\overline{T}$ similarly with $\Gamma/(1+\Gamma)$ and $1/(1+\Gamma)$ interchanged.

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- **Bounds**: Under Fisher's H_0 and the sensitivity model with a fixed $\Gamma \geq 1$:

$$\Pr\left(\overline{T} \geq k \middle| \mathcal{F}, \mathcal{Z}\right) \leq \Pr\left(T \geq k \middle| \mathcal{F}, \mathcal{Z}\right) \leq \Pr\left(\overline{\overline{T}} \geq k \middle| \mathcal{F}, \mathcal{Z}\right) \text{ for all } k,$$

with equality for $\Gamma = 1$. Bounds attained for particular π_{ij}.

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- **Approximate bounds**: As $I \to \infty$,

$$\Pr\left(\overline{\overline{T}} \geq k \,\middle|\, \mathcal{F}, \mathcal{Z}\right) \approx 1 - \Phi\left[\frac{k - \{\Gamma/(1+\Gamma)\}\sum_{i=1}^{I} q_i}{\sqrt{\left\{\Gamma/(1+\Gamma)^2\right\}\sum_{i=1}^{I} q_i^2}}\right] \quad (1)$$

if $\left(\sum_{i=1}^{I} q_i^2\right) / \left(\max_{1\leq i\leq I} q_i^2\right) \to \infty$. ($\Phi(\cdot)$ is Normal cdf)

The new U-statistic, described informally

- **Name**: Fix three integers, m, $\underline{m}$, $\overline{m}$ with $1 \leq \underline{m} \leq \overline{m} \leq m < I$. Then $(m, \underline{m}, \overline{m})$ is the name of one U-statistic.

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- **One good choice:** $(8, 7, 8)$. Look at 8 pairs. Find the two largest $|Y_i|$'s, and score 0, 1, or 2 depending upon whether neither, one or both Y_i's are positive.

Sensitivity analysis for the NHANES data about blood lead levels

- Compare sign test $(1, 1, 1)$, Wilcoxon test $(2, 2, 2)$, and the new U-statistic with $(m, \underline{m}, \overline{m}) = (8, 7, 8)$ for $I = 679$ smoker-nonsmoker pair differences Y_i in blood lead levels.

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Γ	1	2	2.5	3	3.5	3.8
Sign test	0.0000	0.0083	0.5961	0.9918	1.0000	1.0000
Wilcoxon	0.0000	0.0000	0.0004	0.0510	0.4224	0.7160
(8,7,8)	0.0000	0.0000	0.0000	0.0009	0.0142	0.0444

Additional sensitivity analyses for the NHANES data about blood lead levels

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$$T = \sum_{i=1}^{I} \operatorname{sgn}(Y_i)\ q_i \tag{2}$$

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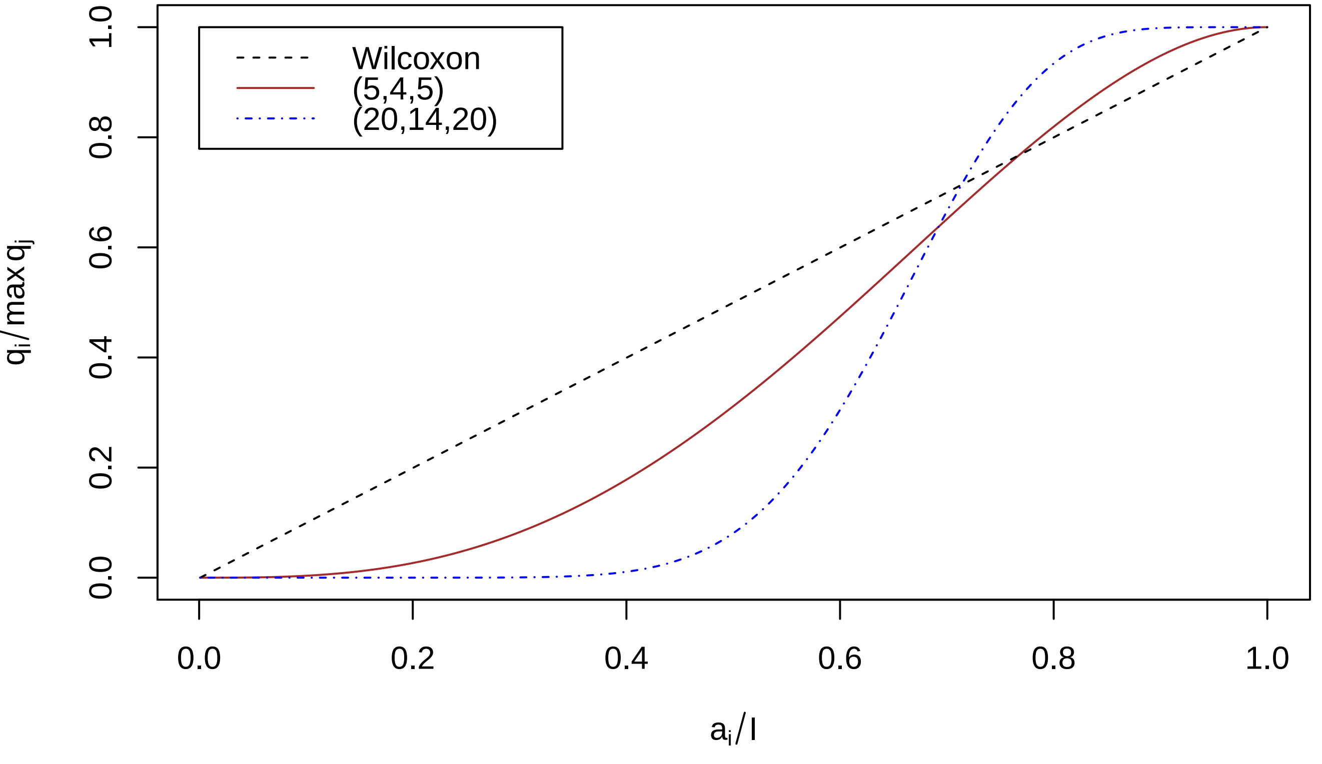
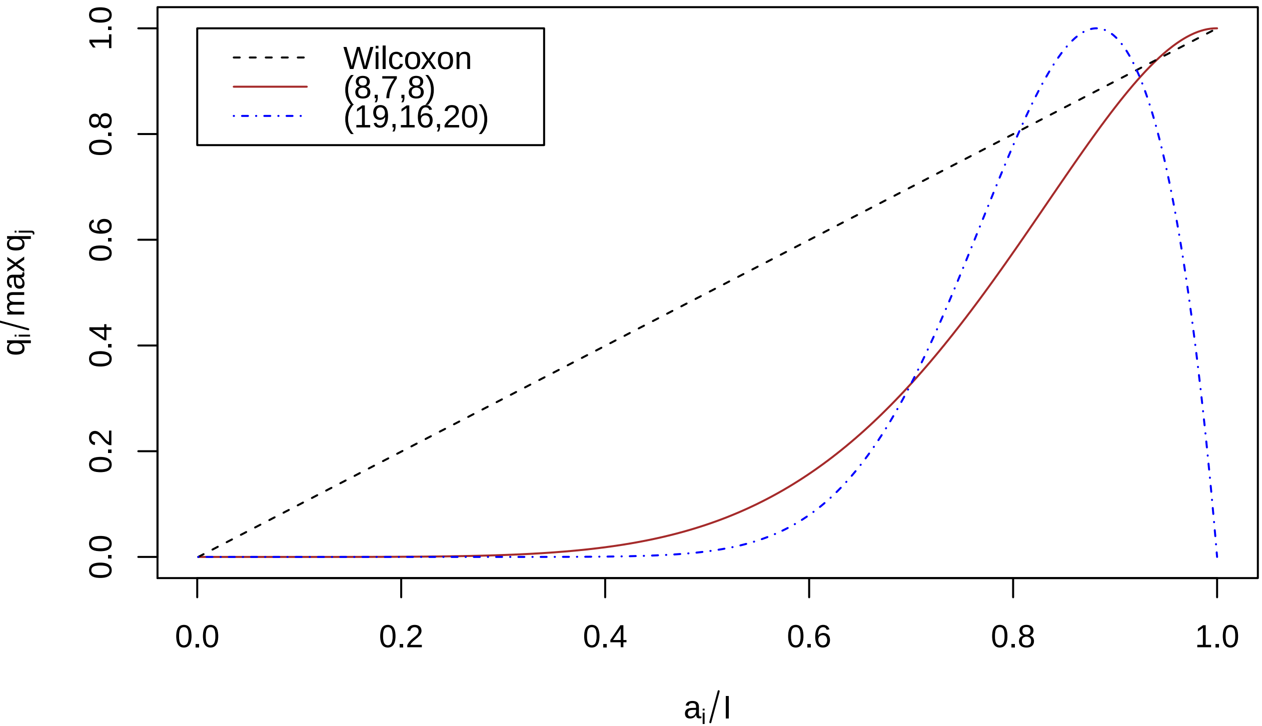
- Will plot $q_i / \max q_j$ against a_i / I.



Wilcoxon
(5,4,5)
(20,14,20)
0.0
0.2
0.4
0.6
0.8
1.0
$q_i/\max q_j$
a_i/I



Wilcoxon
(8,7,8)
(19,16,20)
1.0
0.8
0.6
0.4
0.2
0.0
$q_i/\max q_j$
0.0
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Power of sensitivity analysis

- If the treatment had an effect and if there was no bias in treatment assignment, $\Pr\left(Z_{ij} \mid \mathcal{F}, \mathcal{Z}\right) = \frac{1}{2}$, then we could not see this in the observed data. The best we can hope to say is that rejection of H_0 at level α is insensitive to small and moderate bias as measured by Γ. The power is the probability that we will be able to say this.

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- **Power is**: the probability that the upper bound on the P-value testing H_0 will be less than or equal to α at this Γ when the Y_i are sampled from some probability model in which there is an effect an no bias, $\Pr(T \mid \mathcal{F}, \mathcal{Z}) = \frac{1}{2}$, e.g., $Y_i \sim_{iid} N(\tau, 1)$.

Simulated Power

- **Sampling situation**: $Y_i = \tau + \epsilon_i$ where ϵ_i is standard Normal, standard logistic or t-distributed with 4 degrees of freedom, and no unmeasured bias, $\Pr\left(Z_{ij} = 1 \mid \mathcal{F}, \mathcal{Z}\right) = \frac{1}{2}$.

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Table: Power of a one-sided 0.05 level sensitivity analysis with additive effect τ conducted with $\Gamma = 3$ and $I = 250$ pairs. Errors are standard Normal, standard logistic or t-distributed with 4 degrees of freedom. The highest powers in a column are in **bold**.

Errors Statistic	Normal $\tau = 1/2$	Logistic $\tau = 1$	t with 4 df $\tau = 1$
Wilcoxon	0.08	0.40	0.43
(5,4,5)	0.34	0.67	**0.65**
(8,7,8)	**0.63**	**0.74**	0.57
(20,14,20)	0.53	**0.74**	**0.65**
(20,16,19)	0.52	0.69	0.61

Design sensitivity

- **Definition**: For a given sampling situation with a treatment effect and no unmeasured bias, and for a given test statistic, there is a number $\widetilde{\Gamma}$ such that, as $I \rightarrow \infty$, the power of an α-level sensitivity analysis tends to 1 if performed with $\Gamma < \widetilde{\Gamma}$ and to 0 if $\Gamma > \widetilde{\Gamma}$.

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- **Illustration**: For an additive effect of $\tau = 1$ with errors from the t-distribution with 3 degrees of freedom, the Wilcoxon statistic has design sensitivity $\widetilde{\Gamma} = 6.0$ while $(m, \underline{m}, \overline{m}) = (5, 4, 5)$ has design sensitivity $\widetilde{\Gamma} = 6.8$.

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- **Example**: If $I = 100,000$ differences $Y_i = \tau + \epsilon_i$ are sampled from this distribution, the upper bound on the P-value from Wilcoxon's statistic is 0.016 at $\Gamma = 5.8$ and 0.997 at $\Gamma = 6.1$, consistent with $\widetilde{\Gamma} = 6.0$. If $(m, \underline{m}, \overline{m}) = (5, 4, 5)$ is used instead, the P-value bound is 0.0028 for $\Gamma = 6.5$ and 0.98 for $\Gamma = 6.9$, consistent with $\widetilde{\Gamma} = 6.8$.

Formula for the design sensitivity of the U-statistic

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- **Cases**: If $\theta = \overline{m} - \underline{m} + 1$ then $\widetilde{\Gamma} = \infty$. If $\widetilde{\Gamma} < 1$, then the power tends to zero as $I \to \infty$ for all $\Gamma \geq 1$)

Table of Design Sensitivities

Table: Design sensitivities $\widetilde{\Gamma}$ with additive effect τ. Errors are standard Normal, standard logistic or t-distributed with 3 or 4 degrees of freedom. The largest $\widetilde{\Gamma}$s in a column are in **bold**.

Errors Statistic	Normal $\tau = 1/2$	Logistic $\tau = 1$	t with 4 df $\tau = 1$	t with 3 df $\tau = 1$
Wilcoxon	3.2	3.9	6.8	6.0
(5,4,5)	3.9	4.7	8.4	6.8
(8,7,8)	**5.1**	5.5	9.1	6.8
(20,14,20)	4.6	5.3	9.4	7.3
(20,16,19)	4.9	**5.6**	**10.1**	**7.8**

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- What $|Y_i|$ would you pick?

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- If $\mathrm{abz}(y) > \Gamma/(1+\Gamma)$, then at $|Y_i| = y$, positive Y_i occur with a frequency $\mathrm{abz}(y)$ that is too high to be attributed to a bias of magnitude Γ.

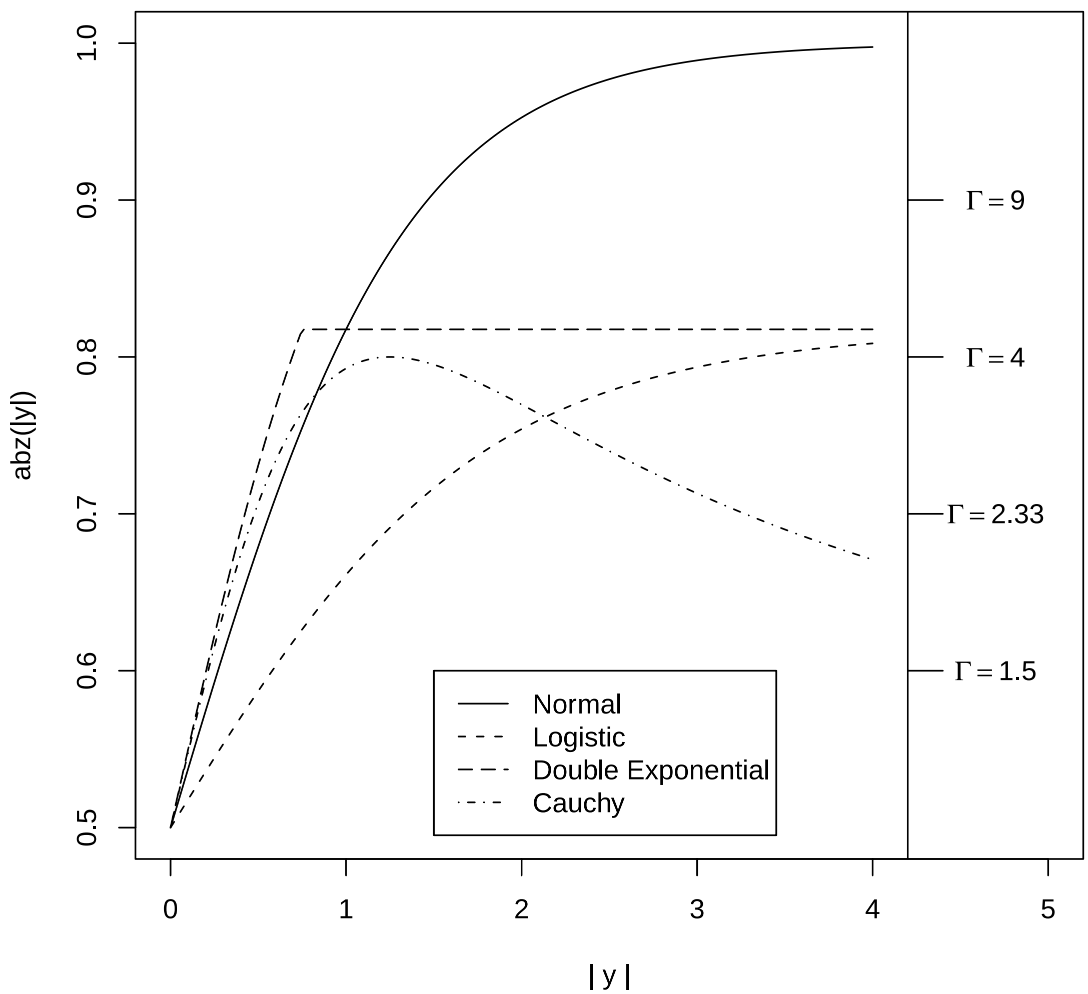

Figure 2: Conditionally given various values of $|Y_i|$, the figure shows the probability of a positive treatment-minus-control difference, $Y_i > 0$, for an additive treatment effect τ = ¾ in the standard forms of four distributions.

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- What you should do with large $|Y_i|$ depends on the distribution G which you typically do not know.

Stephenson's test: useful when only some people respond to treatment

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- **The U-statistic**: is Stephenson's statistic for $(m, \underline{m}, \overline{m}) = (m, m, m)$. That is, look at the sign of Y_i for the one pair of m with the largest $|Y_i|$.

Testing one hypothesis twice

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- **Proposition**: Both alternative 1 and alternative 2 achieve the best design sensitivity $\widetilde{\Gamma}$.

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- **In terms of** $\widetilde{\Gamma}$: several choices of $(m, \underline{m}, \overline{m})$ increase $\widetilde{\Gamma}$ relative to Wilcoxon's statistic for all of these sampling situations.

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$$
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&= \tau + \epsilon_i' \text{ where } \epsilon_i' = \epsilon_i + \xi_i' \\
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- Because ξ_{ij} is independent of everything else and symmetric about 0, $\xi_i' = (Z_{i1}\xi_{i1} - Z_{i2}\xi_{i2})$ has the same distribution as ξ_{ij}, is symmetric about 0, and is independent of the Z_{ij}.

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The new U-statistic

- Fix three integers, m, $\underline{m}$, $\overline{m}$ with $1 \leq \underline{m} \leq \overline{m} \leq m < I$. Let $\mathcal{K}$ be the set containing the $\binom{I}{m}$ sequences $\mathcal{I} = \langle i_1, \ldots, i_m \rangle$ of m distinct integers $1 \leq i_1 < \cdots < i_m \leq I$, and write $\mathbf{Y}_{\mathcal{I}} = \langle Y_{i_1}, \ldots, Y_{i_m} \rangle$.

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- A U-statistic (Hoeffding 1948) has the form

$$T = \binom{I}{m}^{-1} \sum_{\mathcal{I} \in \mathcal{K}} h\left(\mathbf{Y}_{\mathcal{I}}\right)$$

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- For $\mathcal{I} = \langle i_1, \ldots, i_m \rangle \in \mathcal{K}$, sort $Y_{i_1}, \ldots, Y_{i_m}$ to $Y_{[\mathcal{I},1]}, \ldots, Y_{[\mathcal{I},m]}$ to be increasing in absolute value, $0 < \left| Y_{[\mathcal{I},1]} \right| < \cdots < \left| Y_{[\mathcal{I},m]} \right|$.

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- In the new u-statistic, $h\left(\mathbf{Y}_{\mathcal{I}}\right)$ is the number of positive differences among $Y_{[\mathcal{I},\underline{m}]}, \ldots, Y_{[\mathcal{I},\overline{m}]}$, so $h\left(\mathbf{Y}_{\mathcal{I}}\right)$ is an integer in $\{0, 1, \ldots, \overline{m} - \underline{m} + 1\}$.

Familiar instances of the new U-statistic

- To repeat: $0 < \left|Y_{[\mathcal{I},1]}\right| < \cdots < \left|Y_{[\mathcal{I},m]}\right|$, $h\left(\mathbf{Y}_{\mathcal{I}}\right)$ is the number of positive differences among $Y_{[\mathcal{I},\underline{m}]}, \ldots, Y_{[\mathcal{I},\overline{m}]}$, $T = \binom{I}{m}^{-1} \sum_{\mathcal{I} \in \mathcal{K}} h\left(\mathbf{Y}_{\mathcal{I}}\right)$

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  $T = \binom{I}{m}^{-1} \sum_{\mathcal{I}\in\mathcal{K}} h(\mathbf{Y}_{\mathcal{I}})$
- **Sign test**: if $m = \overline{m} = \underline{m} = 1$, then
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- **Wilcoxon's signed rank**: If $m = \overline{m} = \underline{m} = 2$, then $h\left(\mathbf{Y}_{\mathcal{I}}\right) = \text{sgn}\left(Y_{[\mathcal{I},2]}\right)$, and T is the u-statistic that closely approximates Wilcoxon's signed rank statistic (Lehmann 1975, p. 337).

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- **Stephenson's statistic**: If $m = \overline{m} = \underline{m} \geq 1$, then $h(\mathbf{Y}_{\mathcal{I}}) = \text{sgn}\left(Y_{[\mathcal{I},m]}\right)$ and T is Stephenson's (1981) statistic. Excellent power when only a subset of treated subjects respond to treatment; see Conover and Salsburg (1988) and Rosenbaum (2007; 2010a, §16).