Economic and Statistical Uncertainty in Cost-Effectiveness Inference

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Yin = Dark = Evil = Risk

Yang = Light = Good = Benefit

In statistical inference, the shadow price of health, lambda, is a nuisance parameter. The wedge-shaped confidence regions resulting from either the “count outwards” bootstrap approach or from Fieller’s theorem are equivariant (commutative) under changes in lambda. Every outcome within the ICE uncertainty scatter thus remains inside of, right on or else outside of the resulting ICE ray confidence limits. These regions thus quantify only the statistical uncertainty in patient level cost and effectiveness data about the location of the true ICE outcome difference.

The shadow price of health, lambda, has been given various names but is invariably described as an “unknown constant.” When lambda is varied over a wide numerical range, “uncertainty” about lambda is emphasized by ignoring the key “technical” assumption that lambda is some FIXED value. This swamps statistical uncertainty and injects inconsistency and subjectivity.

Unfortunately, widely practiced economic approaches, such as Net Benefit confidence intervals and acceptability curves, are highly sensitive this sort of subjective variation in lambda.

These concepts are illustrated graphically using functions from my R-package “ICEinfer.”

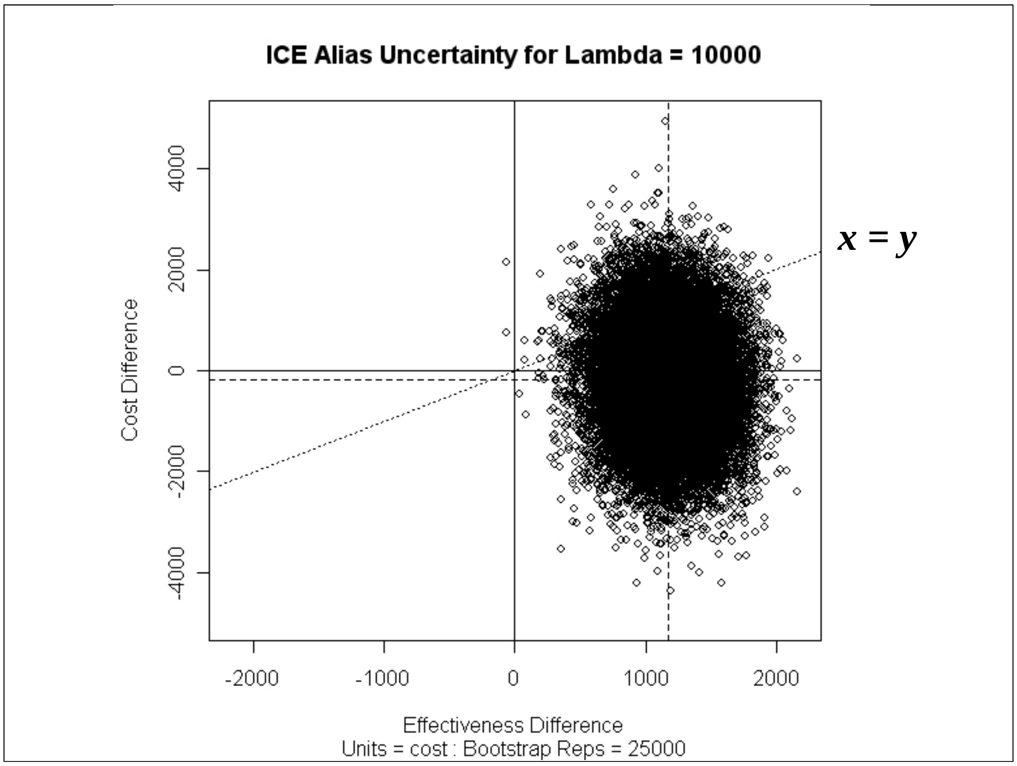
Expressing (ΔE, ΔC) in cost units

A positive λ different from +1 represents here a change in scale along the “first” or “horizontal” or “x” axis in which:

ΔE in effectiveness units
becomes $\lambda\ \Delta E$ in cost units

Standardized coordinates: **(x, y) = ($\lambda\Delta E$, ΔC)**

Given patient level data on 2 variables (effectiveness and cost) in two treatment arms, “new” a



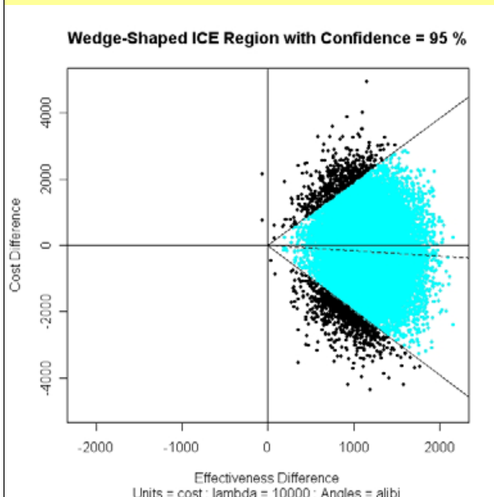
25,000 bootstrap replications for the fluox vs tca example published in PharmacoEconomics in 1997. The horizontal effectiveness measure is a binary indicator (Yes=1, No=0) of whether on not the patient remained on the chosen medication for at least six months, and the vertical cost measure is total health care costs over those same six months.

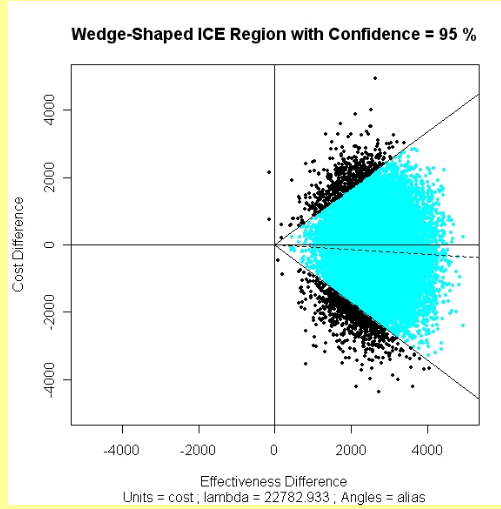
These calculations and the above graph were produced using the “ICEuncrt” function in the ICEinfer R-package. Under the restriction that the ICE origin, (0, 0), must appear in the exact center of the plot (Xmin = -Xmax and Ymin = -Ymax), this graphic uses the minimum range (both horizontally and vertically) that displays all 25,000 replications. In other words, to show as much detail as possible, the plot has zoomed in (by possibly different amounts horizontally and vertically) as much as is possible

This is called a ALIAS plotting perspective, because all points would appear to remain “fixed in space” if the scaling along either the vertical axis or the horizontal axis or both axes were to change.

Wedge-Shaped **Equivariant** Confidence Region

Why does it appear to be Invariant here?





Alias Only @ λ =10K **Alias & Alibi @ λ =23K**

Wedge-Shaped Confidence Intervals for the ICE Ratio are produced by Fieller's theorm, but this method fails in many interesting cases because the central polar angle can never exceed 180 degrees. This angle is slightly less than 90 degrees in this particular example.

The above regions, derived from ICE Bootstraping, clearly suggest upper and lower limits for ICE radius as well as counter-clockwise (upper?) and clockwise (lower?) ICE ray limits on the unknown, true (x, y) outcome. The equivariant method illustrated here is my "count outwards" algorithm published in J Biopharm Stats in 1999.

These calculations and the above graph were produced using the "ICEwedge" function in the ICEinfer R-package.

Equvariant Confidence Wedge: The counter-clockwise and clockwise limiting ICE rays are defined in such a way that, if λ were to change, each bootstrap outcome within (on, or outside) the wedge would remain within (on, or outside) the wedge.

Alibi Perspective (Mathematics): Axes and Tick Marks on Axes are Fixed; Points Move as λ Changes.

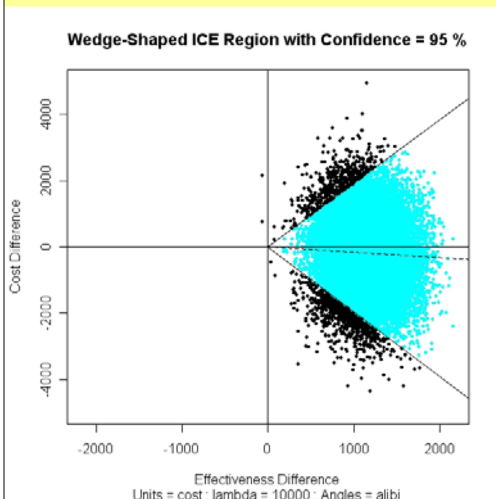
Alias Perspective (Physics & CS): Points are Fixed; Tick Marks on at least one Axis then Change if λ Changes.

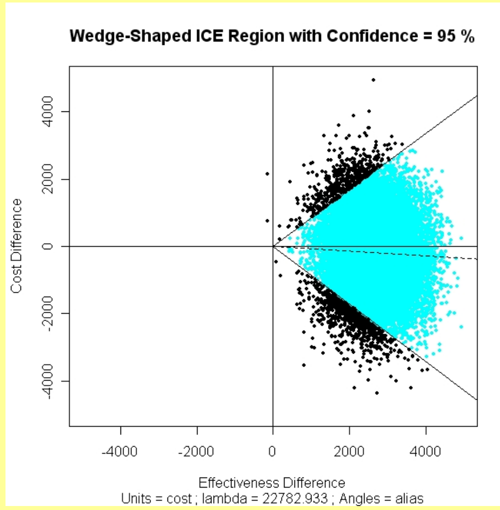
Xmax = Max(Abs(Min(X)),Max(X))
Ymax = Max(Abs(Min(Y)),Max(Y))

Equivariant => Actions of transforming the data and computing a summary statistic are commutative. The arithmetic mean and sample standard deviation are equivariant under the group of transformations consisting of translations and scale changes.

By using an alias plotting perspective, equivariance is much easier to see as a form of invariance.

Conclusion: **When using an <u>Equivariant</u> Confidence Region for <u>Statistical Inference</u>, the Shadow Price of Health, λ, is a mere Nuisance Parameter.**





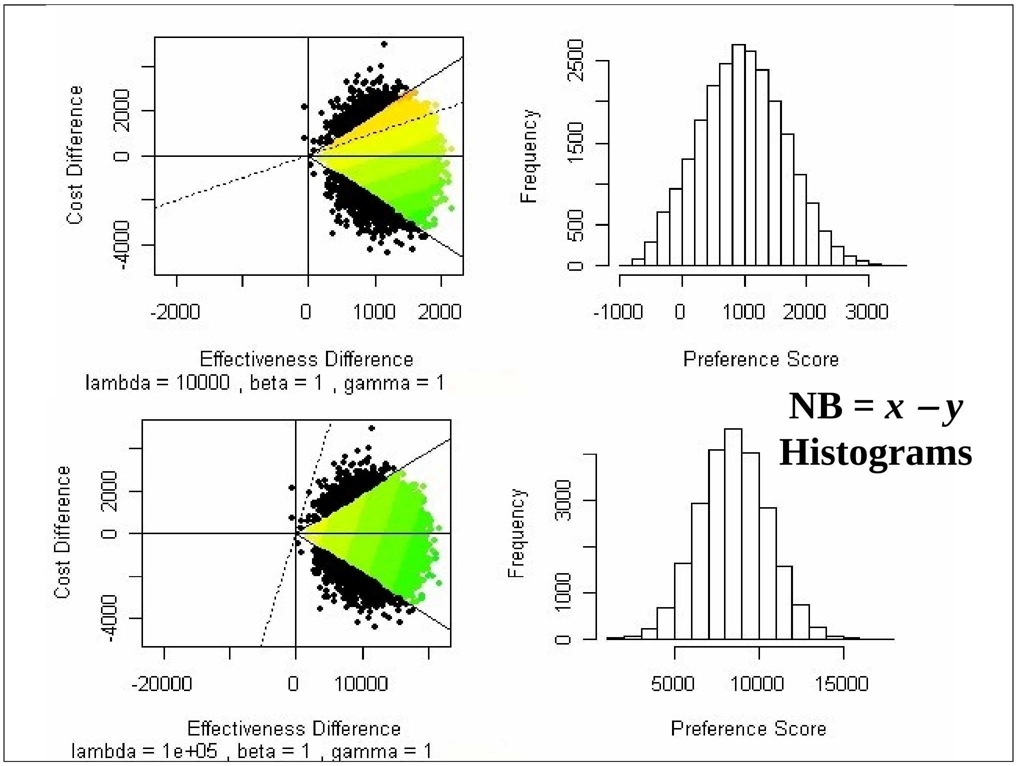
Alias Only @ λ =10K **Alias & Alibi @ λ =23K**

Functions in the ICEinfer R-package always <u>compute</u> the polar angle of a bootstrap ICE outcome from the alibi (mathematical) perspective.

Because ICEinfer functions always <u>display</u> plots from the alias perspective, computed ICE angles can appear to be VERY WRONG!!!

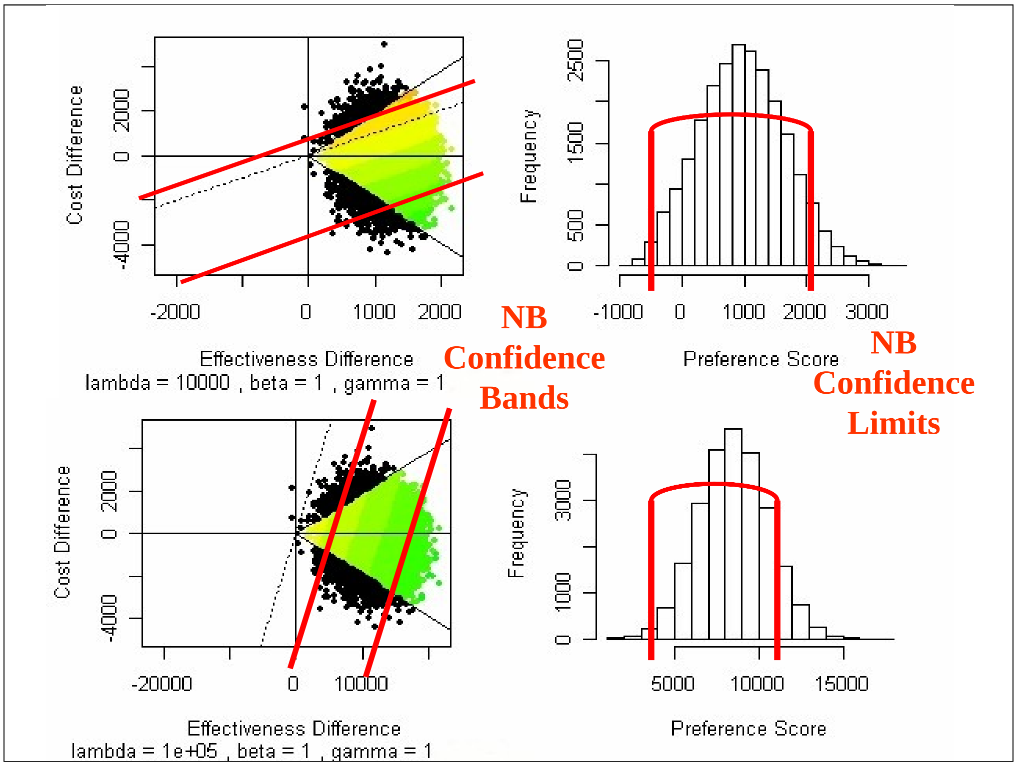
As λ changes, Net Benefit = x–y calculations can be used to interpret the Economic Meaning of the Bootstrap ICE outcomes within an Equivariant Confidence Region.

Economic Uncertainty about the Shadow Price of Health, λ, can introduce inconsistencies that totally SWAMP Statistical Uncertainty.



Here, linear preferences (NBs) are used [1] to color the outcomes within the equivariant confidence wedge (RED = highly negative, TAN = mildly negative, YELLOW = mildly positive, GREEN = strongly positive) or else [2] displayed as preference histograms (distributions.)

Note the inconsistent conclusions resulting from the two alternative choices for lambda! The new treatment is not cost-effective (with 95% confidence) when lambda = 10,000 but is when lambda = 100,000.



Relative to preferences computed only for outcomes within the equivariant wedge, traditional NB calculations (depicted here in RED) are clearly biased. In the above example, the bias is towards lower benefit for new over standard and lower variability (uncertainty.)

Obenchain RL, Melfi CA, Croghan TW, Buesching, DP. Bootstrap analyses of cost effectiveness in antidepressant pharmacotherapy. ***PharmacoEconomics*** 1997; 11: 464-472.

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Obenchain RL. **ICEinfer:** R package for Statistical Inference (wedge-shaped, equivariant confidence regions; VAGR acceptability and ALICE curves) and Economic Preference variation in Incremental Cost-Effectiveness (ICE) Analysis. ***http://www.r-project.org*** 2007.

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