SANOFI

My poster in 180 seconds : Evaluation of alternative robust methods for anti-drug antibodies cut-point determination

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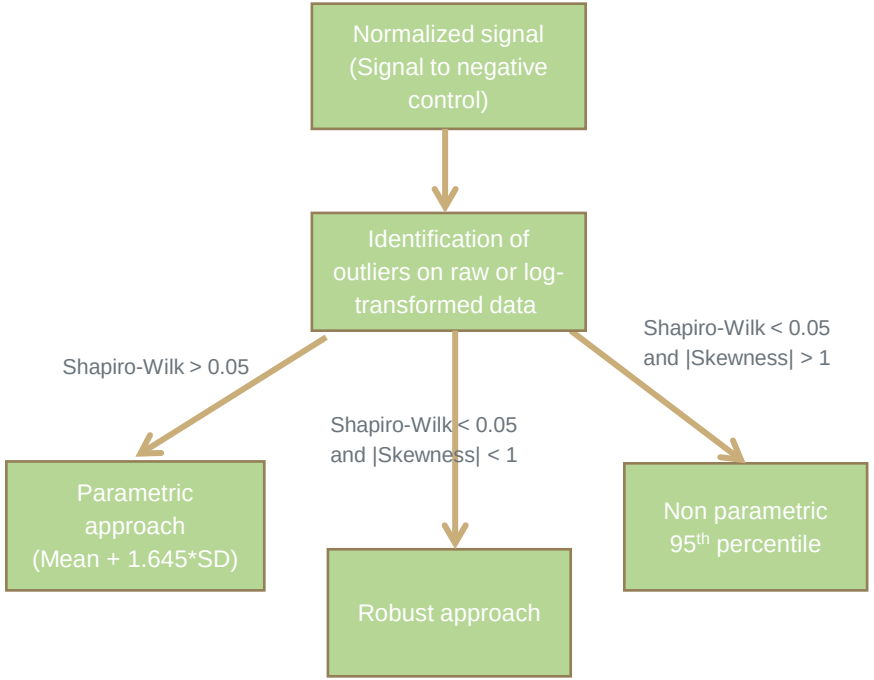
Evaluation of alternative robust methods for anti-drug antibodies cut-point determination

Context

- With the increase of new biological drugs, immunogenicity testing is a key component in drug development as it can lead to potential safety issues and/or loss of efficacy
- Immunogenicity assessment usually performed using multi-tiered approach
  - Screening assay to detect all antibodies binding to the protein (sensitive assay)
    - Based on screening cutpoint (SCP) determined to have a 5% false positive rate on average
    - Samples above cutpoint are considered as reactive, negative otherwise
  - Confirmatory assay
    - For samples considered as reactive
    - Based on specificity cutpoint (CCP) determined to have 1% false positive rate
    - Samples above cutpoint are considered as positive
  - Titration



Current algorithm for SCP based on Devanarayan et al (2017)

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Simulations

- **Simulations scheme**
  - Sample size : N=30 / 50 / 100
  - Distributions evaluated : Normal / Lognormal / Cubic / Gamma
  - % of outliers : No outliers / 5% / 10% / 20% close and far outliers
  - Management of outliers :
    - No criterion (keep all data)
    - Remove outside median +/- 1.5*IQR
    - Remove outside median +/- 3*IQR
  - Methods evaluated :
    - Parametric : Mean + 1.645*SD
    - Non parametric 95th percentile
    - Robust approach alone using Median +1.645 nMAD / Robust estimator Qn / M-estimator with median
    - Shapiro-Wilk test and skewness (current algorithm) to evaluate normality in raw and log-transformed data
    - Box-Cox (B-C) transformation (always determined on data w/o outliers) before Parametric or Robust approach

- **Main results for SCP evaluation (95th percentile)**

Median cut-point estimation (N=50)			Boxplot crieria for outlier removal							
			No		1.5 x IQR					3 x IQR
			Robust Median	B-C + Robust Median	Non para.	B-C + Robust Median	B-C + para-metric	Shapiro-Wilk + Skewness Raw	Shapiro-Wilk + Skewness Log	B-C + Robust Median
	Outliers	Location								
Normal	No		95.10%	95.20%	93.90%	95.30%	94.20%	94.20%	96.30%	95.40%
	5%	Close	96.40%	96.50%	94.50%	95.10%	94.70%	94.60%	97.30%	98.40%
		Far	96.20%	96.30%	93.40%	95.00%	94.50%	94.50%	96.50%	95.20%
	10%	Close	97.20%	97.40%	95.60%	95.70%	95.00%	94.70%	98.70%	99.50%
		Far	96.90%	96.90%	93.30%	95.30%	94.70%	94.50%	96.50%	95.30%
	20%	Close	99.40%	100.00%	100.00%	99.20%	99.70%	99.30%	100.00%	100.00%
		Far	98.40%	98.50%	94.20%	95.20%	94.80%	94.70%	96.60%	95.70%
Log Normal	No		84.20%	93.30%	90.70%	90.30%	87.80%	85.60%	94.20%	93.10%
	5%	Close	85.30%	95.80%	93.30%	91.50%	90.00%	88.80%	97.80%	93.30%
		Far	85.30%	95.00%	91.30%	91.50%	90.00%	88.80%	94.50%	93.30%
	10%	Close	86.10%	97.30%	95.20%	92.30%	90.80%	89.90%	98.80%	94.00%
		Far	86.10%	96.40%	91.80%	92.30%	90.80%	89.90%	95.40%	94.00%
	20%	Close	88.30%	99.70%	99.60%	94.90%	93.60%	93.70%	99.40%	99.70%
		Far	88.30%	99.80%	98.00%	94.50%	93.60%	93.70%	99.50%	94.70%
Cubic	No		91.20%	94.40%	93.10%	93.60%	92.00%	88.80%	96.30%	95.00%
	5%	Close	92.40%	96.50%	95.50%	94.10%	93.30%	90.40%	99.10%	95.80%
		Far	92.40%	95.80%	93.10%	94.10%	93.30%	90.40%	96.50%	94.90%
	10%	Close	93.30%	97.70%	97.10%	94.80%	93.70%	90.50%	99.80%	97.90%
		Far	93.30%	96.60%	93.30%	94.80%	93.70%	90.50%	96.80%	95.10%
	20%	Close	95.20%	99.90%	100.00%	97.30%	97.40%	93.80%	100.00%	100.00%
		Far	95.10%	99.00%	97.00%	95.00%	94.10%	91.40%	99.90%	95.20%
Gamma	No		92.00%	92.60%	93.60%	92.10%	91.80%	91.10%	95.40%	93.70%
	5%	Close	93.20%	94.80%	94.50%	93.20%	92.90%	91.80%	96.90%	96.40%
		Far	93.20%	94.60%	93.70%	93.20%	92.90%	91.80%	95.60%	94.00%
	10%	Close	94.20%	96.10%	95.20%	93.30%	93.20%	92.10%	98.70%	98.40%
		Far	94.10%	95.70%	93.70%	93.30%	93.20%	92.10%	95.60%	93.80%
	20%	Close	96.90%	100.00%	100.00%	97.90%	98.90%	98.10%	99.90%	100.00%
		Far	96.30%	97.90%	94.80%	93.70%	94.10%	93.10%	97.40%	93.90%

Under-estimation — Over-estimation

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Conclusion and remarks

- **Using Box-Cox transformation to symmetrize the distribution**
  - allow further automatization of cutpoint calculation
  - avoid check on normality (Shapiro-Wilk and/or skewness cutoff) to choose cutpoint calculation method (parametric, robust, non-parametric) which had lower performance on skewed distribution
- **The Box-Cox + robust median (after removing 1.5*IQR outliers) is the method that gives results closer to real 95th percentile (with less overestimation)**
- **Box-Cox + parametric approach being quite close to Box-Cox + robust median could be a simpler alternative and allow adjustement for plate effect**
- **For few cases where Box-Cox model does not work well, the non-parametric 95th percentile (after removing 1.5*IQR outliers) would be a relevant alternative**

THANK YOU

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