Testing a trend effect for count variables which are bounded by another count variable

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Context

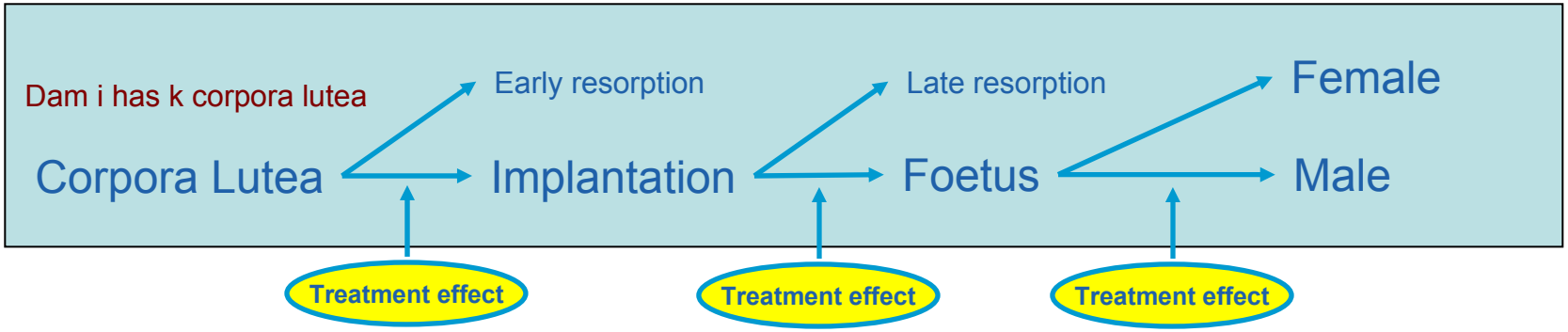
- End user statistical computerized application

- Review of statistical methods
- Reproductive toxicology

Context

- Count parameters
  - Number of corpora lutea
  - Number of implants
  - Number of embryos
  - Number of males

Objective



Taking the example of the number of fetuses :

Toxicologists are interested by the potential effect of the drug on the number of fetuses, independently to the number of implantation.

If we note as Y the count variable to be analyzed, and X the number of opportunities, the toxicologist is interested by the conditional probability of Y|X

Statistical methods

- **Select the best statistical method in term of coverage and power among**
  - **Parametric methods based on generalized linear model**
    - Anova on the ratio Y/X
    - Ancova (X being the covariate)
    - Logistic regression
    - Poisson model (with X as offset variable)

    Trend test is performed using a linear contrast
  - **Non parametric methods**
    - Cochran-Mantel-Haentzel (CMH) with X as stratification variable
    - Jonckere-Terpstra (JT) on the ratio Y/X
  - **Mixture of parametric and non-parametric methods**
    - Regression of Y on X ($Y_{ij} = \mu + \beta X_{ij} + \varepsilon_{ij}$) followed by JT on residuals
    - ANCOVA followed by JT Test on adjusted values ($Y_{ij} = \mu + \alpha_i + \beta X_{ij} + \varepsilon_{ij}$)

Statistical methods

GLM Models	Linear Contrast test from ANOVA on Y/X	ANOVA_ratio
	Linear Contrast test from ANCOVA on Y with X as covariate	ANCOVA
	Linear Contrast test from Poisson model on Y with X as offset variable	Poisson
	Linear Contrast test from Logistic Model	Logit
Non Parametric	CMH	CMH
	JT on the ratio Y/X	JT_ratio
Mixture of parametric and non parametric methods	JT test on residuals from the regression of Y on X	JT_Residus
	JT test on residuals from the regression of Y1/2 on X1/2	JT_Root_Residus
	JT test on adjusted values from ANCOVA on Y with X as covariate	JT_adjusted1
	JT test on adjusted values from ANCOVA on Yrank with Xrank as covariate	JT_adjusted2

Simulations

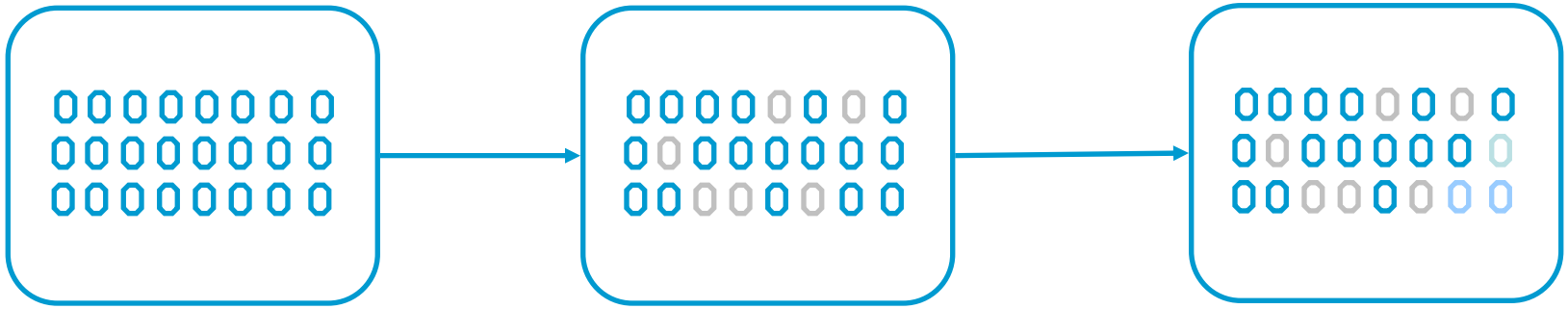
Simulations in four situation :

- **Situation 1:** X independent on the treatment dose
  - **Situation 1a -** “no dose group effect on Y conditionally to X”
  - **Situation 1b -** “trend effect on Y conditionally to X”
- **Situation 2:** X dependent on the treatment dose
  - **Situation 2a -** “no dose group effect on Y conditionally to X”
  - **Situation 2b -** “trend effect on Y conditionally to X”

Situation 1a and 2a are used to assess the type I error of the statistical methods in competition whereas situations 2a and 2b are used to assess power

Simulations

Variables simulated :



Corpora lutea

simulated by bootstrap, using historical control data

Implants

Simulated by a binomial distribution $B(X,p_{ij})$, p_{ij} being simulated using a beta-binomial distribution

Fetuses

Simulated by a binomial distribution $B(X,p_{ij})$, p_{ij} being simulated using a beta-binomial distribution

Simulations

- **Corpora lutea is simulated by bootstrap using historical control data**
- **Implants and embryos are simulated using a binomial distribution:**
  - **The parameter p of the binomial distribution is simulated, for each dam, using a beta-binomial distribution**
    - Parameters α and β of the binomial distribution are determined using historical control data of implants => E[p]=0.9, Var[p]=0.01
    - No treatment effect : $E[p_{ij}] = E[p_{ij}] = E[p_{ij}] = 0.90$
    - Treatment effect : $E[p_{1j}]=0.9$ $E[p_{2j}]= 0.82$, $E[p_{3j}]= 0.74$, $E[p_{4j}] = 0.66$

Simulations

- **Implants and embryos are simulated using a binomial distribution (continued):**
  - **Queues of distribution are truncated**
    - p values drawn from the beta-binomial distribution must be included in [0.5, 1[(the algorithm is looping until the p value is within the specified range).
    - The number of implantations drawn from the binomial distribution must be greater or equal to 21 which was the maximum value observed in the HCD ((the algorithm is looping until the number of implantations is within the specified range).

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Simulation

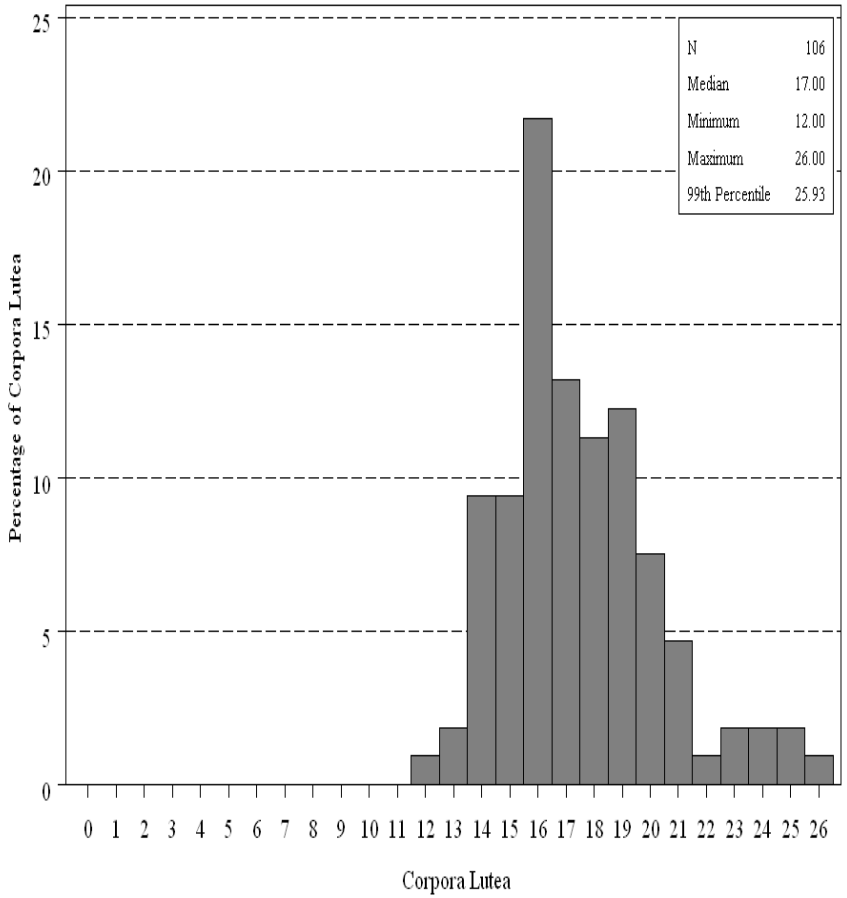
Summary of simulations

	Corpora Lutea	Implantations	Fetuses
Case 1a	No treatment effect	No treatment effect	No treatment effect
Case 1b	No treatment effect	No treatment effect	Treatment effect
Case 2a	No treatment effect	Treatment effect	No treatment effect
Case 2b	No treatment effect	Treatment effect	Treatment effect

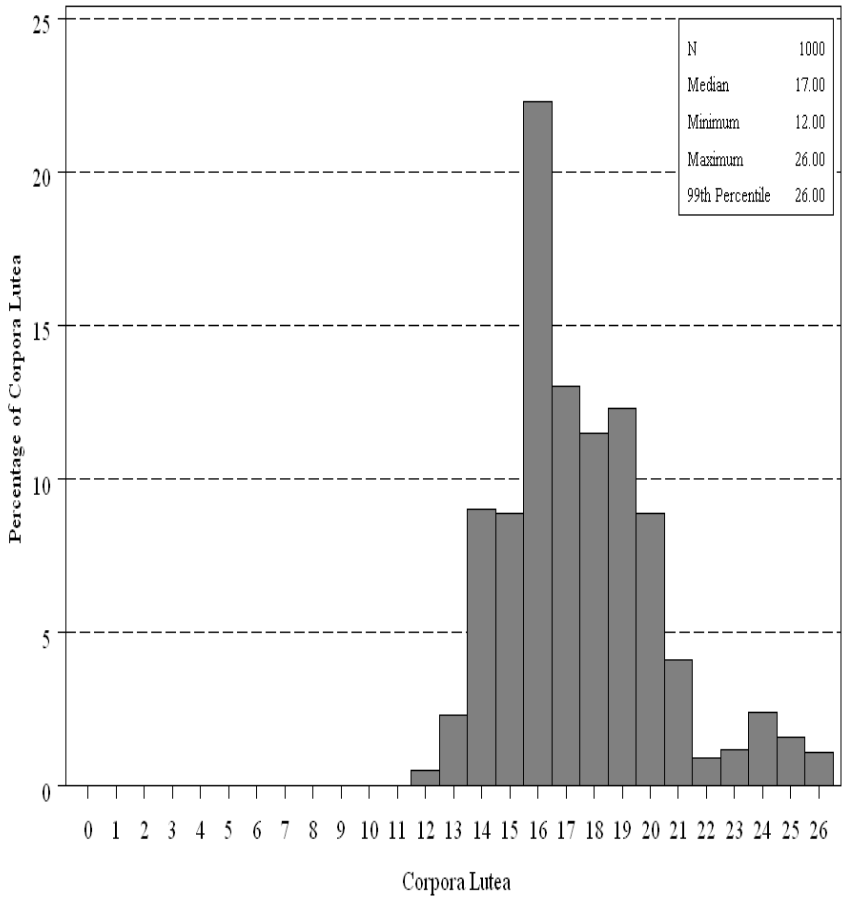
In each case, 4 groups of 5 animals and 4 groups of 10 animals

Historical control data vs. simulated data

Historical Control Data



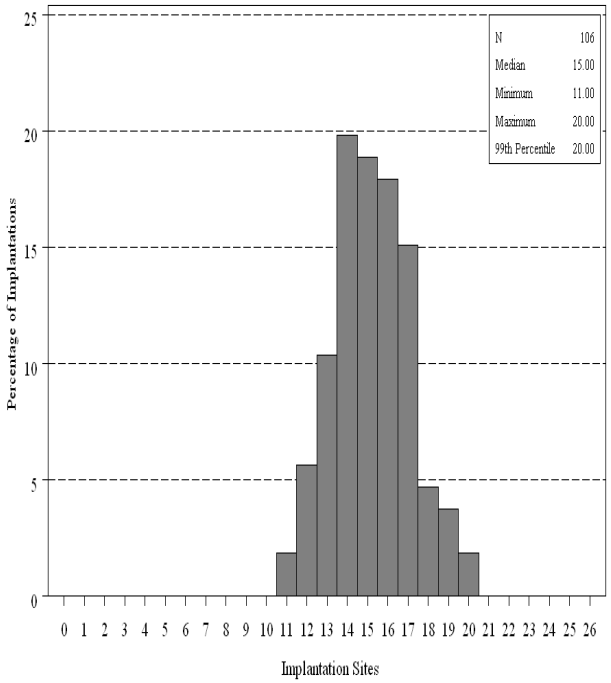
Simulated data (bootstrap)



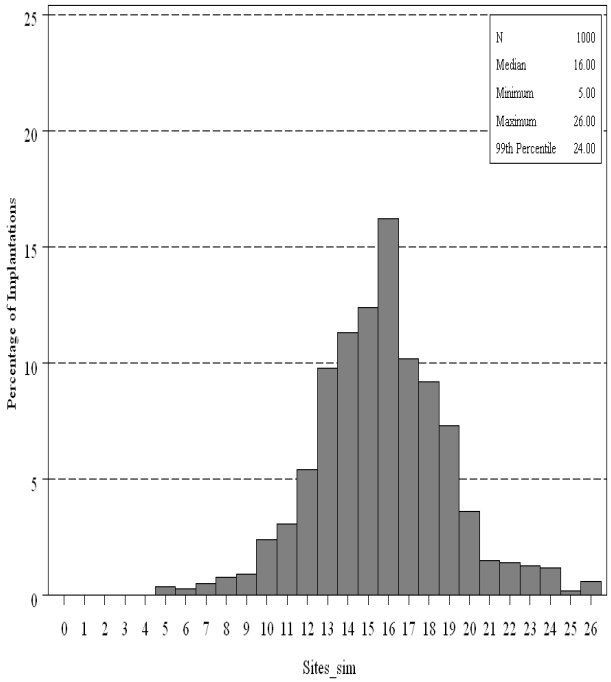
Historical control data vs. simulated data

Implantation sites

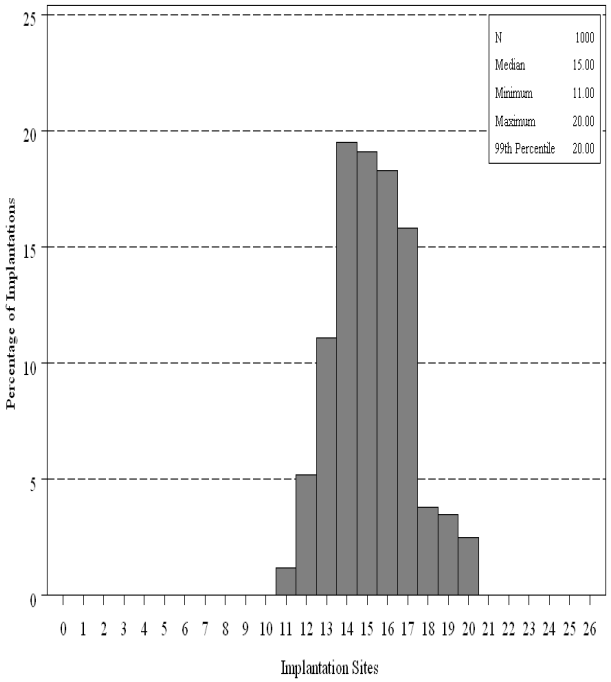
Historical Control Data



Simulated data (binomial)



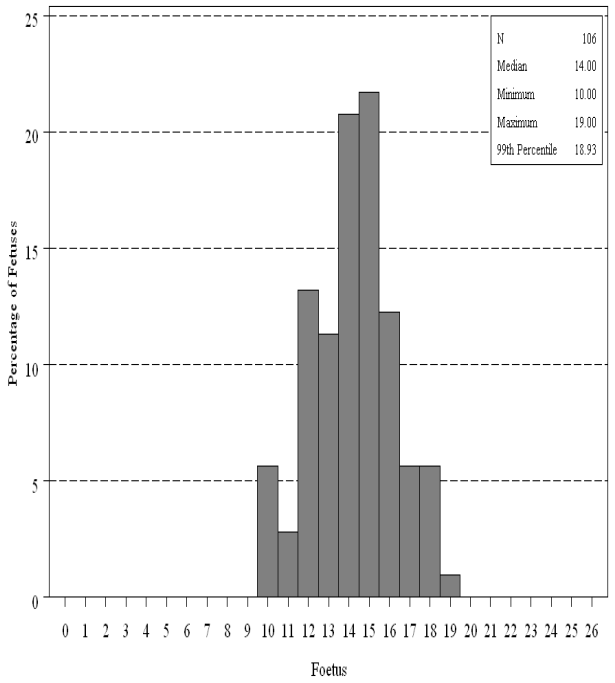
Simulated data (binomial) with truncation



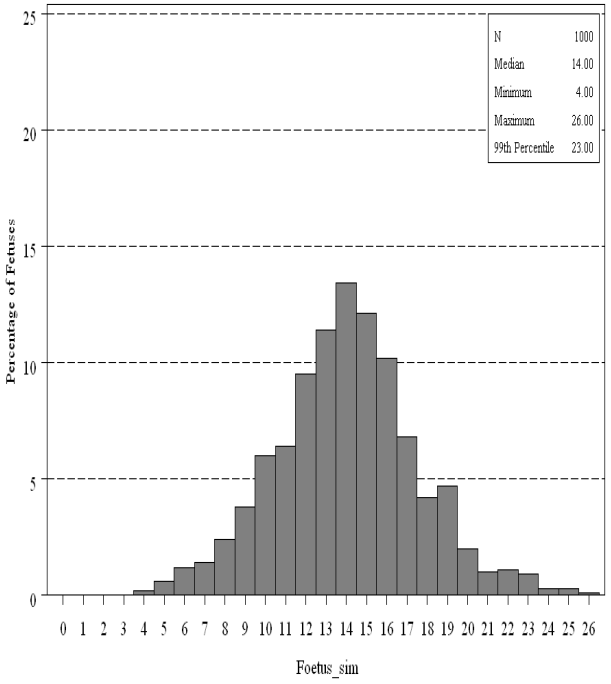
Historical control data vs. simulated data

Fetuses

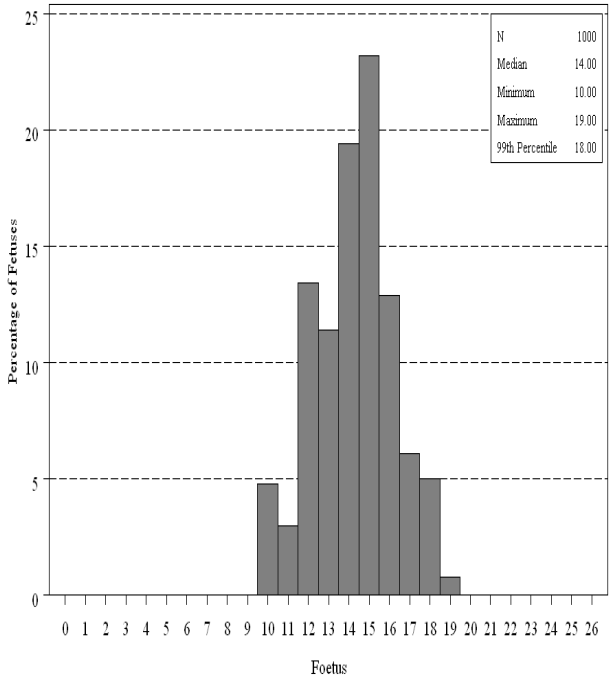
Historical Control Data



Simulated data (binomial)

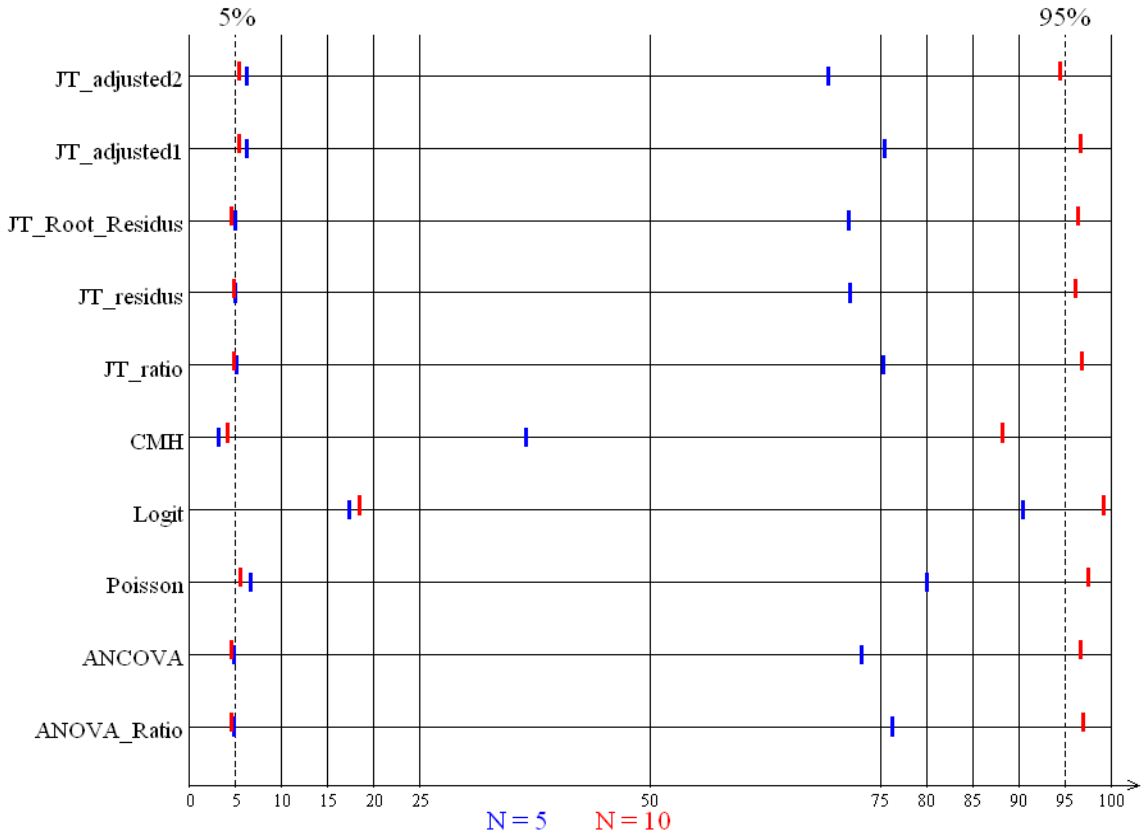


Simulated data (binomial) with truncation



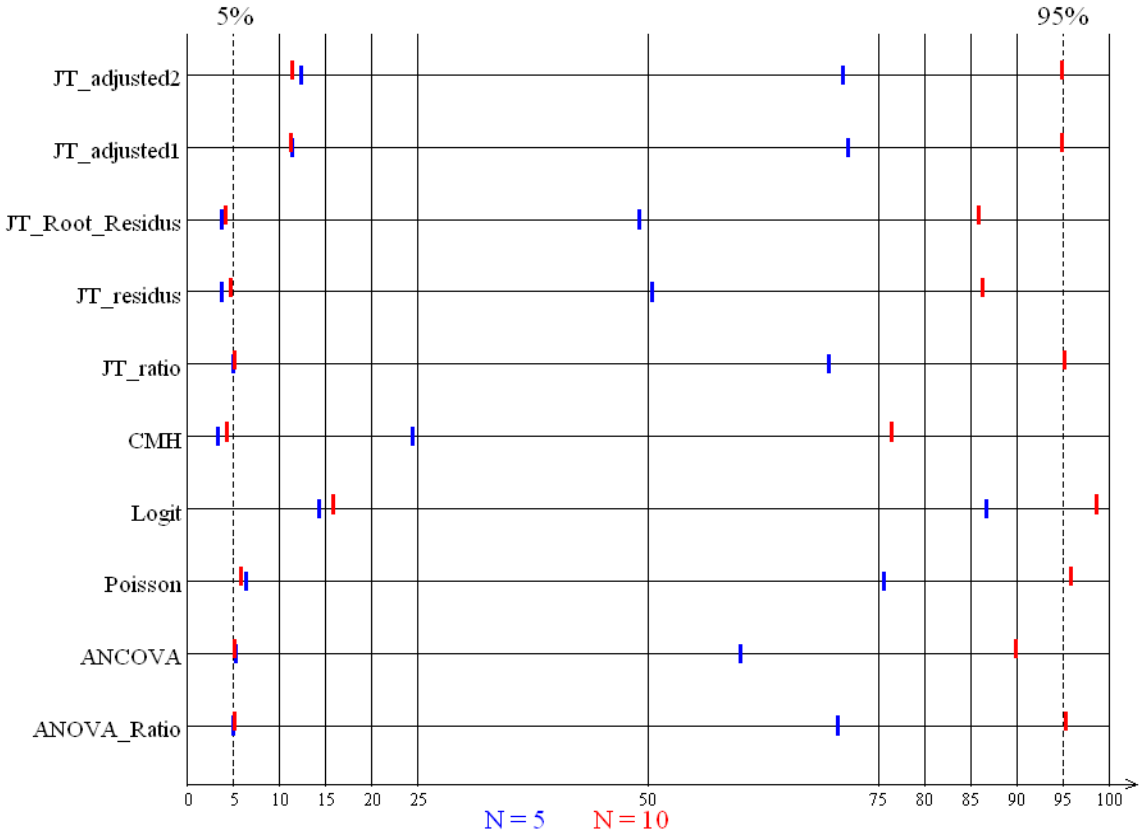
Results

Fetuses - No treatment effect on implantations



Results

Fetuses - Treatment effect on implantations



Conclusion

- Logit model is too liberal – the model does't take into account the dam effect.
  - GEE models ?
  - Exact conditional distributions
- CMH is conservative and not powerful
- Mixture methods do not show any advantages
- Poisson is performing well but slightly too liberal
- JT on ratio and Anova on ratio give the better results

References

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