Mixed models using the SAS® PROC MIXED procedure:

A simulation based approach to assess sample size and resolve a daily biostatistician's dilemma for preclinical trials…

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Our context: preclinical research area

- Seen by the biologist
  - Comparison between treatments
  - Limited number of subjects
  - Repeated measures over time

- Seen by the statistician
  - Many experiments related to longitudinal data
  - Small sample size
  - Potentially missing data

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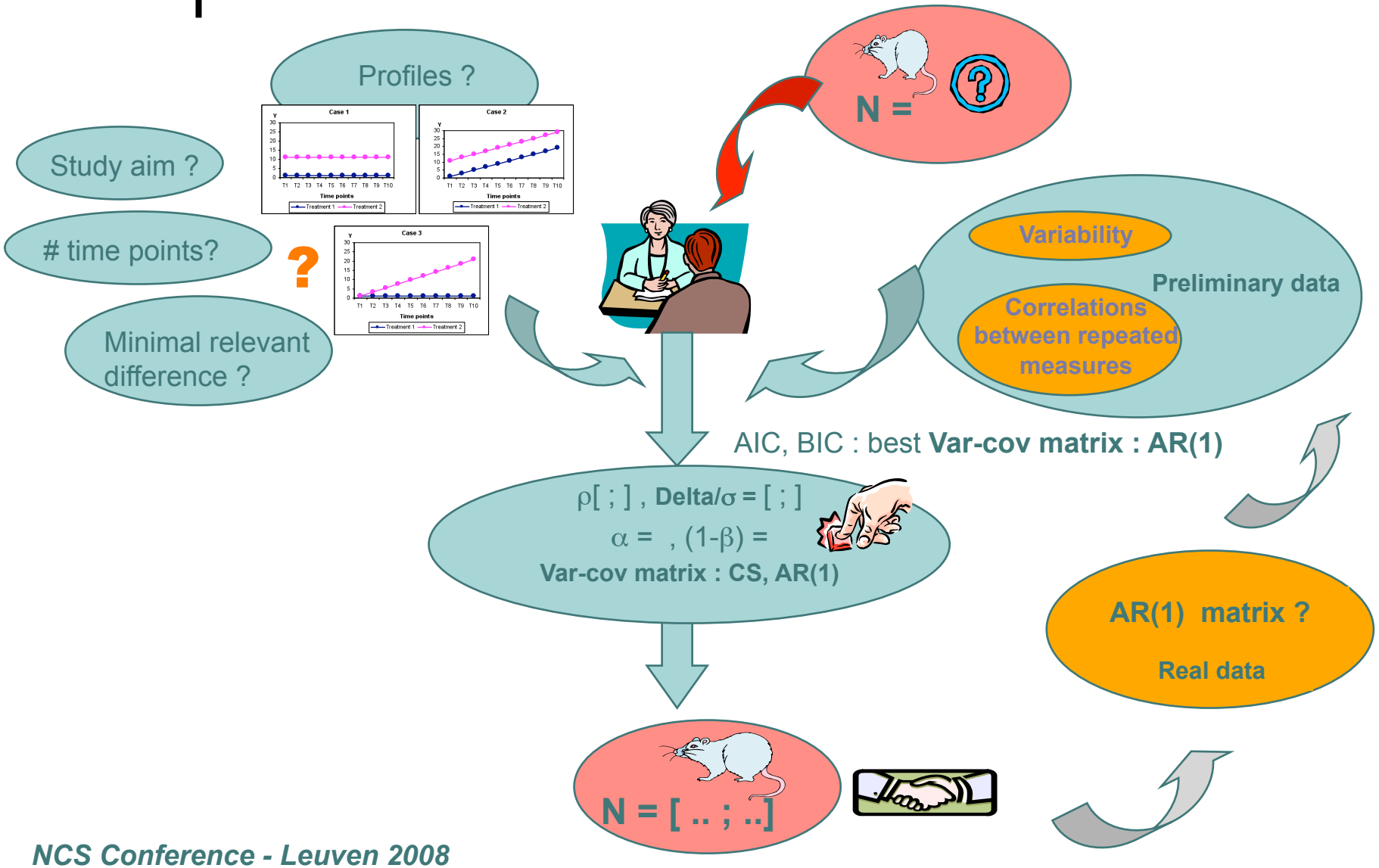
  ↳ Proc mixed is commonly used
    - More suitable than GLM for repeated measures
    - Management of missing data
    - Better modeling of the correlations between observations
  - But
    - Multiple options not well understood to date
    - Choice of the var/cov structure sometimes tricky

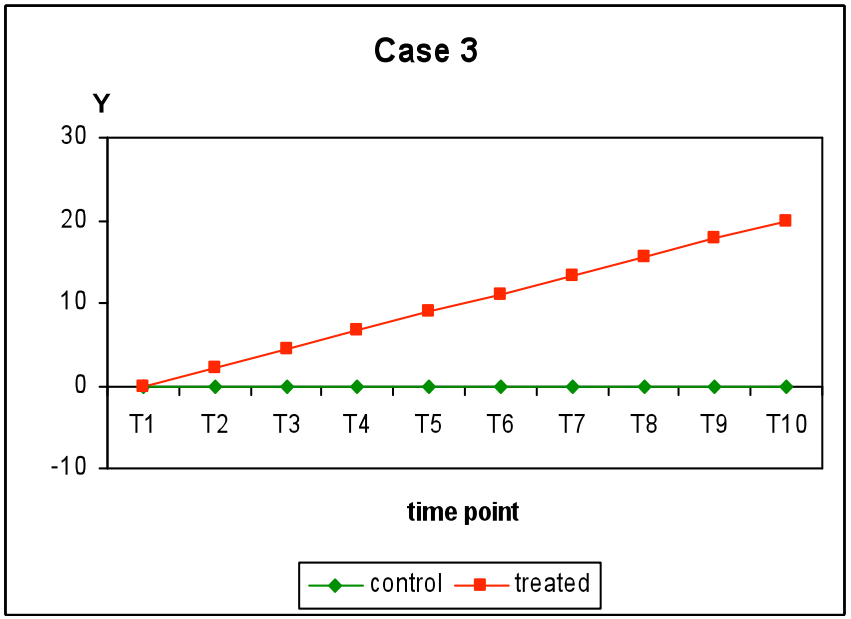
Objectives

- Evaluate the impact of various options in the proc mixed
  - on alpha
  - on power
- Provide sample size evaluation by a simulation program

Strategy for sample size evaluation



Studied designs



- Classical and simple experimental design
  - 2 groups (control and treated)
  - Repeated measures over time
- Focus on 4 common response profiles
  - With or without interaction and effect
  - 3 and 10 time points

	case 0	case 1	case 2	case 3
interaction	0	0	0	X
treatment	0	X	X	X
time	0	0	X	X

Simulation approach for each case

1000 to 2000 times

Simulation

- 2 samples with CS or AR(1) structure
- Corr = 0.2 or 0.8
- 3 or 10 time points
- n = 4 to 14 by 2
- Delta = 10, Sigma = 10

X

Analysis

- ML or REML **method**
- CS or AR(1) Var-covar **matrix**

model

=

Result

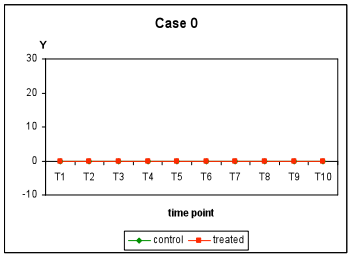
Count of significant p-values for :

- Group effect according to interaction
- Interaction
- Time effect

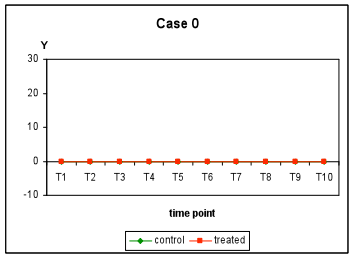
α-level control

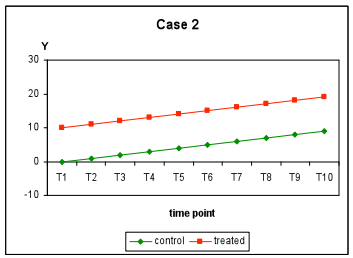
- Simulations under H0
  - α threshold: 10%

No group effect

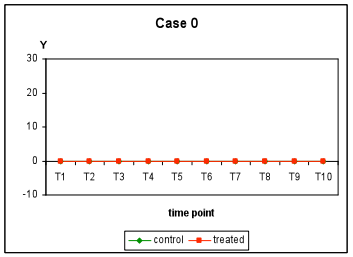


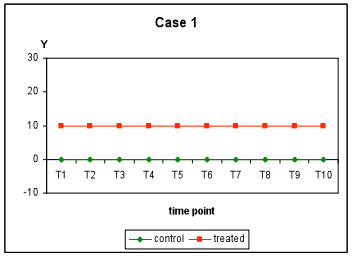
No interaction effect





No time effect





α-level control

- Results (1): method

α-level control

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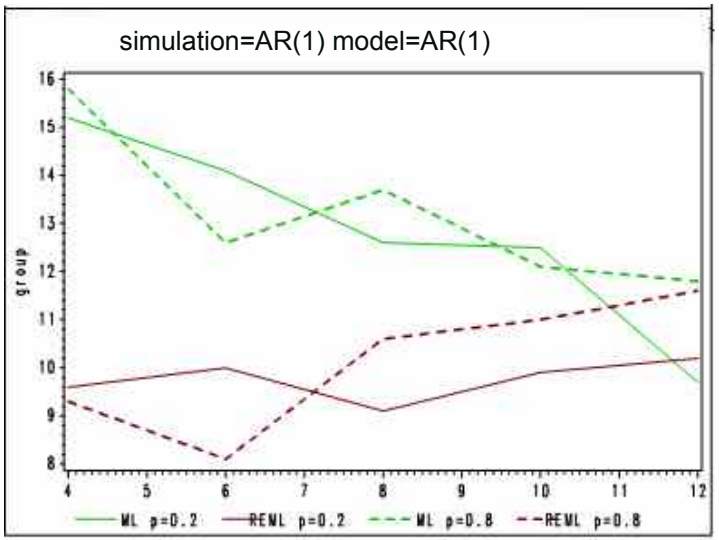
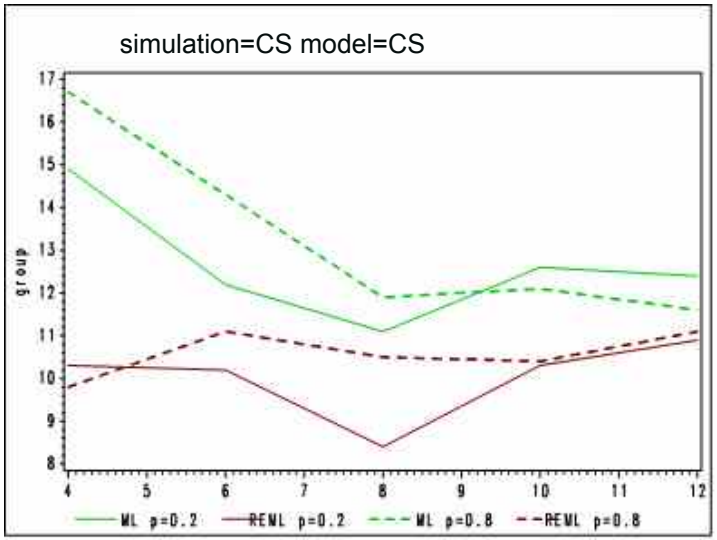
  - With ML, α is uncontrolled for some very low sample size!





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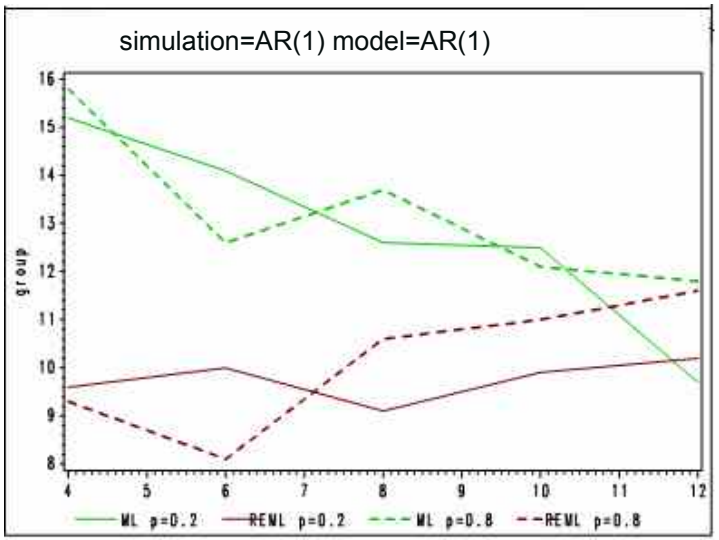

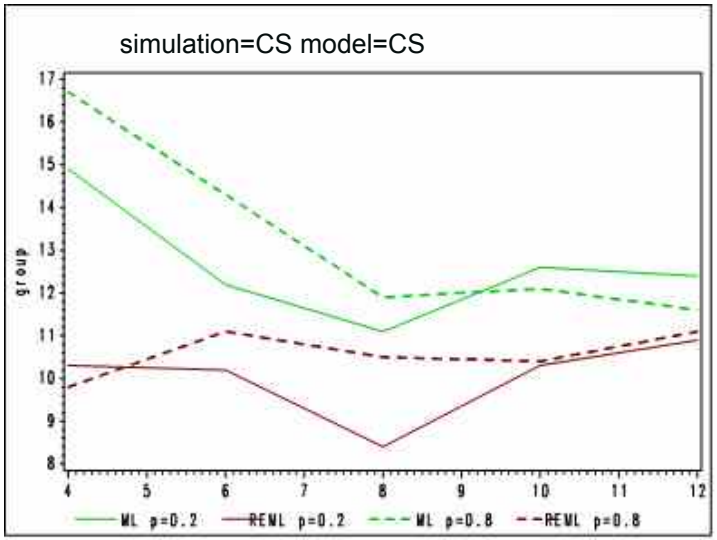

↳ REML is kept afterwards

α-level control

- Results (2): variance-covariance matrix

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  - For group effect:

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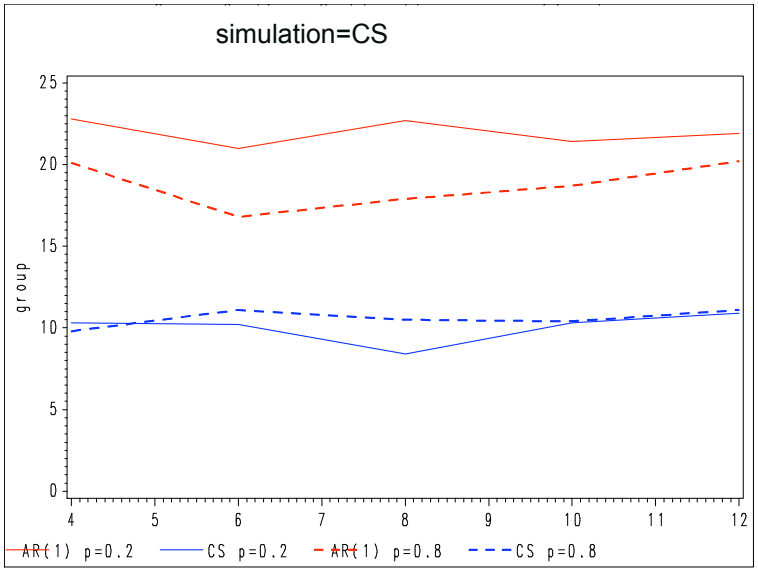
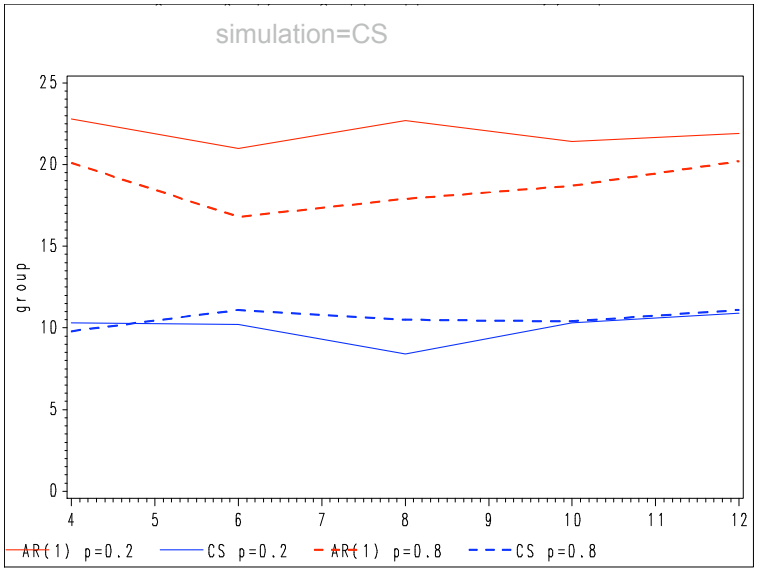
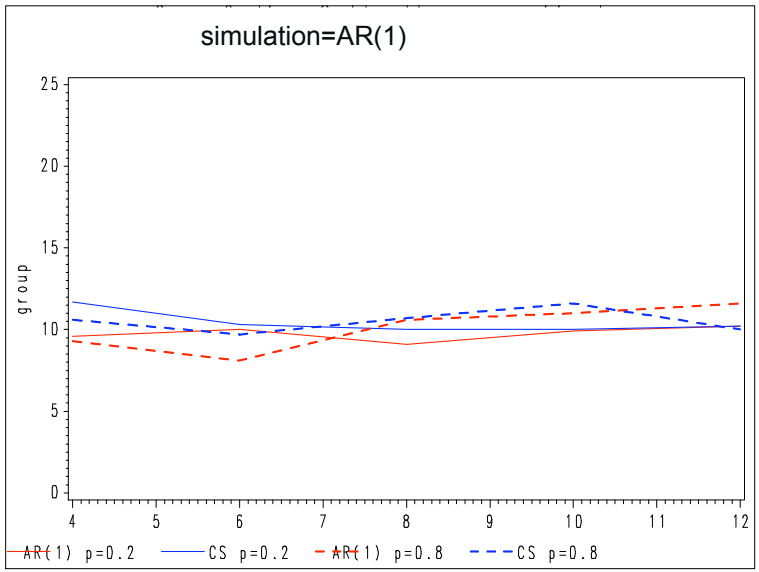
    - If analyzed with AR(1), α risk is increased for a CS structure



α-level control

- Results (2): variance-covariance matrix
  - For group effect:
    - If analyzed with AR(1), α risk is increased for a CS structure
    - No impact of the matrices for a AR(1) structure





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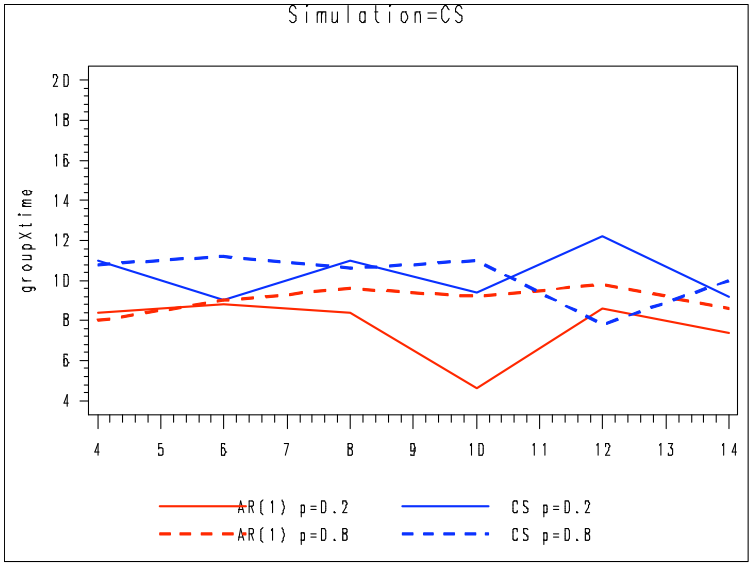
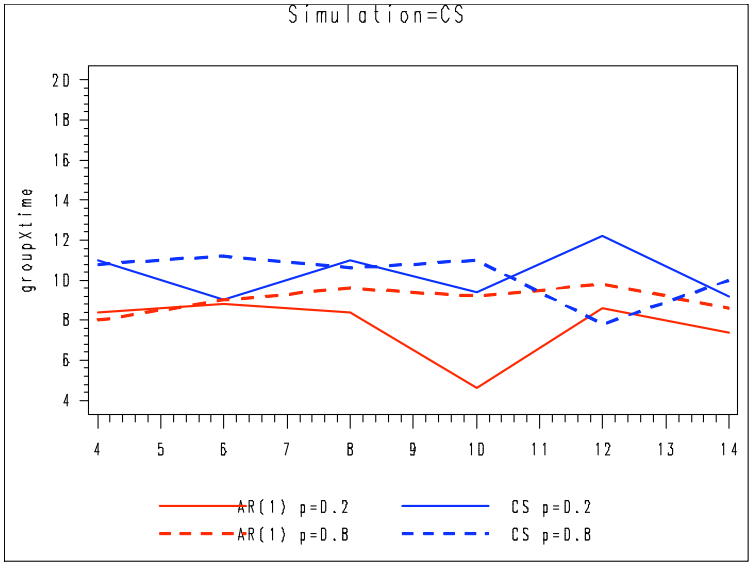
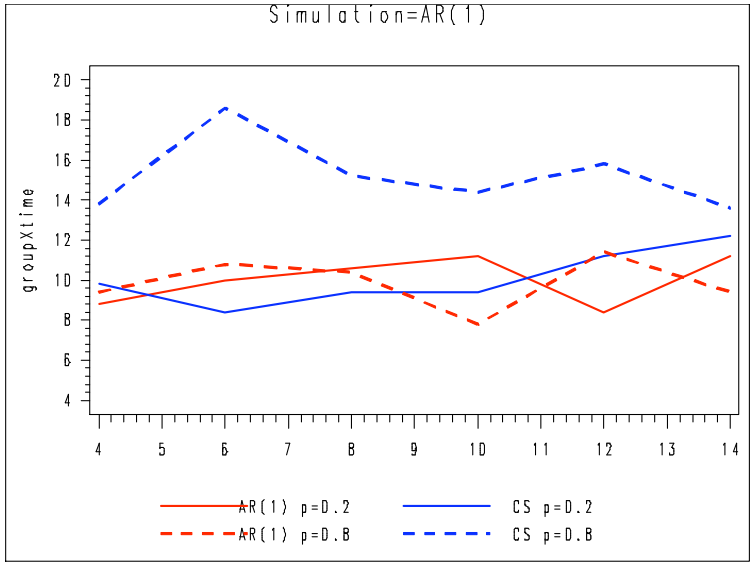


α-level control

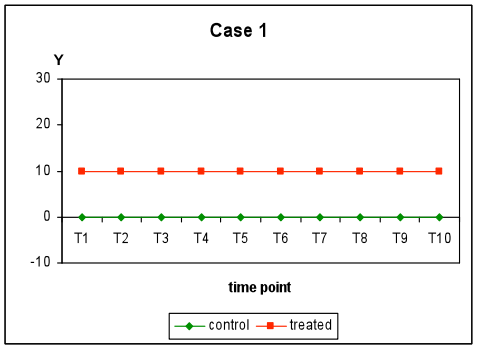
- Results (2): variance-covariance matrix
  - For interaction effect:
    - No impact of the matrices for a CS structure
    - If analyzed with CS α risk is increased for a AR(1) structure when ρ is high
  - Conclusions are the same for time effect

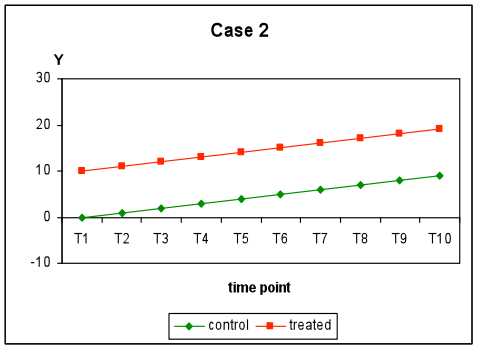




Impact of the variance-covariance matrix on power for the group effect

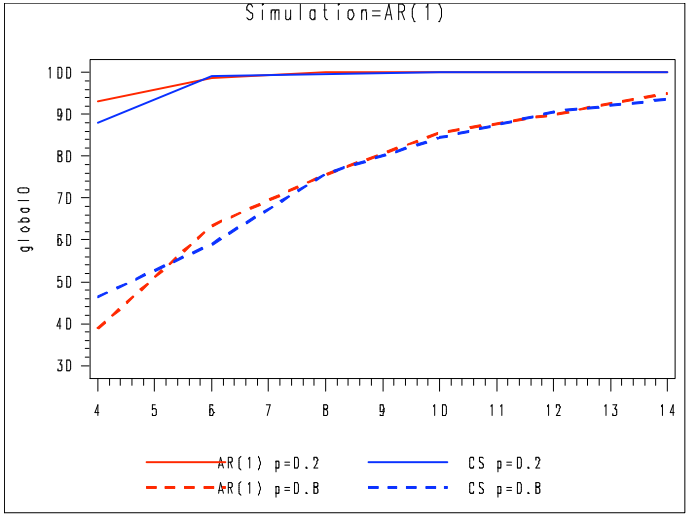
- Without interaction (cases 1 and 2)





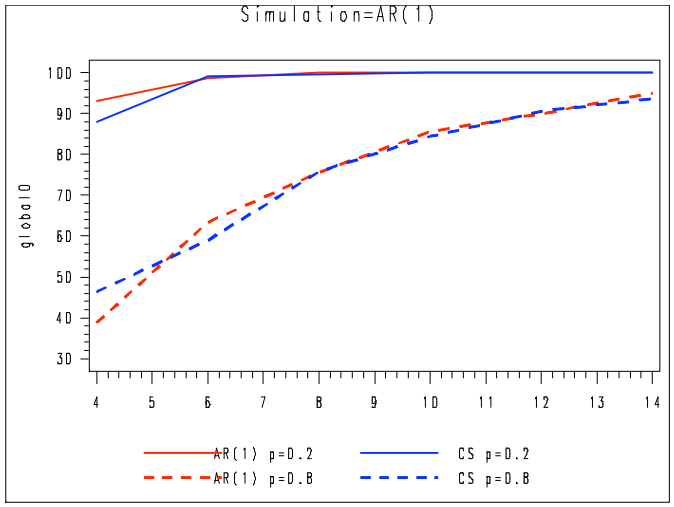
Impact of the variance-covariance matrix on power for the group effect

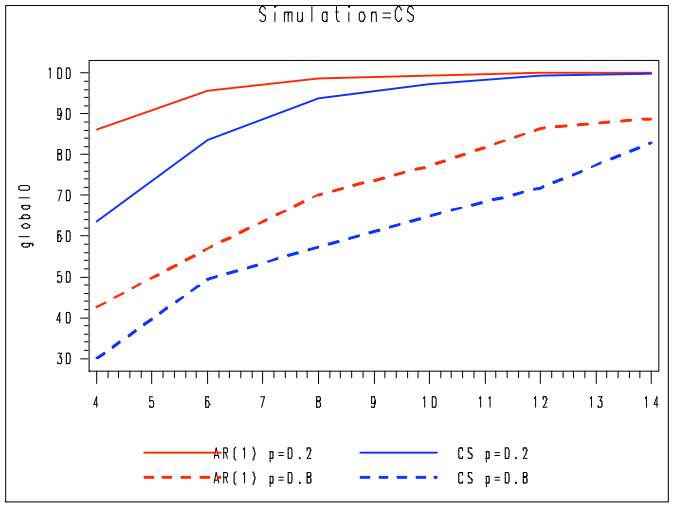
- Without interaction (cases 1 and 2)
  - For a data structure AR(1)
    - no impact of the matrices
    - power is higher as ρ is lower



Impact of the variance-covariance matrix on power for the group effect

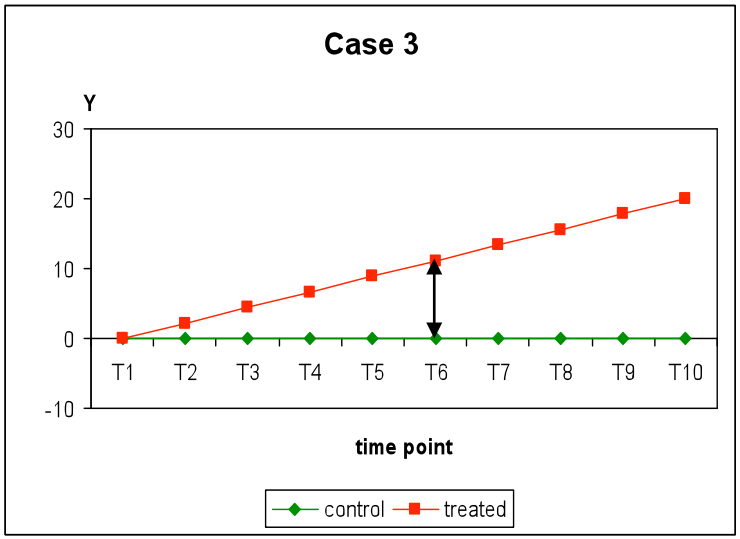
- Without interaction (cases 1 and 2)
  - For a data structure AR(1)
    - no impact of the matrices
    - power is higher as ρ is lower
  - For a data structure CS
    - AR(1) analysis gives a higher power
    - power is higher as ρ is lower





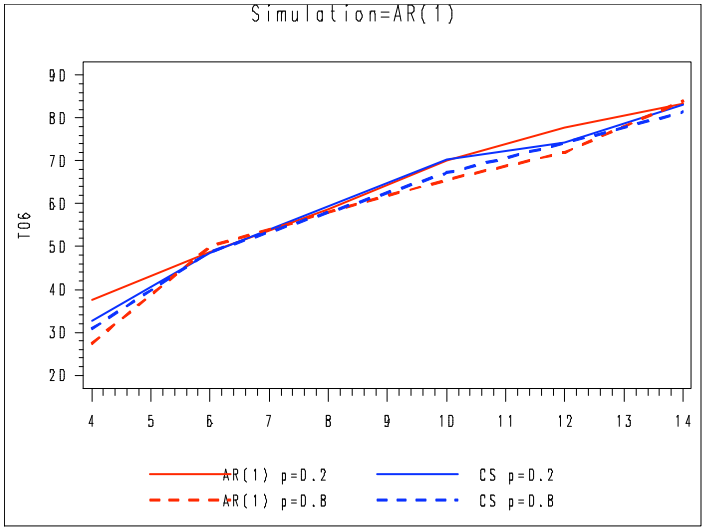
Impact of the variance-covariance matrix on power for the group effect

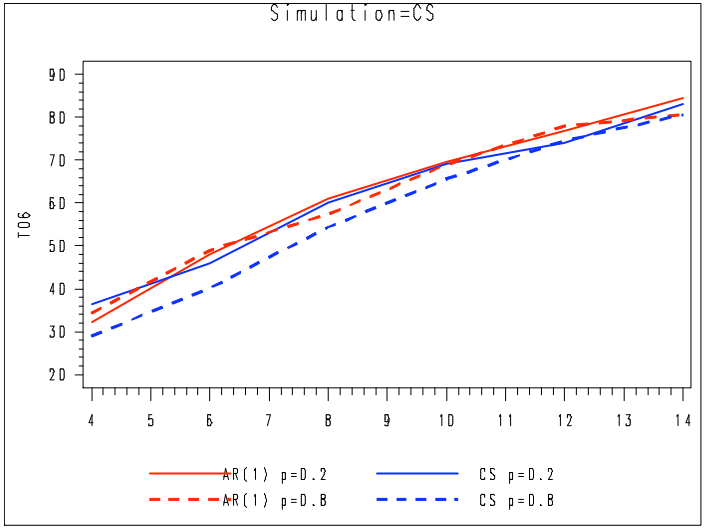
- With interaction (case 3)
  - At the middle time-point (T6)



Impact of the variance-covariance matrix on power for the group effect

- With interaction (case 3)
  - At the middle time-point (T6)
    - no impact of ρ and matrices





Impact of the variance-covariance matrix on power for the interaction and time effect

- Interaction effect (case 3)
  - Whatever the data structure is
    - power is higher with **CS**
    - especially when ρ is high

Impact of the variance-covariance matrix on power for the interaction and time effect

- Interaction effect (case 3)
  - Whatever the data structure is
    - power is higher with **CS**
    - especially when ρ is high

- Time effect without any interaction (case 2)
  - Whatever the data structure is
    - power is higher with **CS**
    - especially when ρ is high

Conclusion

- REML has to be chosen to control the α-risk

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	To control α	To maximize (1-β)
Group effect	CS	AR(1)
Interaction or time effect	AR(1)	CS

Conclusion

- REML has to be chosen to control the α-risk
- It is recommended to choose the matrix according to the primary objective

	To control α	To maximize (1-β)	To estimate n *(worst case)*
Group effect	CS	AR(1)	CS
Interaction or time effect	AR(1)	CS	AR(1)

Perspectives

- Missing and/or unbalanced data
- Heterogeneous variances
- More than 2 groups and α adjustment
- Time as a continuous variable
- Other types of variance matrix

References

- Linear Mixed Models for Longitudinal Data, Verbeke G., Molenberghs G., Springer Series in Statistics, 2000
- Applied Mixed Models in Medicine, Brown H., Prescott R., Statistics in practice, 1999
- Tutorial in Biostatistics: Modelling covariance structure in the analysis of repeated measures data, Littell R. C. and al., Statistics in Medicine, 2000
- SAS institute, Inc. (1999) SAS/STAT user's Guide, V8. Cary, NC: SAS Institute

Model

- Analysed using proc mixed with repeated statement

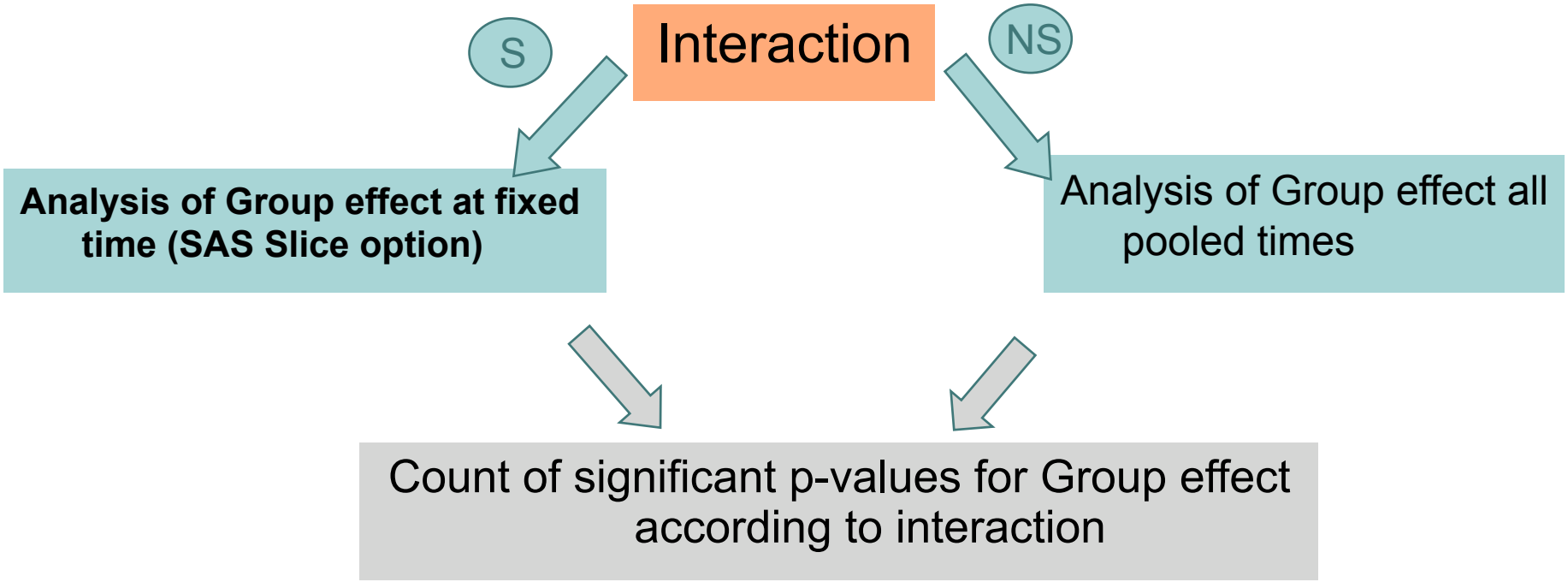
$Y_{ijk} = \mu + group_i + time_j + groupxtime_{ij} + \varepsilon_{ijk}$

$\varepsilon \sim iid(0,R)$

```
proc mixed method=&method. ;
        class group time animal ;
        model Y = group time group*time / ddfm=satterth;
        repeated time / subject=animal(group) type=&typvarmixed.;
```

back

Simulation approach for each case



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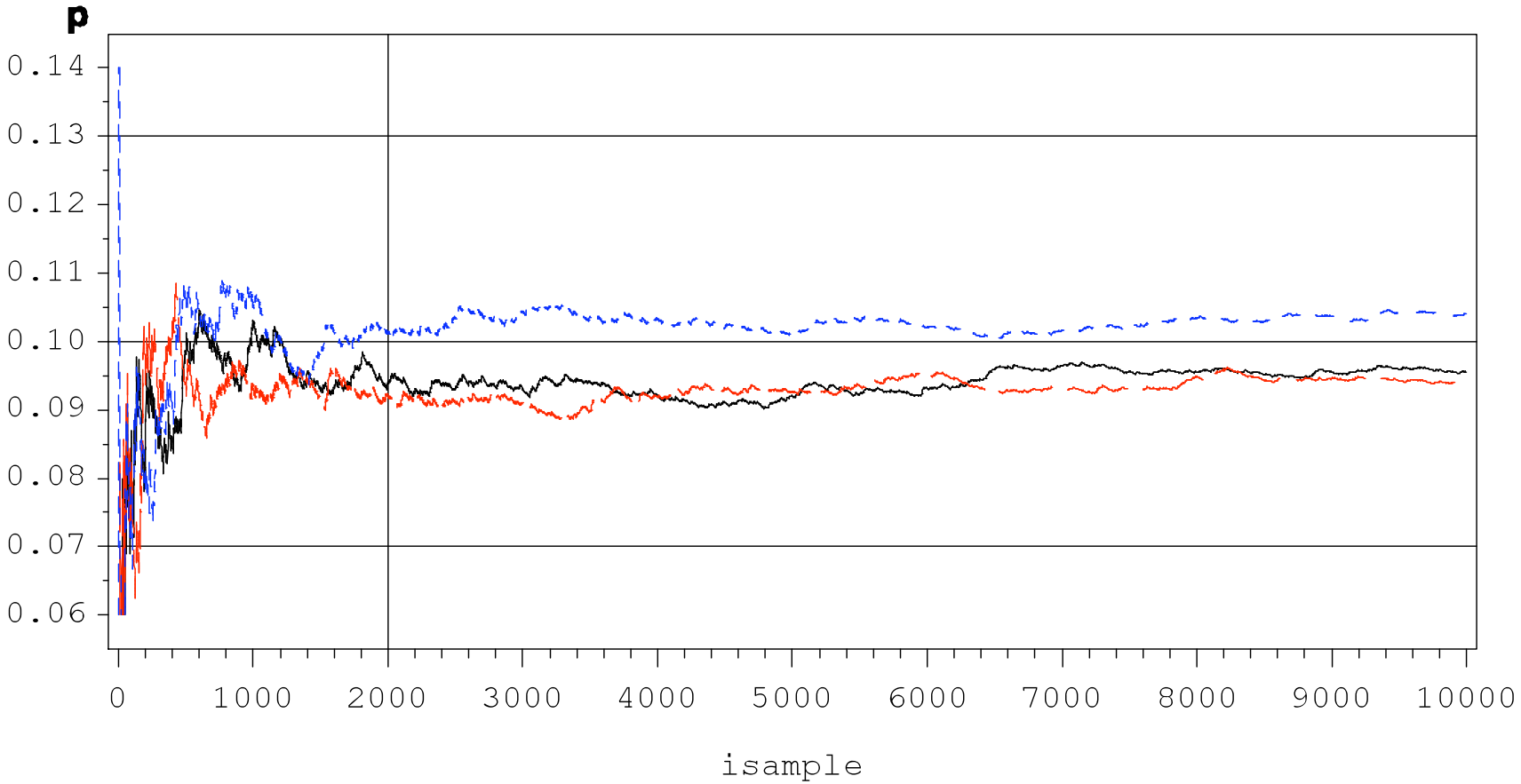
3 times : rejection frequency of time effect



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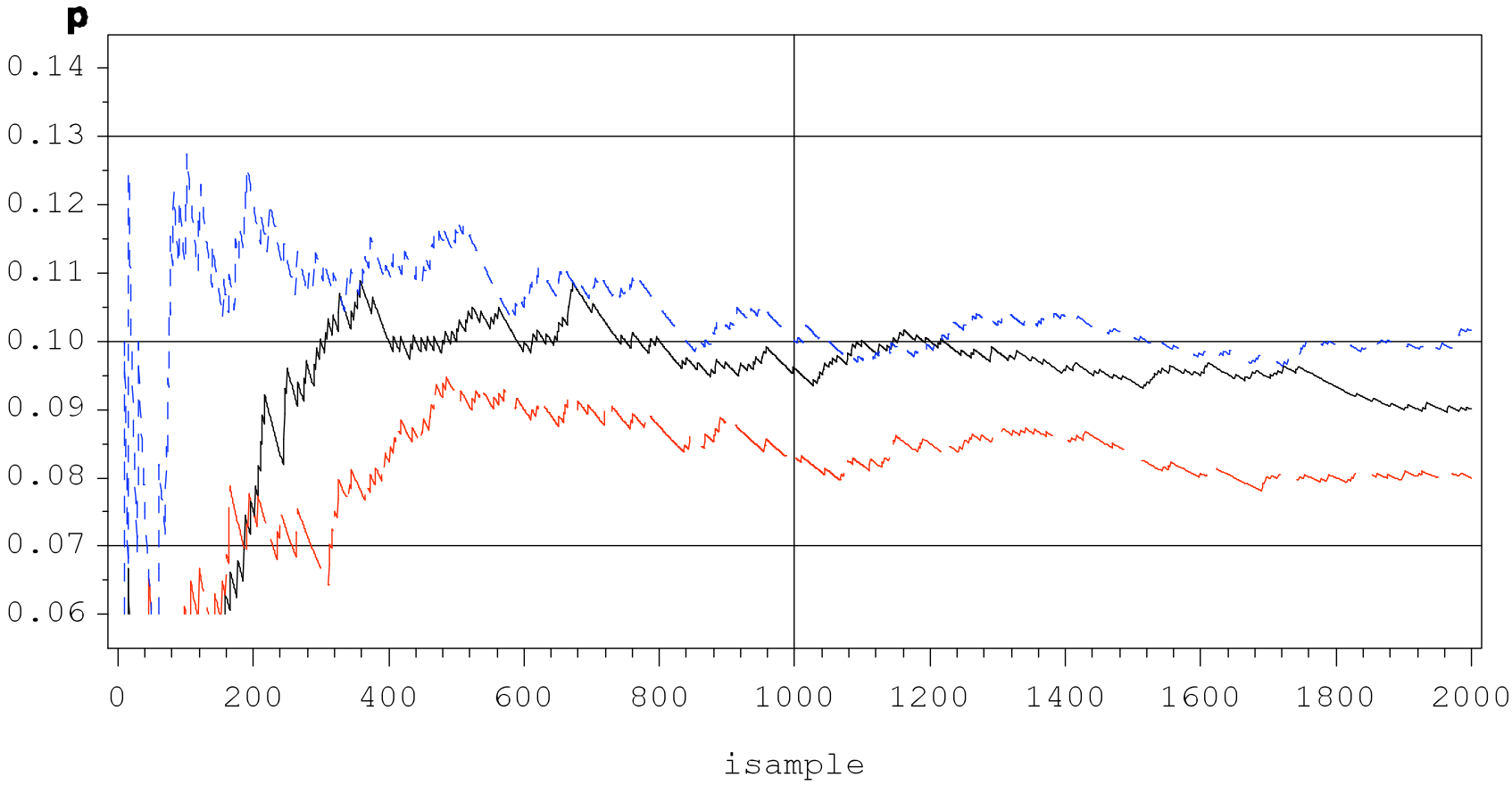
10 times →

10 times : rejection frequency of time effect



← 3 times

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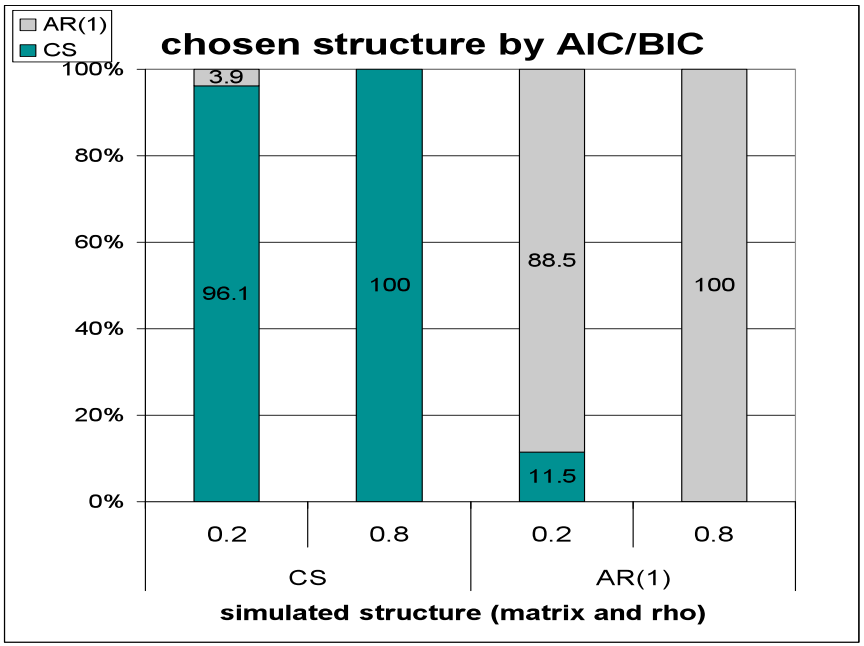
Use of AIC / BIC to select the suitable matrix



- Simulations are validated for these two simple structures
- **But it is possible to make mistakes is case of low correlation !**

Impact of ML and REML on α level (10 times)

1000 simulations
n = 5

			model_simul					
			AR(1)			CS		
			Effect			Effect		
			group	group*time	time	group	group*time	time
model	method	ddfm						
AR(1)	ML	Déf(BW)	11.30%	22.80%	22.10%	24.40%	18.50%	18.30%
AR(1)	ML	KR	14.20%	20.10%	19.50%	27.90%	16.30%	16.60%
AR(1)	ML	Satterth	13.20%	23.20%	22.30%	26.70%	18.50%	18.30%
CS	ML	Déf(BW)	13.30%	25.10%	23.60%	12.90%	22.70%	22.30%
CS	ML	KR	13.90%	26.00%	24.20%	14.10%	23.40%	22.90%
CS	ML	Satterth	13.90%	26.00%	24.20%	14.10%	23.40%	22.90%

			AR(1)			CS		
			Effect			Effect		
			group	group*time	time	group	group*time	time
model	method	ddfm						
AR(1)	REML	Déf(BW)	8,10%	11,00%	10,10%	20,30%	8,70%	9,00%
AR(1)	REML	KR	10,00%	8,70%	7,90%	22,20%	6,80%	7,10%
AR(1)	REML	Satterth	8,90%	10,30%	9,50%	21,60%	8,40%	8,70%
CS	REML	Déf(BW)	9,80%	16,10%	14,90%	9,50%	9,90%	10,00%
CS	REML	KR	9,80%	16,10%	14,90%	9,50%	9,90%	10,00%
CS	REML	Satterth	9,80%	16,10%	14,90%	9,50%	9,90%	10,00%