

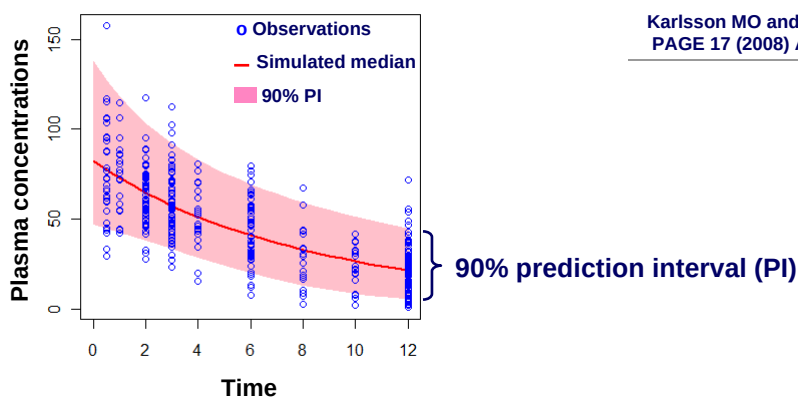
You have problems to interpret VPC? Try VIPER!

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UMR181 Physiopathologie et Toxicologie Expérimentales, INRA, ENVT



Visual Predictive Checks (VPC)

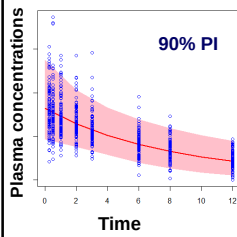


Karlsson MO and Holford N.
PAGE 17 (2008) Abstr 1434

⇒ Under the correct model, **approximately 90%** of observations should be included in the 90% PI (**subjective** interpretation).

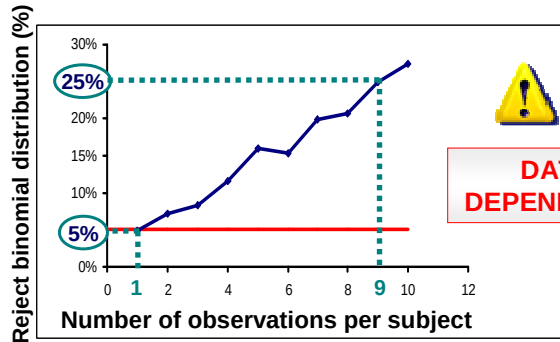
⇒ No strict rule of decision exists to clearly assess a model.

VPC and rule of decision



n: total number of observations

⇒ Does the number of observations outside the 90% PI follow a **binomial distribution** $B(n, p=0.1)$? (nominal level of 5%)

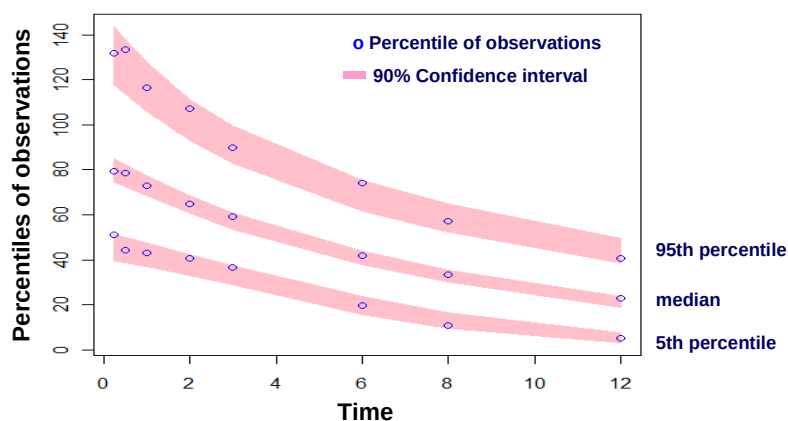


⇒ With ≥ 2 observations per subject, the correct model is rejected more than it should (here $>5\%$) with the binomial distribution.

⇒ These results are in agreement with previous findings*.

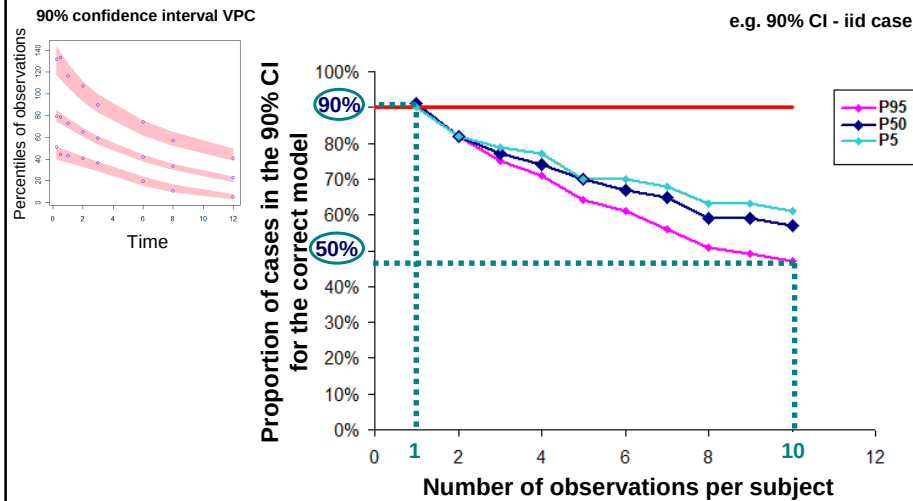
* Brendel et al (2010) J Pharmacokinet Pharmacodyn

Confidence interval (CI) VPC



⇒ People might expect that all percentiles of observations over time should be in the 90% CI in 90% of cases for the correct model.

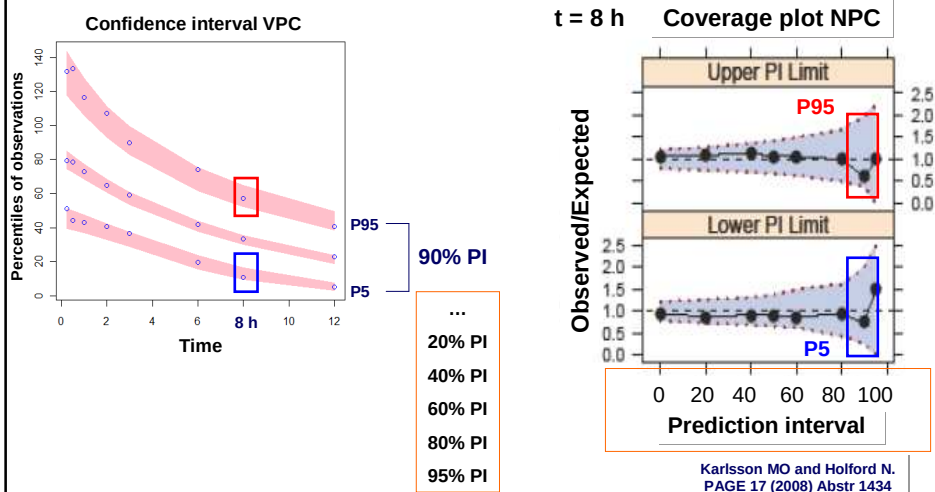
Confidence interval VPC and rule of decision



⇒ With the increase of number of observations per subject, the **correct model is frequently rejected (>10%)** !

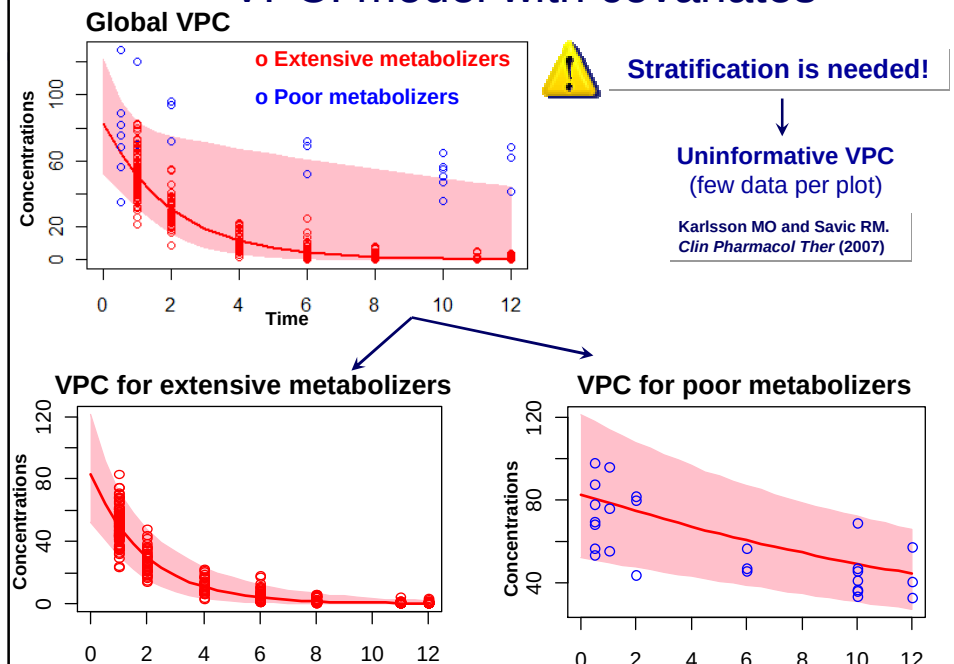
Numerical Predictive Checks (NPC)

Wilkins J et al. PAGE 15 (2006) Abstr 1029

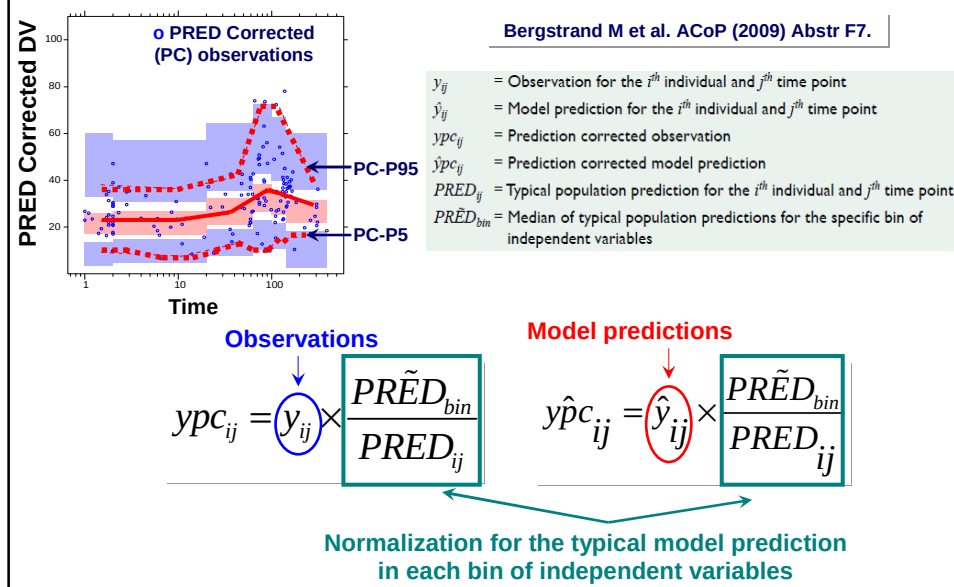


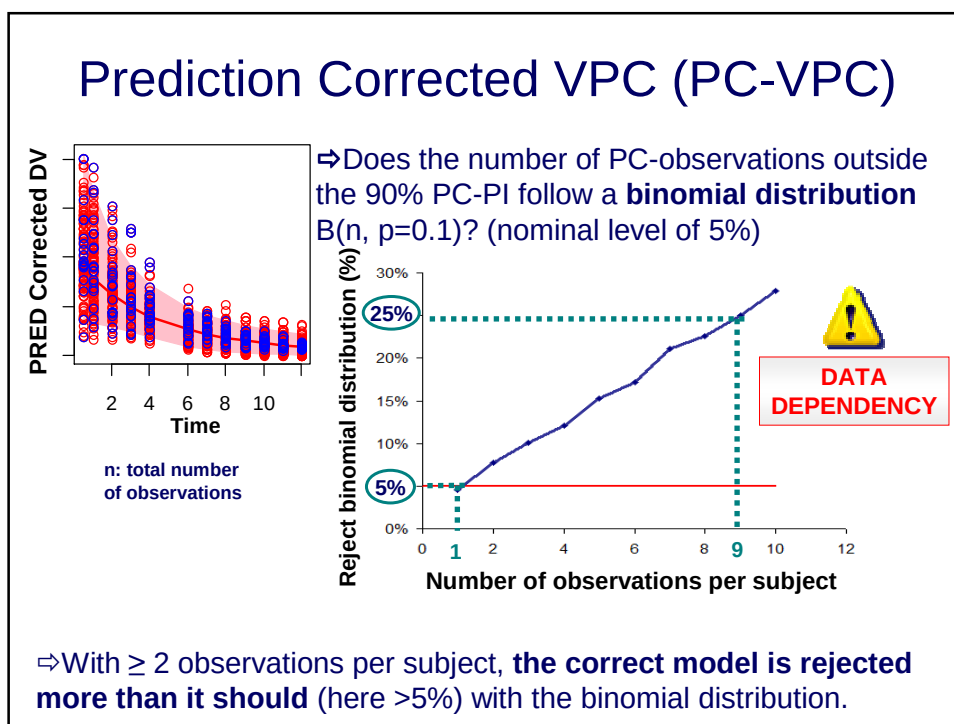
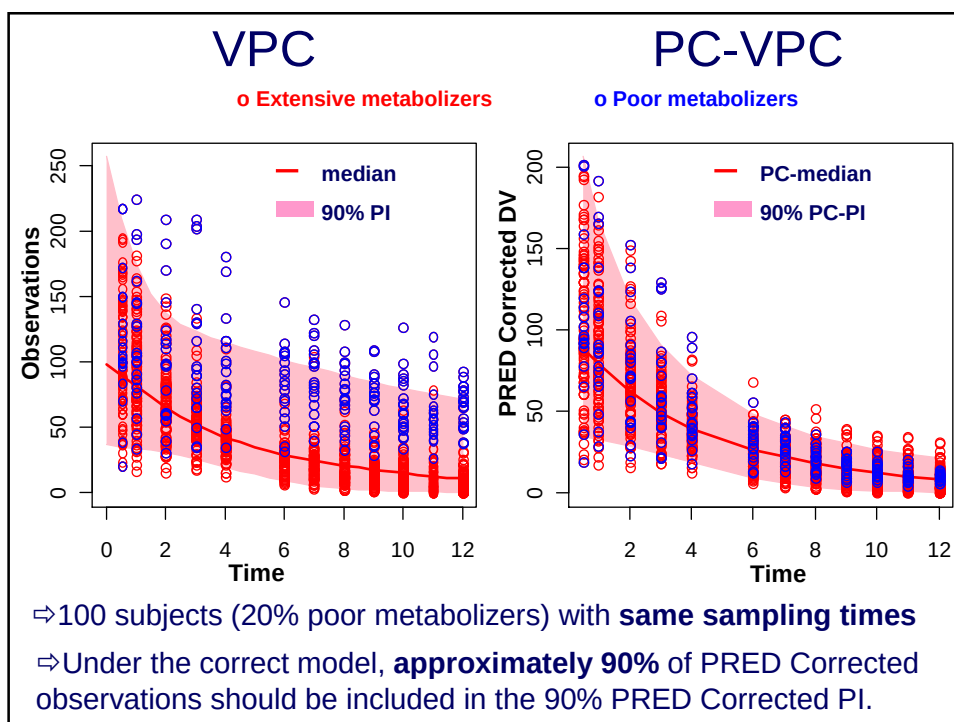
⇒ The issue about the rule of decision obtained for the 90% prediction interval is also valid for other prediction intervals (NPC).

VPC: model with covariates



Prediction Corrected VPC (PC-VPC)





VPC, confidence interval VPC, NPC, PC-VPC

- ☹ **Subjective** interpretation (no exact result)
- ☹ Problem with **rules of decision**
- ☹ Problem of **stratification** (excepted PC-VPC)
- ☹ Problem of **binning** (excepted VPC)

A solution: VIPER

➤ VPC graphs: very popular tool for model evaluation but present some drawbacks

Karlsson MO and Holford N.
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➤ We propose a new tool which **looks like VPC** but presents the advantage to be **easy** and **exact** for interpretation:

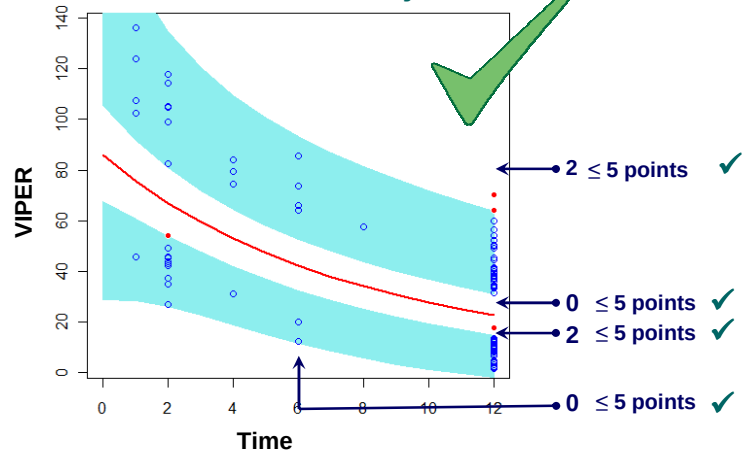
☐ **VIPER**: **V**isual **P**redictive **E**xtended **R**esiduals

VIPER: example (1)

N=100 subjects $\Rightarrow$ 100 points

$\Rightarrow$ The model is not rejected

$\Delta < 0.05 \times N$
 $= 0.05 \times 100$
 $= 5 \text{ points}$

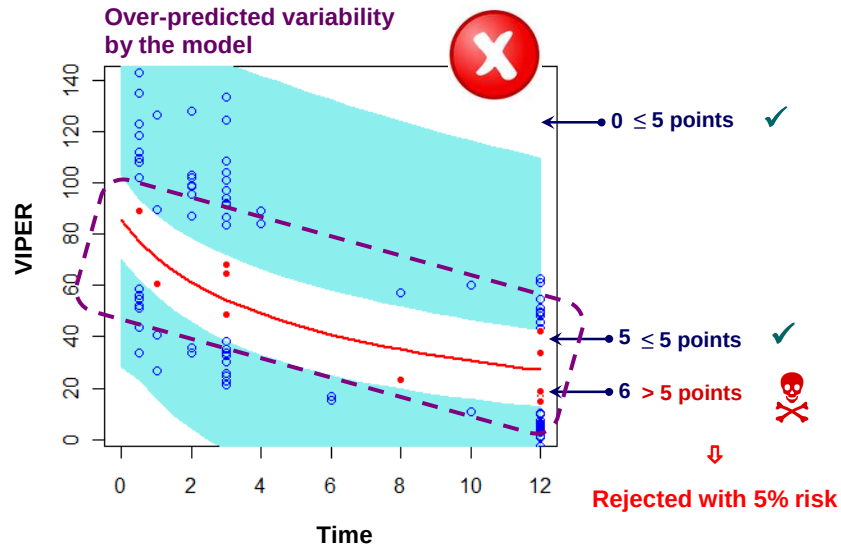


Rule: A model is rejected with 5% risk when there are $>0.05N$ points in a white area

VIPER: example (2)

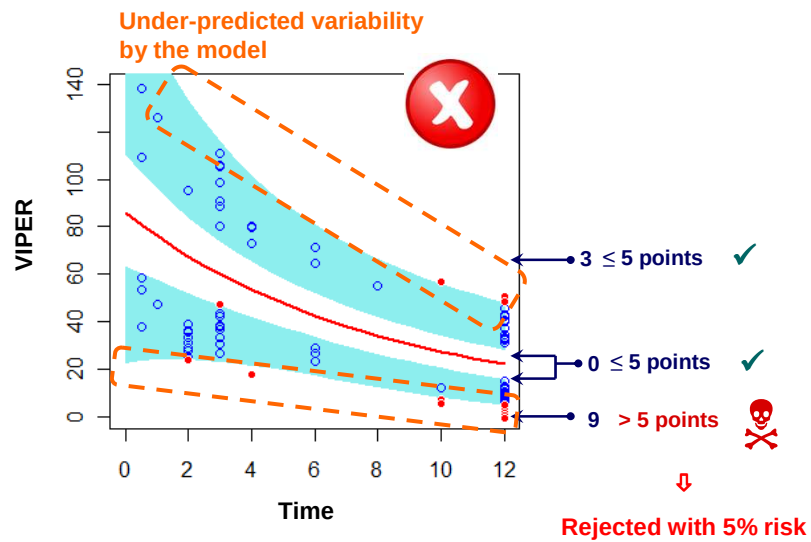
N=100 subjects $\Rightarrow$ 100 points

Over-predicted variability
by the model

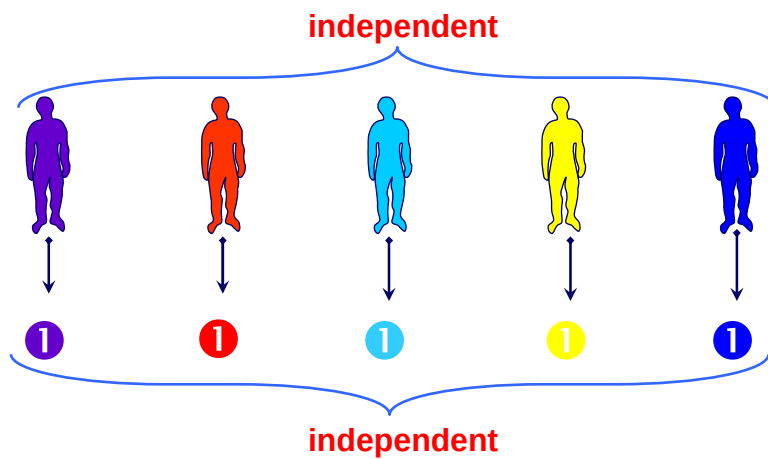


VIPER: example (3)

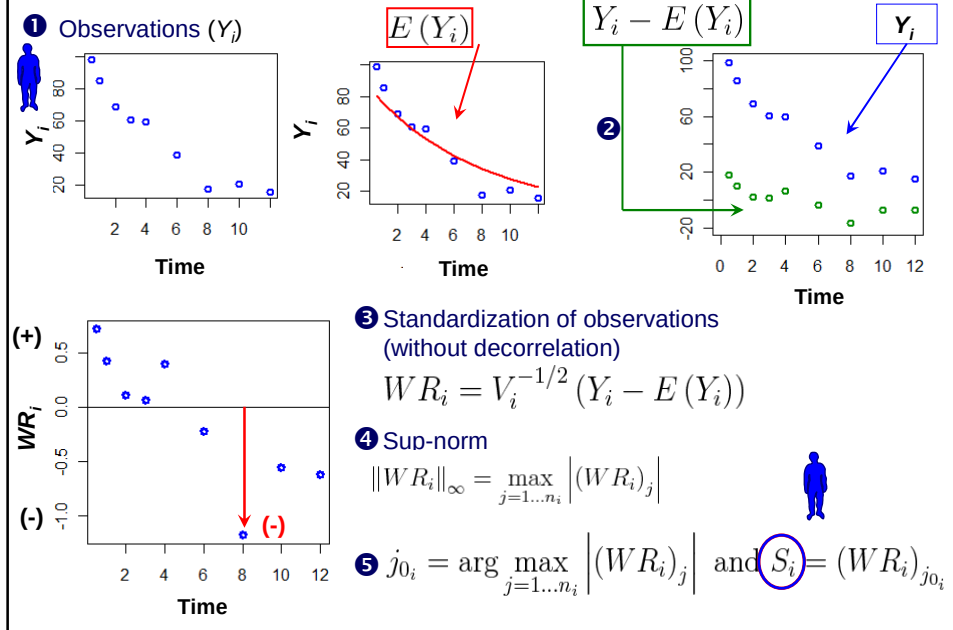
N=100 subjects $\Rightarrow$ 100 points



VIPER: basic idea

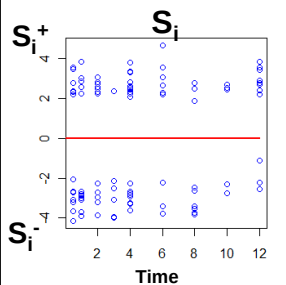


VIPER: computation (1)



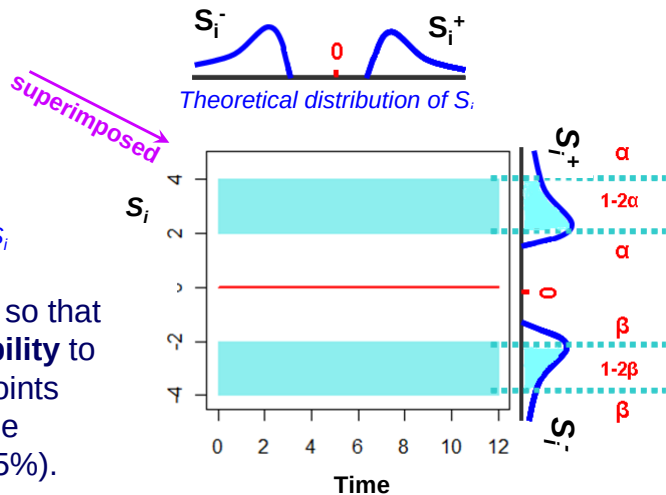
VIPER: computation (2)

$N = 100$ subjects



For iid case:

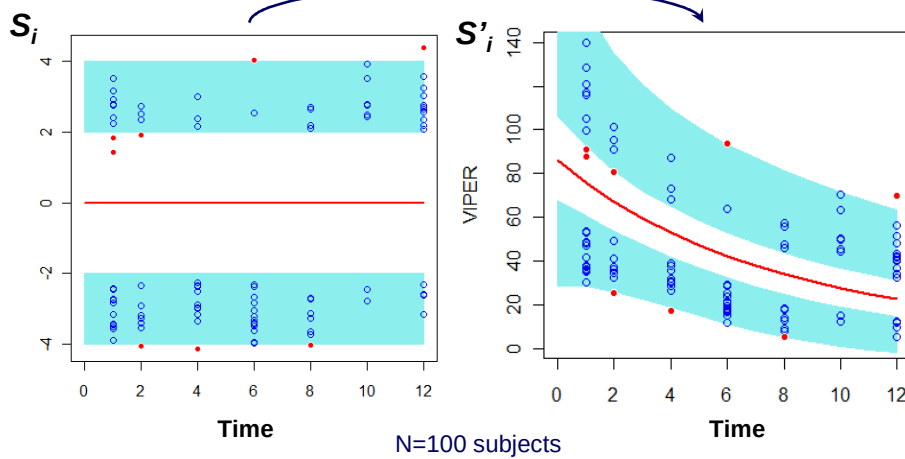
With the assumed model, we obtain the following distribution of S_i :



VIPER: computation (3)

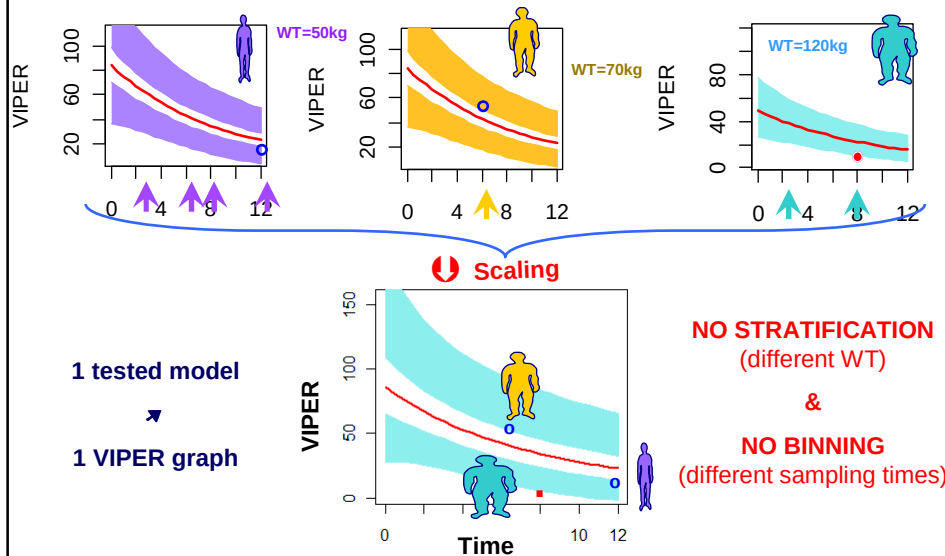
$$S'_i = S_i \times V_i^{1/2} + E(Y_i)$$

Reverse of standardization



VIPER: computation (4)

For non-iid case (i.e. different sampling times, model with covariates...):

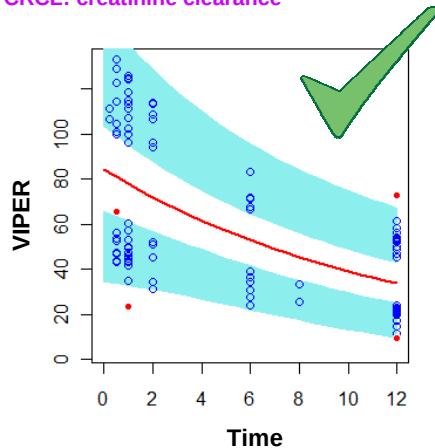


VIPER: application for a model with covariate

N=100 subjects with **different sampling times**

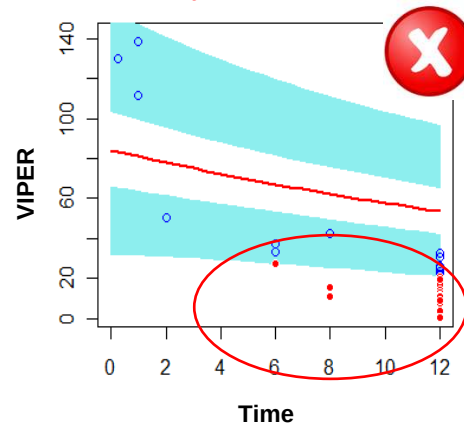
Correct model: $CL = 4.32 + 2 \times CRCL$

CRCL: creatinine clearance



False model: $CL = 4.32$

Rejected with 5% risk



Conclusion

You have problems to interpret VPC? Try VIPER!

Model evaluation tools	VPC	Confidence interval VPC, NPC	PC-VPC	VIPER
Diagnostic of structural and random effects	✓	✓	✓	✓
Illustrative graph	✓	✓	✓	✓
Suggestion of model improvements	✓	✓	✓	✓
No stratification needed	✗	✗	✓	✓
No binning needed	✓	✗	✗	✓
No issue of data dependency	✗	✗	✗	✓
Easy interpretation (strict rule of decision)	✗	✗	✗	✓
Exact test	✗	✗	✗	✓

🔍 More work is needed to evaluate VIPER in real conditions (PK/PD model, real-case data, effect of censoring data BLQ...).