

Getting your data in good shape for Non Linear Mixed Effects Modeling

PHUSE 2010

SP07

Vincent Buchheit

Introduction

- Non Linear Mixed Effects Modeling is used in Modeling and Simulation (M&S)
- Non linear mixed effects models is about analyzing repeated measurements data by taking into consideration variability as well as the nonlinear relationship between the explanatory variable (time,...) and the response variable (drug concentration...)
- What is M&S?



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Introduction

- What is Nonmem?
 - Software, developed in the 70's
 - Main methodology for modeling and simulation
 - Industry Standard for Non Linear Mixed Effects Modeling

Nonmem file structure – Time event dataset

Need to be harmonized and clean

Sort by calendar date, clock time	For all dose events: Patient ID, calendar date, clock time, dose amount	Nonmem variables: Time since first dose Elapse time	Covariates time dependant: Lab Comedication 	Covariates : Study ID Age Gender Race Height Weight BMI BSA.....
	For all PK samples: Patient ID, calendar date, clock time, PK concentration	Days since first dose 		
	For all PD events: Patient ID, calendar date, clock time, PD value			

Nonmem file structure – Time event dataset

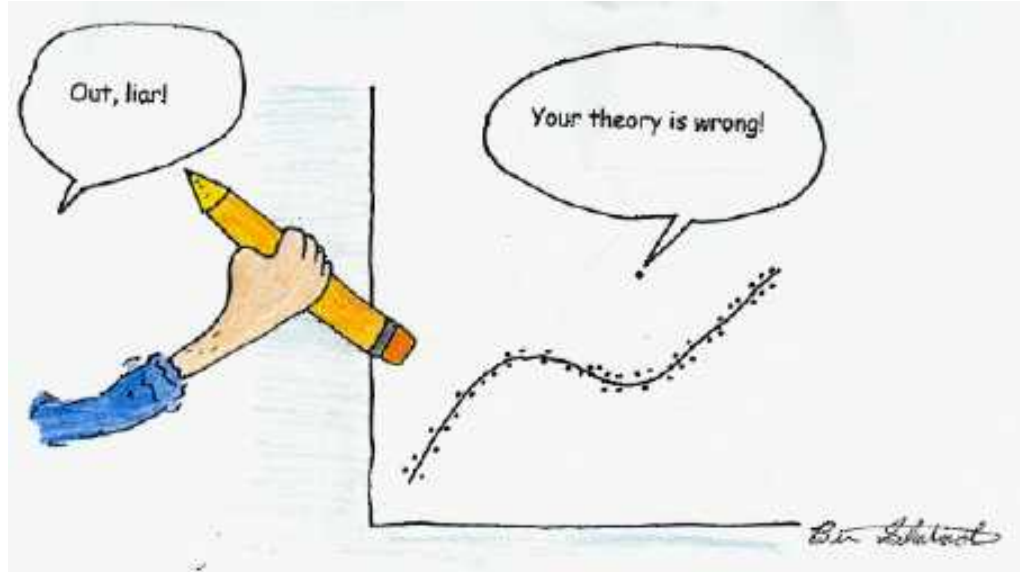
- Each row = one single event (dose administation, drug concentration, biomarker....)

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	
STUD	CENT	SUB	ID	TIME	TAD	NT	RATE	AMT	DV	MDV	dose	COUN	AGE0	SEX	RACE	ETH	HT0	WT0	BSA0	BMI0	
2101	1	101	1	-8588.43			4	0	0	2.286692	0	0	2	64	1	1	88	179	77	1.964281	24.03171
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2101	1	101	1	3	3	3	0	0	78.13956	0	100	2	64	1	1	1	88	179	77	1.964281	24.03171
2101	1	101	1	4.016667	4.016667	4	0	0	96.86545	0	100	2	64	1	1	1	88	179	77	1.964281	24.03171
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2101	1	101	1	24.03333	0.583333	24	0	0	64.5573	0	100	2	64	1	1	1	88	179	77	1.964281	24.03171
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2101	1	101	1	119.45	0	0	-2	100	0	1	100	2	64	1	1	1	88	179	77	1.964281	24.03171
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2101	1	101	1	503.45	0	0	-2	0	0	1	0	2	64	1	1	1	88	179	77	1.964281	24.03171
2101	1	101	1	527.45	0	0	-2	0	0	1	0	2	64	1	1	1	88	179	77	1.964281	24.03171

Nonmem input dataset

- Quality of the Nonmem input dataset drives the quality of the modeling outputs
- The quality of the simulation
- And hence the quantitative input to drug development decision making
- Careful attention needs to be paid for harmonization and cleaning the data
- We are interested in time profile compare to change from baseline

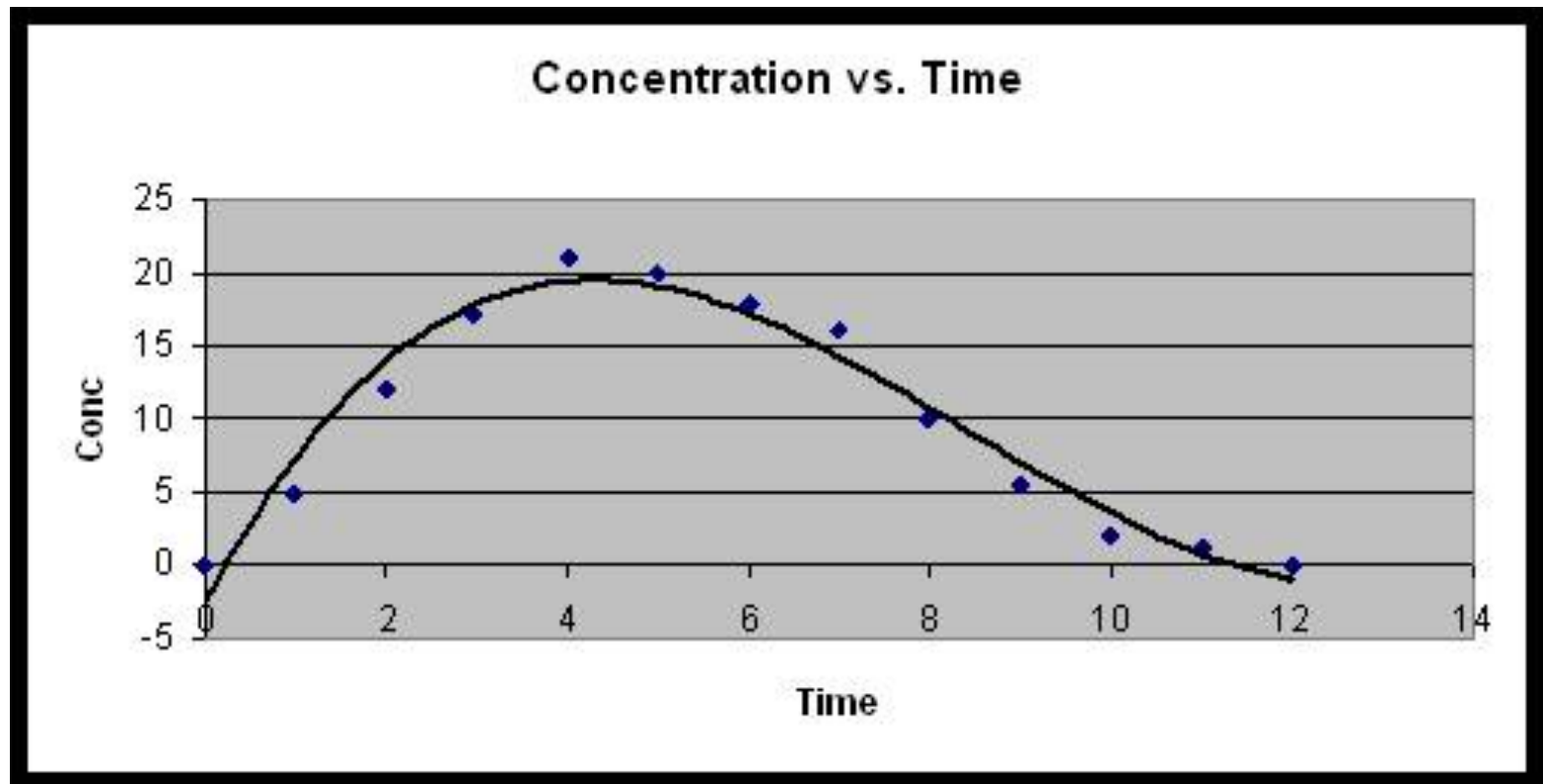
A) Outliers



- No database will be 100% correct and accurate
 - Mistakes happen and will always exist – clinical programmers always encounter outliers
 - What are the impacts from a modeling point of view?
- <http://davidmlane.com/hyperstat/outlier.jpg>

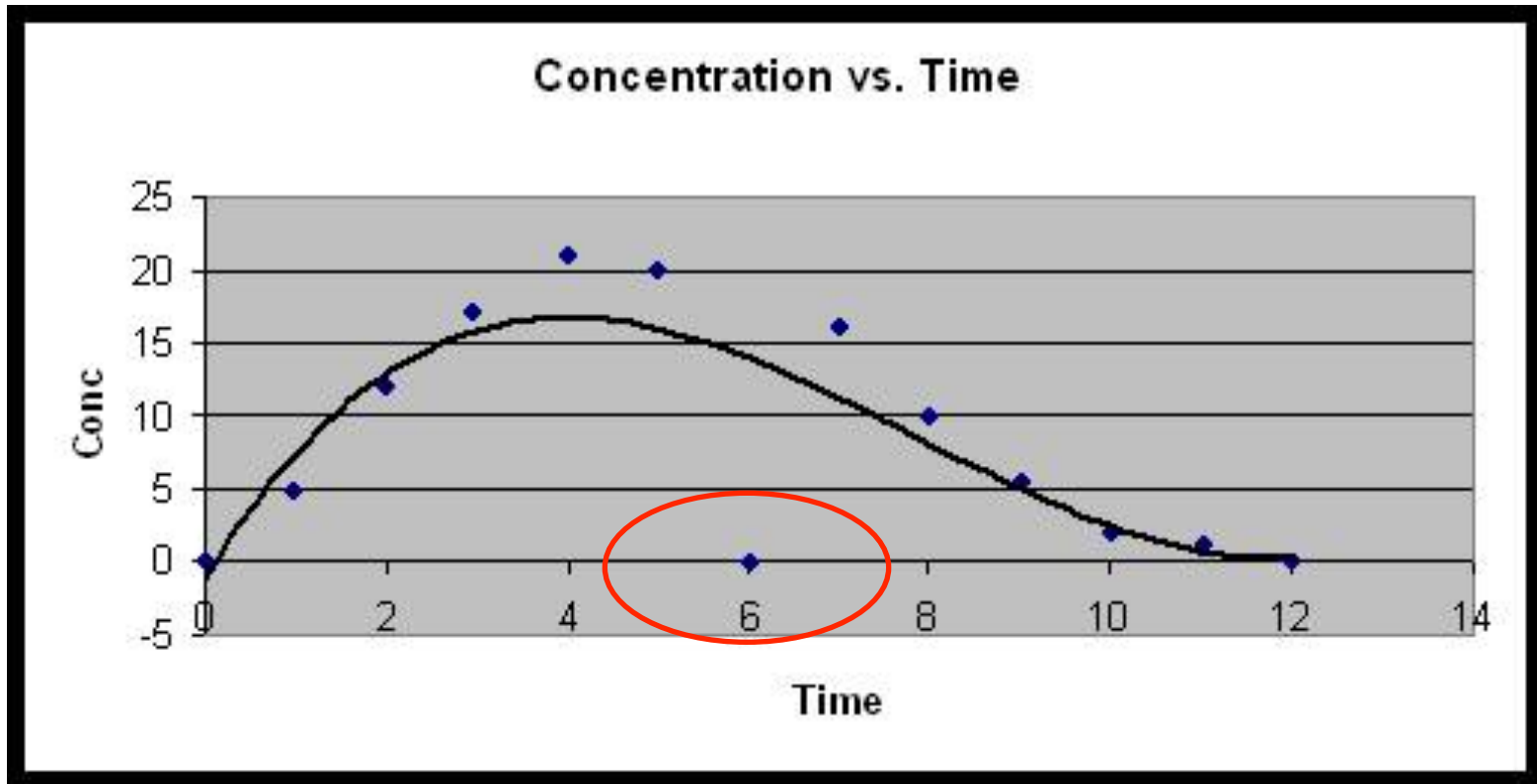
A) Outliers

- Standard 12 hours pharmacokinetic profile



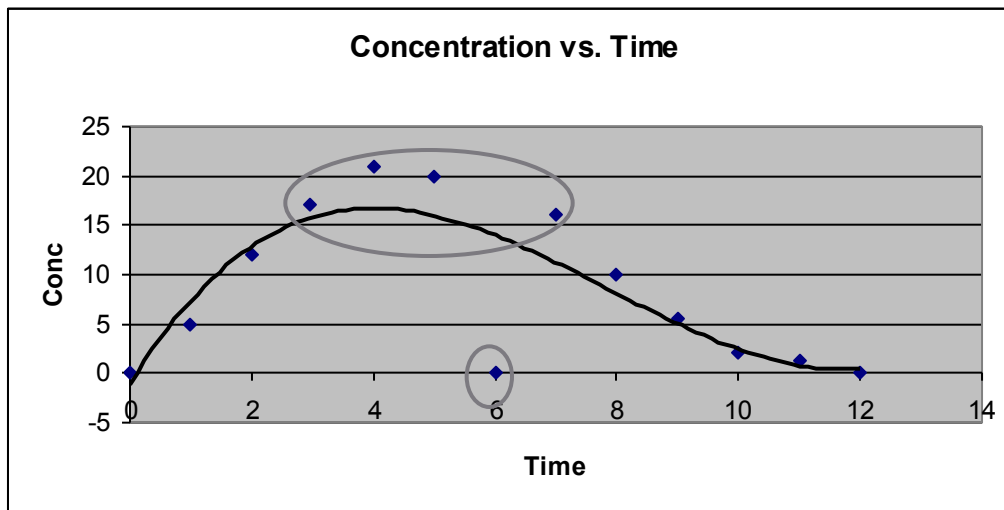
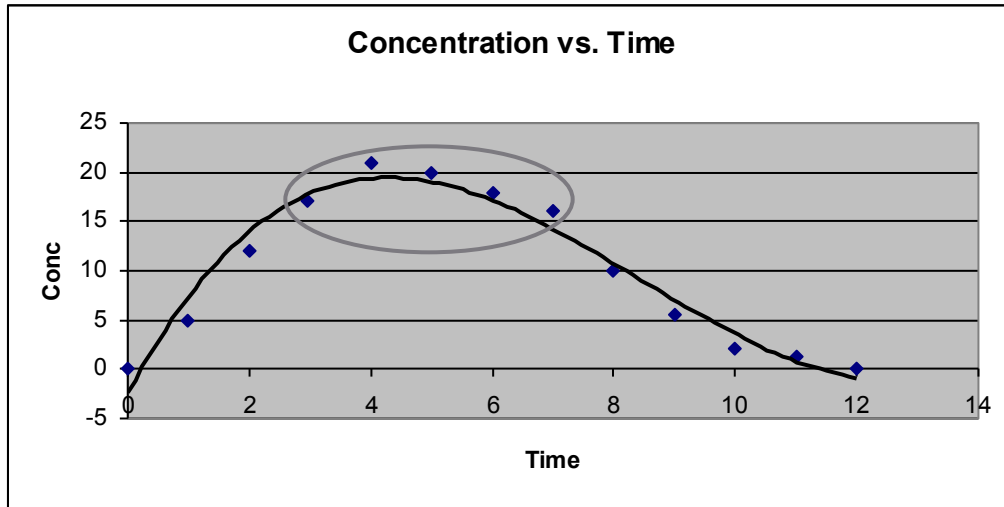
A) Outliers

- Now if one of the values is not correct

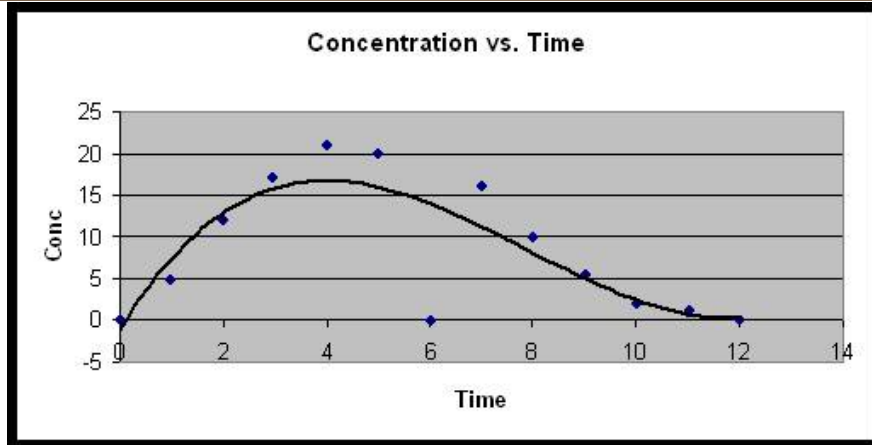


- The model that fits the data is different

A) Outlier



A) Outliers

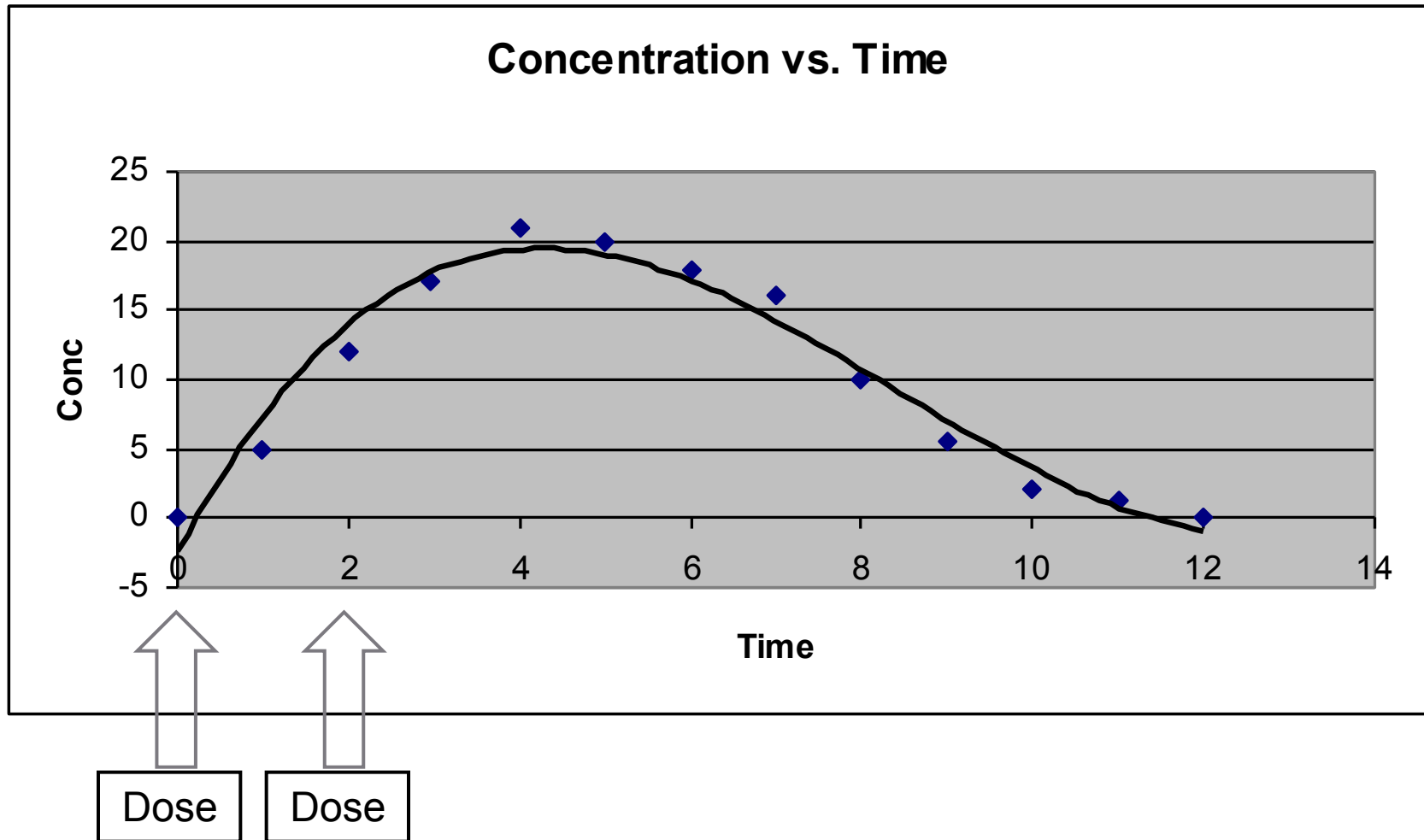


- Predictions based on the model likely to be incorrect
- What do you do, What is wrong?
- Time? Does this PK concentration belong to the 14 hours post-dose profile?
- PK concentration value? PK concentration Unit?

B) Data consistency

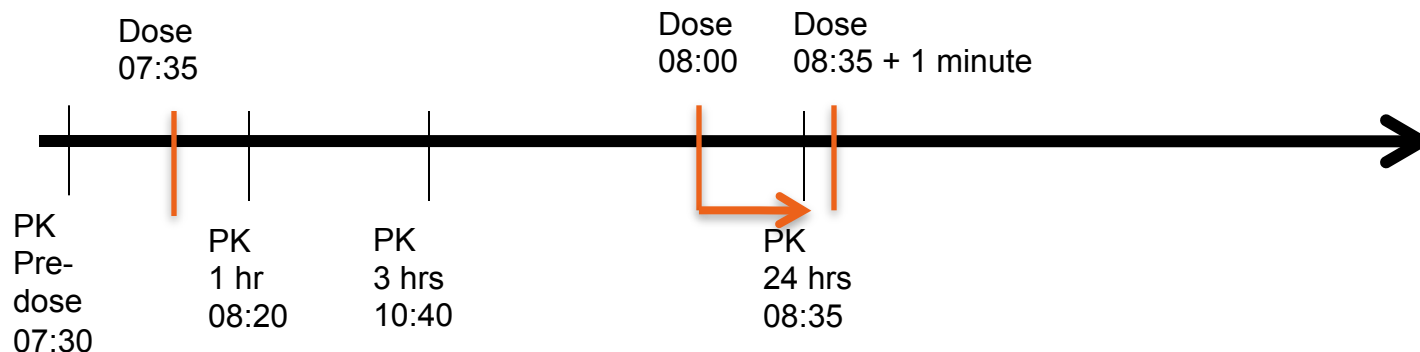
- We combine all types of data: dose history, PK, PD, adverse events, comedication....
- Because we combine all types of data, we'll identify discrepancies... That you may not identify without pooling all data together
- For a same patient, data needs to be coherent
-
- Example: positive PK concentrations before the first dose is a problem

B) Data consistency



C) Missing data

- Because not all data are known, you may need to impute some of them
- The time sequence in a modeling input dataset is critical
- For example: study where patients are treated for 6 months. We only collect the dose clock time at certain visits
- Cannot use one single default values for all patients (08:00)



D) Open entry fields in CRF

- In some clinical studies, you may find useful information in some of the open entry fields
- For example dose regimen
- Why?
- Because the database allow user to select dose regimen=other and allow user to type in what they want in the comment field like:
 - Mon Tue Wen every other week
 - Sat Sund
 -
- Because this information is key to us, we have to include it

Conclusions

- Data quality drives the quality of modeling results.
- If you do not pay attention to all potential data issues, you may lose some important information.
- The role of the modeling and simulation programmer is fundamental
- It's not just only about following a set of rules containing in the data set specification! It goes beyond that.