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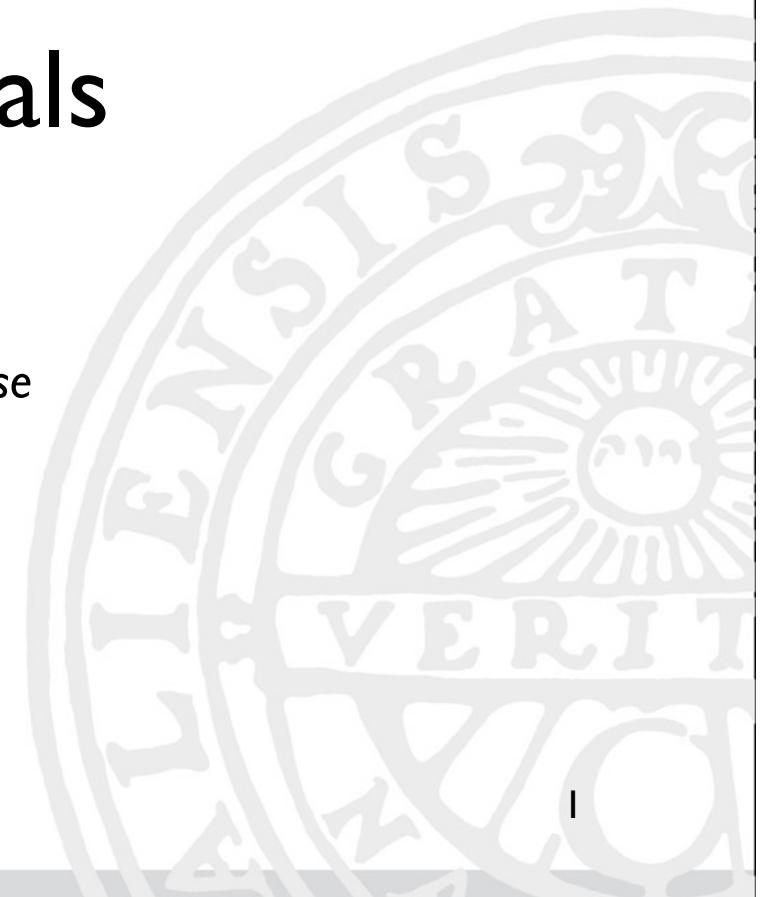
Modelling & Simulation of Clinical Trials

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Clin PKPD spring 2022

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Uppsala University*





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Outline

Learning objectives

- Why modelling (and simulation) of clinical trials?
- What does a model consist of?
- What does a clinical trial simulation consist of?
- How can drug development benefit from M&S?



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Modelling & Simulation

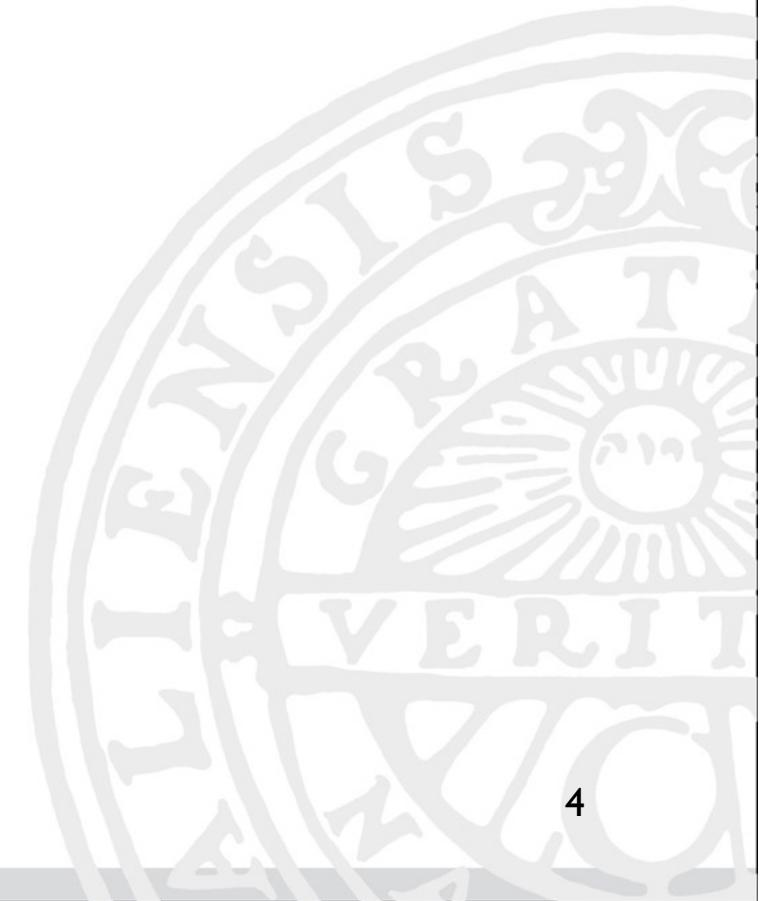
WHY M&S OF CLINICAL TRIALS?



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Why M&S?

For every winner, there are more losers



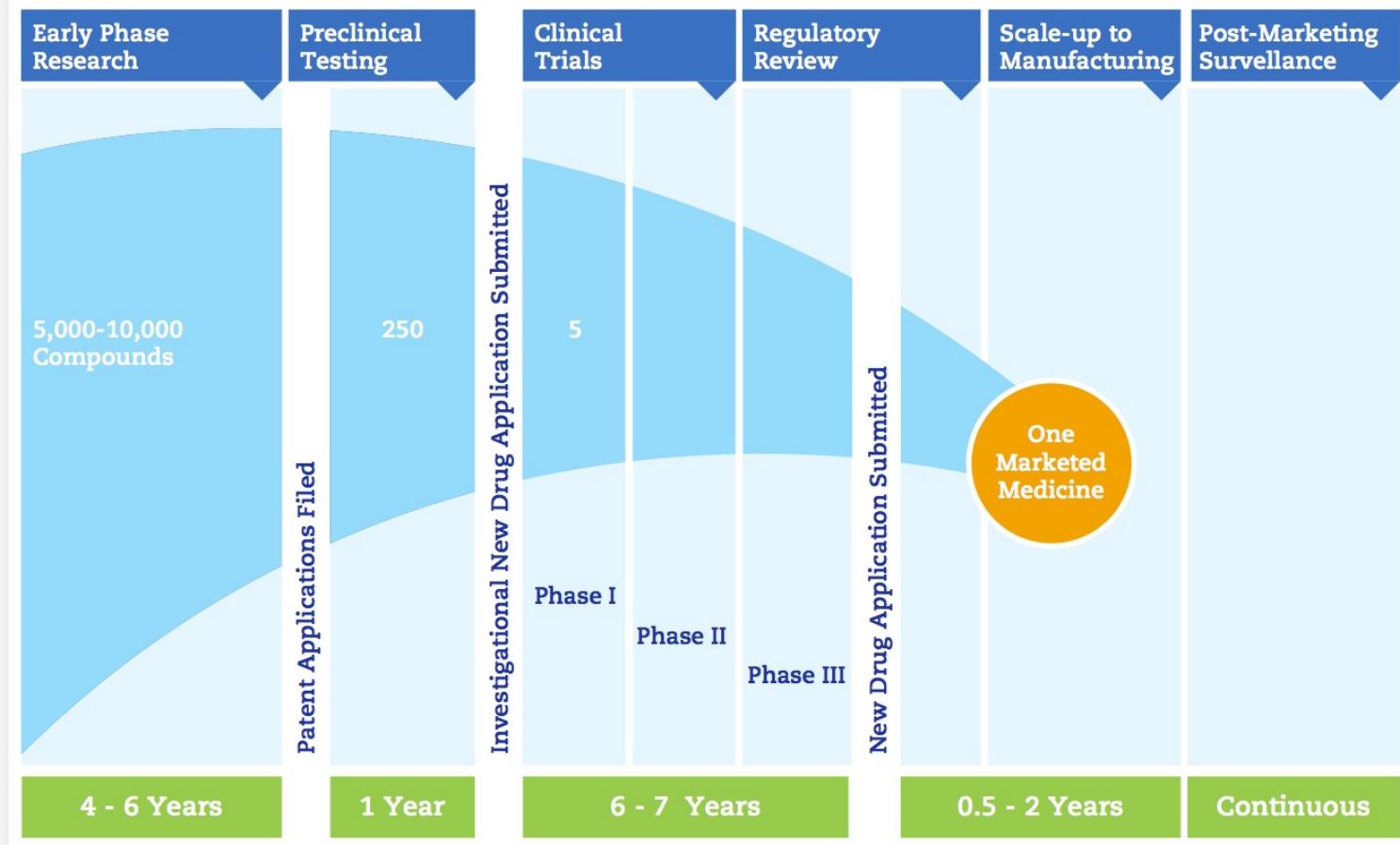


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Why M&S?

Drug development holds many risks...

Figure 1: The research and development process³



*IFPMA, Facts and Figures 2012. The Pharmaceutical Industry and Global Health

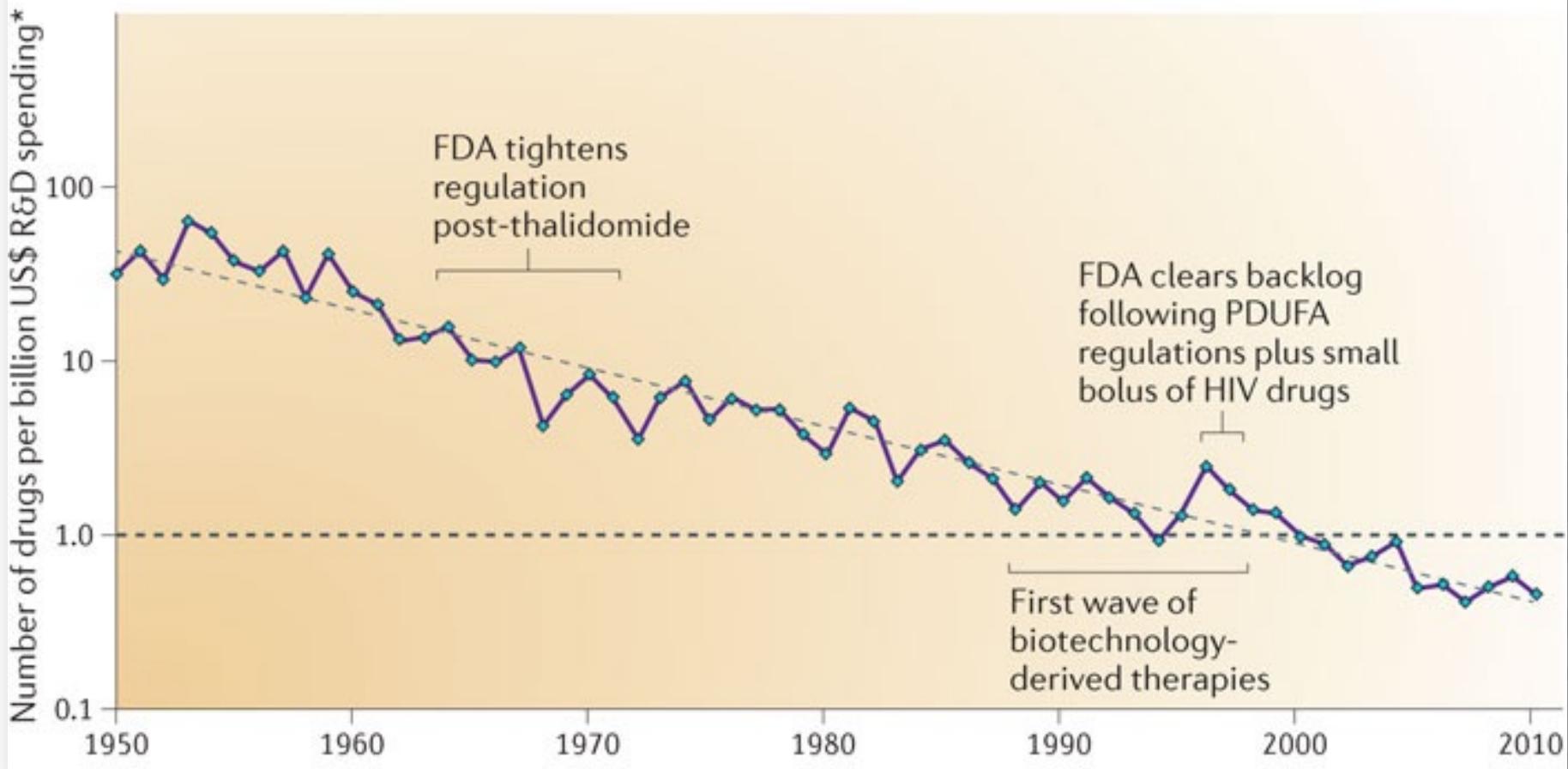


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Why M&S?

Probably no news for you, drug development is expensive

a Overall trend in R&D efficiency (inflation-adjusted)



*Scannell JW et al. Nature Rev Drug Disc, 2012; 11: 191-200.



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Why M&S?

Late failures and uninformative trials contribute to expensive DD

Drug d.

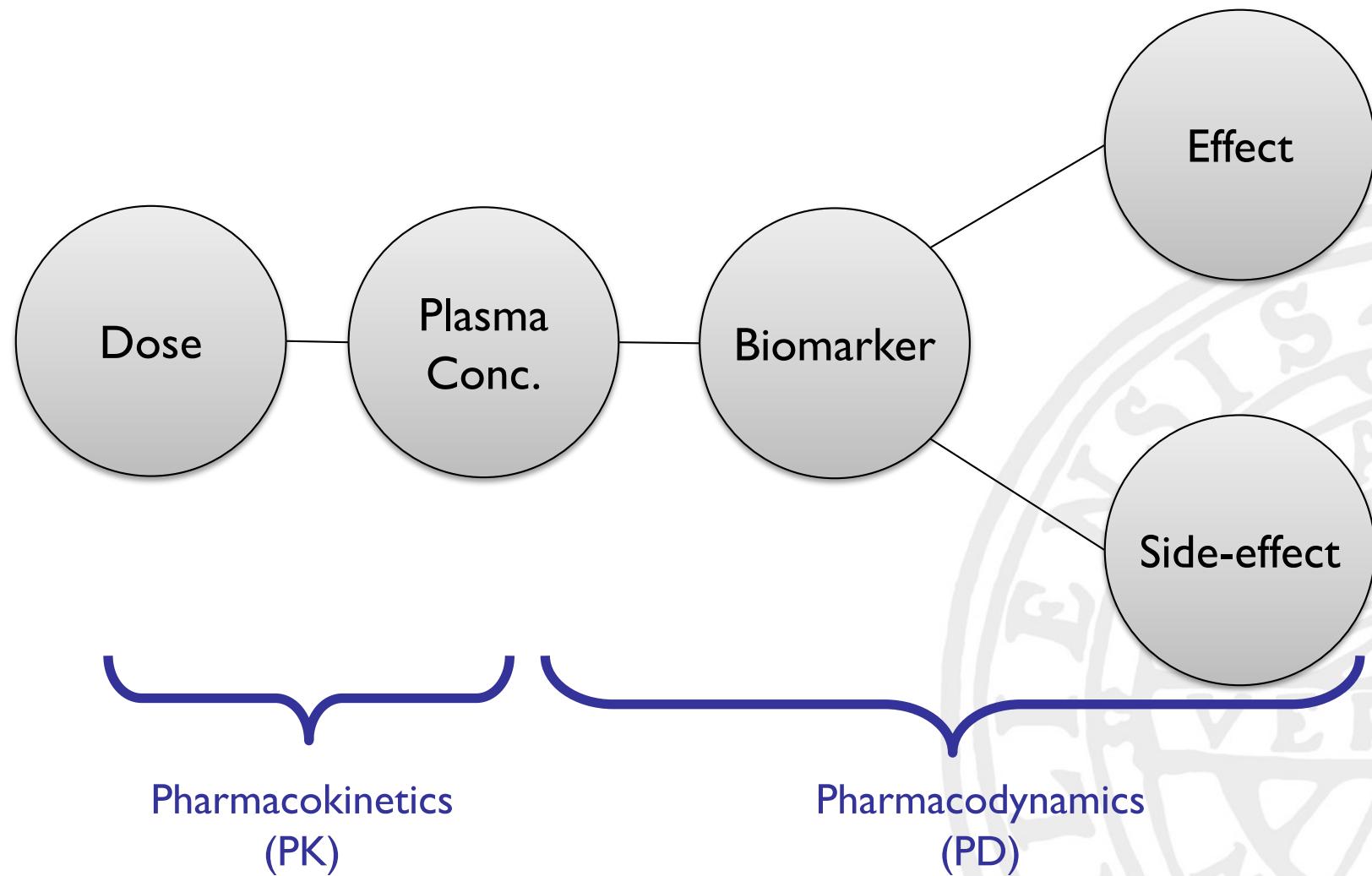
Many of these challenges can be handled through modelling and simulations! Could be made more efficient!

- Fewer, smaller studies – requires good design
- Early assessment of individualization – requires identification of important effects
- Earlier kills – requires early assessment of achievable effects
- Assess certainty of changes in disease effects over time – measurement of how confident we are in certain outcome



Modelling

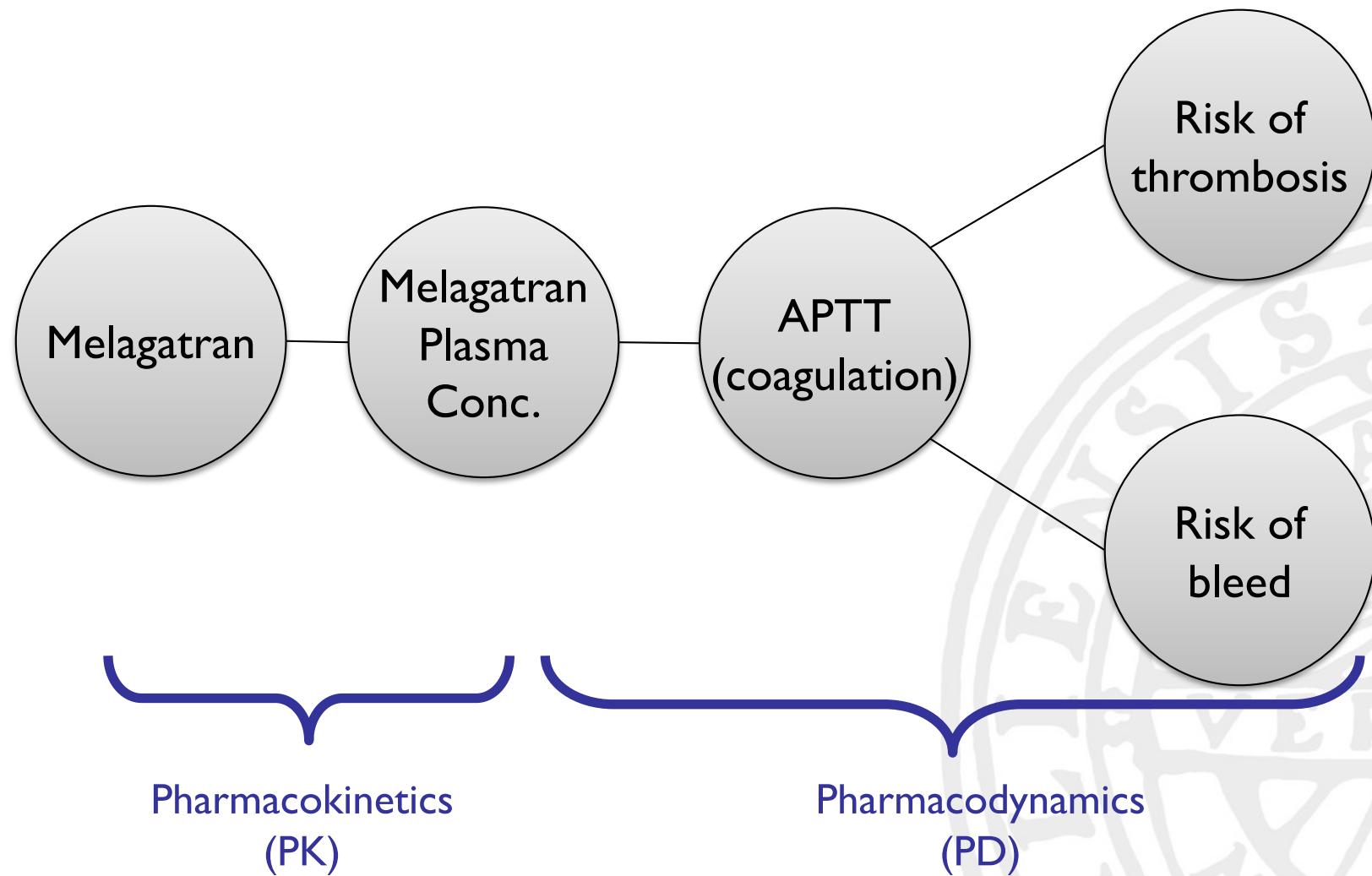
Principles of PK and PD: describing dose → effect/side-effect





Modelling

Principles of PK and PD: describing dose → effect/side-effect

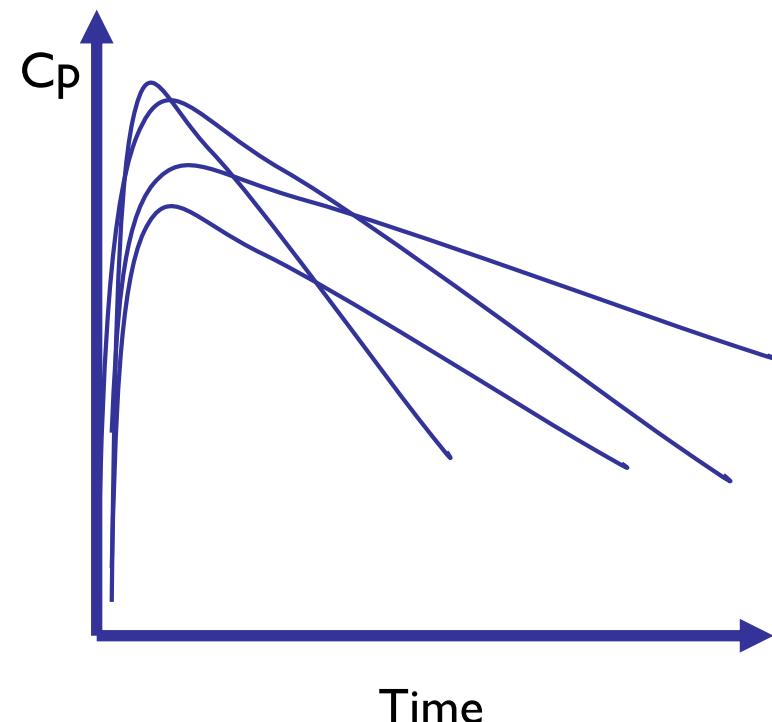
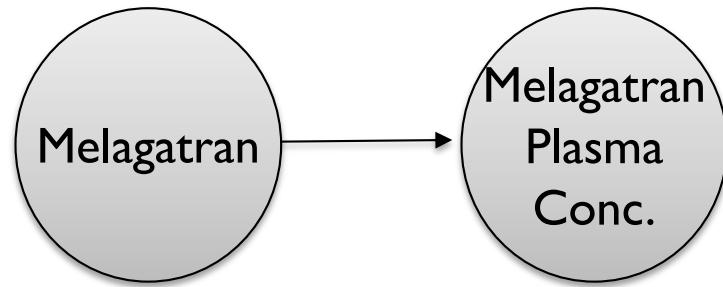




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Modelling

PK model describes main trend and variability



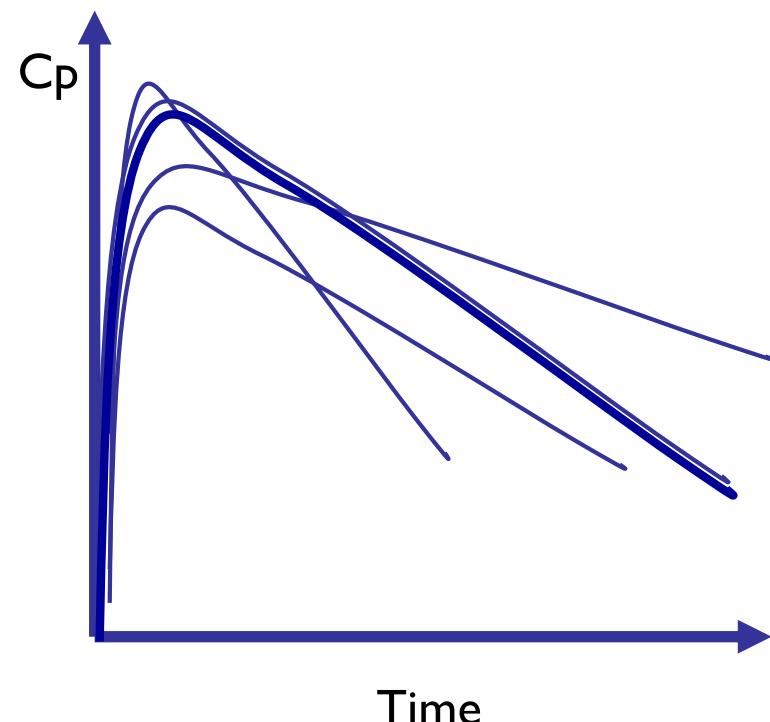
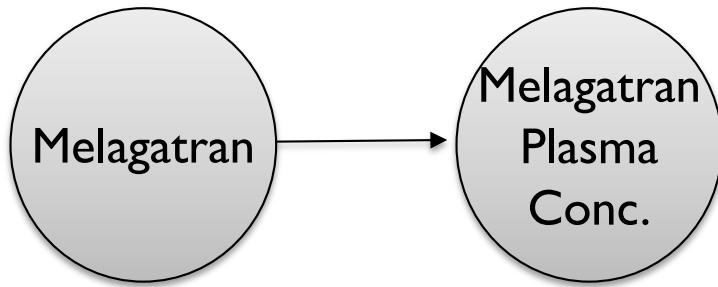
The PK Model describes



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Modelling

PK model describes main trend and variability



The PK Model describes

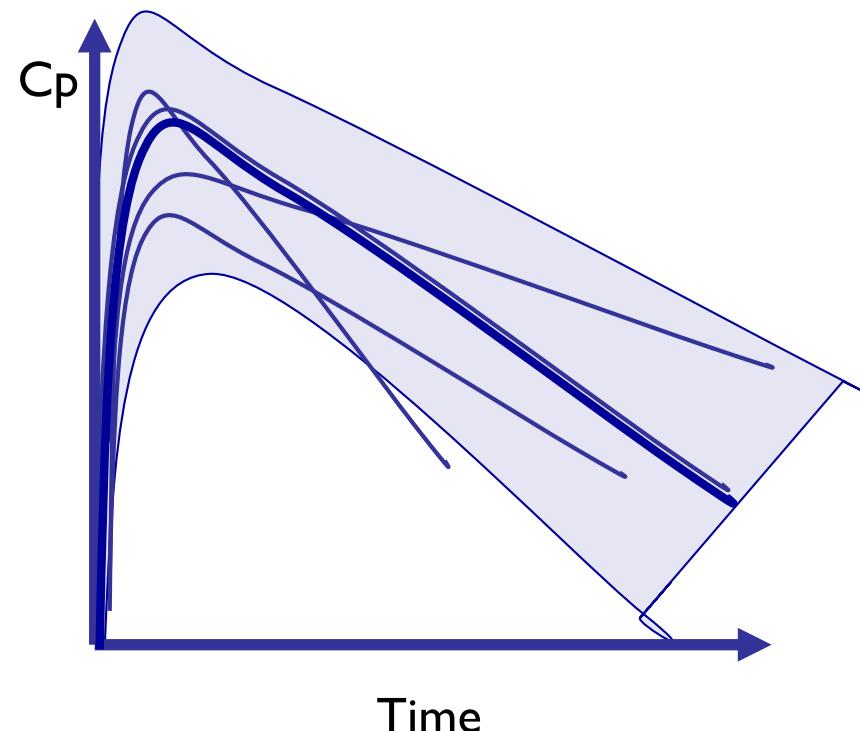
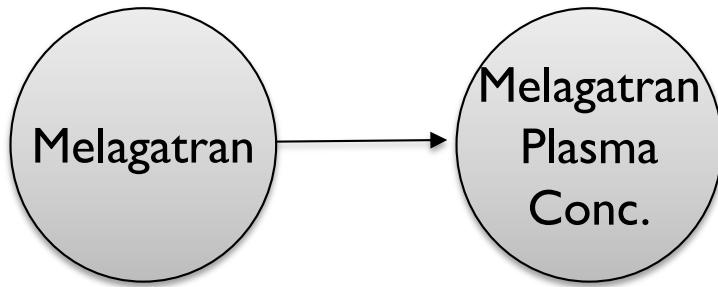
- Time-course of conc.



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Modelling

PK model describes main trend and variability



The PK Model describes

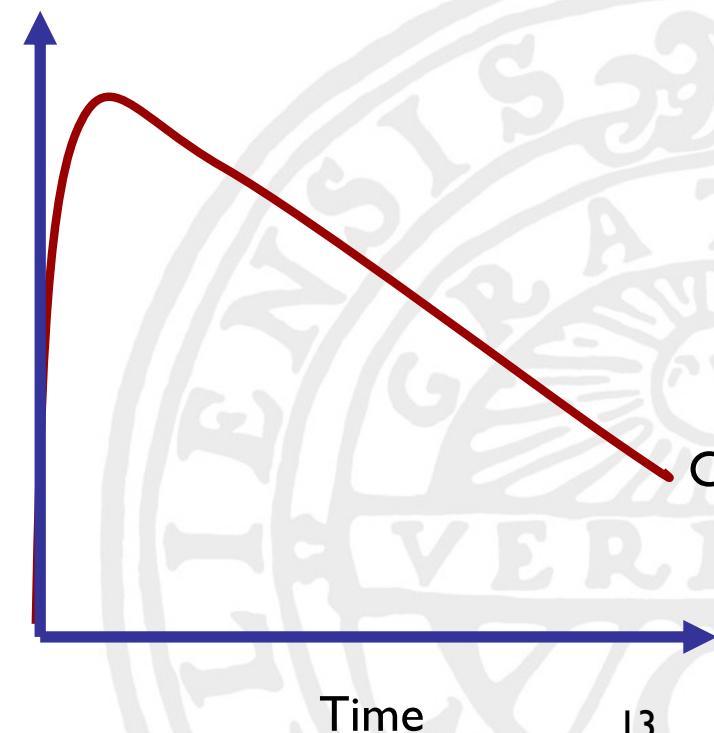
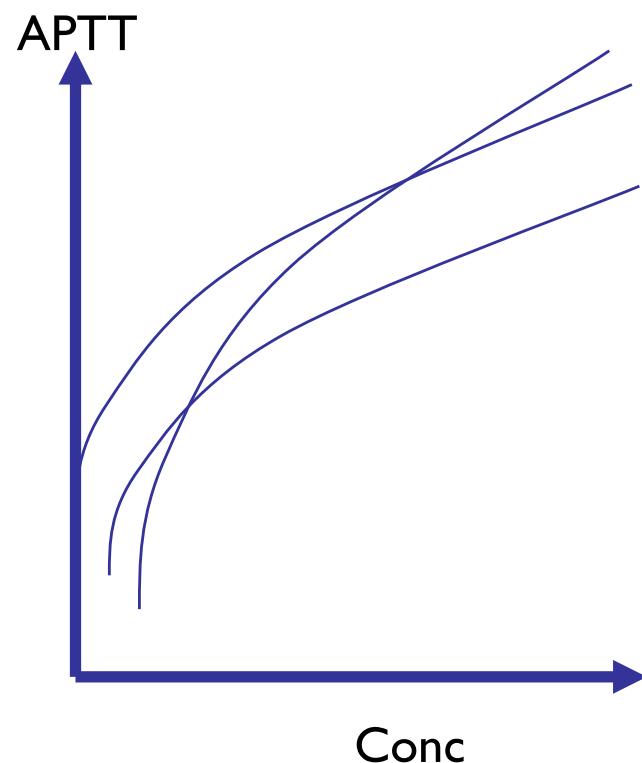
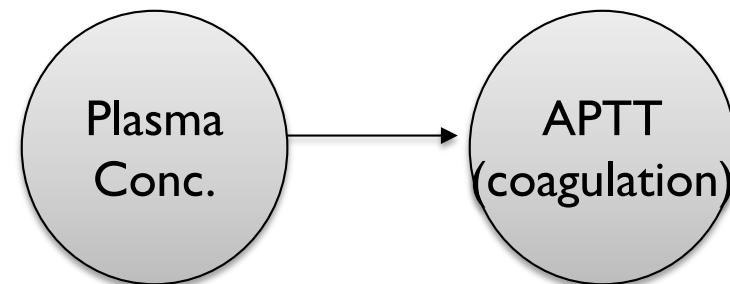
- Time-course of conc.
- Variability in conc.



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Modelling

PD model describes concentration vs. biomarker

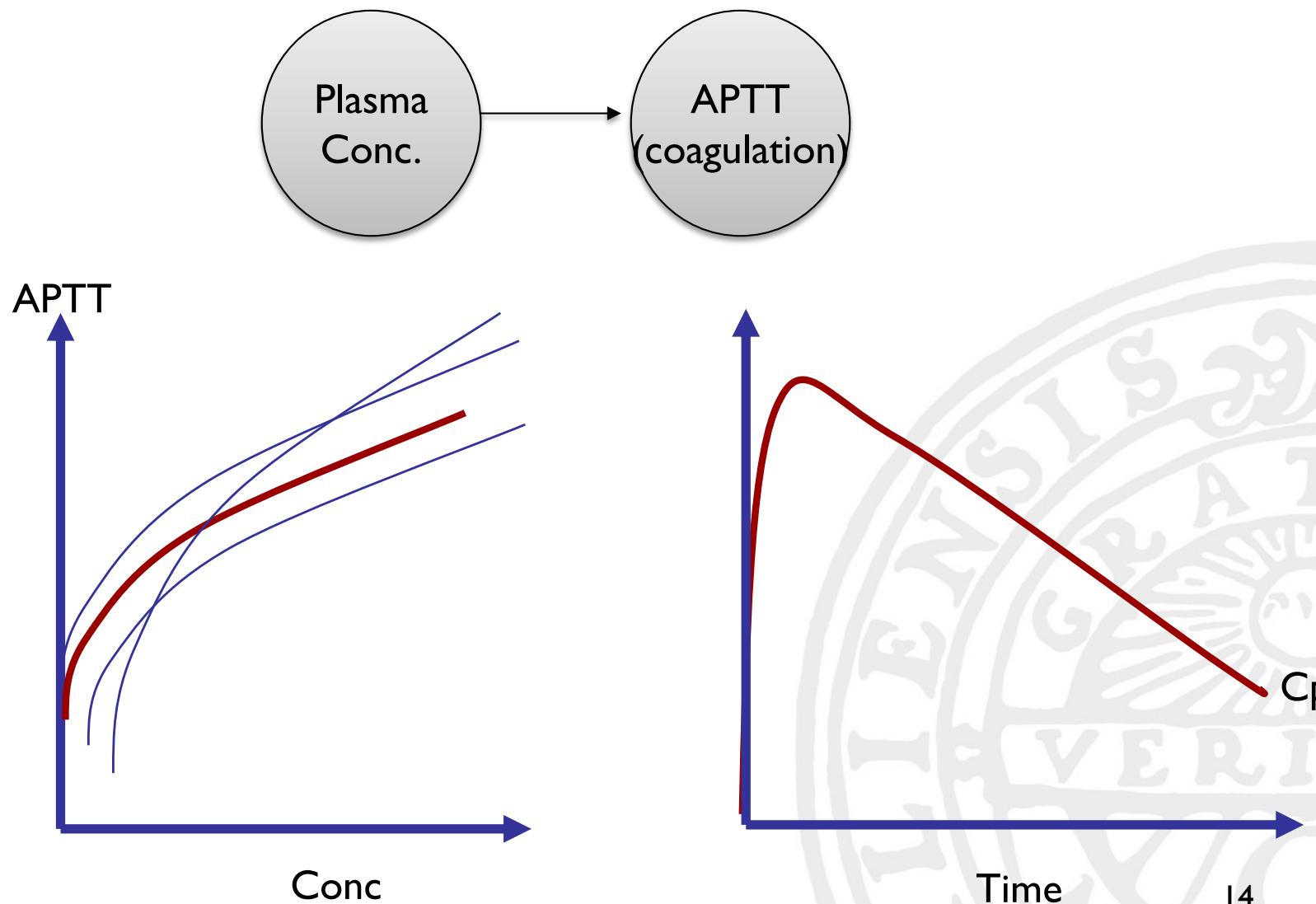




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Modelling

PD model describes concentration vs. biomarker

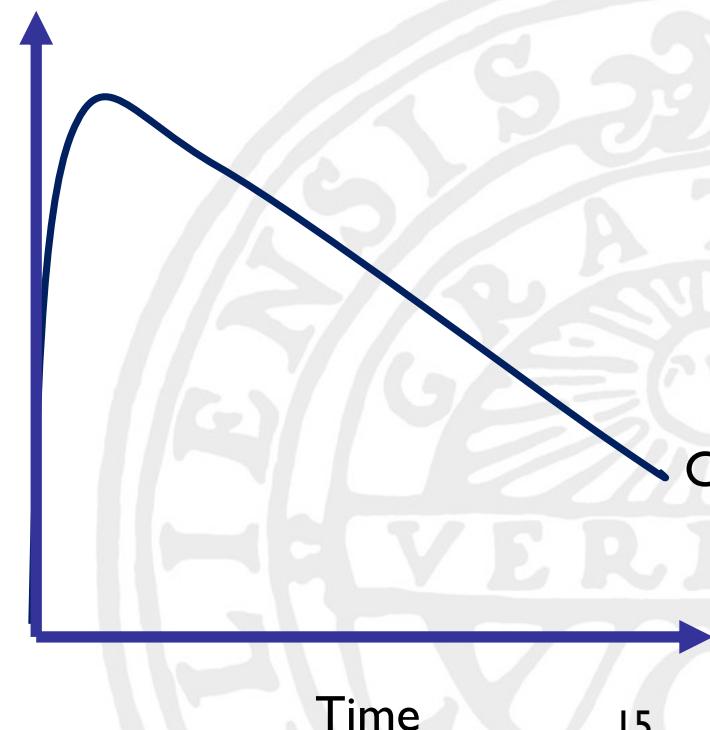
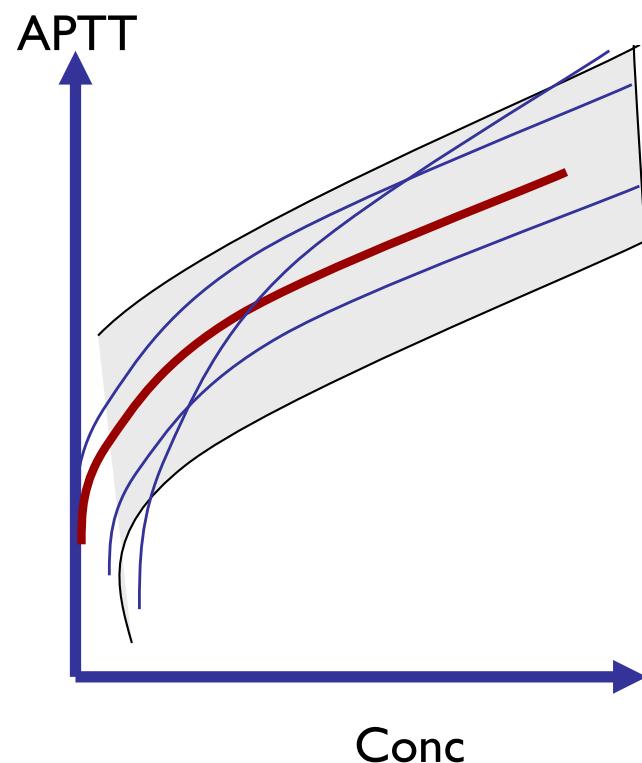
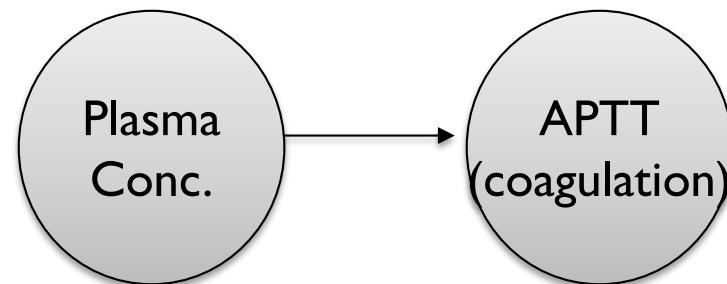




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Modelling

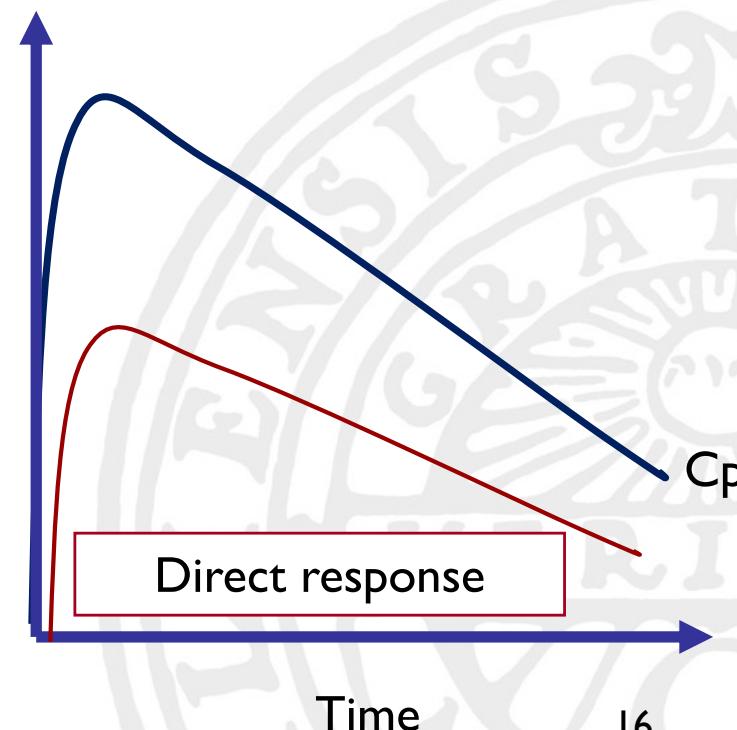
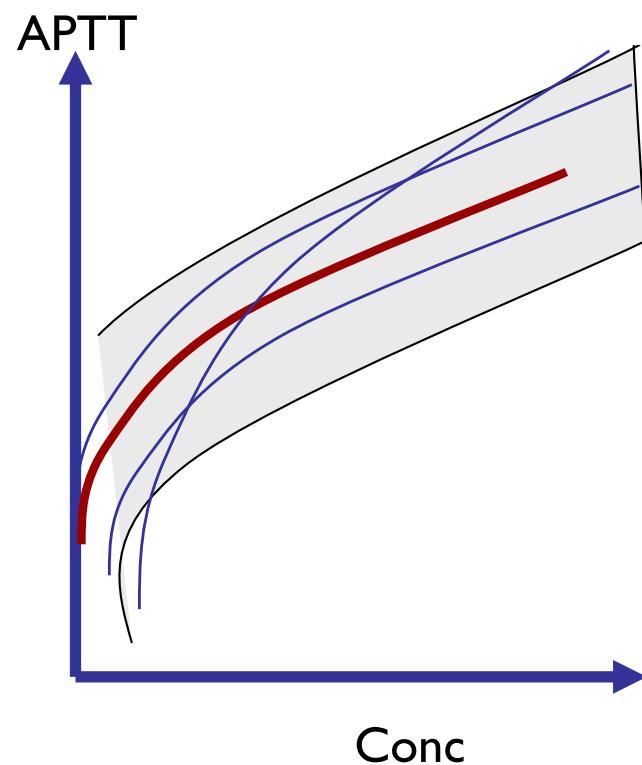
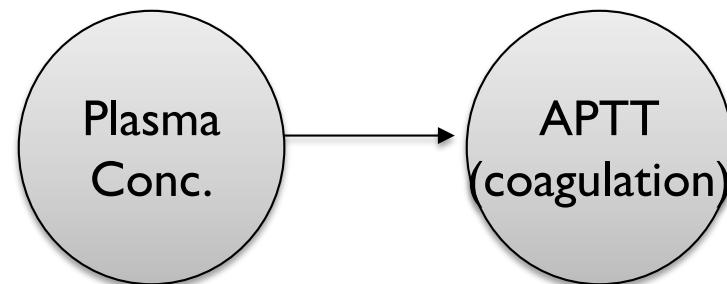
PD model describes concentration vs. biomarker





Modelling

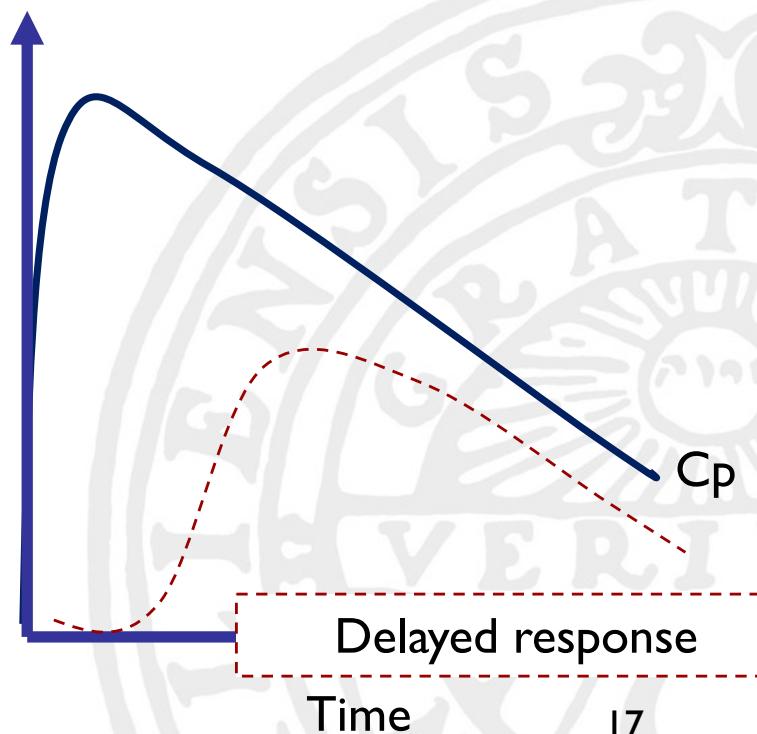
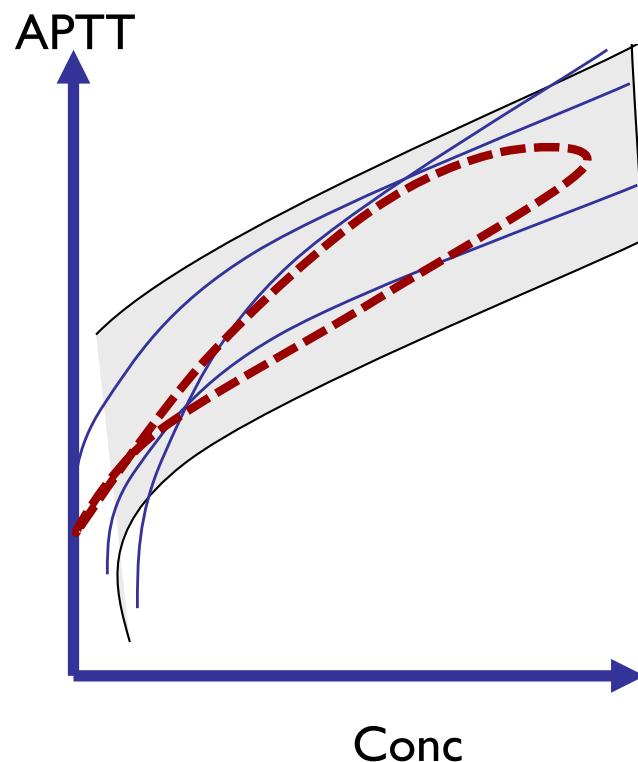
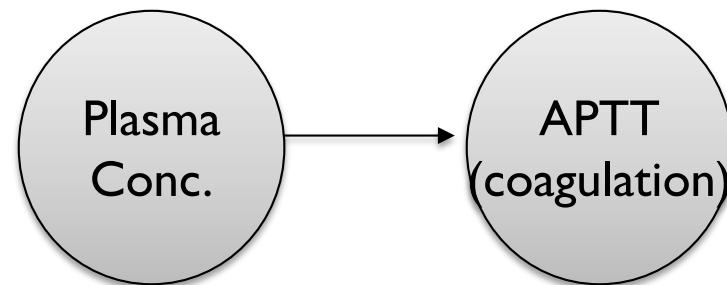
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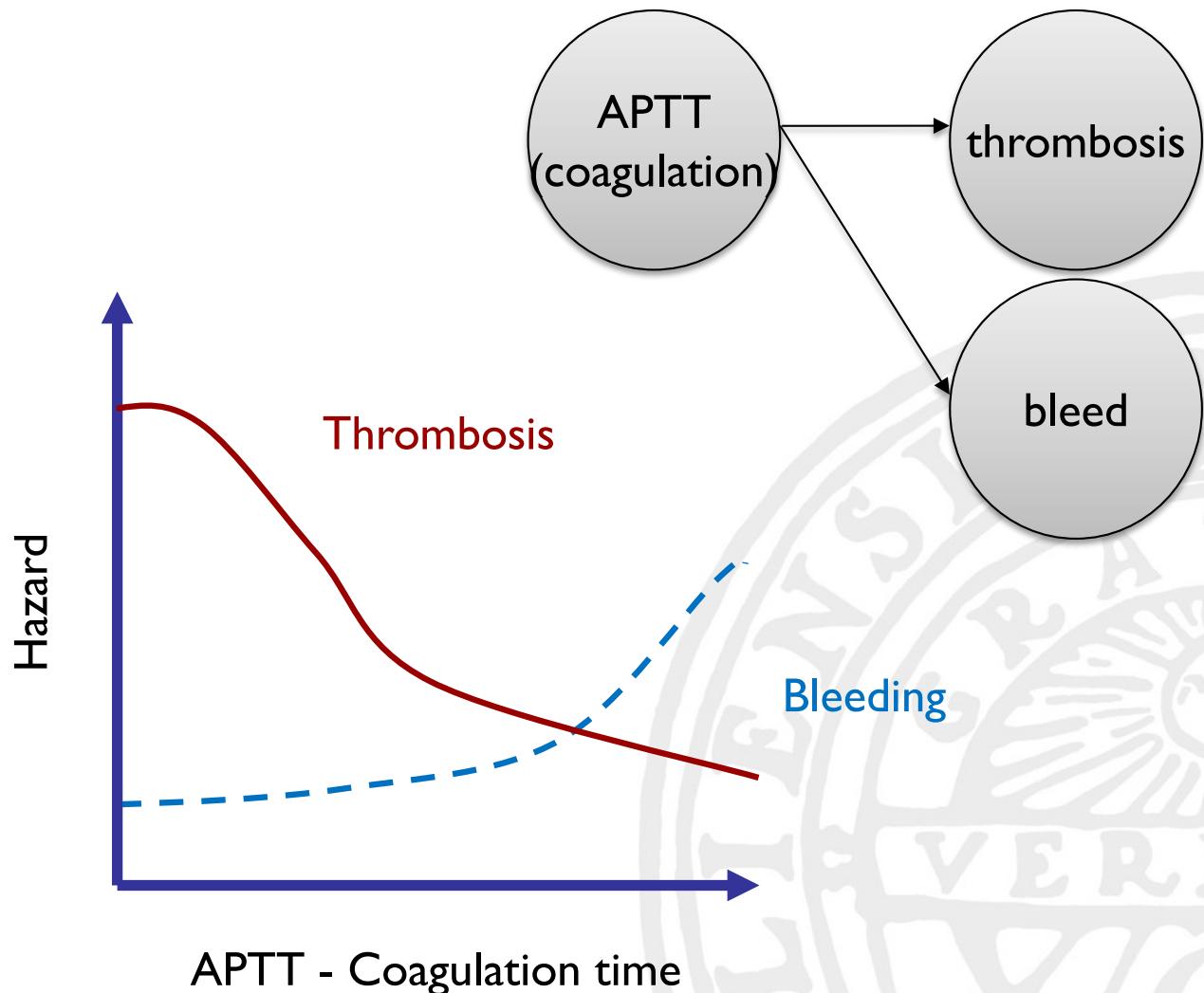
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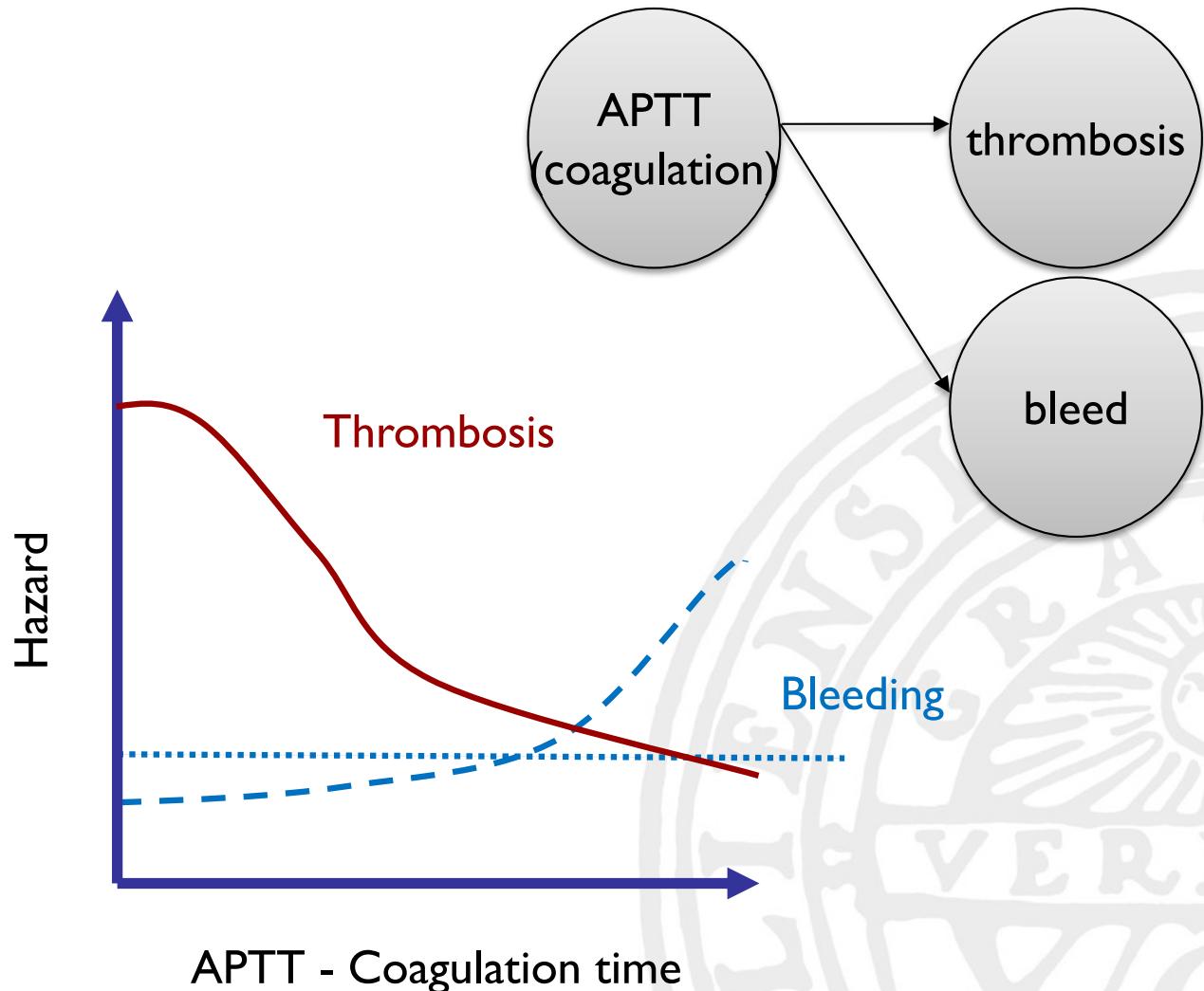
Biomarker model describes biomarker vs. effect/side-effect





Modelling

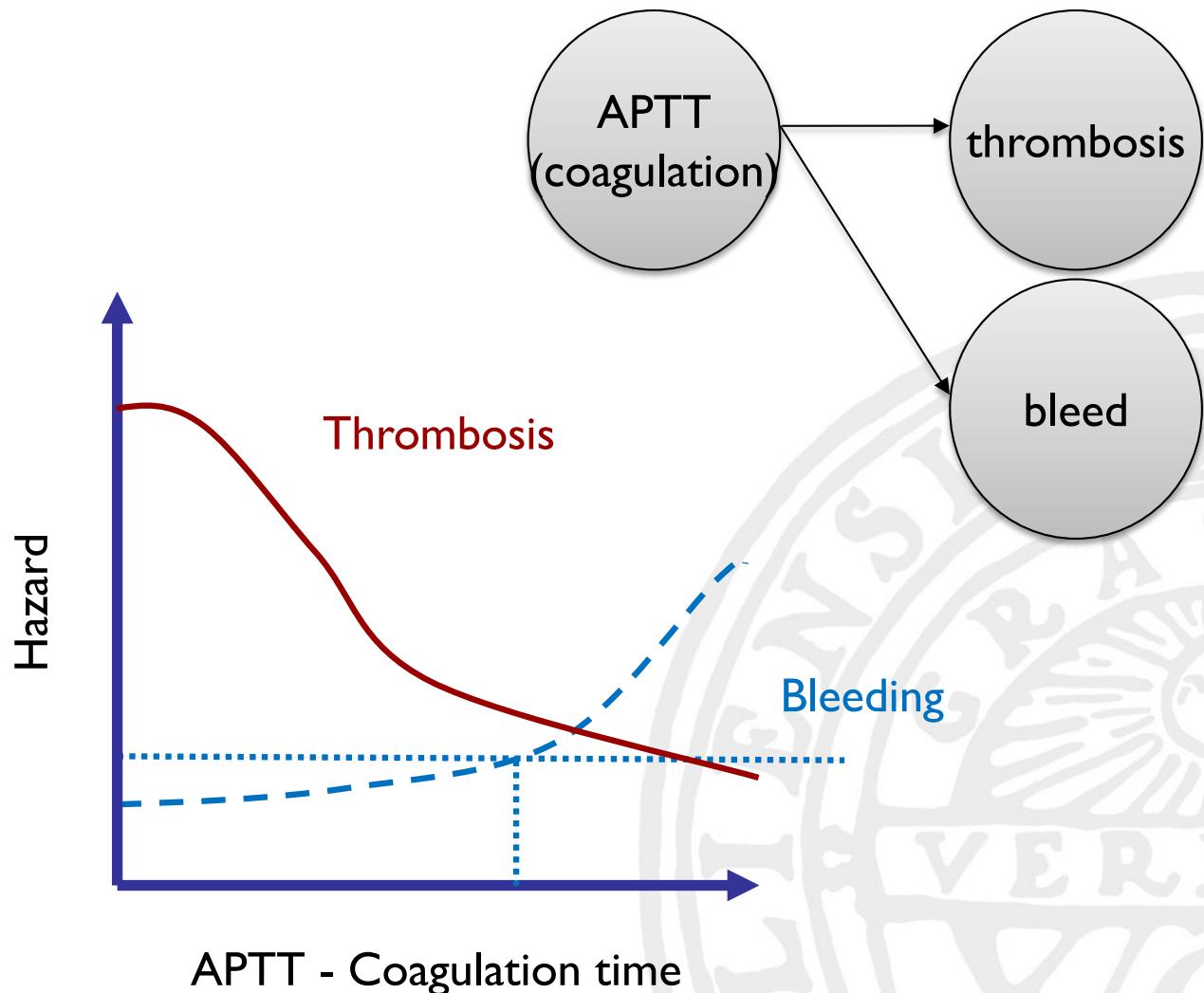
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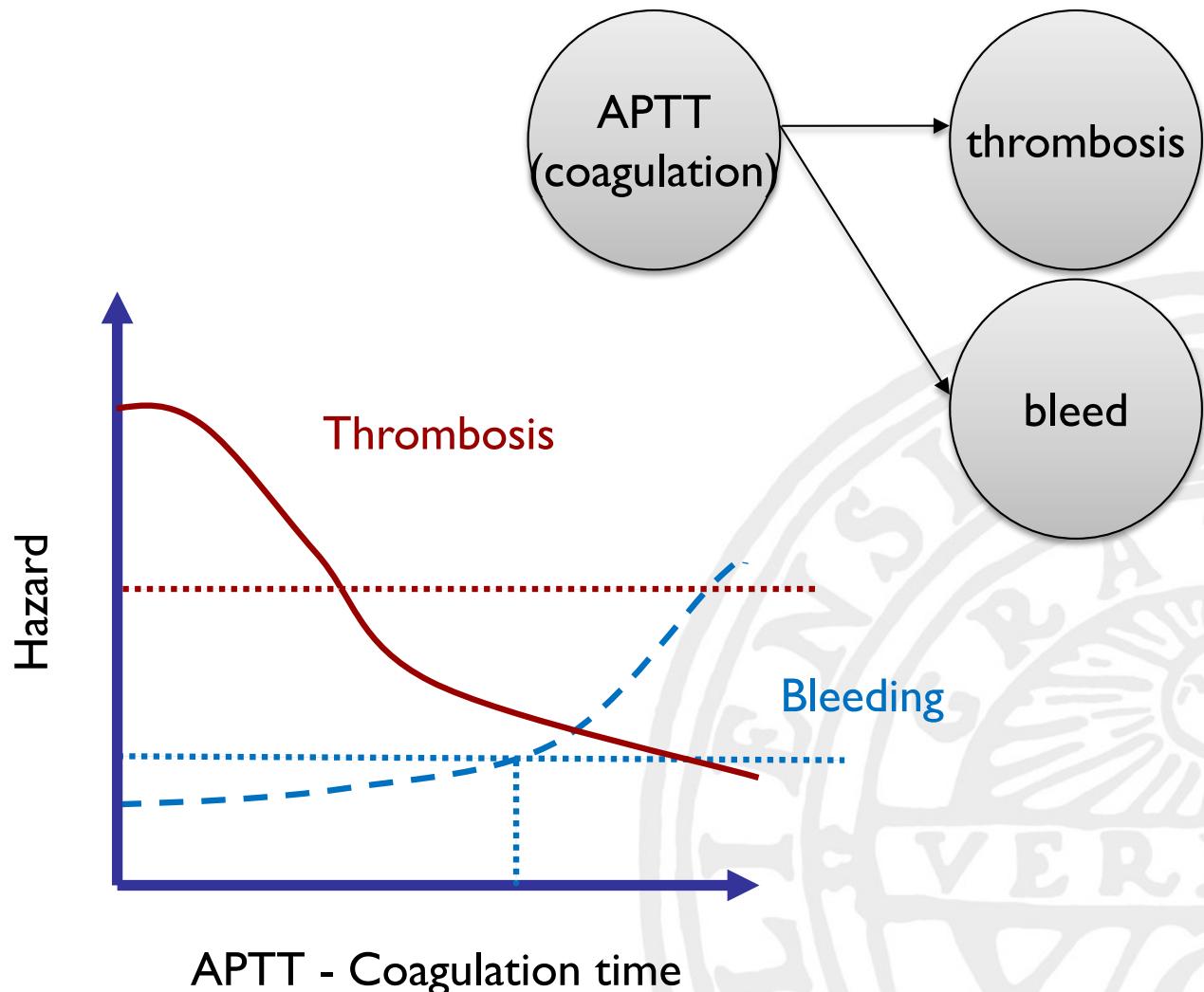
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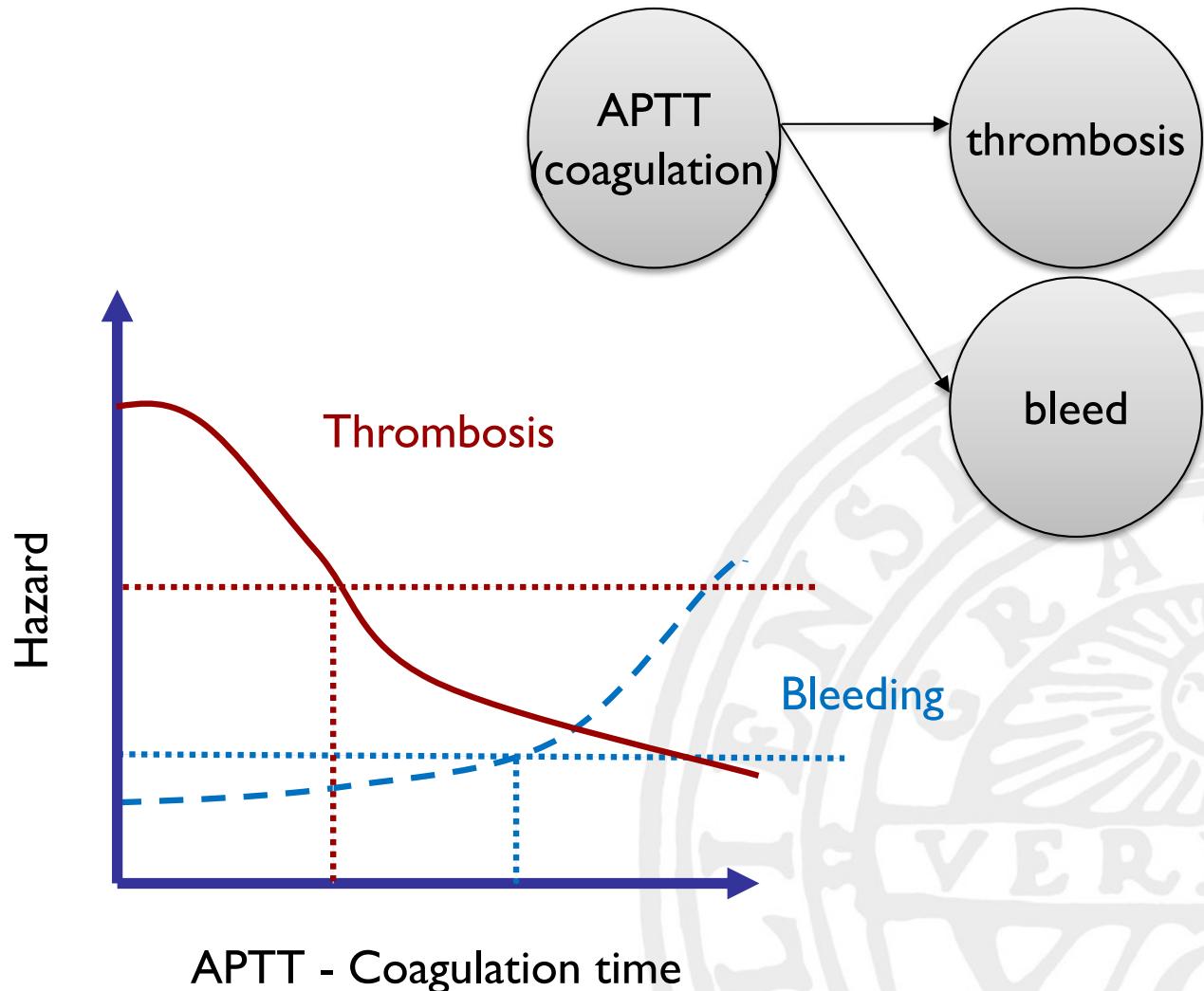
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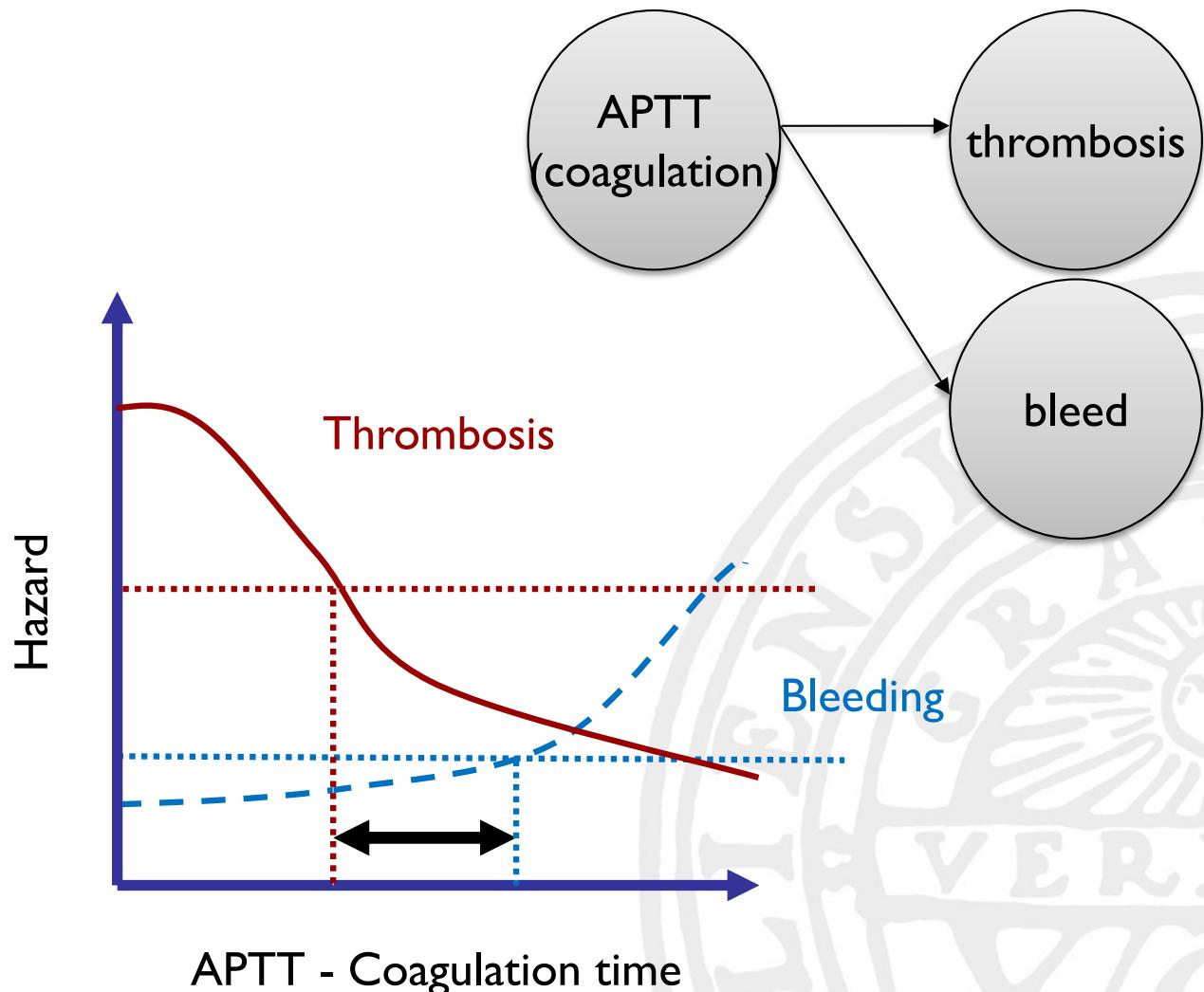
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Modelling

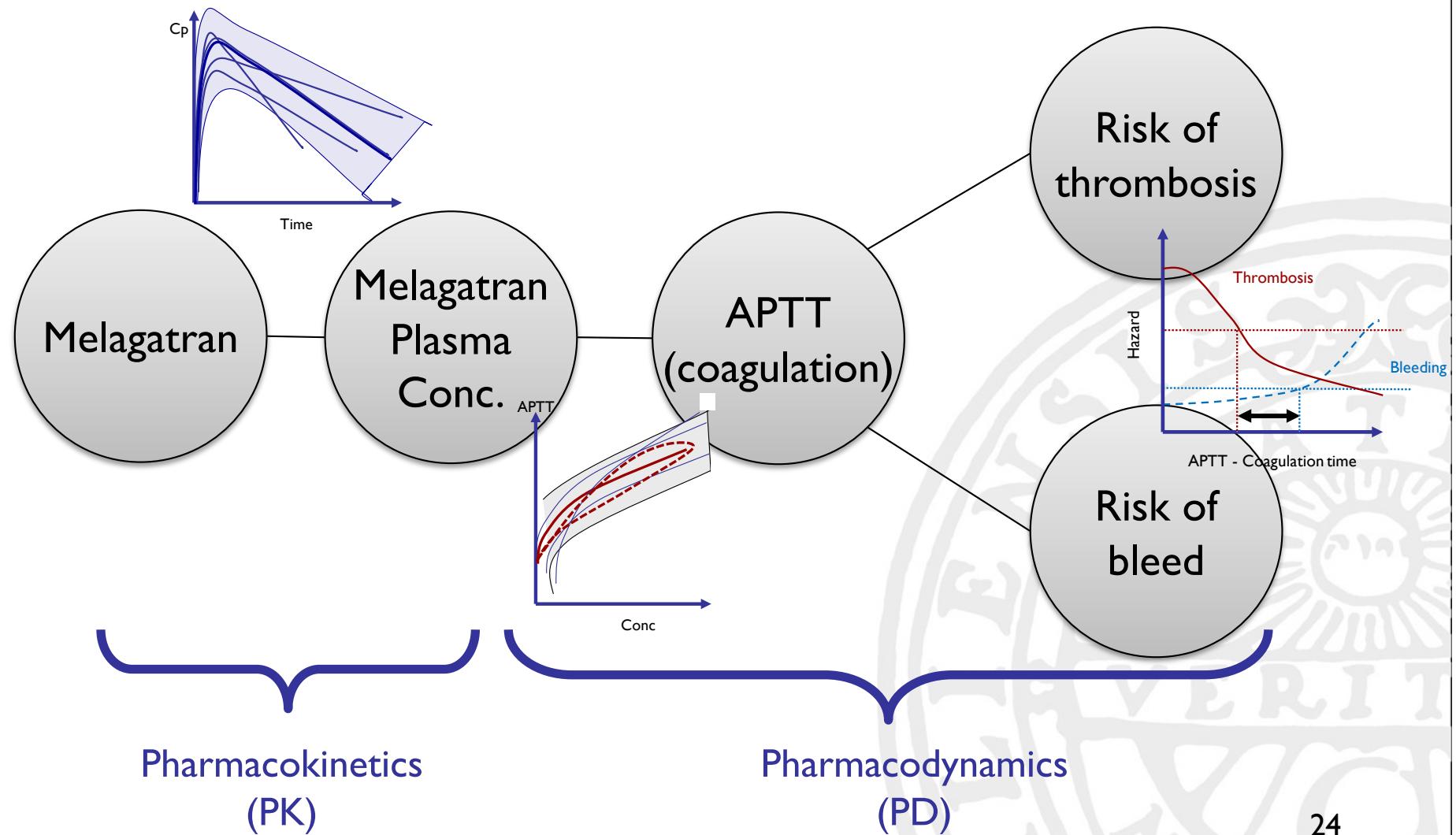
Biomarker model describes biomarker vs. effect/side-effect





Modelling

Example: Thrombin inhibitor





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Modelling

WHAT DOES A MODEL CONSIST OF?





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The model components

A model consists of several components

- Structure - shape
- Parameters - magnitude
- Unexplained variability in parameters –
Inter-Individual variability
- Unexplained variability in sample –
Residual error
- Relationships between parameters and patients characteristics (covariates)
- Uncertainty in models and parameters

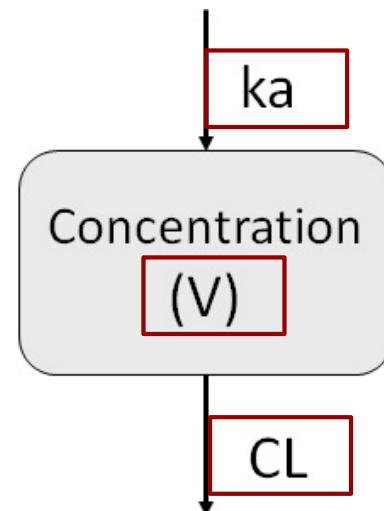


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The model components

Example of structures with associated parameters

- PK: One-compartment with 1st order absorption
 - CL, V, F, ka (oral and IV data)
 - CL/F, V/F, ka (oral data only)





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The model components

Example of structures with associated parameters

- PD: Emax model with baseline
 - Baseline, EC₅₀, E_{max}

$$Effect = \boxed{Baseline} + \frac{\boxed{E_{\max}} \cdot Conc}{\boxed{EC_{50}} + Conc}$$



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The model components

A model consists of several components

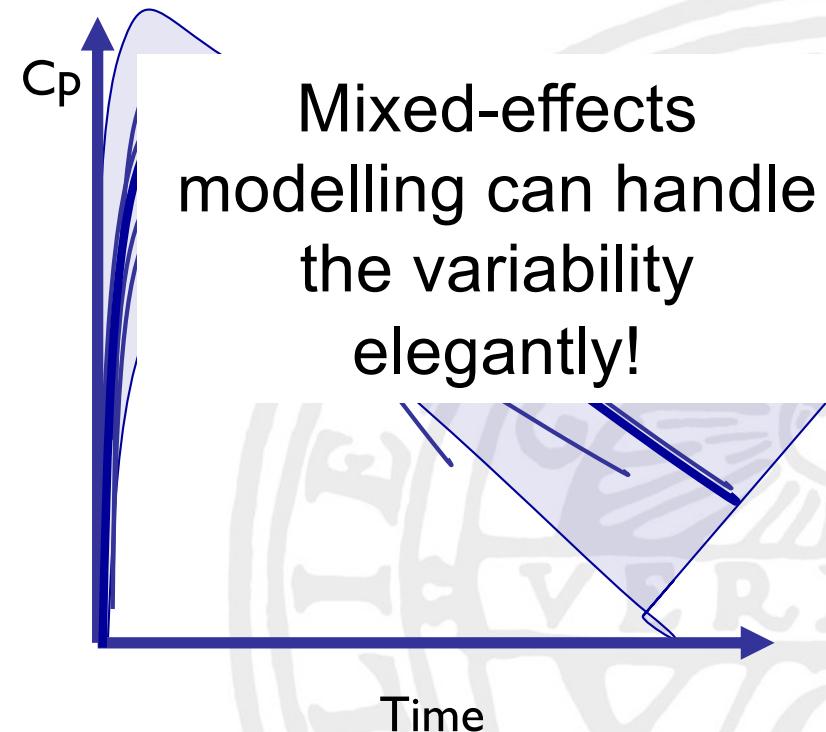
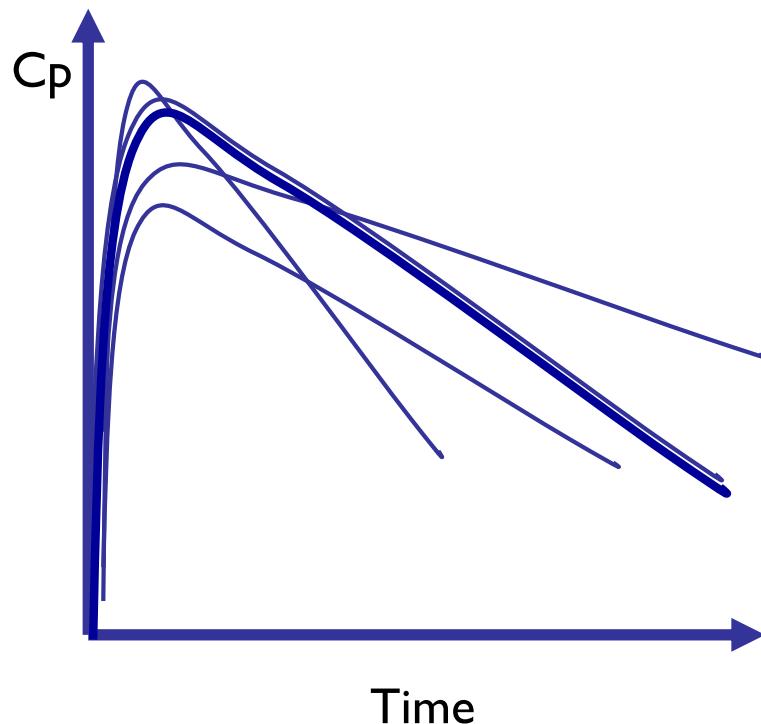
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The model components

PK model describes main trend through typical parameters but what about differences between individuals?





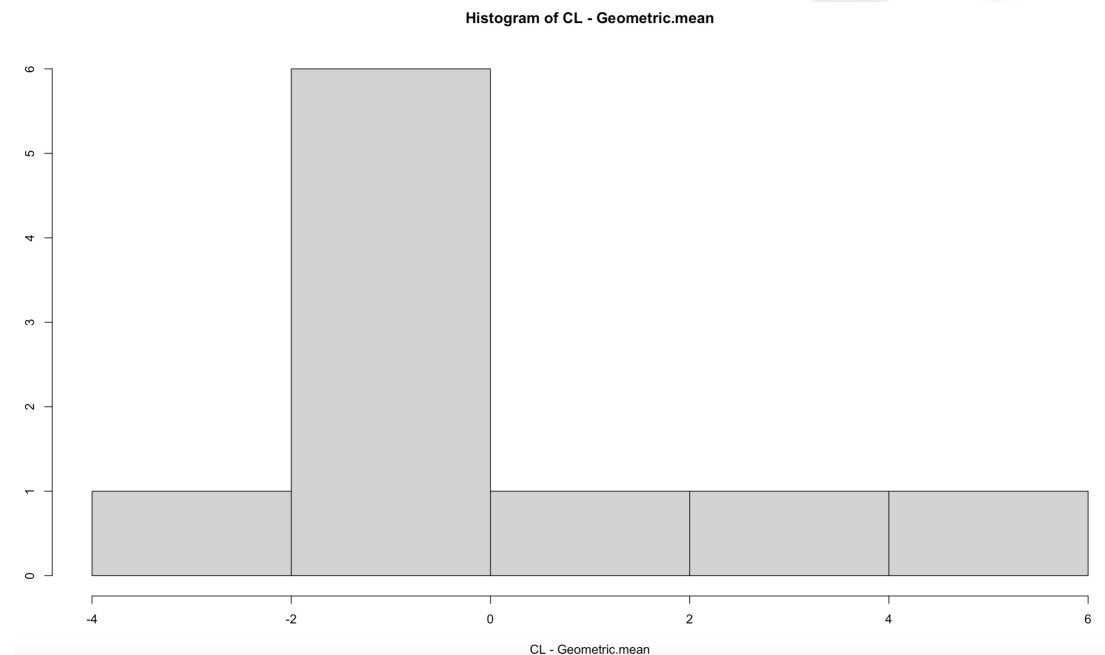
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The model components

*Between-individual variability describe difference in parameters
between individuals*

Person	Clearance (L/h)
1	3.62
2	5.63
3	4.84
4	4.18
5	3.52
6	10.2
7	7.81
8	5.00
9	4.83
10	2.81

Geometric mean = 5 L/h

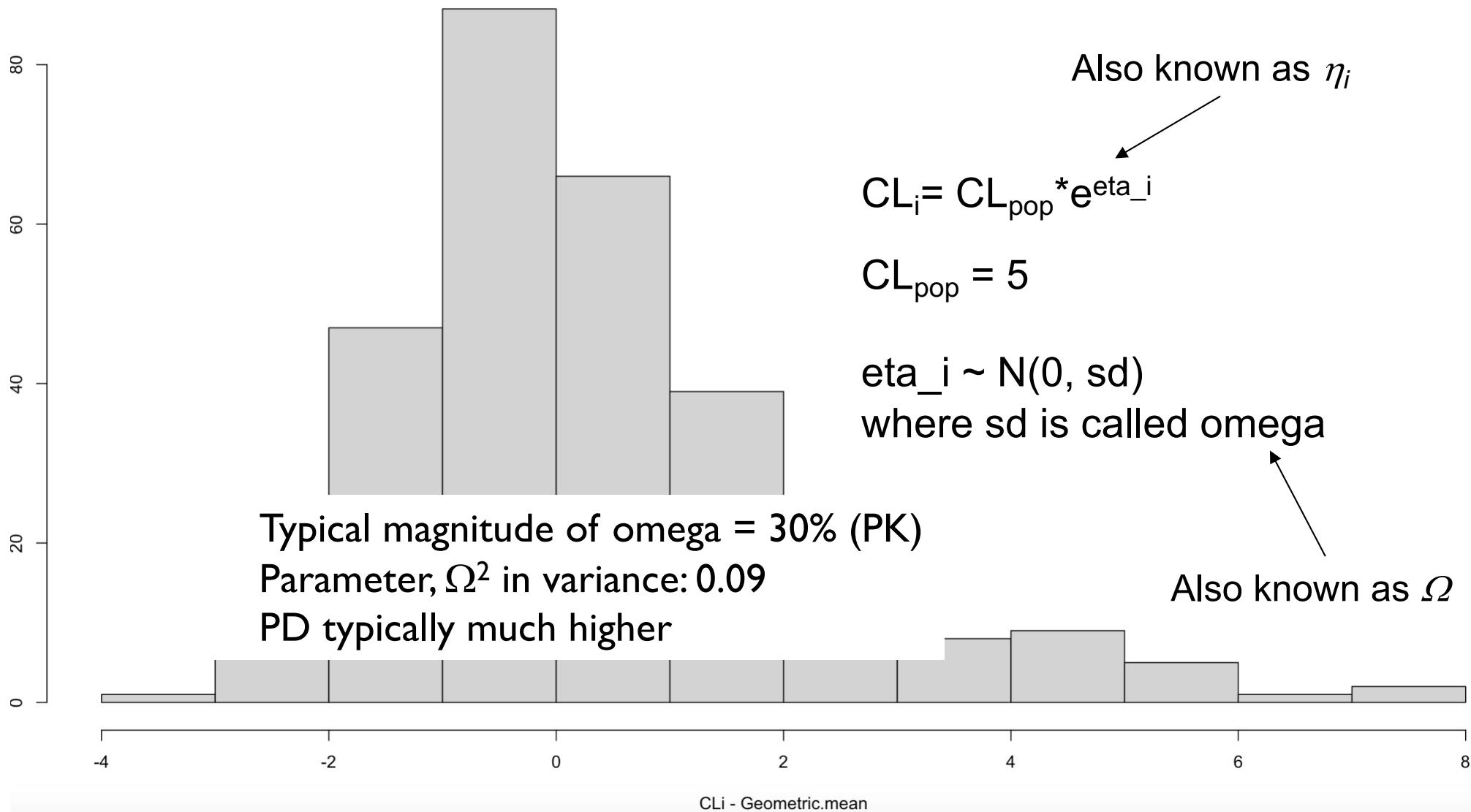




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The model components

*Between-individual variability describe difference in parameters
Histogram of CL_i - Geometric.mean
between individuals*

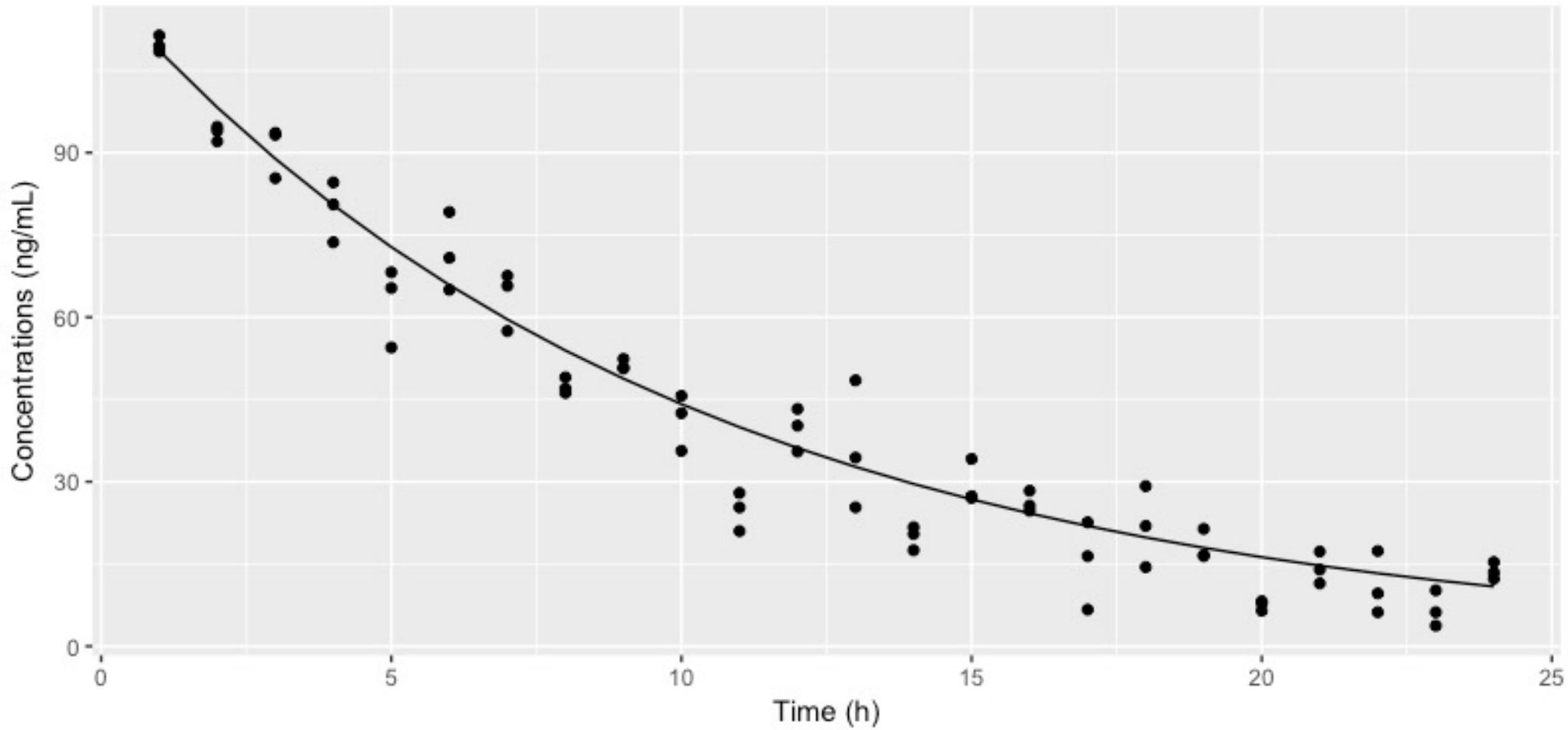




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The model components

Residual error describe deviation between model prediction and observations

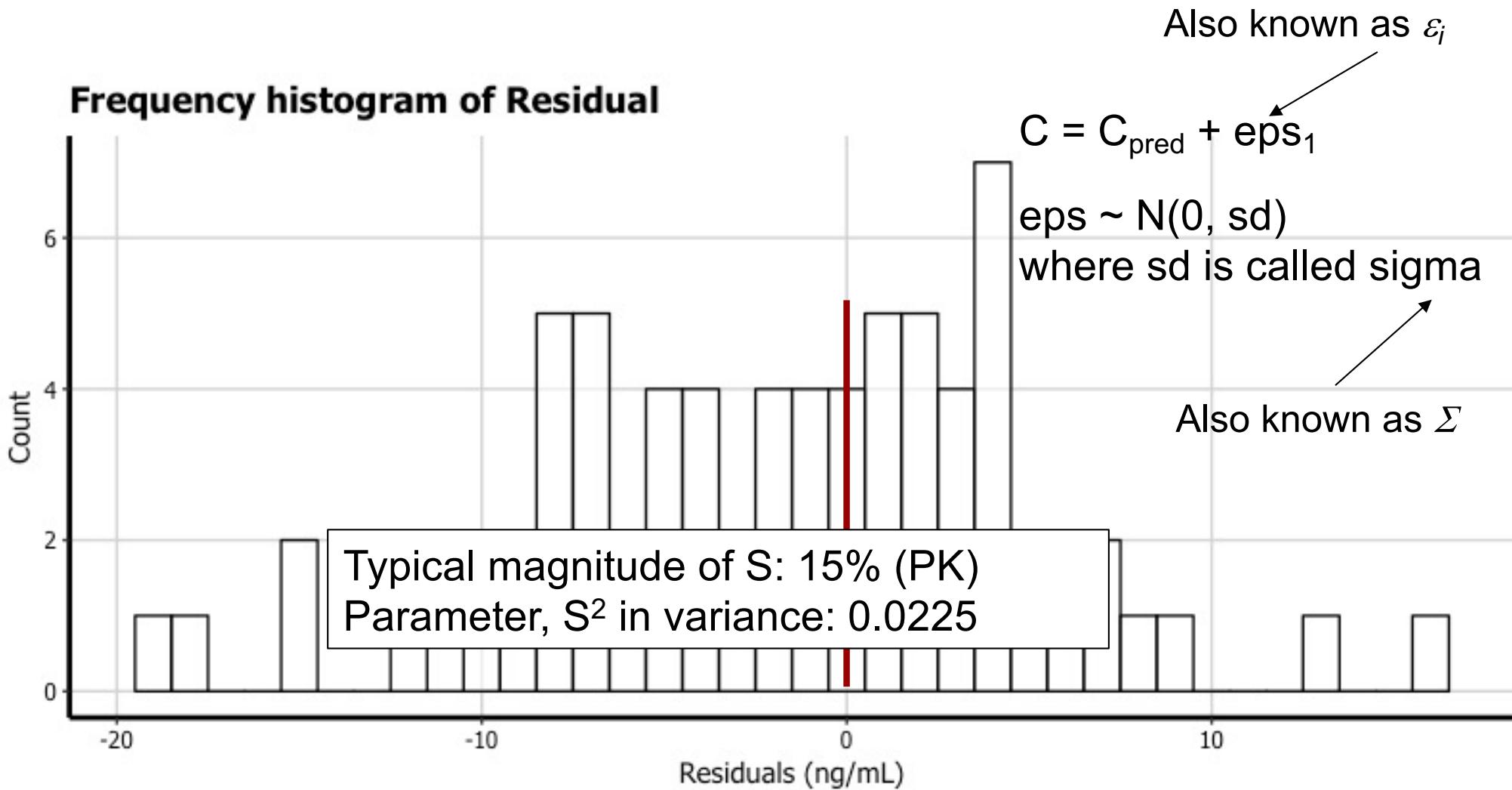




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The model components

Residual error describe deviation between model prediction and observations





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The model components

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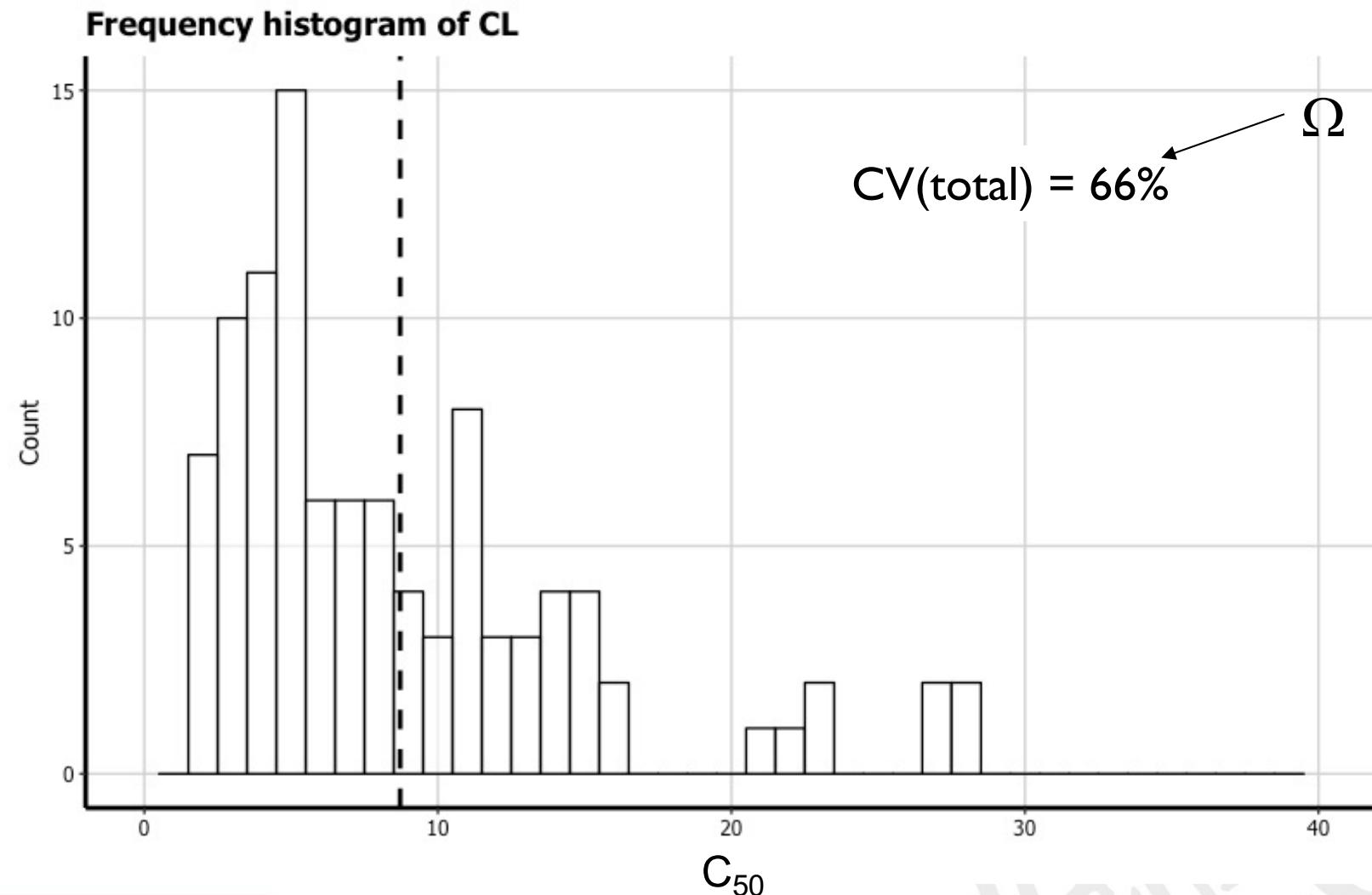
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The model components

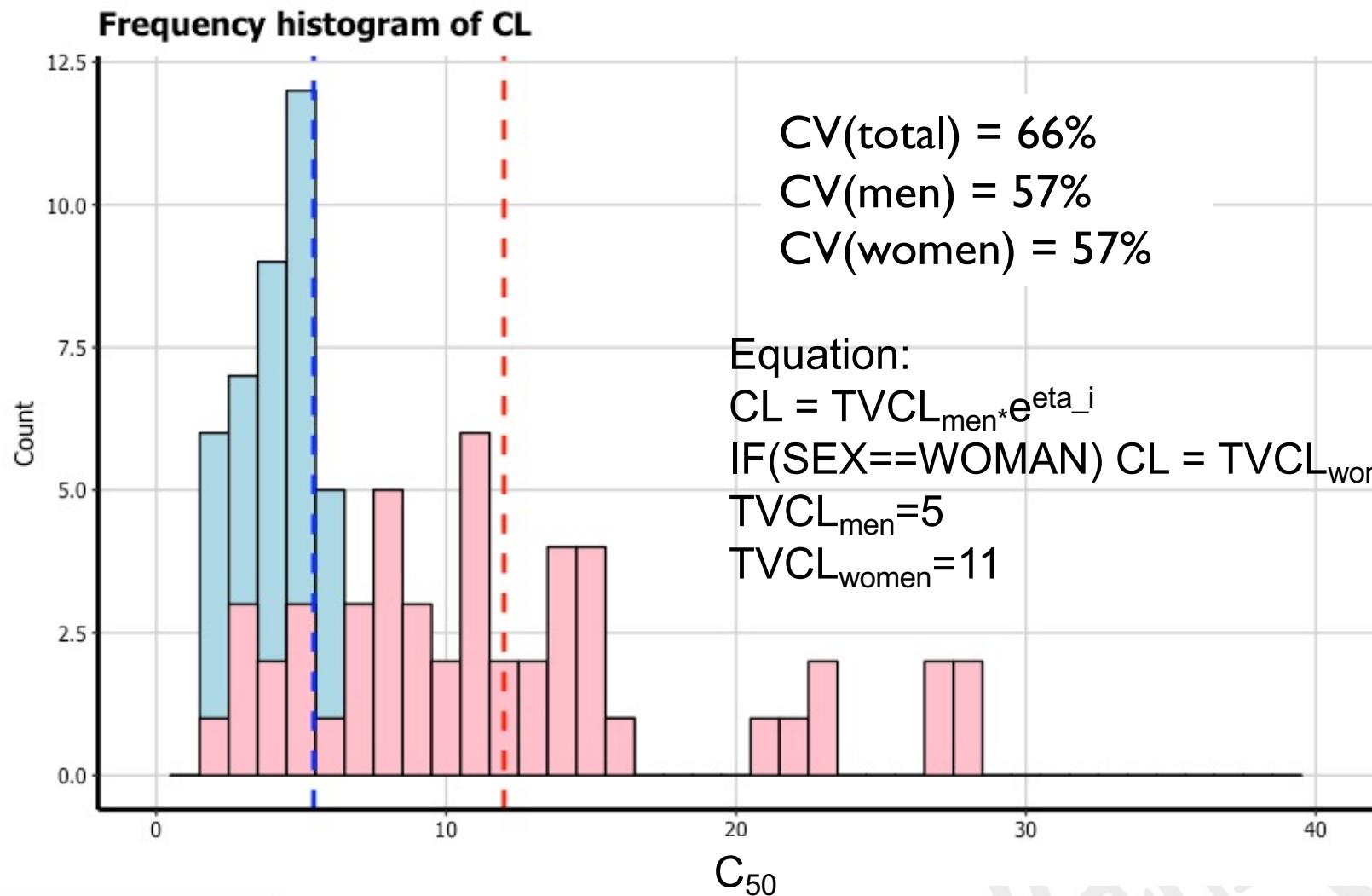
Example of covariate relationship





The model components

Example of covariate relationship

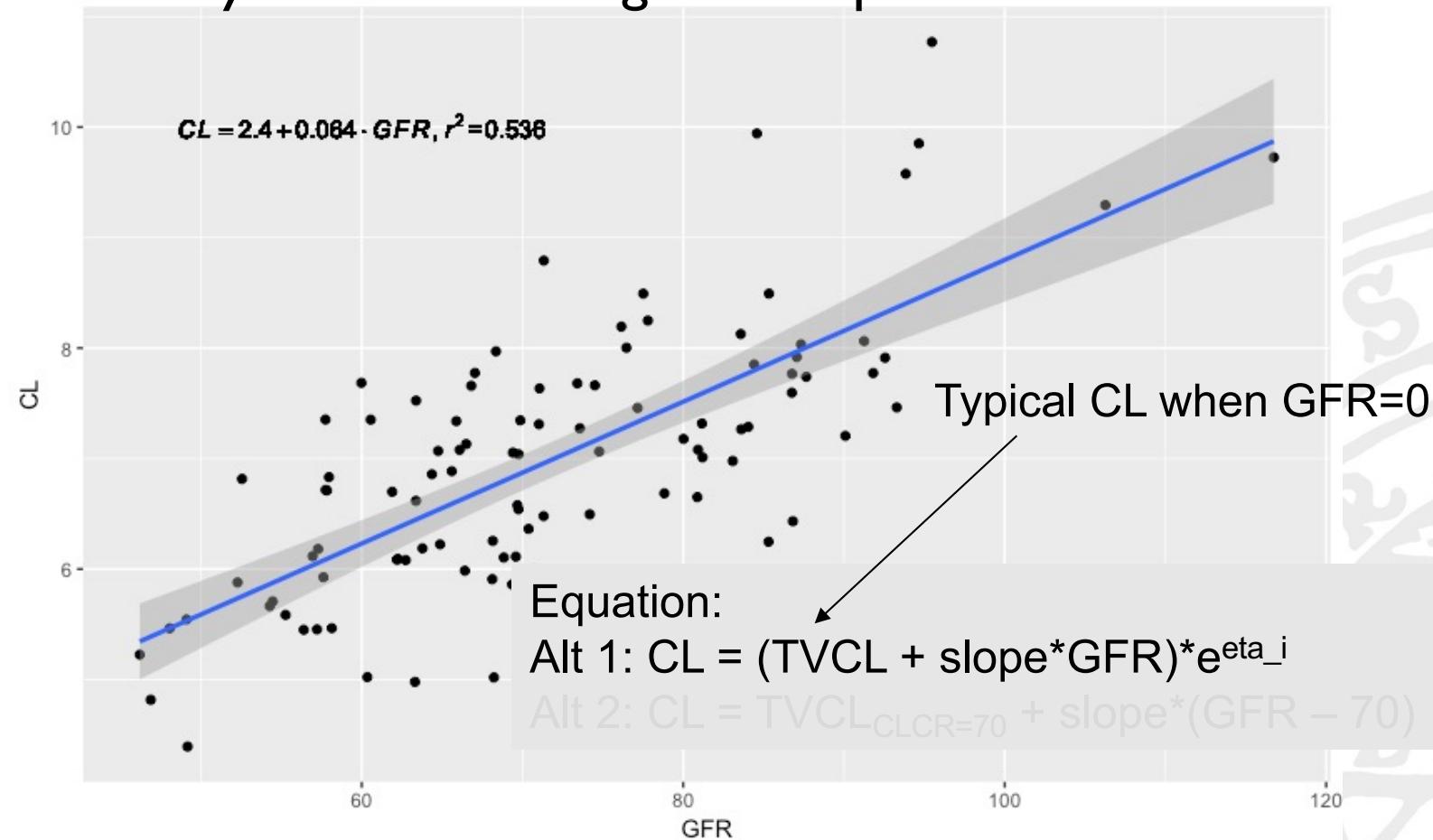




The model components

Example of covariate relationship

For renally eliminated drugs: CL depends GFR

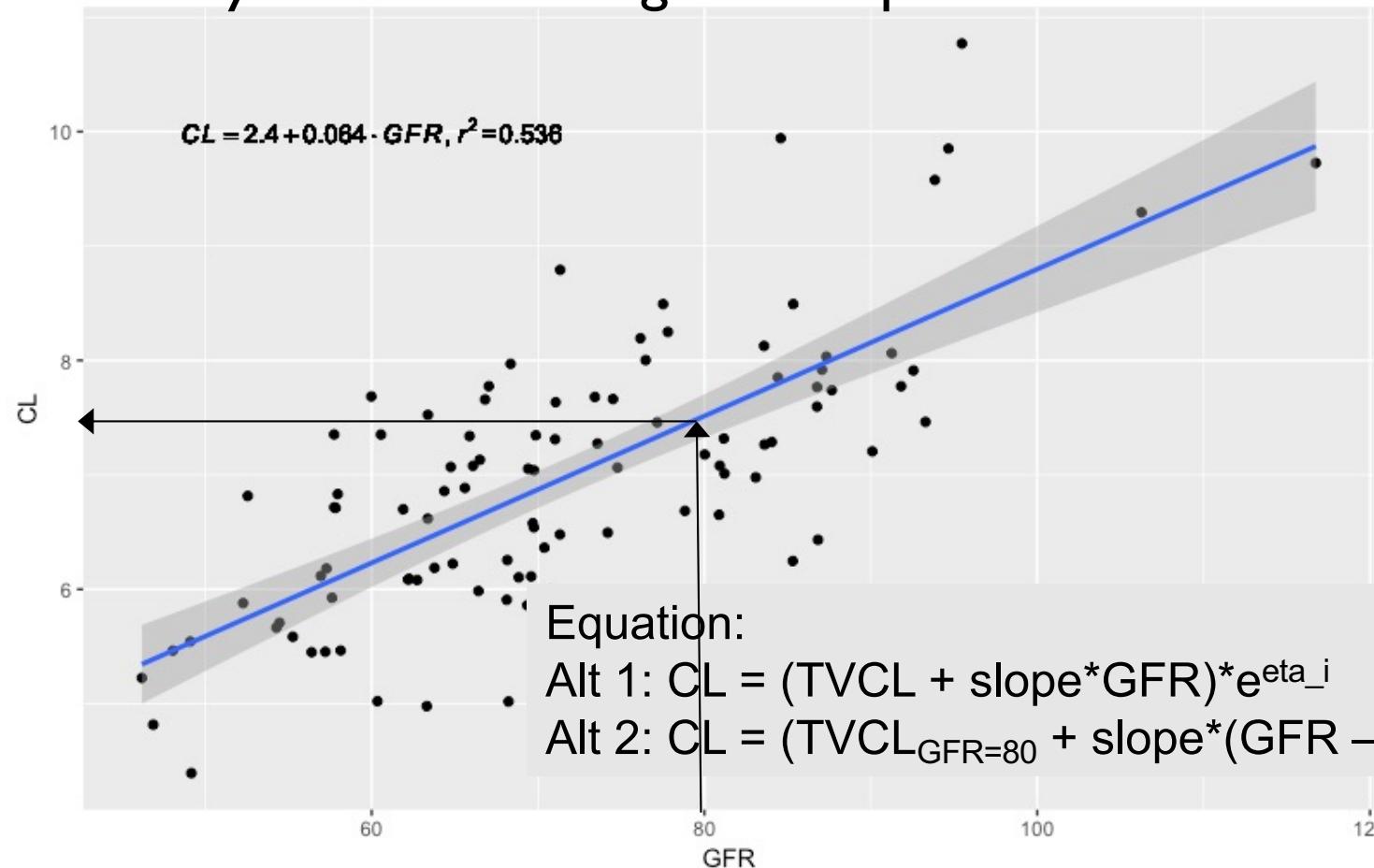




The model components

Example of covariate relationship

For renally eliminated drugs: CL depends GFR





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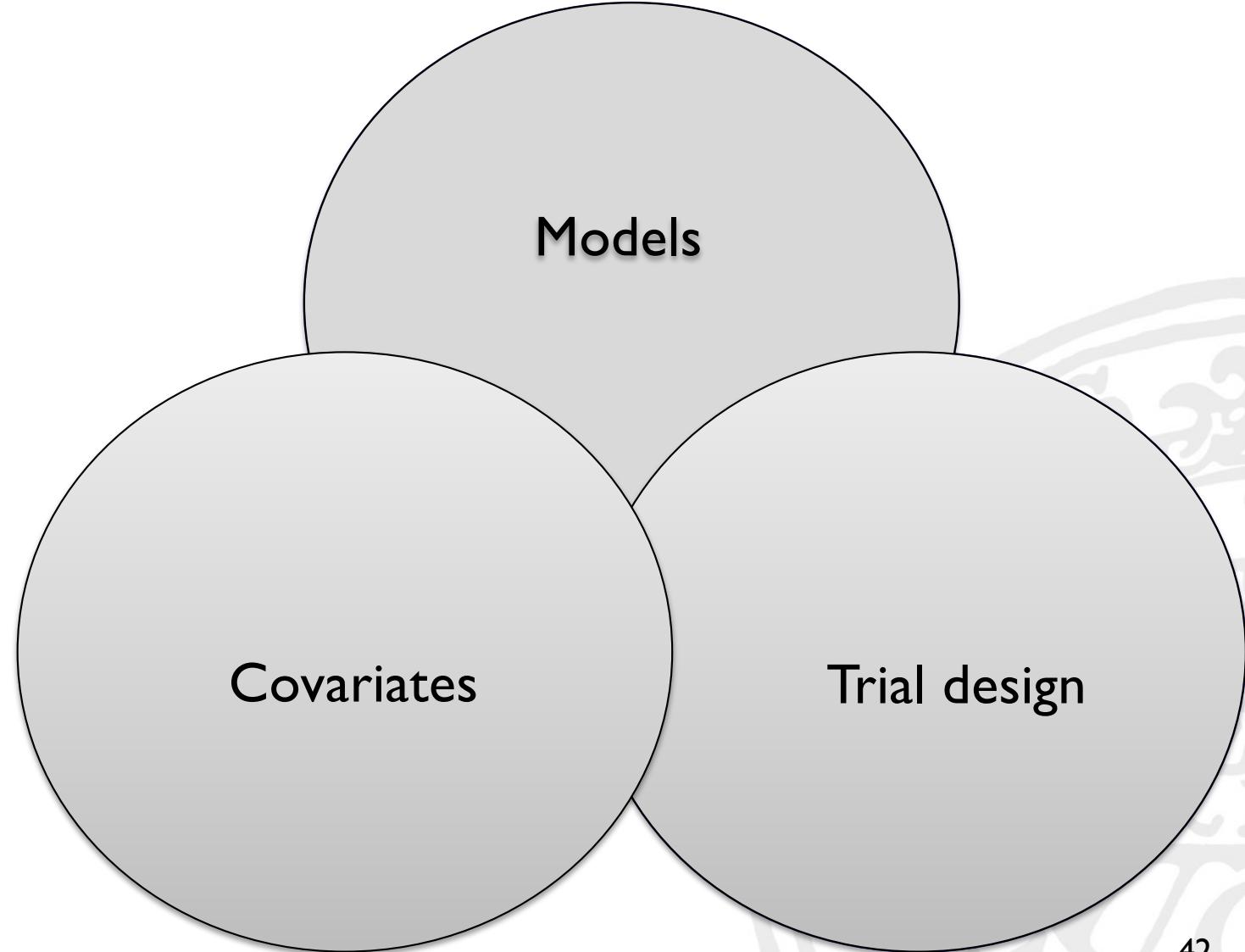
Clinical Trial Simulations

WHAT DOES CTS CONSIST OF?



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Components of Clinical Trial Simulations





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Clinical Trial Simulations

CTS is used to design good studies

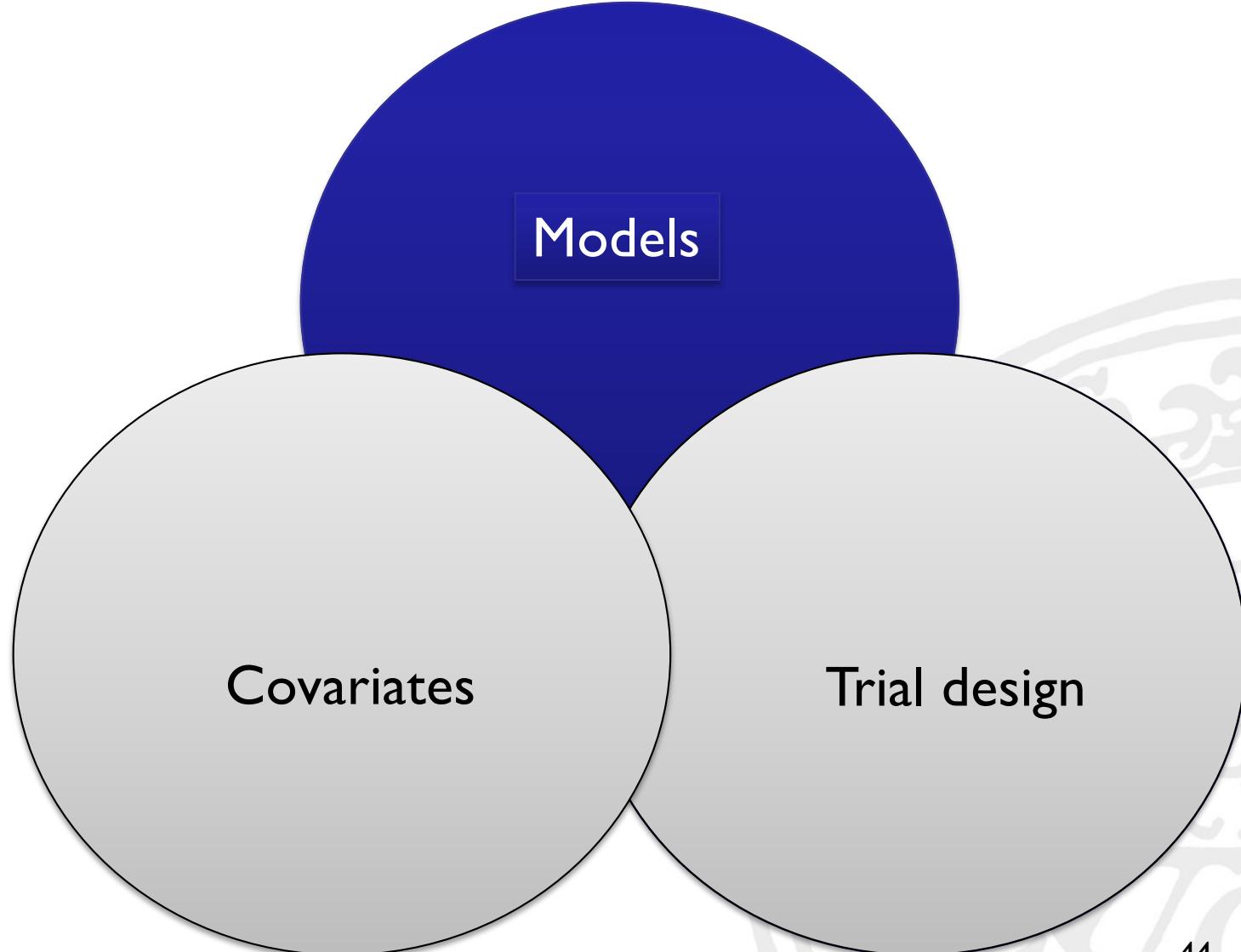
- What should we study?
 - When should we take samples?
 - How long should we study?
-
- Cross-over or parallel study – power and duration differ
 - Treatments – number of doses and schedules
 - Number of patients per arm for a particular power



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Components of CTS

The drug model





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Components of CTS

A model is needed for each piece in the trial

Models required for CTS:

- **Pharmacokinetic** – what the body does with the drug
- **Pharmacodynamic** – what the drug does with the body



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Components of CTS

A model is needed for each piece in the trial

Models required for CTS:

- **Pharmacokinetic** – what the body does with the drug
- **Pharmacodynamic** – what the drug does with the body
- **Baseline/Disease progression** – how biomarkers change
- **Drop-out** – how participation in trial change
- **Placebo** – how people respond to being treated
- **Adherence** – how people follow directions



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Components of CTS

Disease progression may be important in certain situations

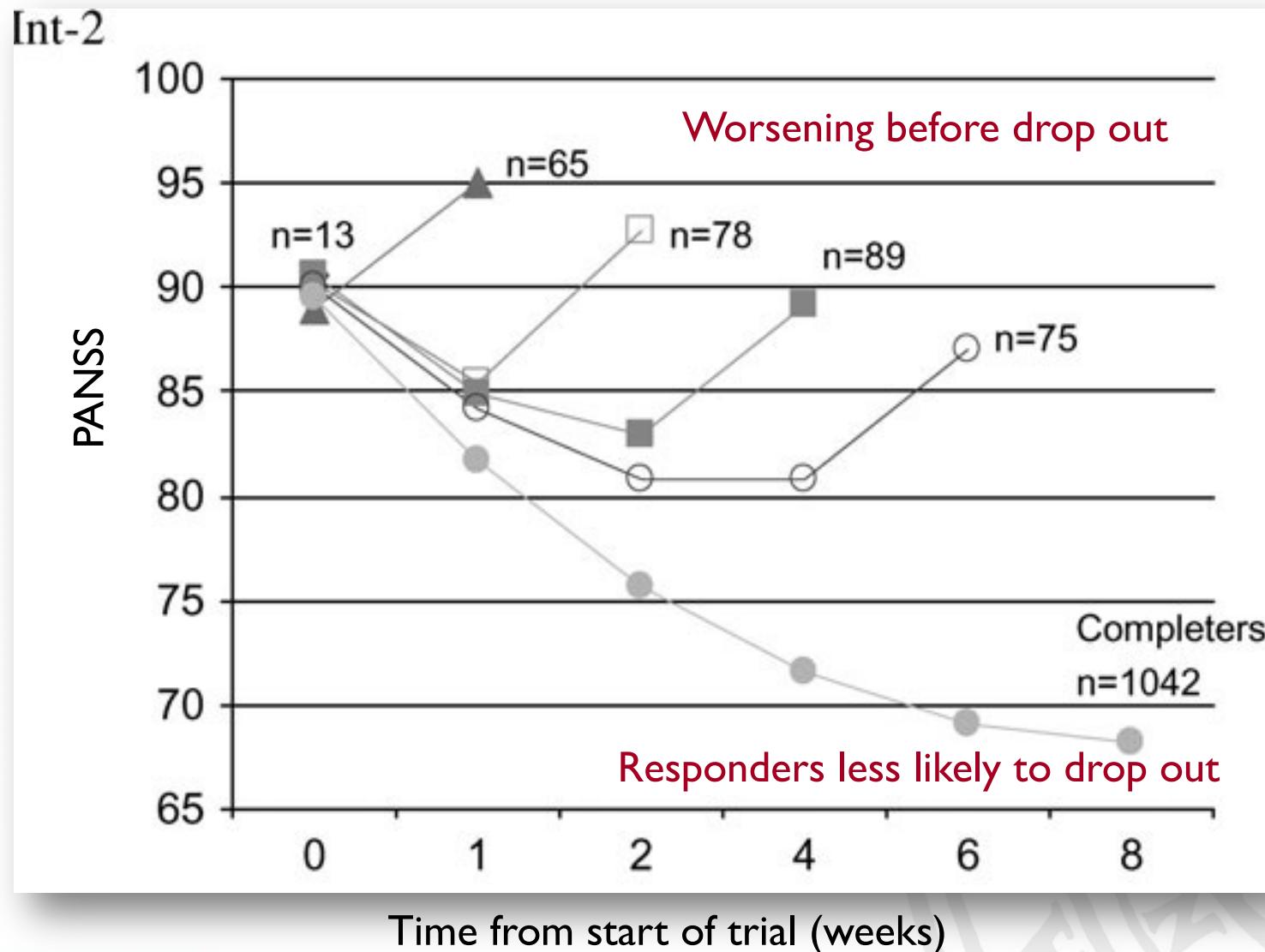
- Disease progression may be needed as a separate model
 - Certain diseases are progressing
e.g. Parkinson's, Alzheimer's, MS, Diabetes
 - Studies of long duration
e.g. phase 3 studies, observational studies



Components of CTS

Dropout may need to be accounted for

*Rabinowitz and Davidov. *Schizophrenia Bull.* 2008



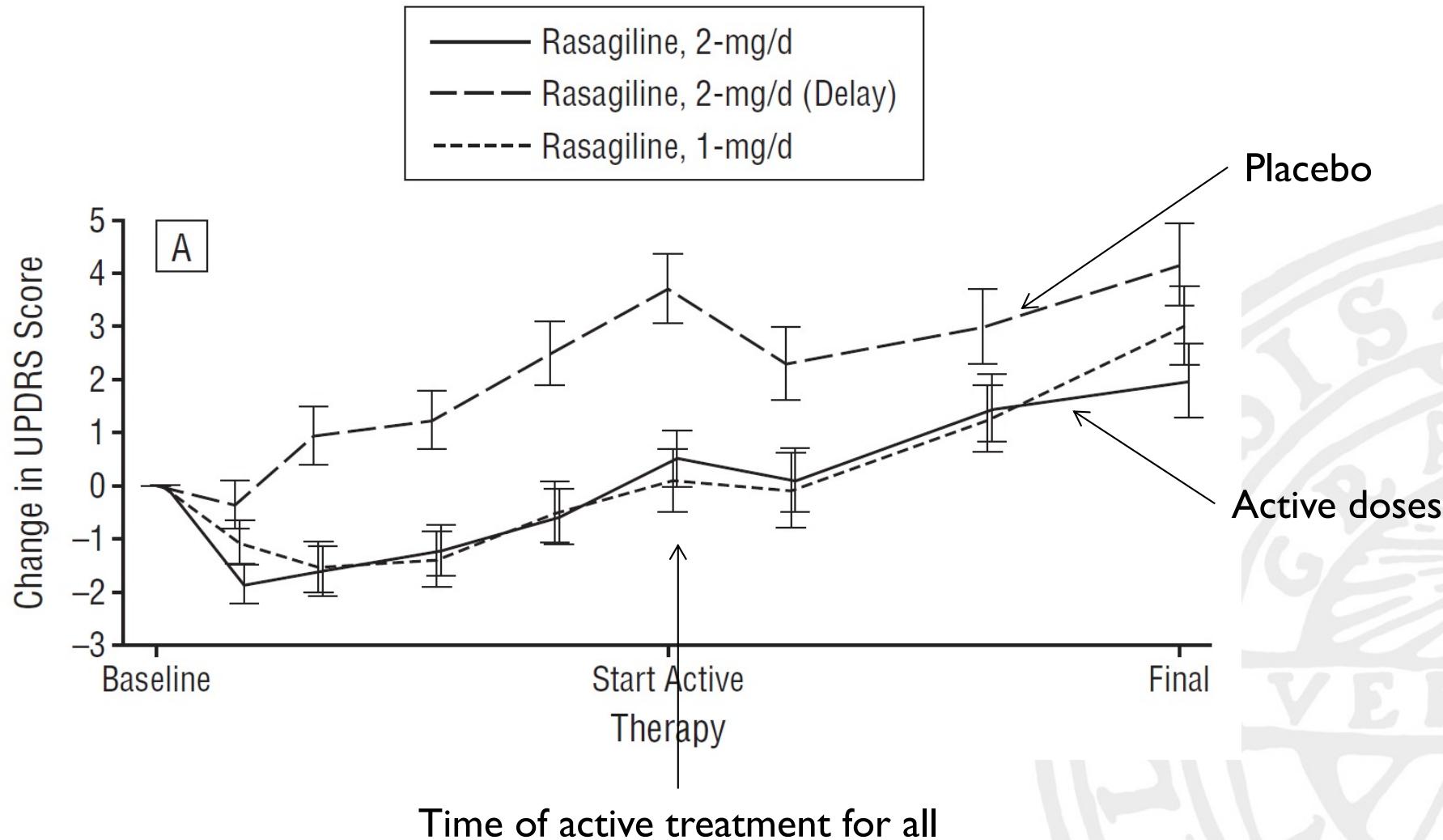


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Components of CTS

Placebo response is always present in drug trial data

*Parkinson Study Group, Arch Neurol, 2004.

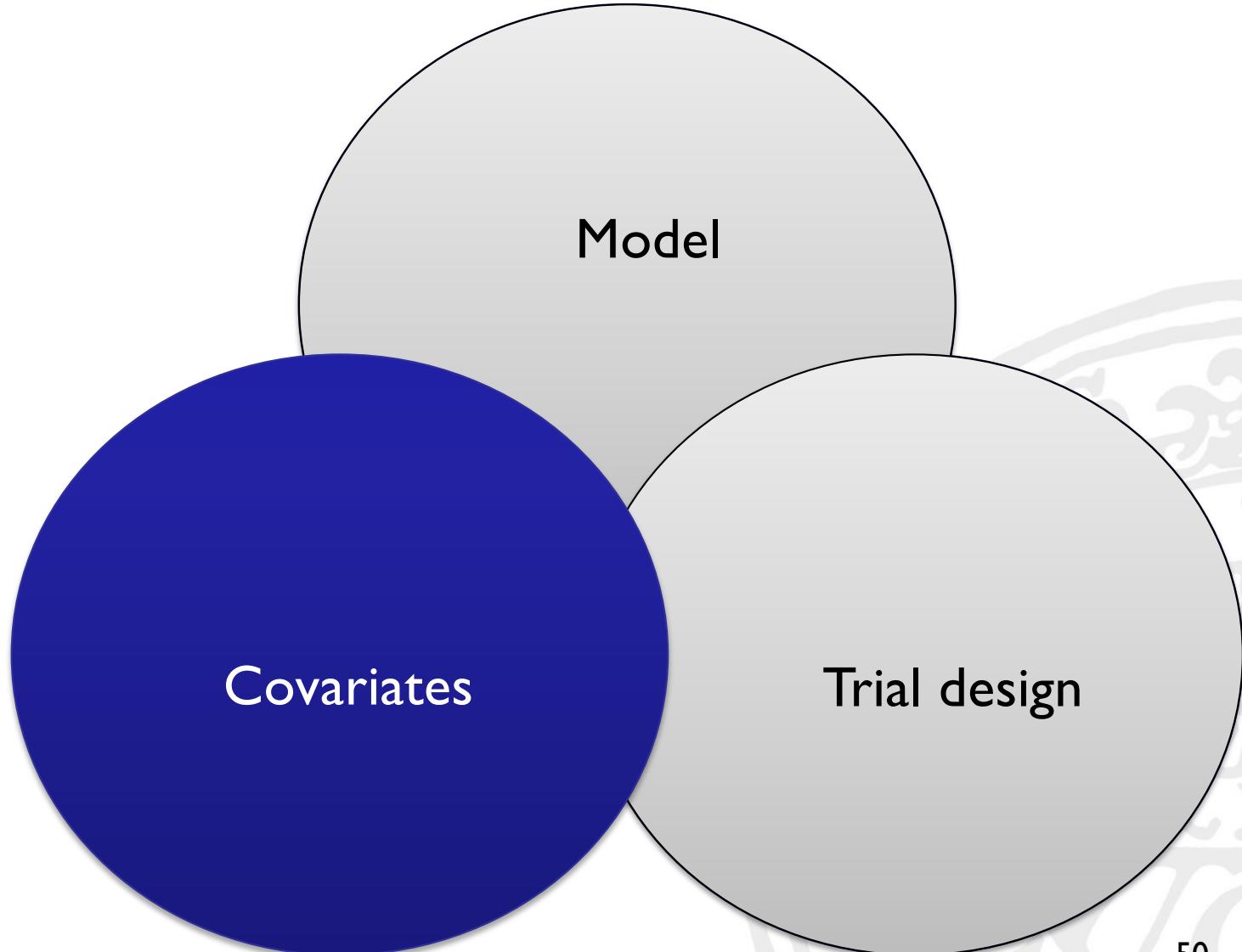




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Components of CTS

Covariates





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Covariates

Covariates may explain IIV

If the models contain covariates, realistic values needs to be simulated

Consider:

- Expected mean
- Distribution shape
- Natural limits
 - e.g. $\text{weight} > 0$
- Inclusion/exclusion criteria puts boundaries on covariates
- Correlation between covariates
 - e.g. sex and weight, age and weight in children



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Modelling & Simulation

HOW CAN DRUG DEVELOPMENT BENEFIT FROM M&S?



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Example: CTS with Ivabradine

Ivabradine

- Reduction of heart rate leads to
 - Decreased risk of angina pectoris attack
 - Increase risk of excessive bradycardia

Purpose:

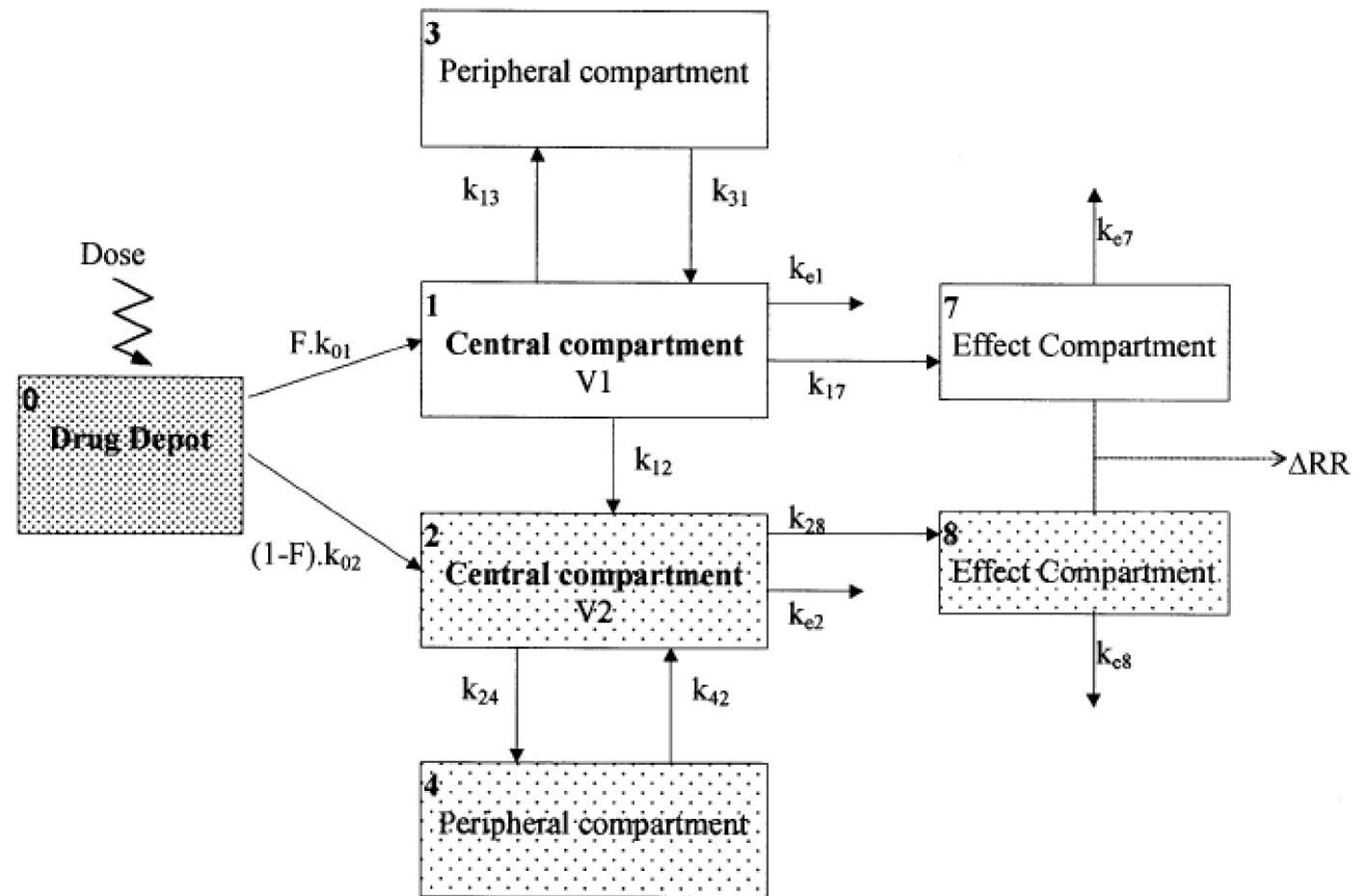
Determine for a phase III study, the expected response of treatment, the choice of dose, and the number of patients required for a specific power.

The main efficacy outcome was reduction in number of patients with angina attack(s) over 24 hours compared to untreated patients

Chabaud S, et al. J PKPD 29; 2002



PK-PD model





PK-PD model

$$\Delta RR(t) = \frac{E_{\max_p} \cdot \left(\frac{Ce_p(t)}{Ce50_p} \right)^{\gamma_p} + E_{\max_m} \cdot \left(\frac{Ce_m(t)}{Ce50_m} \right)^{\gamma_m}}{1 + \left(\frac{Ce_p(t)}{Ce50_p} \right)^{\gamma_p} + \left(\frac{Ce_m(t)}{Ce50_m} \right)^{\gamma_m}},$$

$$HR(t) = \frac{60,000}{RR_0(t) + \Delta RR(t)}$$

Probabilistic model related to $HR(t)$:

1. Probability of at least one angina pectoris attack
2. Probability of at least bradycardia



PK-PD model

Dx Py	Efficacy						Safety		
	% Patients with at least one episode of chest pain			Number of Patients to include in a future trial			% Patients with at least one adverse event		
	Median	Interquartile interval		Median	Interquartile interval		Median	Interquartile interval	
	Median	Lower	Upper	Median	Lower	Upper	Median	Lower	Upper
Placebo	68	65	71	—	—	—	4	3	6
D2.5 P1	67.5	65	70	2552 ^a	1235	11333	5	3	6
D2.5 P2	64	61	68	1967 ^a	554	11139	5	4	6
D5 P1	63	60	67	1771 ^a	453	5342	5	3	6
D5 P2	60	55.5	62.5	715 ^a	233	1772	6	4	7
D10 P1	58	53	61	478 ^a	198	1326	6	4.5	7
D10 P2	52	49	57	220	112	588	8	6	10
D20 P1	52	47	55	196	100	398	8	6	9.5
D20 P2	47.5	43	41	11	61	213	10	8	12
D40 P1	46	41	49	91	56	159	10	8	12
D40 P2	41	38	45.5	72	42	106	13	10.5	15



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Example:

Ivabradine

- Placebo: 68% of patients would have chest pains
- Dose = 20 mg, once daily
 - 200 patients per group with alpha = 5% and power = 90%
 - 16% reduction of risk of chest pains (Risk of chest pain = 52%)
 - Risk of adverse event doubles (from 4% to 8%)



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Summary

Learning objectives

- Why modelling (and simulation) of clinical trials?
 - Make drug development more efficient
- What does a model consist of?
 - Structure, parameters, covariate relationships, variability
- What does a clinical trial simulation consist of?
 - Model, Covariates, Study design
- How can drug development benefit from M&S?
 - Support for more informed decisions



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Questions?





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References

- International Federation of Pharmaceutical Manufacturers & Association. Facts and Figures 2012. The Pharmaceutical Industry and Global Health. http://www.ifpma.org/fileadmin/content/Publication/2013/IFPMA_Facts_And_Figures_2012_LowResSinglePage.pdf (assessed Nov 2014)
- Jack W. Scannell¹, Alex Blanckley¹, Helen Boldon¹ & Brian Warrington. Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Rev Drug Disc*, 2012; 11: 191-200.
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