Grand Challenges
African Drug Discovery Accelerator

Drug Discovery and Development Course

CERTARA | SIMCYP

PK/PD Relationships

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Learning Objectives

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Simcyp

- Understand key concepts of PK/PD modelling
- Recognise the differences between basic types of PK models
- Differentiate between direct and indirect PK/PD relationships
- Understand the impact PK/PD relationship on study designs

Popular Quotes

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Simcyp

- “All models are wrong, but some are useful”
  - George Box (Statistician)
- “Perfect is the enemy of the good”
  - Voltaire (Philosopher)
- “The goal is to build the simplest useful model with minimal data/cost”
  - A PKPD modeller

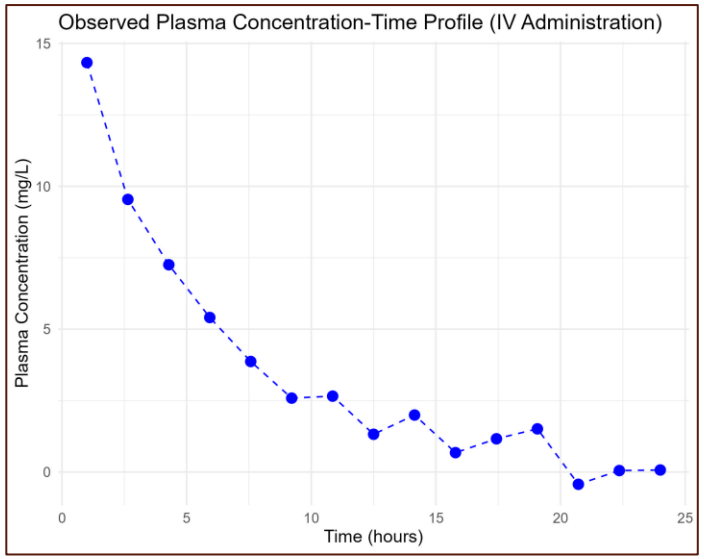
What is a useful model?

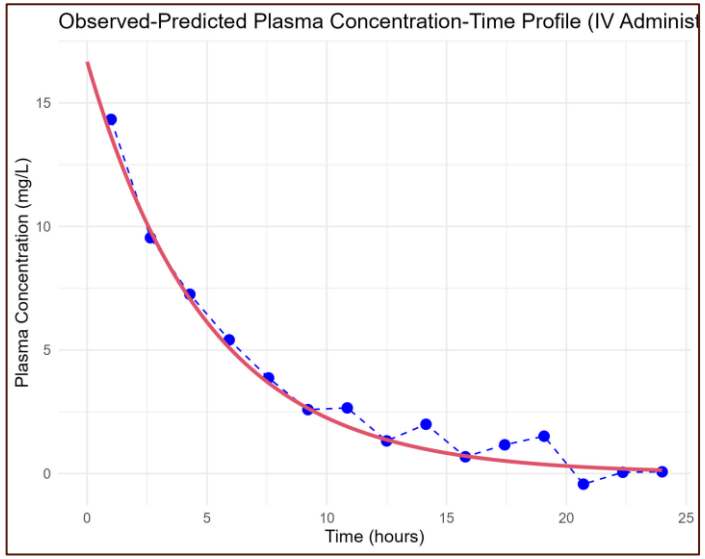
CERTARA Simcyp

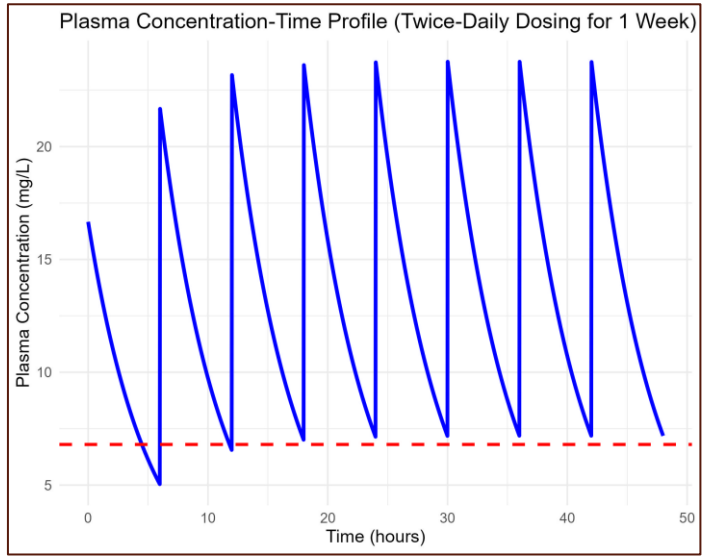
- Models are based on data and assumptions.
  - A simple model often has more assumptions but require less data.
  - Replacing assumptions with data incurs cost/time/effort.
- If either data or assumptions are wrong, the model will likely not be useful.
- “Useful” depends on the question to be answered.

A useful model example

- Assume you have plasma exposure data following a single IV administration
- Need to predict steady-state concentrations after multiple IV dosing.

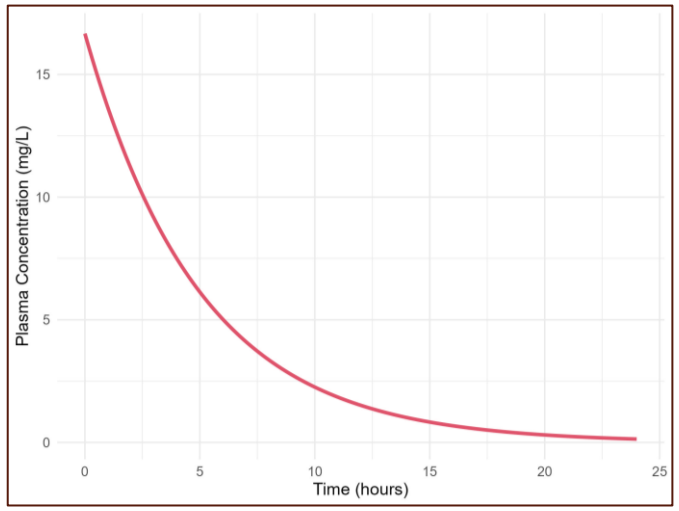




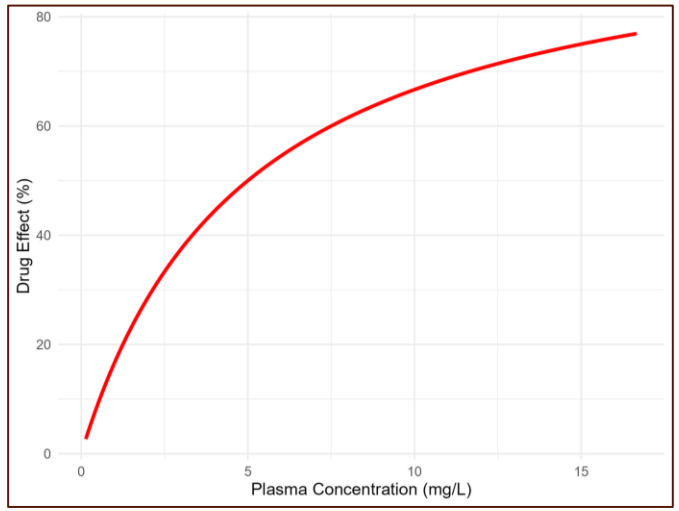


What is PK/PD?

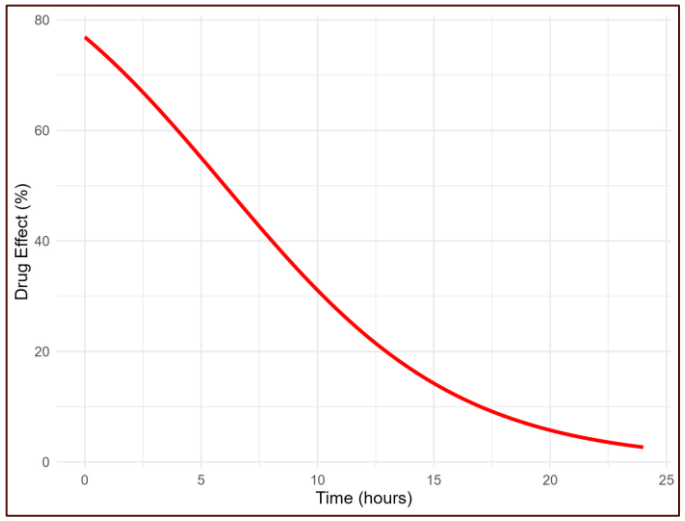
Pharmacokinetics



Pharmacodynamics



PK/PD

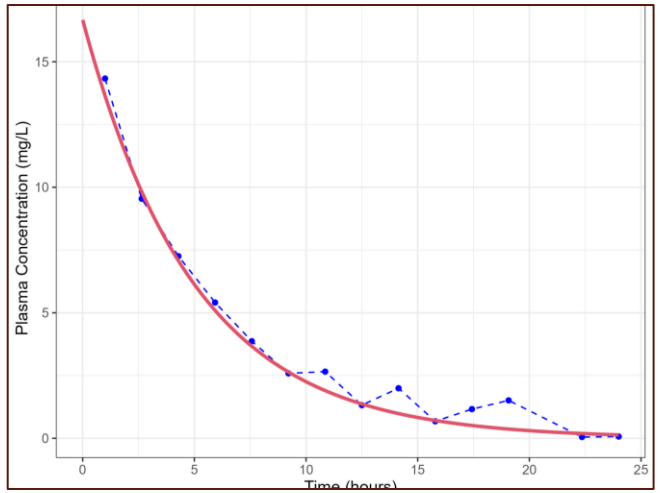


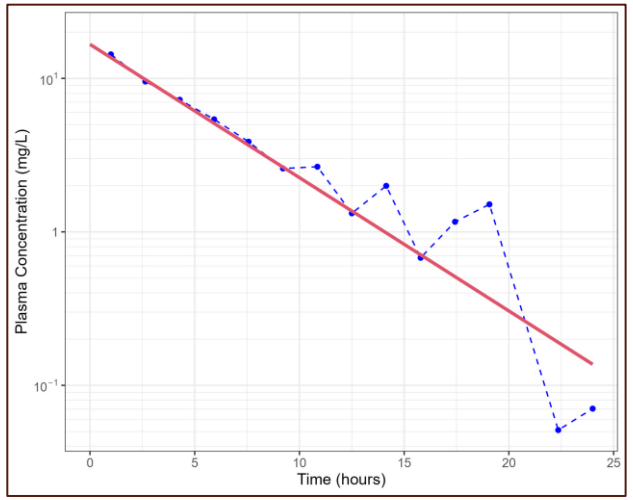
- If PK/PD is well understood, we can predict PD changes under different PK conditions.

PK models: 1 Compartment IV

- Whole body is represented by a single compartment with volume (V)
- Drug is eliminated from the compartment in a first-order fashion with and elimination rate constant (k)

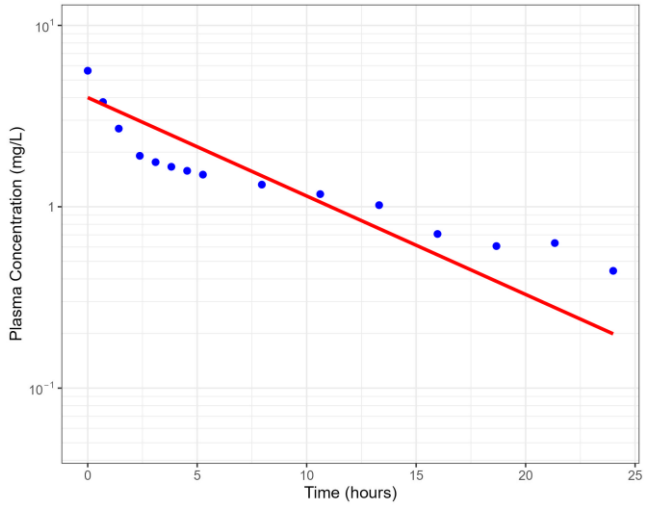
$$C(t) = \frac{D}{V} \cdot e^{-k_e t}$$



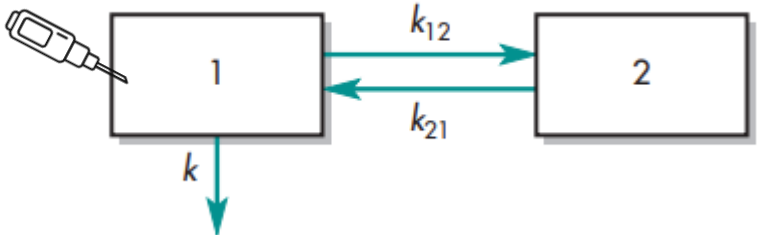


PK models: 2 Compartment IV

- Some data won't fit to a single compartment model.
- A more complex model (with relaxed assumptions) would be needed.



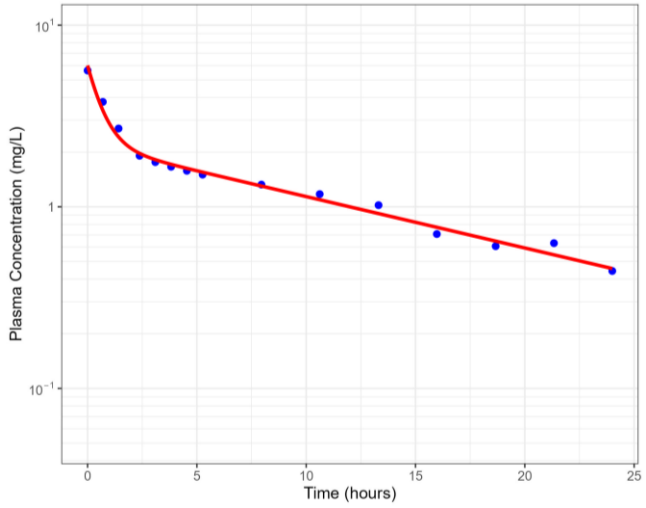
Two-compartment open model, IV injection.



$$C_1(t) = A\,e^{-\alpha t} + B\,e^{-\beta t}$$

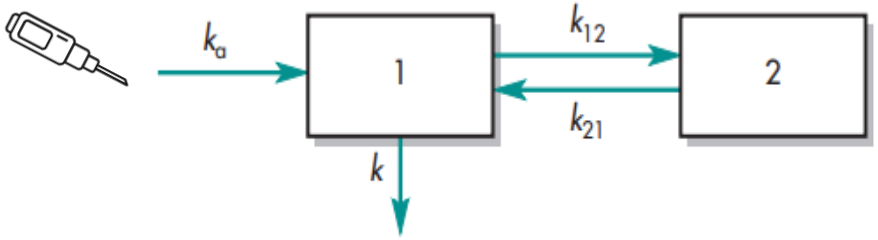
$$A = \frac{\text{Dose} \cdot (\alpha - k_{21})}{V_1 \cdot (\alpha - \beta)} \qquad B = \frac{\text{Dose} \cdot (k_{21} - \beta)}{V_1 \cdot (\alpha - \beta)}$$

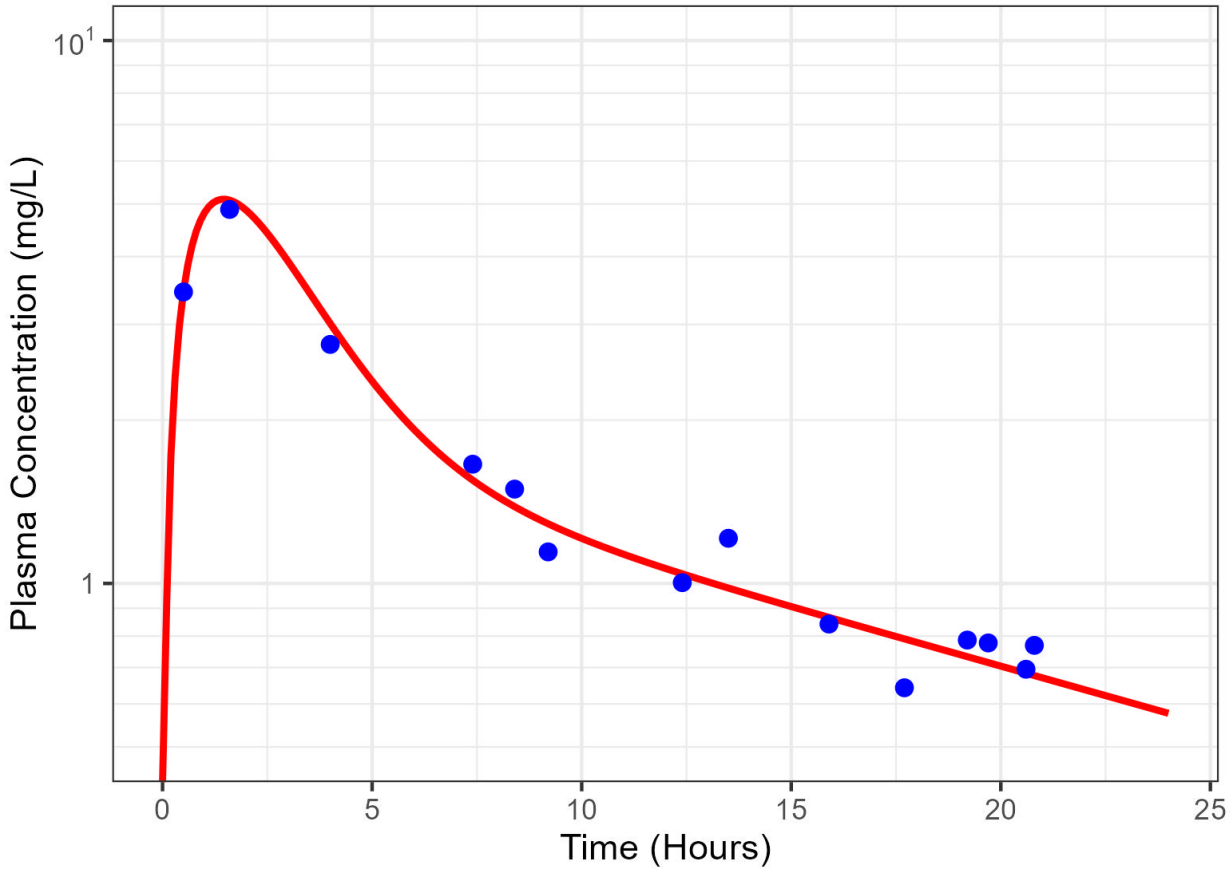
$$\alpha, \beta = \frac{1}{2}\left[(k_{10} + k_{12} + k_{21}) \pm \sqrt{(k_{10} + k_{12} + k_{21})^2 - 4k_{10}k_{21}}\right]$$



PK models: 2 Compartment Extravascular

- To model absorption process in case of extravascular administration
  - Oral
  - Intramuscular
  - Subcutaneous, etc.





PK models: Summary

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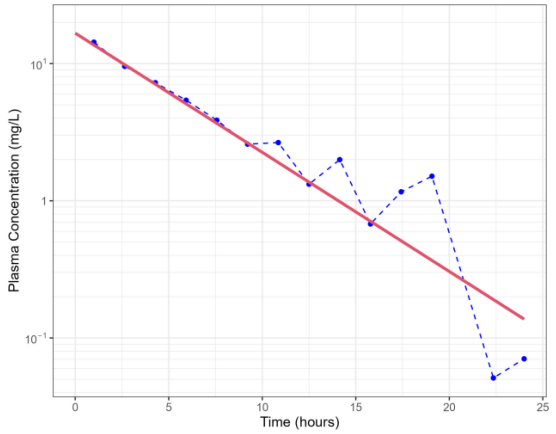
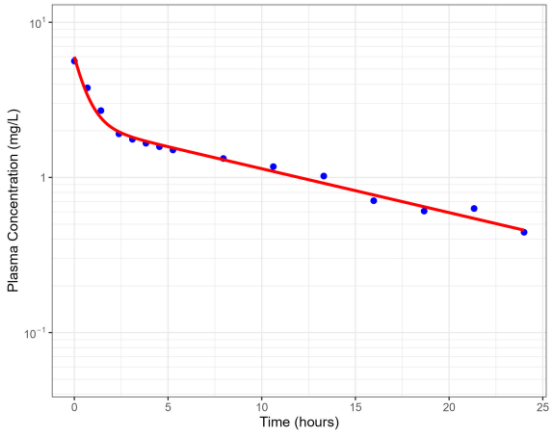
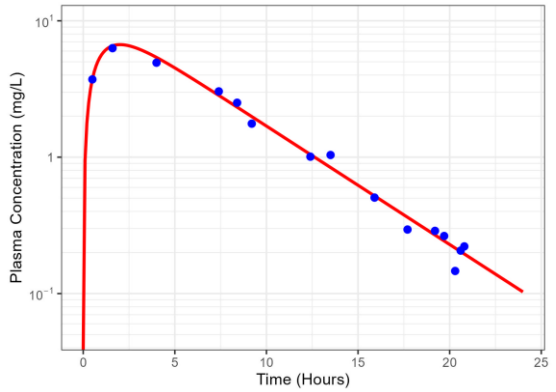
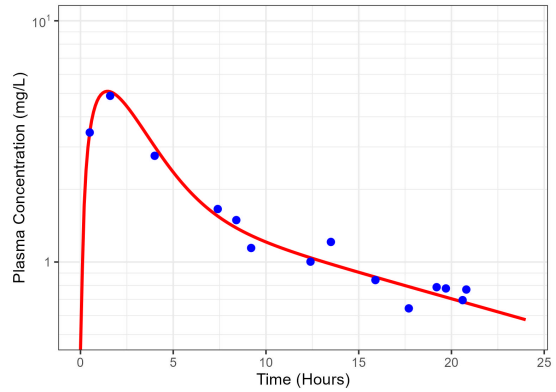
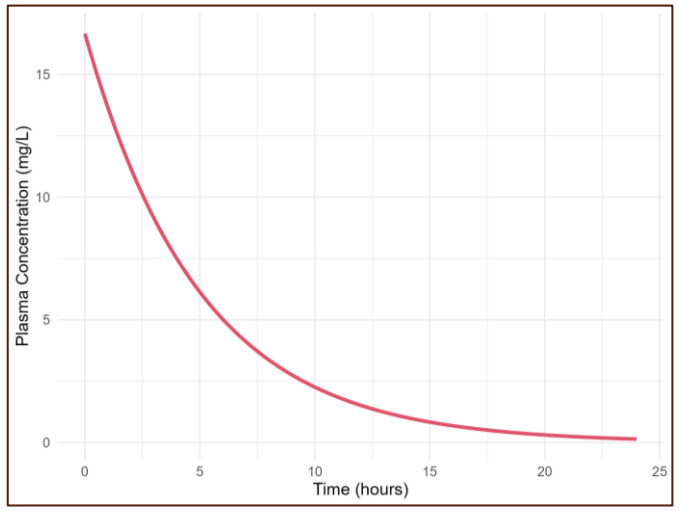
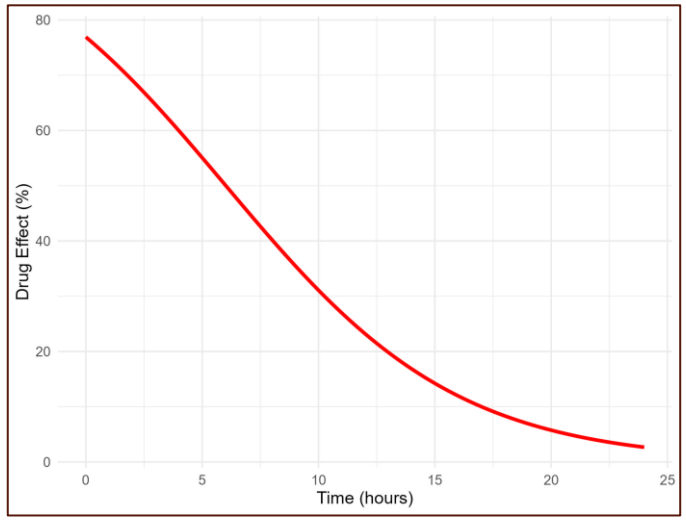
	1 Compartment	2 Compartment
Intravenous		
Extravascular		

PD model: Direct Emax Model

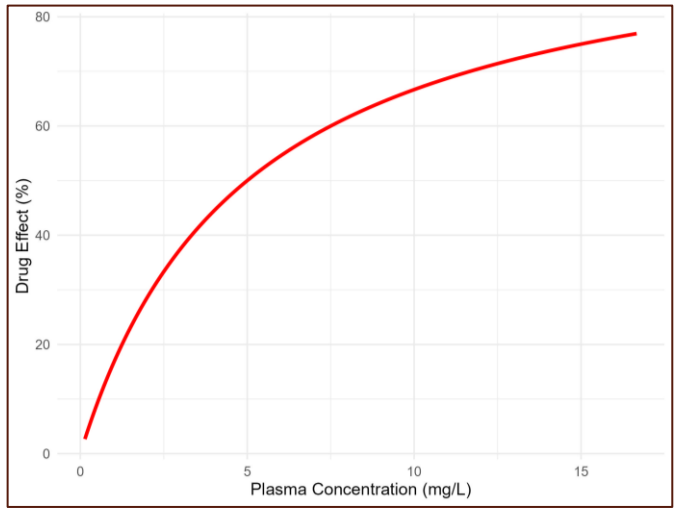
1 Compartment IV



PK/PD



PD



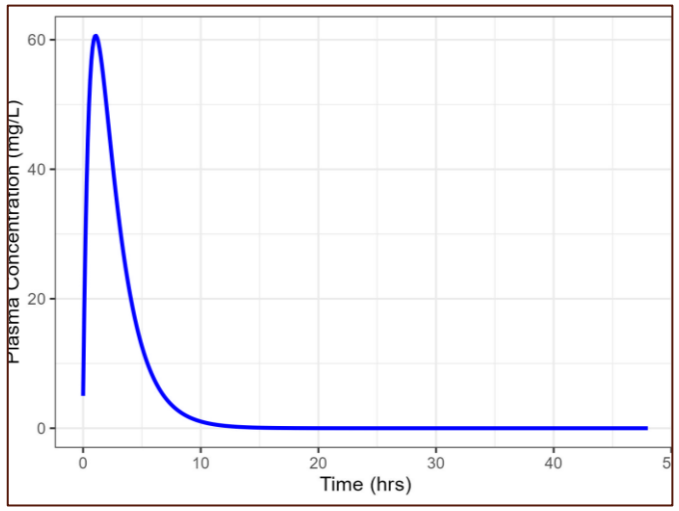
$$C = \frac{Dose}{V} \times e^{-\frac{k}{V} \times t}$$

$$E(C) = \frac{E_{\max} \cdot C}{EC_{50} + C}$$

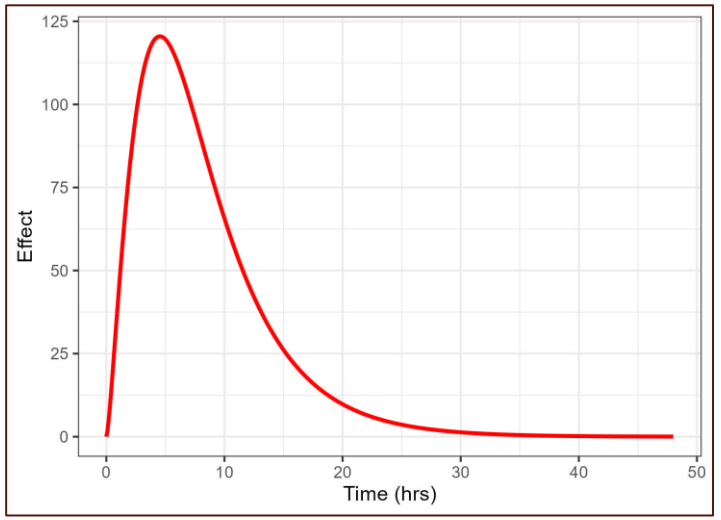
$$E(C) = E_0 + \frac{E_{\max} \cdot C}{EC_{50} + C}$$

PD model: Indirect Emax Model

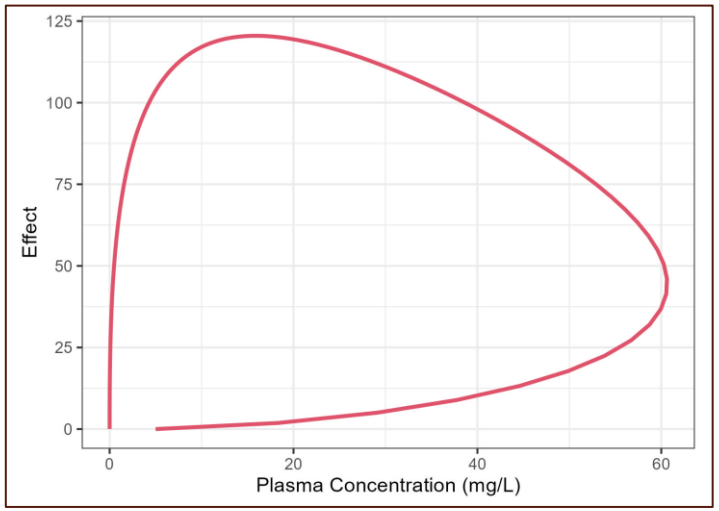
1 Compartment Extravascular



PK/PD



PD



- Accounts for time delay in response
- Maximum effect is later than plasma maximum concentration
- Effect versus time shows hysteresis

Impact of direct vs indirect PKPD

- Indirect PKPD relationship:
  - The duration of effect maybe significantly greater than the duration of exposure.
- Dosing frequency Consideration:
  - Less frequent dosing may be needed than for direct PK/PD
- Modelling the single dose PK/PD data would allow for the optimal design of the repeat dose study

Recommendations

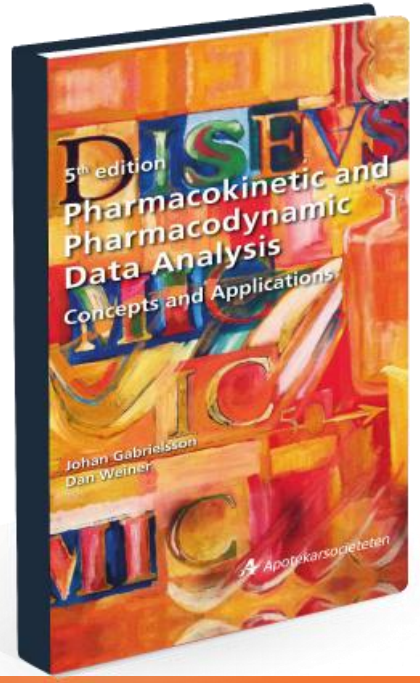
- PK/PD experiments should be designed:
  - Integrate all available knowledge (PK, in vitro pharmacology and biology) and design studies to test hypothesis.
  - Select dose levels and sample times to investigate concentration-effect and time dependence.
- Avoid simple dose-effect interpretation
  - Exposure derives efficacy, dose is just a tool to achieve exposure
- Obtain exposure-time and effect-time data where possible.
- Integrate modelling and simulation into PK/PD design to maximise value of studies.

Summary

- Model integrate knowledge of a drug and can help support decision making throughout the drug discovery process.
- A model doesn’t have to be perfect to be useful.
- Refine models as more data become available to replace assumptions and make them even more useful.
- Models should be used in combination with biological knowledge/hypotheses to optimise PK/PD study designs.

References/further resources

- PK/PD Data Analysis: Concepts and Application
  - Johan Gabrielsson and Dan Weiner
  - https://www.certara.com/ebook/pharmacokinetic-and-pharmacodynamic-data-analysis/#main



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Thank You

Any Questions?

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