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Development of a Whole-Body Physiologically Based Pharmacokinetics Model for Children with Severe Malnutrition

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Pharmacokinetics (PK)

- Describes the movement of drugs in and out of the body through the following processes:

  i. Absorption: the movement of drug from the site of oral or extravascular administration into the systemic circulation

  ii. Distribution: the reversible transfer of drug between the systemic circulation and the tissues

  iii. Elimination: the removal of drug from the body by processes such as renal excretion or hepatic metabolism

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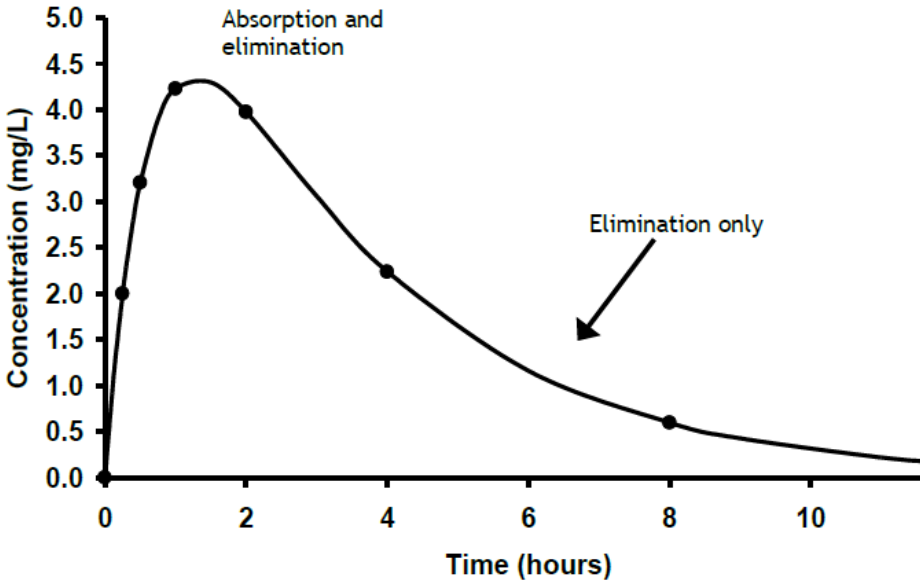
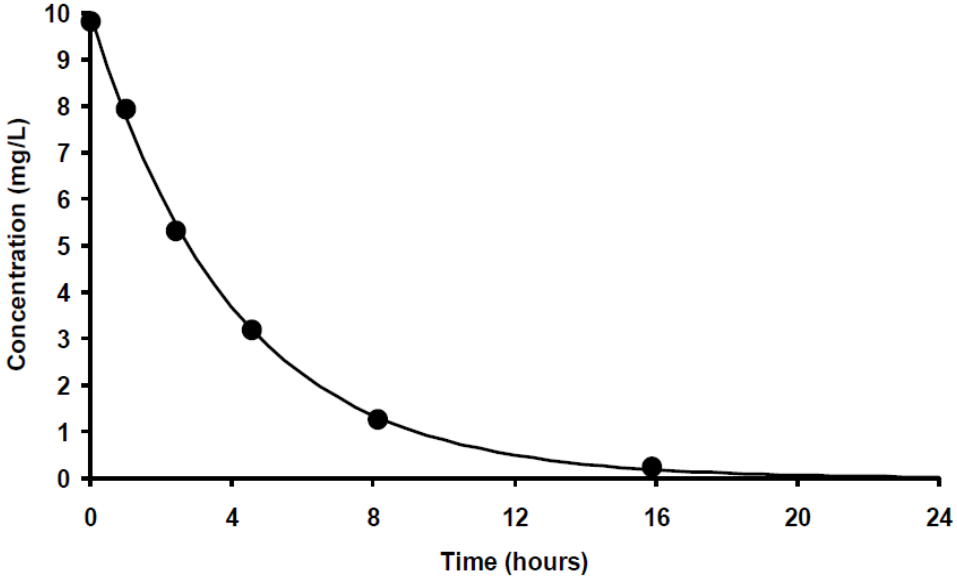
Concentration-time profile

Oral administration



Intravenous administration

(IV bolus)



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PK model

- Hypothetical structures used to describe and predict the disposition of drugs

For example:

If the desired target range of **Drug X** is 10-20 mg/L

- What loading dose should be used to achieve a serum concentration of 15 mg/L?
- What is the maximum concentration if an oral loading dose of 1000 mg is given?
- What concentration would you expect to measure 8 hours after the dose?

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How to develop PK models?

- PK models can be developed by two approaches:

  i. Empirical approach (traditional method)

  ii. Mechanistic approach

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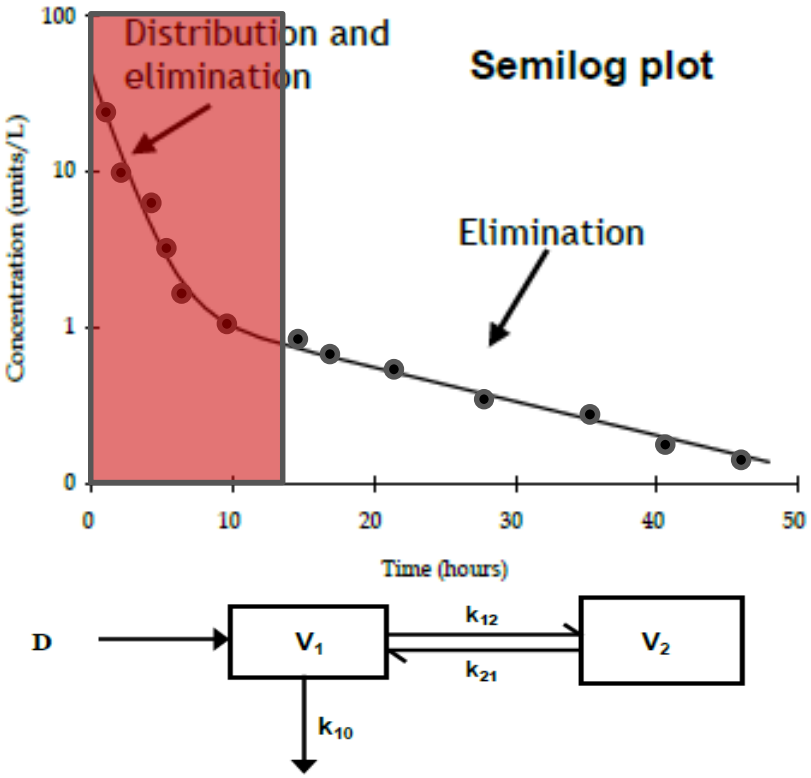
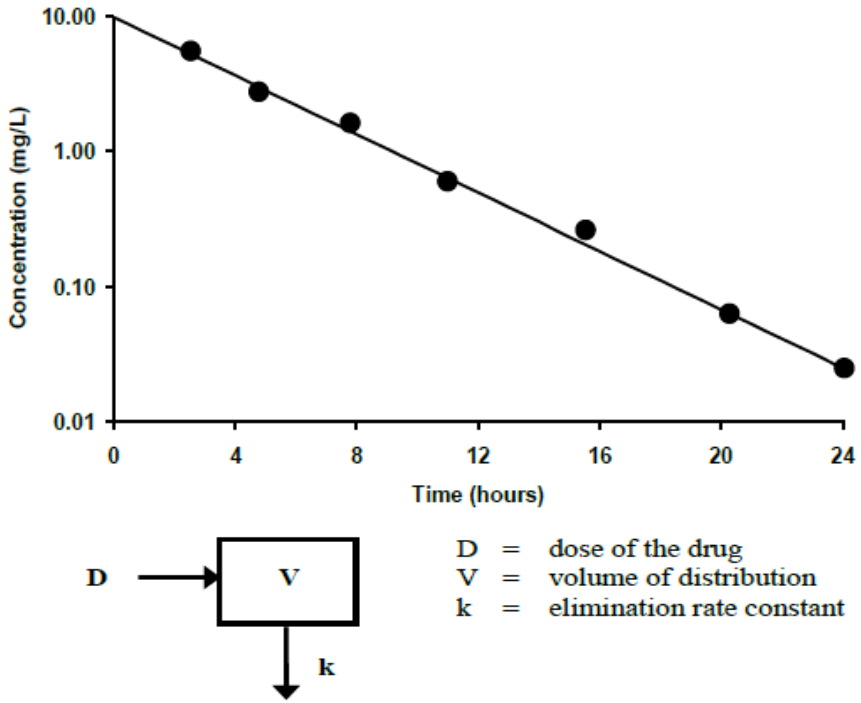
Empirical approach

- Compartmental model e.g. one- and two-compartment models





- Simple but the models have no physiological meaning
- Derived from the experimental data (drug concentrations)
- Complexity of the model depends on the data available

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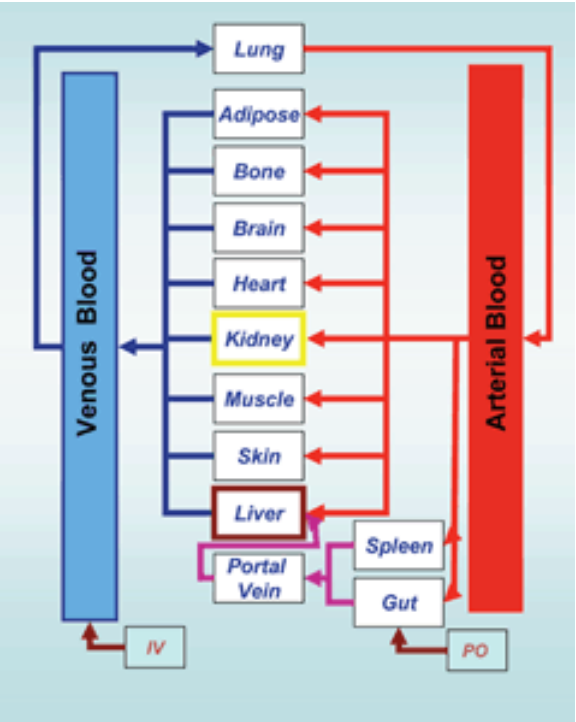
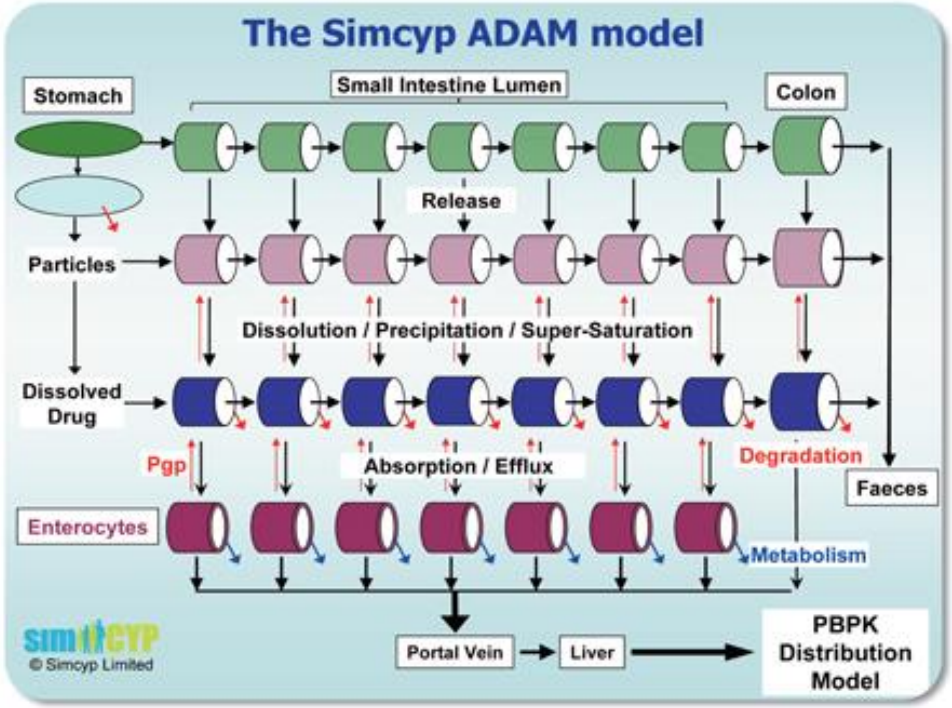
Mechanistic approach

- PK processes of drugs are described by physiologically realistic compartment (anatomy of organism).
- E.g. Whole-body physiologically based pharmacokinetic (PBPK) models, liver metabolism models, absorption model.





PBPK models implemented in Simcyp simulator (www.simcyp.com)

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Mechanistic approach

- The main use is for predicting drug concentrations with the extrapolation techniques
  - i. Inter-species (e.g. rat to human)
  - ii. Inter-tissue (e.g. plasma to less accessible organs)
  - iii. Inter-route (e.g. IV to oral)
  - iv. Inter-drug (e.g. other drug in the same class)

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Example

A whole-body physiologically based pharmacokinetic (WBPBPK) model for children with severe malnutrition

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General method [1]

Input parameters

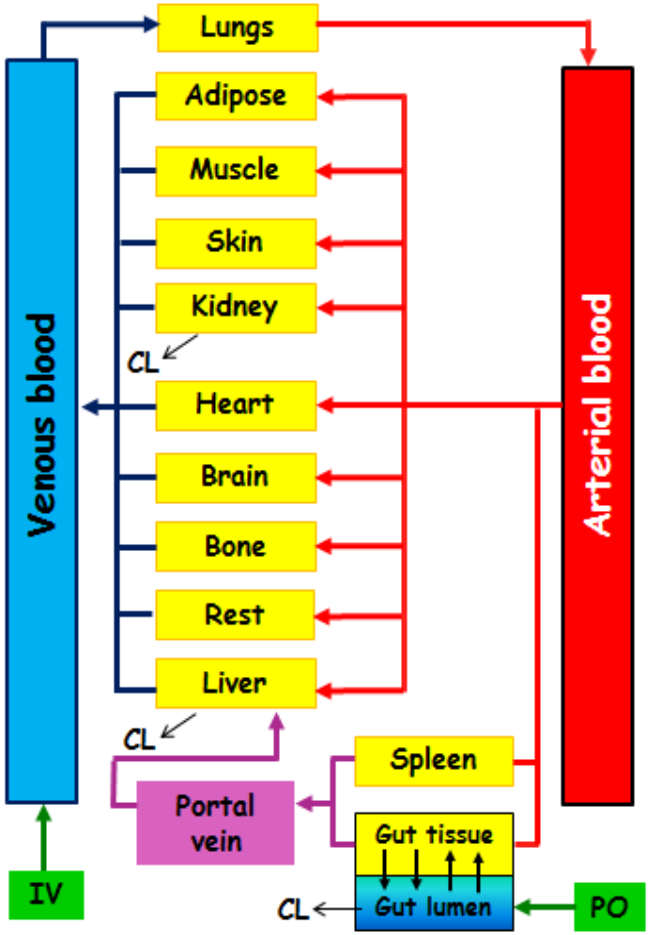
1. Drug specific
- Tissue:plasma partition coefficient (Kp)
- LogP, pKa
- Protein binding (R, fu)
- Solubility, Permeability
- Rate and extent of absorption
- Clearance
- Dosage form, particle size

2. Species specific
- Organ volume
- Organ blood flow

Trial design

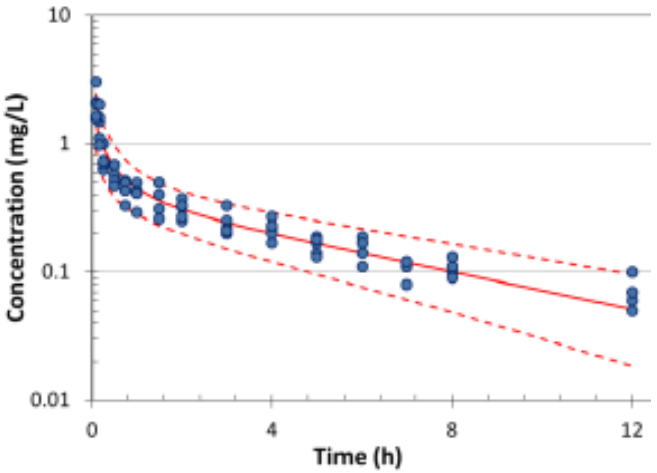
- Dosing regimen
- *n* doses
- *n* subjects
- Demographic data

PBPK model



Output

- Incorporate uncertainty and variability
- Simulate *n* times to obtain median and PIs



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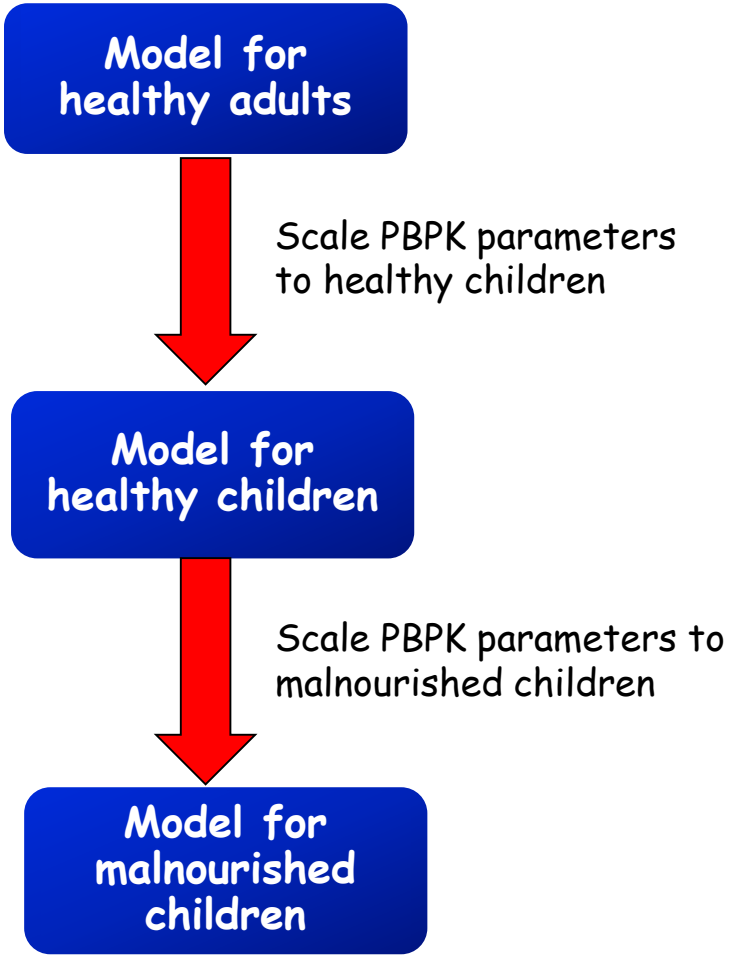
General method [2]



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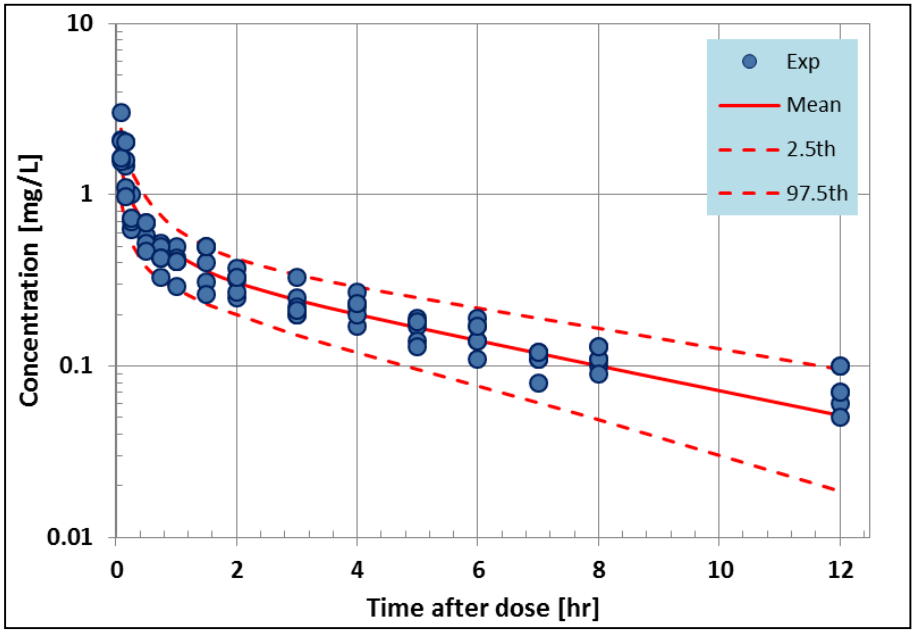
Results: healthy adults

1) IV bolus model (ciprofloxacin 100 mg)

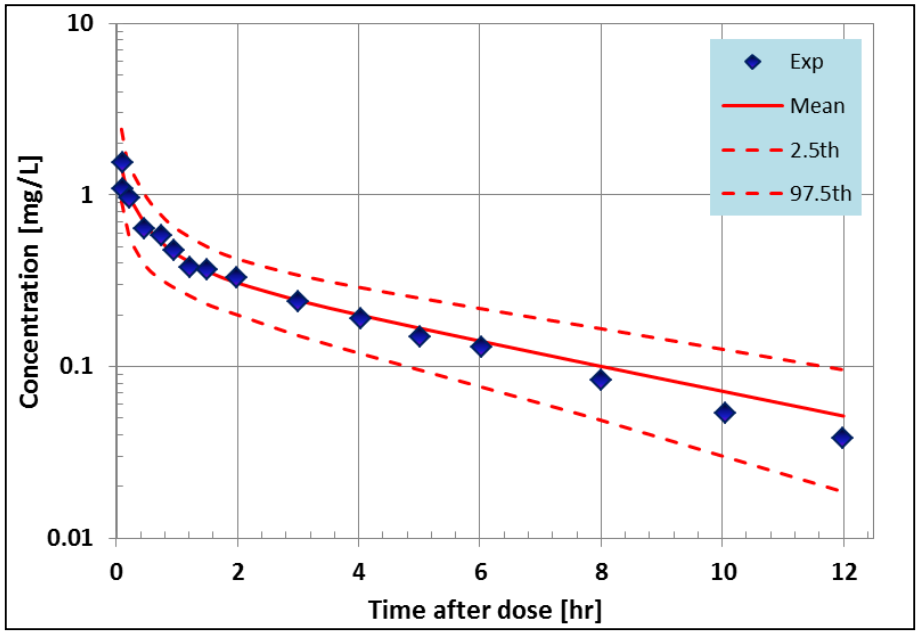
Observed data

Mean simulated data

Prediction interval



Wise et al. Pharmacokinetics of intravenously administered ciprofloxacin. Antimicrob Agents Chemother, 1984; 26:8-10.



Bergan et al. Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses. Eur J Clin Microbiol, 1986;5: 187-92.

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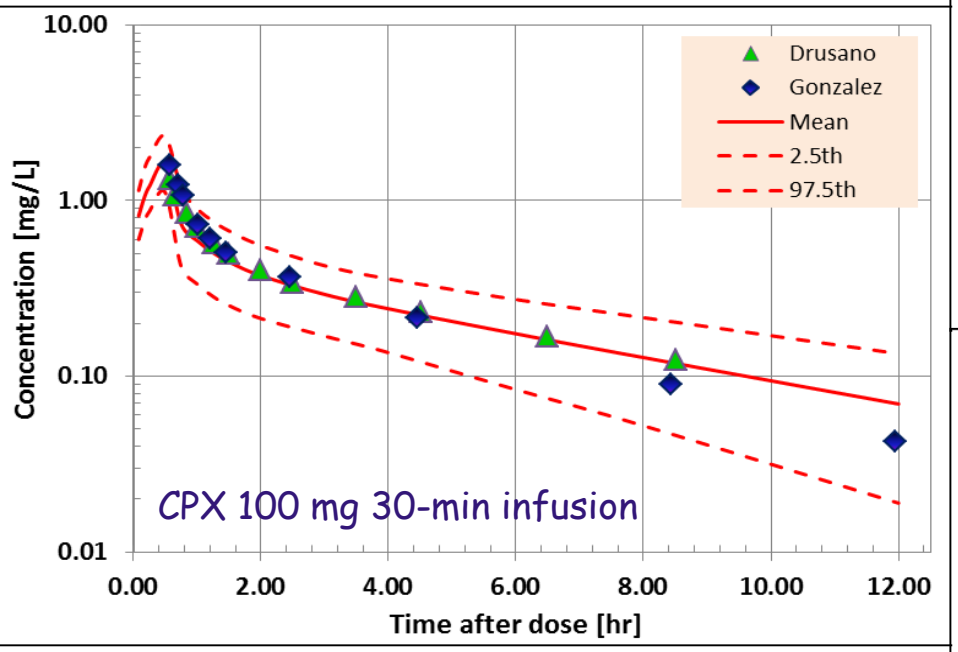
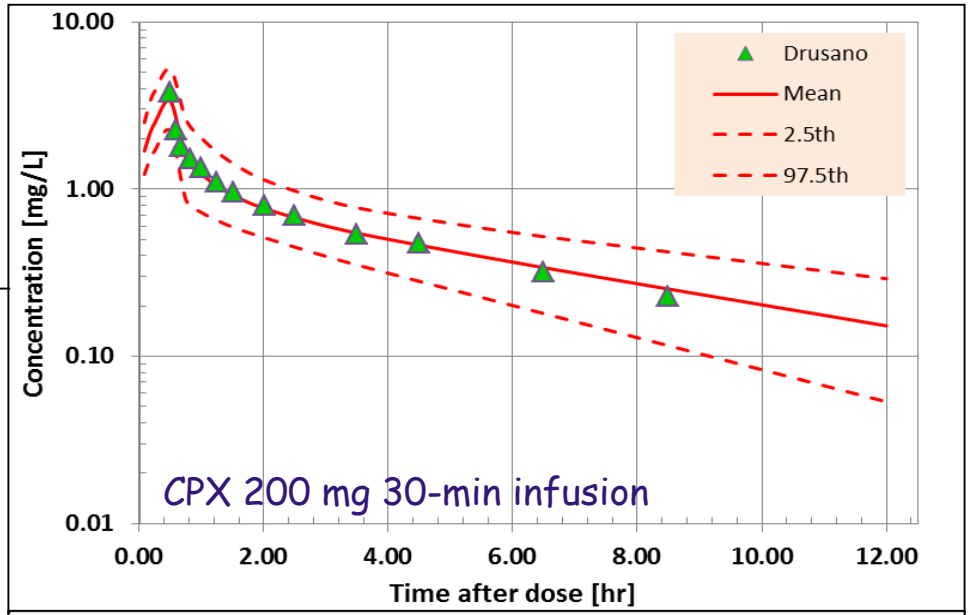
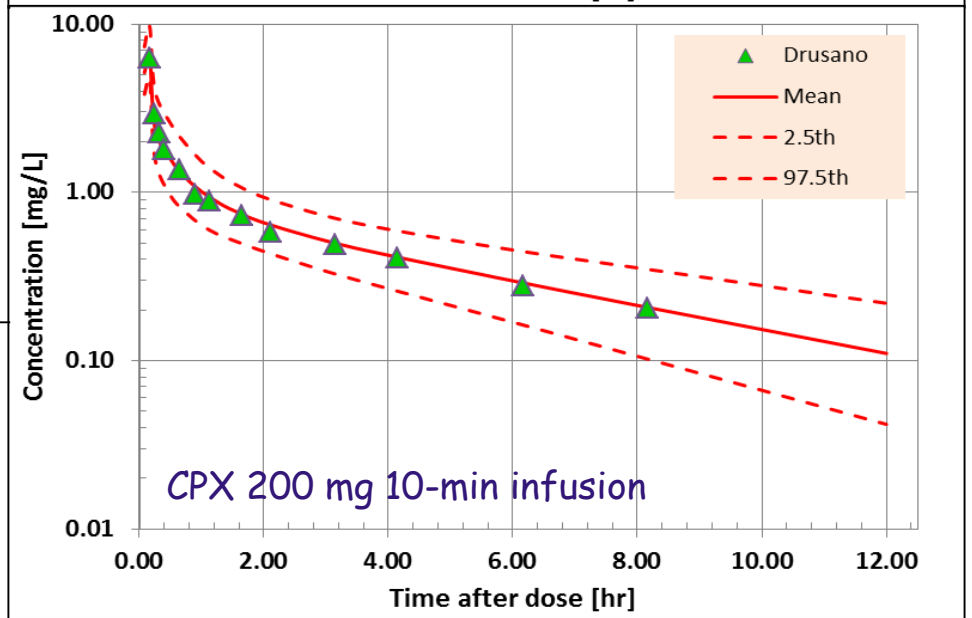
Results: healthy adults

2) IV infusion model







Drusano et al. Antimicrob Agents Chemother, 1986;30: 440-3.

Drusano et al. Antimicrob Agents Chemother, 1987;31: 860-4.

Gonzalez et al. Antimicrob Agents Chemother, 1985;28: 235-9.

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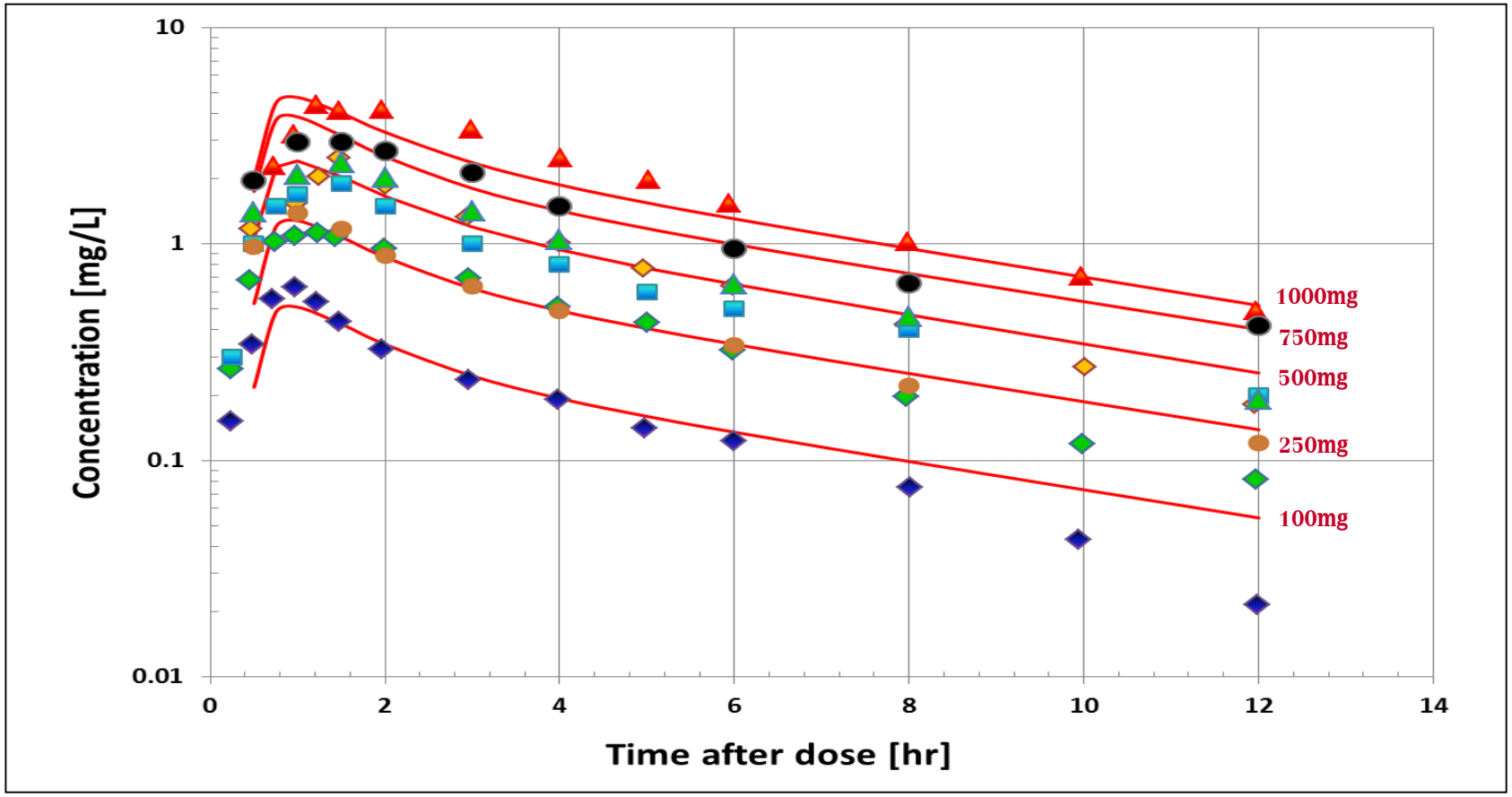
Results: healthy adults

3) Oral model



Bergan et al Pharmacokinetics of ciprofloxacin after intravenous and increasing oral doses. Eur J Clin Microbiol, 1986;5:187-92.

Crump, et al Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob Agents Chemother, 1983;24:784-6.

Gonzalez et al Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother,1984;26:741-4.

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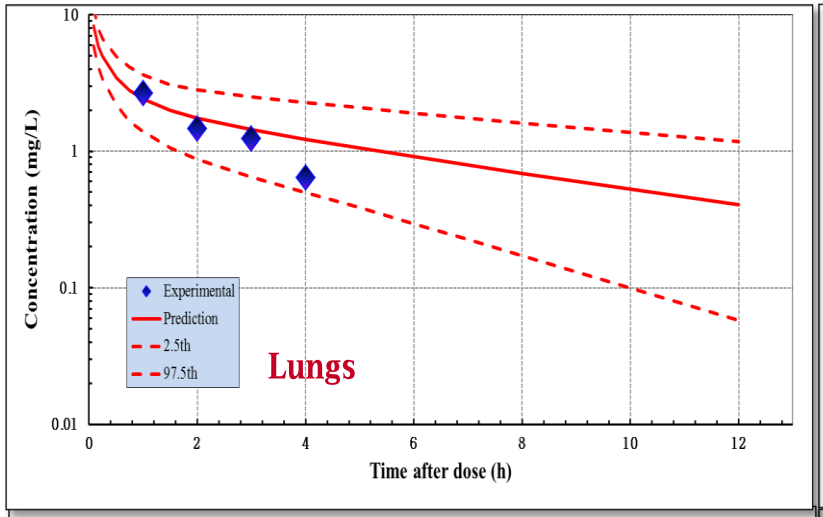
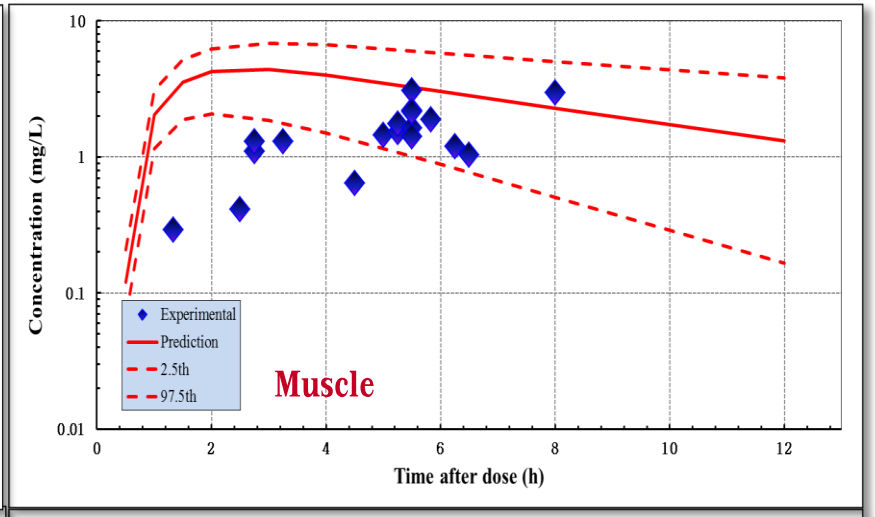
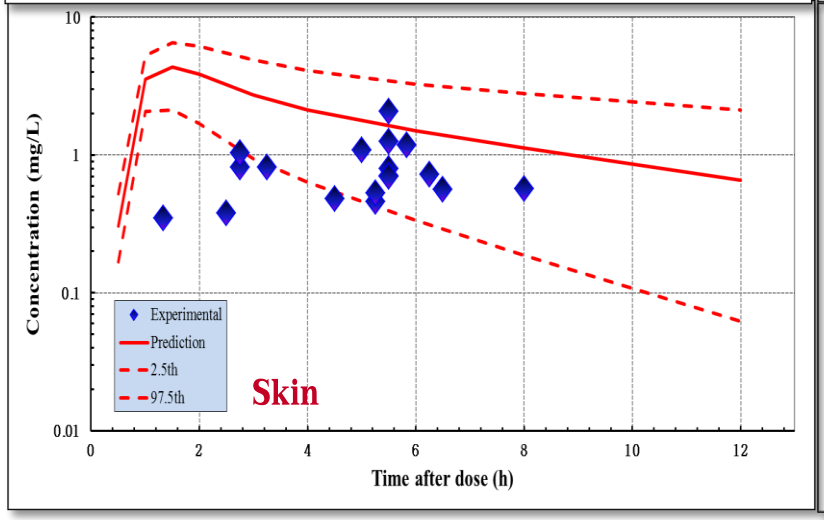
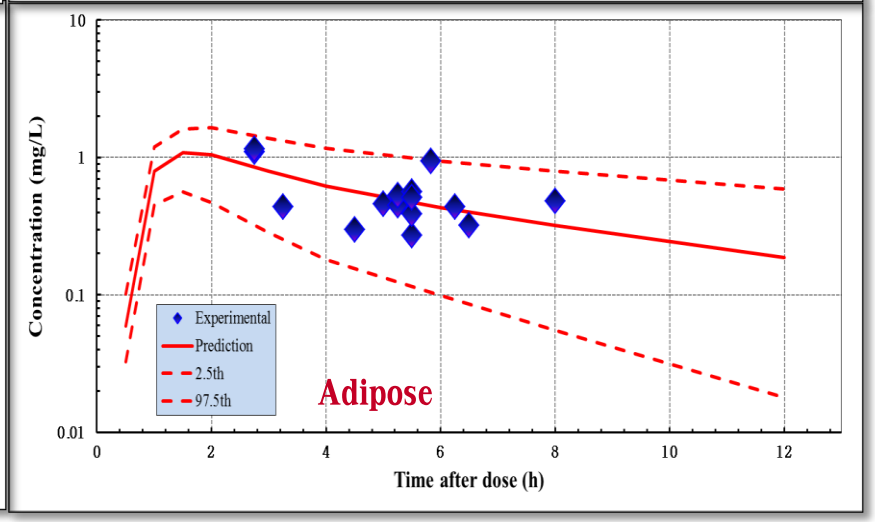
Results: organ concentrations









Aigner, K. R. & Dalhoff, A. 1986. Penetration activities of ciprofloxacin into muscle, skin and fat following oral administration. J Antimicrob Chemother, 18, 644-5.

Schlenkhoff, D., Dalhoff, A., Knoff, J. & Opferkuch, W. 1986. Penetration of ciprofloxacin into human lung tissue following intravenous injection. Infection, 14, 299-300.

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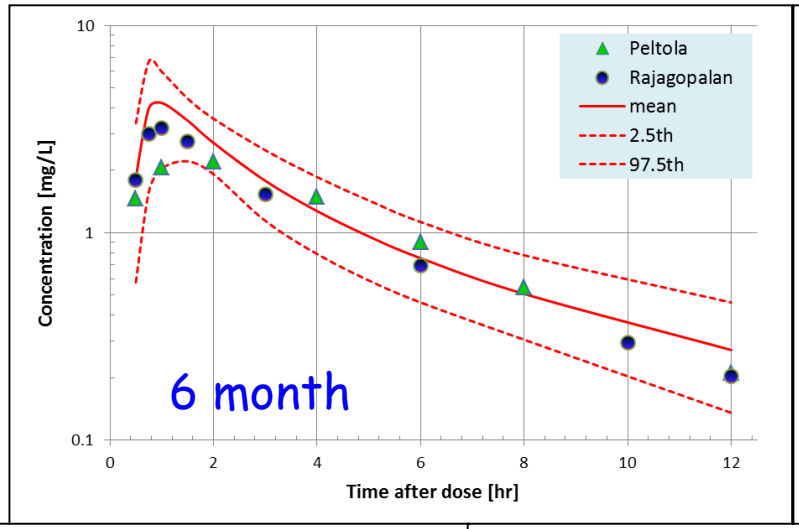
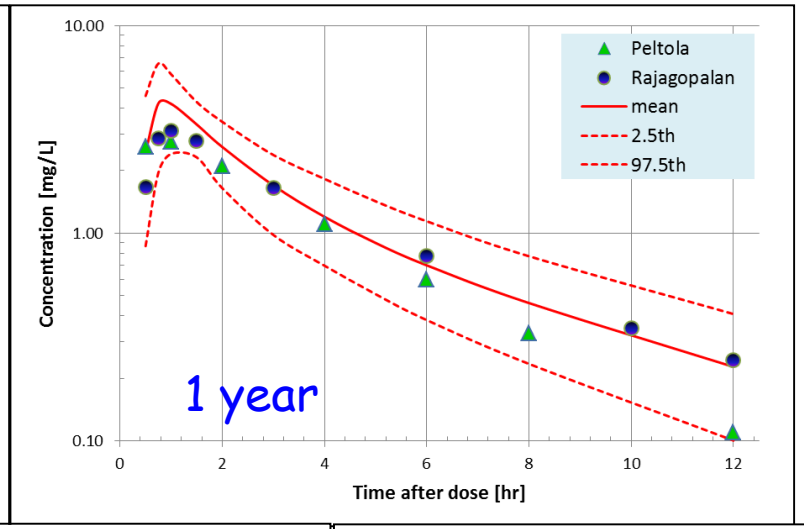
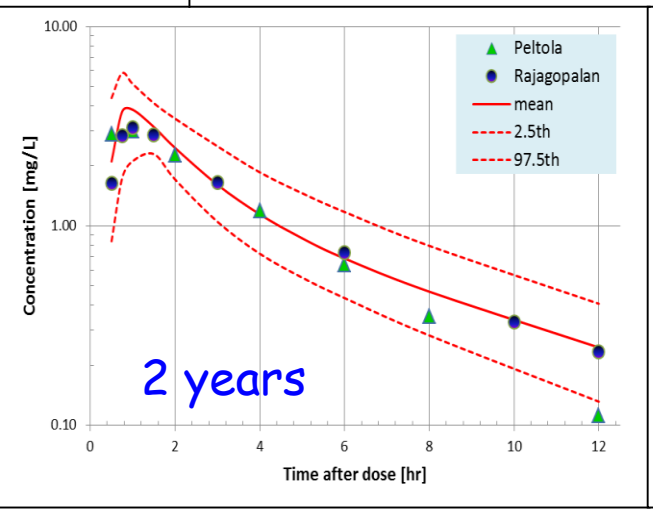
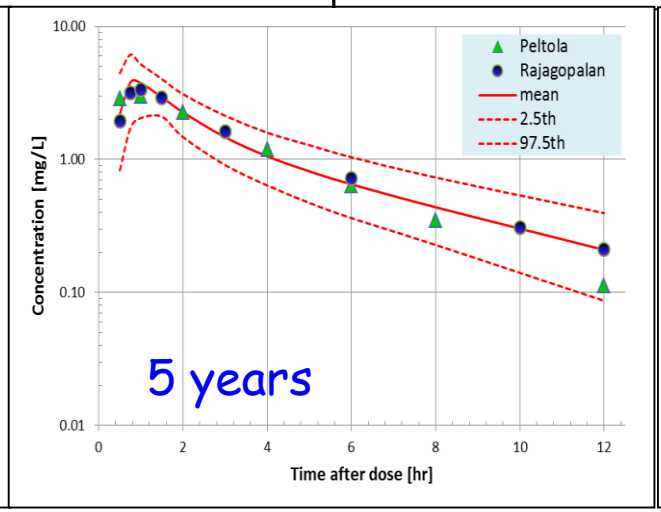
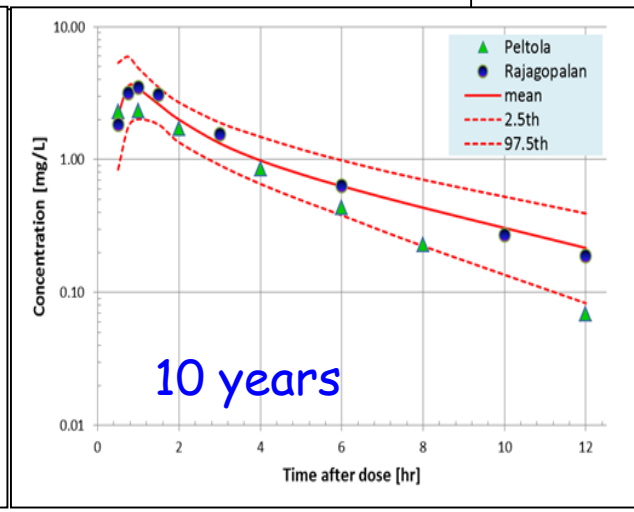
Results: oral model for healthy children











PELTOLA, H., UKKONEN, P., SAXEN, H. & STASS, H. 1998. Single-dose and steady-state pharmacokinetics of a new oral suspension of ciprofloxacin in children. Pediatrics, 101, 658-62.
RAJAGOPALAN, P. & GASTONGUAY, M. R. 2003. Population pharmacokinetics of ciprofloxacin in pediatric patients. J Clin Pharmacol, 43, 698-710.

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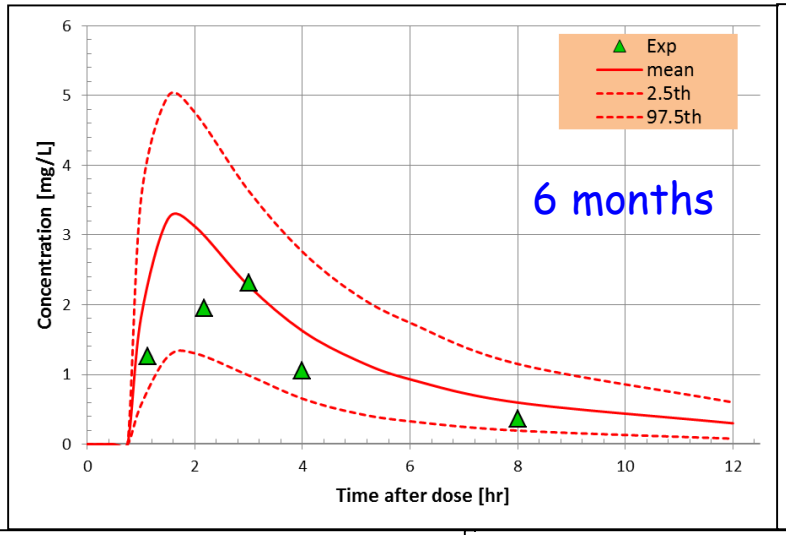
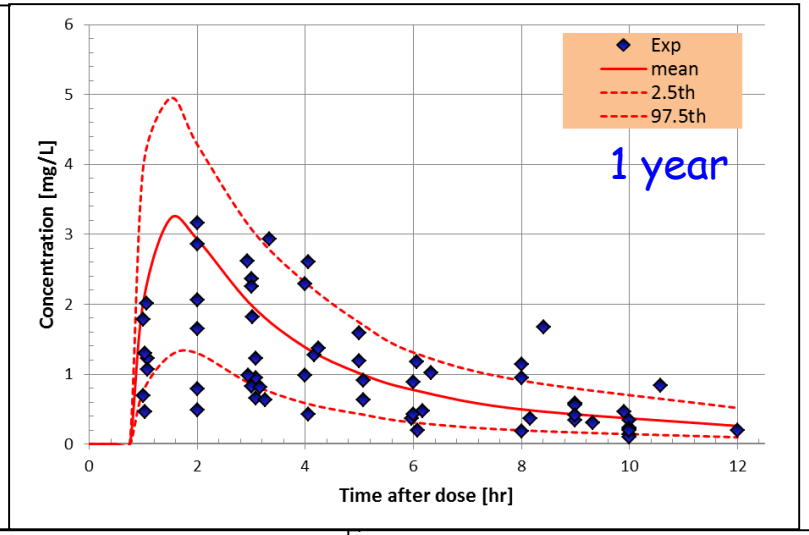
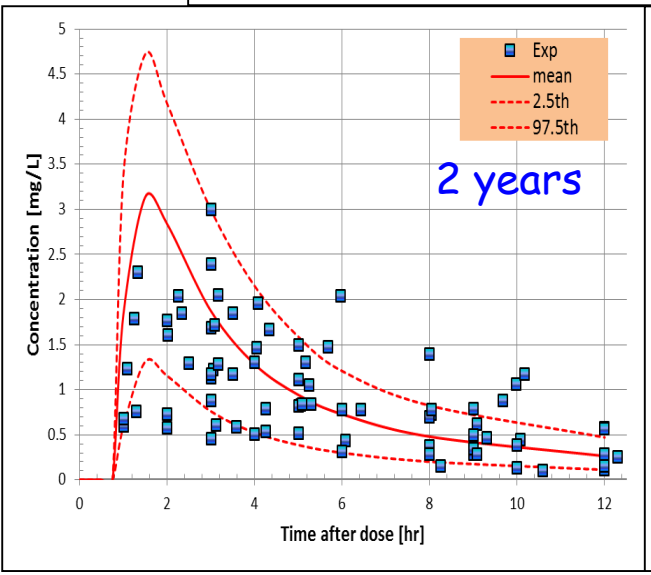
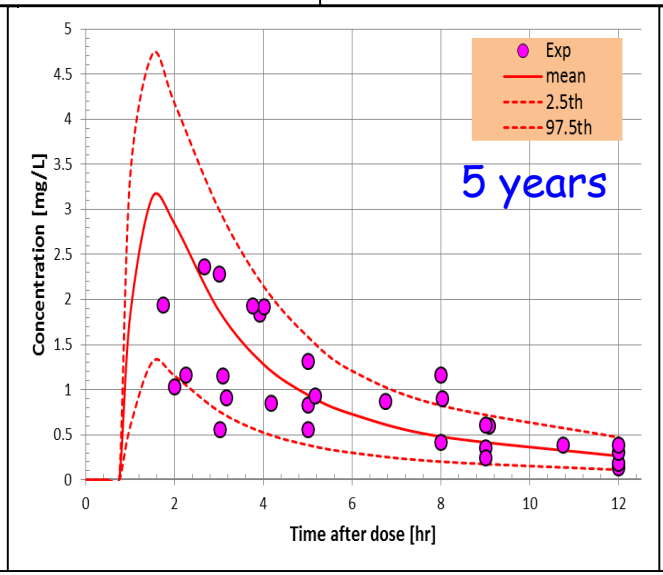
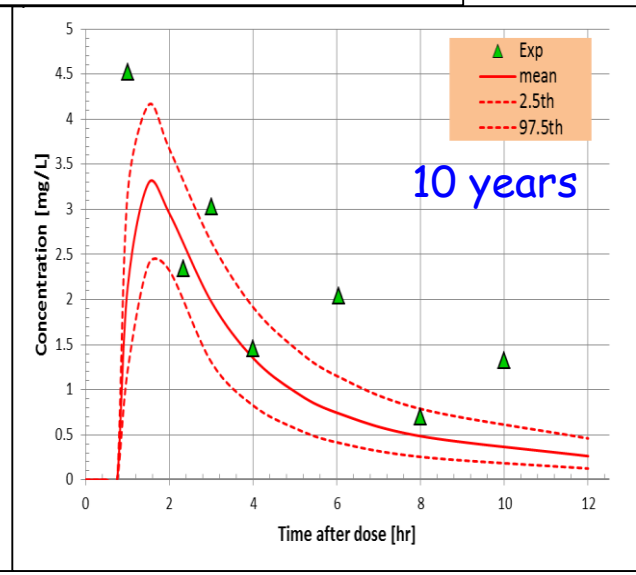
Results: oral model for malnourished children











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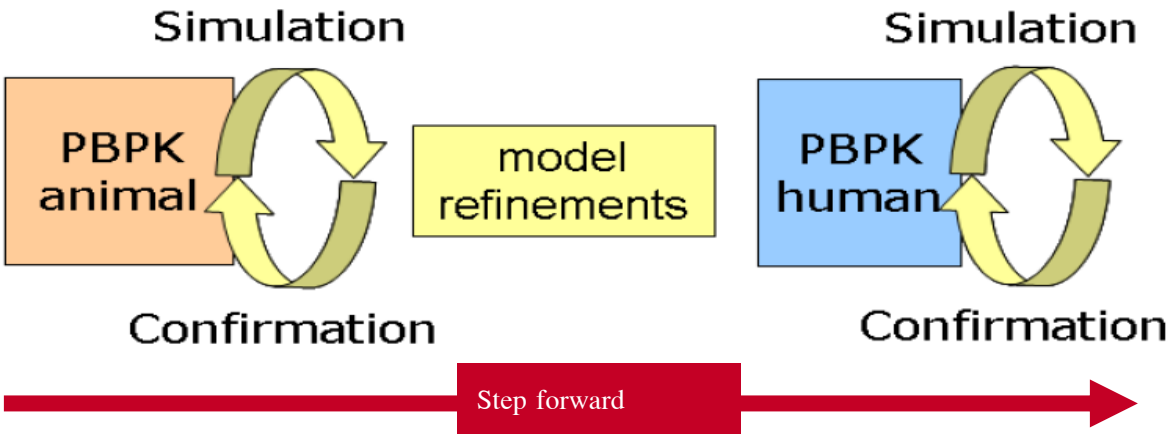
Application

i. Drug discovery and development: ”*learn & confirm*”



If the model prediction is adequate, then do step forward.

If the model prediction is inadequate, there are some systems that we do not know yet.

ii. Patient care

Predict drug concentrations, efficacy and toxicity for special popualtions

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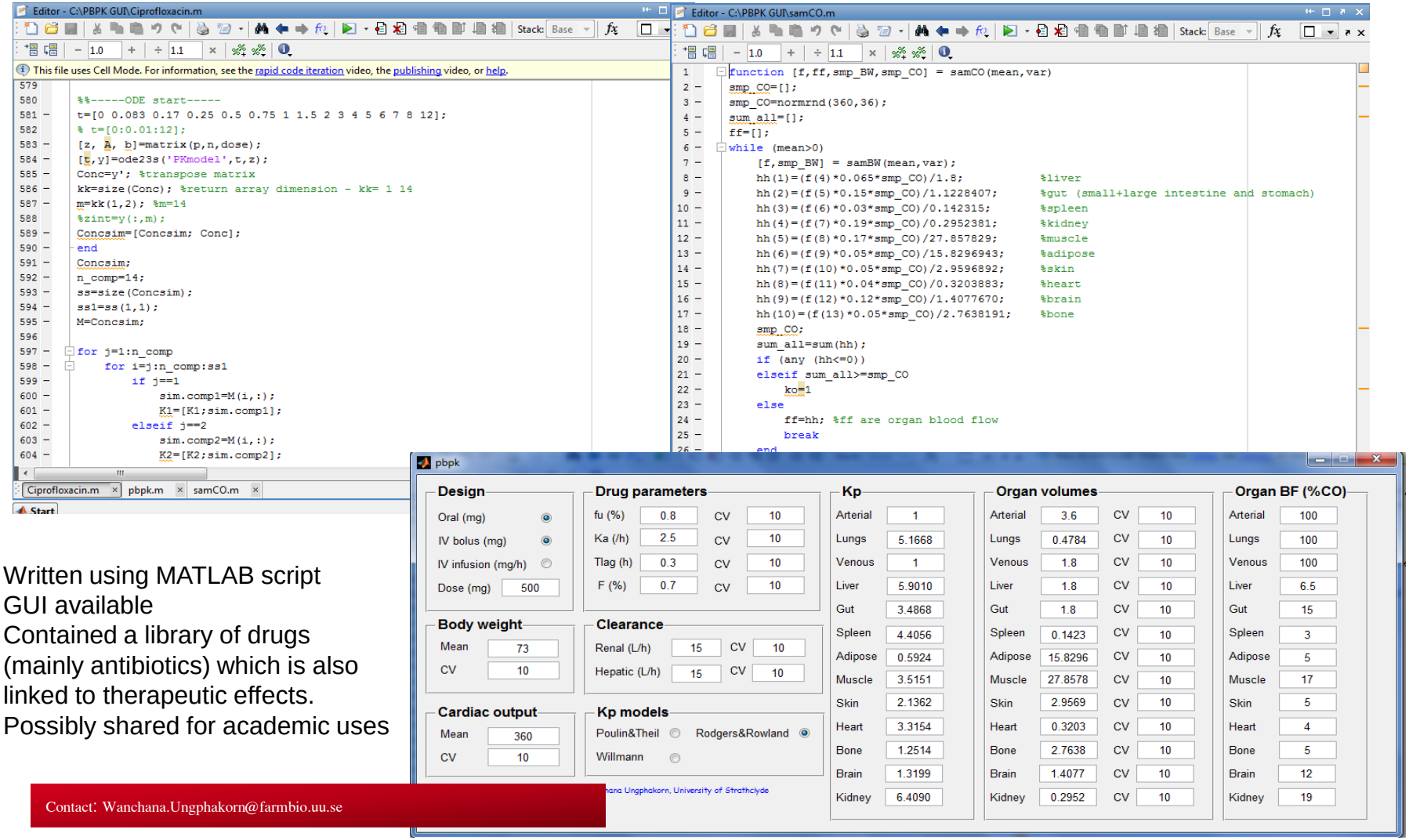
Program for PBPK simulation



- Written using MATLAB script
- GUI available
- Contained a library of drugs (mainly antibiotics) which is also linked to therapeutic effects.
- Possibly shared for academic uses

Contact: Wanchana.Ungphakorn@farmbio.uu.se

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Pharmacometrics research group, Uppsala University

- World's largest with more >60 members devoted to both methodological development and applications in drug development and therapy.

- Collaboration projects:
  1. DDMoRe – The Drug Disease Model Resources
  2. PreDiCT-TB - Model-based preclinical development of anti-tuberculosis drug combinations
  3. OrBiTo – Oral Biopharmaceutics Tools
  4. AIDA – preserving old antibiotics for the future

- Visiting student and researcher are welcome

- UPSS – Uppsala Pharmacometrics Summer School

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Uppsala: Sweden's old capital city (~70 km from Stockholm)

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Model equations

- Mass of the drug in each organ was calculated using Linear ordinary differential equations (LODE)

1) Non-eliminating organs:

$$V_{T,i} \frac{dC_{T,i}}{dt} = Q_{T,i} \times (C_A - \frac{C_{T,i}}{Kb_i})$$

2) Eliminating organs (kidney, liver, gut):

$$V_{T,i} \frac{dC_{T,i}}{dt} = \left[Q_{T,i} \times (C_A - \frac{C_{T,i}}{Kb_i}) \right] - CL_{int} \times \frac{C_{T,i}}{Kpu_i}$$

C = concentration (mg/L), Q = blood flow (L/h), Kb = tissue:blood partition coefficient, Kpu = tissue:plasma unbound partition coefficient, CLint = intrinsic clearance (L/h), V = volume (L), T = tissue, A = arterial blood, i = each organ in the model

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in silico Kp prediction

- Based on in vitro data of i. drug lipophilicity ($LogP_{O:W}$), ii. protein binding (fu, R) and iii. tissue composition

Tissues	Tissue composition (fraction of tissue wet weight)					
	Water	Extracellular water	Intracellular water	Neutral lipids	Neutral phospholipids	Acidic phospholipids
Bone	0.45	0.074	0.0011	0.346	0.100	0.67
Brain	0.78	0.051	0.0565	0.620	0.162	0.40
Gut	0.76	0.0487	0.0163	0.475	0.282	2.41
Heart	0.78	0.0115	0.0166	0.456	0.320	2.25
Kidney	0.76	0.0207	0.0162	0.483	0.273	5.03
Liver	0.73	0.0348	0.0252	0.573	0.161	4.56
Lung	0.78	0.003	0.009	0.446	0.336	3.91
Muscle	0.71	0.022	0.0072	0.630	0.079	2.42
Skin	0.67	0.0284	0.0111	0.291	0.382	1.32
Spleen	0.79	0.0201	0.0198	0.579	0.207	3.18
Adipose	0.15	0.79	0.002	0.017	0.135	0.4
Plasma	0.95	0.0032	0.0021	-	-	-
Blood cells	0.63	0.0012	0.0033	0.603	-	0.57

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1) Poulin and Theil method

$$Kp = \frac{\left[P \cdot (V_{nl} + 0.3V_{ph}) + V_w/fu_t + 0.7V_{ph}\right]_{\text{-tissue}}}{\left[P \cdot (V_{nl} + 0.3V_{ph}) + V_w/fu_p + 0.7V_{ph}\right]_{\text{-plasma}}}$$

2) Rodgers and Rowland method

$$Kpu_{BC} = \left[\frac{(Hct - 1) + R}{fu + Hct}\right]$$

$$X = 10^{pKa_{BASE} - pH_{iw}} + 10^{pH_{iw} - pHa_{ACID}};\ Y = 10^{pKa_{BASE} - pH_p} + 10^{pH_p - pHa_{ACID}};\ Z = 10^{pKa_{BC} - pH_{iw}} + 10^{pH_{iw} - pHa_{BC}}$$

$$Ka_{AP} = \left[Kpu_{BC} - \left(\frac{1+Z}{1+Y} \cdot V_{iw,BC}\right) - \left(\frac{P \cdot V_{nl,BC} + (0.3P+0.7) \cdot V_{nl,BC}}{1+Y}\right)\right] \cdot \left(\frac{1+Y}{AP_{BC} \cdot Z}\right)$$

$$Kpu = \left[\left(\frac{1+X \cdot V_{iw}}{1+Y}\right) + V_{ew} + \left(\frac{Ka_{AP} \cdot AP \cdot X}{1+Y}\right) + \left(\frac{P \cdot V_{nl} + (0.3P+0.7) \cdot V_{ph}}{1+Y}\right)\right]$$

P = $P_{O:W}$ and $D_{VO:W}$ for lean and adipose tissues, respectively. $D_{VO:W}$ were estimated using linear regression and Henderson-Hasselbalch equations. Kp = Kpu·fu

3) Empirical method

$$Vss = V_{plasma} + (V_{BC} \cdot RBC_u \cdot fu) + \sum_{i=i}^{n} V_{t,i} \times 10^{a_{t,i} \times \log Kp_{muscle} + b_{tissue,i} \times \log X_{drug} + intercept_{tissue,i}}$$