WORLDWIDE ANTIMALARIAL RESISTANCE NETWORK

WWARN

Non-compartmental PK-PD analysis

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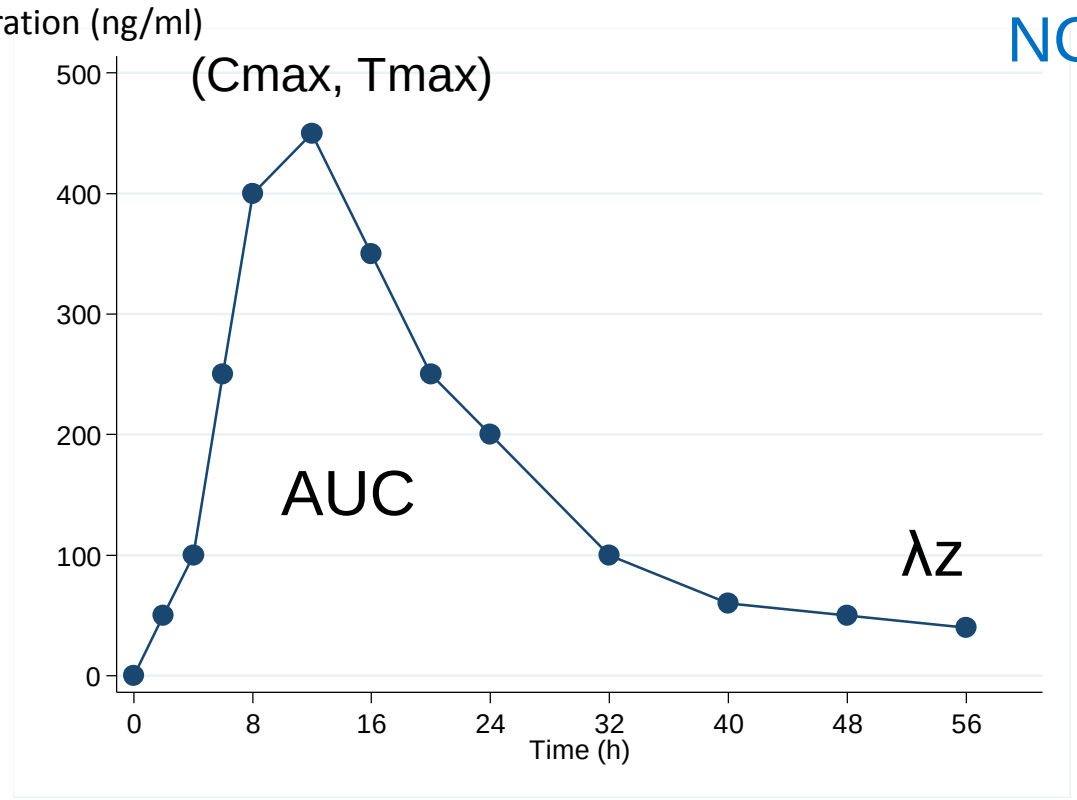
Principles of NCA

No assumptions made about kinetic model

Based on estimation of total drug exposure

Dependent on sampling frequency and timing

Principles of NCA



NCA gives estimates of:

Drug absorption
Total drug exposure
Drug elimination

Total body clearance
Volume of distribution

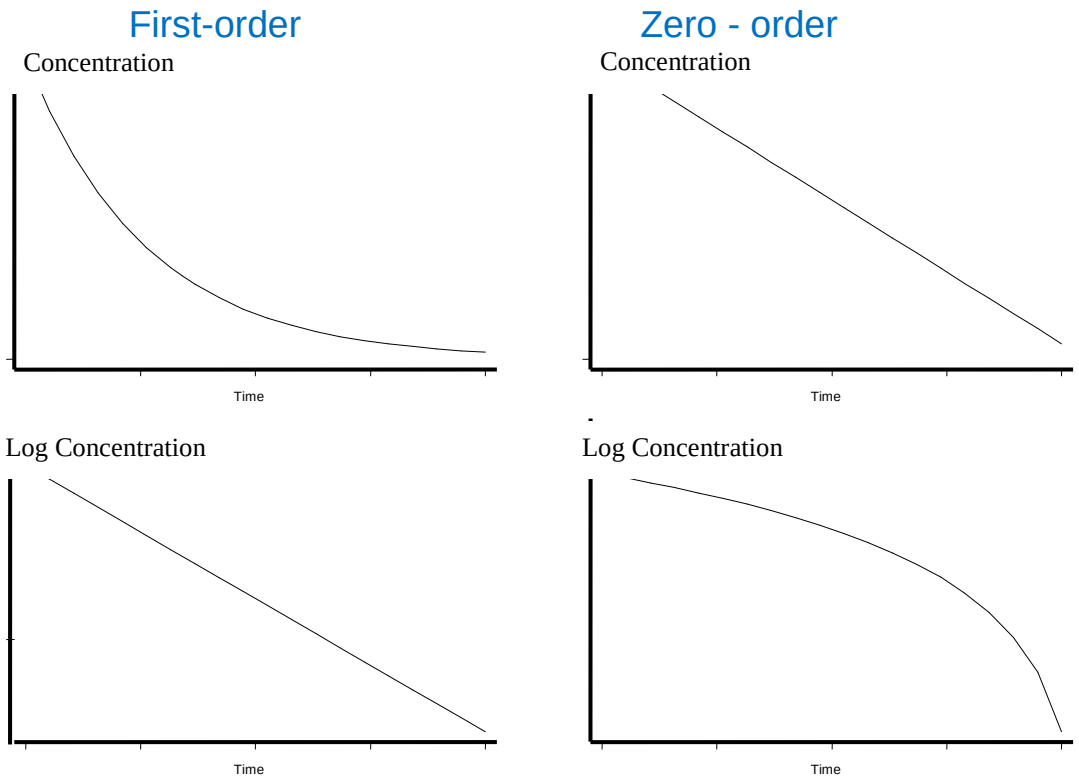
First order process

First-order process = a fixed <u>fraction</u> of the drug is absorbed, metabolised or eliminated per unit time.
Zero-order process = a fixed <u>amount</u> of the drug is processed per unit time.

Original Scale

↓

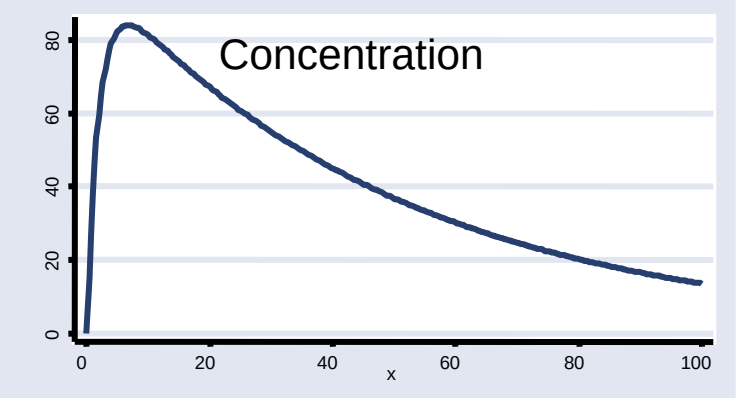
Log Scale

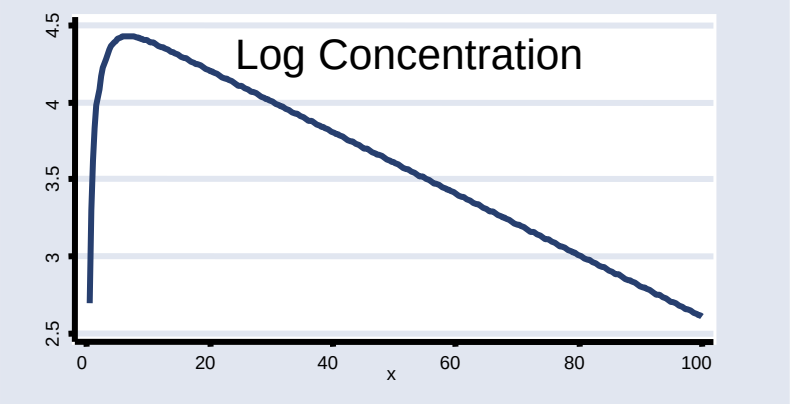


First order process: Time taken for the concentration to change by half (reduced by 50%) is always the same = Elimination half life $T_{1/2}$

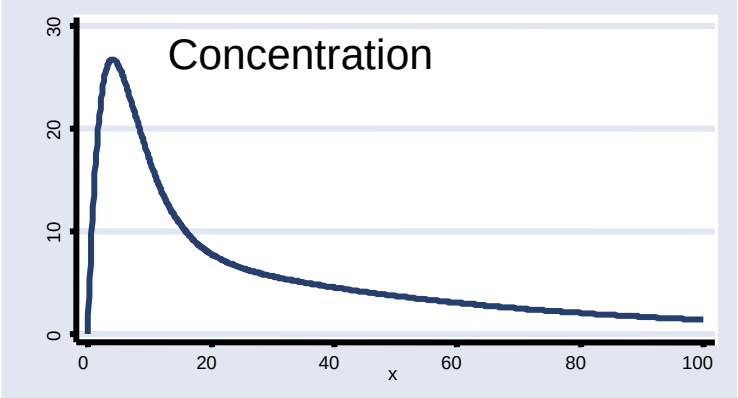
Drug elimination – first order process

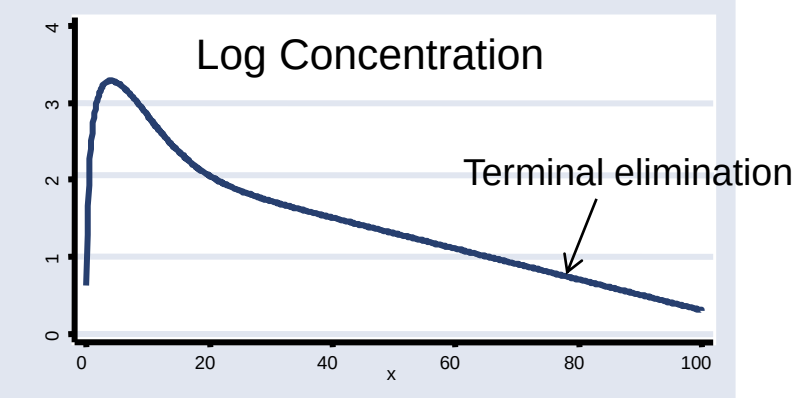
Constant elimination rate ~ One compartment model



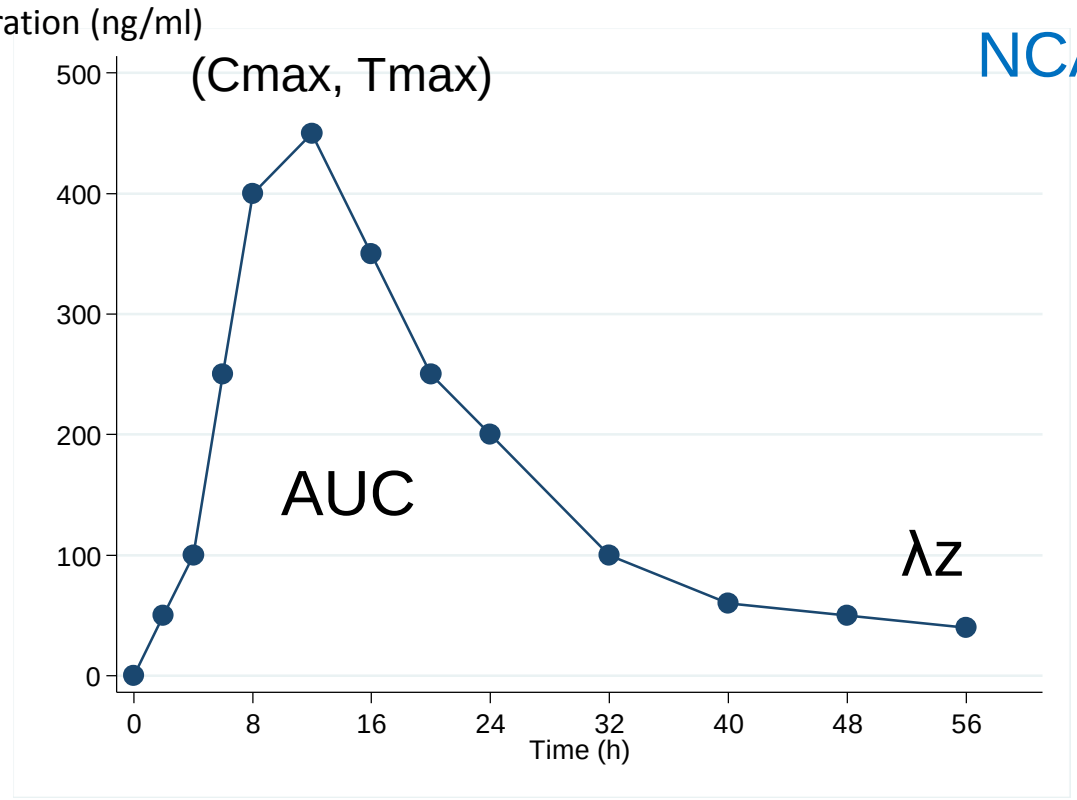


Fast elimination rate initially ~ Two compartment model





Principles of NCA



NCA gives estimates of:

Drug absorption
Total drug exposure
Drug elimination

Total body clearance
Volume of distribution

Measures of absorption/exposure: Tmax Cmax

Cmax = maximum concentration

Peak drug concentration obtained directly from the data without interpolation

Tmax = time of maximum concentration

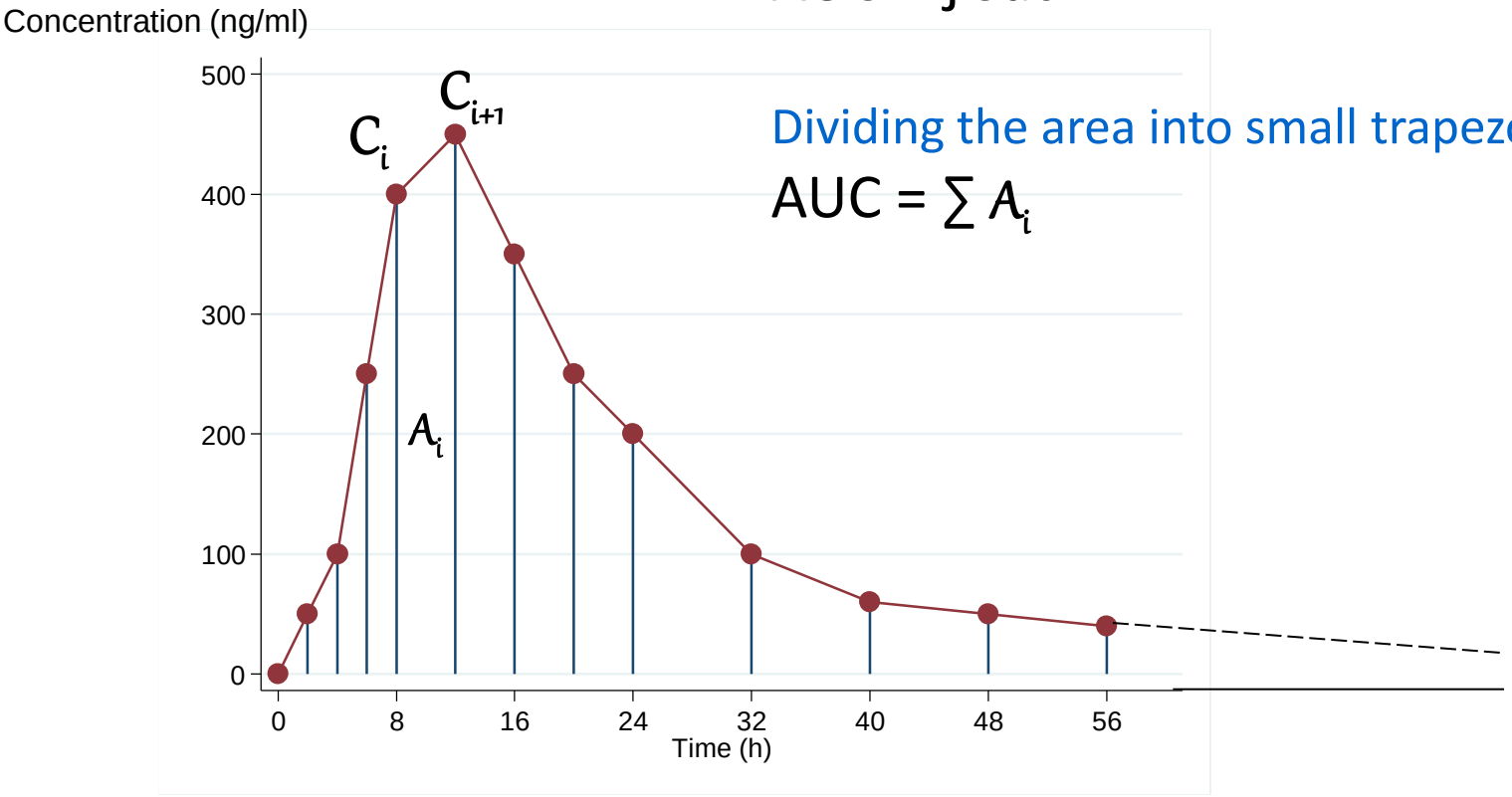
Actual time when the peak concentration was measured

- Sampling around expected concentration peak is required to provide adequate estimation of Cmax

- Precision of Tmax determined by frequency of sampling

Area under Concentration-Time curve

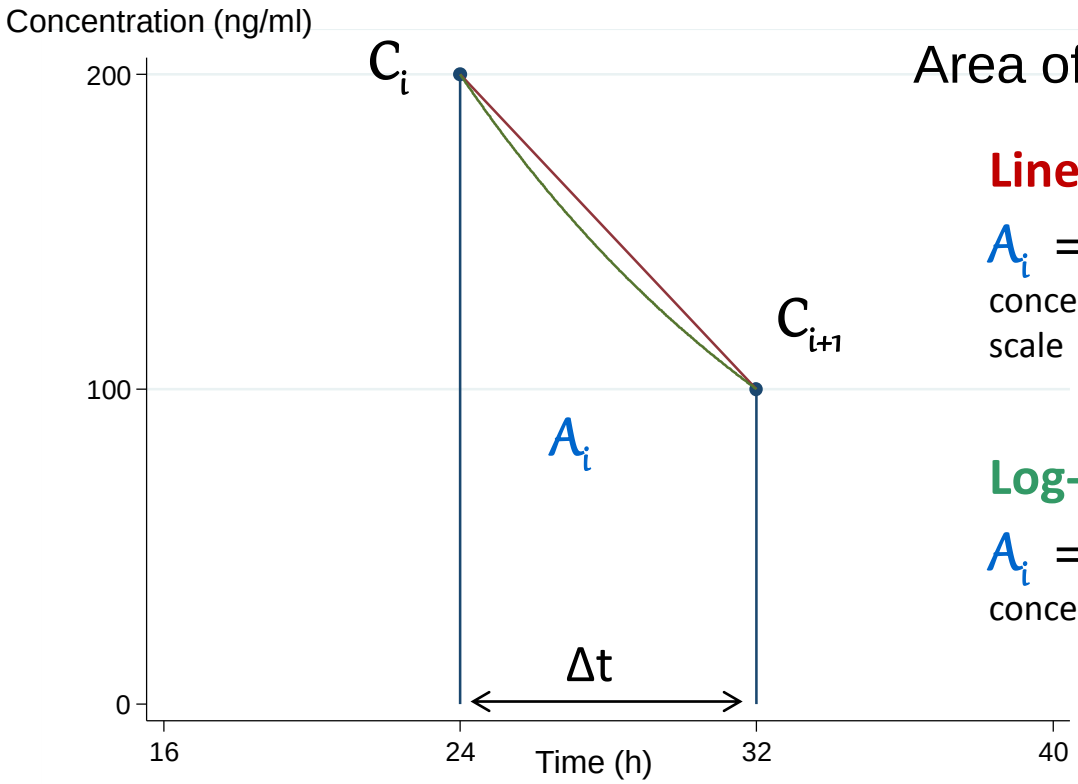
$$AUC = \int C dt$$



Dividing the area into small trapezoids A_i

$$AUC = \sum A_i$$

Estimation of AUC observed – trapezoid method



$$AUC = \sum A_i$$

Area of A_i can be calculates as:

Linear trapezoid method

$$A_i = (C_i + C_{i+1}) / 2 \times \Delta t$$

concentrations connected by straight line on the original scale

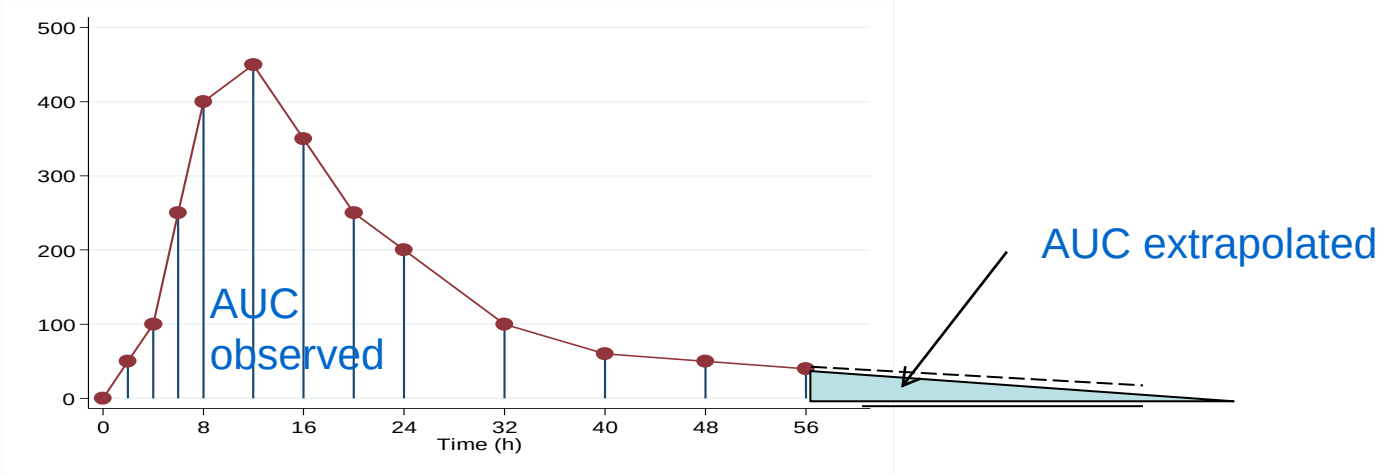
Log-linear trapezoid method

$$A_i = (C_i - C_{i+1}) / ln(C_i / C_{i+1}) \times \Delta t$$

concentrations connected by straight line on the log scale

UNITS: concentration × time so for example: ng/ml × h

Estimation of AUC to infinity: $AUC_{0-\infty}$



$AUC_{0-\infty}$ = AUC observed + AUC extrapolated

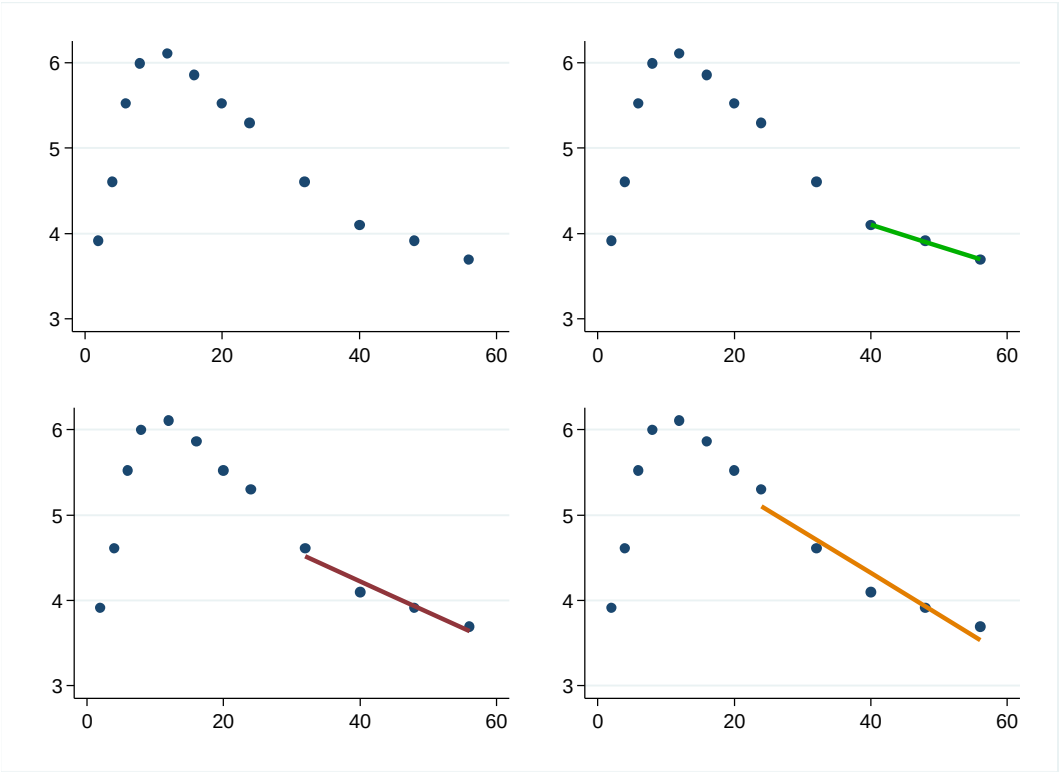
$AUC_{0-\infty} = AUC_{0-t_{last}} + C_{last} / \lambda z$

$AUC_{0-t_{last}}$ = AUC observed – calculated as before using tapezoid or log-trapezoid rule

C_{last} = last measured concentration

λz = terminal elimination rate constant **NEED TO ESTIMATE**

Estimation of terminal elimination rate constant



Slope= -0.0275
$T_{1/2}$ = 25h

Slope=-0.0366
$T_{1/2}$ = 19h

Slope = -0.0489
$T_{1/2}$ = 14h

Regression line fitted to terminal phase datapoints on log-scale

Terminal elimination rate constant λz = - slope (UNITS: h^{-1})

Elimination half life $T_{1/2}$ = log(2)/ λz (UNITS: h)

Estimation of AUC to infinity: $AUC_{0-\infty}$

- Selection of points to estimate terminal rate constant:

very important; at least 3-4 points; strategy for selection should be clear; individual concentration profiles should be visually examined

- Measured last concentration can be different from the predicted terminal regression line

estimated last concentration should be used instead

- % AUC extrapolated is an useful measure of precision of estimates:

$$AUC_{ext} = = AUC_{t_{last}-\infty} / AUC_{0-\infty} \times 100\%$$

<25% - good estimate

< 20% - required for bioequivalence studies

Physiological parameters

Clearance = volume of blood (or plasma) cleared completely of drug per unit time.

C_L = Dose / $AUC_{0-\infty}$ (UNITS: L/s or L/s/kg if dose per kg)

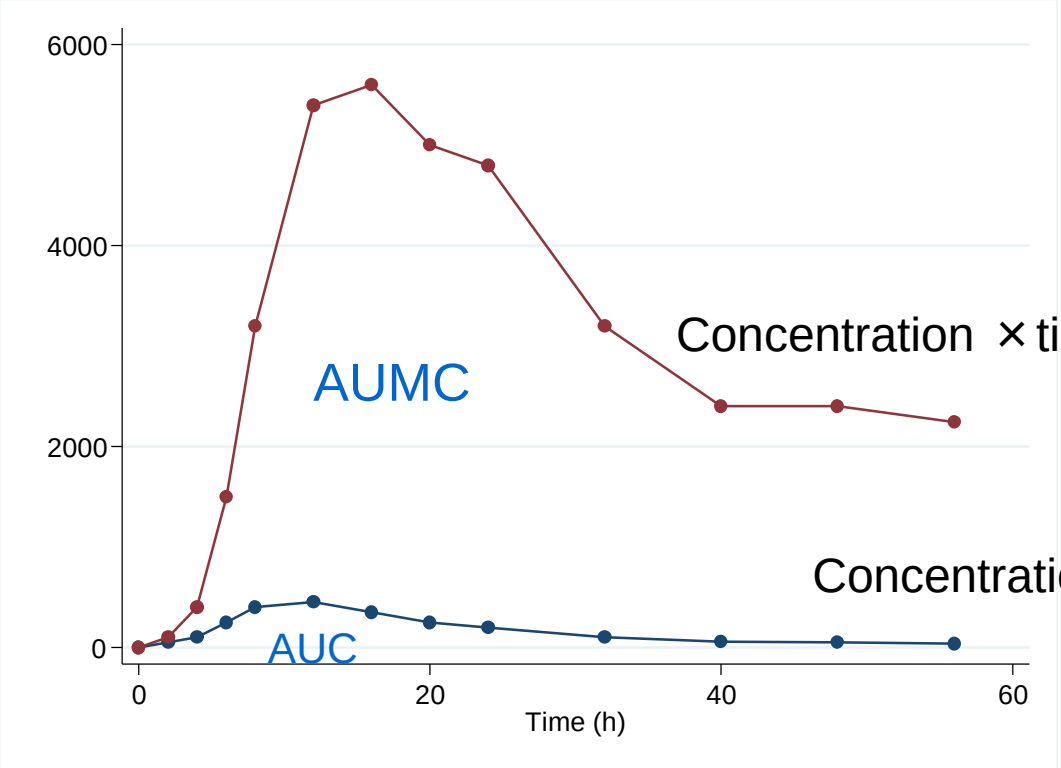
any administration, model independent

Volume of distribution = apparent volume the drug is distributed in

$V = CL / \lambda z$ (UNITS: L or L/kg if dose per kg)

any administration,
volume of distribution in one compartment model OR
volume of distribution during the terminal phase

Mean Resisidence Time: MRT



AUMC = area under Concentration × time - time curve

AUC = area under Concentration - time curve

Mean Residence Time: MRT

Mean residence time

$$MRT = AUMC / AUC \qquad \text{(UNITS: s)}$$

$$AUMC_{t_{last}-\infty} = C_{last} \times t_{last} / \lambda z + C_{last} / \lambda z^2$$

MRT = average length of time a drug molecule stays in circulation.

MRT = time needed for 63.3% of the dose to be eliminated via all routes of elimination

$MRT_{bolus} = 1.44\ T_{1/2}$ - one compartment model, bolus injection

$MRT_{bolus} \approx 1.44\ T_{1/2\beta}$ - two compartment model, $\alpha >> \beta$

$MRT_{oral} = MRT_{bolus} + 1/Ka$ Ka- absorption rate constant

Sampling strategies

Sampling schedule crucial for reliable NCA estimates

- Based on the shape of concentration-time curve, if known
- At least 3 half-lives covered
- Unevenly spaced over time
- More sampling points around the expected curve shape changes
- Depends on the primary aim of the study
- Record the real time