Mathematics & Biostatistics

Lecture 4

Applications of Area Under the Curve (AUC) in Pharmacy

First Year – College of Pharmacy

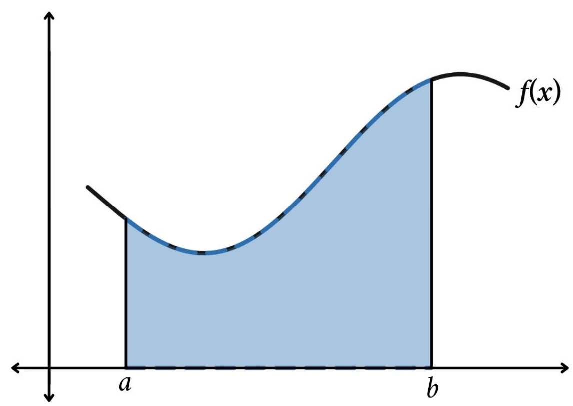
Saif M. Hassan

Ph.D. Pharmacology and Therapeutics

What is AUC?

Mathematical Definition

$$\text{AUC} = \int_{t_1}^{t_2} C\,(t)\,dt$$



$$Area = \int_a^b f(x)dx$$

Where:

- $C(t)$ = Concentration at time t
- t_1, t_2 = Time interval limits

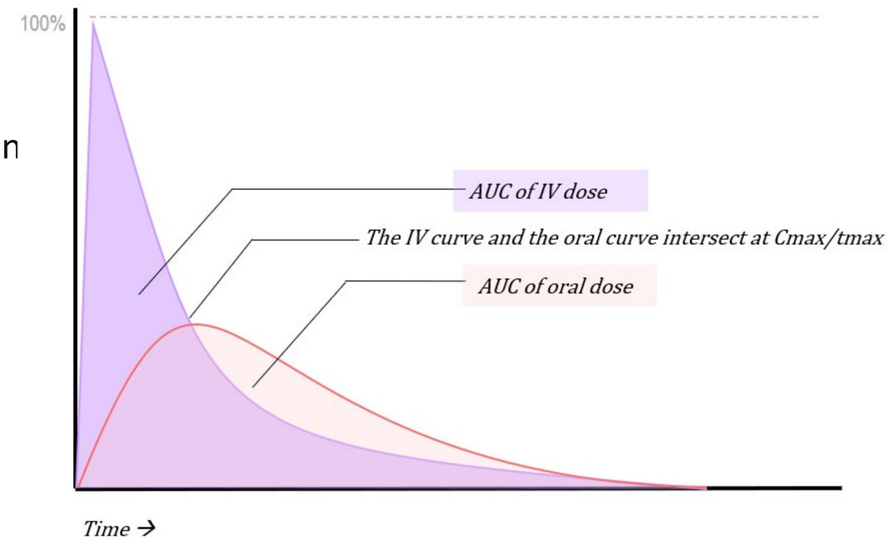
Geometric Meaning: Area between concentration-time curve and time axis

Primary Applications

1 - Bioavailability (F)

Comparing Drug Formulations

Bioavailability: Fraction of administered dose reaching systemic circulation



Formula:

$$F = \frac{AUC_{oral} \times Dose_{IV}}{AUC_{IV} \times Dose_{oral}}$$

Example:
IV dose: 100 mg, AUC = 500 mg·h/L
Oral dose: 200 mg, AUC = 300 mg·h/L

$$F = \frac{300 \times 100}{500 \times 200} = 0.30 = 30\%$$

Only 30% of oral dose reaches circulation due to first-pass metabolism

Primary Applications

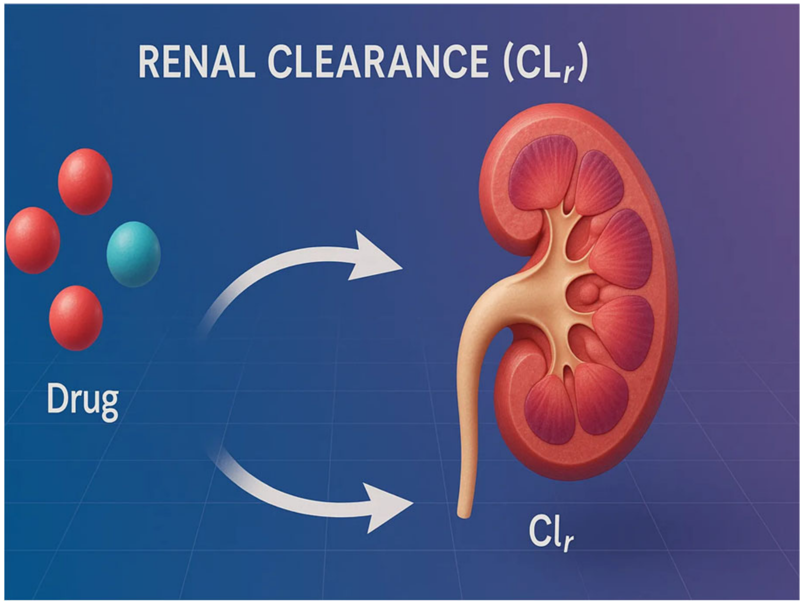
2 - Clearance Calculation

Fundamental PK Relationship

$$\text{Clearance (CL)} = \frac{Dose}{AUC}$$

Where:

- CL = Volume cleared per unit time (L/h)
- Dose = Administered amount (mg)
- AUC = Area under concentration-time curve (mg·h/L)



Clinical Significance:

- Renal impairment → ↓ CL → ↑ AUC
- Liver disease → ↓ CL → ↑ AUC
- Drug interactions → ↑ or ↓ CL → AUC changes

Primary Applications

CL:
Normal pt 2.5-3
Renal problem ≤ 2

Clearance Example - Gentamicin

Therapeutic Drug Monitoring

Patient Data: Dose: 80 mg IV

•Measured AUC_{0-12}: 30 mg · h/L

Calculate the Clearance Calculation and dose adjacent if you need in following patients

1- normal

2- renal impairment

Primary Applications

3 - Bioequivalence Studies

Generic vs. Brand-Name Drugs

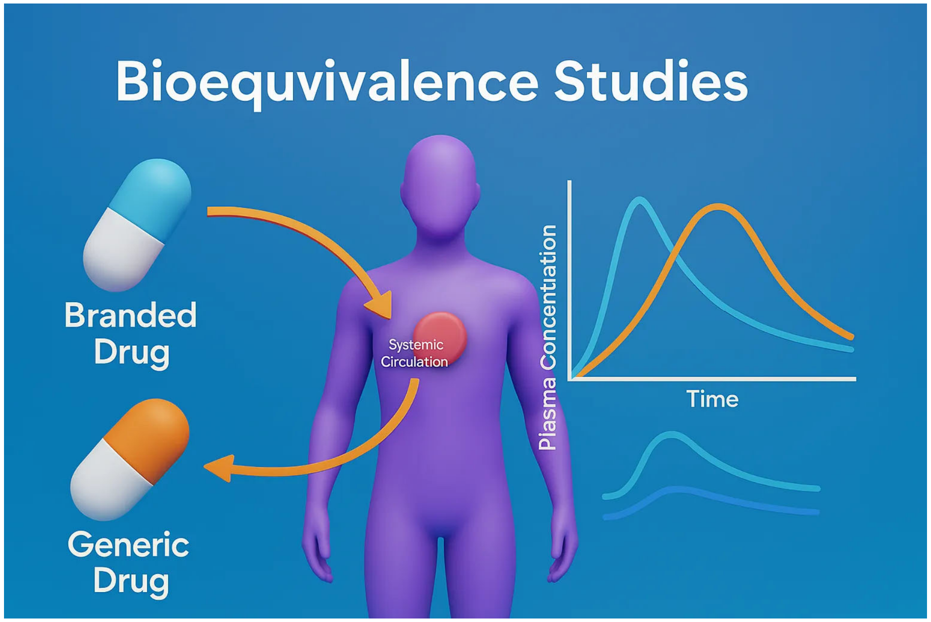
Regulatory requirement (FDA/EMA): Generic must have AUC within 80–125% of reference product

Study Design:

- Administer test and reference products
- Measure AUC_{0-t} (to last measurable point)
- Calculate $AUC_{0-\infty}$ (extrapolated to infinity)

Acceptance Criteria:

$$0.80 \le \frac{AUC_{test}}{AUC_{reference}} \le 1.25$$



Primary Applications

Bioequivalence Example

Two Formulations of Metformin

Reference (Brand): AUC = 10,500 ng·h/mL
Test (Generic): AUC = 9,800 ng·h/mL

Ratio:

$$\frac{9{,}800}{10{,}500} = 0.933 = 93.3\%$$

Interpretation:
93.3% is within 80–125% → **Bioequivalent**
Patients can safely switch between formulations

Primary Applications

4 - Dose Adjustment

Linear Pharmacokinetics Assumption

For most drugs: AUC ∝ Dose

Formula:

$$\text{New Dose} = \frac{Target\ AUC}{Observed\ AUC} \times Current\ Dose$$

Example - Gentamicin:
Current: 160 mg/day → AUC = 0.75 mg·h/L

Target: AUC = 1 mg·h/L (for better bacterial control)

$$\text{New Dose} = \frac{1}{0.75} \times 160 = 120\ mg/day$$

Mathematics & Biostatistics

Lecture 5

Samples, Confidence Intervals, Dependent and independent variables in Pharmacy

First Year – College of Pharmacy

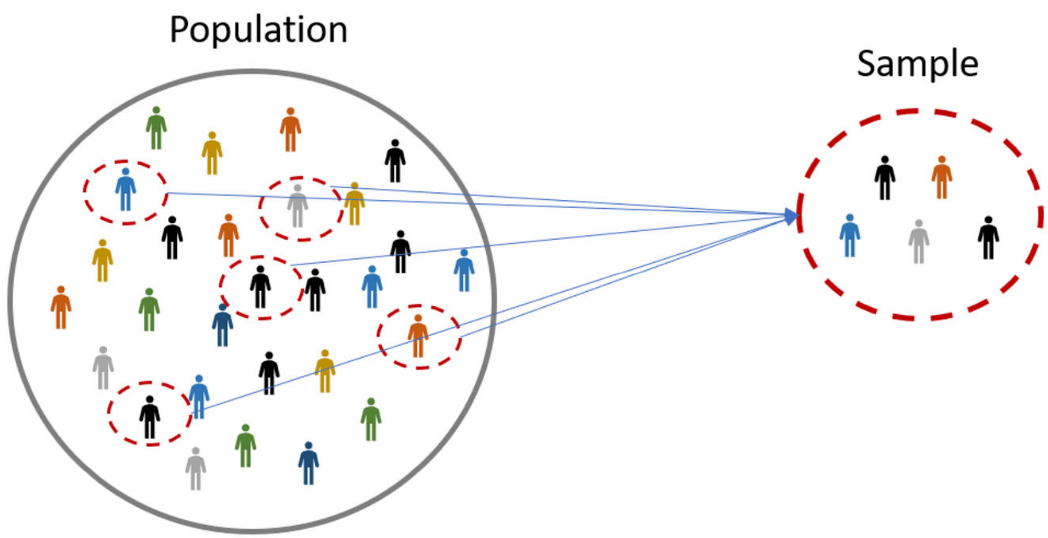
Saif M. Hassan

Ph.D. Pharmacology and Therapeutics

Population vs. Sample

Population: Complete set of items/individuals of interest
Examples:

- All diabetic patients in a country
- All tablets in a production batch
- All possible blood concentrations after a dose

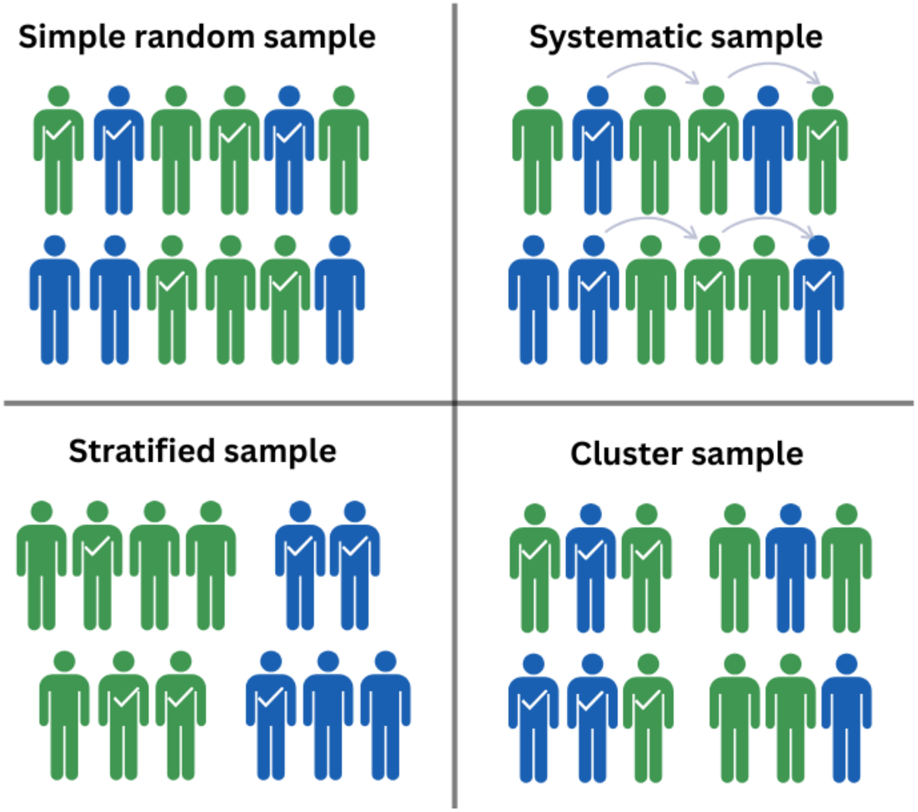


Sample: Subset selected from the population
Examples:

- 100 diabetic patients in a clinical trial
- 20 tablets tested for dissolution
- 5 blood samples drawn over 24 hours

Sampling Methods in Pharmacy

1. **Simple Random Sampling**: Equal chance for all units
   1. *Example*: Randomly selecting vials from a batch
2. **Systematic Sampling**: Every nth item
   1. *Example*: Testing every 50th tablet on production line
3. **Stratified Sampling**: Divide population into subgroups
   1. *Example*: Sampling equal numbers of tablets from beginning, middle, and end of production run
4. **Convenience Sampling**: Readily available subjects
   1. *Example*: First 50 patients who visit clinic (potential bias)



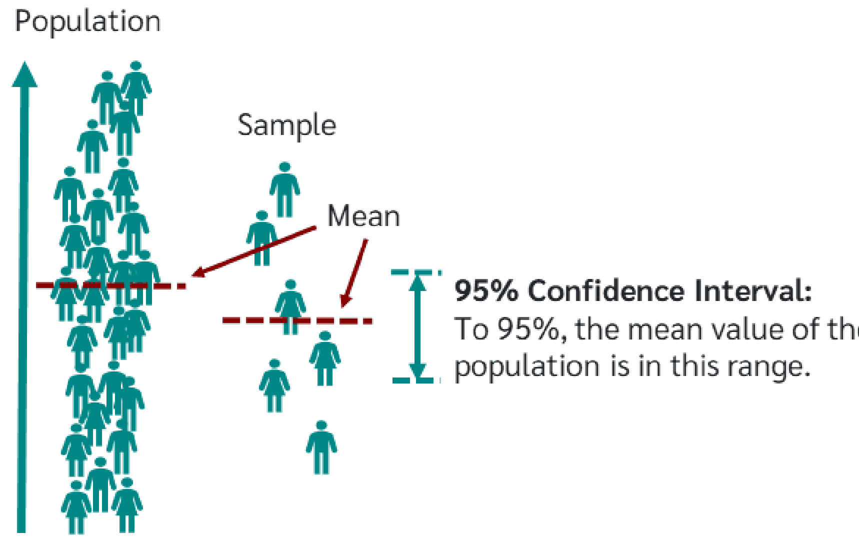
Confidence Intervals - Concept

The "Plausible Range" Approach

Problem: Sample mean ≠ Population mean
Solution: Estimate a range likely to contain population mean

Confidence Interval (CI):
Range of values that, with specified confidence level, contains the true population parameter

Interpretation:
"We are 95% confident that the true mean lies between X and Y"



Confidence Interval Formula

For Means (Large Samples or Known σ)

$$CI = \bar{x} \pm z_{\alpha/2} \times \frac{\sigma}{\sqrt{n}}$$

Where:

- $\bar{x}$ = sample mean
- $z_{\alpha/2}$ = critical value (1.96 for 95% CI)
- σ = population standard deviation
- n = sample size

Margin of Error: $E = z_{\alpha/2} \times \frac{\sigma}{\sqrt{n}}$

Application 1 - Tablet Potency

Manufacturing Quality Control

Scenario: Test 20 tablets from batch for active ingredient
Data: Mean = 99.8 mg, Standard deviation = 1.2 mg
Required: 95% CI for true batch mean (assume target = 100 mg)

Calculation (using t-distribution, df = 19, t = 2.093):

$$\begin{aligned} CI &= 99.8 \pm 2.093 \times \frac{1.2}{\sqrt{20}} \\ &= 99.8 \pm 2.093 \times 0.268 \\ &= 99.8 \pm 0.56 \\ &= (99.24, 100.36)\ mg \end{aligned}$$

Conclusion: CI contains 100 mg → Batch meets potency specification

Dependent and independent variables Concepts

Independent Variable (IV)

•The **cause** or **predictor**

•The variable that is **manipulated** or **selected**

•Plotted on the **x-axis** of graphs

•Also called: **Explanatory variable**, **Predictor variable**, **Treatment variable**

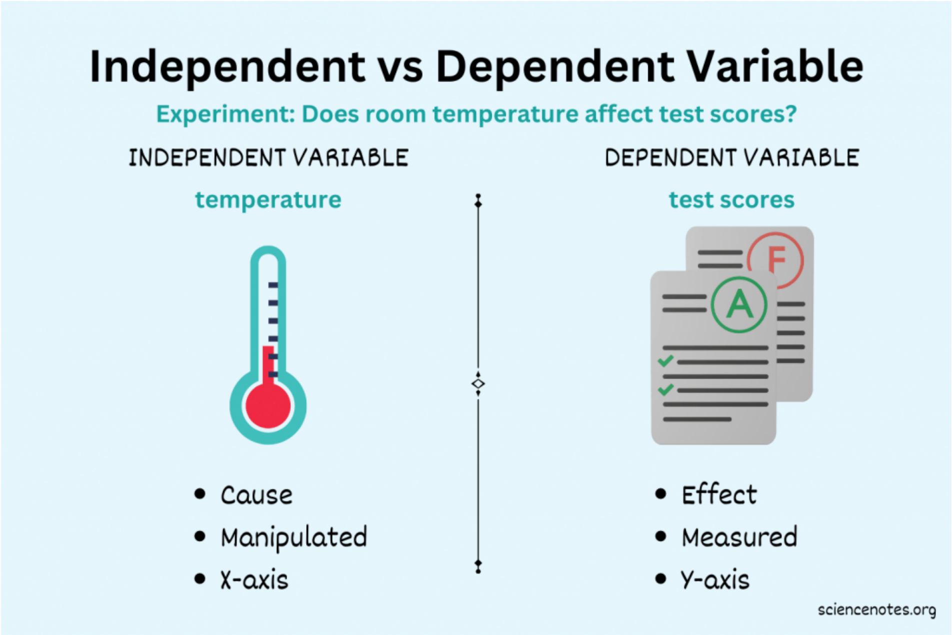
Dependent Variable (DV)

•The **effect** or **outcome**

•The variable that is **measured**

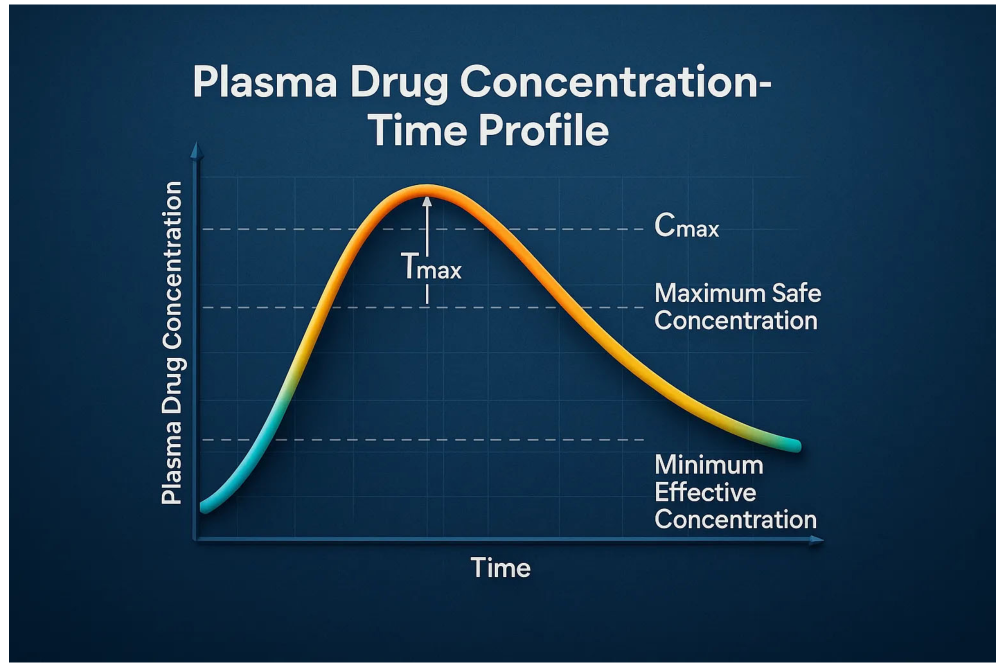
•Plotted on the **y-axis** of graphs

•Also called: **Response variable**, **Outcome variable**



Dependent and independent variables Concepts

Pharmacokinetics Example



Drug Concentration Over Time

Study: IV bolus administration

Variables:

•**Independent Variable**: Time (hours)

•**Dependent Variable**: Plasma drug concentration (mg/L)

Equation:

$$C(t) = C_0 e^{-kt}$$

Concentration **depends on** time

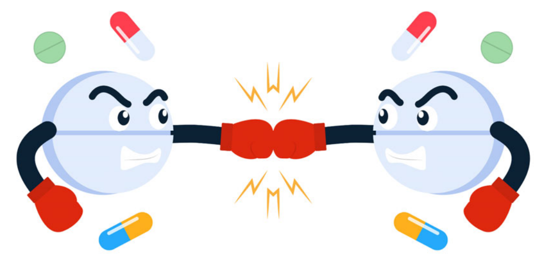
Dependent and independent variables Concepts

Hospital Pharmacy

IV Compatibility Study:

•IV: Drug combination (A alone, B alone, A+B)

•DV: Precipitation (yes/no), pH change, concentration loss



Study: Compare oral vs. rectal formulation

Identify:

•IV: Formulation type (oral tablet, rectal suppository)

•DV: AUC (Area Under Curve), Cmax, Tmax

•Controlled: Dose (same mg), Subjects (same patients, crossover)