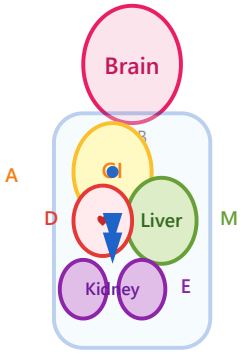
ADMET Prediction



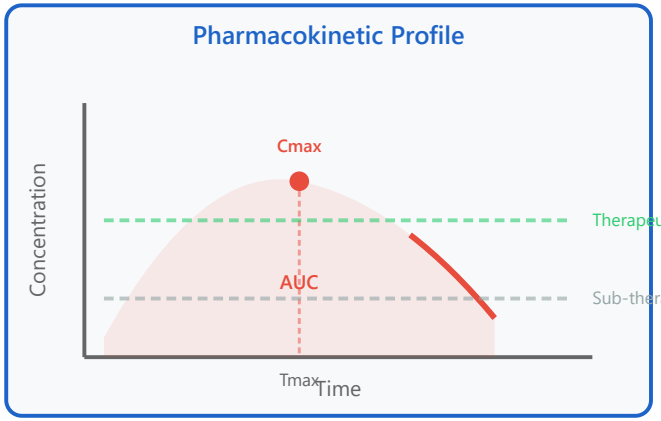
Absorption
Caco-2, LogP

Distribution
Vd, PPB

Metabolism
CYP450

Excretion
Clearance

Toxicity
hERG, LD50



Absorption models
Oral bioavailability prediction

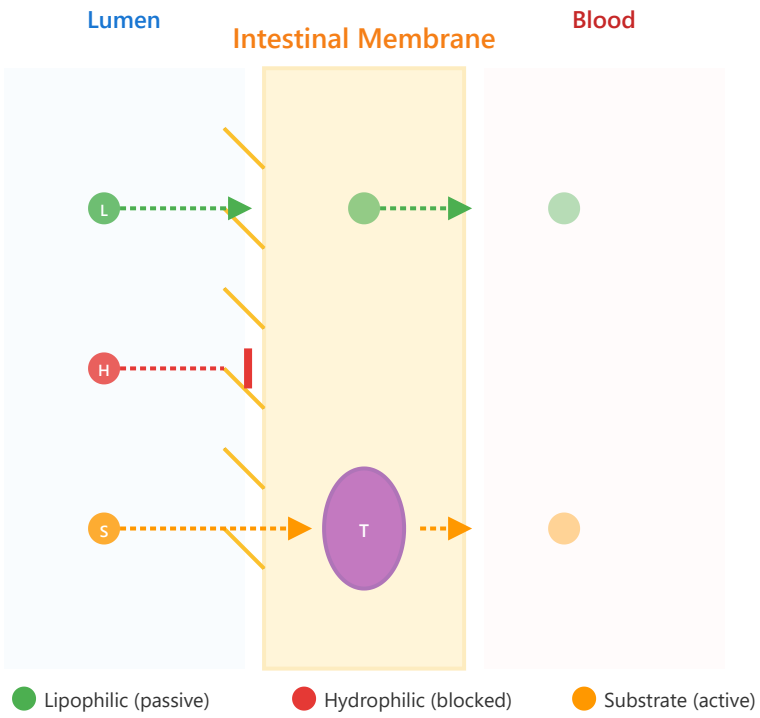
Distribution (BBB, Vd)
Tissue distribution modeling

Metabolism (CYP)
Drug metabolism prediction

Excretion (clearance)
Elimination pathway modeling

Toxicity endpoints
Safety assessment

Absorption



Definition

Absorption refers to the process by which a drug moves from the site of administration into the bloodstream. For oral drugs, this primarily occurs in the gastrointestinal tract.

Key Parameters

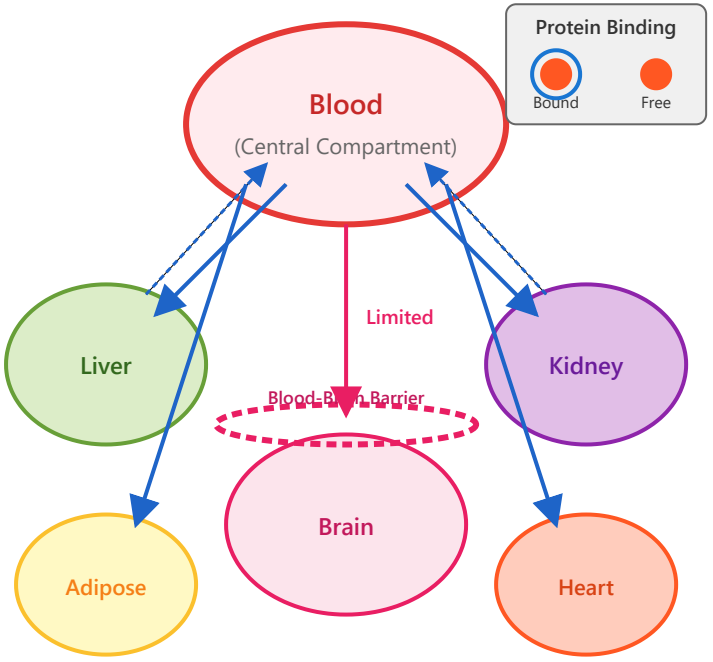
- **Caco-2 permeability:** In vitro model using human colon carcinoma cells to predict intestinal absorption
- **LogP/LogD:** Lipophilicity measures that correlate with membrane permeability
- **Oral bioavailability (F%):** Fraction of administered dose reaching systemic circulation
- **PAMPA:** Parallel artificial membrane permeability assay for passive diffusion

Prediction Methods

- QSAR models based on physicochemical properties
- Machine learning approaches (RF, SVM, DNN)
- Lipinski's Rule of Five screening
- PBPK modeling for dynamic predictions

Clinical Importance: Poor absorption is a major cause of drug candidate failure. Approximately 40% of new chemical entities fail due to inadequate absorption or bioavailability.

Distribution



Definition

Distribution describes how a drug disperses throughout the body fluids and tissues after entering the bloodstream. It determines drug concentration at the site of action.

Key Parameters

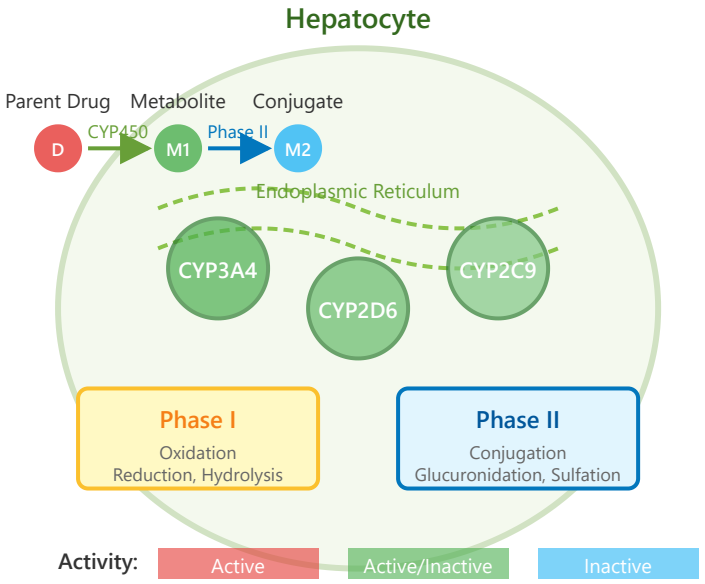
- **Volume of Distribution (Vd):** Apparent volume in which drug is distributed (L or L/kg)
- **Plasma Protein Binding (PPB):** Percentage bound to albumin or other proteins
- **BBB Penetration:** Ability to cross blood-brain barrier (LogBB, PS product)
- **Tissue:Plasma ratio:** Drug concentration in tissue vs. plasma

Prediction Approaches

- Physiologically-based pharmacokinetic (PBPK) models
- BBB permeability prediction using molecular descriptors
- Deep learning for multi-compartment modeling
- In silico estimation of tissue partition coefficients

Clinical Relevance: Distribution determines drug efficacy and safety. High Vd suggests extensive tissue binding, while high protein binding can lead to drug-drug interactions and reduced free drug concentration.

Metabolism



Definition

Metabolism is the biochemical transformation of drugs, primarily in the liver, converting them into more polar, water-soluble compounds for elimination. This process can activate, inactivate, or create toxic metabolites.

Key Parameters

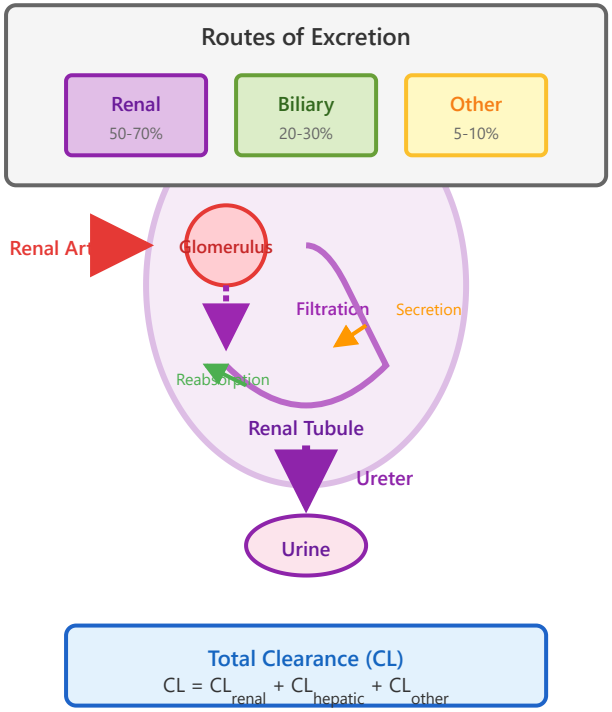
- **CYP450 substrate/inhibitor:** Interaction with cytochrome P450 enzymes (3A4, 2D6, 2C9, etc.)
- **Metabolic stability:** Half-life in liver microsomes or hepatocytes
- **Intrinsic clearance (CLint):** Rate of metabolism normalized by enzyme concentration
- **Metabolite identification:** Structure and activity of biotransformation products

Computational Methods

- Site of metabolism (SOM) prediction using graph neural networks
- CYP450 substrate/inhibitor classification models
- Metabolite structure prediction
- Metabolic pathway simulation

Drug-Drug Interactions: CYP450 inhibition/induction is a major cause of adverse drug reactions. Predicting metabolic interactions early can prevent clinical failures and improve patient safety.

Excretion



Definition

Excretion is the removal of drugs and their metabolites from the body, primarily through kidneys (urine) and liver (bile). The rate of excretion determines drug half-life and dosing frequency.

Key Parameters

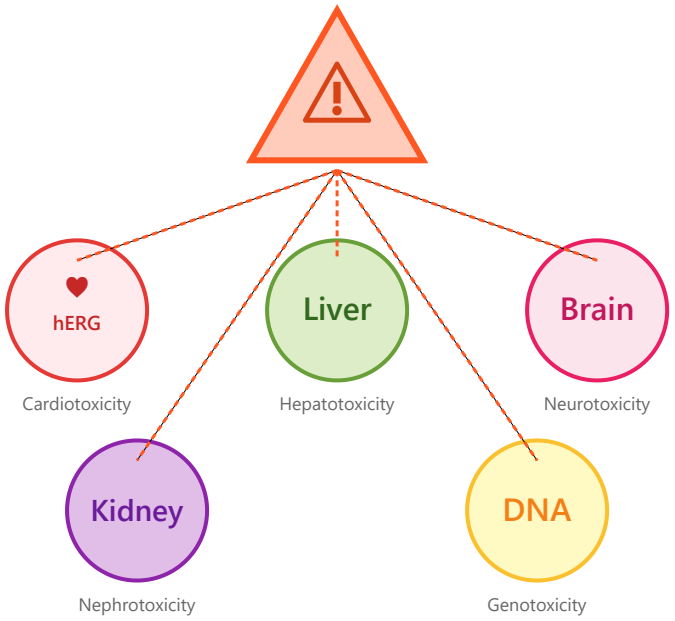
- **Renal clearance (CL_R):** Volume of plasma cleared per unit time via kidneys
- **Total clearance (CL):** Sum of all elimination pathways
- **Half-life ($t_{1/2}$):** Time for plasma concentration to decrease by 50%
- **Urinary excretion ratio:** Fraction of dose recovered in urine

Prediction Strategies

- Renal clearance models based on GFR and molecular properties
- Transporter-mediated secretion prediction (OAT, OCT, P-gp)
- Allometric scaling for cross-species extrapolation
- Population PK models for special populations

> **Clinical Consideration:** Impaired renal function significantly affects drug clearance. Dose adjustment is critical in patients with kidney disease to prevent toxicity from drug accumulation.

Toxicity



LD_{50}: Lethal Dose 50% - Acute Toxicity Measure

Definition

Toxicity assessment evaluates the potential of a drug to cause adverse effects or harm to living organisms. Early prediction of toxicity endpoints is crucial for drug safety and reducing attrition rates.

Key Endpoints

- **hERG inhibition:** Blockage of cardiac potassium channels leading to QT prolongation and arrhythmia
- **Hepatotoxicity:** Liver damage (DILI - Drug-Induced Liver Injury)
- **Acute toxicity (LD50):** Median lethal dose in animal models
- **Mutagenicity (Ames test):** Potential to cause genetic mutations
- **Carcinogenicity:** Long-term cancer risk assessment

In Silico Approaches

- Structure-activity relationship (SAR) alerts for toxic moieties
- QSAR models for specific endpoints (hERG IC50, Ames, etc.)
- Deep learning classification for multi-endpoint toxicity
- Read-across and chemical similarity methods

Regulatory Impact: Toxicity is the leading cause of drug attrition in clinical trials (>30% failures). Early computational screening can reduce development costs by identifying toxic candidates before expensive in vivo studies.