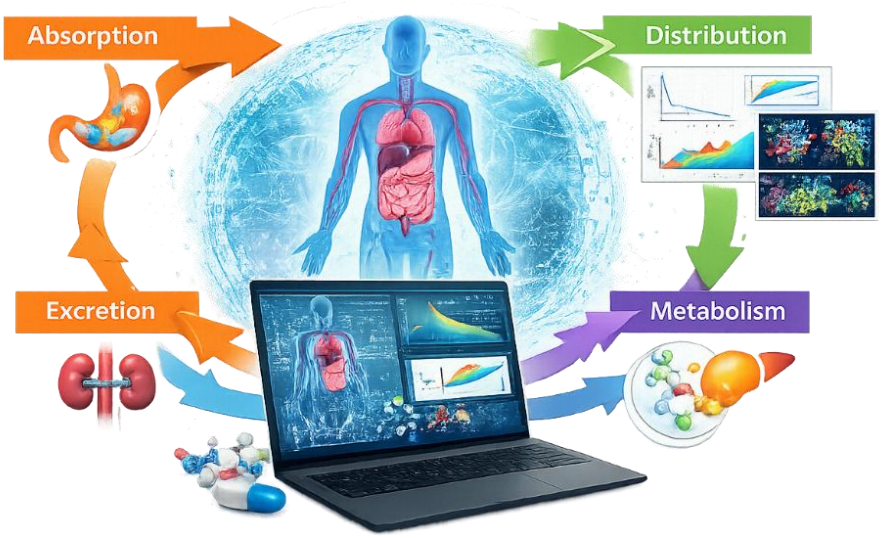
Computational Modeling of Drug Disposition

Computational Modeling of Drug Disposition: Introduction

- Computational modeling of drug disposition refers to the use of **mathematical models and computer simulations** to understand and predict how a drug behaves inside the body.



What is Drug Disposition?

- **Drug disposition** includes all processes that affect the **drug after administration:**
  - Absorption
  - Distribution
  - Metabolism
  - Excretion (ADME)

Purpose of Computational Modeling

- Predict drug concentration over time
- Reduce need for animal and human testing
- Optimize drug design and dosage
- Understand variability between patients

Types of Models Used

1. **Compartmental Models**
   - ➢ Body divided into compartments
   - ➢ Simple and widely used
2. **Physiologically-Based Pharmacokinetic (PBPK) Models**
   - ➢ Based on real anatomy and physiology
   - ➢ Include organs, blood flow, enzyme activity

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3. Empirical Models

- Based only on observed data
- Do not include biological mechanisms

Advantages

- Cost-effective
- Faster drug development
- Ability to simulate different scenarios

Limitations

- Depend on quality of input data
- May oversimplify biological systems

Applications

- Predict drug concentration over time
- Study variability among patients
- Evaluate drug-drug interactions
- Support regulatory submissions

Modeling Techniques: Drug Absorption

- Drug absorption refers to how a drug enters the bloodstream from the site of administration (e.g., oral, injection).

Key factors affecting absorption

- Drug solubility
- Membrane permeability
- Gastrointestinal pH
- Gastric emptying time

Modeling approaches

- **First-order absorption models:** Drug enters bloodstream at a rate proportional to remaining amount
- **Zero-order absorption models:** Drug enters at a constant rate
- **Advanced models:** Include physiological details like intestinal transit time

Applications

- Predict oral bioavailability

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- Optimize dosage forms (tablet, capsule, etc.)

Important Parameters

- Absorption rate constant (ka)
- Bioavailability (F)

Modeling Techniques: Solubility

- Solubility is the ability of a drug to dissolve in a solvent (usually GI fluids).

Importance

- Only dissolved drug can be absorbed
- Poor solubility → poor absorption

Factors Affecting Solubility

- pH of environment
- Drug's chemical structure
- Temperature

Modeling methods

- **Quantitative Structure–Property Relationships (QSPR):** Predict solubility from molecular structure
- **Thermodynamic models:** Based on energy and molecular interactions
- **Empirical models:** Based on experimental data

Modeling Techniques: Intestinal Permeation

- Permeation is the movement of drug across the intestinal membrane.

Mechanisms

- Passive diffusion
- Active transport
- Facilitated diffusion

Factors Affecting Permeation

- Lipophilicity
- Molecular size
- Charge of molecule

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Modeling approaches

- Caco-2 cell models (in vitro + computational)
- Permeability equations based on diffusion laws
- PBPK models incorporating intestinal layers

Key parameters

- Permeability coefficient
- Surface area of intestine
- Blood flow

Importance

- Predicts oral drug absorption
- Helps classify drugs (e.g., BCS classification system)

Modeling Techniques: Drug Distribution

- Distribution refers to how a drug spreads from blood to tissues.

Key factors

- Blood flow to tissues
- Binding to plasma proteins
- Tissue permeability
- Lipophilicity of drug

Important Parameters

- Volume of distribution (Vd)
- Tissue partition coefficients

Modeling approaches

- **Compartmental models:** Simple representation of tissue distribution
- **PBPK models:** Detailed organ-specific distribution
- **Volume of distribution (Vd):** calculations

Example

- Highly lipophilic drugs accumulate in fat tissue
- Hydrophilic drugs remain in plasma

Importance

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