Student Objectives for This Chapter

- To understand the development and use of physiologically based pharmacokinetic (PBPK) models
- To understand the different types of concentration - effect relationships
- To understand the mathematical relationships involved with direct reversible pharmacological effect kinetics
Goals of Modeling

• Codify current facts
• Testing competing hypotheses
• Predicting system response under new conditions
• Estimating inaccessible system variables

F. Eugene Yates (1973)

Pharmacokinetics (PK)

➢ Description of the time course and factors affecting the handling of drugs by the body.

Important are:
- \( F \) = Bioavailability
- \( CL \) = Clearance
- \( V \) = Volume of Distribution

➢ Specific models are needed to make predictions of kinetic behavior of drugs at any dosages
  - Compartmental Models (e.g., 1 CM, 2 CM)
  - Physiologic Models (e.g., PBPK)
Physiologically Based Pharmacokinetic Models (PBPK)

PBPK model segregates the body into separate compartments representing organs interconnected by the blood circulation.

PBPK Model Requirements:
- Experimental data
- Physiological Parameters (Tissue size, blood flow)
- Model construction
- Program for numerical solution of differential equations

Model of Simple Tissue Distribution

Fick’s Law of Perfusion

\[
\frac{dA_T}{dt} = Q_T \cdot (C_a - C_{vT})
\]

\[
C_T = K_p \cdot C_{vT}
\]

\[
\frac{dA_T}{dt} = Q_T \cdot (C_a - \frac{C_T}{K_p})
\]

Assumptions:
- Rapid equilibrium between tissue & venous blood

\\
A_T = \text{Amount in tissue} \\
Q_T = \text{Tissue blood flow} \\
C_a = \text{Conc. arterial blood} \\
C_{vT} = \text{Conc. tissue venous blood} \\
K_p = \text{Tissue/plasma partition coefficient}

Initial uptake (amount/time) = Q_T \times C_a
Drug Distribution within Tissue – Permeability Issues

Tissue Subcompartments

Fick’s Law of Diffusion

\[
\frac{dA_T}{dt} = PS \cdot (C_1 - C_2)
\]

\(A_T = \) Amount in tissue
\(PS = \) Permeability/Surface area constant
\(C_1, C_2 = \) Concentration

Initial uptake (amount/time) = PSxC_1

→ Size, nature, permeability, binding and transporters can determine tissue uptake

PBPK Model Example: Thiopental

Figure 23.3.4 Some Results for Thiopental Bischoff and Dedrick 1968
(http://www.boomer.org/c/p4/c23/c2303.html)
PBPK Models: Pros vs. Cons

- **Advantages:**
  - The prediction of plasma (blood) and tissue PK of drug candidates prior to *in vivo* experiments
  - Support a better mechanistic understanding of PK properties from tissue kinetic data predicted, facilitating a more rational design during clinical candidate selection.
  - Extrapolation across species, routes of administration, duration and timing of drug input and dose levels.

- **Limitations:**
  - Considerable experimental and computational effort
  - Difficulty in obtaining realistic parameters

Pharmacodynamics (PD)

Description of the time-course and factors controlling drug effects on the body.

**Important are:**

- $E_{\text{max}}$ = Capacity constant
- $EC_{50}$ = Sensitivity constant
- $k_{e0}, k_{in}, \tau$ = Various time constants for specific models

SC Doses

![Graph showing serum rHuEPO concentration over time for different doses.](image)

Reticulocytes%

![Graph showing reticulocyte percentage over time.](image)

EPO stimulates production of RBC.
Basic Tenets of Pharmacodynamics

**Capacity-Limitation**

\[ E = \frac{E_{\text{max}} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma} \]

Hill Function

The Law of Mass Action \( (D + R \rightleftharpoons DR) \) and small quantity of targets leads to capacity-limitations in most responses.

**Turnover and Homeostasis**

\[ \frac{dR}{dt} = k_{\text{production}} - k_{\text{loss}} \cdot R \]

Biological Factor (R)

Both diseases and therapeutic agents often interfere with the homeostasis in the body resulting from the natural turnover of biological substances or functions.

**Biological Turnover Rates of Structures or Functions**

**Fast**
- Electrical Signals (msec)
- Chemical Signals (min)
- Mediators, Electrolytes (min)
- Hormones (hr)
- mRNA (hr)
- Proteins / Enzymes (hr)
- Cells (days)
- Tissues (mo)
- Organs (year)
- Person (.8 century)

**Slow**

BIO

MARKERS

CLINICAL EFFECTS
Components of PK/PD Models

Drugs

C_p

C_e

H

H

k_in

k_out

Disposition Kinetics
Biophase Distribution
Biosensor Process
Biosignal Flux
Transduction
Response

Pharmacokinetics
Pharmacodynamics

Review article:

Jusko et al., *JPB* **23**: 5, 1995

Types of Drug Effects

**Reversible**
- **Direct**
  - Rapid
  - Slow
- **Indirect**
  - Synthesis, secretion
  - Cell trafficking
  - Enzyme induction

**Irreversible**
- Chemotherapy
- Enzyme inactivation
Clark’s Occupancy Theory: A. J. Clark (1933) proposed the first model to account for the quantitative behavior of a receptor-mediated process.

\[ R + L \overset{k_{on}}{\underset{k_{off}}{\rightleftharpoons}} RL \rightarrow \text{Effect} \]

\[ RL = \frac{R_{TOT} \cdot L}{K_D + L} \]

The “Law of Mass Action”

\[ R = \text{Receptor}, \ L = \text{Ligand}, \ R_{TOT} = \text{Total Receptor} \]
\[ K_D = \text{Equilibrium Dissociation Constant} \ (K_D = \frac{k_{on}}{k_{off}}) \]

Hill Function: \[ E = \frac{E_{max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma} \]

\[ E_{max} = \text{Capacity} \]
\[ EC_{50} = \text{Sensitivity} \]
\[ \gamma = \text{Hill Factor} \]

Properties of Hill Function

\[ E = \frac{E_{\text{max}} \cdot C^\gamma}{E_{\text{C}50}^\gamma + C^\gamma} \]

- When \( C \ll E_{\text{C}50} \)
  \[ E = S \cdot C \]
  \[ S = \frac{E_{\text{max}}}{E_{\text{C}50}^\gamma} \]

- When \( C = E_{\text{C}50} \)
  \[ E = \frac{1}{2}E_{\text{max}} \]

- When \( C \gg E_{\text{C}50} \)
  \[ E = E_{\text{max}} \]

LINEAR MODEL

\[ E = E_0 \pm S \cdot C \]

\[ S = \frac{E_{\text{max}}}{E_{\text{C}50}^\gamma} \]

Slopes of $E$ vs. $\log C$ Plots are Often Linear

\begin{align*}
\text{Slope} &= m = \frac{E_{\max} \cdot \gamma}{4} \\
\text{Intercept} &= \ln EC_{50} - \left(\frac{2}{\gamma}\right)
\end{align*}

Simple Direct Effect: Inhibition of Cyclooxygenase Enzyme Activity in Blood by Dexamethasone

\[ E = E_0 \left(1 - \frac{I_{\max} \cdot C}{IC_{50} + C}\right) \]

$IC_{50} = 1.42 \text{ nM}$
PK/PD Expectations For Simple Direct Effects

\[ C = C_0 \cdot e^{-k \cdot t} \]

\[ E = \frac{E_{\text{max}} \cdot C}{EC_{50} + C} \]

Profiles based on \( k = 0.4, E_{\text{max}} = 100, EC_{50} = 100 \).

PK/PD Expectations For Simple Direct Effects, con’t

\[ E = \frac{E_{\text{max}} \cdot C}{EC_{50} + C} \]

“No hysteresis”
Kinetics of Pharmacologic Effects


\[ E = E_0 - k \cdot m \cdot t \]

**PK**

![PK Graph]

\[ \log C = \frac{-k}{2.3} t \]

**Pharmacology**

\[ m = \frac{E_{\text{max}} \cdot \gamma}{4} \]

**PD**

\[ E = E_0 - k \cdot m \]

\[ \text{Slope} = m = \frac{E_{\text{max}} \cdot \gamma}{4} \]

NB: Half-life applies in PK but not PD!

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**Decline of Effect: Derivation**

\[ E = m \cdot \log A + e \]

\[ \log A = \frac{E - e}{m} \]

\[ k = \text{elimination constant} \]

**Kinetics:**

\[ \log A = \log A^o - \frac{kt}{2.3} \]

**Combine:**

\[ \frac{E - e}{m} = \frac{E^o - e}{m} - \frac{kt}{2.3} \]

\[ E = E^o - \frac{km \cdot t}{2.3} \]

\[ E^o = \text{Peak effect} \]

A = Amount of drug

\[ m = \text{Slope} \]

\[ e = \text{Intercept} \]
Pharmacodynamic Models Producing Delayed Responses

- **Direct Effect:** Active Metabolite
- **Direct Effect:** Biophase Distribution
- **Direct Effect:** Slow Receptor \( k_{on}/k_{off} \)
- **Antibody-Ligand Interaction**
- **Indirect Response:** Inhibition of \( k_{in} \)
- **Indirect Response:** Stimulation of \( k_{out} \)
- **Indirect Response:** Inactivation
- **Indirect Response:** Cell Life-Span Loss
- **Irreversible Effect:** Regeneration
- **Transduction Process**

**Paralysis by Mechanical Twitch Response, %**

\[
\frac{dC_e}{dt} = k_{eo}(C_p - C_e)
\]

\[
E = \frac{E_{max} \cdot C_e}{EC_{50} + C_e}
\]

Furchgott R (1955)
Segre, IL Pharmaco (1968)
Sheiner et. al., CPT (1979)
Role of $k_{eo}$ in Determining Simple Drug Effects

PK/PD Model: 

\[ \begin{align*}
C_P & \xrightarrow{k_{eo}} C_e \\
\downarrow k_{el} & \\
\text{CONCENTRATION} & \text{EFFECT}
\end{align*} \]

\[ E = \frac{E_{max} \cdot C_e}{EC_{50} + C_e} \]

Simulations of Plasma Drug Concentrations ($C_P$, dashed line) for monoexponential kinetics ($C_o = 1000$, $k_{el} = 0.4$), Effect Site Concentrations ($C_e$, solid lines) for the indicated values of $k_{eo}$, and Effect profiles for the $E_{max}$ model with $E_{max} = 100$ and $EC_{50} = 100$.

Basic Indirect Response Models

Production \[ k_{in} \] \[ \rightarrow \] Response (Mediator) (R) \[ \rightarrow \] Removal \[ k_{out} \]

Drugs can alter the production ($k_{in}$) or dissipation ($k_{out}$) process normally controlling endogenous levels of R. Drugs can inhibit (폐) or stimulate (▲) any of these processes.

(Daynaka et al., JPB 21: 457 1993).
Irreversible Drug Effects: Antibiotics on Cell Killing

Effects of Various Intraperitoneal Doses of Piperacillin on Killing and Growth Kinetics of Pseudomonas Aeruginosa in Neutropenic Mice

\[
\frac{dR}{dt} = k_s \cdot R - k \cdot C \cdot R
\]

(Jusko, *JPS* 60: 892 1971)
(Zhi et al, *JPB* 16: 1988)

Factors Affecting PK/PD: Covariates

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Disease</th>
<th>Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE: Young/Old</td>
<td>Hepatic</td>
<td>Inhibitors</td>
</tr>
<tr>
<td>Sex</td>
<td>Renal</td>
<td>Inducers</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Thyroid</td>
<td>Joint Mechanisms</td>
</tr>
<tr>
<td>Race</td>
<td>Cystic Fibrosis</td>
<td>Opposing Mechanisms</td>
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<tr>
<td>Genetics</td>
<td>Obesity</td>
<td></td>
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<tr>
<td>Stress</td>
<td></td>
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</tbody>
</table>
Pharmacokinetics and Pharmacodynamics of \( d \)-Tubocurarine in Infants, Children, and Adults


**Infants show both reduced clearance (related to GFR) and greater sensitivity to dTC.**

Influence of extreme obesity on the body disposition and neuromuscular blocking effect of atracurium


**PK Parameters:**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Obese</th>
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</thead>
<tbody>
<tr>
<td>( V_{ss} ), L/kgTBW</td>
<td>0.141</td>
<td>0.067</td>
</tr>
<tr>
<td>CL, ml/min/kgTBW</td>
<td>6.6</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**PD Parameters:** \( (E_{max} = 100) \)

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<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2} ), min</td>
<td>8.3</td>
<td>7.4</td>
<td>312</td>
</tr>
<tr>
<td>EC_{50}, ng/ml</td>
<td>470</td>
<td>312</td>
<td>470</td>
</tr>
</tbody>
</table>
PK/PD and Pharmacogenetics

The $\beta_2$-adrenergic receptor gene polymorphism was assessed by PCR and found to be a major determinant of bronchodilator response to albuterol. J.J. Lima et al, CPT 65: 519 (1999).

Pharmacodynamic Caveats

- Measurements should be sensitive, gradual, reproducible, objective, and meaningful.
- Studies should include baseline and span 2 or 3 dose levels with effects from 0 to $E_{\text{max}}$.
- Measure major intermediary steps.
- Models should recognize mechanism(s) of drug action.
- Covariates are important!
# Modeling Dynamic Effects

<table>
<thead>
<tr>
<th>PHARMACOKINETICS</th>
<th>TRANSDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOPHASE</td>
<td>ADAPTATION</td>
</tr>
<tr>
<td>MECHANISM</td>
<td>PATHOPHYSIOLOGY</td>
</tr>
<tr>
<td>MODEL TYPE</td>
<td>DISEASE PROGRESSION</td>
</tr>
<tr>
<td>TURNOVER</td>
<td>COMPLEXITIES</td>
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</tbody>
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*Requires Integration of Diverse Components*