OVERVIEW OF MECHANISTIC PK/PD MODELING

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Outline: PK/PD Modeling

- Definitions
- Purposes of Modeling
- Model Components
- Array of Models
- Complications
- Applications

Pharmacokinetics (PK)

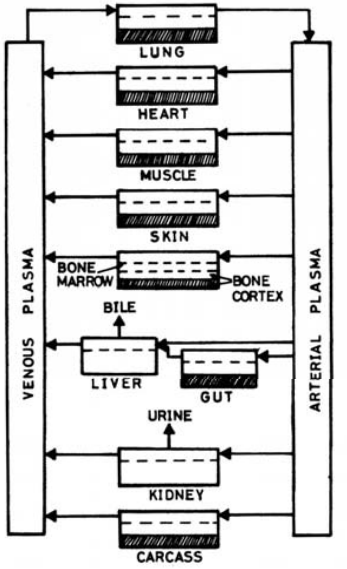
Description of the time - course and factors affecting the handling of drugs by the body.

Important are:

F = Bioavailability

V = Volume of Distribution

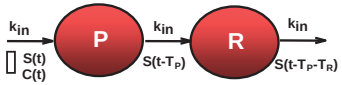
CL = Clearance



Physiological Model

Pharmacodynamics (PD)

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

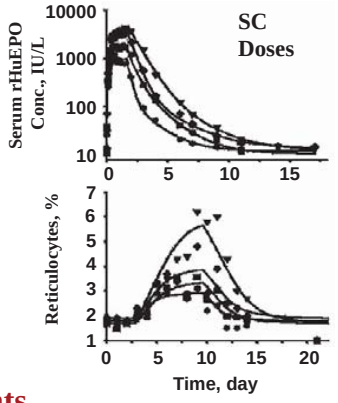


Important are:

E_{max} = Capacity constant

EC_{50} = Sensitivity constant

k_{eo}, k_{in}, τ = Various time constants for specific models



EPO stimulates production of RBC.

PK vs. PD

Whole body influence	Alters specific subsystem
Zero baseline	Starts from steady-state
'Simple' determinants	Complex controls
Usually linear	Predominately nonlinear

Components and processes can be described with models and equations allowing conceptualization, quantification, and prediction.

Why Do Modeling?

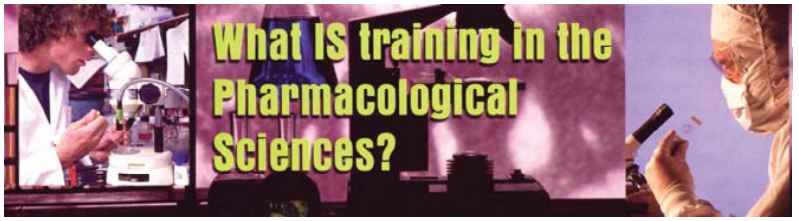
"Modeling is a fundamental procedure underlying scientific knowledge. The entire breadth and depth of human understanding of our perceived world is based on models."

Westwick DT and Kearney RE (1994)
Adv. Meth. Physiol. System Modeling, Vol. 3, Plenum Press, NY

Goals of Modeling

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

On the Mathematical Modeling of Biological Systems: A Qualified "Pro",
F. Eugene Yates, In: *Physiological Adaptation to the Environment*, F. John Vernberg
Intext Educational Publishers, New York, 1973.



"There was remarkable consensus that the core subject matter of pharmacology remains the principles of pharmacokinetics and pharmacodynamics."

NIGMS Pharmacological Sciences Training Grant Meeting
Molecular Interventions 2: 270 (Sept 2002).

Preusch PC, *Pharm. Res.* 19: 1771 (2002).

Drug Development and Model Building
Learning and Confirming

Lalonde RL et al., *CPT* 82: 21 (2007).

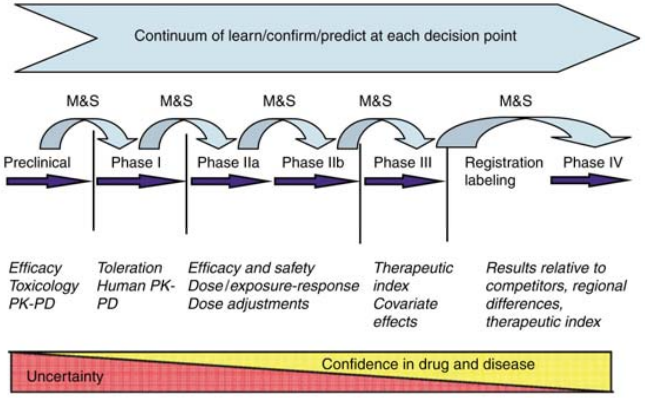
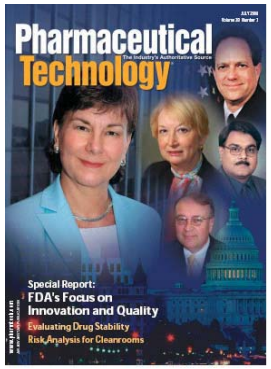
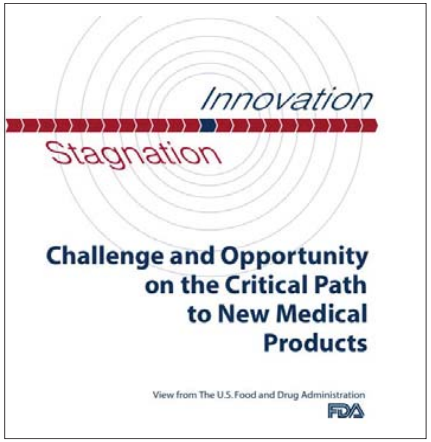


Figure 1 Modeling and simulation (M&S) are performed before each decision point to quantitatively assess risk in moving forward. The drug and disease model is continuously updated to include new information acquired during drug development.



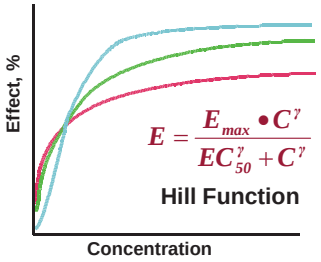
Guidance for Industry on Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications for the Food and Drug Administration (http://www.fda.gov/cder/guidance/index.htm).



- **Biomarkers**
- **PK/PD Modeling**

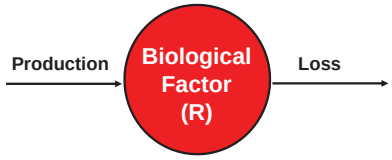
Basic Tenets of Pharmacodynamics

Capacity-Limitation



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

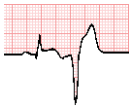
Turnover and Homeostasis



$$\frac{dR}{dt} = k_{production} - k_{loss} \bullet R$$

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

Slow

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

BIOMARKERS

CLINICAL

Direct Effect Models

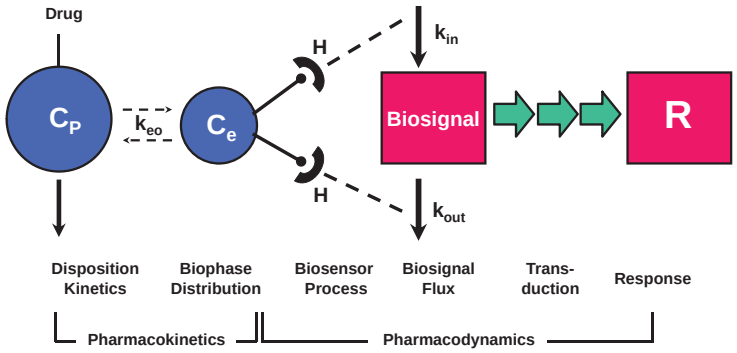
Turnover Models

Transduction Models

SYSTEMS MODELS

12

Components of PK/PD Models



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

Review article:
Mager DE, Wyska E, Jusko, WJ, Diversity of Mechanism-Based Pharmacodynamic Models, *Drug Met. Disp.* 31: 510 (2003).

Types of Drug Effects

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

Irreversible
- Chemotherapy
- Enzyme inactivation
- Suicide inhibitors

Paul Ehrlich (1913)

"Corpora non agunt nisi fixata."

(Substances do not act unless bound.)

Lexicon: Types of Models

- Time-variant
- Deterministic
- Static
- Lumped
- Linear
- Continuous
- Empirical
- Reversible
- Basic

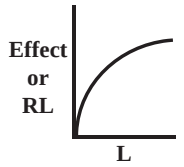
- Time-invariant
- Stochastic
- Dynamic
- Distributed
- Nonlinear
- Discrete
- Mechanistic
- Irreversible
- Systems

Clark's Occupancy Theory

A. J. Clark (1933) proposed the first model to account for the quantitative behavior of a receptor-mediated process.

$$R + L \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RL \bullet\bullet\bullet\bullet\bullet \text{Effect} \qquad K_D = \frac{k_{-1}}{k_1}$$

$$DR = \frac{B_{max} \cdot L}{K_D + L} \qquad E = \frac{E_{max} \cdot C}{EC_{50} + C}$$



….Translation……

Intrinsically Nonlinear Pharmacologic Processes

Transformation	Binding
Transport	Transduction

Intrinsic Activity: ε

Ariëns (1954), Stephenson (1956)

$$R + L \underset{}{\overset{\varepsilon}{\rightleftharpoons}} RL \bullet\bullet\bullet\bullet\bullet \text{ Effect}$$

Transduction

ε = proportionality constant between receptor occupancy and biological response.

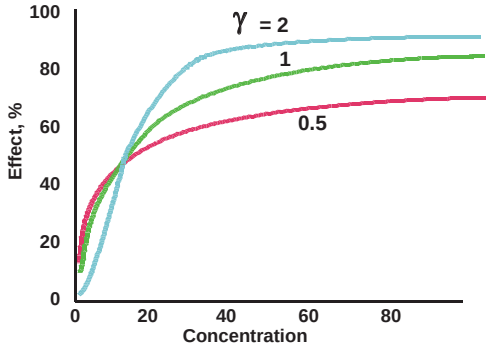
$$\frac{Effect}{E_{max}} = \varepsilon \cdot \frac{DR}{B_{max}}$$

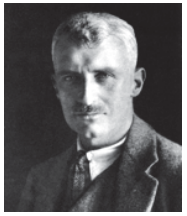
E.J. Ariëns
Univ. of Nijmegen, NL

Hill Function:

$$E = \frac{E_{max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

E_{max} = Capacity
EC_{50} = Sensitivity
γ = Hill Factor





Hill AV , The possible effect of the aggregation of molecules of haemoglobin on its dissociation curve, *J. Physiol.* (London) 40: *iv* (1910).

More Complex Functions

Agonist

$$E = \frac{E_{max} \cdot C_A^{\gamma}}{EC_{50}^{\gamma} + C_A^{\gamma}}$$

Antagonist (C_B)

$$E = \frac{E_{max} \cdot C_A}{C_A + EC_{50A} \cdot \left(1 + \frac{C_B}{EC_{50B}}\right)}$$

Biphasic

$$E = \frac{E_{max} \cdot C}{EC_{50} + C + K_2 \cdot C^2}$$

Transduction

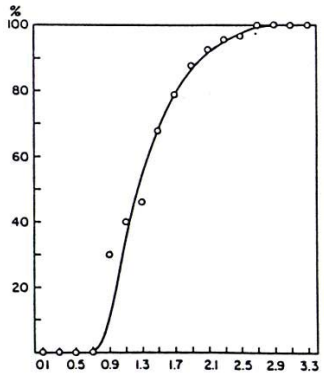
$$E = \frac{E_{max} \cdot \tau^n \cdot C^n}{[K_A + C]^n + \tau^n \cdot C^n}$$

Principles and Applications of Medicolegal Alcohol Determination

BY
PROF. DR. E. M. P. WIDMARK
Medical-Chemical Institute of
the University of Lund
Sweden

Urban & Schwarzsenberg 1932

PERCENTAGE OF DIAGNOSES OF SUBJECTS "INFLUENCED" AT VARIOUS BLOOD ALCOHOL CONCENTRATIONS.
(Total = 558 cases)



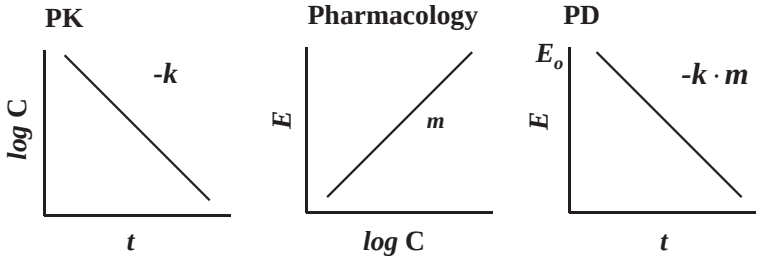
Blood Alcohol Conc., %

Kinetics of Pharmacologic Effects

Gerhard Levy, *Clin. Pharmacol. Ther.* 7:362 (1966)

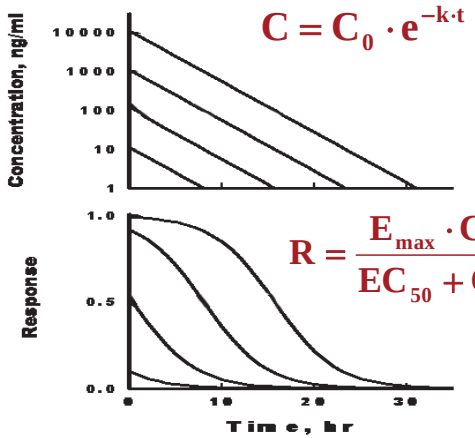
$$E = E_o - k \cdot m \cdot t$$

Father of PD



The first equation to describe drug dynamics.

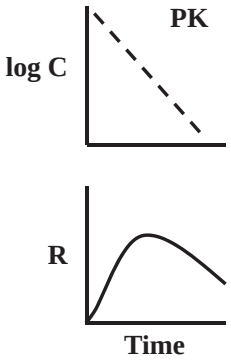
PK/PD Expectations For Simple Direct Effects: Signature Profiles



J. G. Wagner

Kinetics of Pharmacologic Response
J. Theor. Biol. 20: 173 (1968).

Pharmacodynamic Models Producing Delayed Responses



Which model?

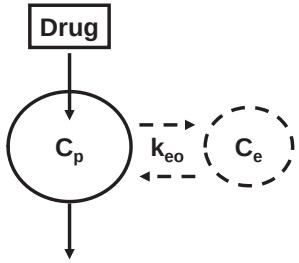
- Direct Effect: Active Metabolite
- Direct Effect: Biophase
- Direct Effect: Slow Receptor k_{on}/k_{off}
- Antibody-Ligand Interaction
- Indirect Response: Inhibition of k_{in}
- Indirect Response: Stimulation of k_{out}
- Indirect Response: Inactivation
- Indirect Response: Cell Life-Span Loss
- Irreversible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

Measure or Model the "Biophase"

Furchgott RF, *Pharmacol. Rev.* 7: 183-265 (1955).

The pharmacology of vascular smooth muscle.

Coined "biophase"



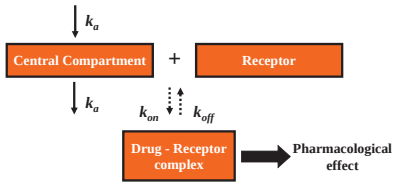
$$\frac{dC_e}{dt} = k_{eo}(C_p - C_e)$$

The "real" biophase?

G. Segre, Il *Pharmaco.* 23: 906 (1968).

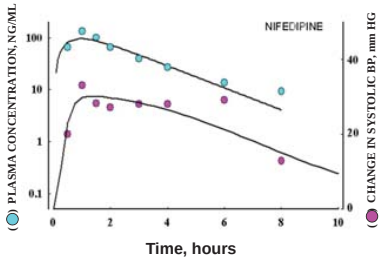
Kinetics of interaction between drugs and biological systems.

DIRECT EFFECTS: Slowly Reversible



$$\frac{d[RC]}{dt} = k_{on} \cdot [C_p] \cdot ([R_T] - [RC]) - k_{off} \cdot [RC]$$

$$\frac{dE}{dt} = k_{on} \cdot [C_p] \cdot (E_{max,R} - E) - k_{off} \cdot E$$



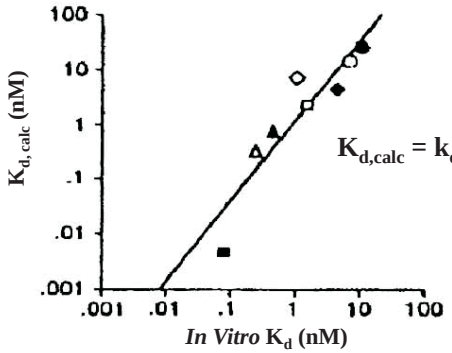
Comparative Pharmacodynamics of Eight Calcium Channel Blocking Agents in Japanese Essential Hypertensive Patients

S. Shimada, Y. Nakajima, K. Yamamato, Y. Sawada, and T. Iga

Biol. Pharm. Bull. 19 430 - 437 (1996)

In Vivo - In Vitro Correlation of PD Parameters of Calcium Channel Blockers

Shimada et al, 1996



$K_{d,calc} = k_{off} / k_{on}$

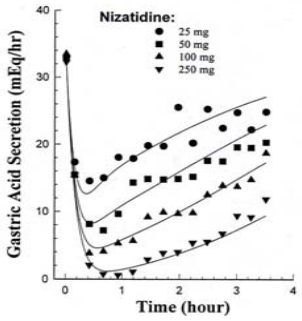
○ nicardipine, ● nifedipine, □ nilvadipine, ■ benidipine,
△ manidipine, ▲ barnidipine, ◆ efonidipine, ◇ nitrendipine

It is often feasible to scale PD from *in vitro* → *in vivo*, animals → man.

Basic Indirect Response Models

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

(Dayneka et al., *JPB* 21: 457 1993).



Basic and Complex Indirect Response Models

Circadian Input

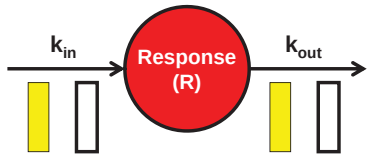
$$k_{in}(t) = R_m + R_b \cdot \cos[(t - t_z) \cdot 2\pi/24]$$

Krzyzanski et al., *Chronobiol Int.* 17:77 (2000)

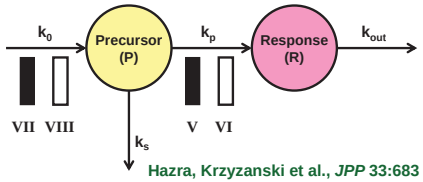
Cell Life-Span IRM

$$k_{out} = k_{in} \cdot (t - TR)$$

Krzyzanski, et al., JPB 27:467 (1999)
Krzyzanski, et al., JPP 33:125 (2006).



Precursor-Dependent IRM



Hazra, Krzyzanski et al., *JPP* 33:683 (2006)

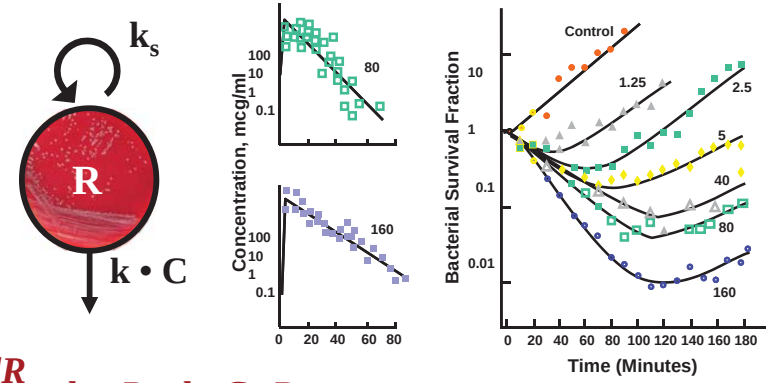
Physiological Limits

$$\frac{dR}{dt} = k_{in} \cdot H(C) - k_{out} \cdot R \cdot \left(1 - \frac{R_L}{R}\right)$$

Yao, Krzyzanski et al., JPP 33:167 (2006)

'Irreversible' Effects: Piperacillin on Killing and Growth Kinetics of Pseudomonas Aeruginosa in Neutropenic Mice

Cell Growth - Cell Killing



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

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

Biophase, Transduction

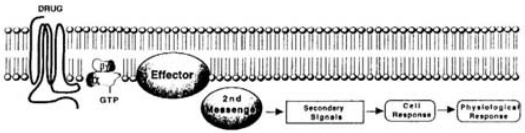
The…. ignorance about the concentration of agonist in equilibrium with receptors and about the relation between receptor activation and tissue response makes the chemical interpretation of concentration - response relations an illusion.

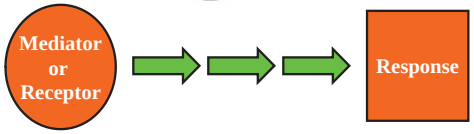
- Sir James Black (1976)

Black J, A Personal View of Pharmacology
Annu. Rev. Pharmacol. 36: 1 (1996).

Modeling Signal Transduction

GPCR



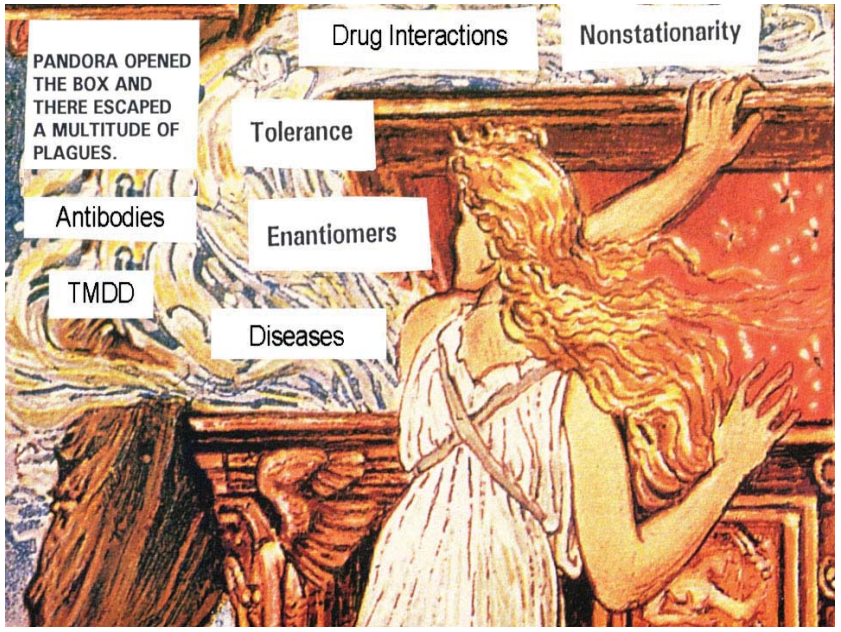


Transduction Processes can be rapid to slow, single to multiple, linear or nonlinear.

Approaches:

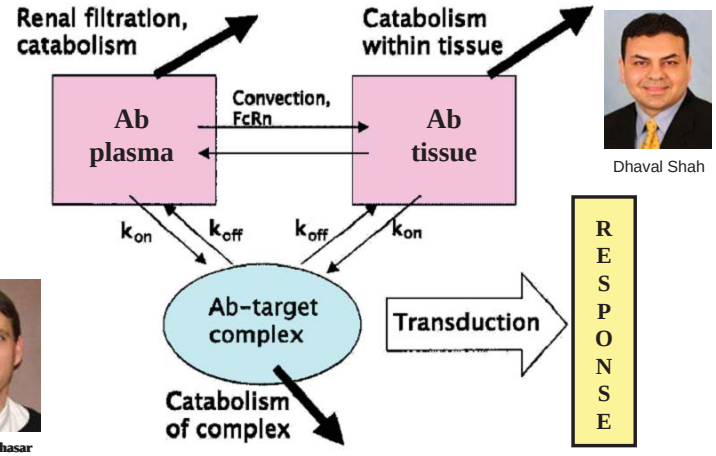
Black JW and Leff P, Operational Models of Pharmacological Agonism, *Proc. Brit. Soc. London* 220: 141 (1983).

Mager DE and Jusko WJ
Pharmacodynamic Modeling of Time-Dependent Transduction Systems, *Clin. Pharmacol. Ther.* 69: 210 (2001).



Protein / Antibody Pharmacokinetics and Pharmacodynamics

Lobo ED, Hanson RJ, Balthasar JP, *J. Pharm. Sci.* 93: 2645 (2004).



Dhaval Shah

Joseph Balthasar

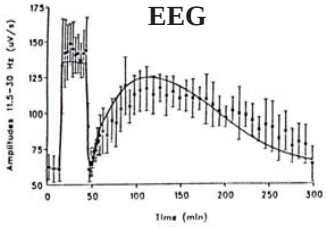
Drug Interactions: Competitive

John Henry Gaddum
Professor of Materia Medica
University of Edinburgh
1942 – 1958

The quantitative effect of antagonistic drugs.
J. Physiol. 89:7 (1937).

$$E = \frac{\frac{E\max_A [A]}{EC_{50,A}} + \frac{E\max_B [B]}{EC_{50,B}}}{1 + \frac{[A]}{EC_{50,A}} + \frac{[B]}{EC_{50,B}}}$$

EEG



Midazolam + Flumazenil

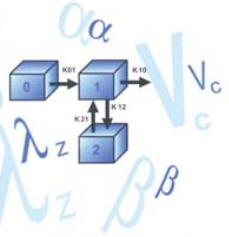
Functional Adaptation Models

Major pharmacodynamic mechanisms responsible for tolerance and rebound phenomena:

- **Counter-Regulation** ····· Effect → Opposing Effect →
- **Desensitization of Receptors** D • R ⇄ (k_t) Inactive DR
- **Up- or Down-Regulation (feed-back)** k_{syn} → mRNA or Receptors → k_{deg} ⊣
- **Precursor Pool Depletion** → P → R →

Computation Methods and Software

D. Weiner



PROFESSIONAL WinNonlin

ADAPT II

D. D'Argenio

D.Z. D'Argenio and A. Schumitzky. A program package for simulation and parameter estimation in pharmacokinetics. *Comput. Prog. Biomed.* 1: 115-194 (1979).

www.pharsight.com

bmsr.usc.edu

Population PK/PD

Journal of Pharmacokinetics and Biopharmaceutics, Vol. 5, No. 5, 1977

Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data

Lewis B. Sheiner, Barr Rosenberg, and Vinay V. Marathe

Jill Fiedler-Kelly

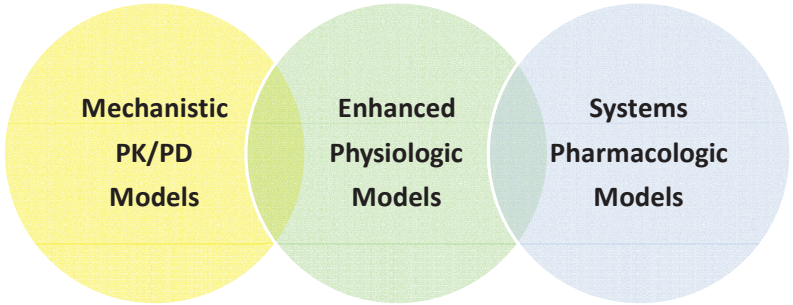
Model:

- **Co-Variate**
- **Statistical**
- **Structural**

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_{max}.**
- **Base models on mechanism(s) of drug action.**
- **Show model with all equations, preferably expressed in mathematical notation conventional for the field.**
- **Justify all assumptions and model components.**

Levels of Modeling Complexity



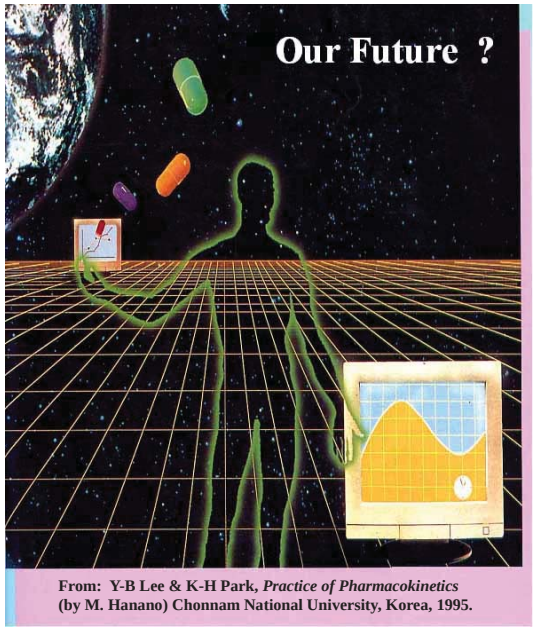
Rigorous analysis of preclinical and clinical data.

Unravel mechanisms of drug action.

Capture rate-limiting steps.

Assemble known physiology and pharmacology.

Robust Fitting ——— **?** ——— **Simulation**



From: Y-B Lee & K-H Park, *Practice of Pharmacokinetics* (by M. Hanano) Chonnam National University, Korea, 1995.

Frontiers in PK/PD Modeling

Mechanistic Models

Signal Transduction

Diverse Interactions

Pharmacogenomics

Disease Progression

Integrative and Systems Pharmacology