PK/PD/Systems Modeling: Lessons from Corticosteroids

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SUNY Distinguished Professor
Department of Pharmaceutical Sciences

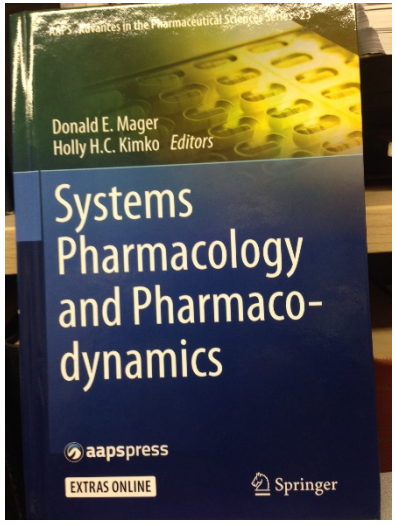
Oscar B Hunter Career Award **ASCPT** **March 23, 2018**

Lecture Outline

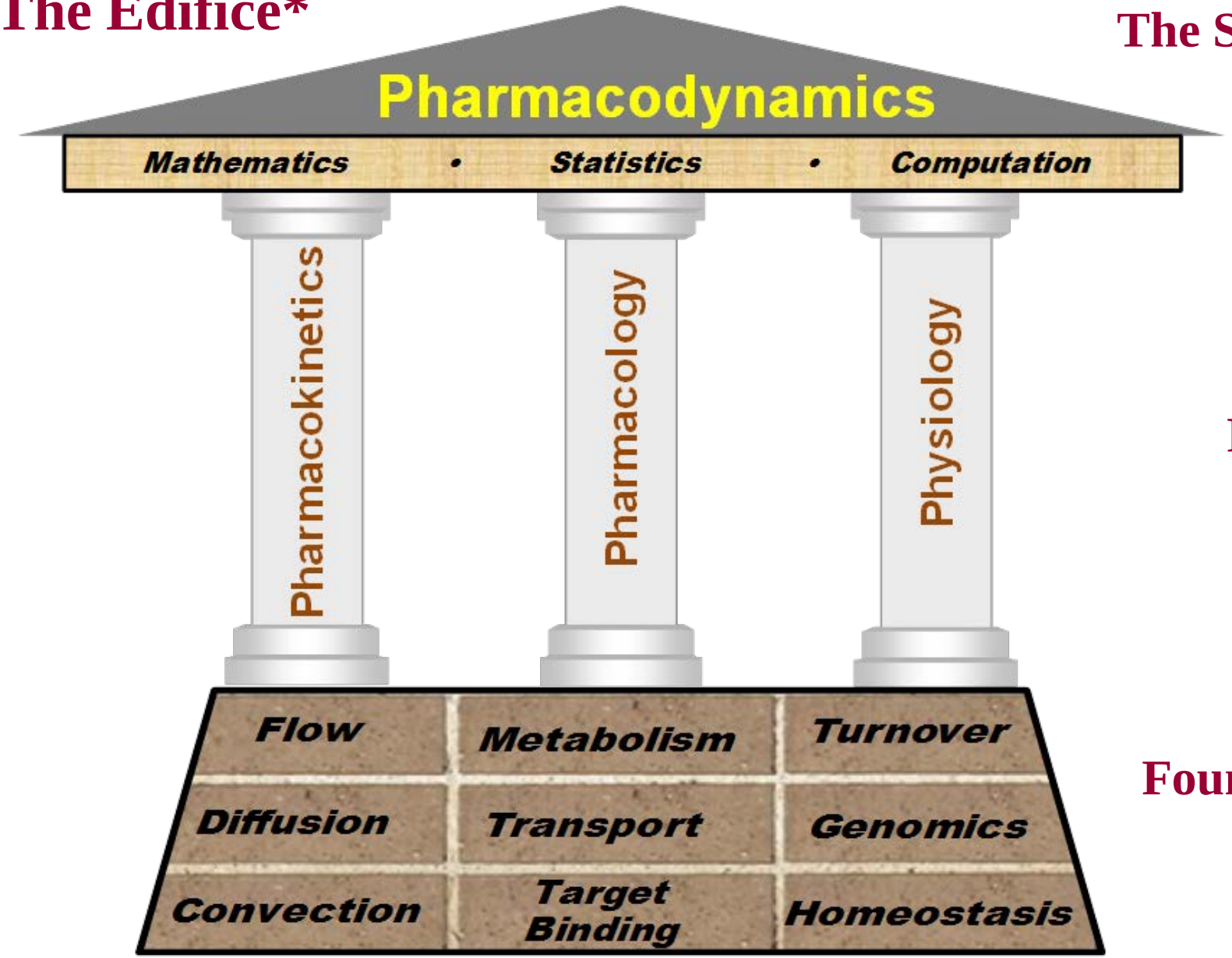
- **How various animal, clinical, and theoretical studies with corticosteroids have provided ideas to advance the fields of PK and PD.**
- **Placement within the array of basic PK and PD model components.**
- **Synthesis of more complex models in moving towards systems pharmacology.**

Partial Reference:

Jusko WJ, *Foundations of Pharmacodynamic Systems Analysis*, In: Systems Pharmacology and Pharmacodynamics, AAPS Advances in the Pharmaceutical Sciences Series 23, ISBN: 978-3-319-44534-2, Chap 8, pp. 161-175, Springer, New York, Editors: DM Mager and H Kimko (2016).



The Edifice*



The Science

Tools

Pillars

Foundation

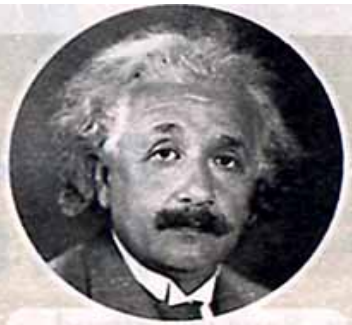
*Definitions: An impressive structure; A complex system of beliefs

The Thrill of Big Ideas

Every so often in the history of science, a theory is presented that transforms our thinking about the universe we inhabit.

The Earth revolves around the Sun. In the 16th century, Copernicus' heliocentric theory of the heavens ushered in the age of modern science.

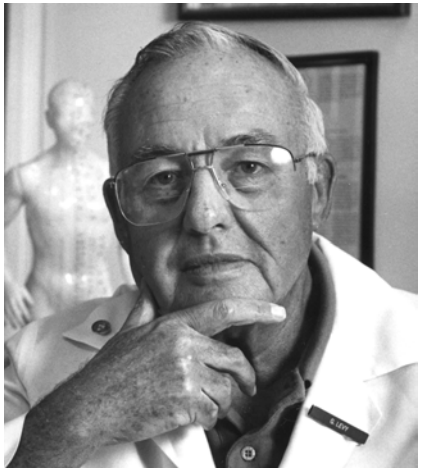
What goes up must come down. In the 17th century, Sir Isaac Newton showed that the Law of Gravity applied to all objects in the universe.



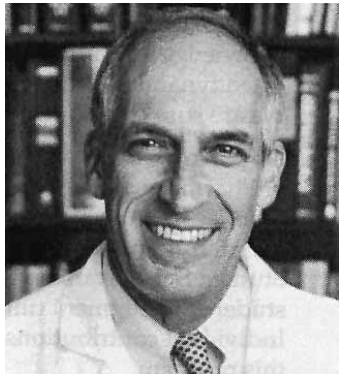
$E=mc^2$. Perhaps the most famous equation ever. Albert Einstein's Theory of Relativity revolutionized ideas about energy.

Think small. Niels Bohr was a contributor to quantum mechanics, which explains the universe at the atomic level and is the basis for our electronic devices.

PARADE • MAY 27, 2007 • PAGE 5



Kinetics of Pharmaco-logical Effects
CPT - 1966



Clearance Concepts in Pharmaco-kinetics
JPB - 1973

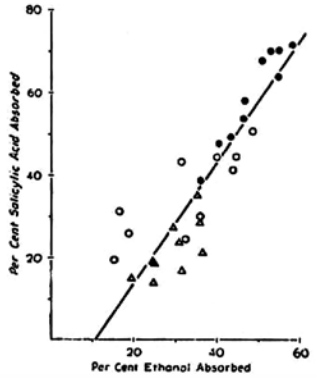
ASCPT Hunter Awards: Levy 1982 — Benet 2010

My Early Publications

J. Pharm. Sci. 54: 219-225 (1965).

Effect of Viscosity on Drug Absorption

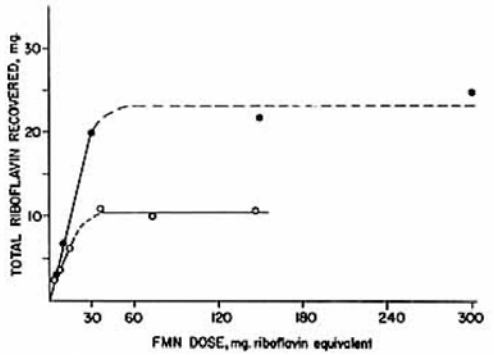
By GERHARD LEVY and WILLIAM J. JUSKO



J. Pharm. Sci. 56: 58-62 (1967).

Absorption, Metabolism, and Excretion of Riboflavin-5′-phosphate in Man

By WILLIAM J. JUSKO and GERHARD LEVY



My UB teachers and mentors.

Milo Gibaldi

Eino Nelson

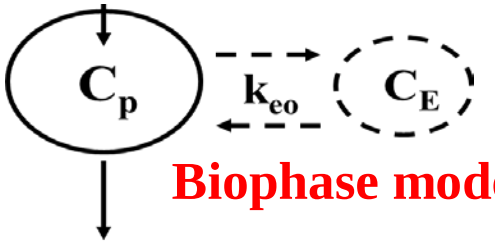
Gerhard Levy

Wm. Jusko

J. Pharm. Sci. 58: 422-424 (1969).

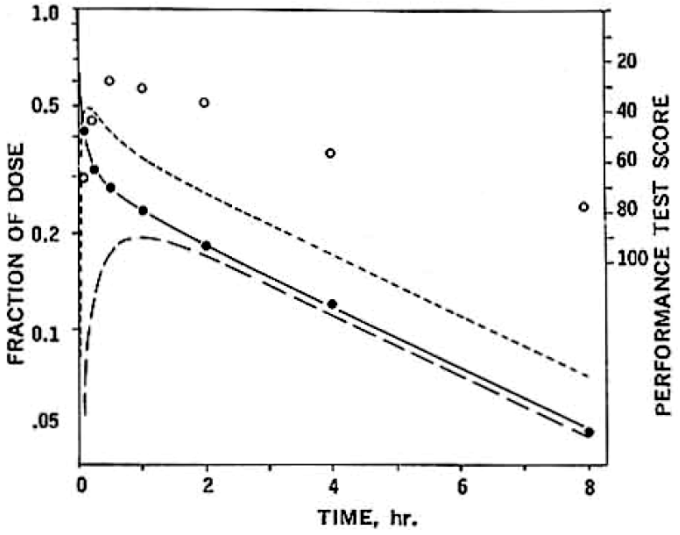
Multicompartment Pharmacokinetic Models and Pharmacologic Effects

GERHARD LEVY, MILO GIBALDI, and WILLIAM J. JUSKO

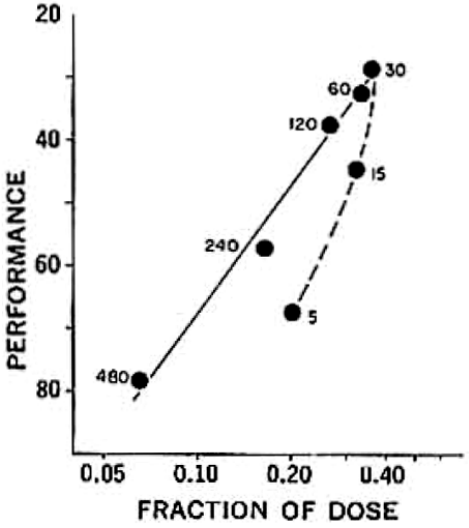


Biophase model

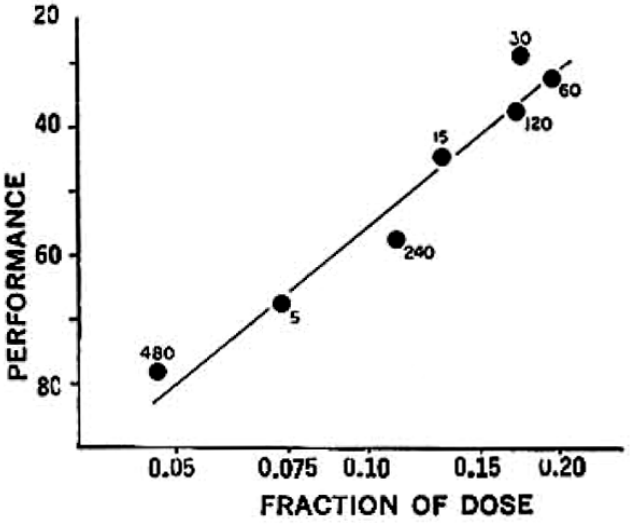
LSD & Tissue Distribution: Hysteresis



Plasma



Slow Comp in 2CM



Reprinted from THE LANCET, *October* 9, 1971, *pp.* 778-781

PREDNISONE SIDE-EFFECTS AND SERUM-PROTEIN LEVELS

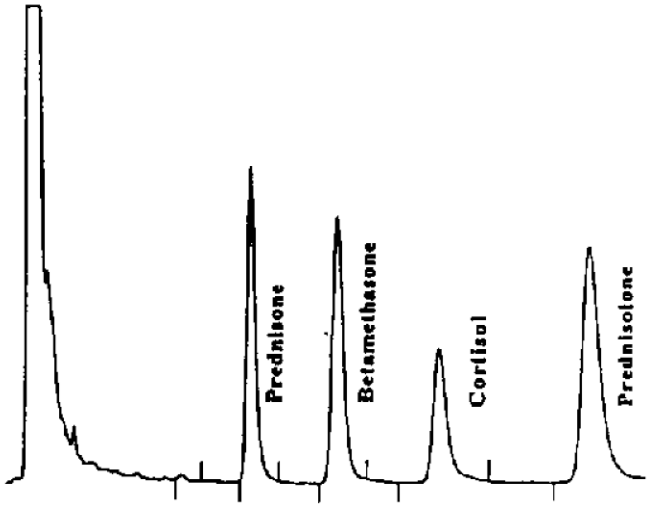
A Collaborative Study

GEORGE P. LEWIS WILLIAM J. JUSKO

Section of Clinical Pharmacology, Veterans Administration Hospital, Boston, Massachusetts, U.S.A.

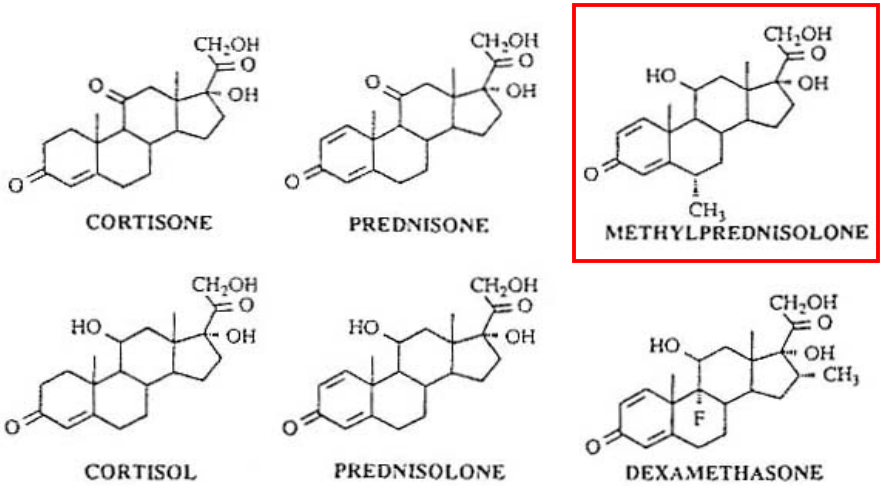
SIDE EFFECTS (in 240 Pts)

Facial Plethora	**14**
Hemorrhage	**12**
Psychoses	**10**
Hyperglycemia	**6**
Myopathy	**1**



Rose JQ & Jusko WJ, HPLC Assay, J Chrom 162: 273 (1979)

Corticosteroid Pharmacological Effects



- **Immunological Effects**
  - **Immunosuppressive**
  - **Anti-inflammatory**

⇒ Treatment for Immune Related Diseases

- **Rheumatoid arthritis**
- **Lupus erythematosus**
- **Bronchial asthma**
- **Organ transplantation**

- **Metabolic Effects**
  - **Carbohydrate metabolism**
  - **Lipid metabolism**
  - **Protein metabolism**

Adverse Effects

⇒ steroid diabetes

⇒ abnormal fat distribution

⇒ muscle wasting

negative nitrogen balance

Corticosteroid Pharmacokinetics in Man

Absorption

F = 2 - 80 %

First-pass

Distribution

Moderate (lipophilic)

PGP Substrates

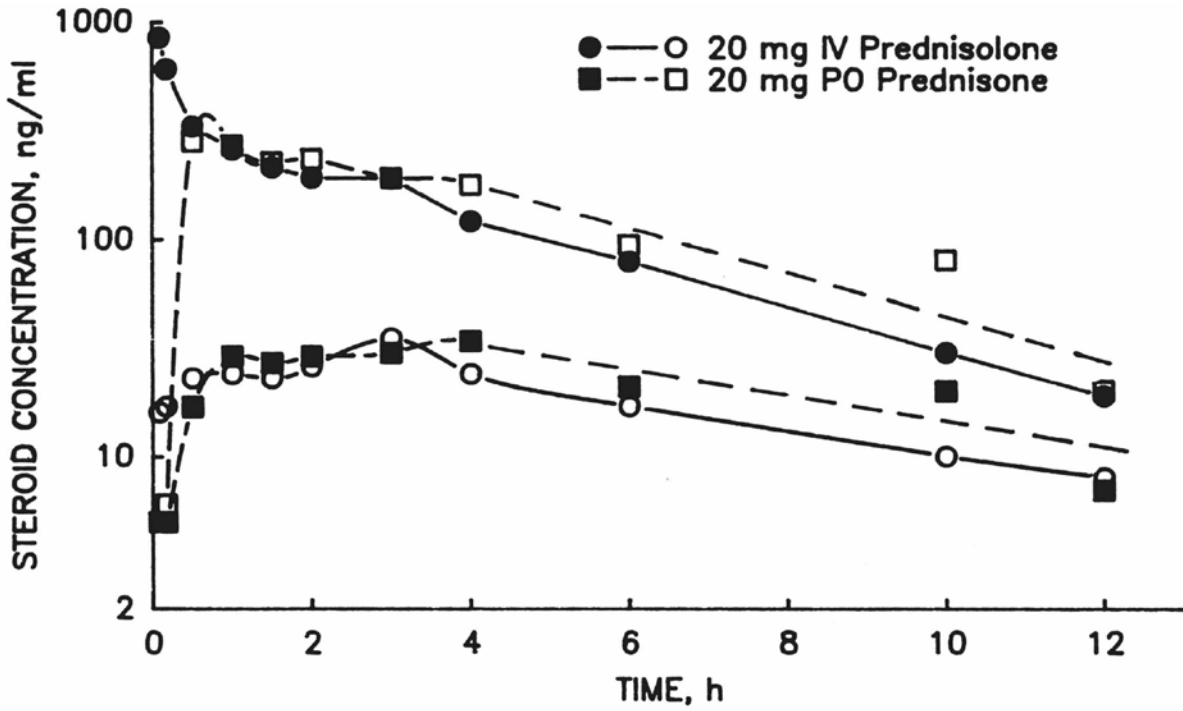
Metabolism

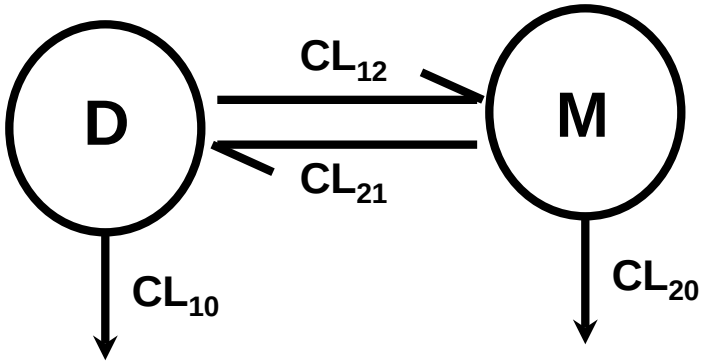
Extensive (Hepatic, Renal)

Reversible

Renal Excretion

Slight



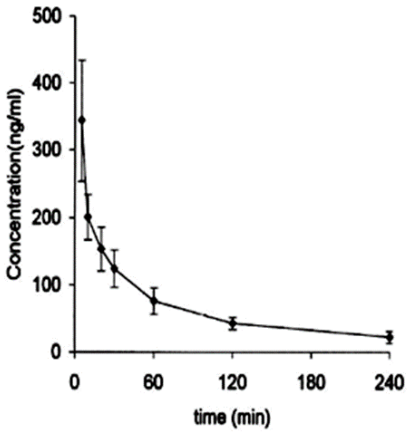


Reversible Metabolism

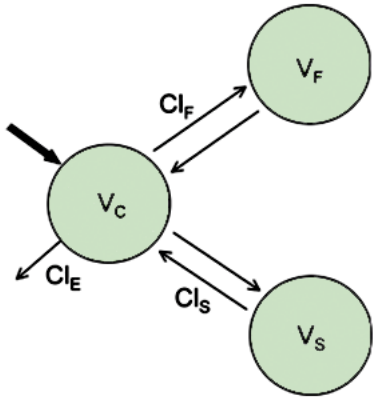
Jusko WJ, Ludwig EA, Corticosteroids Chap. 27, *Applied Pharmacokinetics* (1992).

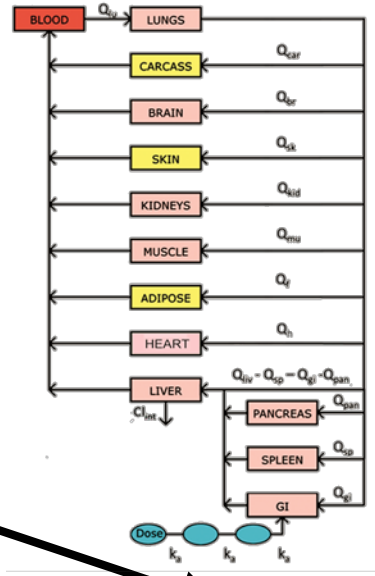
Cheng H, Jusko WJ, *Bioph. Drug Disp.* 14: 721 (1993).

Array of Basic Pharmacokinetic Models



$$CL = \frac{Dose}{AUC} \qquad V_{ss} = \frac{AUMC}{AUC} \cdot CL$$





Plasma Clearance Model

Reversible Metabolism Model

TMDD Model

mPBPK Model

PBPK Model

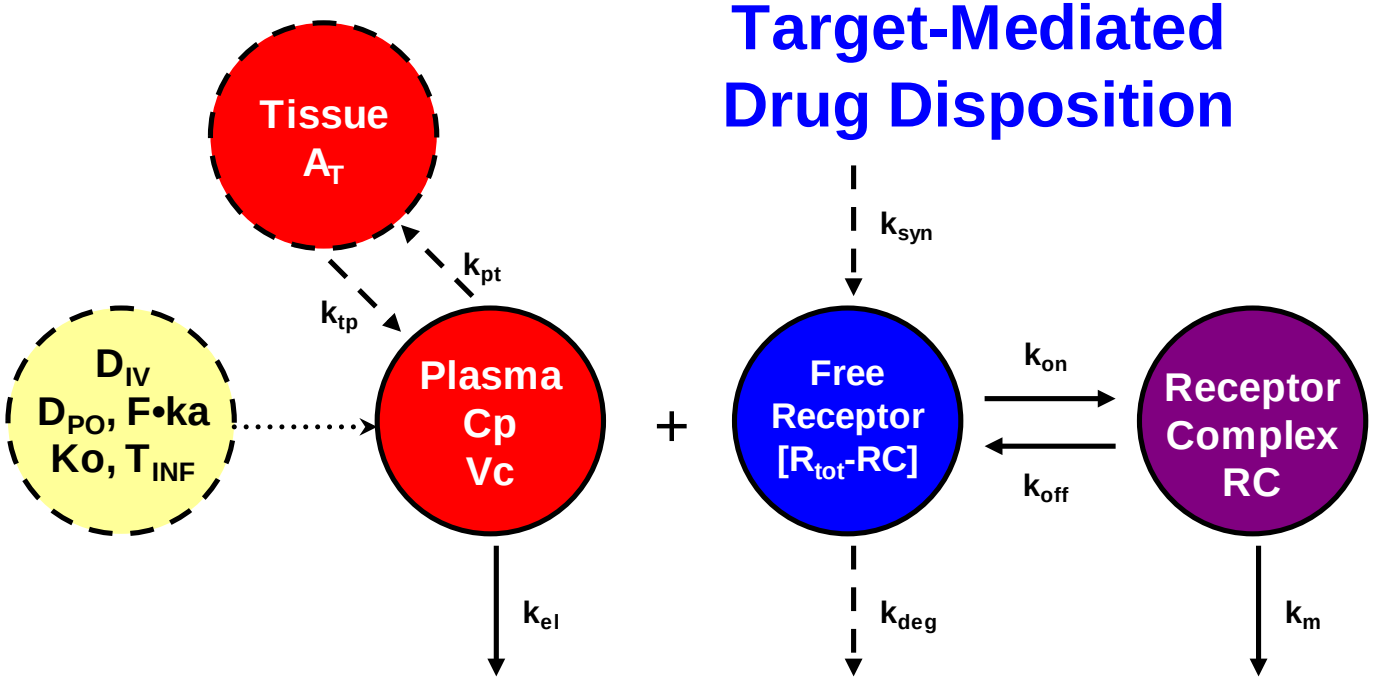
Adapted from Jusko, Guidelines for Pharmacokinetic Analysis, Applied Pharmacokinetics (2005).

Pharmacologic target-mediated drug disposition

Clin Pharmacol Ther. 56:248-52 (1994).

Gerhard Levy, PharmD *Amherst, N.Y.*

Target-Mediated Drug Disposition



$$\frac{dCp}{dt} = In(t) - \left(k_{el} + k_{pt}\right) \bullet Cp + k_{tp} \bullet \frac{A_T}{Vc} - k_{on} \bullet \left(R_{tot} - RC\right) \bullet Cp + k_{off} \bullet RC$$

$$\frac{dRC}{dt} = k_{on} \bullet \left(R_{tot} - RC\right) \bullet Cp - \left(k_{off} + k_m\right) \bullet RC$$

D. Mager

Key Processes in Pharmacokinetics: PBPK

Process	Equation	Origin
Diffusion	$\frac{dA}{dt} = PS\left(C_h - C_l\right)$	Fick (1855)
Perfusion	$\frac{dA}{dt} = Q\left(C_a - C_v\right)$	Fick (1855), Teorell (1937)
Convection	$\frac{dA}{dt} = L\left(1-\sigma\right)\cdot C$	Renkin (1979)
Transit	$\frac{dC_i}{dt} = \frac{1}{\tau}\left(C_{i-1} - C_i\right)$	Bischoff & Dedrick (1973)
Distribution	$CL_D = Q\left(1 - e^{-PS/Q}\right)$	Stec & Atkinson (1981)
Organ Clearance	$CL = \frac{Q \cdot CL_{\text{int}}}{Q + CL_{\text{int}}}$	Rowland, Benet et al (1973)

…….plus metabolism, transport, plasma and tissue binding

Minimal PBPK Models – Small & Large Molecules

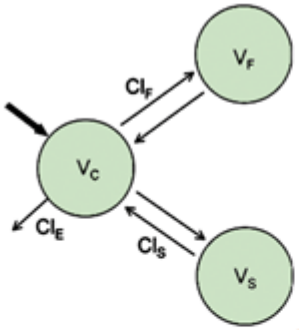
Cao Y and Jusko WJ, JPKPD 2012, 2013.

NCA

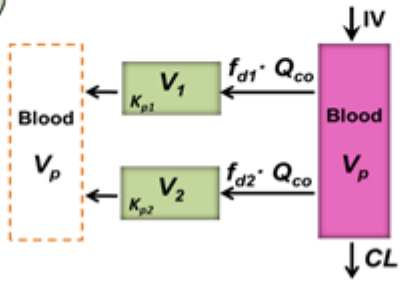
Top-Down

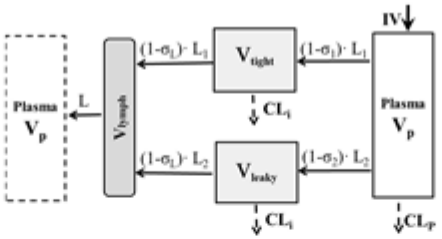
Complexity

Bottom-Up



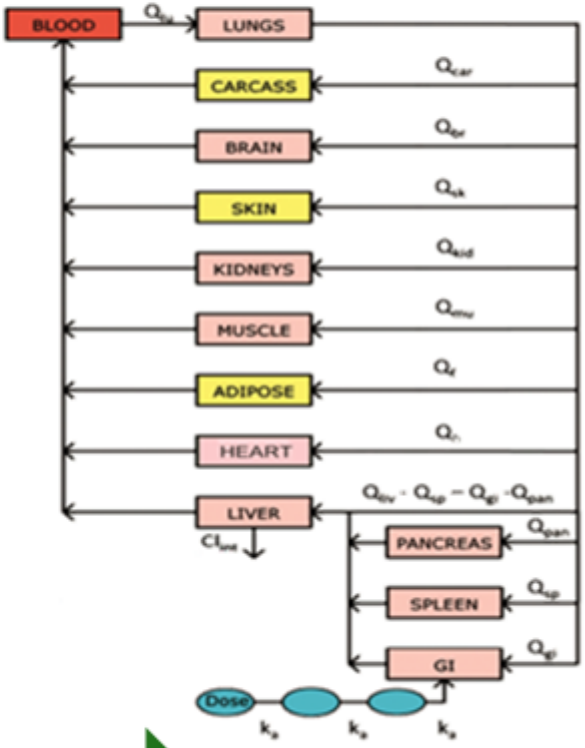
Mammillary model
Empirical approach





Minimal PBPK Models -
An intermediate approach
with only plasma data.

Full PBPK model
with mechanisms



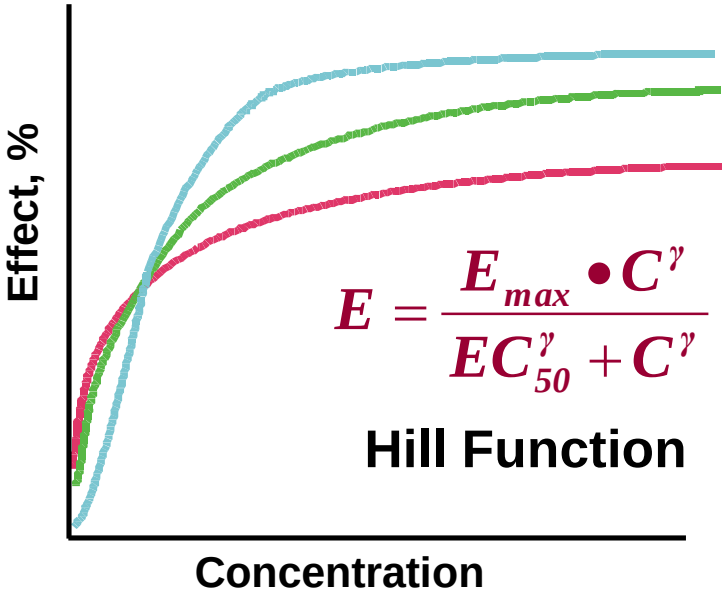
Low

Physiological Information

High

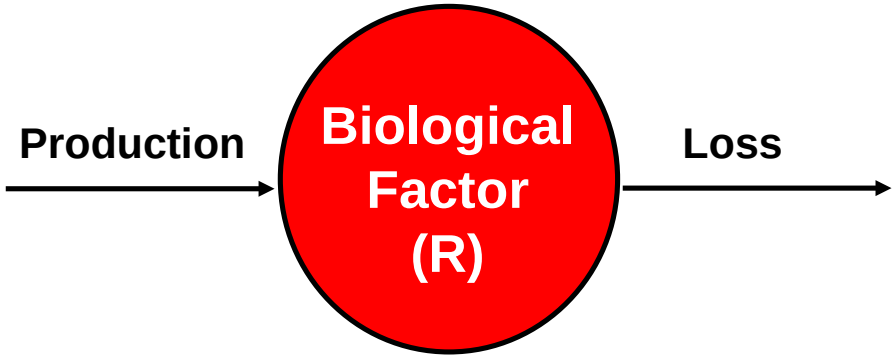
Basic Tenets of Pharmacodynamics

Capacity-Limitation



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

Turnover & Homeostasis



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

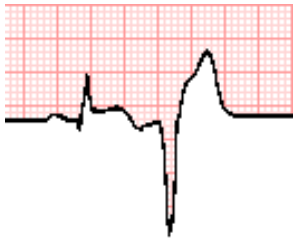
Both diseases and therapeutic agents often interfere with the homeostasis in the body resulting from the natural turnover of biological substances, structures, or functions.

Processes Described by Capacity-Limited Relationships

Process	Equation	Origin
Metabolic Rate	$\frac{dA_m}{dt} = \frac{V_{max} \cdot C}{K_m + C}$	**Michaelis-Menten (1913)**
Transport Rate	$\frac{dAu}{dt} = \frac{T_{max} \cdot C}{K_m + C}$	**Shannon (1939)**
Protein Binding (D_b = Bound Drug)	$D_b = \frac{n \cdot Pt \cdot D_f}{1/K_A + D_f}$	**Goldstein (1949)**
Receptor Binding (B_{sp} = Bound Drug)	$B_{sp} = \frac{B_{max} \cdot D_f}{K_D + D_f}$	**Clark (1933)**
Transduction	$E = \frac{E_m \cdot B_{sp}}{K_E + B_{sp}}$	**Black & Leff (1983)**
Pharmacologic Effect (E)	$E = \frac{E_{max} \cdot C}{EC_{50} + C}$	**Hill (1910)**

WJ Jusko, *J Clin Pharmacol* 29: 488 (1989)

Biological Turnover Rates of Structures or Functions



Fast

Electrical Signals (msec)

Neurotransmitters (msec)

Chemical Signals (min)

Mediators, Electrolytes (min)

Hormones (hr)

mRNA (hr)

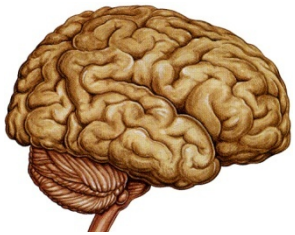
Proteins / Enzymes (hr)

Cells (days)

Tissues (mo)

Organs (year)

People (.8 century)



Slow

BIOMARKERS

CLINICAL

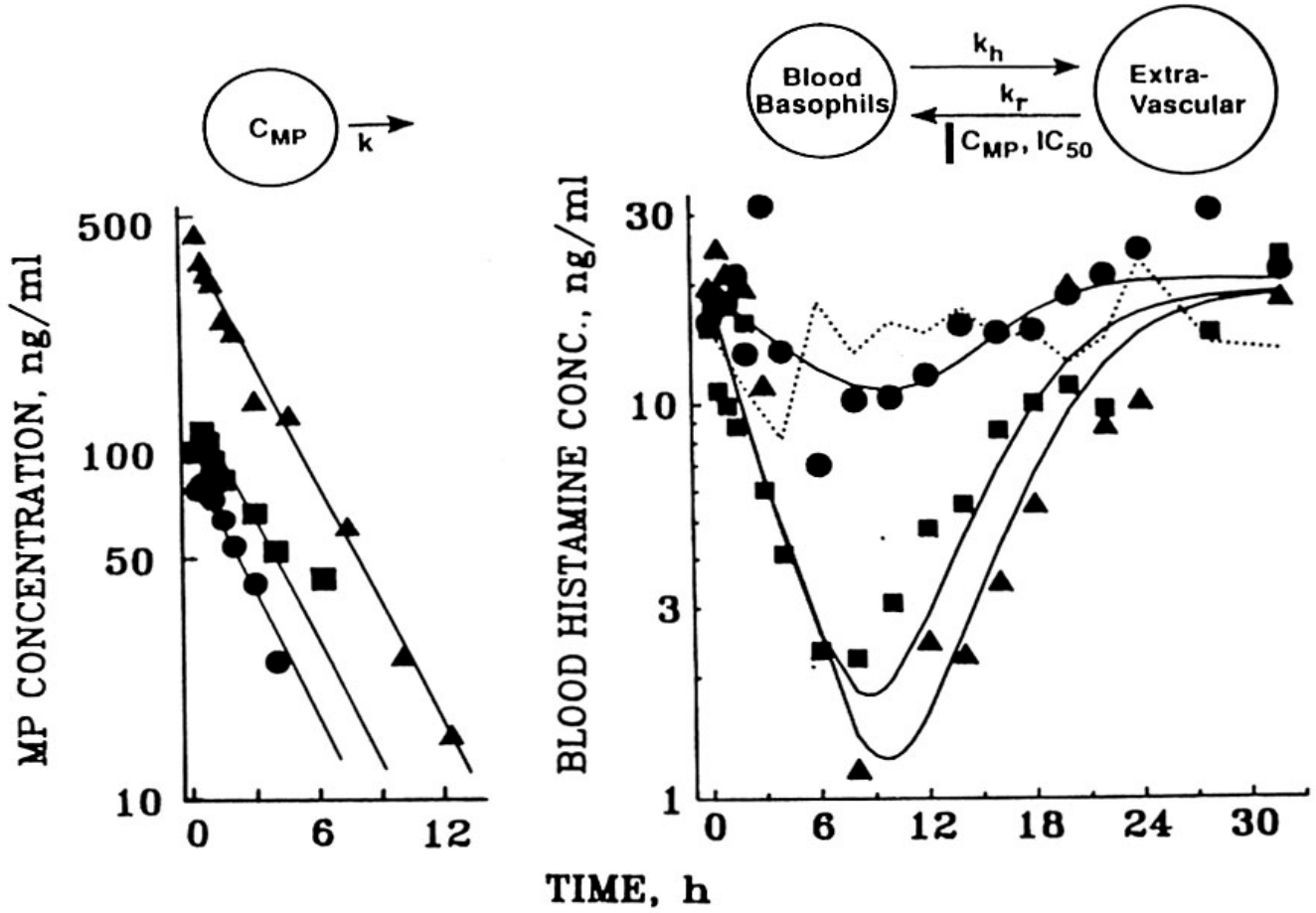
Direct Effect Models

Turnover Models

Transduction Models

SYSTEMS MODELS

CS Effects on Cell Trafficking

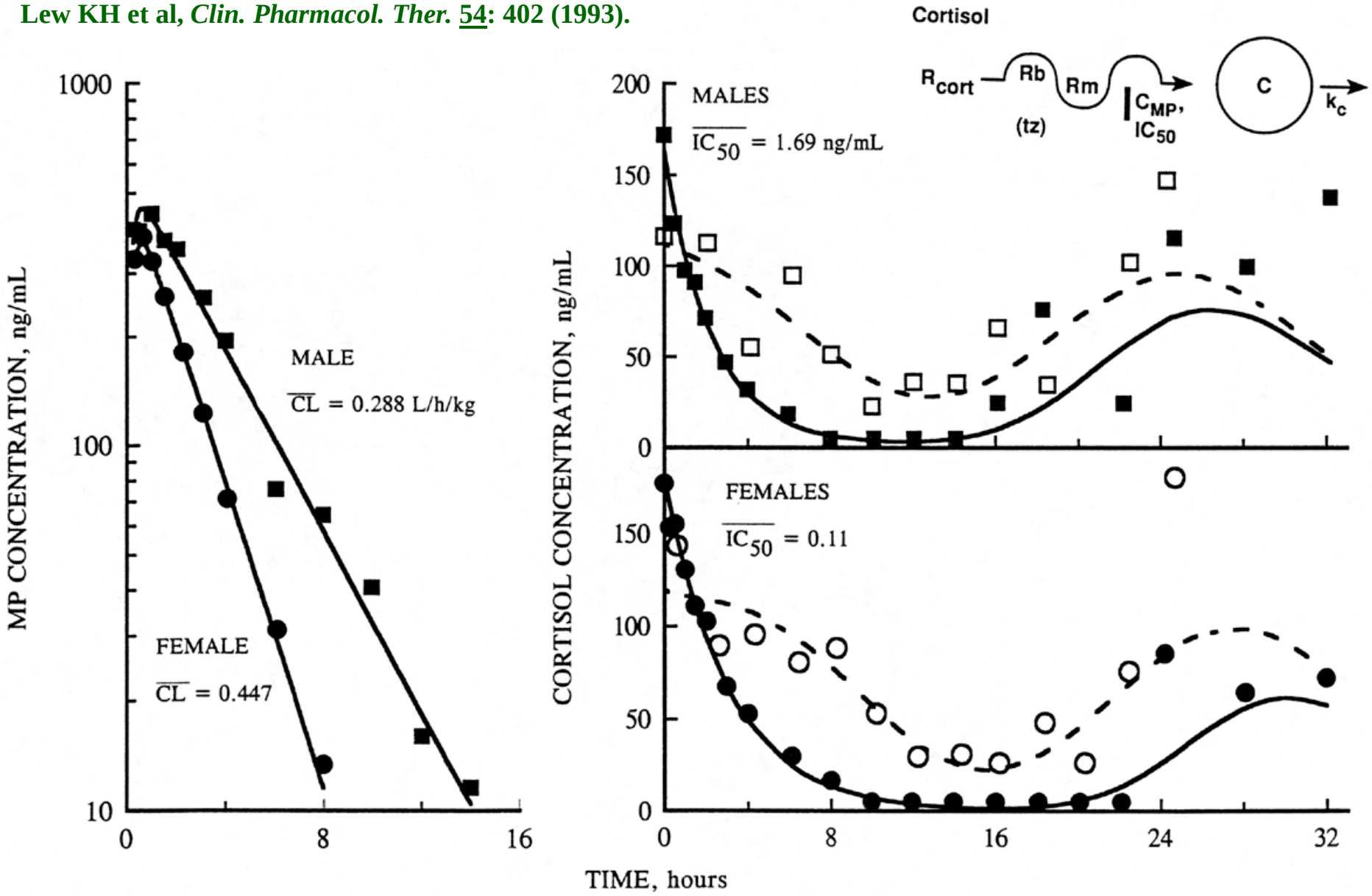


T. Kong

Kong AN, Ludwig EA, Slaughter RL, DiStefano PM, Demasi J, Jusko, WJ. Pharmacokinetics and pharmacodynamics modeling of direct suppression effects of methylprednisolone on serum cortisol and blood histamine in human subjects. Clin. Pharmacol. Ther. 46:616 (1989).

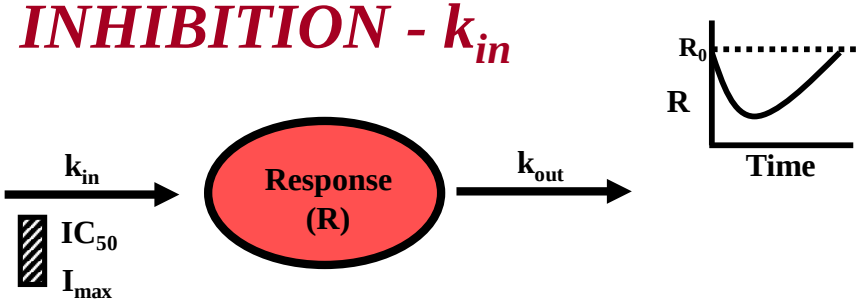
Sex and Methylprednisolone PK/PD

Lew KH et al, *Clin. Pharmacol. Ther.* 54: 402 (1993).



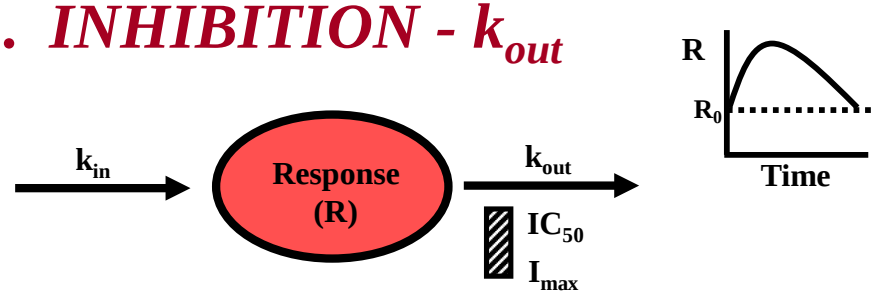
Family of Indirect Response Models

I. *INHIBITION - k_{in}*



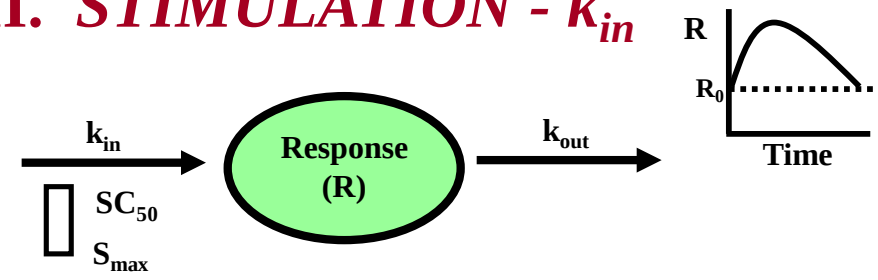
$$\frac{dR}{dt} = k_{in} \cdot \left(1 - \frac{I_{max} \cdot C_p}{IC_{50} + C_p}\right) - k_{out} \cdot R$$

II. *INHIBITION - k_{out}*



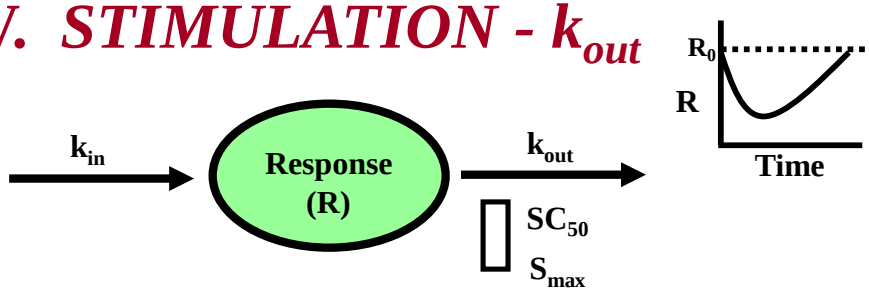
$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 - \frac{I_{max} \cdot C_P}{IC_{50} + C_P}\right) \cdot R$$

III. *STIMULATION - k_{in}*



$$\frac{dR}{dt} = k_{in}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) - k_{out} \cdot R$$

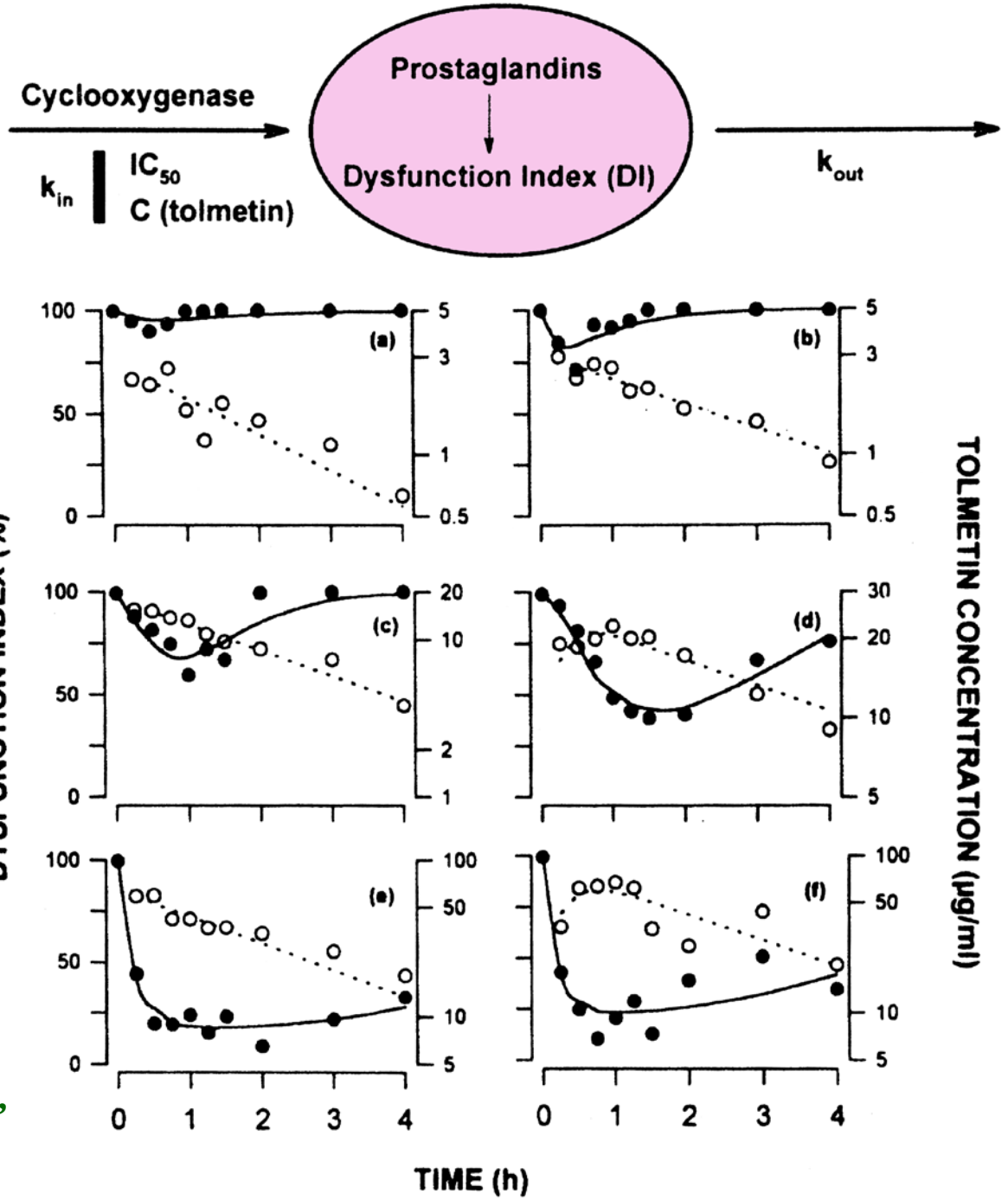
IV. *STIMULATION - k_{out}*



$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) \cdot R$$

Levy et al, CPT 10: 22 (1964); Dayneka, Garg, Jusko, JPB 21: 457 (1993),
Jusko & Ko, CPT 56: 406 (1994); Sharma A and Jusko WJ, *BJCP* 45: 229 (1998).

PAIN: PK/PD of Antinociceptive Drug Effects



Rats received injection of uric acid in knee joint to induce dysfunction.
Lower Index % = less pain.

PK and PD were fitted jointly using population methodology.

Flores-Murrieta, Kimko, Jusko, et al, *JPB* 26: 547 (1998).

Complex Indirect Response Models

Circadian Input

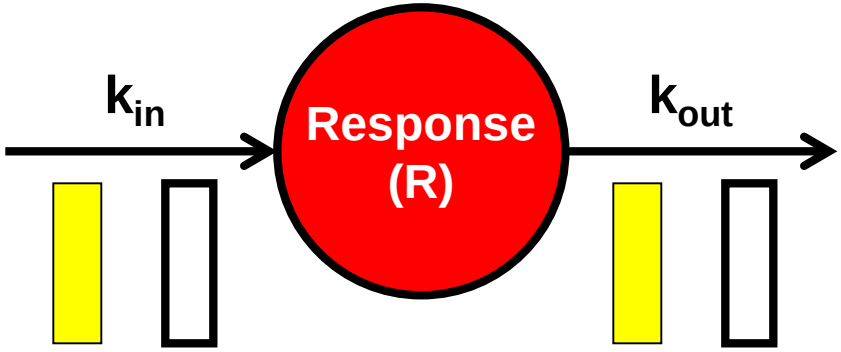
$$k_{in}(t) = R_m + R_b \cdot \cos\left[(t - t_z) \cdot 2\pi/24\right]$$

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

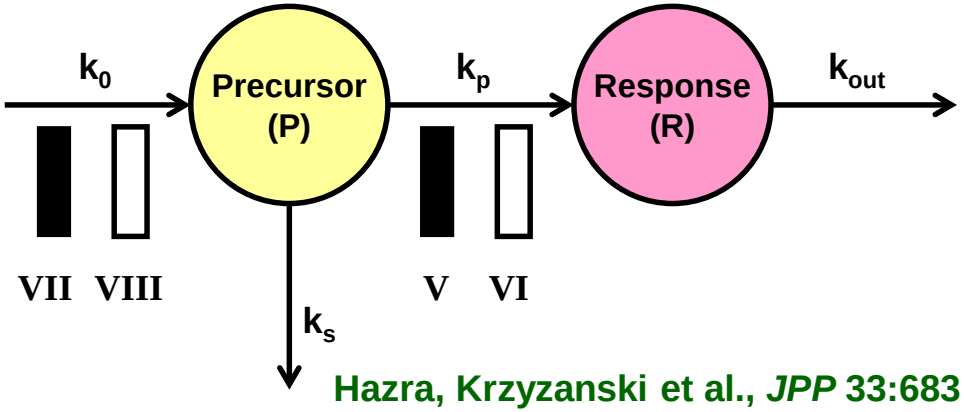
Cell Life-Span IRM

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

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



Precursor-Dependent IRM



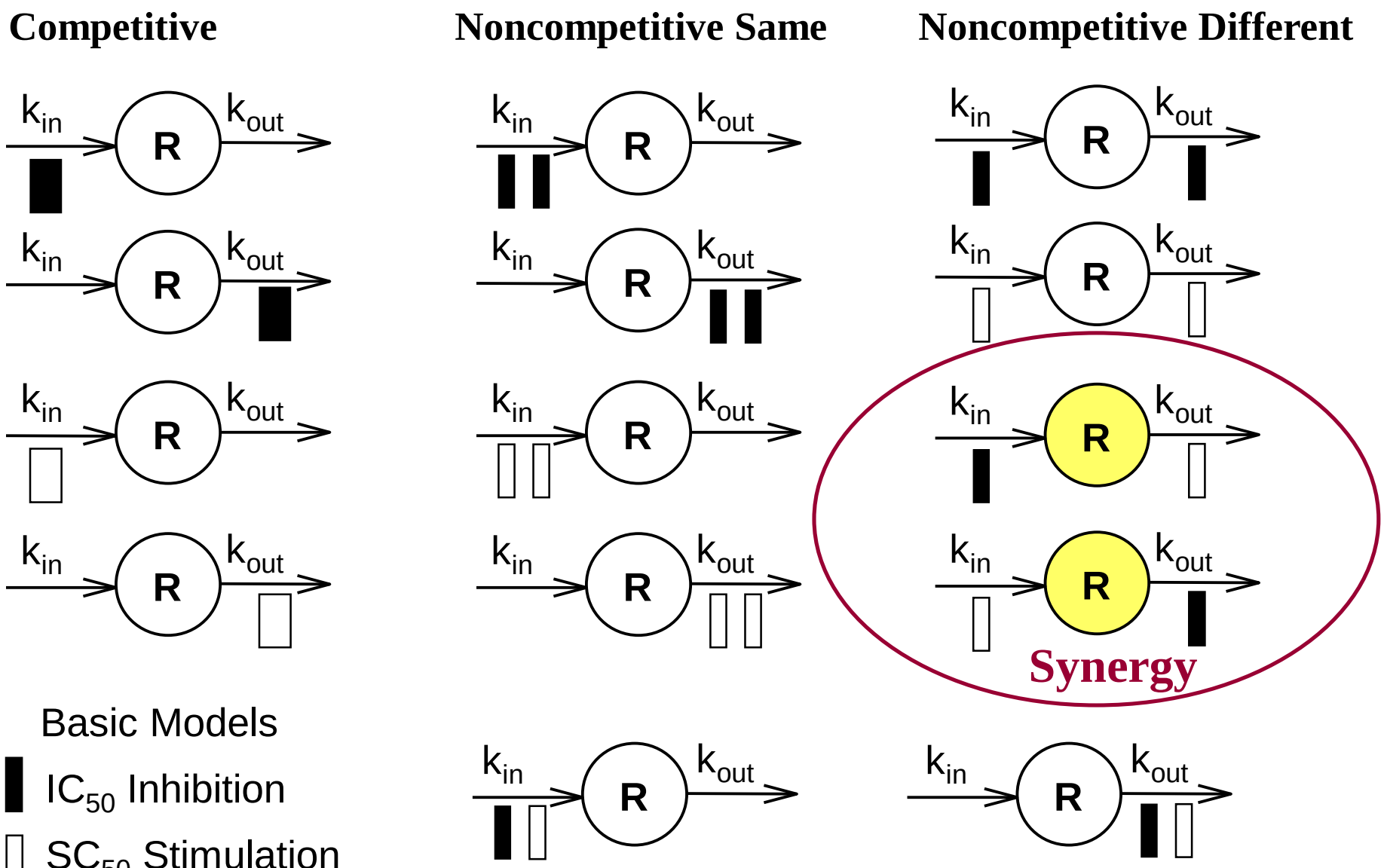
Hazra, Krzyzanski et al., *JPP* 33:683 (2006)

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)

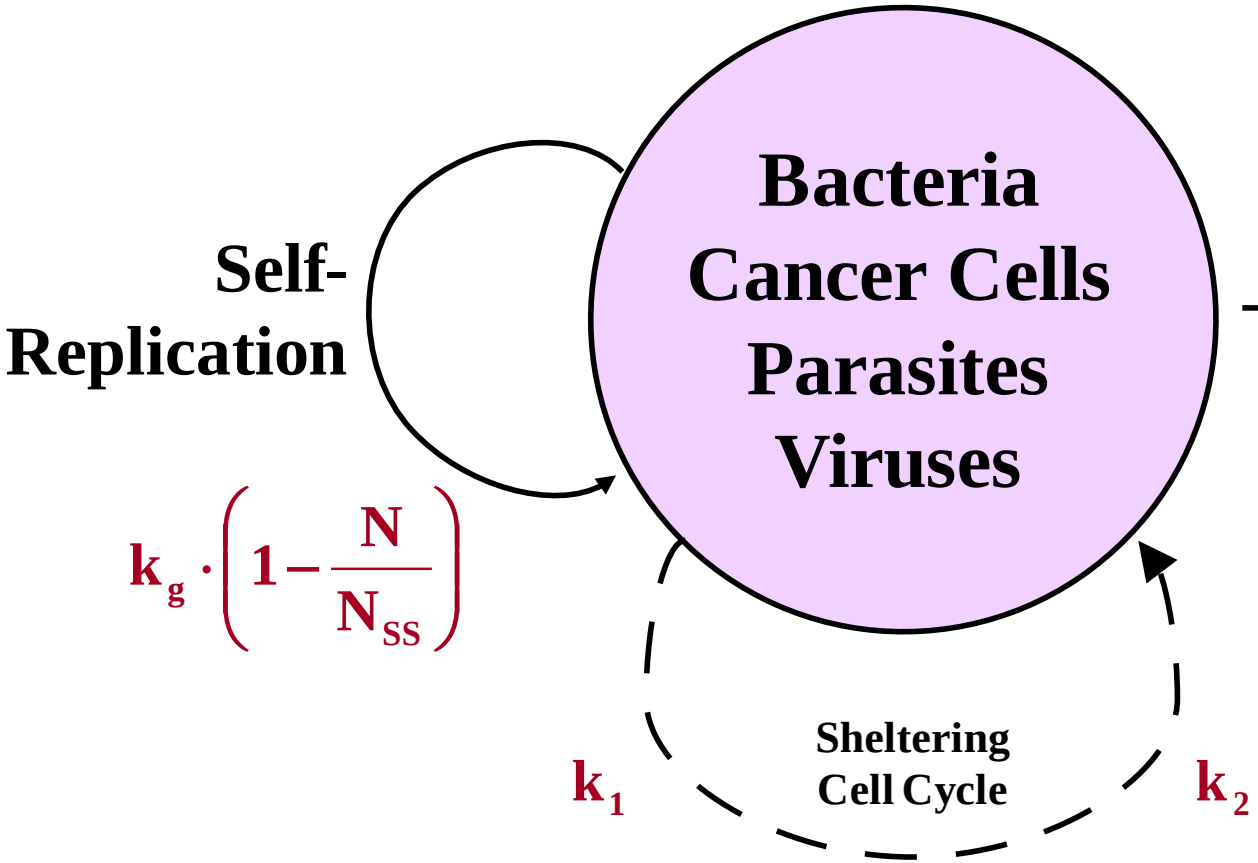
Drug Interactions: Indirect Response Models

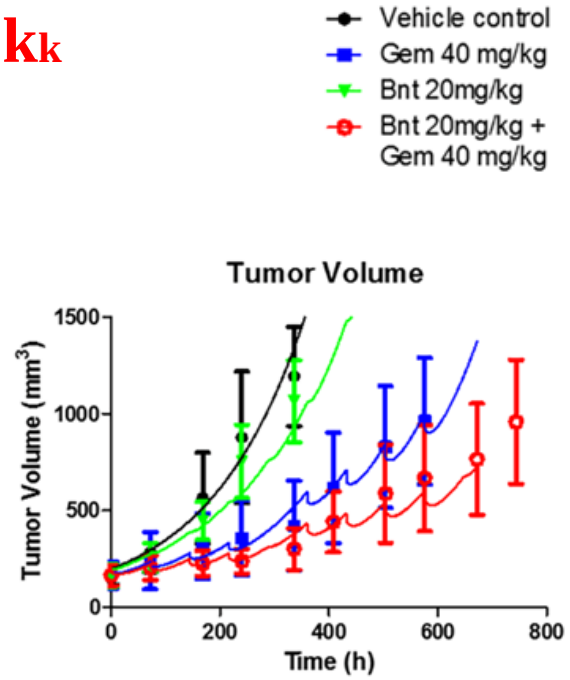


Earp JC, Krzyzanski W, Jusko WJ, *JPKPD* 31: 345 (2004).

Chemotherapeutic Targets: Basic Model Paradigm

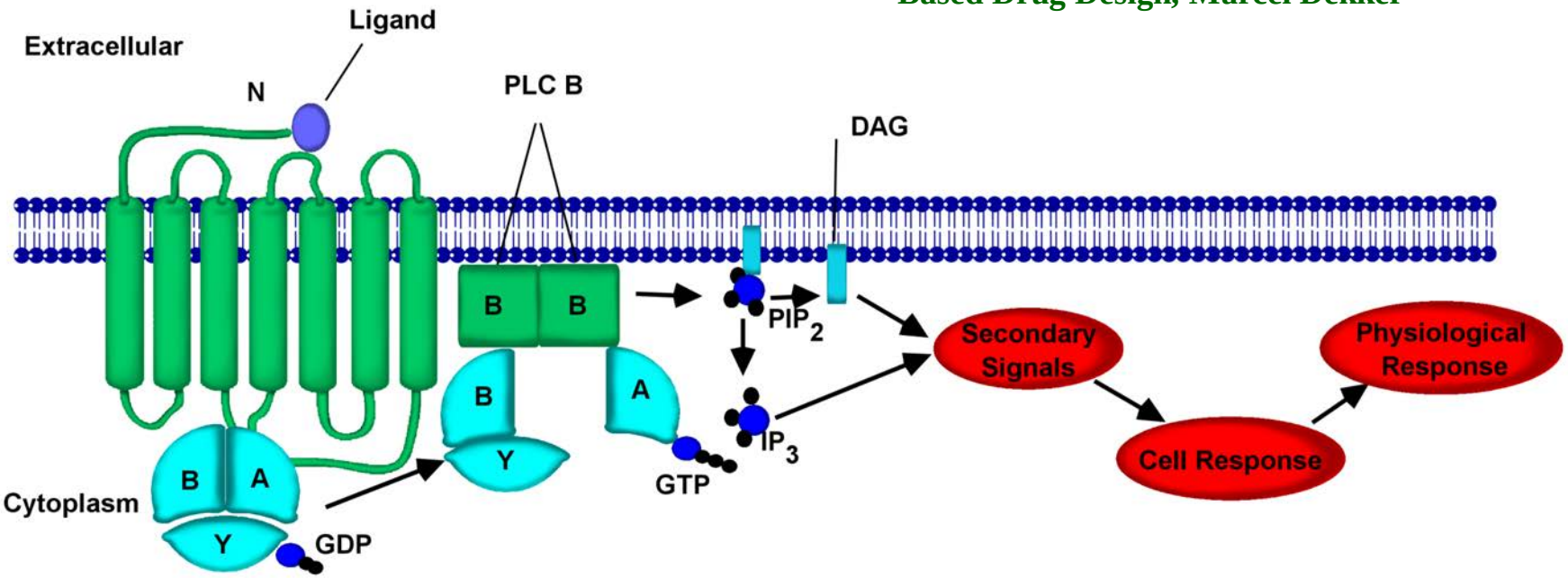
Jusko WJ, A Pharmacodynamic Model for Cell Cycle-Specific Chemotherapeutic Agents, JPB 1: 175 (1973).

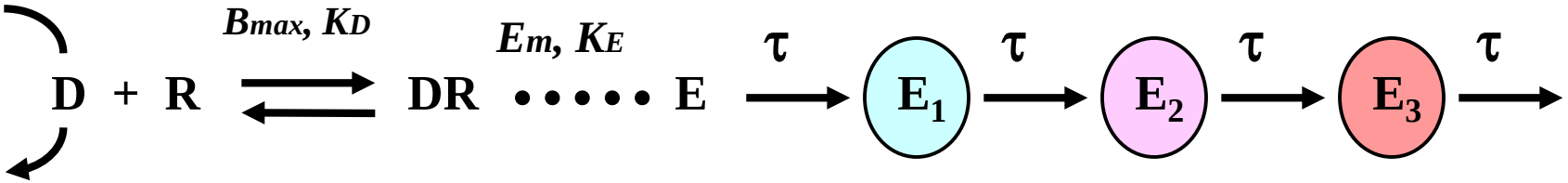




Signal Transduction - Transit Models

Adapted from: Harden TK, Leff P, Receptor-Based Drug Design, Marcel Dekker

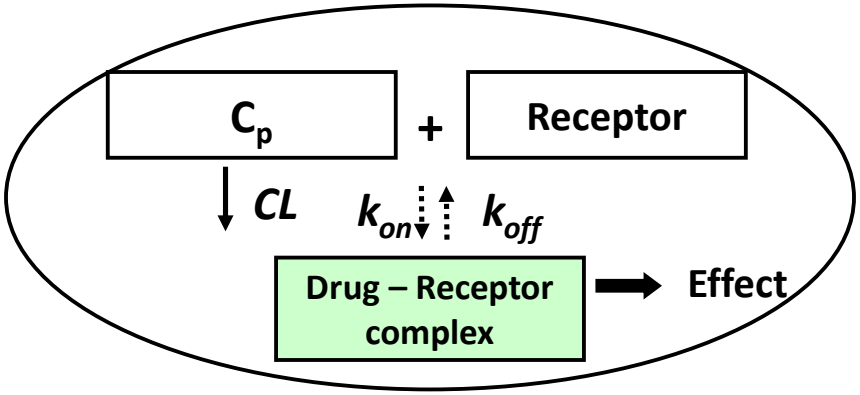




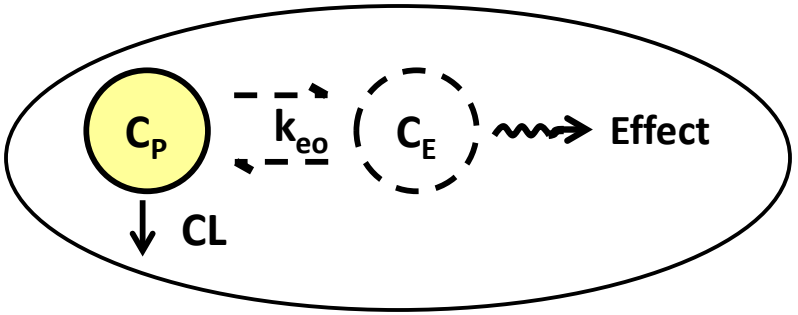
Black JW and Leff P, Operational models of pharmacologic agonism,
Proc Roy Soc London B Biol Sci 220: 141 (1983)

Sun YN & Jusko, JPB, Mager D & Jusko WJ, Pharmacodynamic modeling of time-dependent transduction systems, *CPT* 70: 210 (2001).

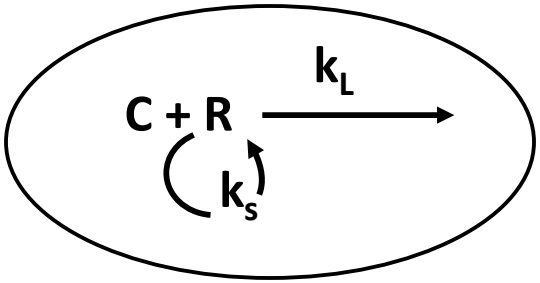
Array of Basic PK/PD Models



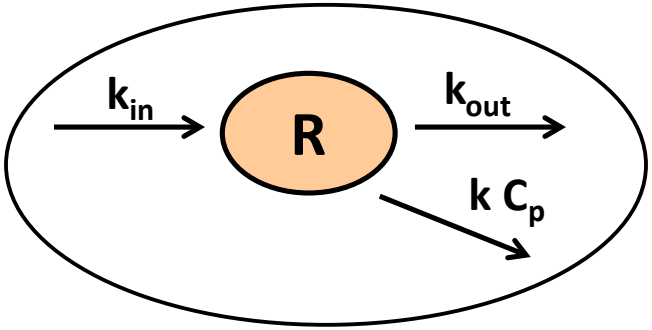
Slow Receptor Binding



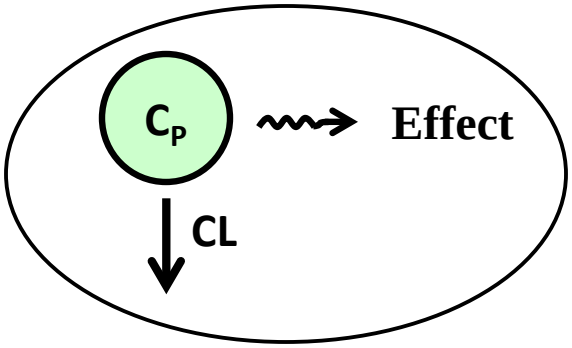
Biophase



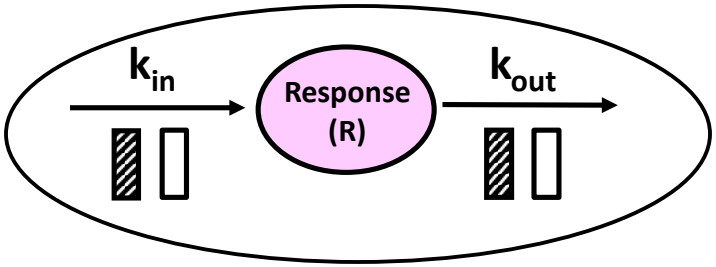
Cell Growth & Loss



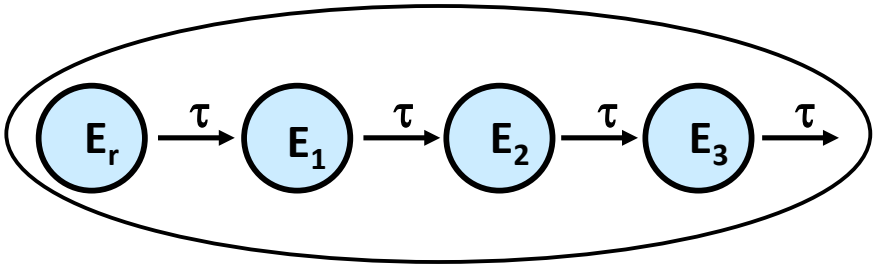
Turnover & Inactivation



Direct

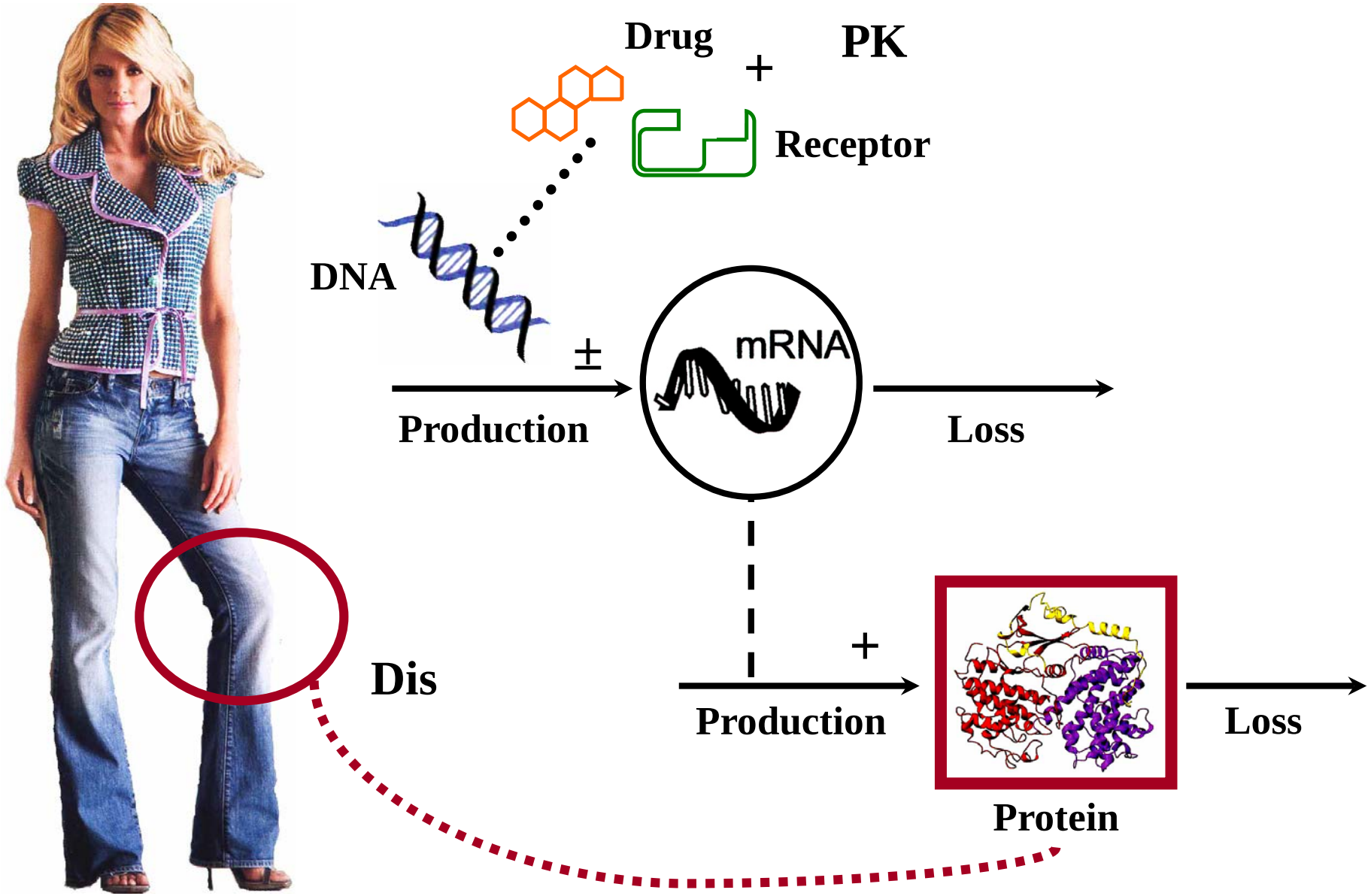


Indirect Response

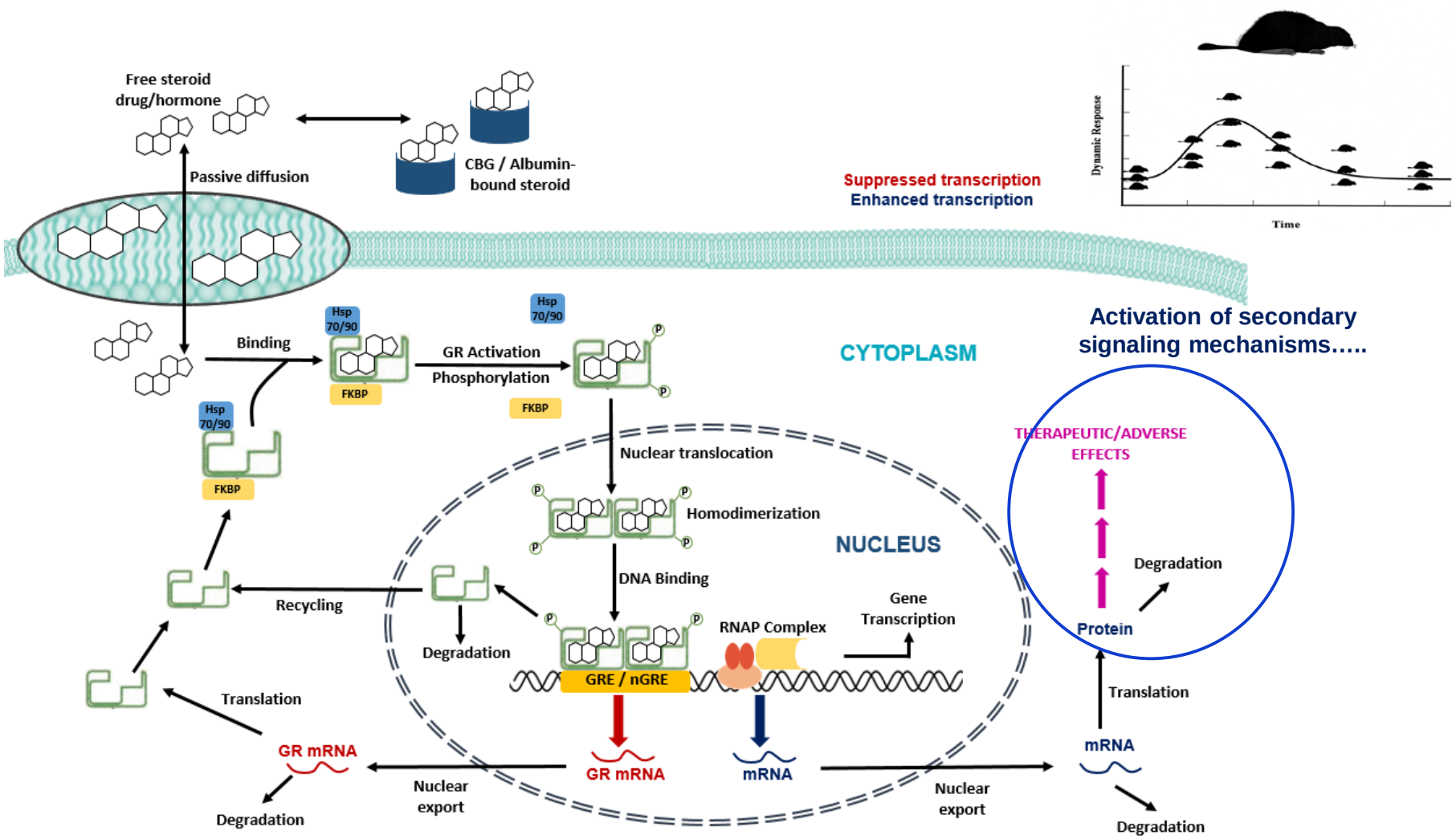


Transduction

CS & Systems PK/PD: Drugs & Genes & Models



Mechanisms of CS Action: Giant Rat Studies



By V Ayyar

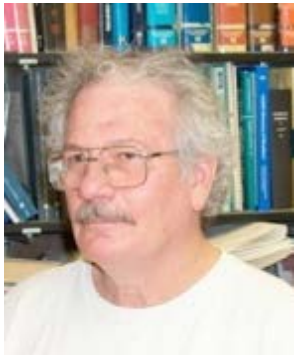
Corticosteroid Pharmacokinetics and Pharmacodynamics
NIH Grant GM 24211-42 (Jusko, Almon, DuBois, Androlakis)

Hypothesis: Realistic and comprehensive PK/PD models of corticosteroid (CS) action are feasible which permit more mechanistic insights into drug, dosage, and interaction factors which determine their effects.

Specific Aims

1. **Assess sex differences in circadian rhythms in rats**
2. **Sex differences in metabolic effects (glucose, lipids, etc)**
3. **Assess sex differences relating to anti-inflammatory and bone turnover systems in response to CS**
4. **Evolve systems pharmacology models to characterize global genomic, proteomic, and biomarker responses to CS in M & F rats**

Almon

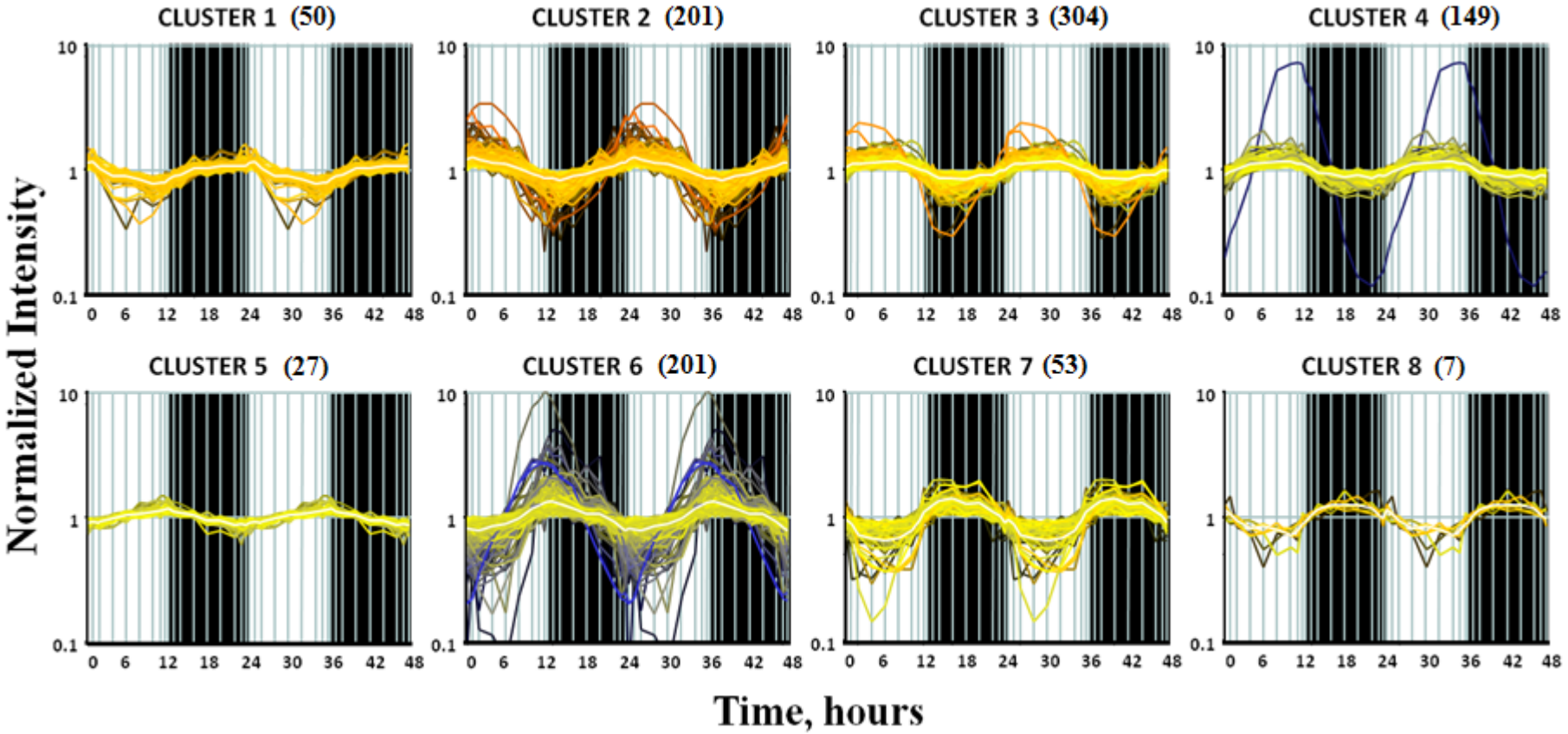


Androlakis

DuBois

Circadian Rhythms in Gene Expression in Rat Lungs

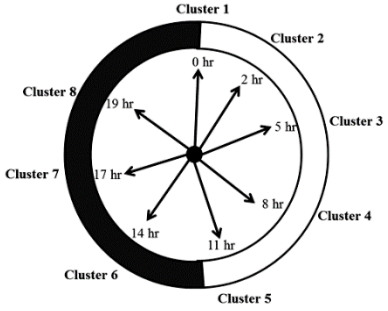
Sukumaran et al., *J. Appl. Physiol.* 110: 1732 (2011).

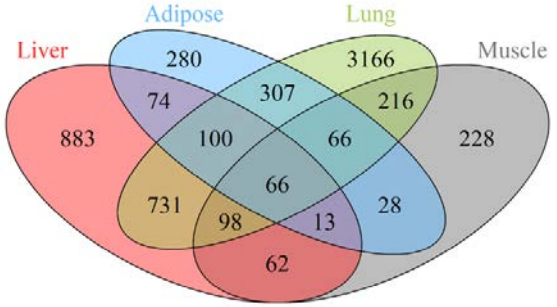


Liver: ***J. Pharmacol. Exp. Ther.*** **326: 700 (2008).**

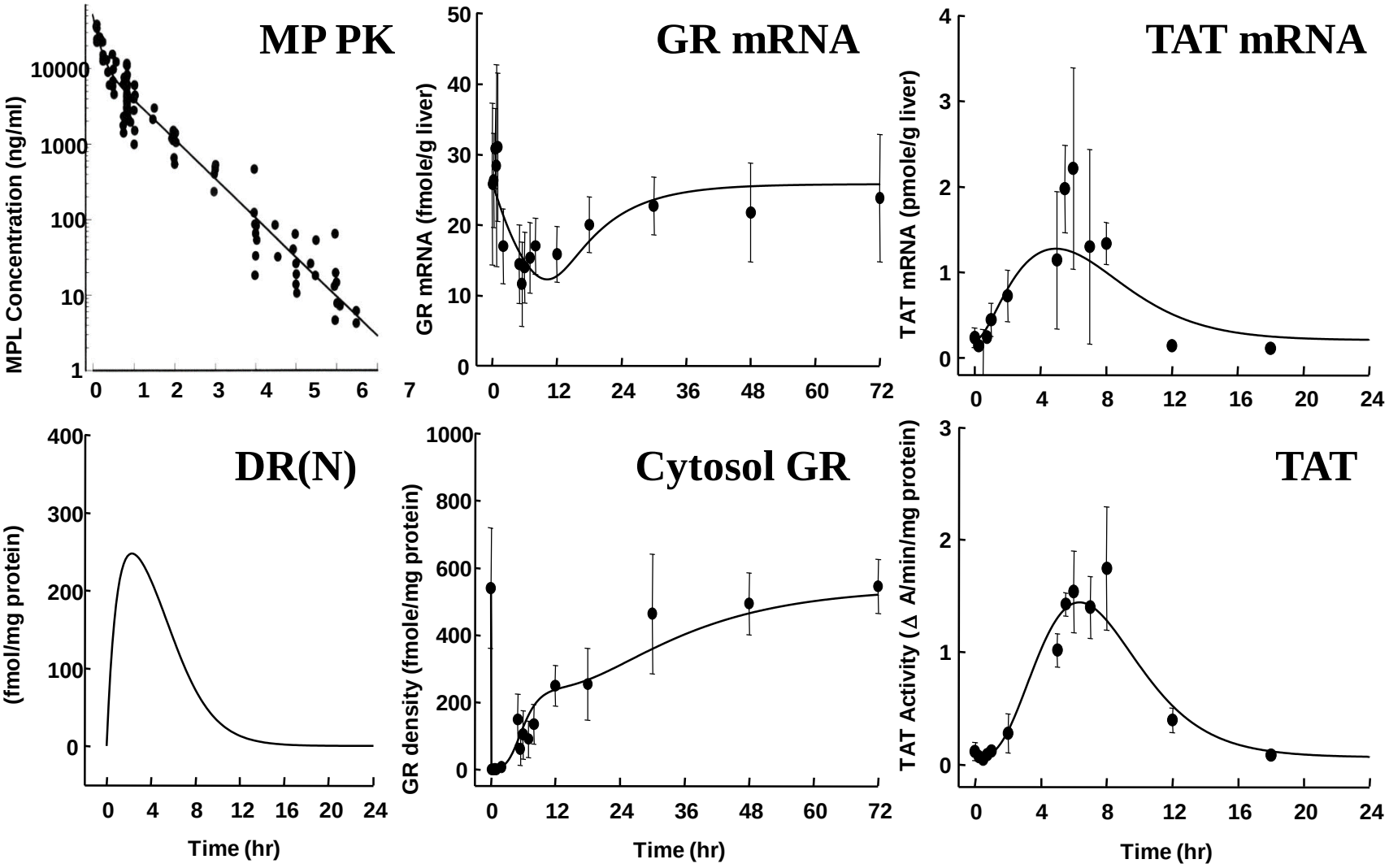
Muscle: ***Am. J. Physiol. Reg Int. Comp. Physiol.*** **295: R1031 (2008).**

Fat: ***Physiol. Genomics*** **42A: 141(2010).**

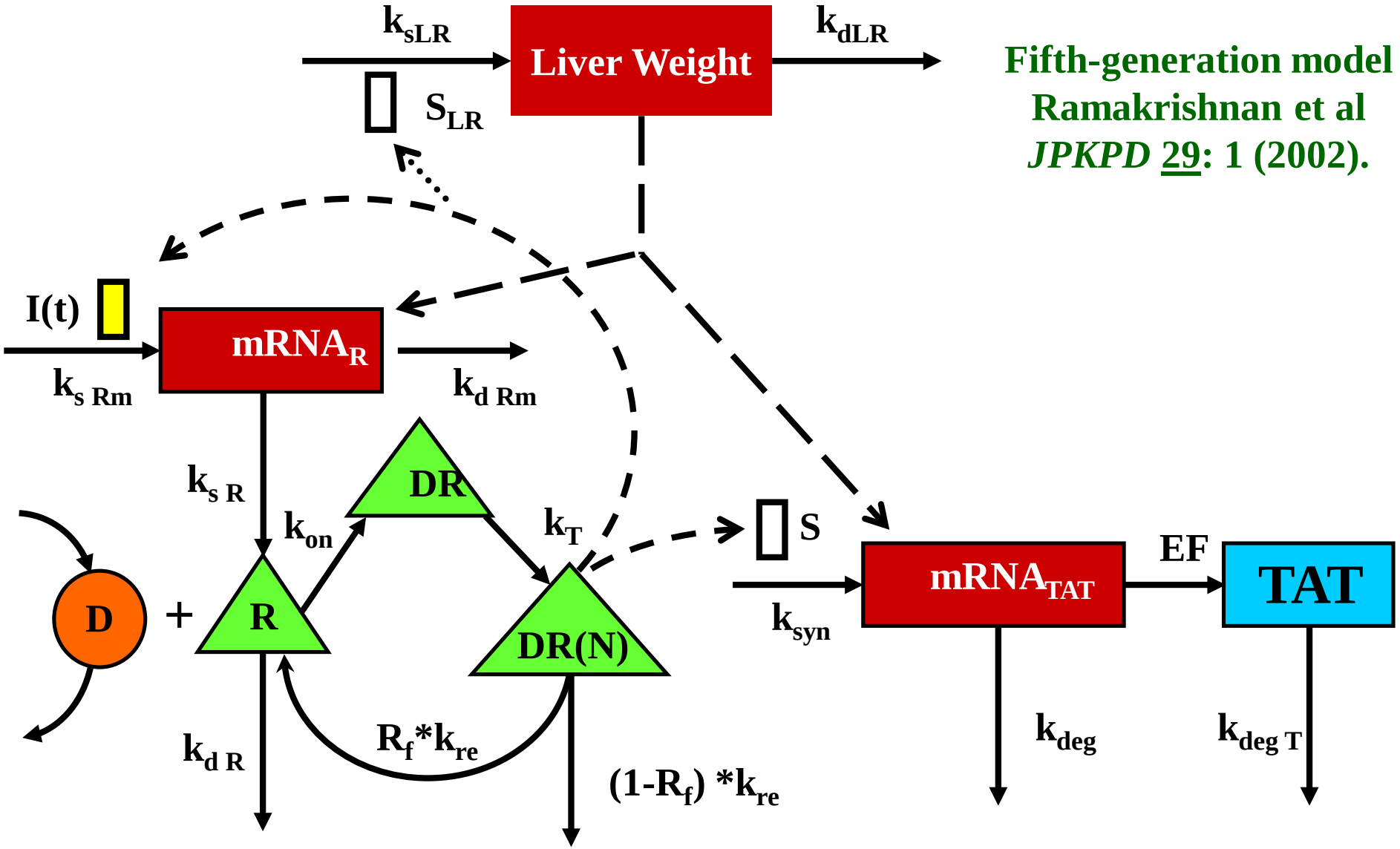




Corticosteroid PK/PD/PG in Rat Liver

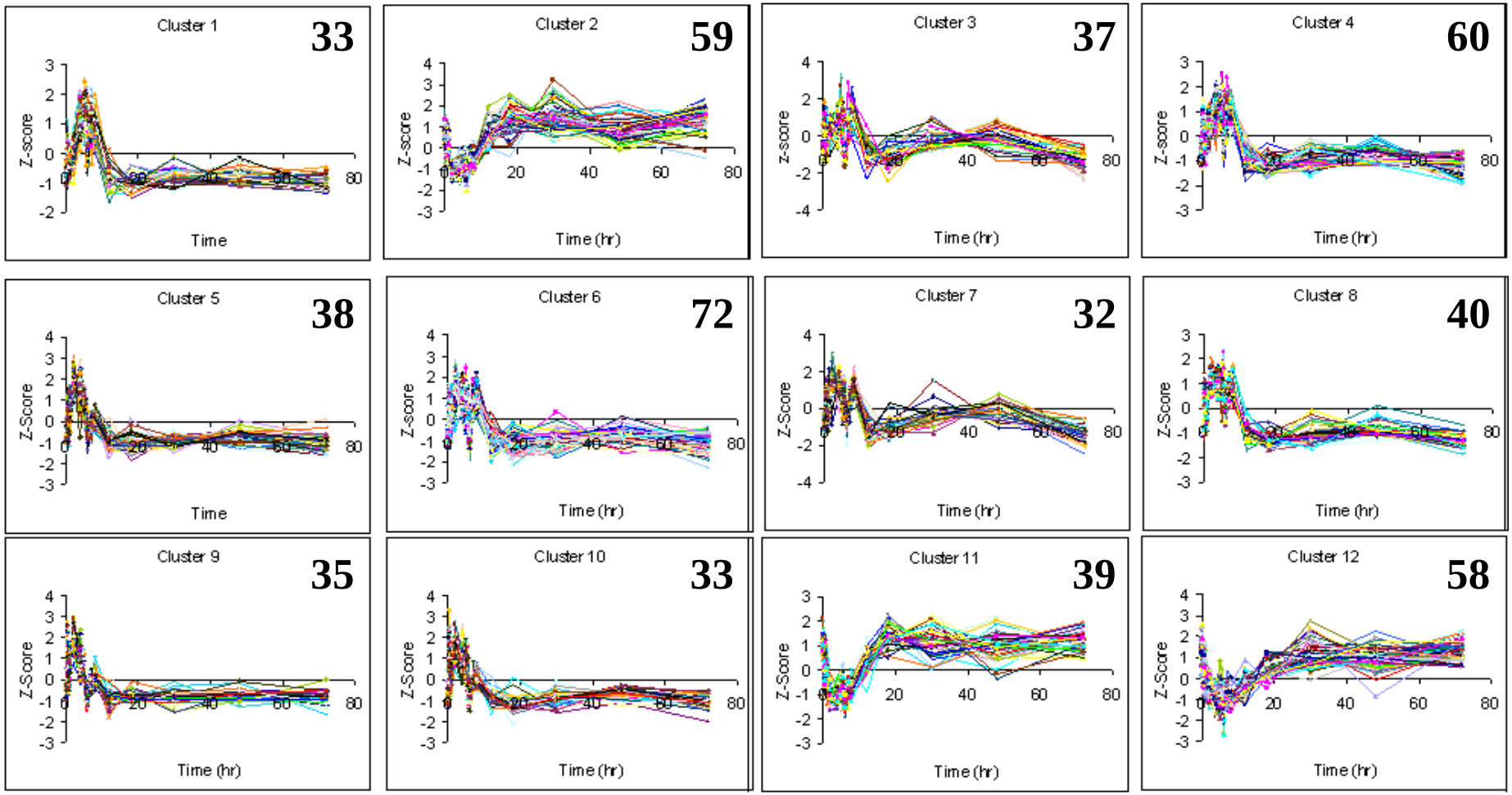


Corticosteroid PK/PD/PG Model



Fifth-generation model
Ramakrishnan et al
JPKPD 29: 1 (2002).

CS Effects on Diverse Genes in Rat Liver

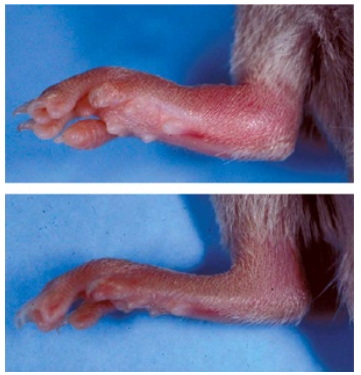


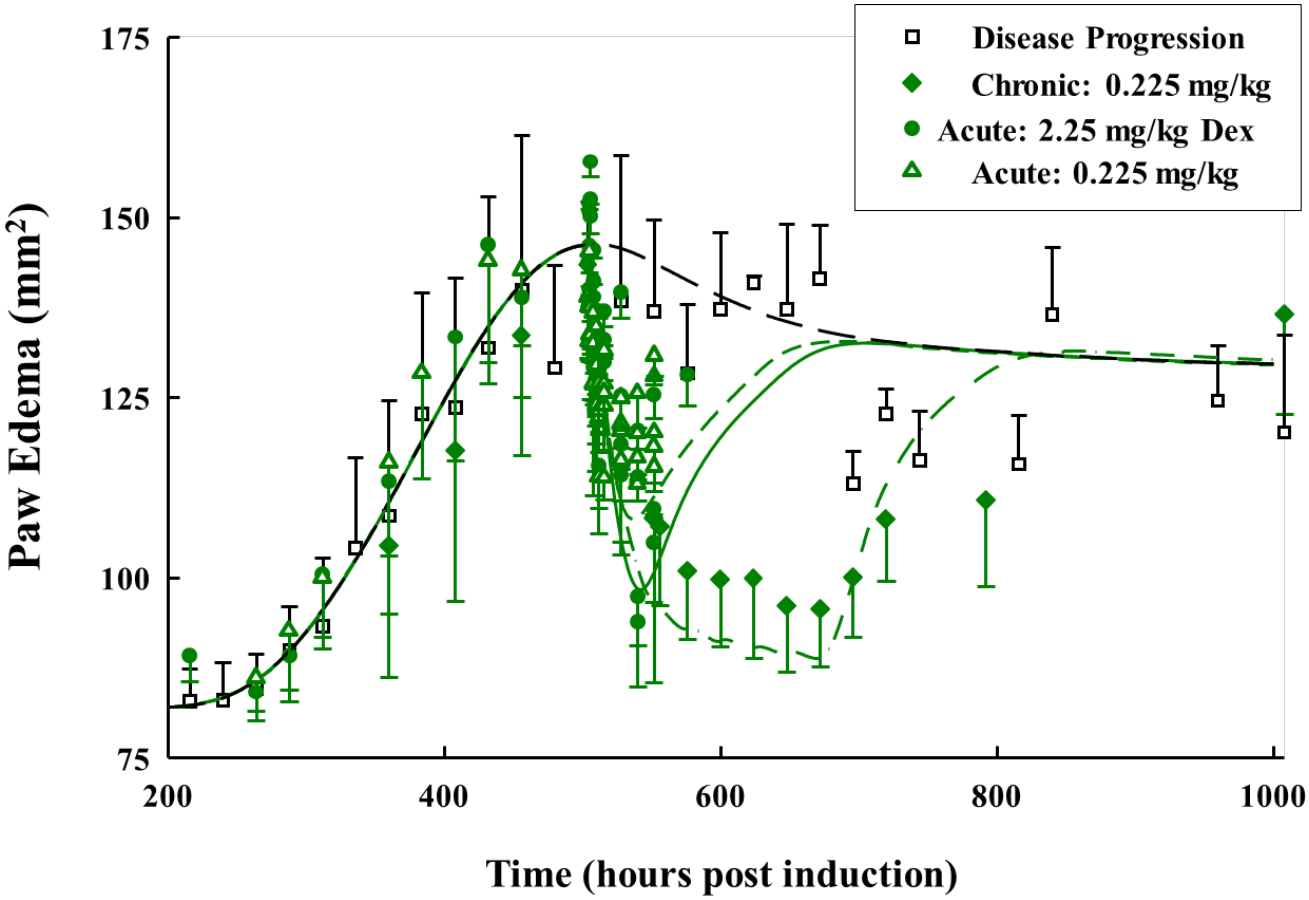
Yang et al, *JPET* 324: 1243 (2008)
Use of Affymetrix Microarrays.

Nouri-Nigjeh E et al, Large-Scale Quantitative Proteomics with Application to Protein Expression Dynamics Induced by Methylprednisolone, Analytical Chem. 86: 8149 (2014).

Arthritis Disease Progression Model

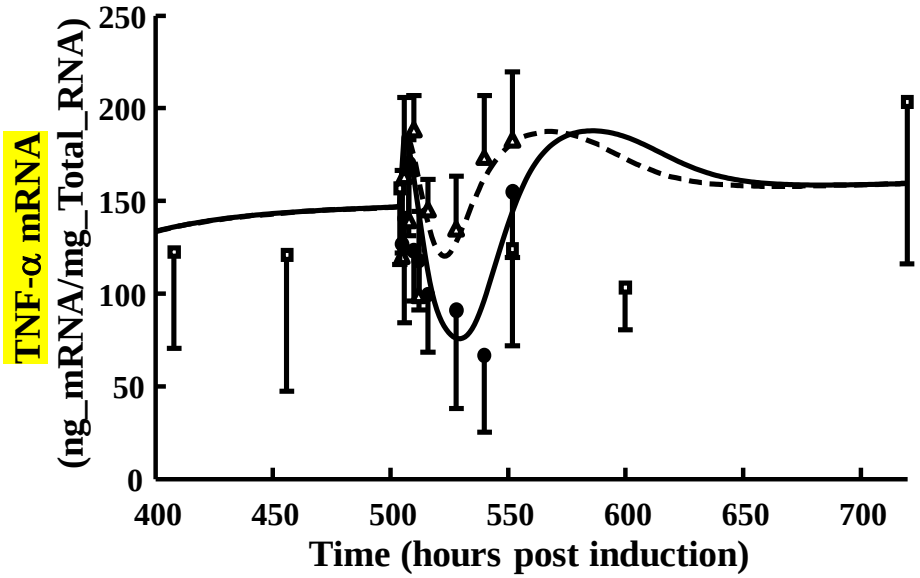
Rats with Collagen-Induced Arthritis - Treatment with Dexamethasone.

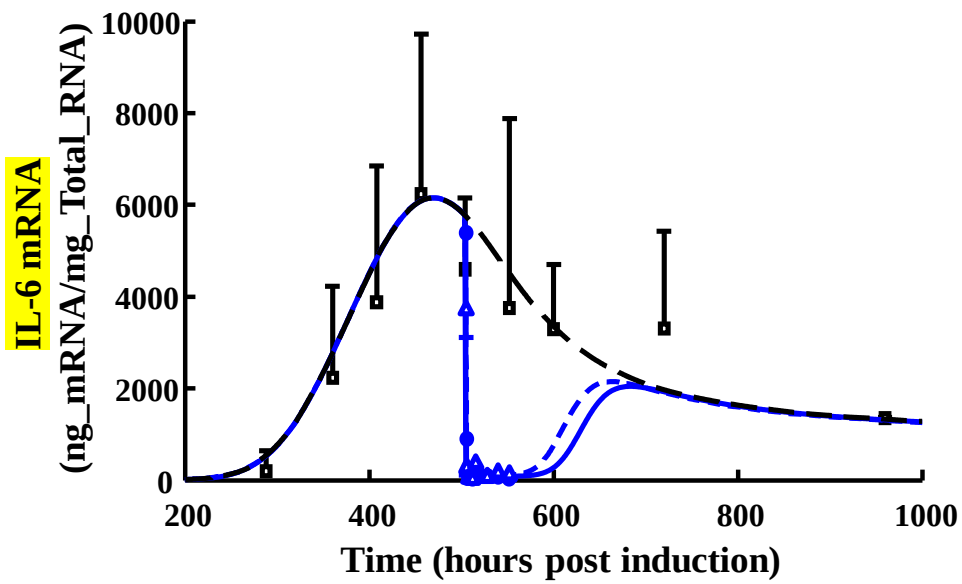




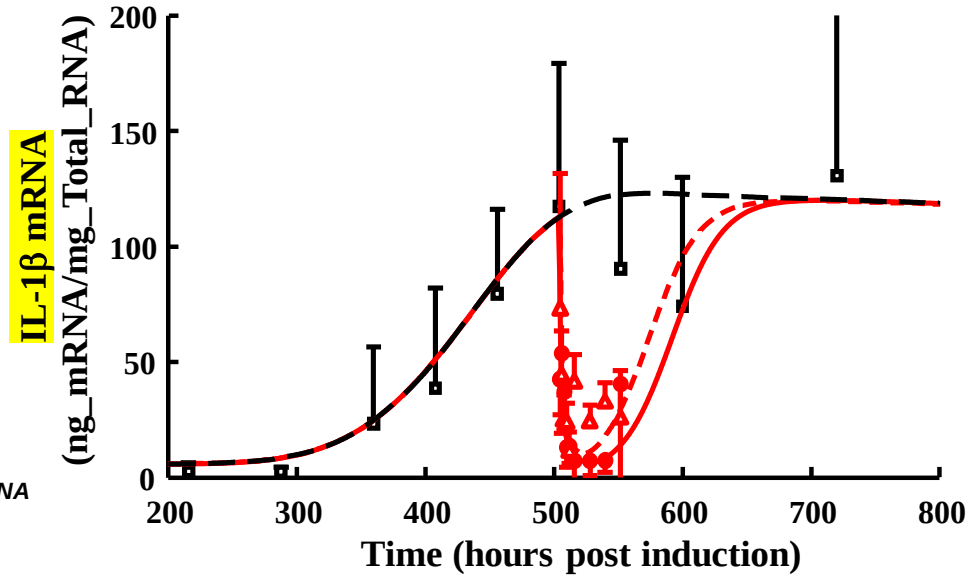
Earp J et al., *JPET* 326: 532 & 546 (2008)

CS PD: Cytokine mRNA – Key MoA





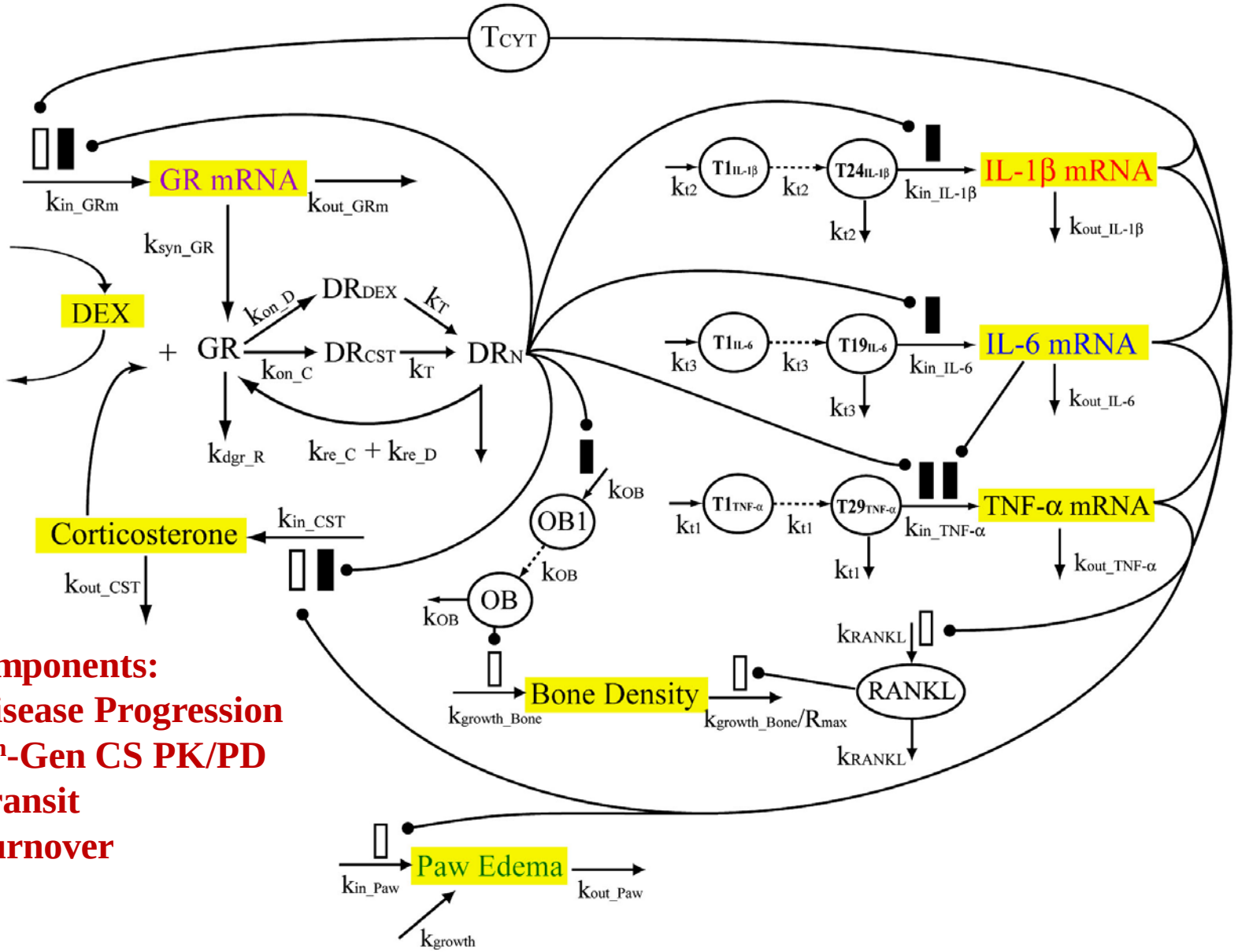
- ● High Dex Dose: 2.25 mg/kg
- △ Low Dose: 0.225 mg/kg
- □ Disease Progression



IDR Eq for Cytokine Inhibition by Dex

$$\frac{dCYT_{mRNA}}{dt} = k_{in} \cdot T29\left(1 - \frac{DR}{IC_{50} + DR}\right) - k_{out} \cdot CYT_{mRNA}$$

RA - CS PK/PD/PG/DIS Model

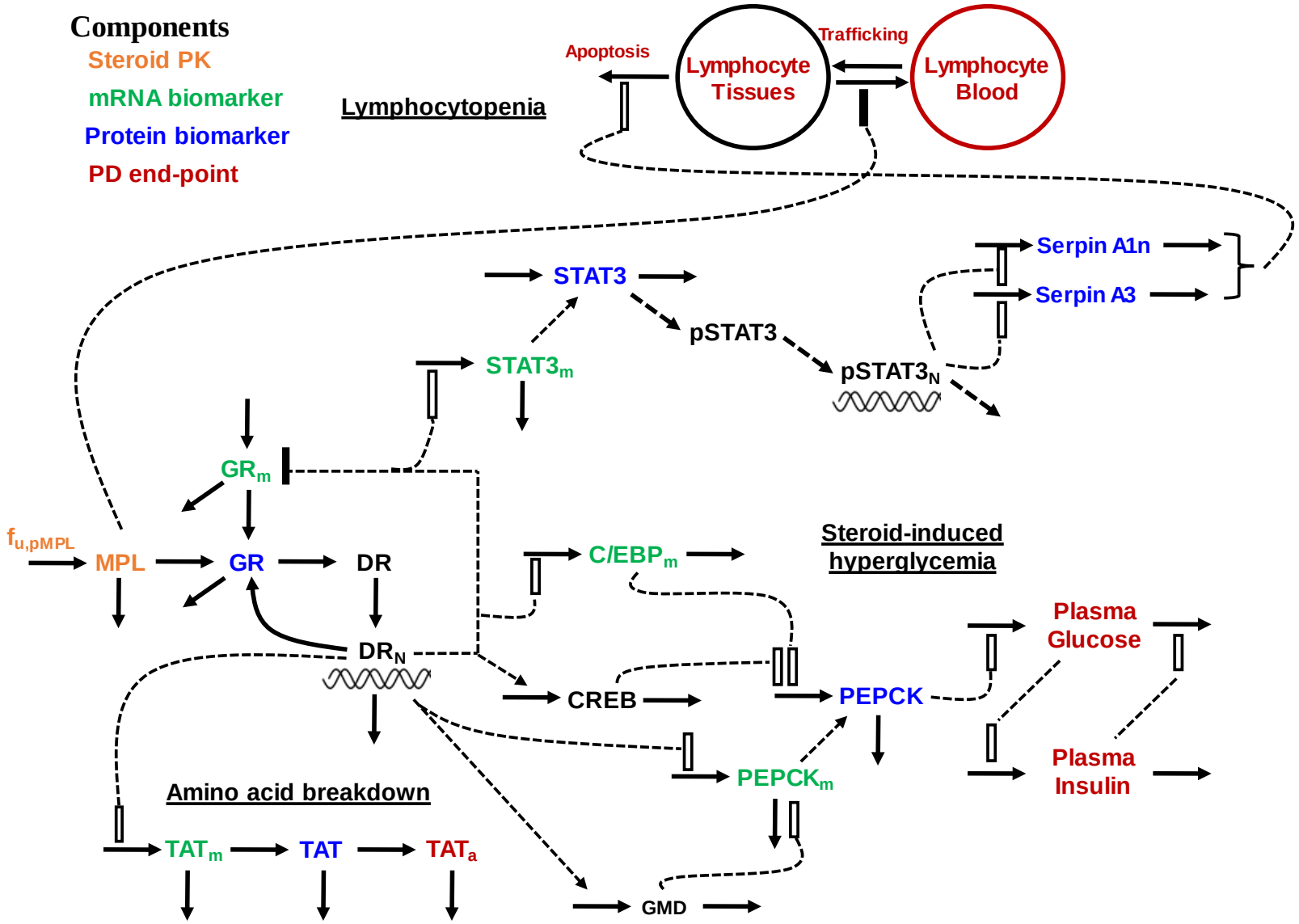


Components:

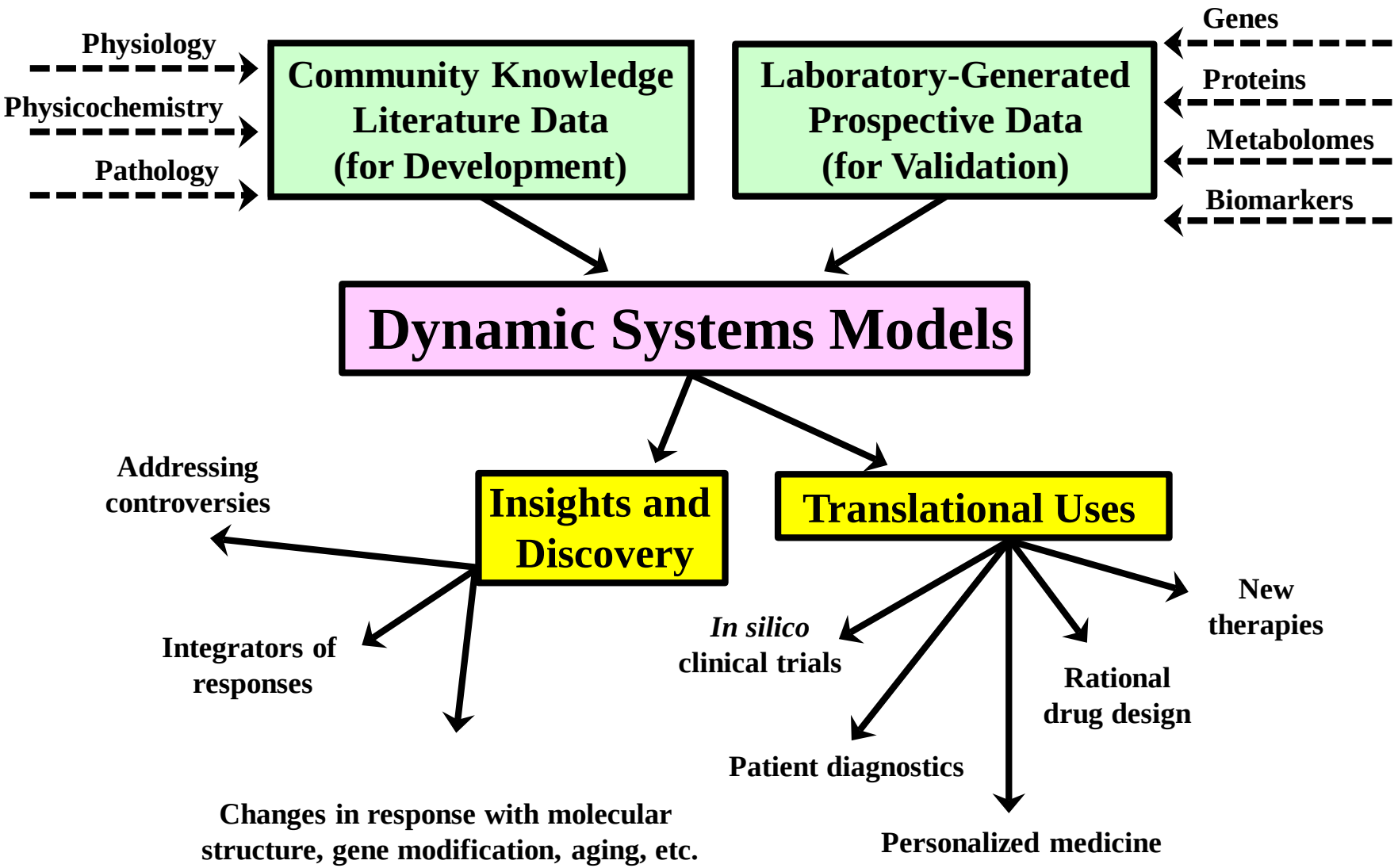
- **Disease Progression**
- **5th-Gen CS PK/PD**
- **Transit**
- **Turnover**

Receptor/Gene/Protein-Mediated Signaling Connects Methylprednisolone Exposure to Metabolic and Immune-Related Pharmacodynamic Actions in Liver

Ayyar VS, Sukumaran S, DuBois DC, Almon RR, Qu J, and Jusko WJ, JPKPD (2018).

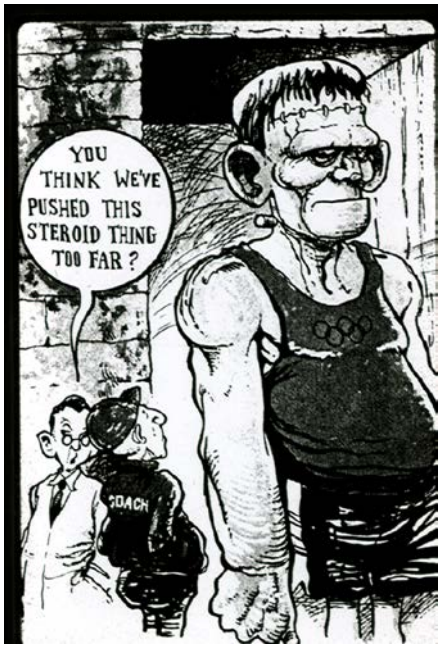


Aspirations of Translational Systems Biology & Pharmacology



Summary

- **PK, PD, and systems pharmacology models are premised on many basic laws of nature, biology, and pharmacology.**
- **Studies of properties of diverse drugs such as steroids have helped evolve PK from empirical NCA and compartment analyses to mechanistic and physiologically-based models.**
- **The principles of capacity-limitation in PK and target occupancy and types & rates of turnover processes serve as tenets for diverse pharmacodynamic and systems models.**
- **Addressing basic and translational aspects of PK/PD has provided me with extremely interesting and enjoyable opportunities and interactions in research, education, training, administration, consulting, and travel.**



With Considerable Thanks