PBPK Modeling: Opportunities for Enhancements

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Presented at the 2021 CRCG PBPK workshop on "Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches." Sept 30 & Oct 1, 2021

Declarations

- **Member of Scientific Advisory Board of Simulations Plus and receives access to all software for UB Pharmaceutical Sciences.**

- **Receives complementary software from Certara on behalf of the UB Department of Pharmaceutical Sciences.**

- **Supported by NIH Grant R35 GM131800 “Mechanistic Pharmacokinetics and Pharmacodynamics”.**

- **Other support: Gates Foundation, GSK.**

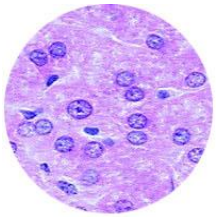
Approaches to Extrapolation

In Silico: QSPR, various software

Bioassays, physicochemical measurements

PK: Allometric Scaling, PBPK Models

In vitro binding, drug metabolism



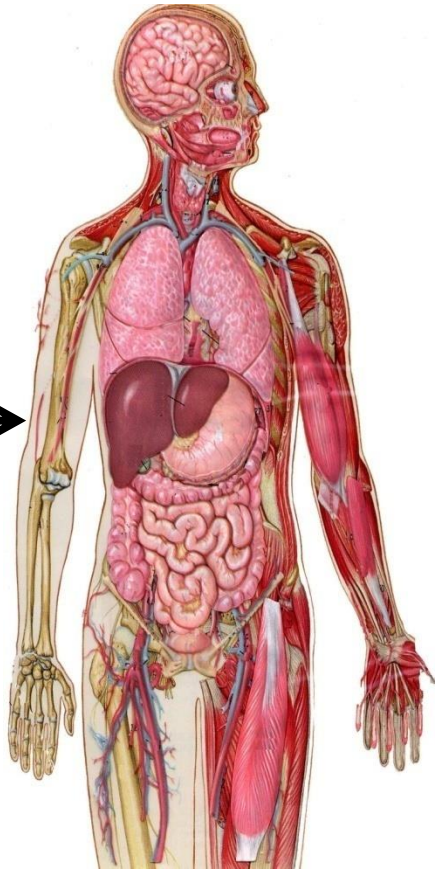
Pharmacology: Assume similar to start

Ex vivo receptor binding, functional assays

Physiology: Allometric scaling, systems biology

Biomarkers; pharmacogenetic screens

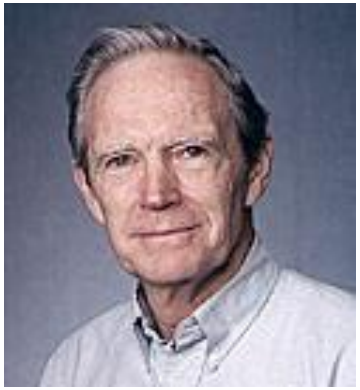
PK/PD Models



Mager DE and Jusko WJ. *Clin Pharmacol Ther*. 83:909 (2008)

PBPK Models

Kenneth Bischoff



Robert Dedrick

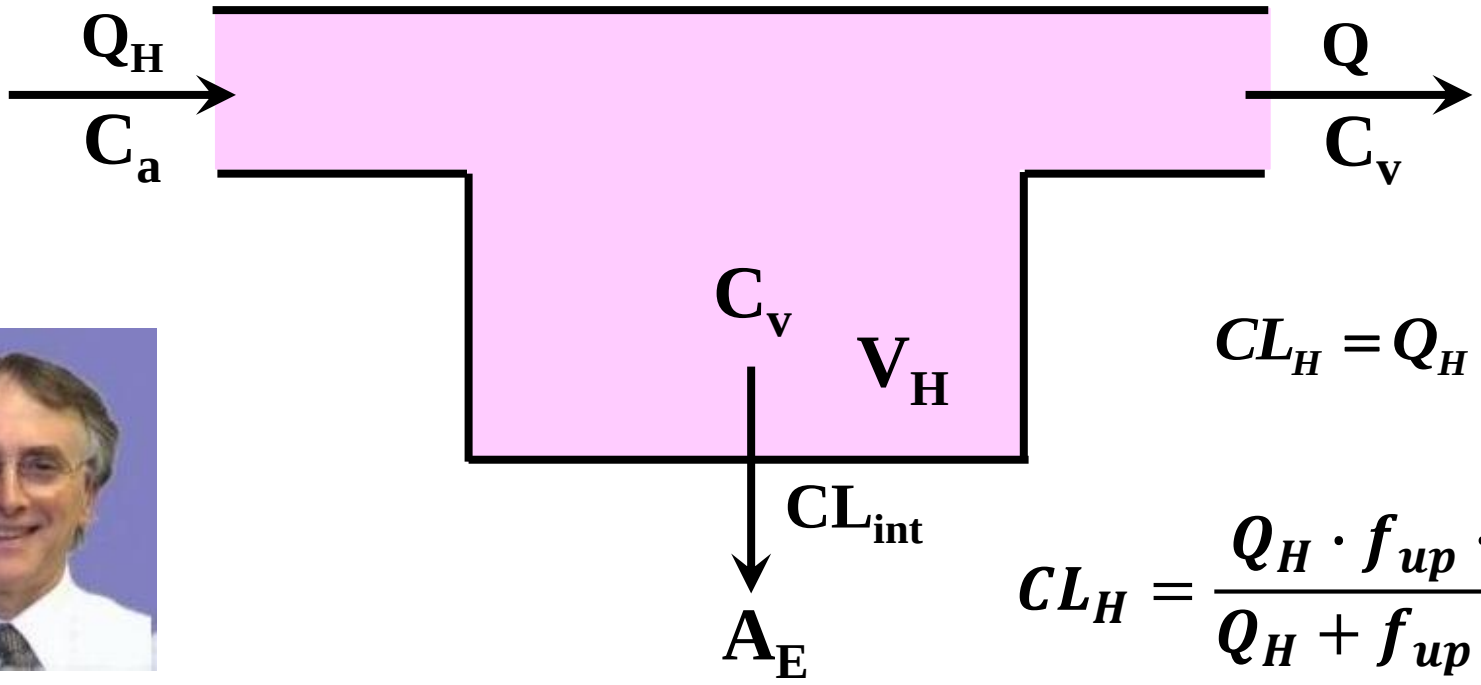
KB Bischoff and RL Dedrick,
J. Pharm. Sci. 57: 1346 (1968)
J. Pharm. Sci. 59: 149 (1970)

"Physiologic modeling enables us to examine the joint effect of a number of complex inter-related processes and assess the relative significance of each."

$$(dCliver)/dt = [Q_H\ (Cin - Cout\ ) - CLint \cdot Cout\ ]/Vliver.$$

Added metabolism/CL to Fick's Law of Perfusion = WSM

Venous Equilibrium Model : WSM



$$CL_H = Q_H \cdot ER$$

$$CL_H = \frac{Q_H \cdot f_{up} \cdot CL_{int}}{Q_H + f_{up} \cdot CL_{int}}$$

Malcolm Rowland

Grant Wilkinson

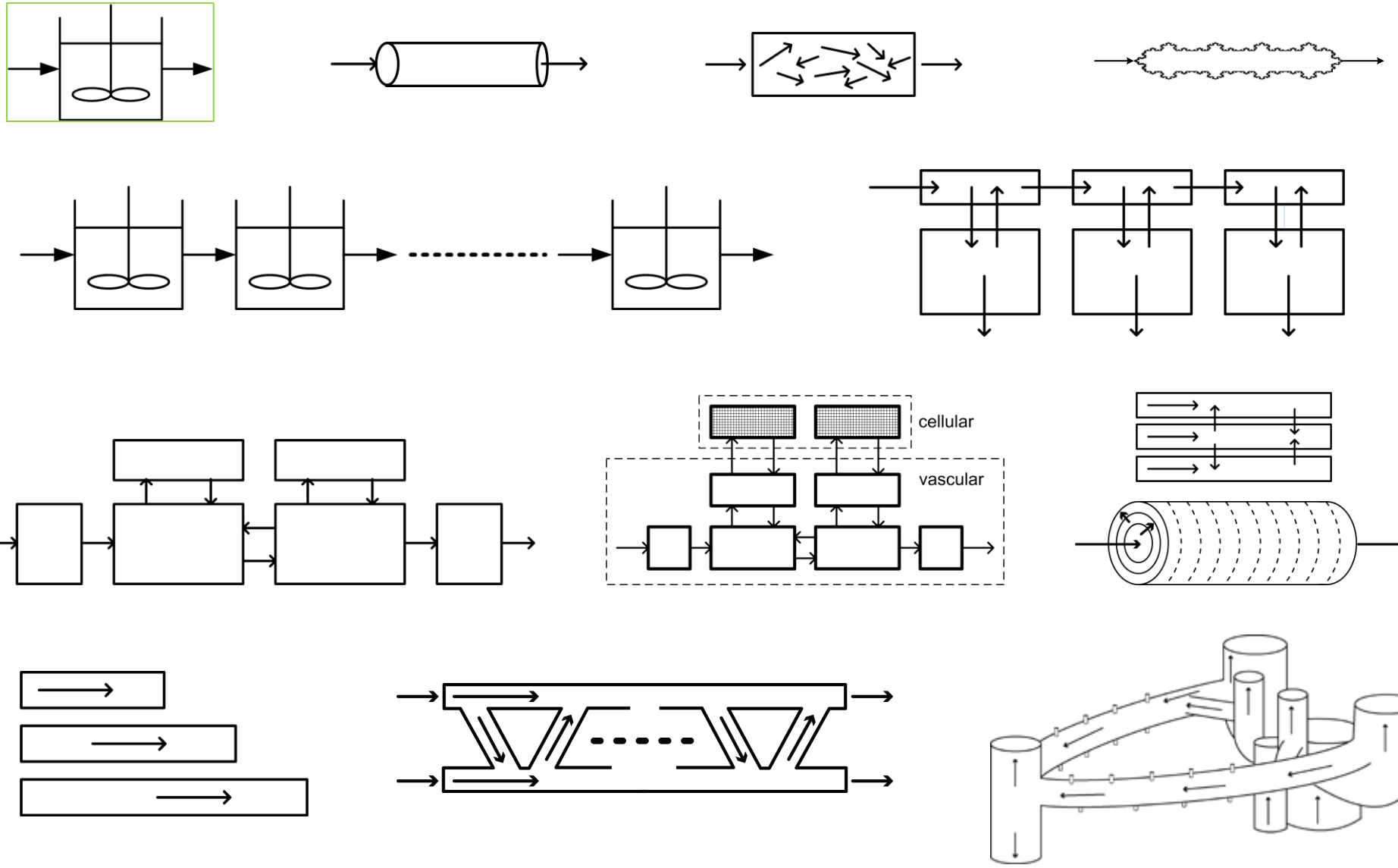
Rowland M, Benet LZ, Graham G: Clearance concepts in pharmacokinetics. J Pharmacokin Biopharm 1: 123 (1973)

Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharm Ther 18: 377 (1975)

Complexities in PBPK & Organ Disposition

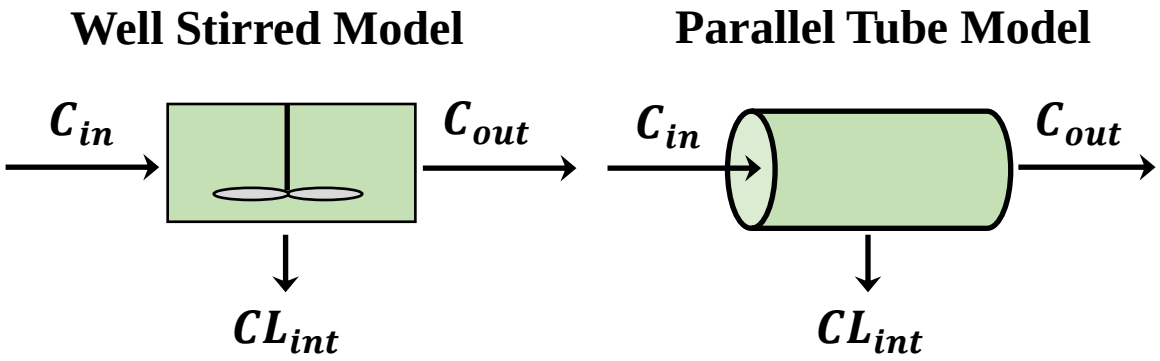
- **Model Assumptions (WSM, PTM, …)**
- **Metabolic site**
- **Reversible metabolism, EHC**
- **Transporters (influx, efflux)**
- **Permeability versus flow**
- **Initial circulatory distribution**
- **Arterial versus venous blood**
- **RBC efflux rate**
- **Albumin-mediated cell uptake**
- **Rapid k_{off} from proteins**
- **Nonspecific binding**
- **Tissue heterogeneity**

Hepatic Models



Ierapetritou et al, *CTS Journal* 2: 228 (2009).

Basic Hepatic Clearance Models



$$\frac{dC_{liver}}{dt} = \left[Q_H(C_{in} - C_{out}) - f_{up}\, CL_{int} \cdot C_{out}\right]/V_{liver}$$

$$\textbf{WSM:} \quad C_{out} = \frac{C_{liver} \cdot R}{K_P} \qquad K_P = \frac{C_{liver,ss}}{C_{P,ss}}$$

$$\textbf{PTM:} \quad \frac{C_{in} - C_{out}}{ln\left(\frac{C_{in}}{C_{out}}\right)} \cdot \frac{R}{K_P} \quad \text{instead of } C_{out}$$

f_{up} = fraction unbound in plasma

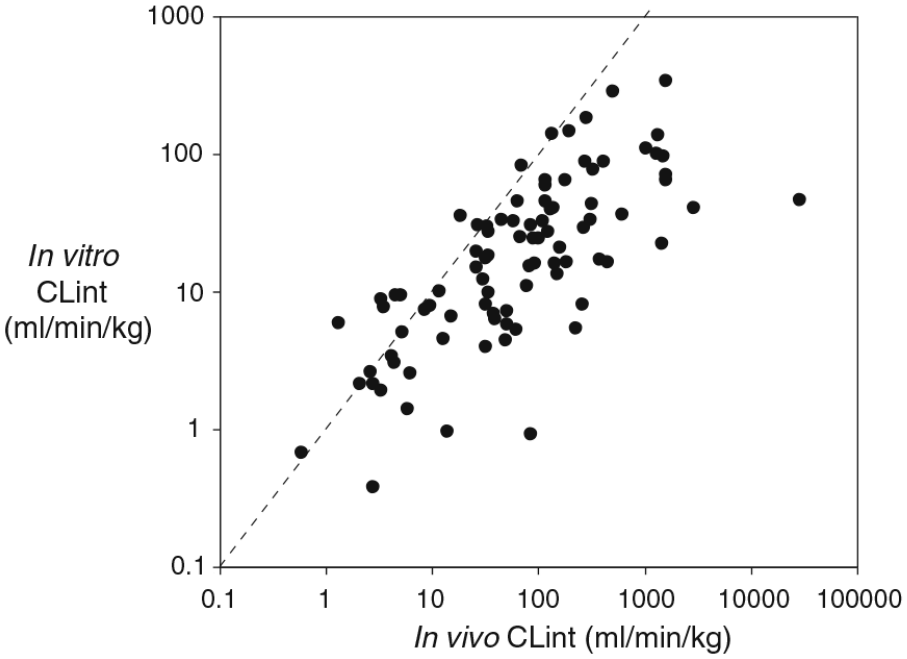
R = Blood/Plasma

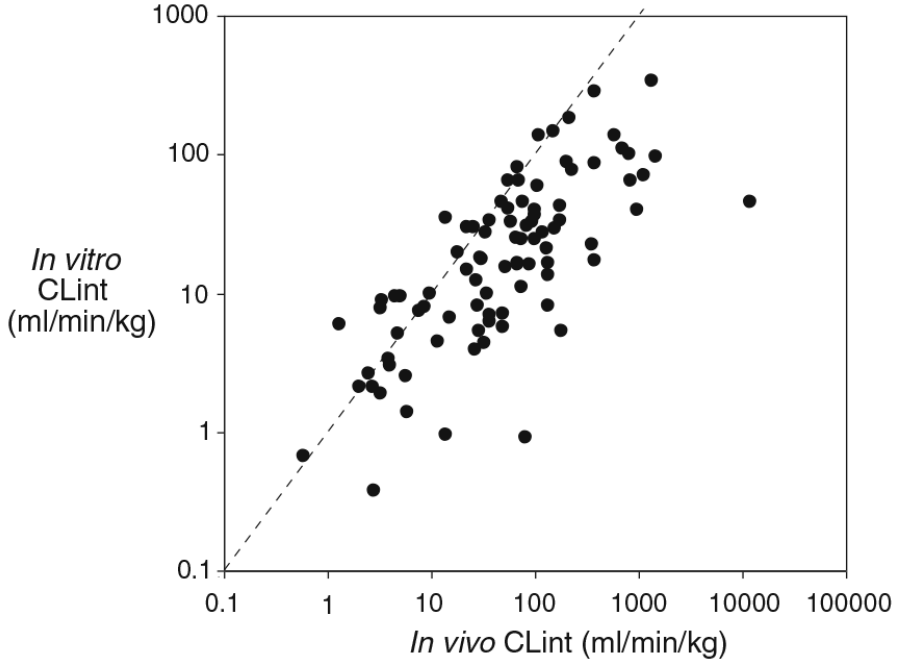
Winkler K, Keiding S, Tygstrup N. Clearance as a quantitative measure of liver function. In, "The Liver: Quantitative Aspects of Structure and Function" pp144-155, Karger-Basel 1973

Pharm Res (2010) 27:2150–2161
DOI 10.1007/s11095-010-0218-3

Prediction of Human Metabolic Clearance from *In Vitro* Systems: Retrospective Analysis and Prospective View

David Hallifax • Joanne A. Foster • J. Brian Houston





$$In\ vivo\ CL_{int} = \frac{CL_b}{fu_b \bullet \left(1 - \frac{CL_b}{Q_H}\right)} \quad \text{(WS liver model)}$$

$$In\ vivo\ CL_{int} = \frac{Q_H}{fu_b} \bullet -\ln\left(\frac{Q_H - CL_b}{Q_H}\right) \text{(PT liver model)}$$

Several assessments show suboptimal IVIVE for many drugs.

Ftorafur Metabolism in Rat Tissues

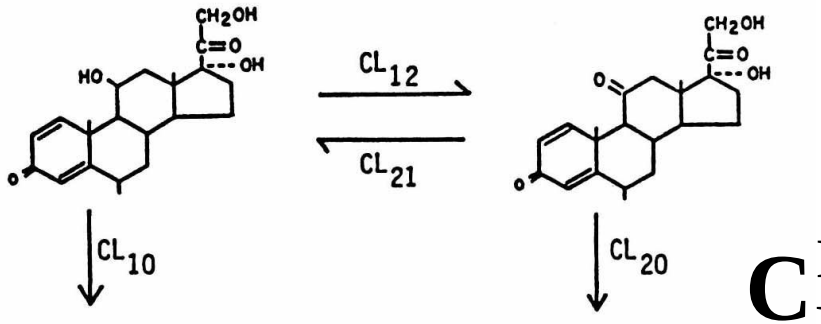
Tissue	CL_{int} [a]	Tissue	CL_{int} [a]
Lung	0.51	Stomach	0.68
Brain	0.72	Small intestine	4.84
Heart	0.69	Adipose tissue	4.20
Liver	78.72	Skin	16.21
Kidney	1.08	Muscle	31.25
Spleen	0.26	Blood	5.48
Pancreas	0.29	Plasma	----

[a] CL_{int} (ml/min) x 10^3 Oxidation
Determined from tissue homogenate measurements.

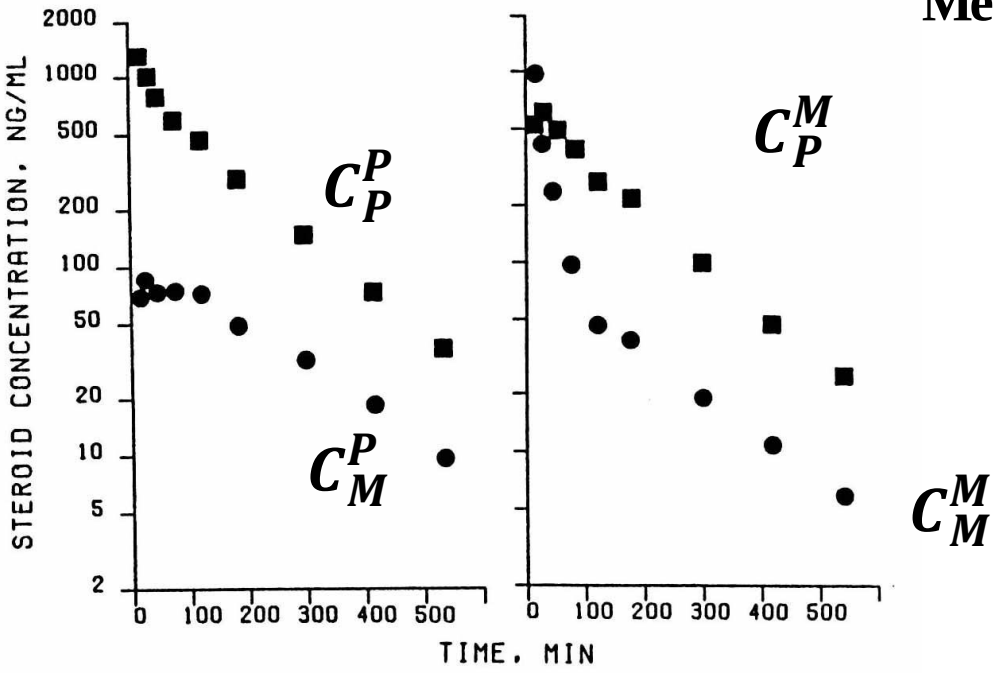
Sakiya Y et al, *Int. J. Pharmaceu.* 25: 347 (1985).

Reversible Metabolism Occurs Often

Methylprednisolone Methylprednisone



$C^{Measured}_{Dosed}$



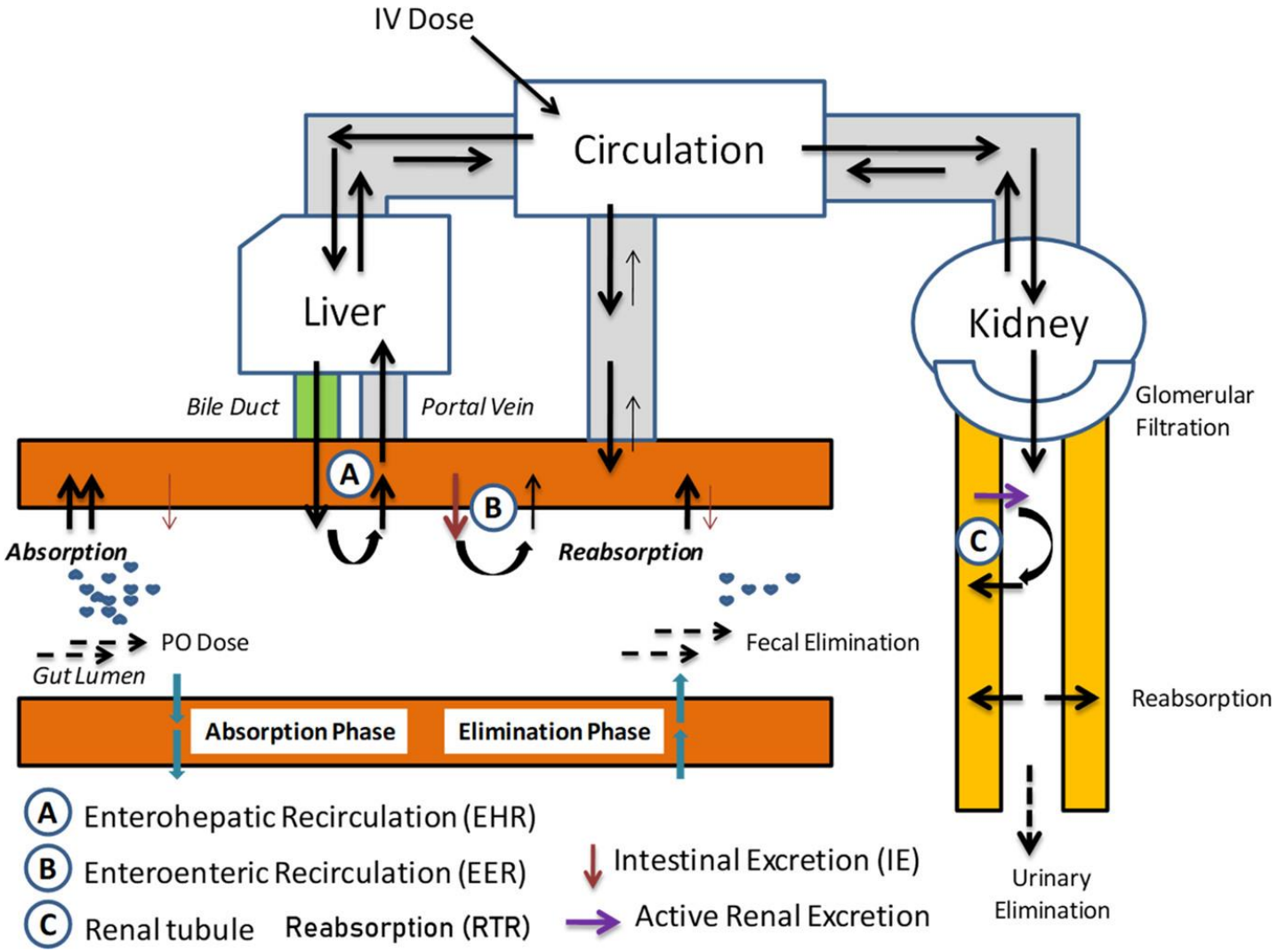
$$\frac{Dose}{AUC} = CL_{10} + \frac{CL_{12} \cdot CL_{20}}{CL_{21} + CL_{20}}$$

Compounds Undergoing Reversible Metabolism

Compound Class	Metabolic Process	Examples
Arylamines	Acetylation	Procainamide, sulfonamides, 2-aminofluorene, dapsone
Tertiary amines	N-oxidation	Imipramine, chlorpromazine, trimethylamine, nicotinamide
Alcohols/ketones aldehydes	Oxidation/reduction	Corticosteroids, estradiol, haloperidol, ketanserin, acetohexamide, trilostane
Lactones	Hydrolysis	Statins, canrenone
Sulfides	Oxidation	Captopril, cimetidine, albendazole, D-penicillamine, metiamide
Sulfoxides	Reduction	Sulindac, Sulfinpyrazone
Phenols	Sulfation	Dehydroisoandrosterone, estrone, dopamine
Carboxylic acids	Conjugation	Clofibric acid, salicylic acid, valproic acid, diflunisal
Hydrazines	Condensation	Hydralazine
Quinones	Epoxidation	Vitamin K_1
Methylxanthines	Demethylation	Caffeine
Alkenes	Isomerization	All-*trans*-retinoic acid, acitretin
Arylpropionic acids	Epimerization	Ibuprofen, 2-phenylpropionic acid

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

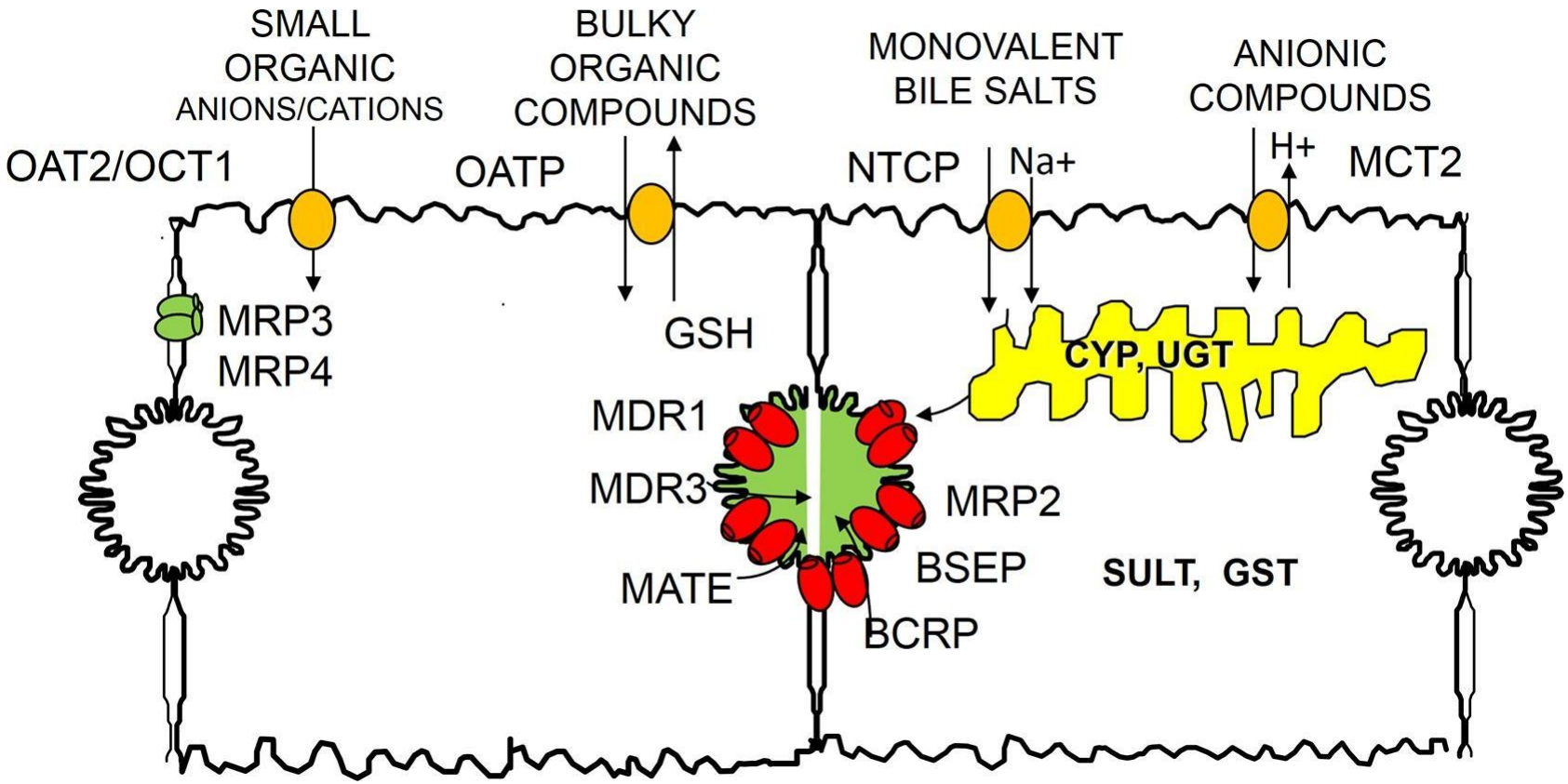
Intestinal Excretion and Recirculation



D Zhang, C Wei, CECA Hop, MR Wright, M Hu, Y Lai, SC Khojasteh, WG Humphreys, J Med Chem, 64:7045 (2021) .

Hepatic clearance concepts and misconceptions: Why the well-stirred model is still used even though it is not physiologic reality?

KS Pang, YR Han, K Noh, PI Lee, M Rowland, Biochem Pharmacol, 169: 2019, 113596.



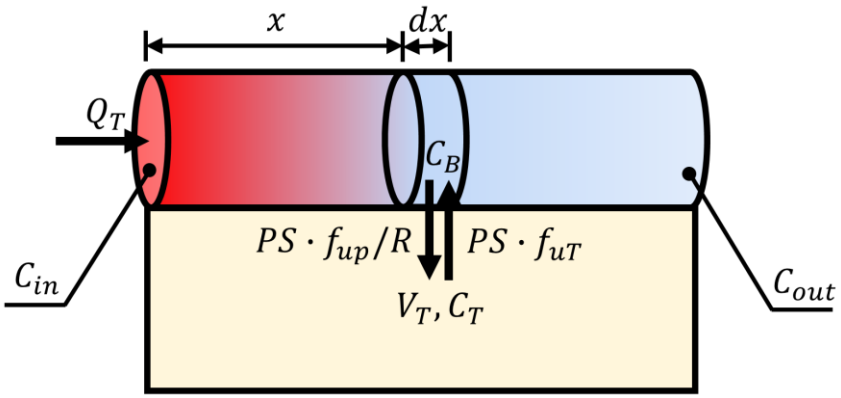
$$CL_H = \frac{Q_H fu_B CL_{influx} CL_{int,H}}{Q_H CL_{efflux} + CL_{int,H}(fu_B CL_{influx} + Q_H)}$$

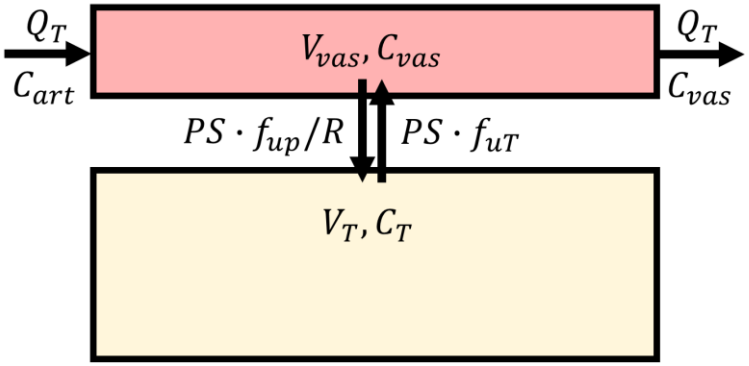
Transporters complicate both CL_H and K_p.

Extending WSM and PTM to Consider Permeability

Estimation of the minimum permeability coefficient in rats for perfusion-limited tissue distribution in whole-body physiologically-based pharmacokinetics, Jeong et al, EJPB 115: 1 (2017).

$$V_T \frac{dC_T}{dt} = Q_T \cdot f_d \cdot \left(C_{art} - \frac{C_T \cdot R}{K_p} \right)$$

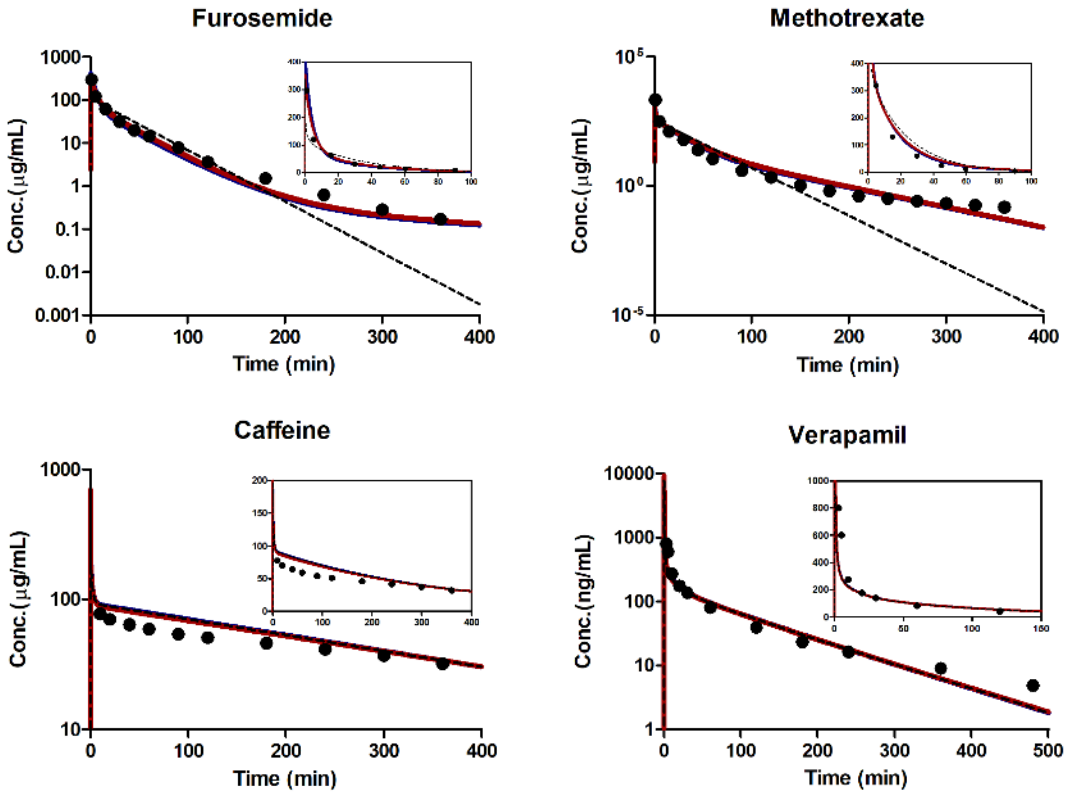




$$f_d = 1 - e^{-\frac{f_{up} PS}{Q_T R}}$$

$$f_d = \frac{f_{up} PS/R}{Q_T + f_{up} PS/R}$$

Prediction of Tissue Permeability *PS* and PK in Rats Using *In Vitro* PAMPA Permeability



Compounds	$f_{up}P/R$ (x 10^{-6} cm/s)
Furosemide	0.00238
Methotrexate	0.0152
Caffeine	1.16
Verapamil	3.33

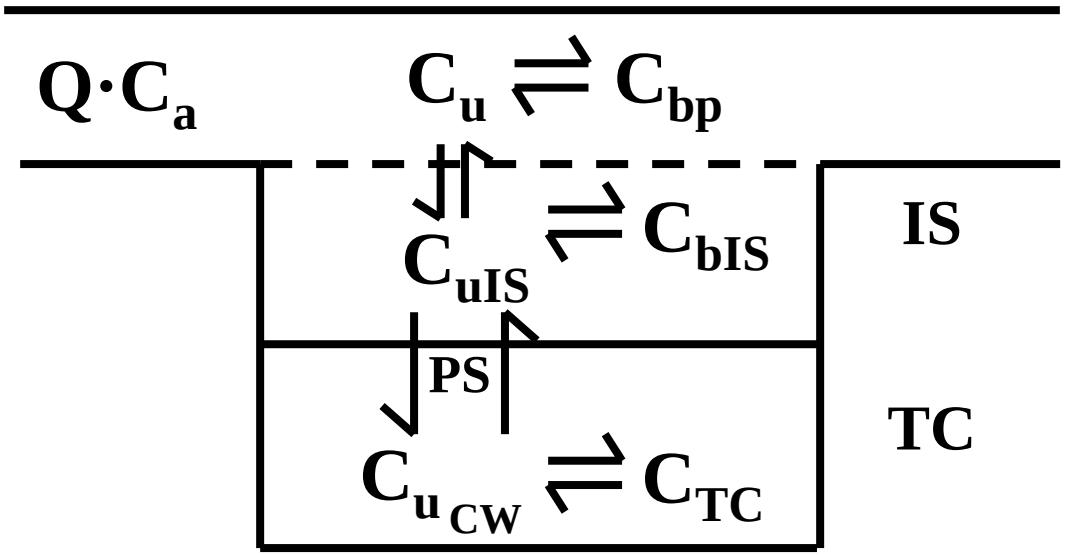
Model 1 (capillary-permeability model)

Model 2 (well-stirred vascular compartment)

Perfusion-limited model

PS & Q jointly determine tissue uptake

Model with Binding and Permeability Issues



Fick's Law of Diffusion : $\dfrac{dA}{dt} = PS\left(C_1 - C_2\right)$

Need :

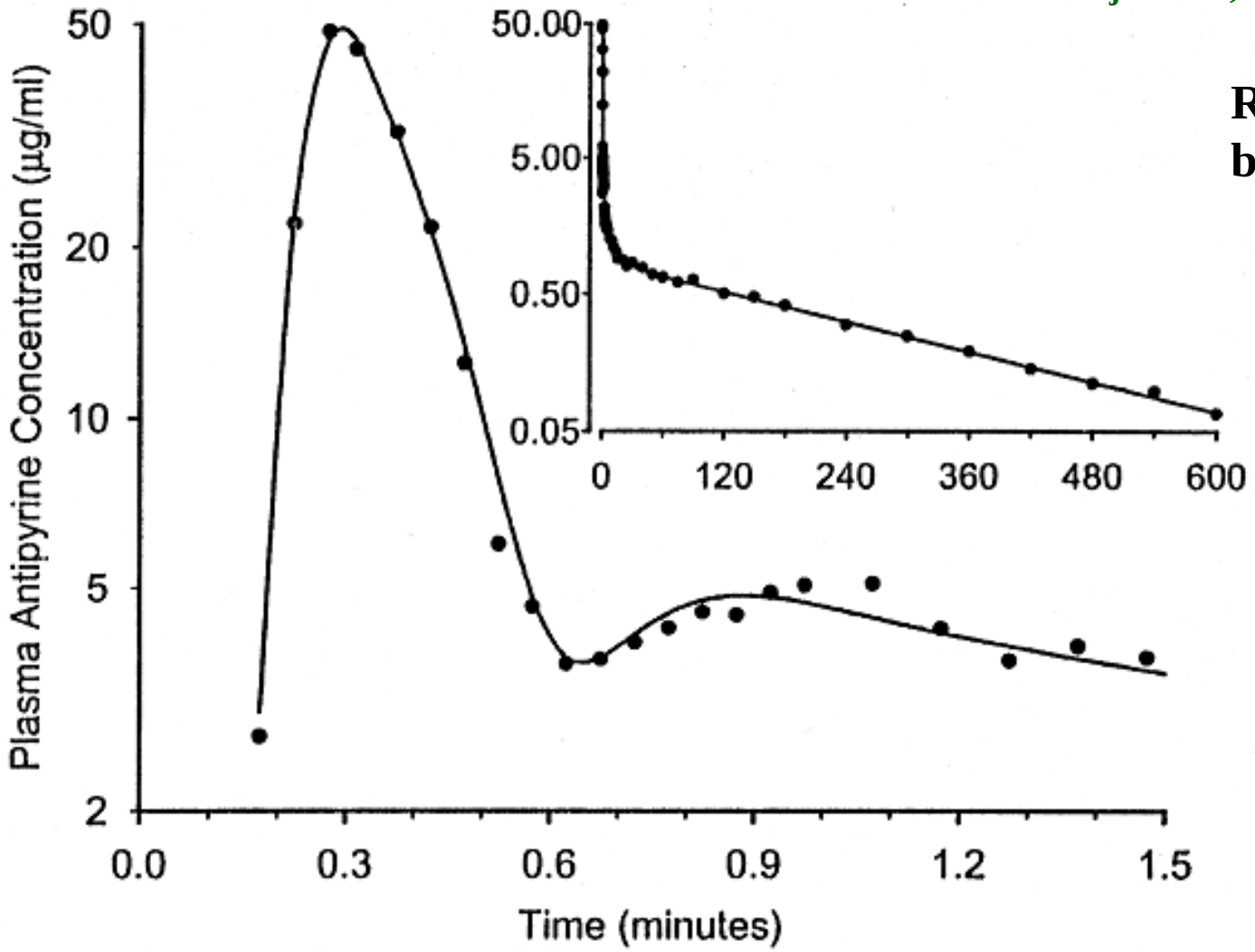
$$V_{IS}\ \frac{dC_{IS}}{dt} = Q\left(f_u \cdot C_a - C_{u_{IS}}\right) - PS \cdot \left(C_{u_{IS}} - \frac{C_{TC}}{K_P}\right)$$

$$V_{TC}\ \frac{dC_{TC}}{dt} = PS \cdot \left(C_{u_{IS}} - \frac{C_{TC}}{K_P}\right)$$

More traditional approach with more components.

Early Distribution Kinetics of Antipyrine in Dogs

Krejcie et al, *JPET* 269: 609 (1994).

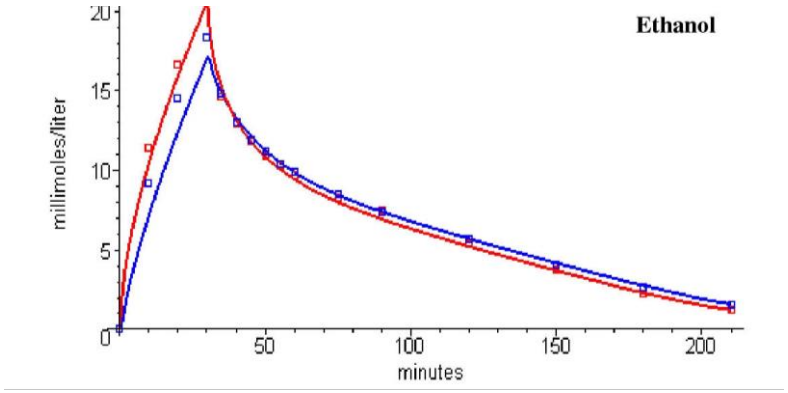


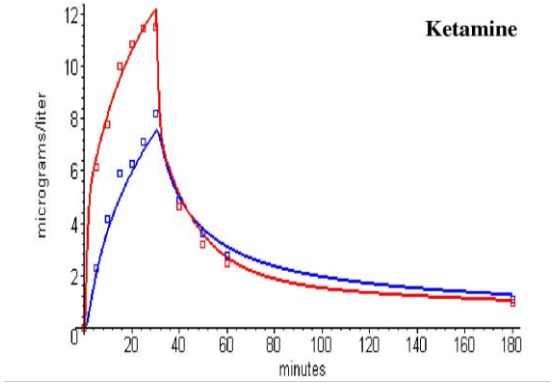
Right atrial bolus injection

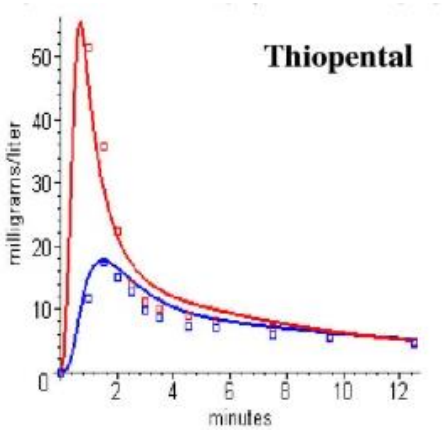
Assuming C_o = Dose / Blood Volume is approximate.

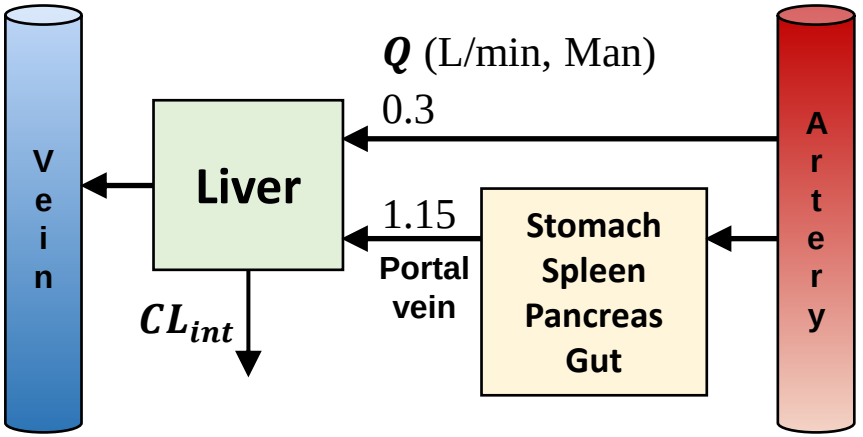
PBPK Modeling of Arterial - Antecubital Vein Concentration Differences

DG Levitt, BMC Clin Pharmacol. 19;4:2 (2004).





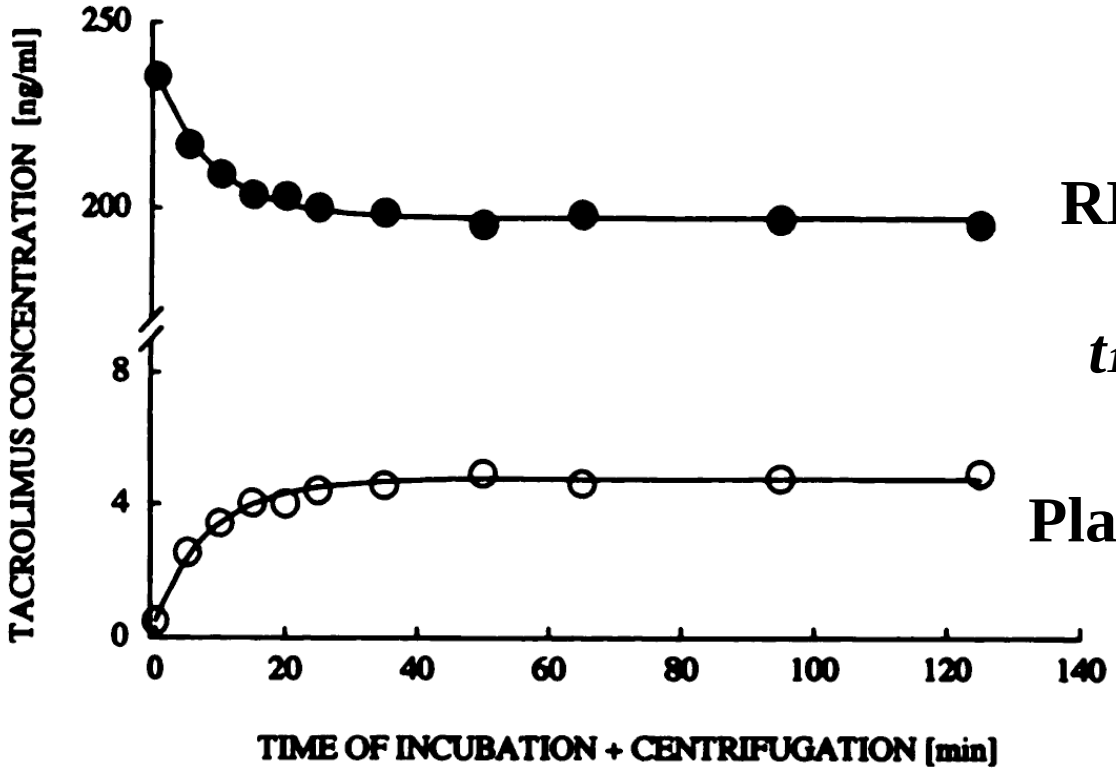




Appreciable A-V differences occur in the first hour and then are close. Liver receives mostly portal venous blood.

DISPOSITION OF TACROLIMUS (FK 506) IN RABBITS
Role of Red Blood Cell Binding in Hepatic Clearance

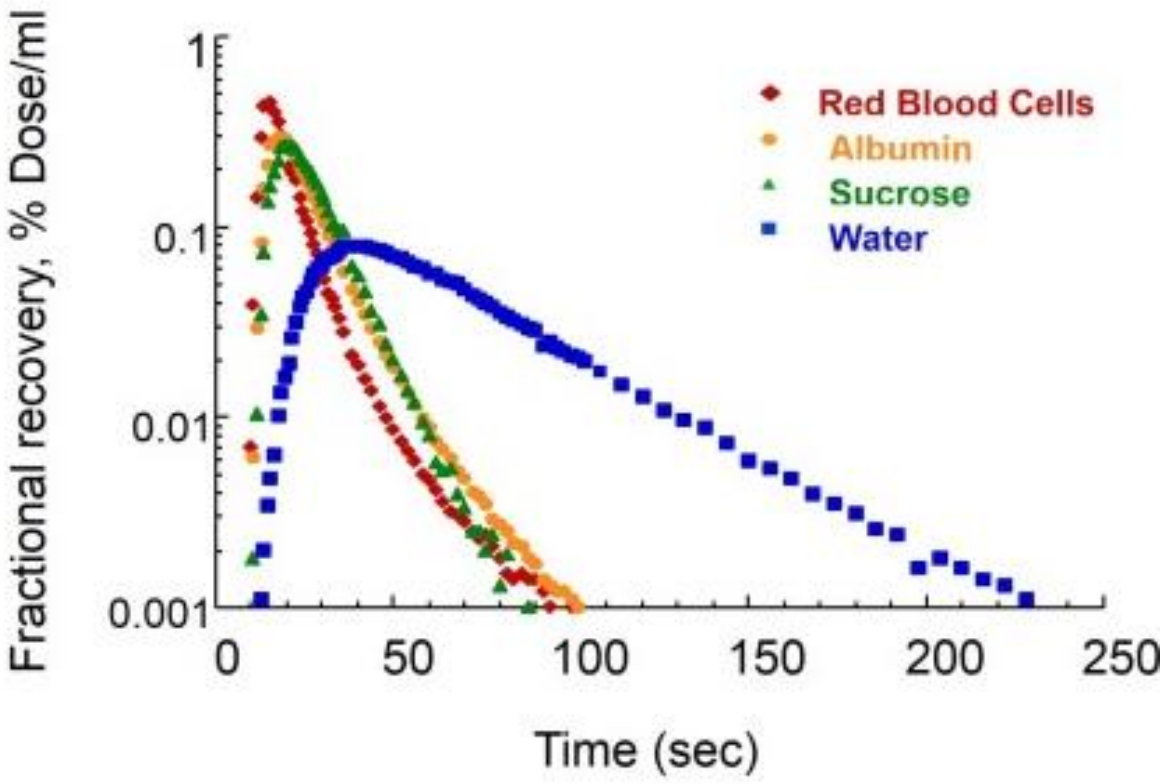
W Piekoszewski, FS Chow and WJ Jusko
Drug Metab Disp 21: 690 (1993)



Efflux of drugs from RBC can be slow and is seldom assessed.

Rapid Transit of Biomarkers in Perfused Rat Liver: Indicator Dilution Studies

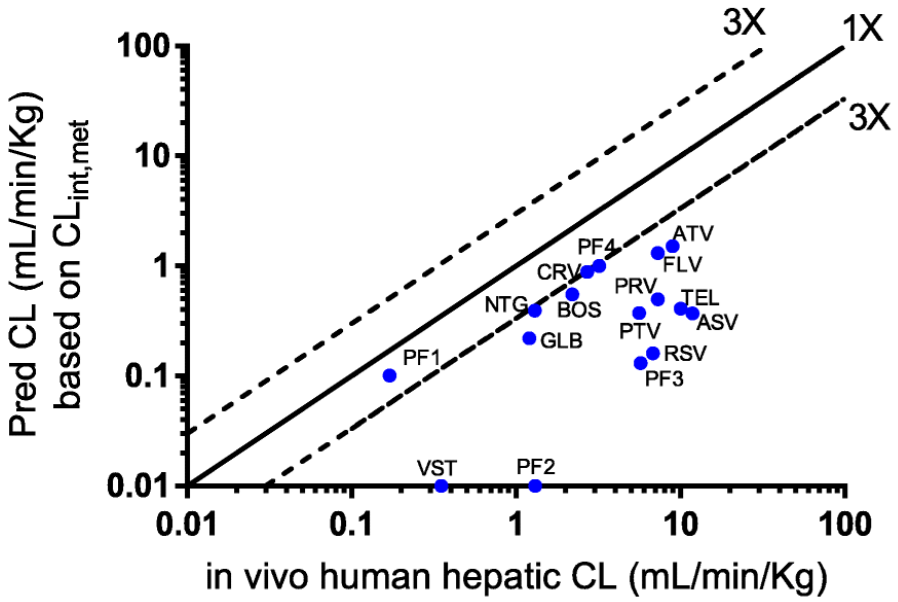
KS Pang, IA Sherman, AJ Schwab, W Geng, F Barker 3rd, JA Dlugosz, G Cuerrier, CA Goresky, Hepatology, 20: 672 (1994).

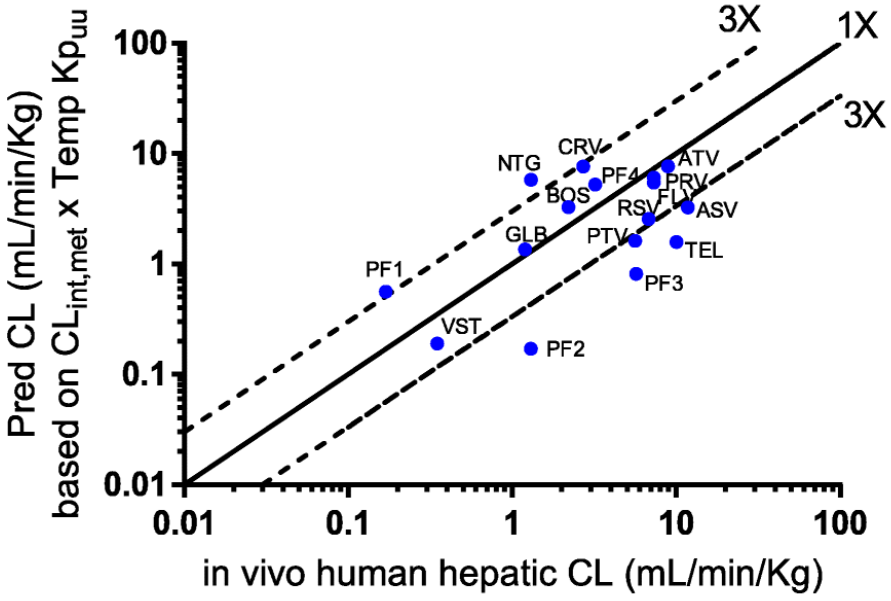


RBC and albumin traverse the rat liver in less than 2 min.

Albumin-Mediated Uptake Improves Human Clearance Prediction

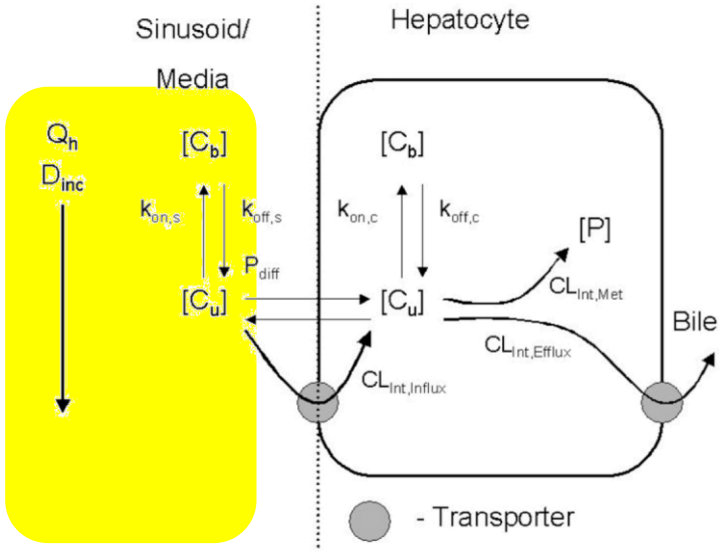
N Li, A Badrinarayanan, K Ishida, X Li, J Roberts, S Wang, M Hayashi & A Gupta *AAPS J* 23, 1 (2021).

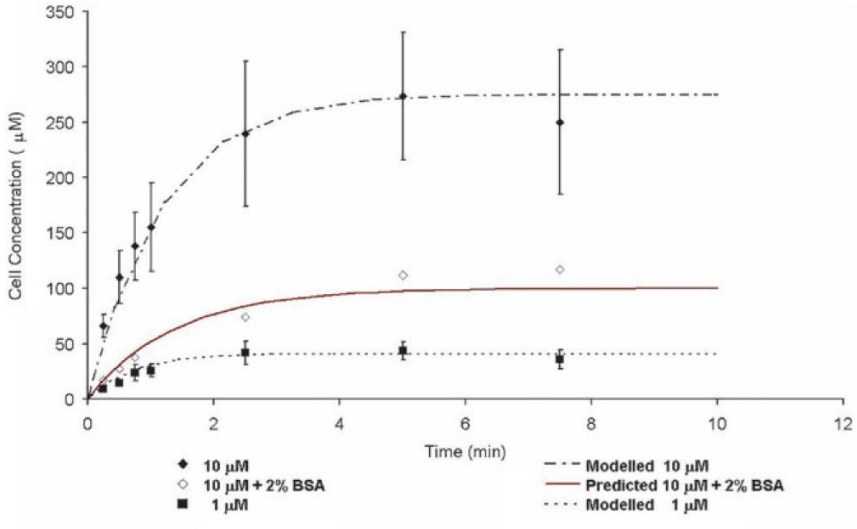




$$f_{u,cell,4^oC} = \frac{C_{u,cell\ (4^oC)}}{C_{cell\ (4^oC)}} = \frac{C_{u,media\ (4^oC)}}{C_{cell\ (4^oC)}} = \frac{1}{Kp_{4^oC}}$$

Kinetic determinants of hepatic clearance: Plasma protein binding and hepatic uptake





Observed hepatic uptake was between total and free drug. Fast *koff* allows tissue uptake of presumed bound drug.

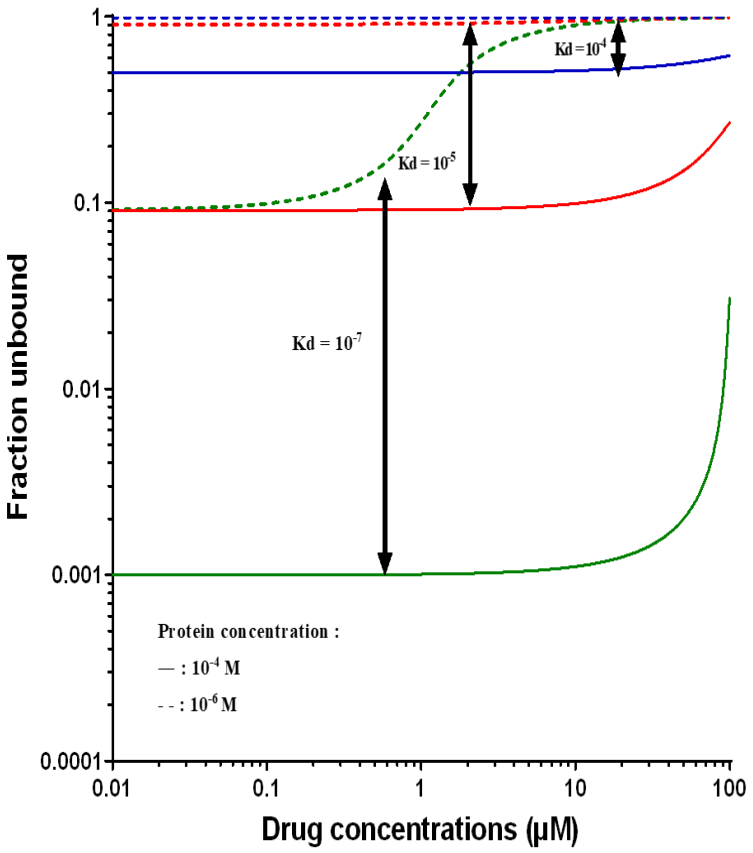
"…some highly bound ligands have more efficient uptake than can be explained by their unbound fraction"

Bowman CM, Benet LZ, EJPS 123: 502 (2018)

M. BAKER & T. PARTON

Xenobiotica, October–November 2007; 37(10–11): 1110–1134

Seeking Nonspecific Binding for In Vitro CL_{int}



$$cf_u = \frac{\left(\frac{1}{Dil}\right)}{\frac{1}{mf_u} - 1 + \left(\frac{1}{Dil}\right)}$$

Caution is needed in the use of the Kalvass-Maurer Equation and interpretation of results from cell and tissue dilution studies.

The *cf*$_u$ correction requires linear binding and is most accurate at low drug and high protein concentrations.

Jusko WJ, Molins EAG, and Ayyar VS, Seeking Nonspecific Binding: Assessing the Reliability of Tissue Dilutions for Calculating Fraction Unbound, Drug Metab. Disp., 48: 894 (2020).

Predicting Tissue:Plasma SS K_p

Poulin & Theil method

$$Kp = \frac{\left[K \cdot \left(V_{nlt} + 0.3V_{pht}\right)\right] + \left[\left(V_{wt} + 0.7V_{pht}\right)\right]}{\left[K \cdot \left(V_{nlp} + 0.3V_{php}\right)\right] + \left[\left(V_{wp} + 0.7V_{php}\right)\right]} \cdot \frac{fu_p}{fu_t}$$

$$\text{adipose} : K = D^*_{vo:w}$$

$$\text{other} : K = P_{o:w}$$

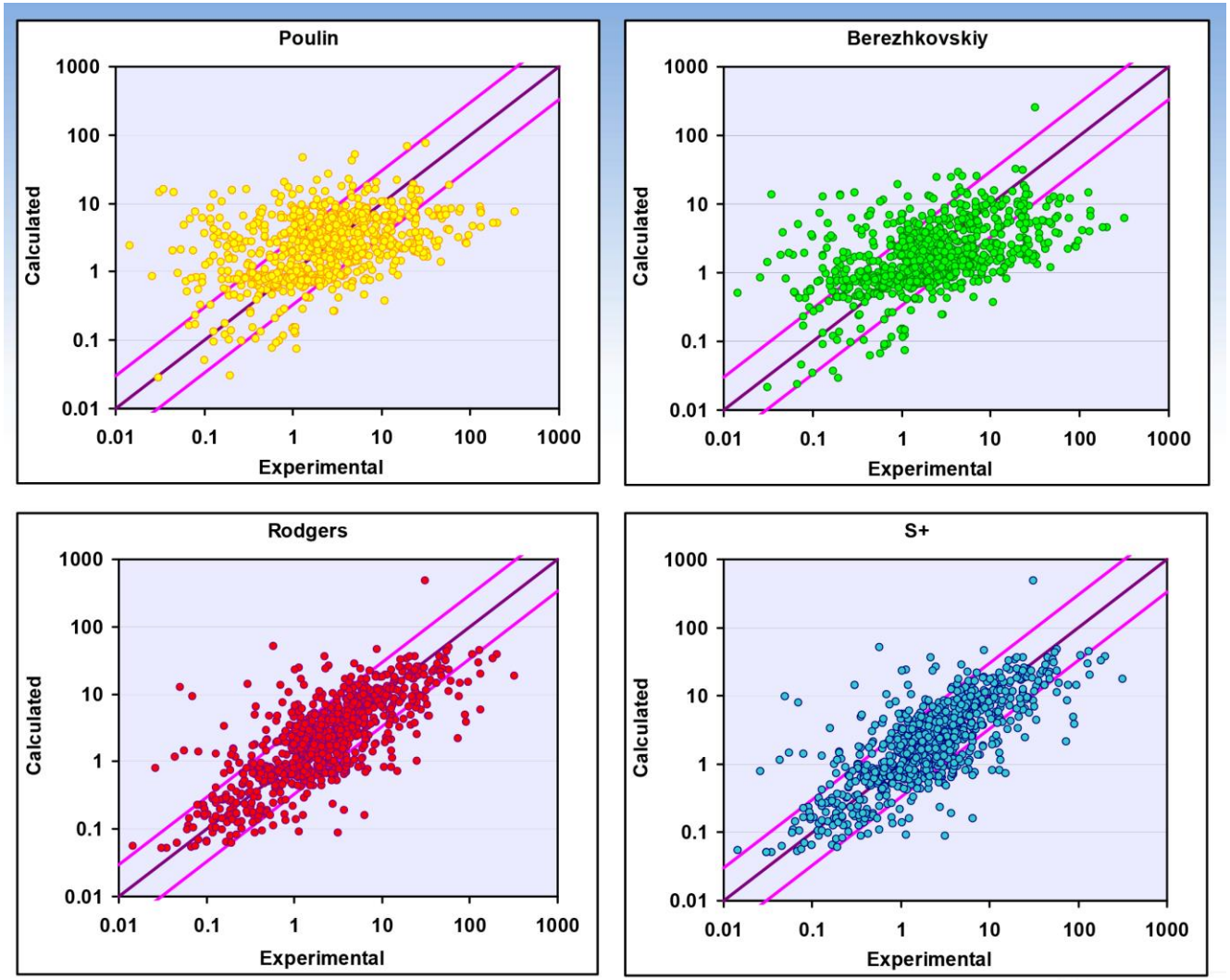
$$\log P_{vo:w} = 1.115 \log P_{o:w} - 1.35 \quad \text{Leo, Hansch}$$

$$fu_t = \left[\left(1 + \left(1 - fu_p\right) / fu_p\right) \cdot RA_{tp}\right]$$

V_{nlt}, V_{pht}, V_{wt} : Volume fraction of neutral lipids, phospholipids, water

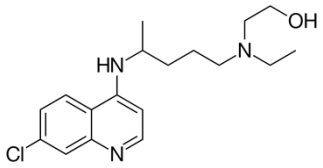
RA_{tp} : Albumin ratio tissue : plasma

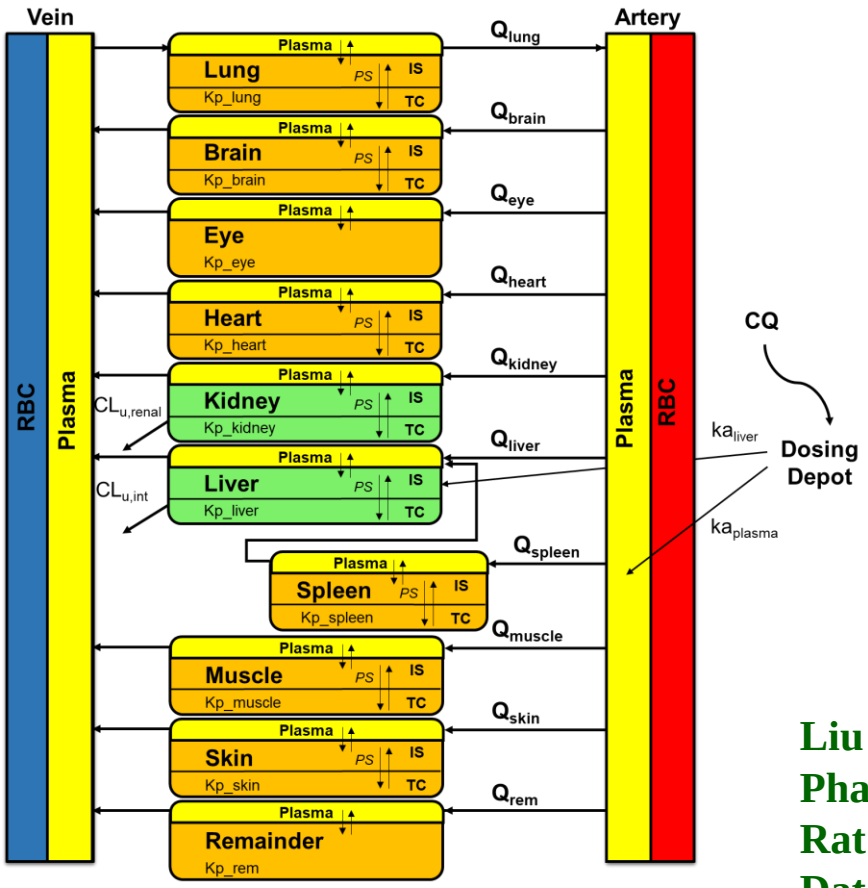
Predicting K_p is Approximate

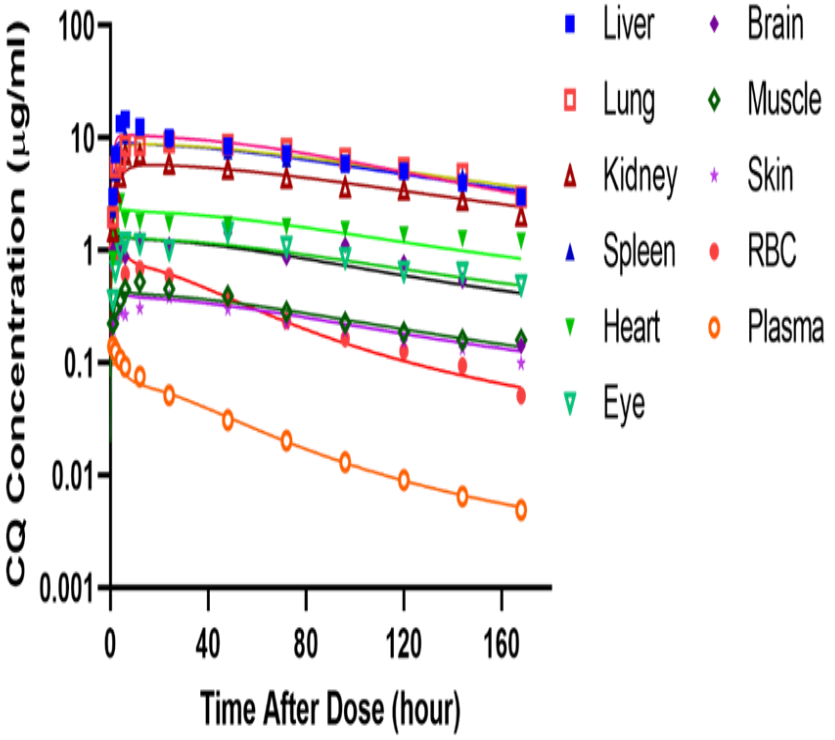


Predictions also do not account for transporters

PBPK Modeling of Chloroquine in Rats

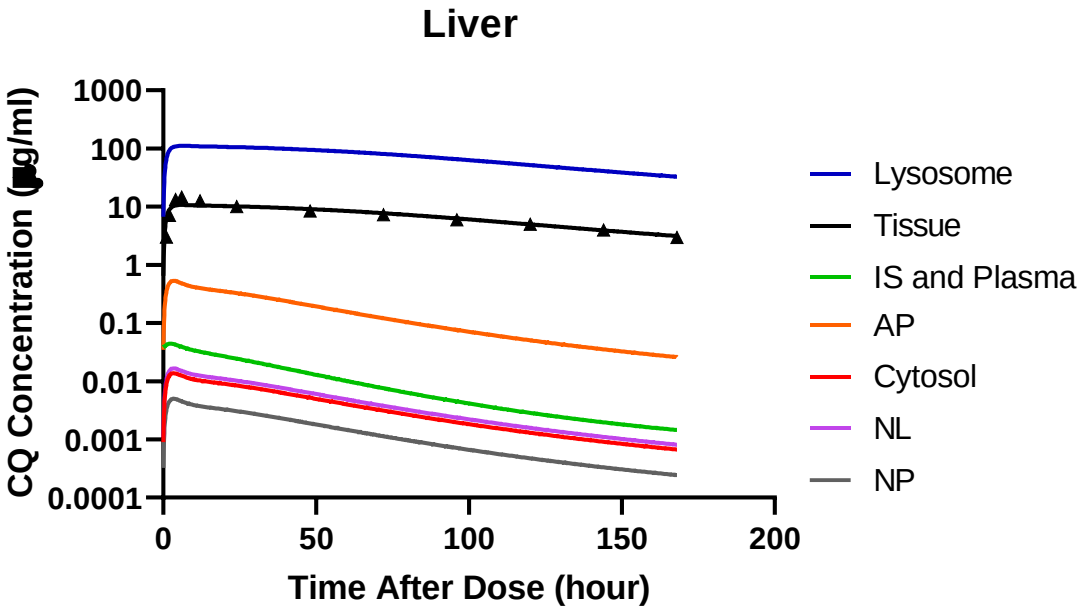




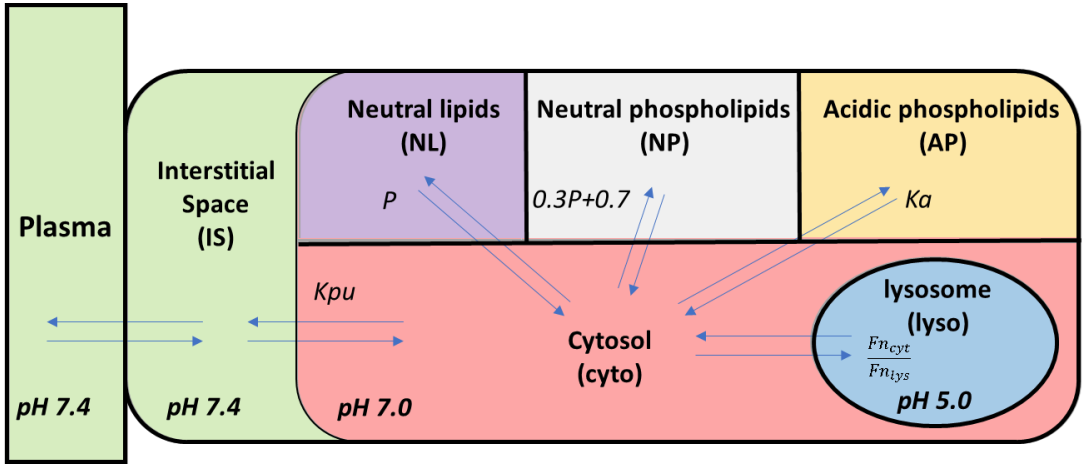


Liu X and Jusko WJ, Physiologically-Based Pharmacokinetics of Lysosomotropic Chloroquine in Rat and Man, JPET 376: 261 (2020).
Data from Adelusi SA and Salako LA, Gen Pharmacol 13:433 (1982).

PBPK of Chloroquine in Rat Tissues



Assmus F, Houston JB ,Galetin A Incorporation of lysosomal sequestration in the mechanistic model for prediction of tissue distribution of basic drugs. Eur J Pharm Sci 109:419 (2017)

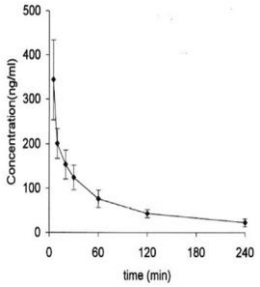


Assessing intra-tissue drug concentrations requires imaging or assumptions.

Minimal PBPK Models May Suffice

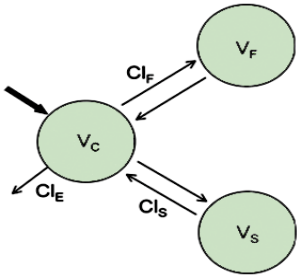
→ V_{SS} —CL→ **Noncompartmental Analysis**

Top-Down

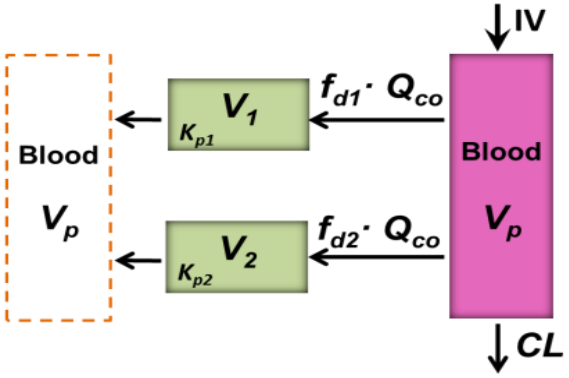


Complexity

Bottom-Up



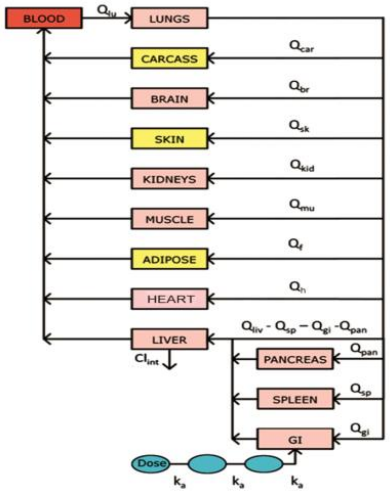
Mammillary Model - Empirical approach



Minimal PBPK Model - An intermediate approach when only plasma data is available.

Cao Y and Jusko WJ, Applications of Minimal Physiologically-Based Pharmacokinetic Models, JPKPD 39: 711 (2012)

Full PBPK Model - Mechanism-Based



Low — **Physiological Information** — High

Summary

- **Basic PBPK models have served well to understand integration of kinetic and physiologic functions.**
- **Prediction methods utilizing in vitro assessed drug properties are helpful but approximate.**
- **Numerous complexities in PBPK need better (enhanced) consideration.**
- **Augment PBPK with rigorous verification.**

PBPK Modeling:

The pot of gold still awaits in seeking perfection, but the journey is highly worthwhile.

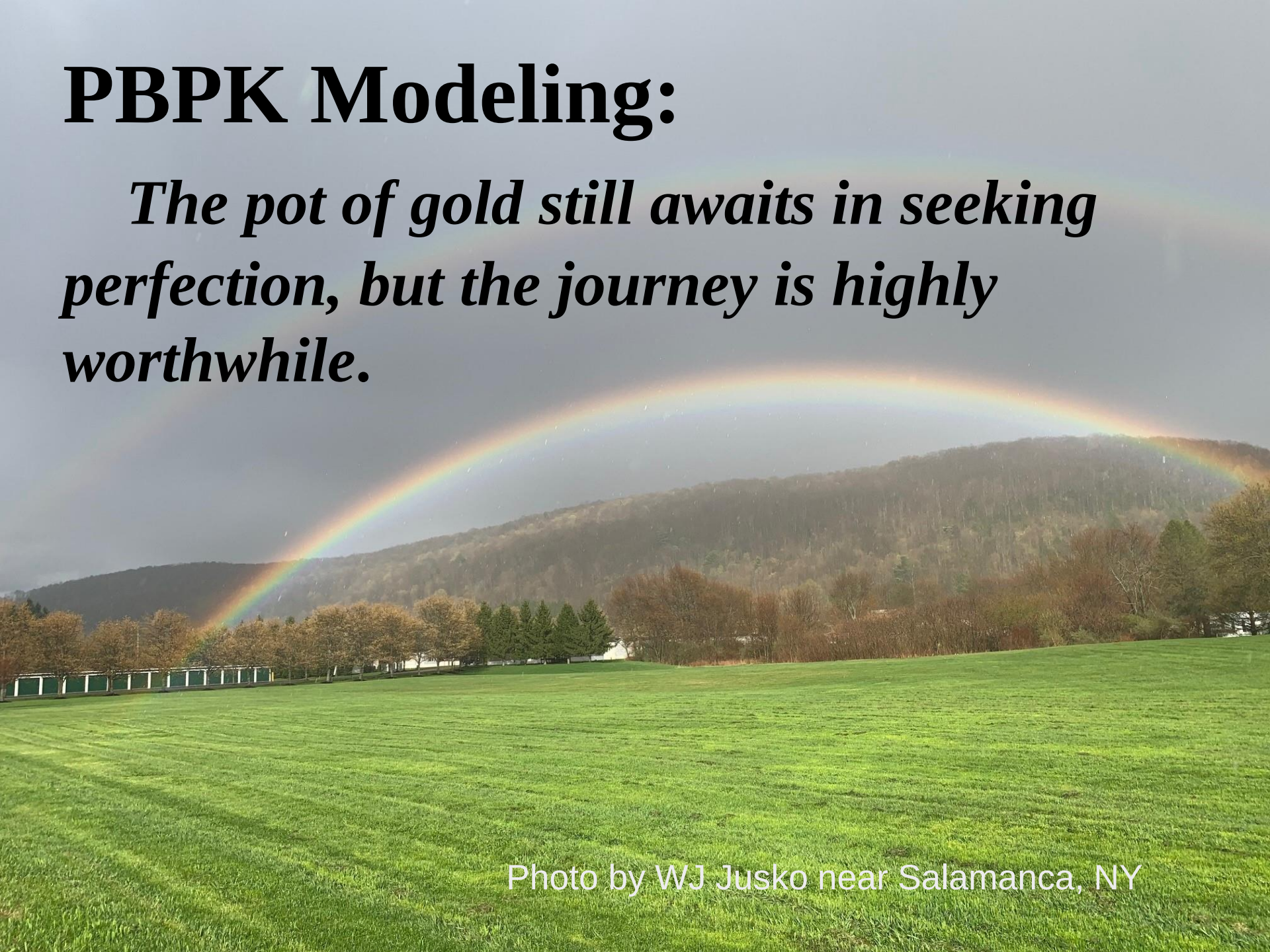


Photo by WJ Jusko near Salamanca, NY