In Vitro In Vivo Extrapolation and its Applications in Predicting PK Population Variability

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Outline

- Clearance concept
- In Vitro In Vivo Extrapolation (IVIVE)
- Linking PBPK and IVIVE, accounting for variability
- Transporters
- Industry/Regulators views
- Future prospects

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Well-stirred liver model

FACTORS AFFECTING DRUG METABOLISM

James R. Gillette, Ann N Y Acad Sci. 1971

Commentary: A physiological approach to hepatic clearance
Wilkinson and Shand , CPT, 1975

$$CL = Q[f_{B,Out}CL_{int}/(f_{B,Out}CL_{int} + Q)]$$

Pang and Rowland, JPK Biopharm 1977

$f_{B,Out}$ = Unbound drug in venous blood / Whole emergent blood concentration

- Unbound concentration of drug in blood cells equates to the unbound concentration in plasma.
- Emergent venous blood is in equilibrium with that in the liver.

Rowland, Benet and Graham, JPK Biopharm 1973 Yang et al., DMD, 2007

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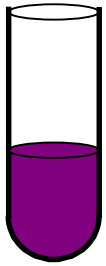
In Vitro - *In Vivo* Extrapolation (IVIVE)

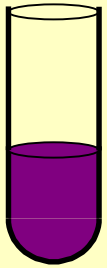


Mechanistic Models

Scaling factors

in vitro
CLu_{int}

in vivo
CLu_{int}



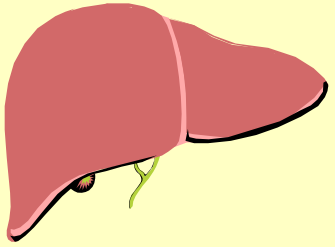
In vitro system

In vitro CLu_{int}

Scaling Factor (MPGGL, HPGL)

CLu_{int} per g Liver

Liver weight



CLu_{int} per Liver

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Accuracy of IVIVE approaches for human CL or CLint

System	AFE	Ref
HLM	2.3	Obach DMD 27, 1350, 1999
	6.2	Ito, Pharm Res, 22, 103, 2005
	2.3	Stringer, Xeno, 38, 1313, 2008
	2.2	Ring, J Pharm Sci, 100, 490, 2011
	5	Hallifax, Pharm Res, 27, 2150, 2010
	2	Jones, Clin Pk, 50, 311, 2011
Heps	2.4	De Buck DMD, 35, 1766, 2007
	5.2	Stringer, Xeno, 38, 1313, 2008
	5	Hallifax 2011
	7.6	Naritomi DMD 31, 580, 2003
Recombinant CYP	1.53 PT 2.15 WS	Stringer DMD, 37,1025, 2009

Generally many literature studies shows under-prediction from *in vitro* systems.
Can be corrected using an empirical scaling factor.
Need to understand for your *in vitro* system if this is necessary.

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IVIVE predictions – Improvements over years

- Non-specific binding (Obach, DMD, 1999, Riley et al., DMD, 2005)
- Recombinant CYPs and ISEF values (Galetin et al., DMD, 2004; Proctor et al. Xenobiotica, 2004)
- In vitro modelling to account for hepatic uptake (Soars et al., DMD, 2007)
- Adding BSA and HAS-FAS to HLM (Rowland et al., DMD, 2008)
- Accounting for the difference in drug ionization in extracellular and intracellular tissue water (Berezhkovskiy, J Pharm Sci, 2011)
- Integrating uptake, metabolism, biliary excretion, and sinusoidal efflux (Umehara and Camenisch, Pharm Res, 2012)
- Incorporating ionisation and protein binding (Poulin et al., J Pharm Sci, 2012)

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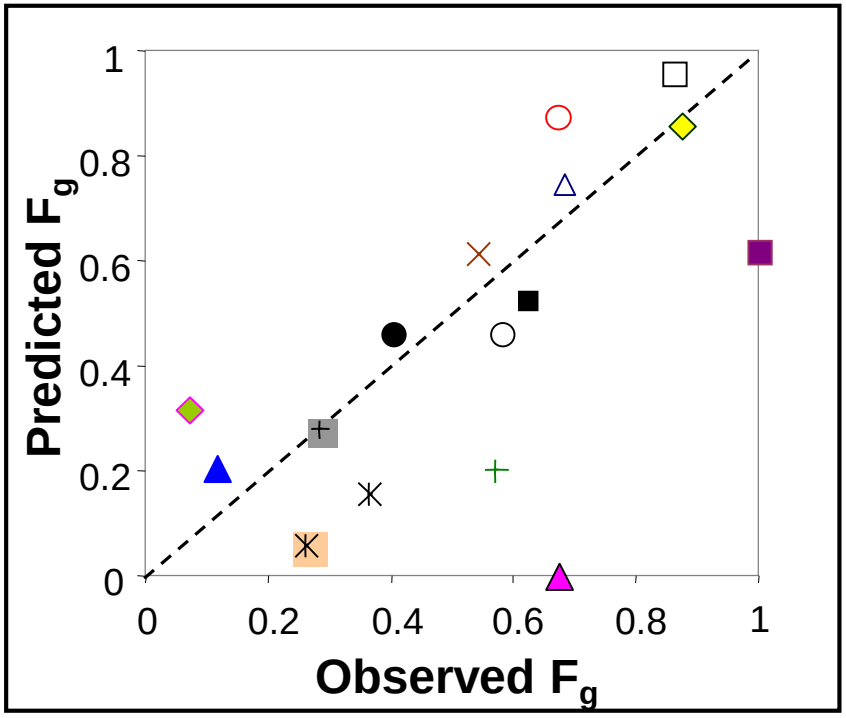
Gut wall metabolism

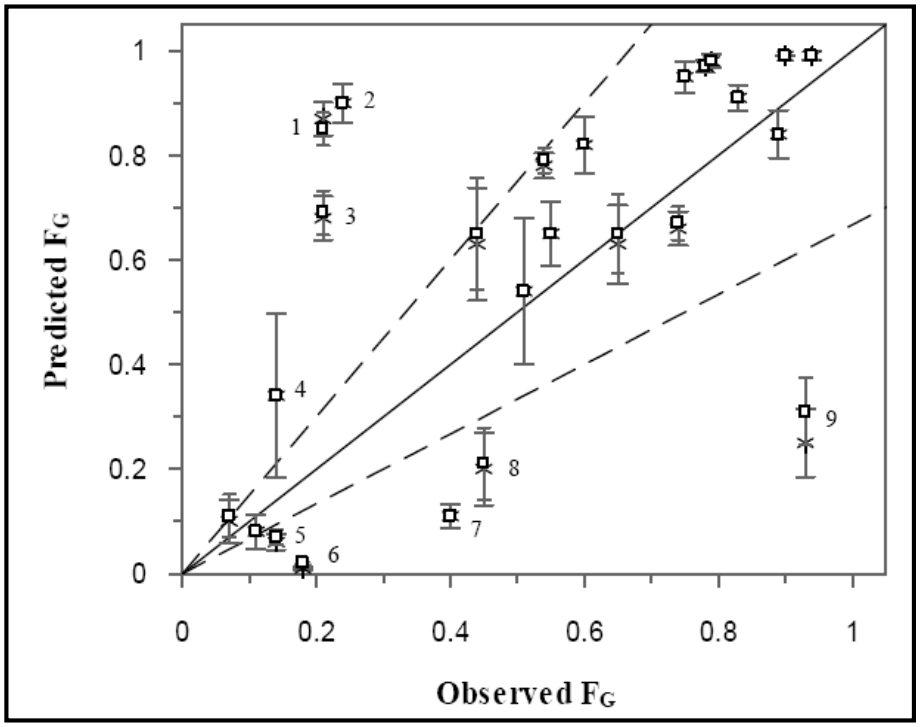
'Q_{gut}' , a minimal model

$$F_g = \frac{'Q_{gut}'}{'Q_{gut}' + fu_{gut}.CLu_{int-gut}}$$

$$'Q_{gut}' = \frac{CL_{perm} \cdot Q_{villi}}{CL_{perm} + Q_{villi}}$$



Yang *et al., CDM, 2007*



Gertz *et al.*, *DMD, 2010*

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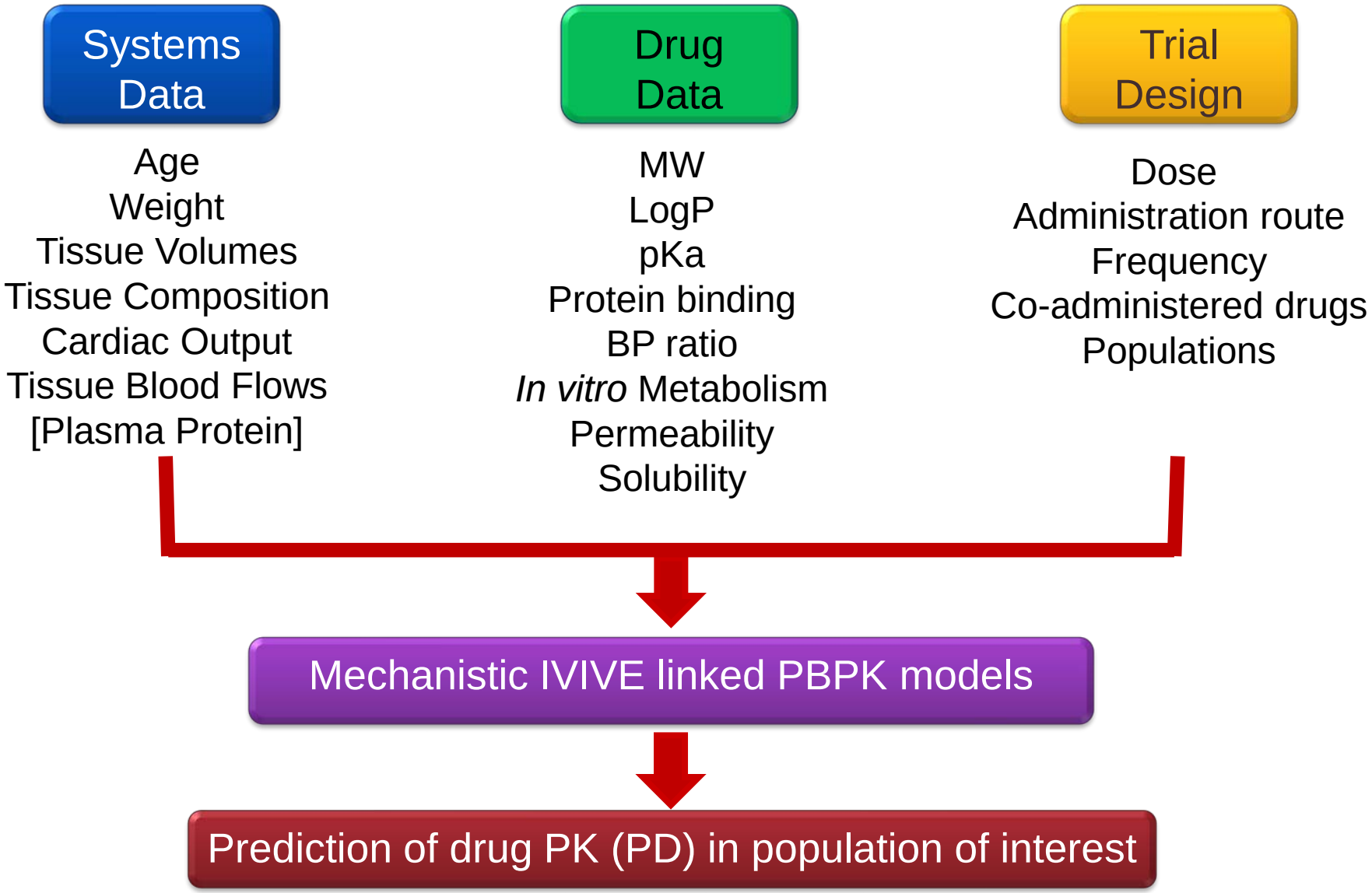
Special populations



Jamei *et al.*, DMPK, 2009, Rostami-Hodjegan, CPT, 2012

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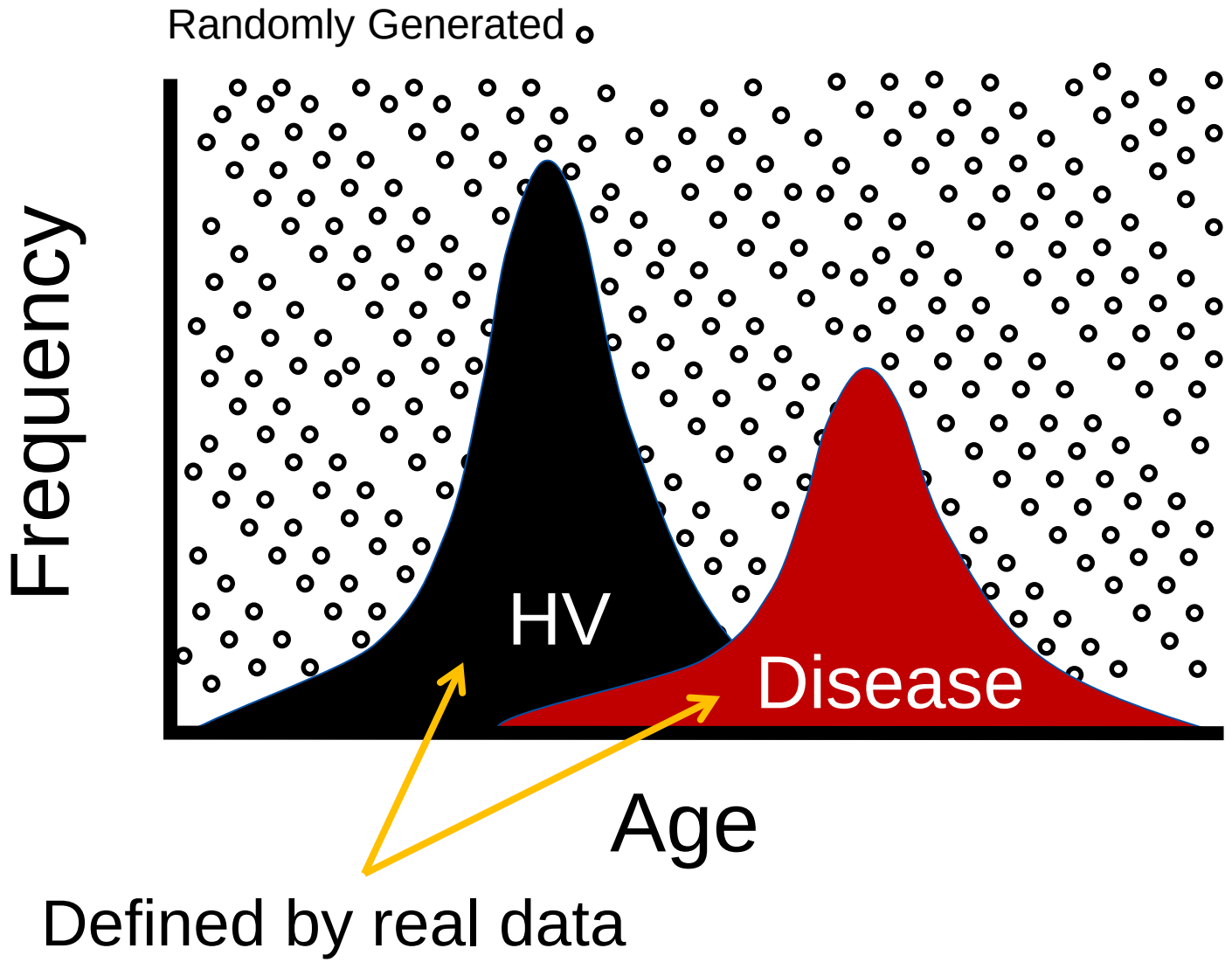
Demographic Features of Healthy and Disease Populations



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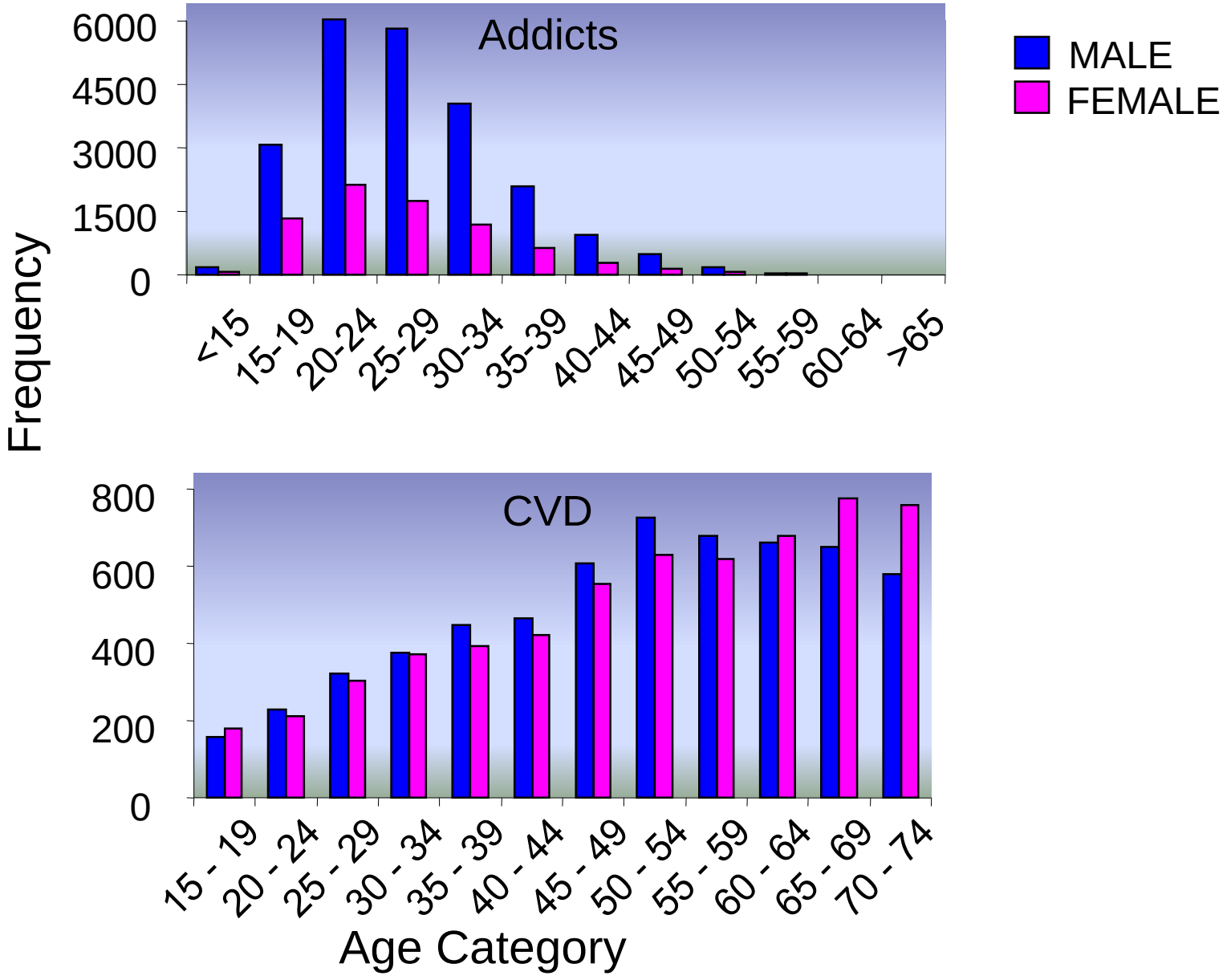
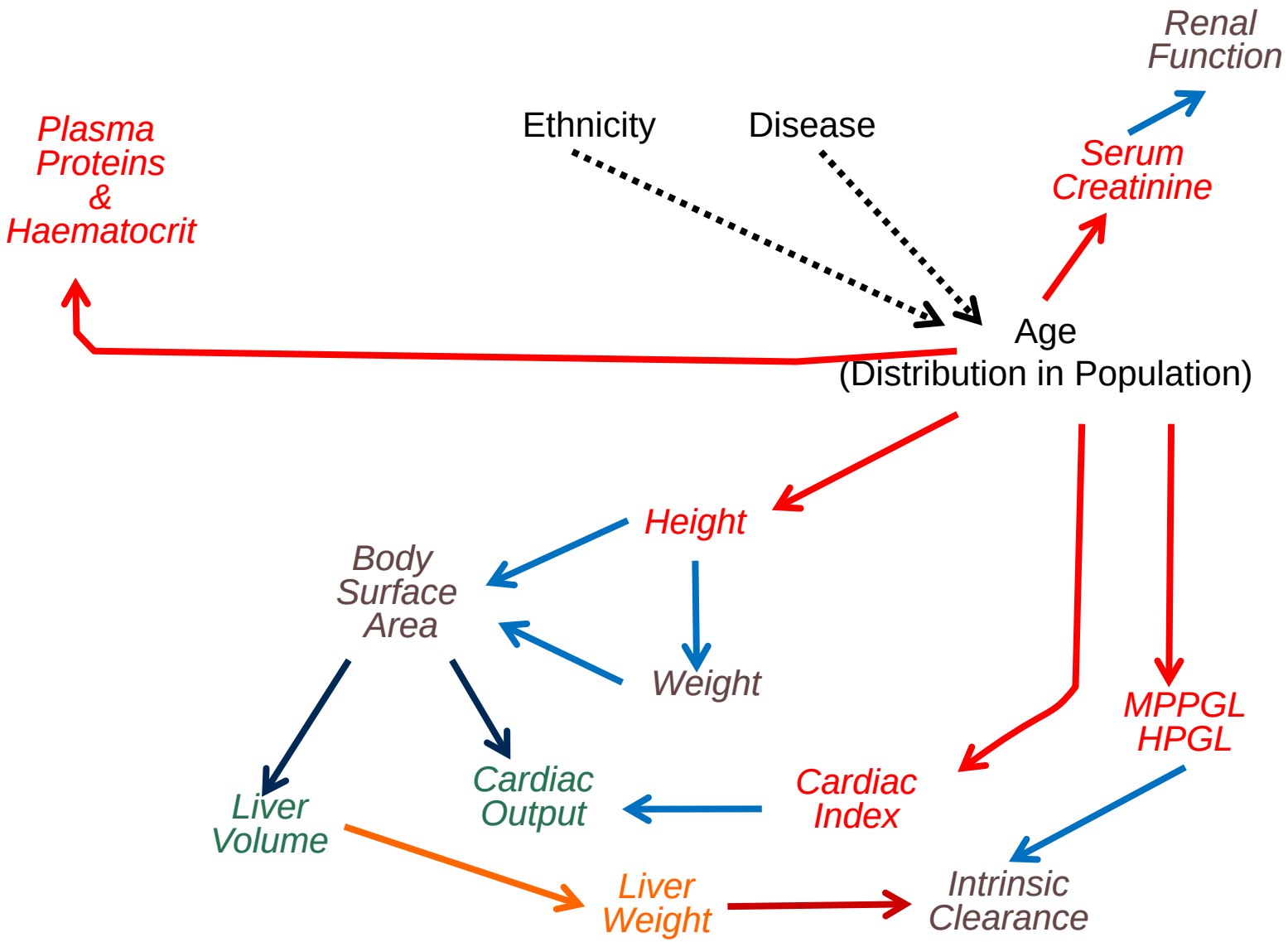
Age Distribution in Target Population



The Complexity of Covariate Effects as Applied to CL



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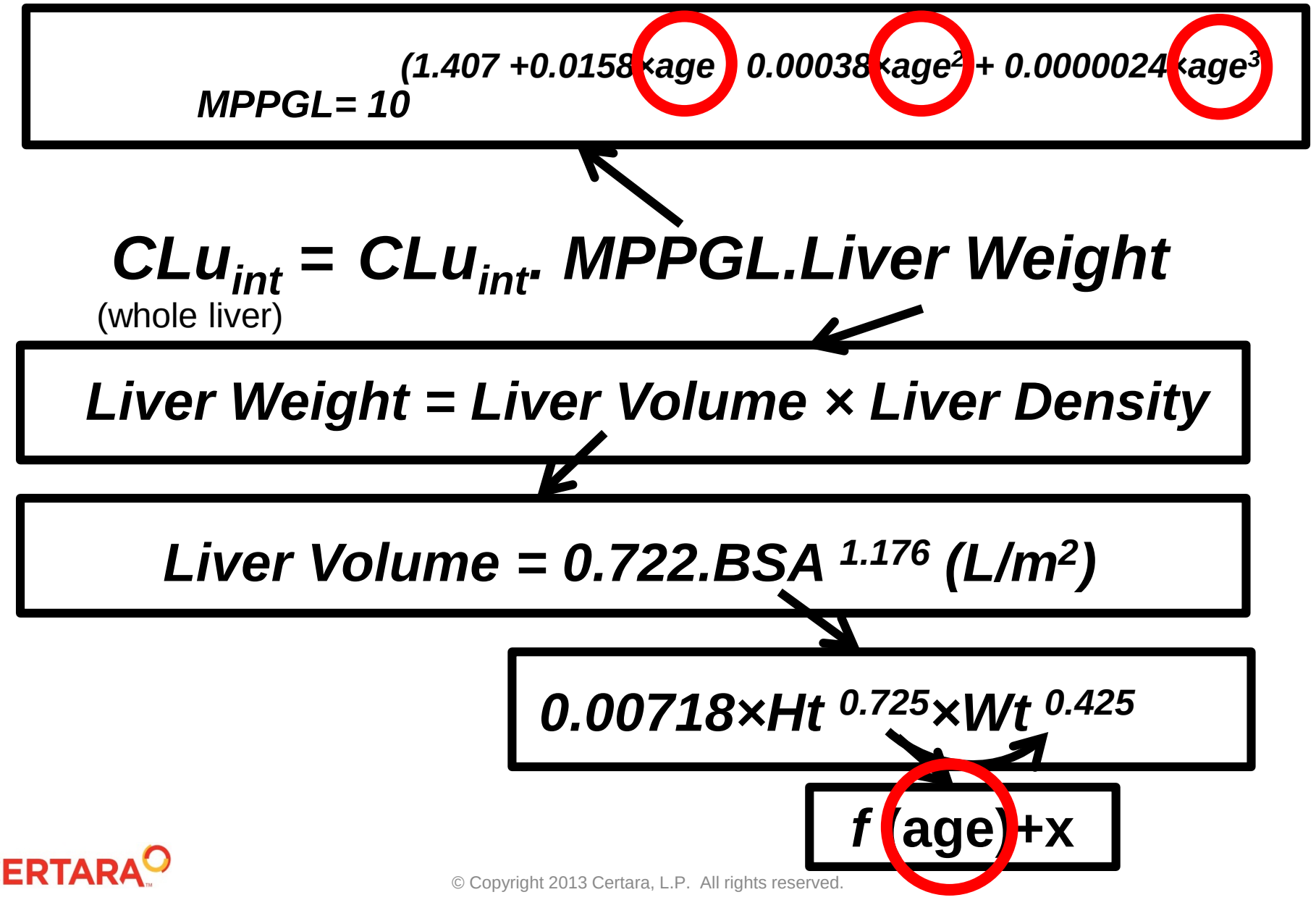
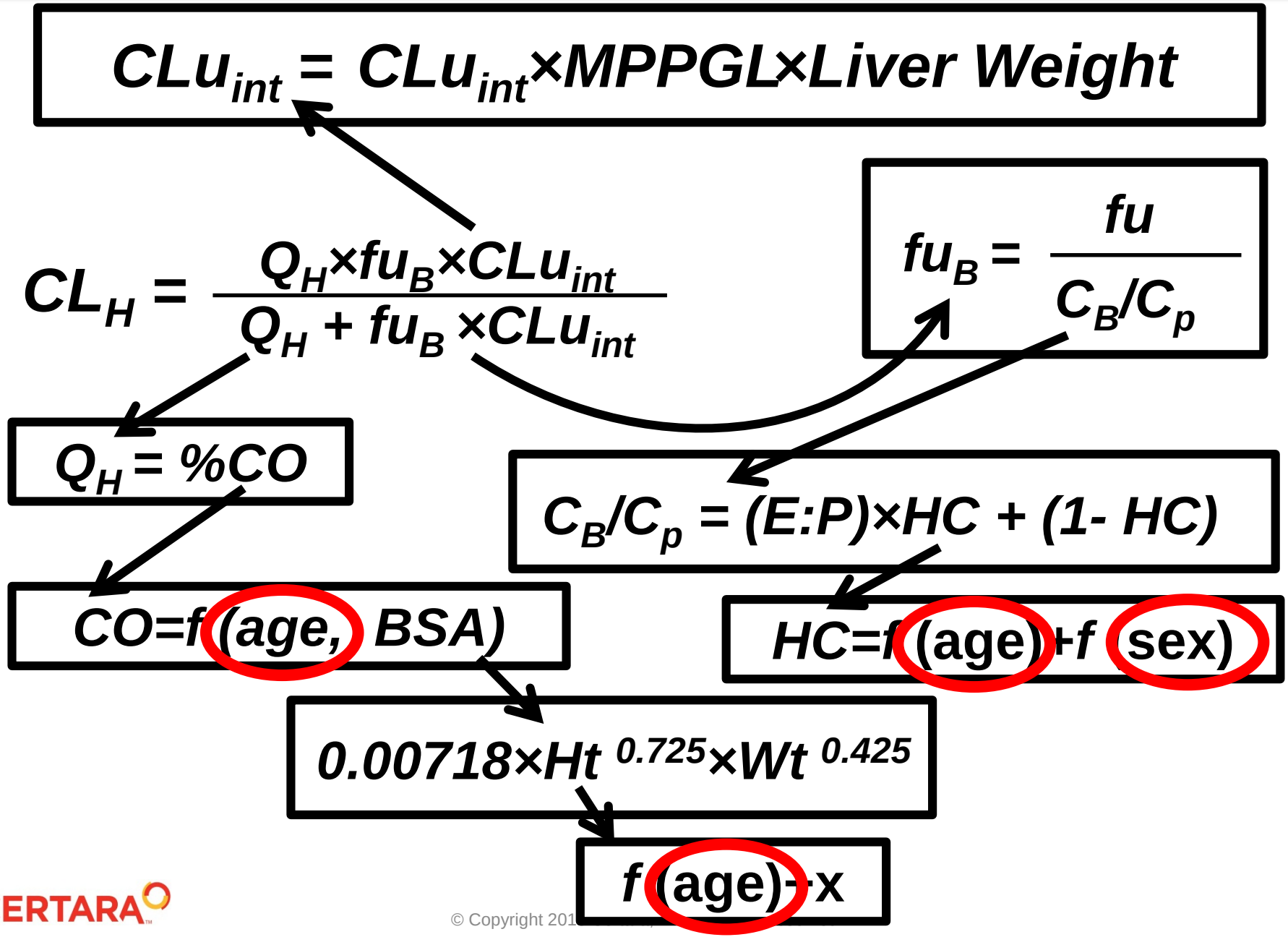
Converting CLu_{int} to CL_H

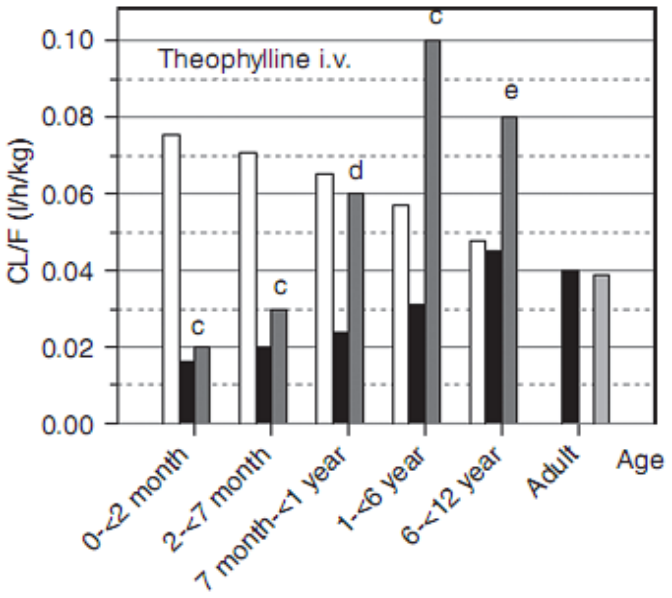


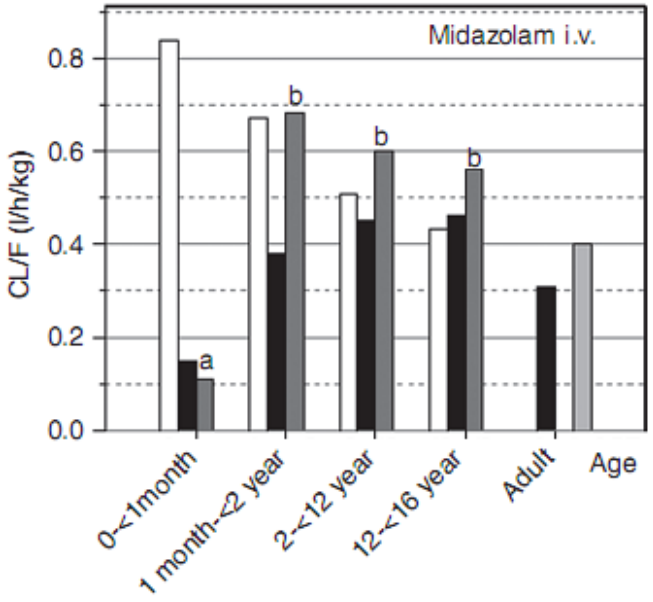
Converting CLu_{int} to CL_H

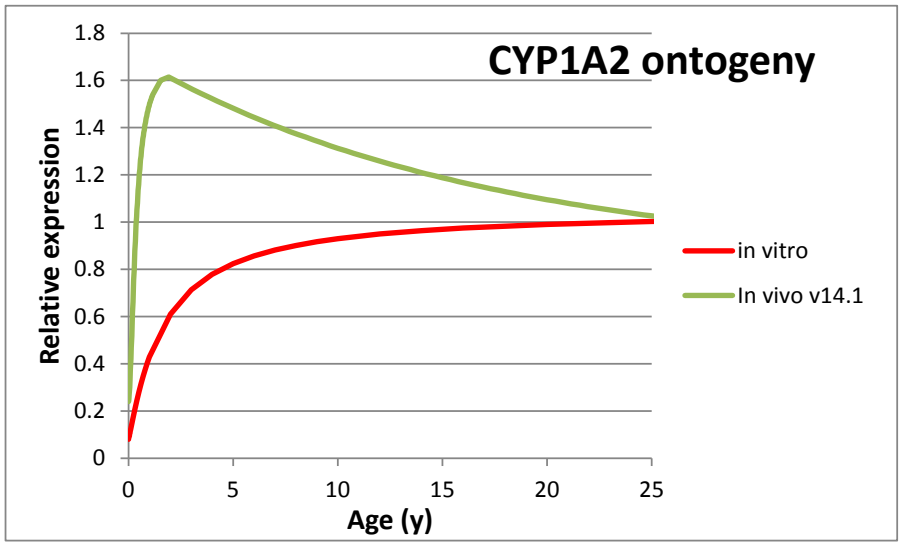


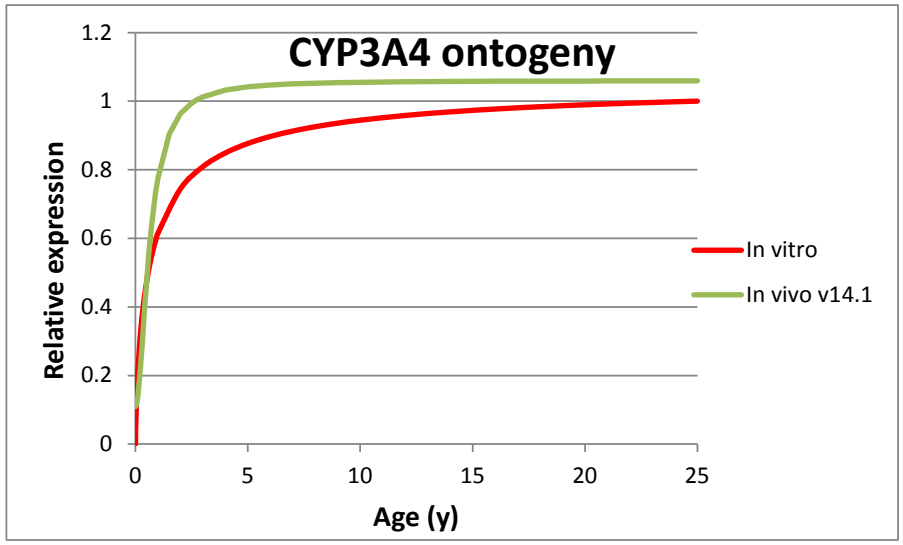
Revised *in vivo* ontogeny functions for CYP1A2 and 3A4

(Leong *et al.*, CPT 2012; 91: 926-931)









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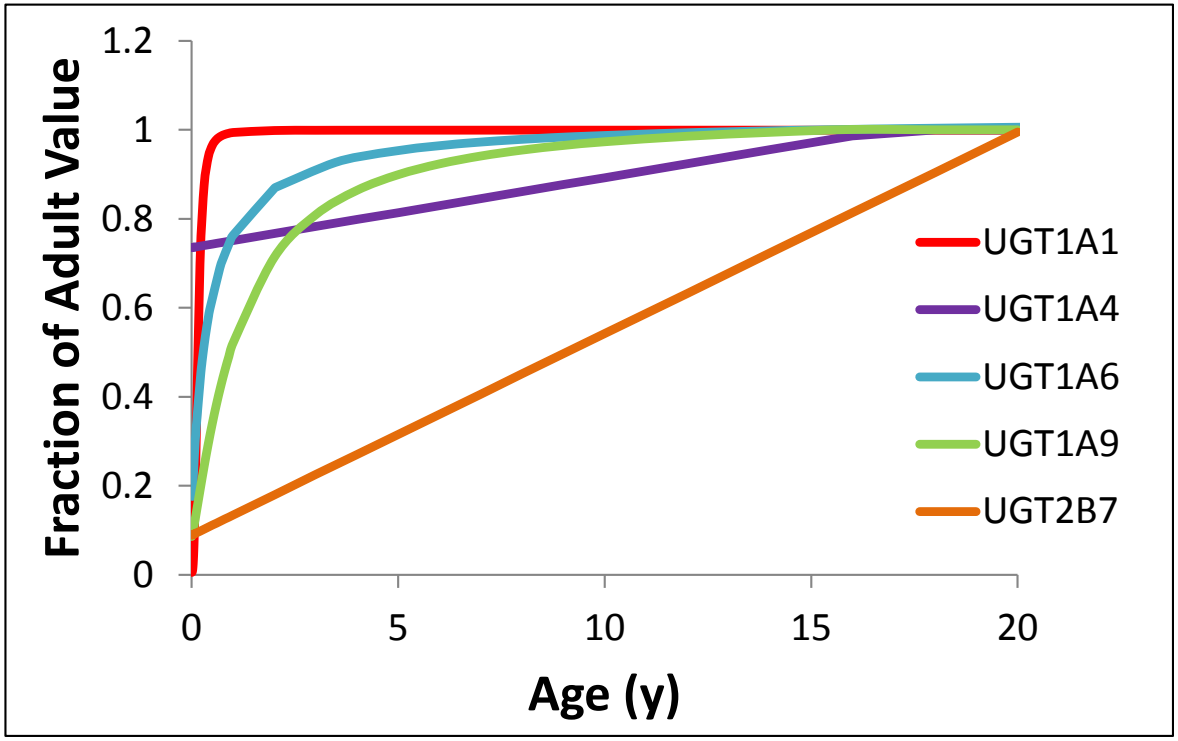
UGT Ontogeny



Strassburg *et al* 2002
Burchell *et al* 1989
Onishi *et al* 1997
Leakey *et al* 1987
Coughtrie *et al* 1988
Miyagi and Collier 2007
Zaya *et al* 2006
Pacifici *et al* 1990
Pacifici *et al* 1982
Choonara *et al* 1989

Leiden Collaboration – Top down *vs* bottom up ontogeny for UGT2B7

- Morphine
- Zidovudine

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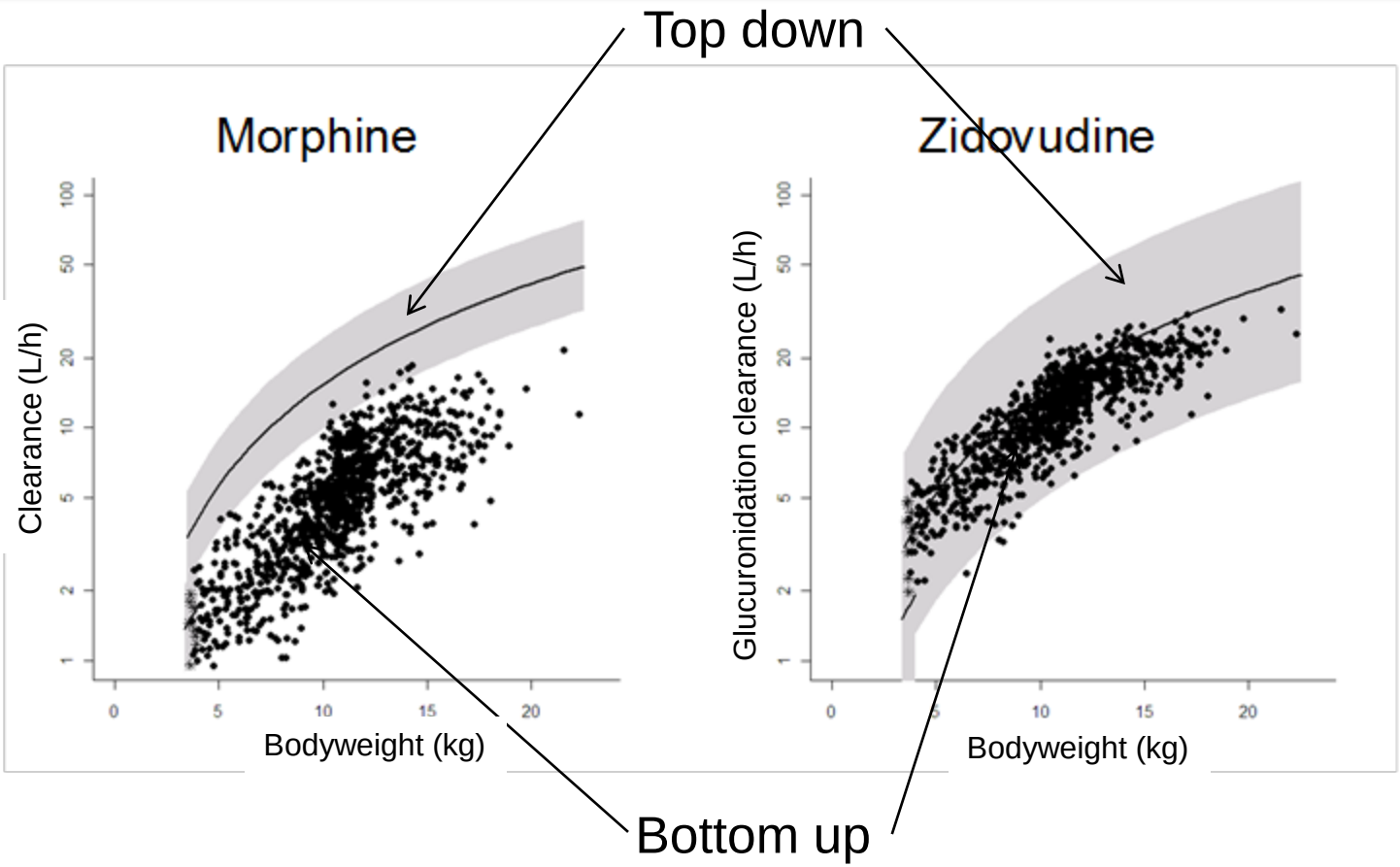
UGT2B7 ontogeny ‘Top down’ vs ‘Bottom up’



- Take home message is that pattern of ontogeny appears to be reasonable except for early neonates
- But under-prediction of CL across age band with morphine.

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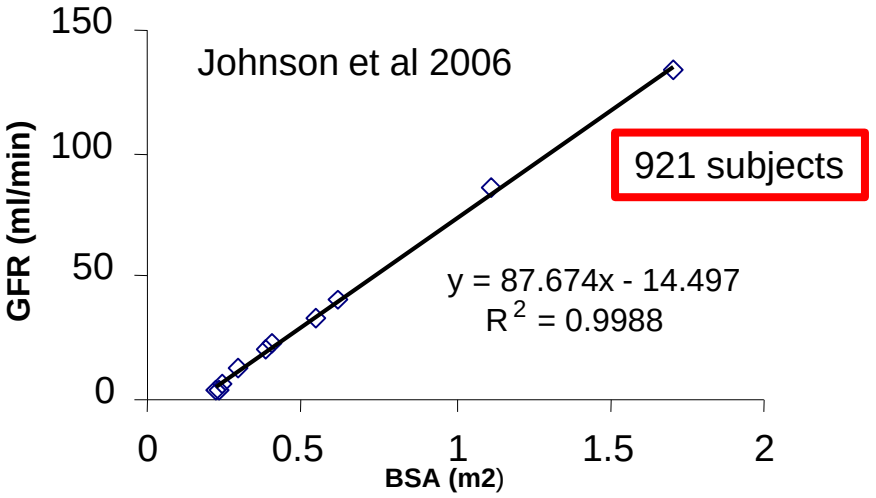
Maturation of Renal Clearance



Pediatr Nephrol (2009) 24:67–76
DOI 10.1007/s00467-008-0997-5

ORIGINAL ARTICLE

Human renal function maturation: a quantitative description using weight and postmenstrual age

Malin M. Rhodin · Brian J. Anderson · A. Michael Peters · Malcolm G. Coulthard · Barry Wilkins · Michael Cole · Etienne Chatelut · Anders Grubb · Gareth J. Veal · Michael J. Keir · Nick H. G. Holford

923 subjects

Pharm Res (2014) 31:2643–2654
DOI 10.1007/s11095-014-1361-z

RESEARCH PAPER

Simultaneous Pharmacokinetic Modeling of Gentamicin, Tobramycin and Vancomycin Clearance from Neonates to Adults: Towards a Semi-physiological Function for Maturation in Glomerular Filtration

Roosmarijn F.W. De Cock · Karel Allegaert · Janneke M. Brussee · Johannes N. van den Anker · Meindert Danhof · Catherijne A. J. Knibbe

1760 subjects

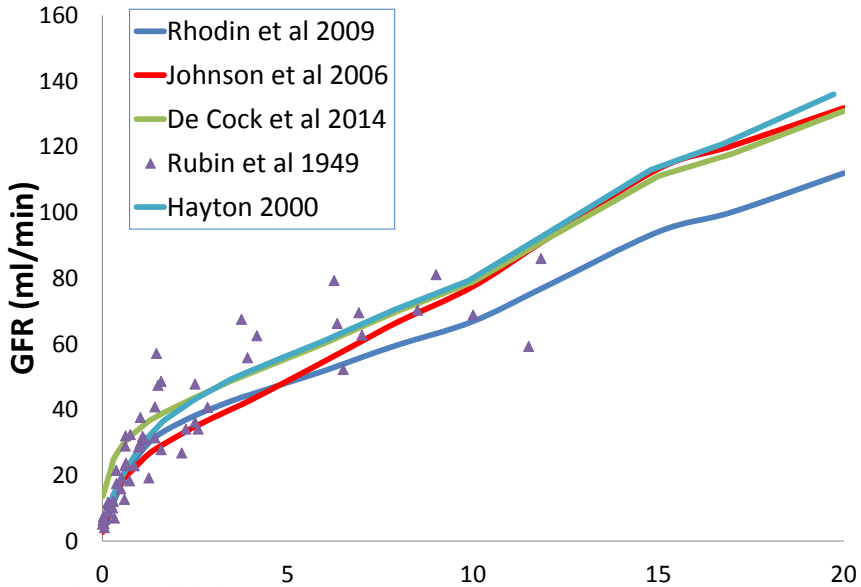
AAPS PharmSci 2002; 2 (1) article 3 (http://www.aapspharmsci.org).

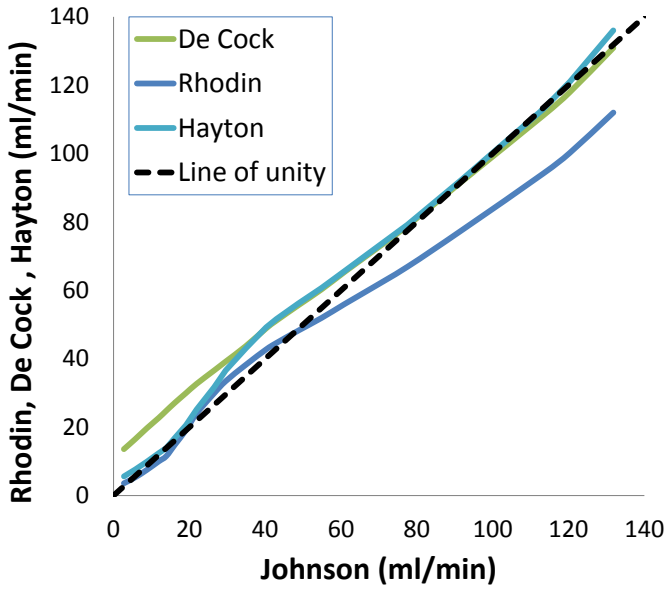
Maturation and Growth of Renal Function: Dosing Renally Cleared Drugs in Children

Submitted: September 6, 1999; Accepted: February 15, 2000; Published: March 3, 2000

William L. Hayton[1]

63 subjects





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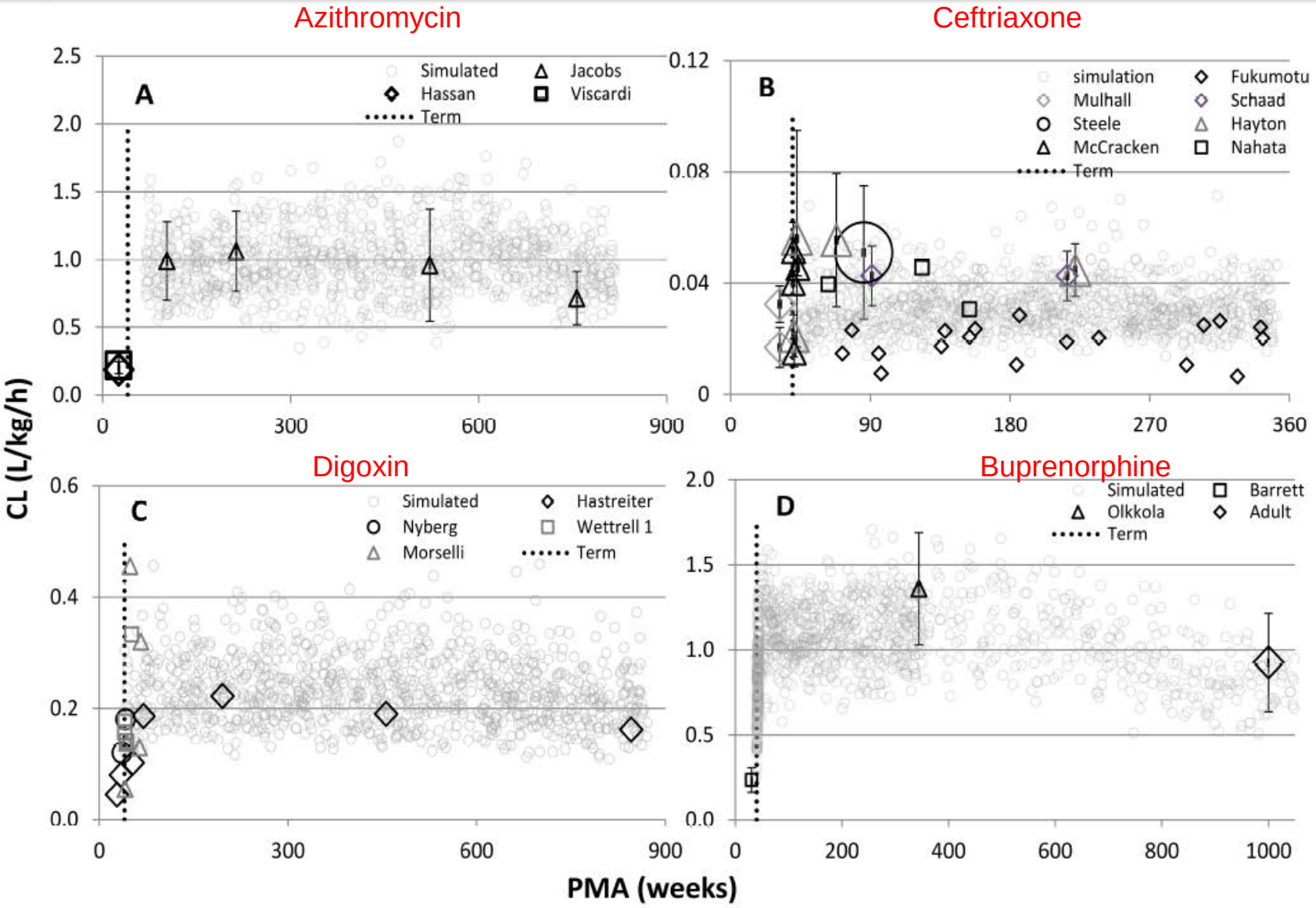
Maturation of Biliary Clearance Appears to be Rapid



Johnson et al Drug Metab Dispos. 2016

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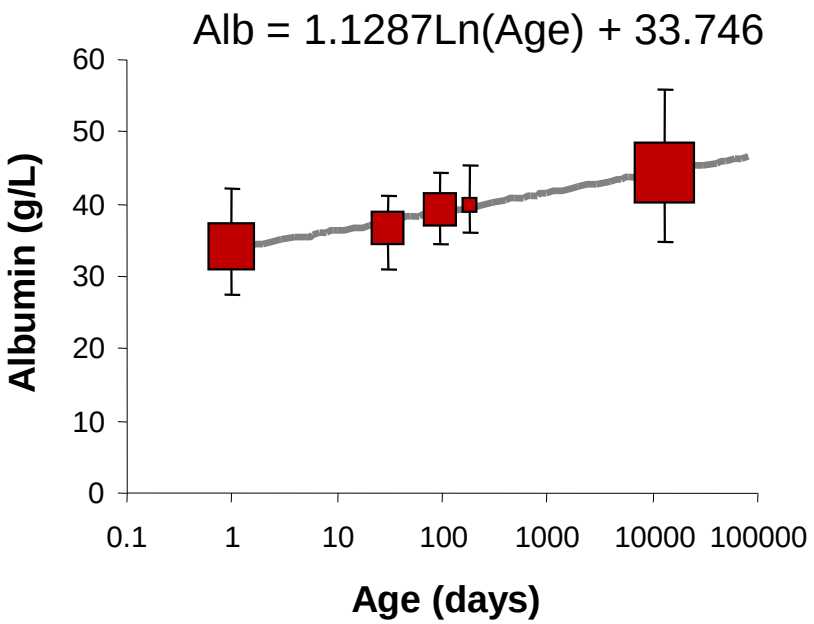
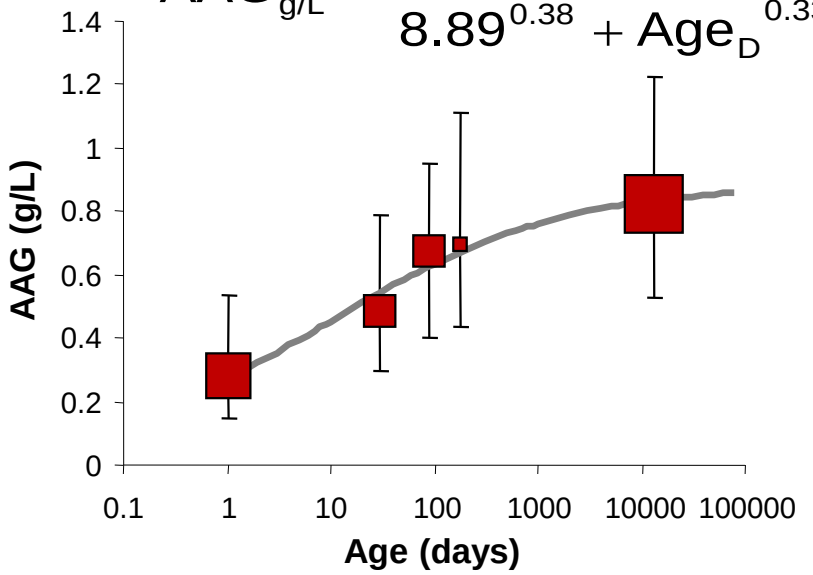
Variation in Protein Binding (fu)



$$AAG_{g/L} = \frac{0.887 \times Age_D^{0.38}}{8.89^{0.38} + Age_D^{0.33}}$$



$$fu = \frac{1}{1 + \frac{[P]}{K_D}}$$

K_D = Dissociation Constant
[P] = Serum Protein Concentration

$$K_D = \frac{[P]}{\frac{1}{fu} - 1}$$

In absence of changes in dynamics of binding:

$$fu = \frac{1}{1 + \left[\frac{[P]}{[P]_{pop*}} \times \frac{(1 - fu_{pop*})}{fu_{pop*}}\right]}$$

*pop is the population under investigation *i.e* paediatric

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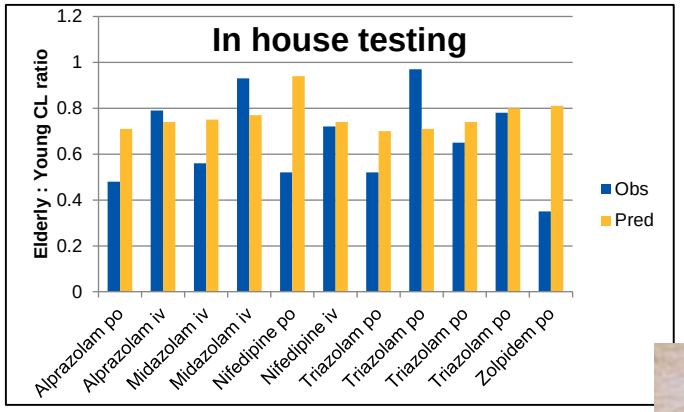
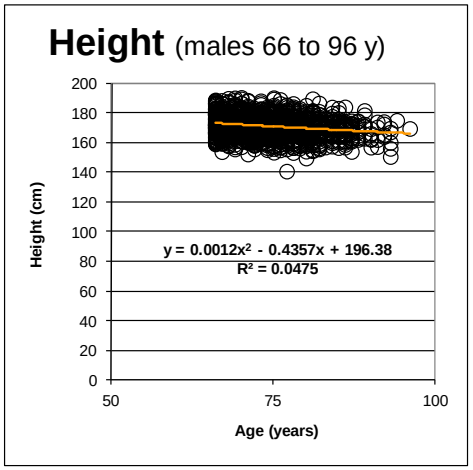
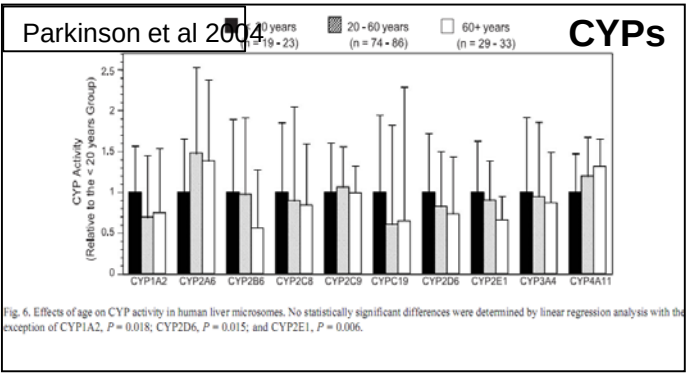
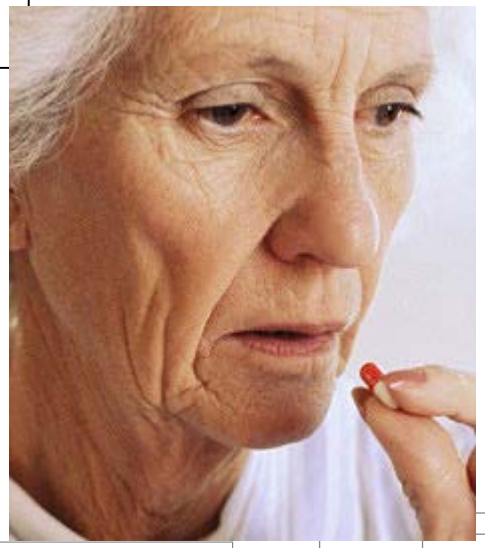
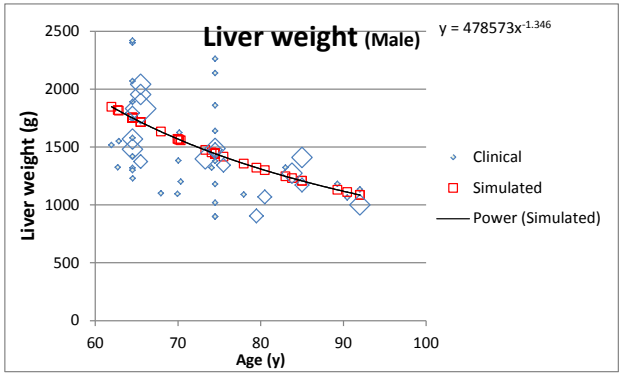
Developing and testing a Geriatric population

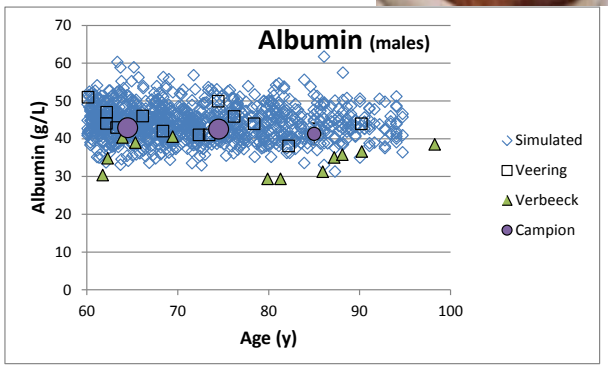


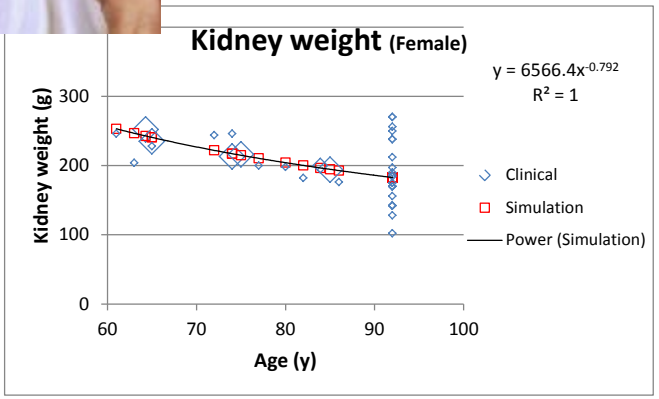








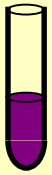




Scaling from in vitro: drug data vs systems data

Liver

In vitro data → J_{max}/K_m or $CLu_{int\ T}$ → HHEP *In vitro* $CLu_{int,\ T}$ → $CLu_{int,\ T}$ per g Liver → $CLu_{int,\ T}$ per Liver



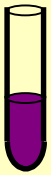
SF 1: REF/RAF_{HHEP}

SF 2: HPGL

SF 3: Liver Weight

Kidney

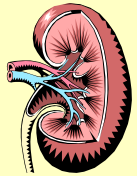
In vitro data → J_{max}/K_m or $CLu_{int\ T}$ → PTC *In vitro* $CLu_{int,\ T}$ → $CLu_{int,\ T}$ per g Kidney → $CLu_{int,\ T}$ per Kidney



SF 1: REF/RAF_{PTC}

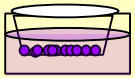
SF 2: PTCPGK

SF 3: Kidney Weight



Brain

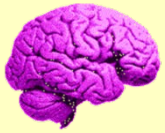
In vitro data → J_{max}/K_m or $CLu_{int\ T}$ → H-BMv *In vitro* $CLu_{int,\ T}$ → $CLu_{int,\ T}$ per g Brain → $CLu_{int,\ T}$ per Brain @ BBB



SF 1: $REF/RAF_{H\text{-}BMv}$

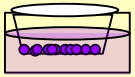
SF 2: H-BMvPGB

SF 3: Brain Weight



Intestine

Caco-2, MDCK- II, $LLC\text{-}PK_1$ *etc.* → J_{max}/K_m or $CLu_{int\ T}$ → $CLu_{int,\ T}$ In Jejunum I



SF 1: $REF/RAF_{Jejunum\ I}$

Scaling via the Permeability and Surface area product

Replacement / Additional Organ

J_{max}/K_m or $CLu_{int\ T}$ → $CLu_{,\ T}$ per whole organ

User needs to scale to whole organ!

SF: Scaling Factor

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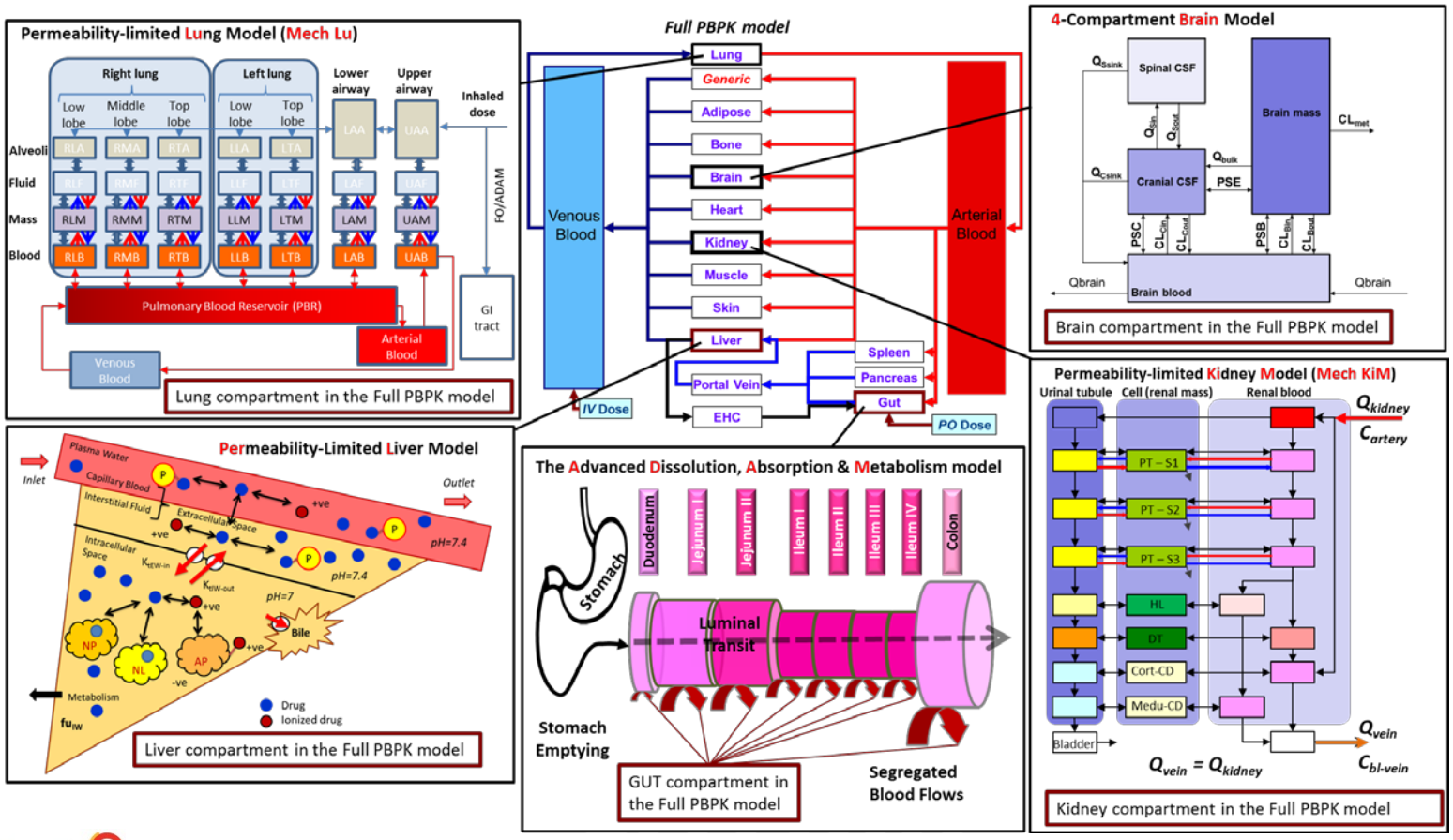
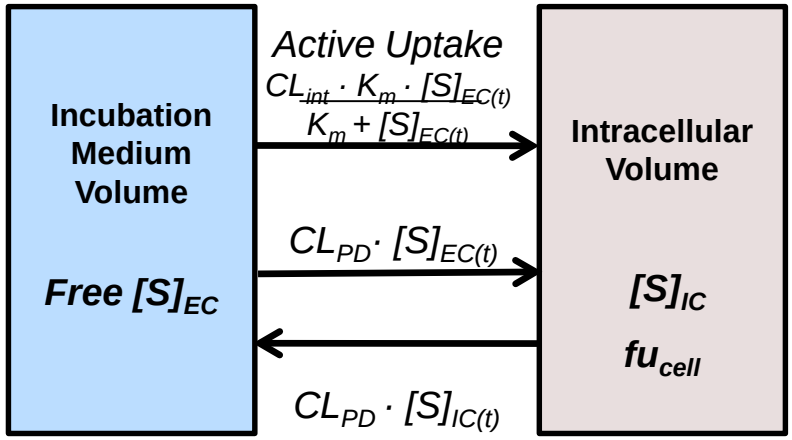
Translating *in vitro* effective concentrations to concentrations at the site of action

- Mechanistic, multi-compartmental tissue models (brain, kidney, liver, lung and intestine) are available
- Enable more reliable estimates of intracellular tissue concentrations



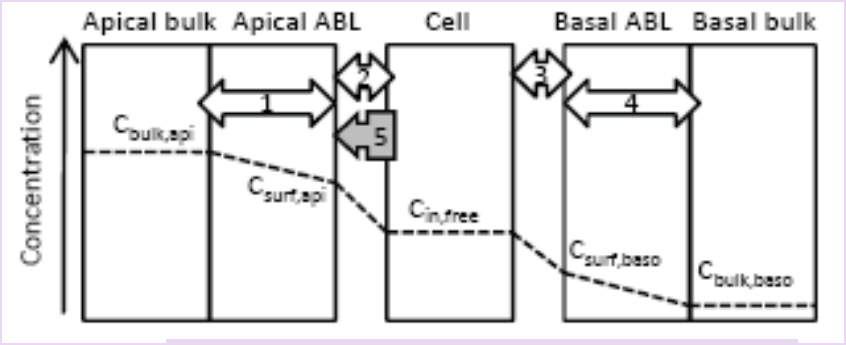
Modelling *in vitro* assays – a must to do!

2 Compartment Model

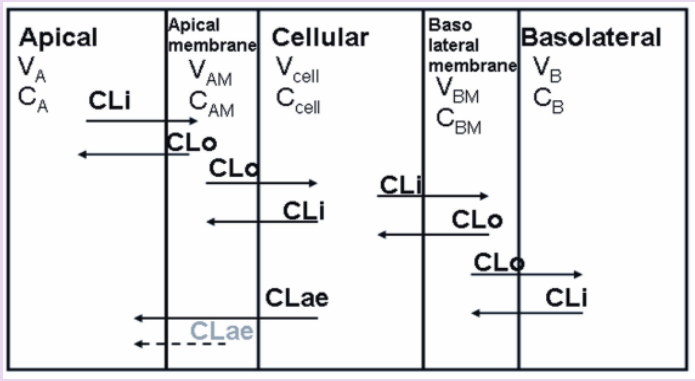


Baker et al., Xenobiotica, 2007; Soars et al., Mol Phar, 2009; Poirier et al., Mol Pharm , 2009; Menochet et al., J Pharm Exp Ther, 2012

5 Compartment Model - Transwell



Heikkinen et al., 2010 Mol Pharmaceutics



Korzekwa et al., 2012 DMD

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PBPK Impact on 19 US Drug Labels in Last 2 Years

Olysio (Simerprevir) Hepatitis C janssen	Xarelto (Rivaroxaban) Thrombosis & Embolism Johnson & Johnson	Edurant (Rilpivirine) HIV infection tibotec	Imbruvia (Ibrutinib) Lymphoma and Leukemia pharmacyclics	Opsumit (Macitentan) Pulmonary Hypertension ACTELION
Zykadia (Ceritinbi) Lung Cancer NOVARTIS	Odozmzo (Sonidegib) Basal Cell Carcinoma NOVARTIS	Farydak (Panobinostat) Multiple myeloma NOVARTIS	Revatio (Sildenafil) Pulmonary Hypertension Pfizer	Bosulif (Bosutinib) Myelogenous Leukemia Pfizer
Lynparza (Olaparib) Advanced Ovarian Cancer AstraZeneca	Movantik (Naloxegol) Opioid Induced Constipation AstraZeneca	Tagrisso (Osimertinib) Metastatic NSCLC AstraZeneca	Iclusig (Ponatinib) Chronic Myeloid Leukemia ARIAD	Cerdelga (Eliglustat) Gaucher Disease genzyme A SANOFI COMPANY
Jevtana (Cabazitaxel) Prostate Cancer SANOFI	Cotellic (Cobimetinib) Metastatic Melanoma Genentech	Lenvima (Lenvatinib) Thyroid cancer Eisai	Aristada (Aripiprazolel) Schizophrenia Alkermes Patient inspired	

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Quantitative *IVIVE* of Tissue Toxicity Supported by European Commission 7th FP Predict-IV Grant

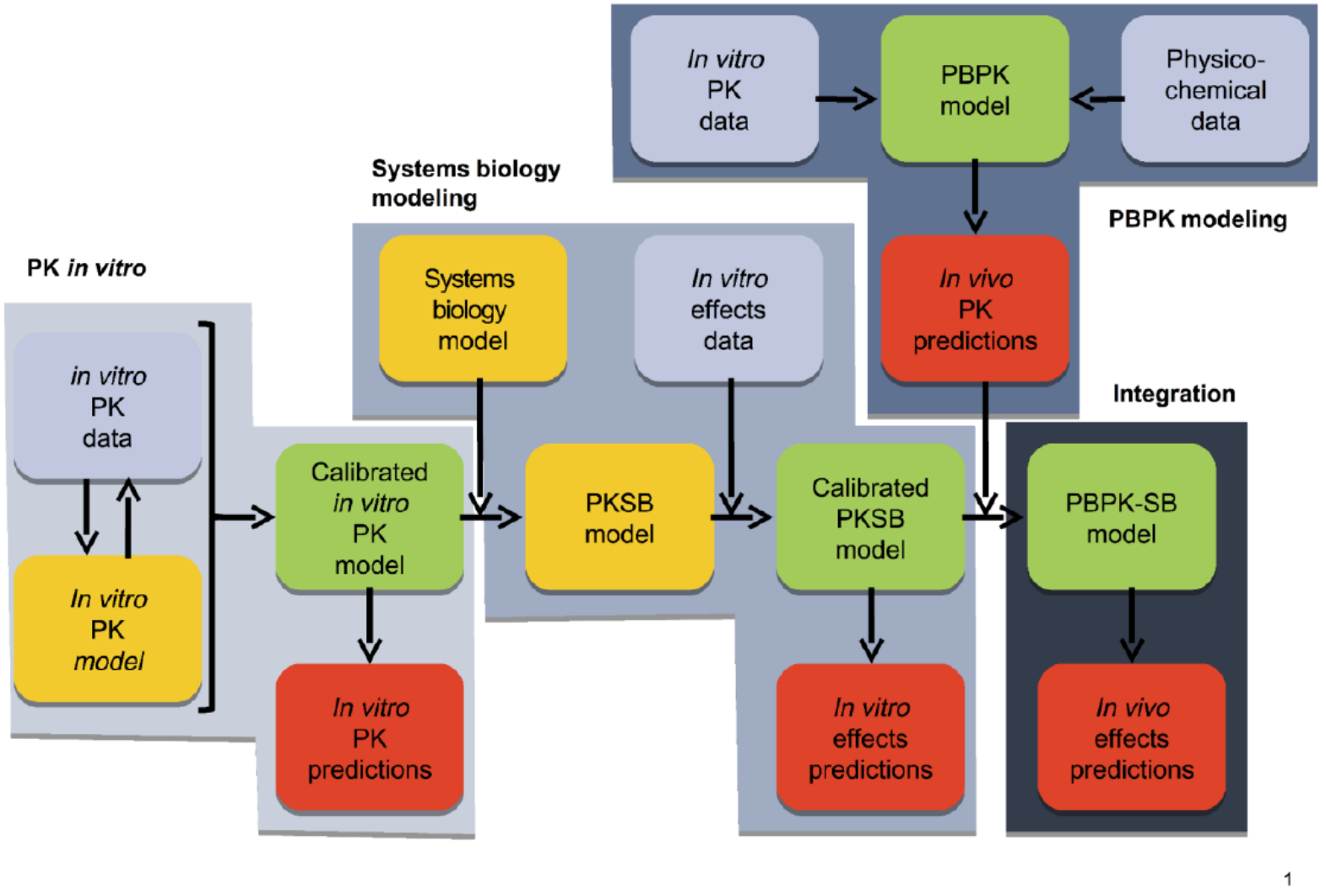

Figure 1: Components of the four integrative modeling steps followed in Predict-IV.

Hamon et al., Toxicology in Vitro, 2015

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Summary

- **In a systems pharmacology paradigm, the bottom-up approach to modeling and simulation of the ADME processes of a chemical, is a valuable tool in integrating available prior information and improving decision making.**
- **Improvement in the in vitro systems which can act as surrogates for in vivo reactions relevant to ADME**
- **Advances in the understanding of the extrapolation factors**
- **Advances in the development of mechanistic models of the human body**
- **Facilitate predicting PK characteristics in a wide range of healthy or disease populations accounting for age, sex, ethnicity, genetic, etc variability**
- **Moving towards PBPK coupling with systems biology models to predict toxicity endpoints/biomarkers and their associated variability from in vitro data**

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