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Implementing Translational Science

SIMCYP
simulator | consultancy | education

Simulating individual variability in pharmacokinetics as a risk factor for drug toxicity

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Simcyp Limited

New Perspectives in DMPK: Informing Drug Discovery,
Royal Society of Chemistry, London
11 February 2014

Tripos SIMCYP Pharsight

Outline of the presentation

- Integrating population variability into PK simulations
  - creation of virtual populations
- Sources of inter-individual variability in Pharmacokinetics
  - Drug Clearance
- Using virtual populations to predict risk factors for drug toxicity
  - Cardiac Safety

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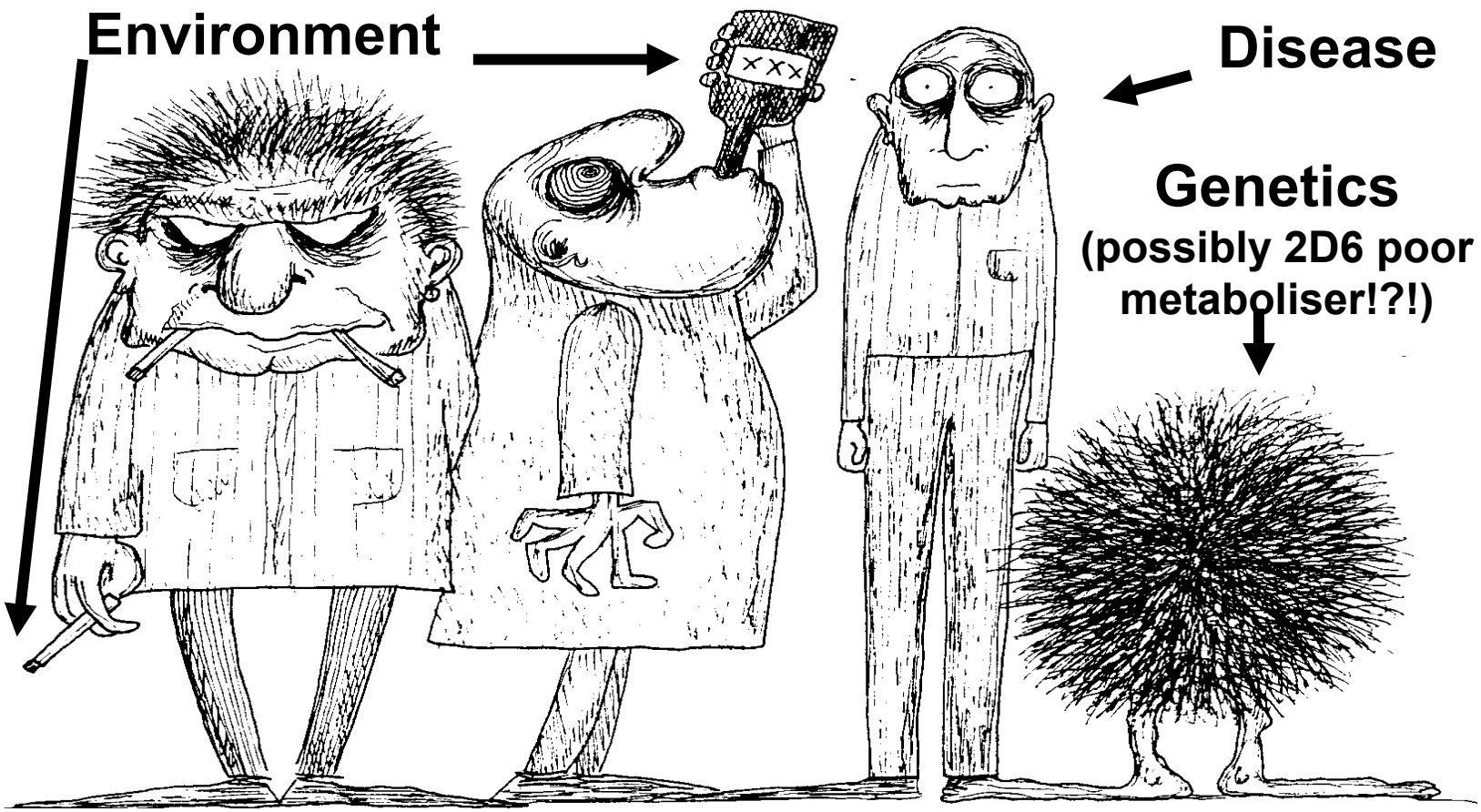
The Challenge of Population Variability



Cross Section of Patients in the Royal Hallamshire Hospital

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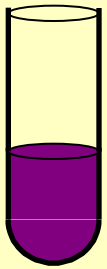
Prediction of human PK (PD) in virtual individuals



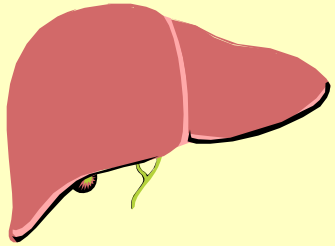
In vitro system

In vitro CLu_{int}

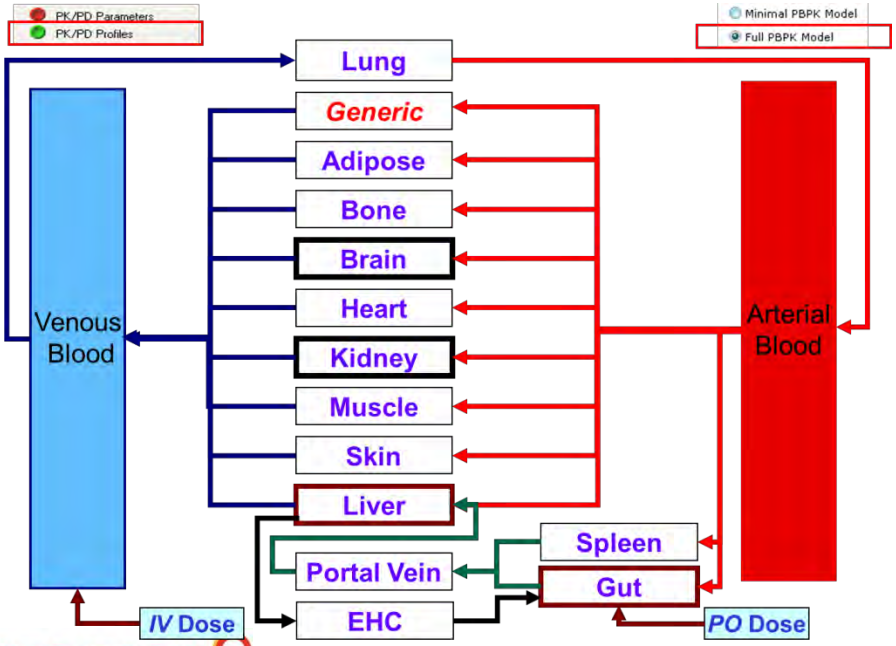
Scaling Factor (MPGGL, HPGL)

CLu_{int} per g Liver

Liver weight



CLu_{int} per Liver



Simcyp approach

Combine in vitro-in vivo extrapolation (IVIVE) and PBPK approaches in virtual individuals to predict drug concentration and effect

Identifying relevant *DISTRIBUTION* of values for demographical, biological, physiological and genetic parameters in target population & the *COVARIATIONS* between the parameters in target POPULATION

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Separating Systems & Drug Information

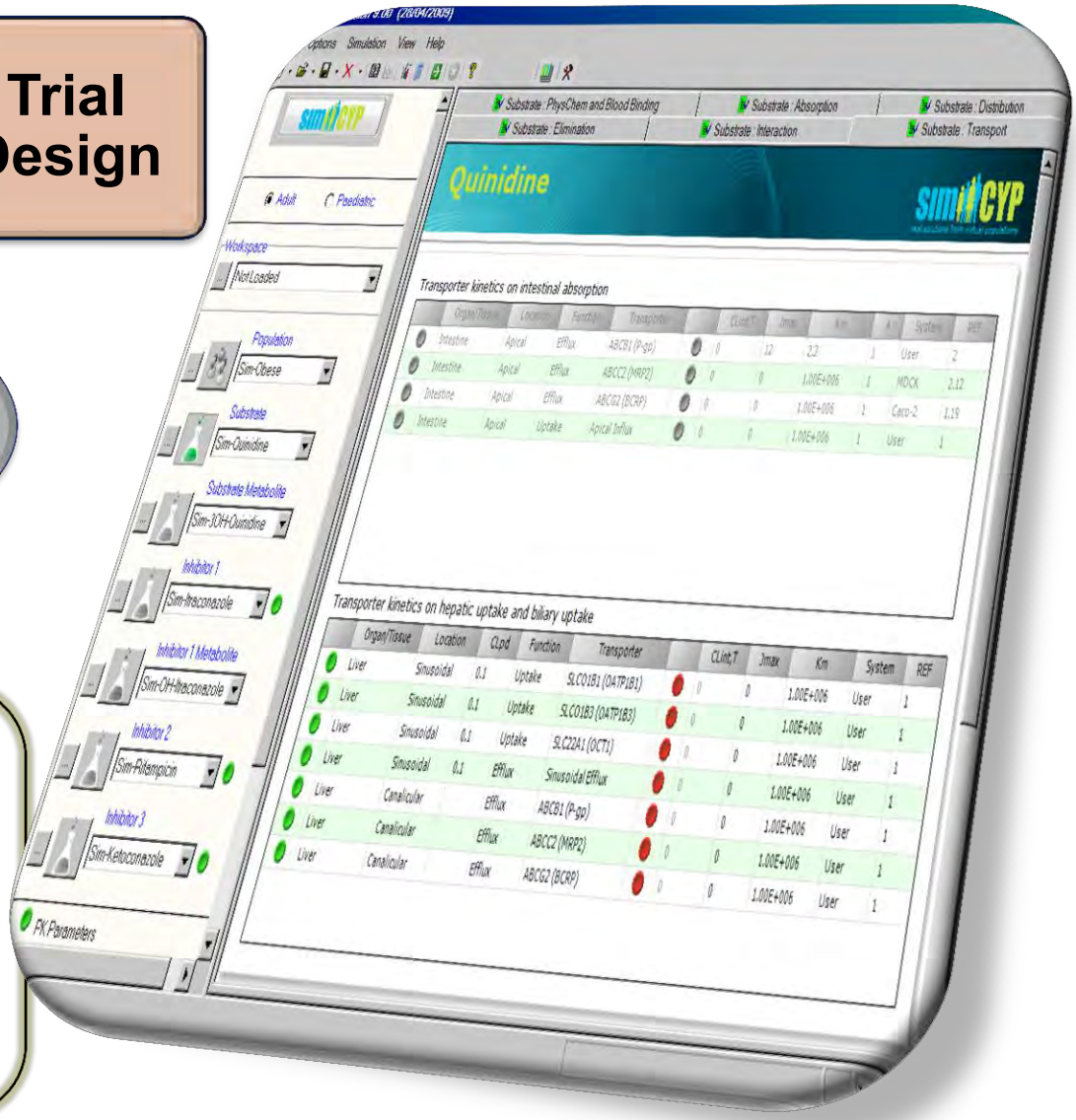
Systems Data

Drug Data

Trial Design

Mechanistic IVIVE & PBPK

Population PK (/PD)
&
Covariates of ADME
&
Study Design



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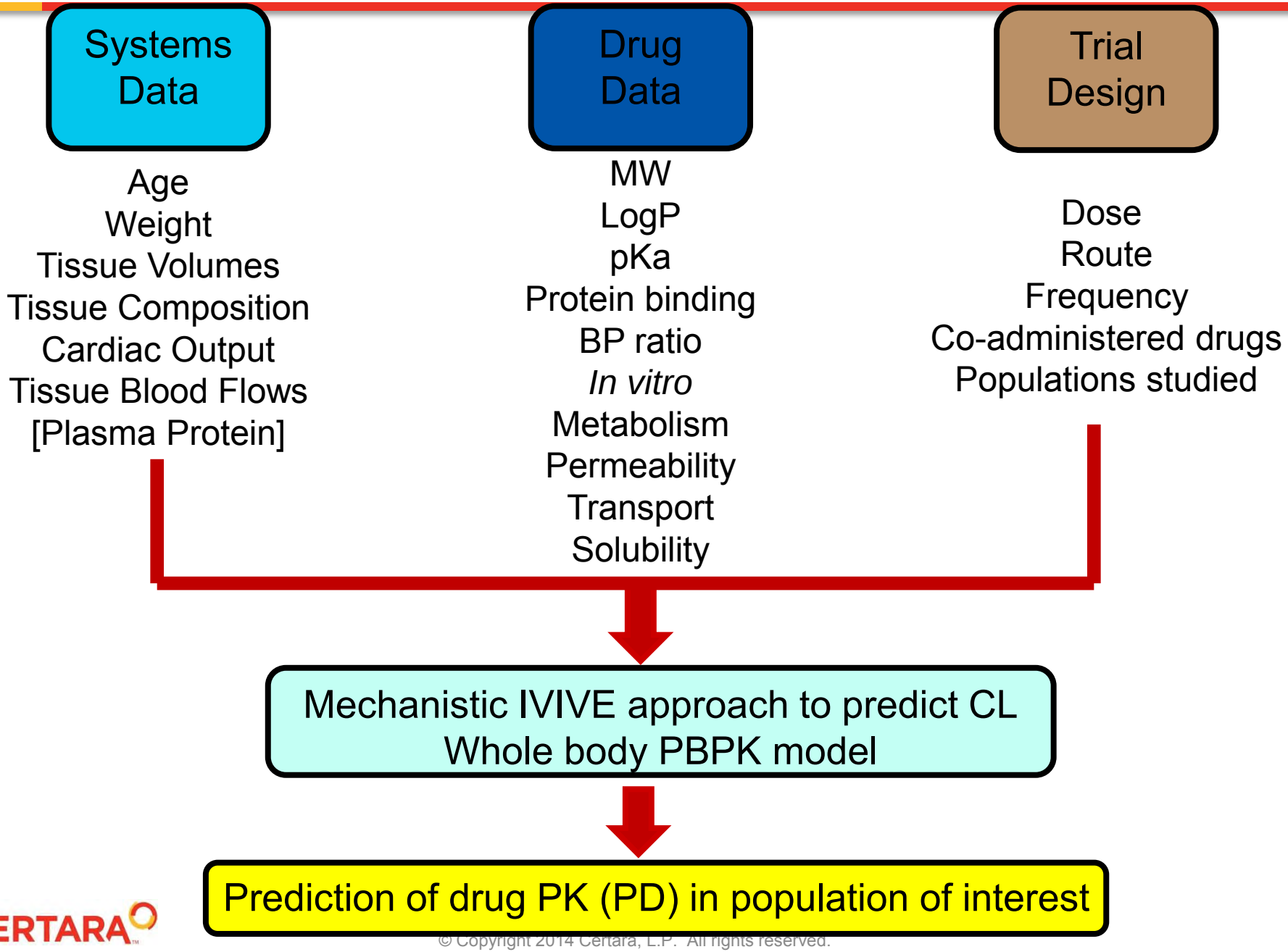
Separating Systems & Drug Information



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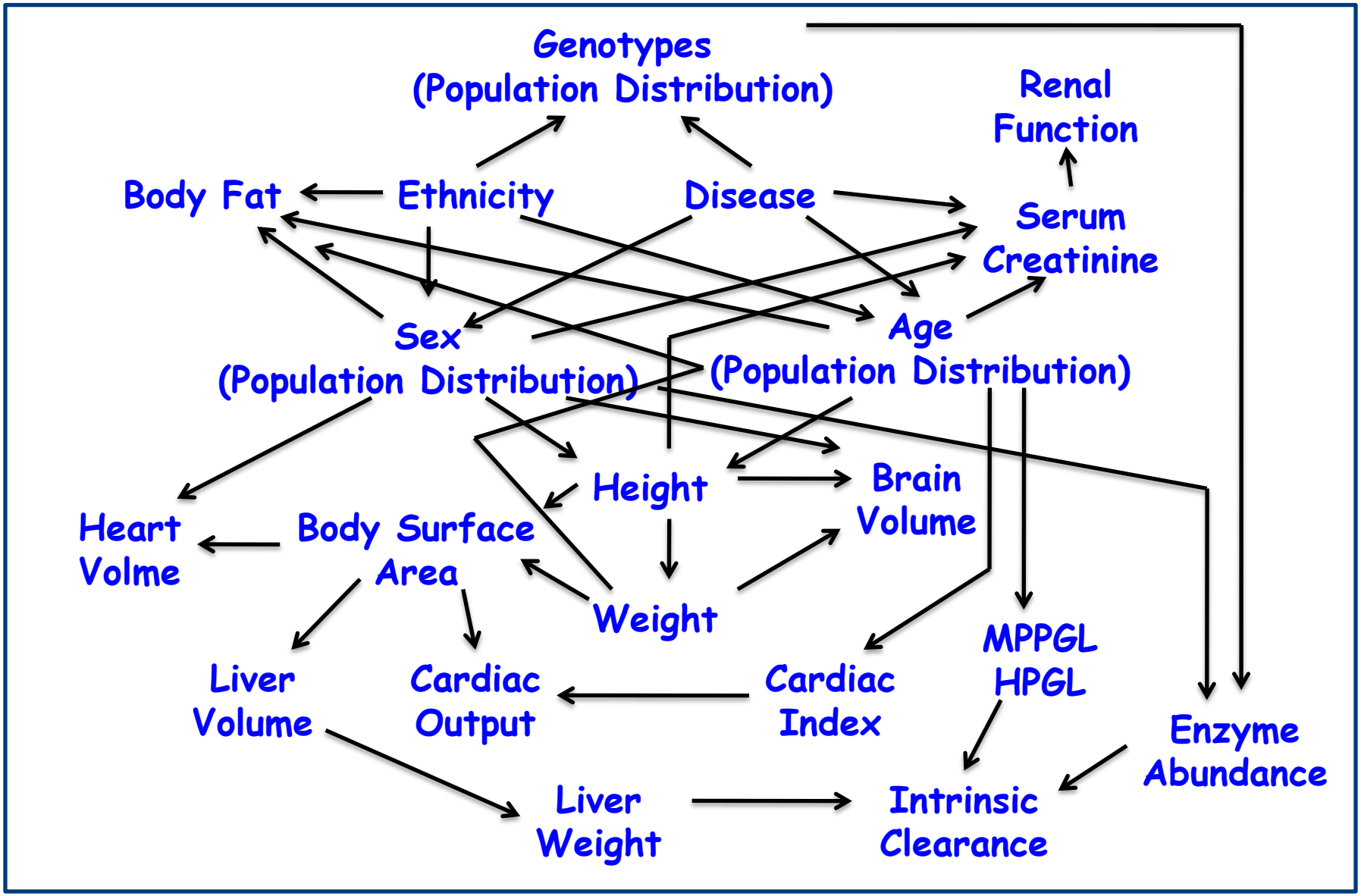
Building virtual populations



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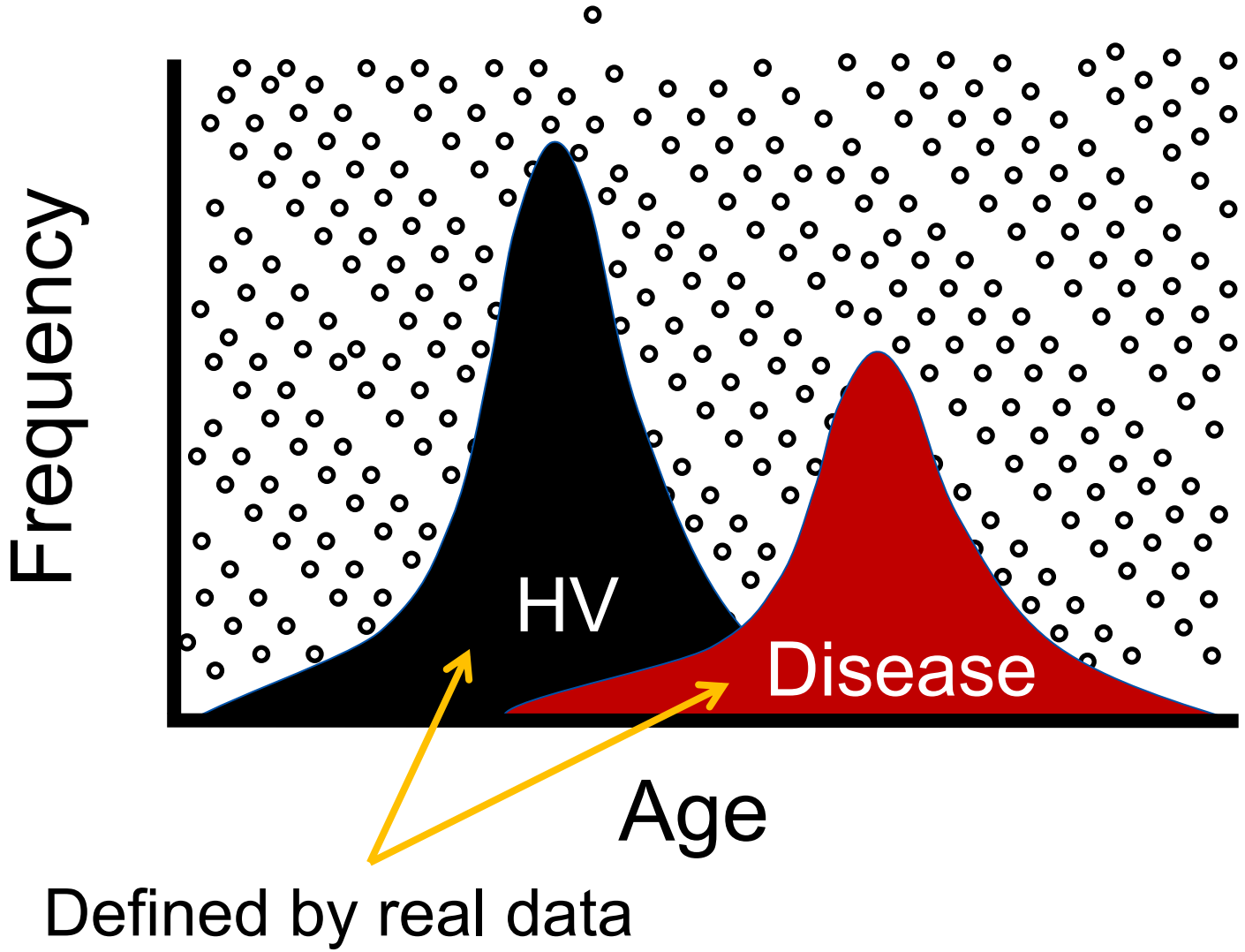
Demographic Features of Healthy and Disease Populations



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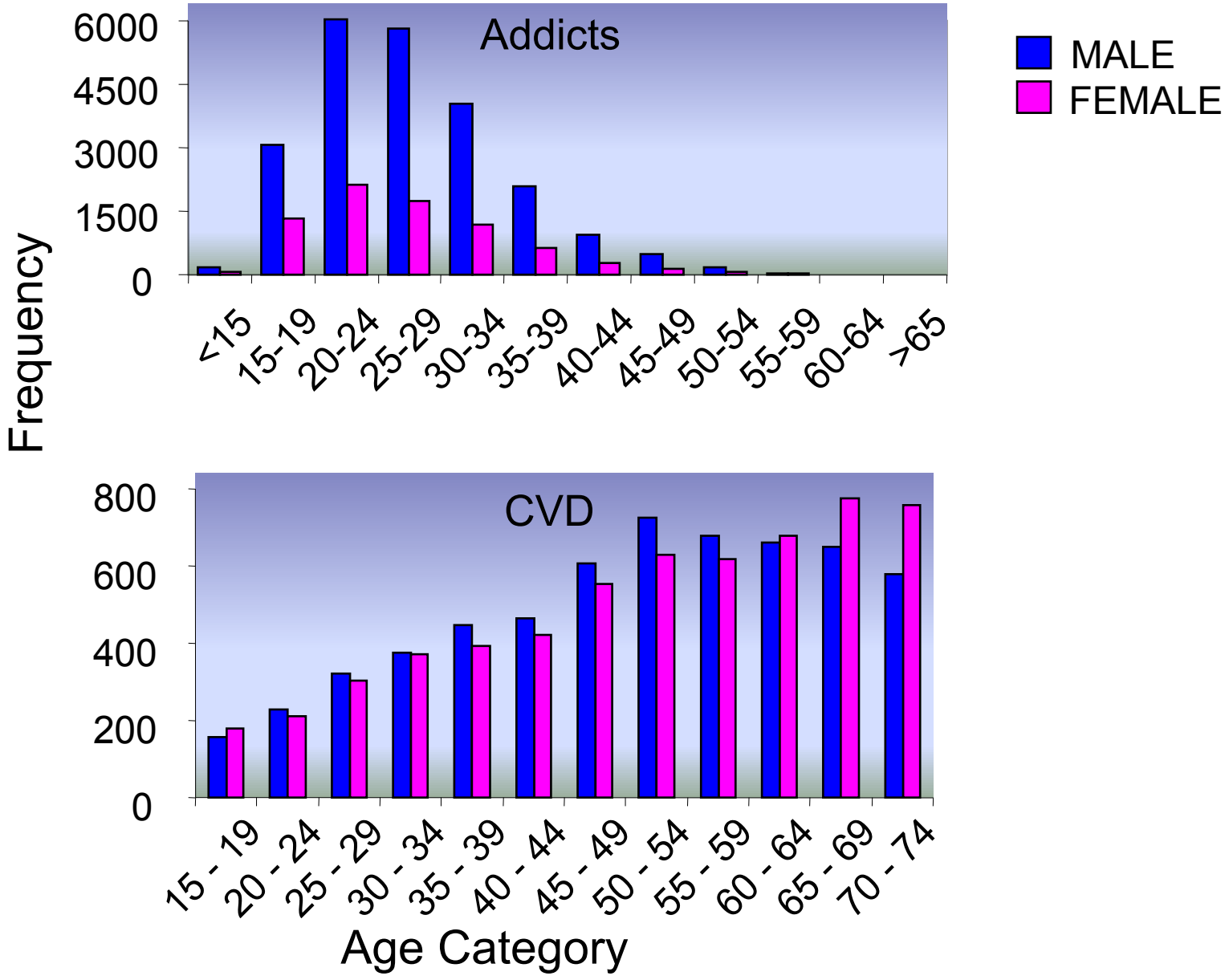
Age Distribution in Target Population



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CLEARANCE: *In Vitro – In Vivo* Extrapolation

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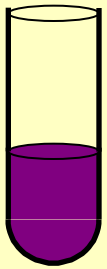
Scaling Factors in Human IVIVE



In vitro system

In vitro CLu_{int}

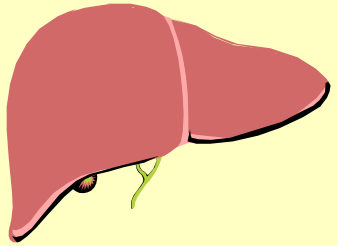
?

Scaling Factor 1

CLu_{int} per g Liver

?

Scaling Factor 2



CLu_{int} per Liver

HHEP	$\frac{\mu L.min^{-1}}{10^6 \text{ cells}}$		X	HPGL	X	Liver Weight
HLM	$\frac{\mu L.min^{-1}}{\text{mg protein}}$		X	MPPGL		
rhCYP	$\frac{\mu L.min^{-1}}{\text{pmol CYP}}$	X	CYP abundance	X	MPPGL	

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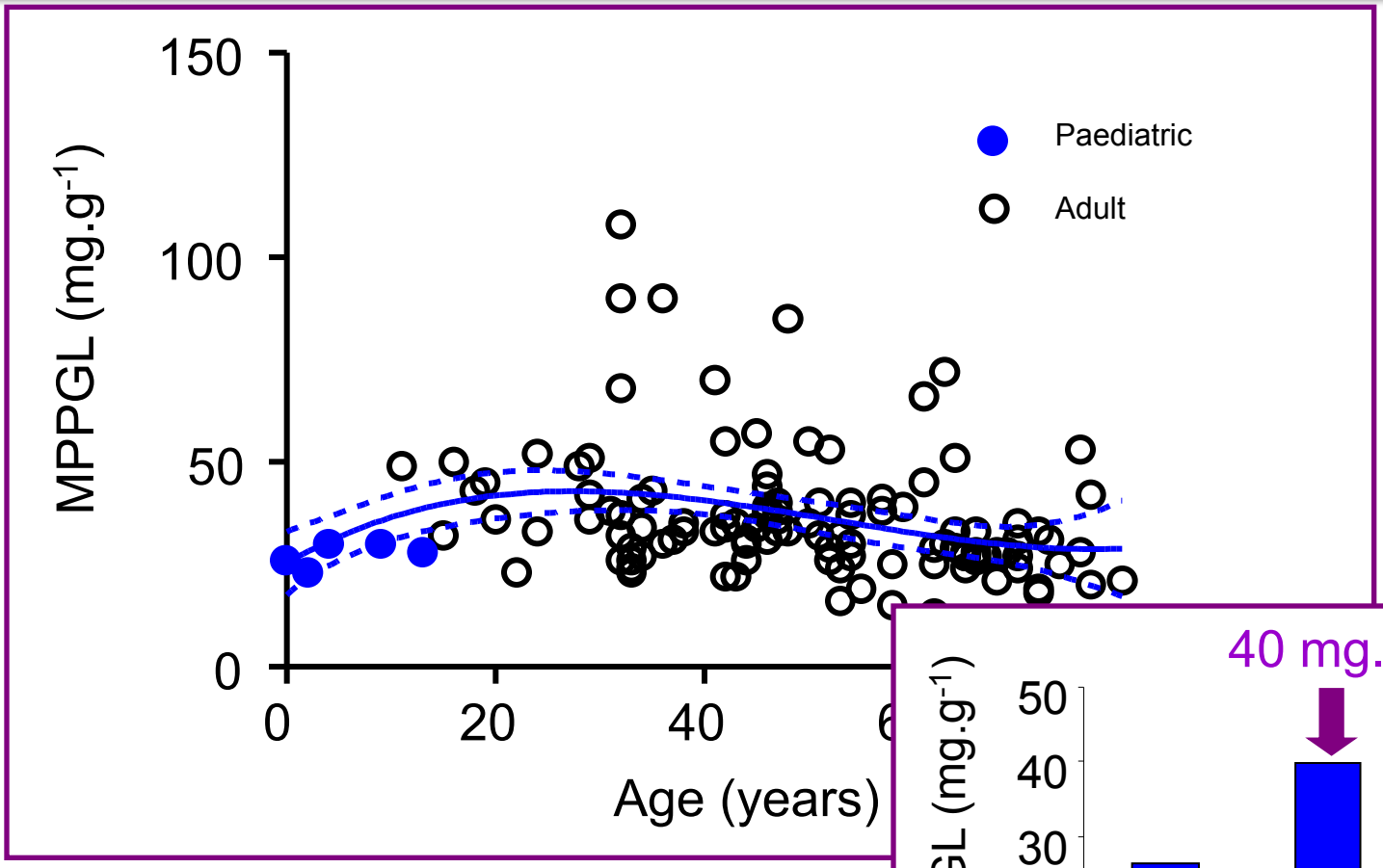
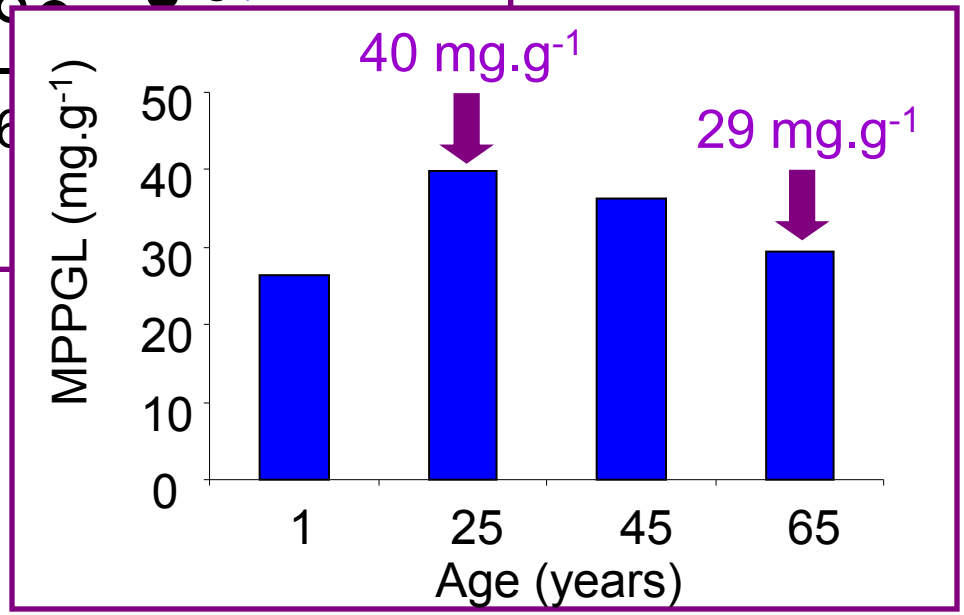
Sources of Variability: MPPGL and Donor Age





Barter *et al*. 2007 Curr Drug Met
Barter *et al*. 2008 Drug Met Disposition

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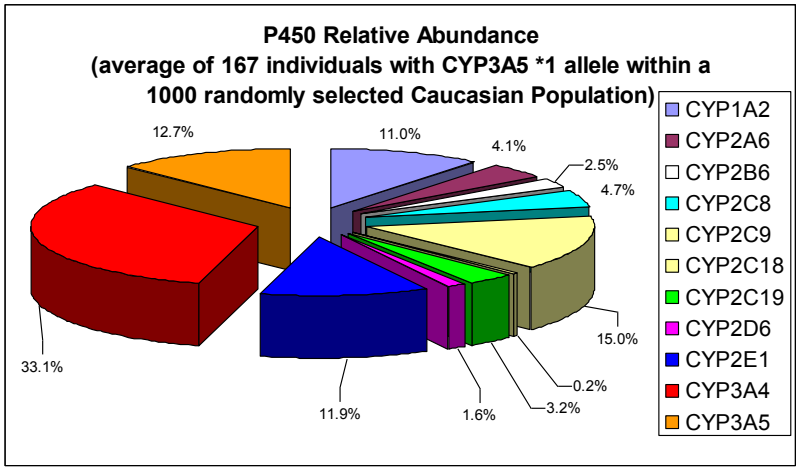
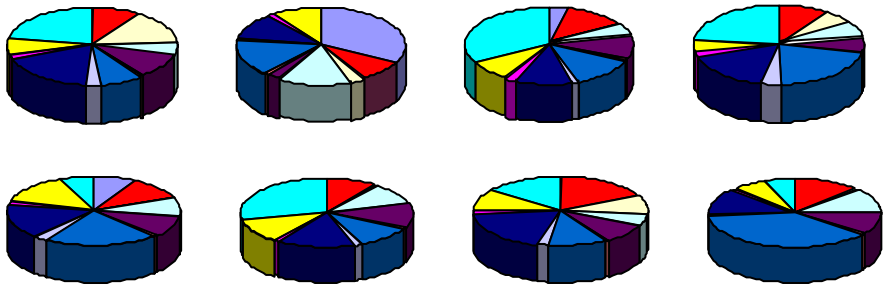
CYP Abundance Variability



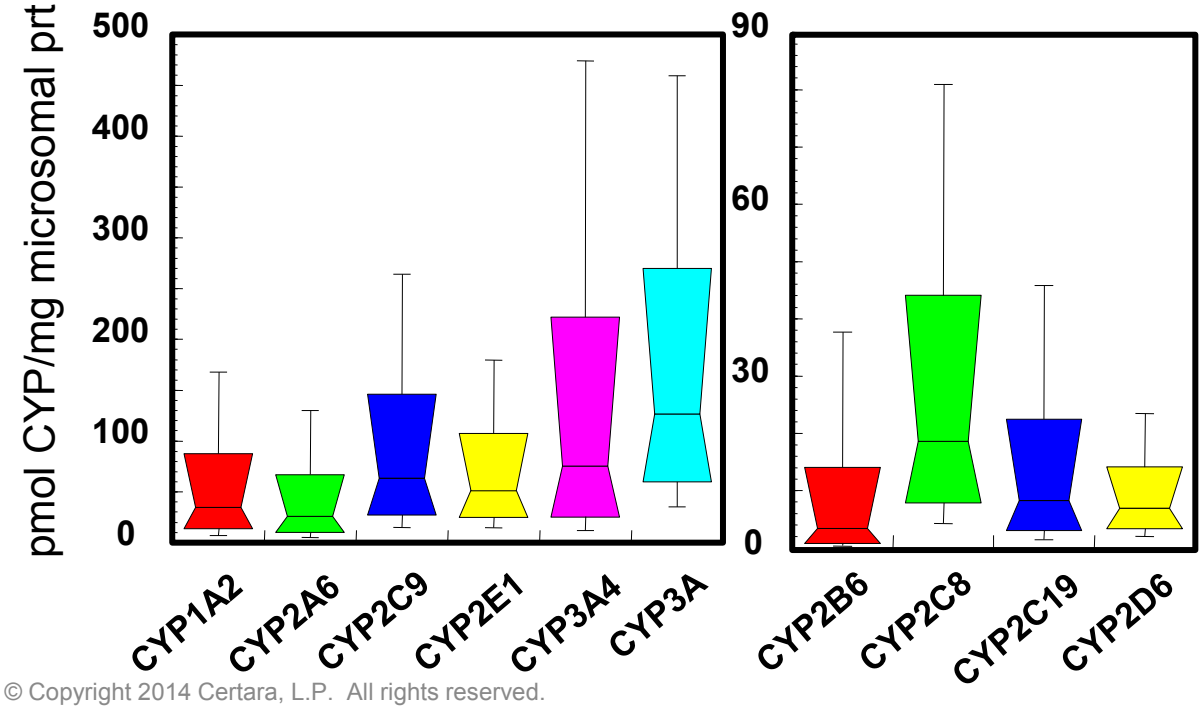


Different Individuals

- Genetics (Ethnicity)

PLUS

-Age (Ontogeny)
- Environment (Ethnicity)
- Sex / Co-medications



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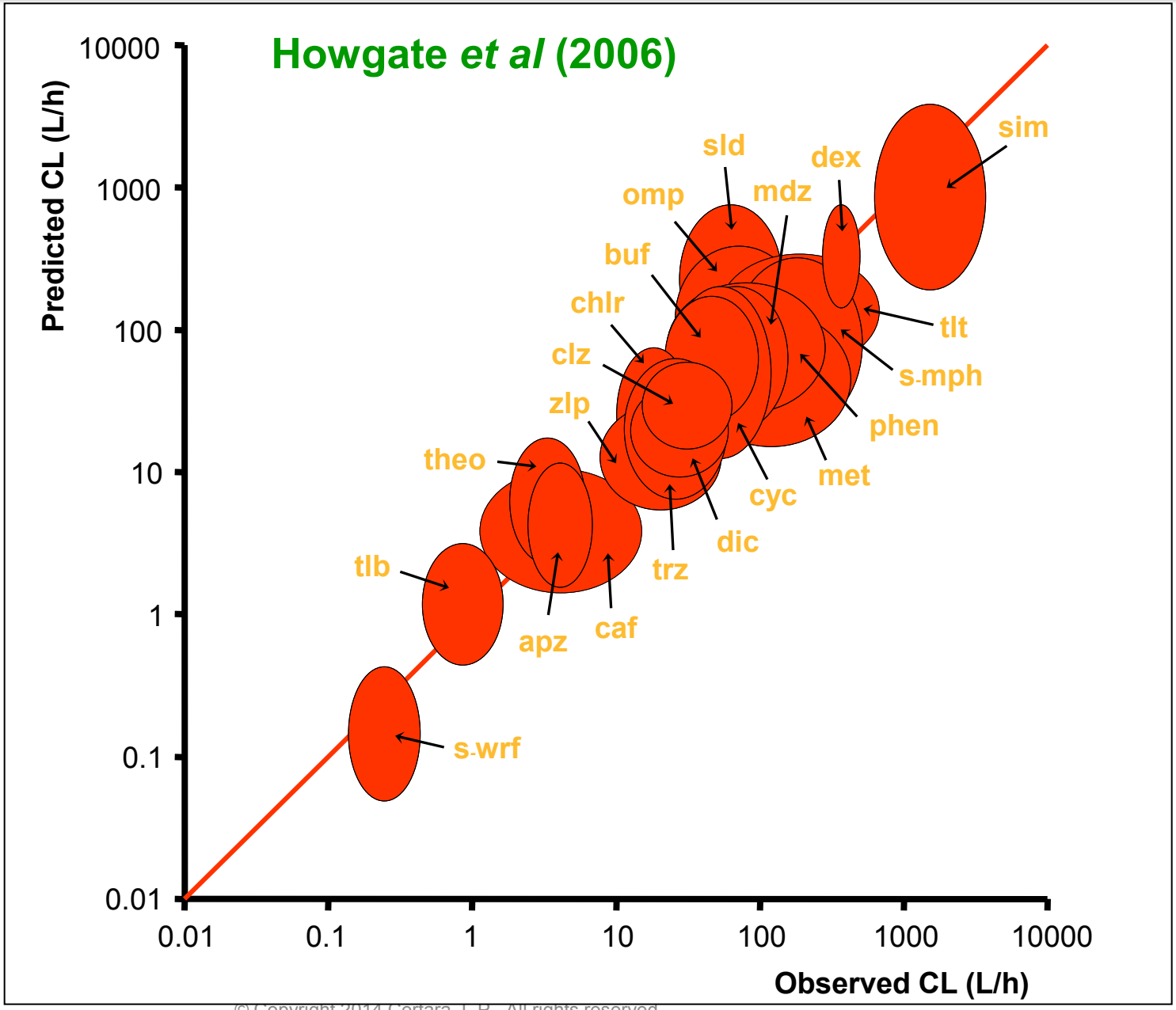
PREDICTION OF CLEARANCE (Oral)

Central tendency

&

Measure of variability



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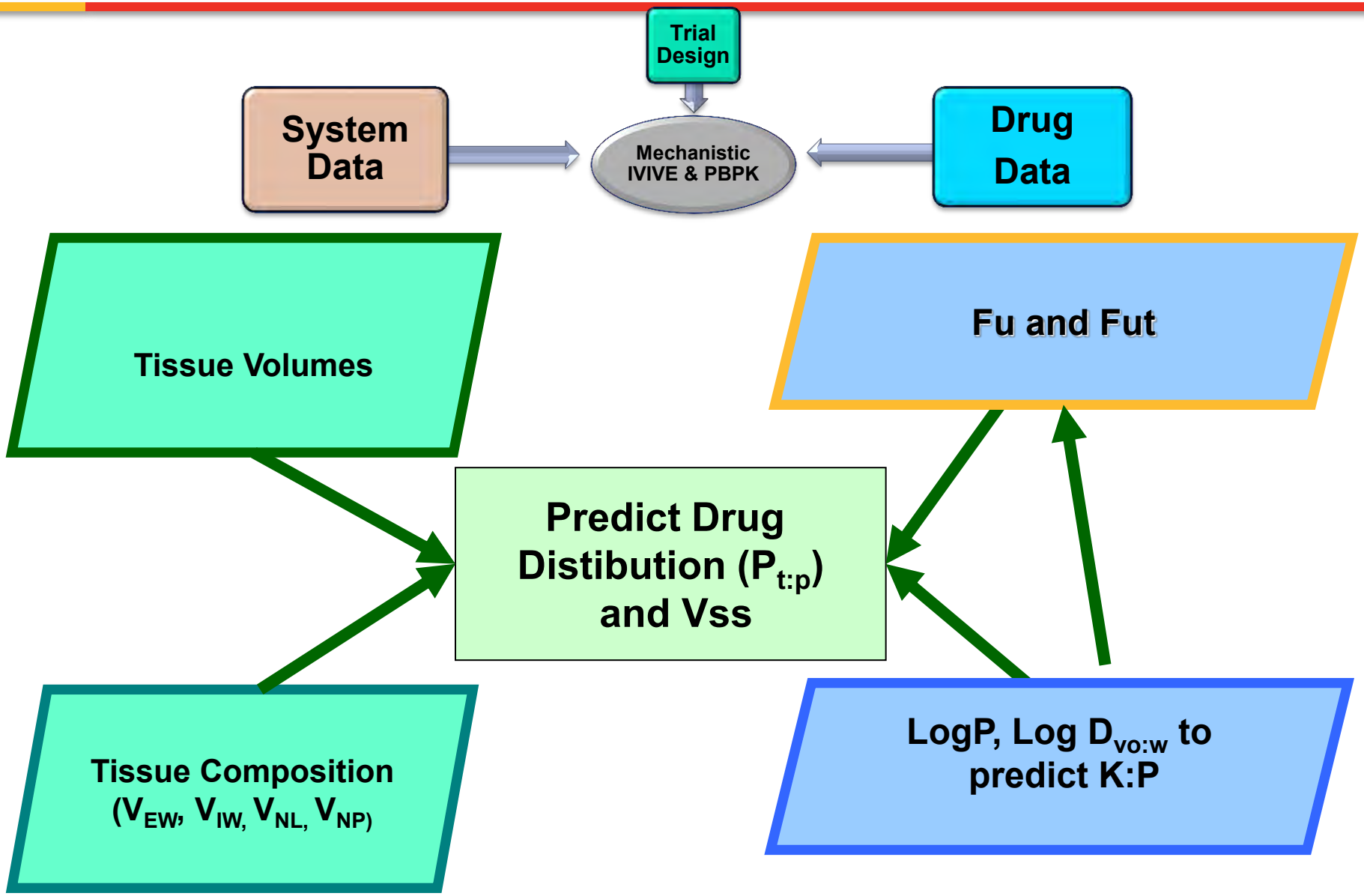
Drug Distribution



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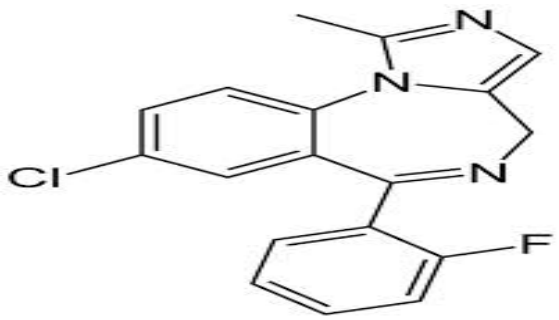
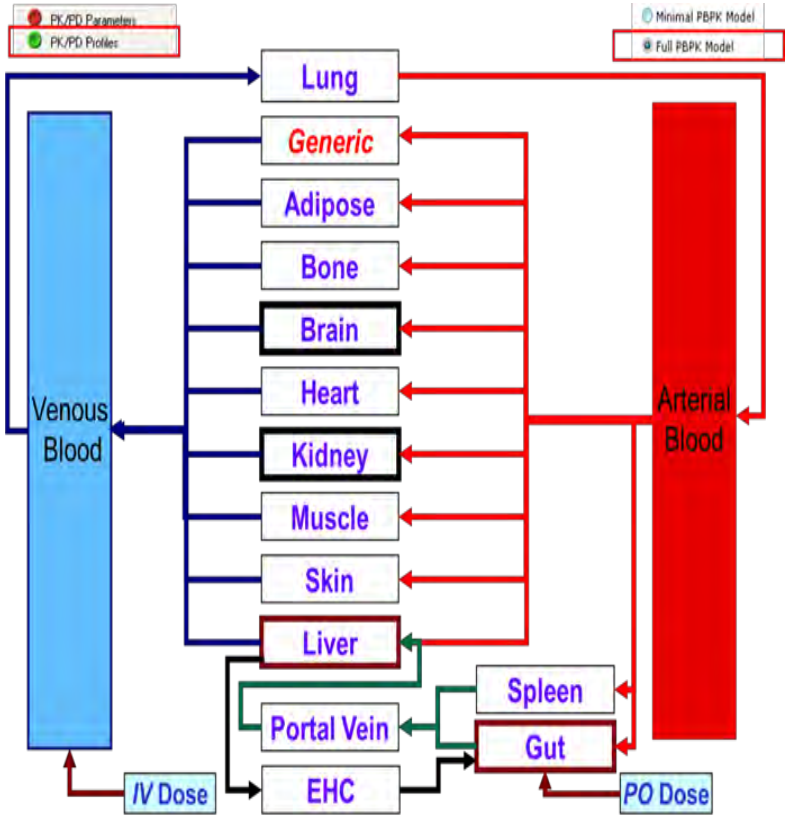
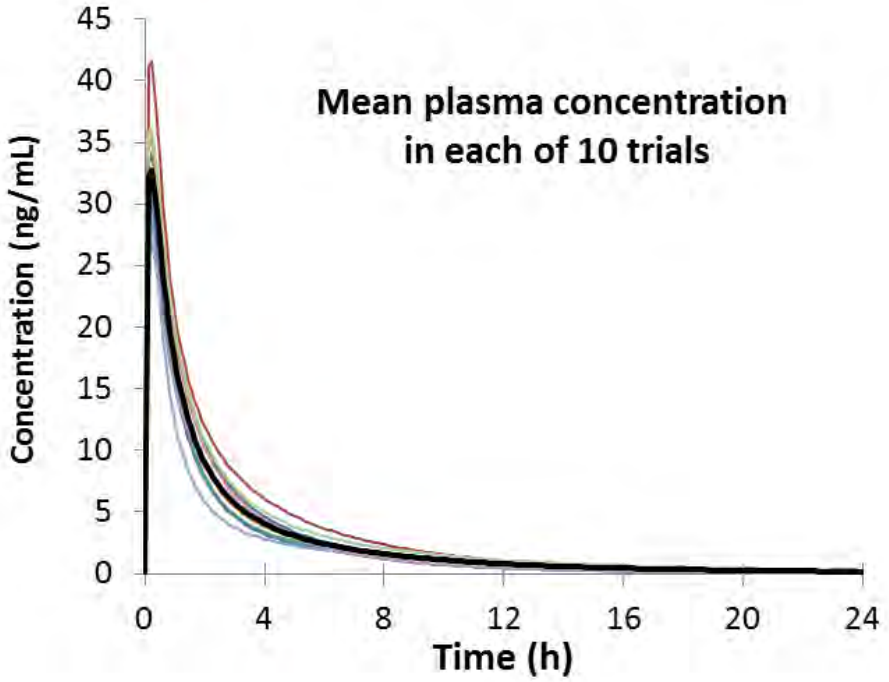
Example: Midazolam pharmacokinetics (simulations in 10 trials of 10 individuals)



Can describe Midazolam Pharmacokinetics using i*n vitro* metabolism data together with systems physiology data





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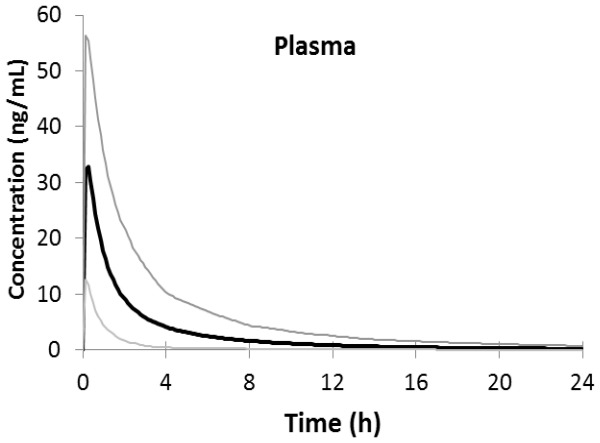
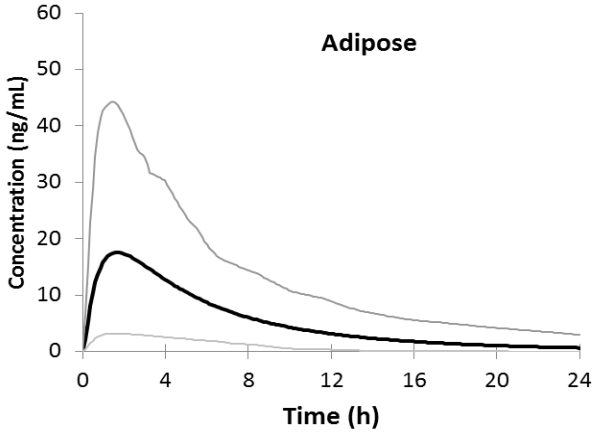
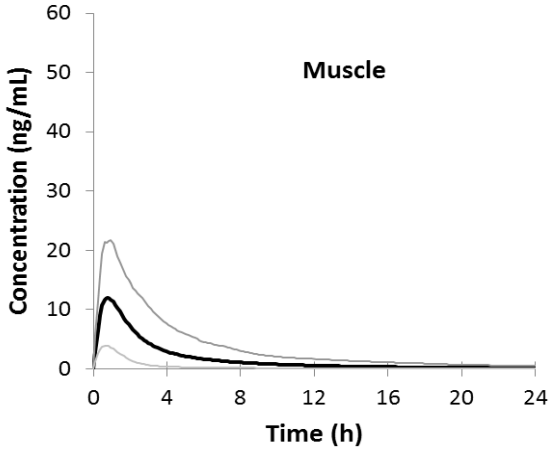
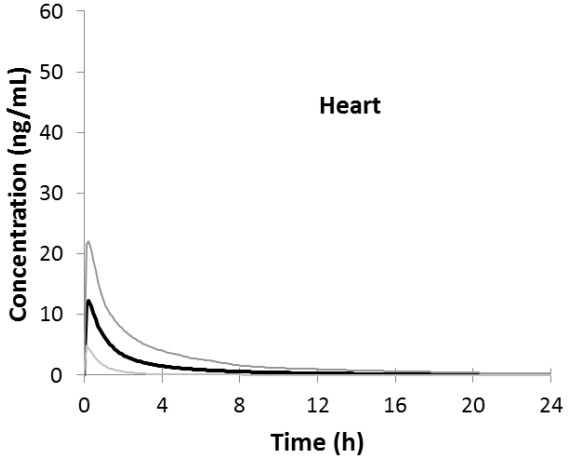
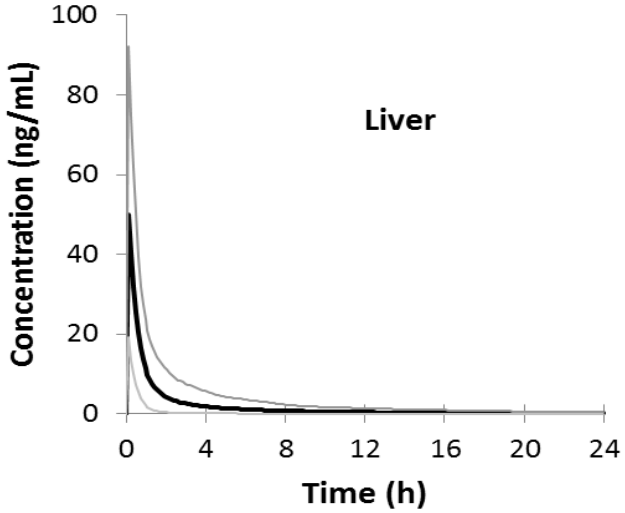
Midazolam Tissue concentrations (mean and 5 and 95 percentiles)











Concentrations in the tissues can also be linked to Pharmacodynamic or Toxicological effects

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Cardiotoxicity

- Cardiac side effects major cause of drug withdrawal (regardless of the development level – from pre-clinical up to the post-approval)
  - E.g. Torsade de points and terfenadine
- Various mechanisms and effects involved
  - pro-arrhythmia, cardiac cell toxicity
- Drug interactions – important element causing serious adverse events
  - E.g. astemizole (CYP related)
- PK variability important for safety assessment
  - E.g. tolterodine (CYP 2D6 mediated metabolism – genetic variability)

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Screening for cardiac safety

- Effects of new compounds on IKR/Herg extensively screened for in drug discovery/development
  - QSAR models
  - IKR binding
  - HERG inhibition
  - Purkinje fiber studies
- Cardiac safety also often investigated in vivo
  - Pre-clinical studies
  - Thorough QT study in humans (~$1000000)

- Can cardiotoxicity also be assessed using mechanistic *in silico* models?

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Links to PD: Assessment of Proarrhythmic Potency

Virtual population generator for human cardiomyocytes parameters: *in silico* drug cardiotoxicity assessment

Toxicology Mechanisms and Methods, 2012

Sebastian Polak[1], Kamil Fijorek[2], Anna Glinka[1], Barbara Wisniowska[1], and Aleksander Mendyk[3]

hERG *in silico* (QSAR) → hERG *in vitro* (measured)

other ion currents *in silico* (QSAR) → other ion currents *in vitro* (measured)

hERG *in vitro* (measured) + other ion currents *in vitro* (measured) → HUMAN HEART LEFT VENTRICULAR CELL MODEL

HUMAN HEART LEFT VENTRICULAR CELL MODEL → action potential (APD90) → pseudoECG (QTc)

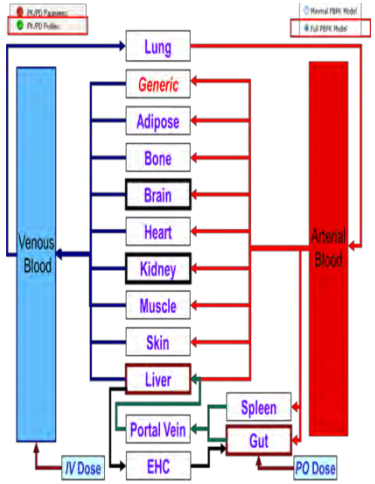
HUMAN HEART LEFT VENTRICULAR CELL MODEL → contractility → electro-mechanical window

HUMAN HEART LEFT VENTRICULAR CELL MODEL → cell metabolism → cell viability

multiple drugs

virtual population

- demography
- physiology
- genetics



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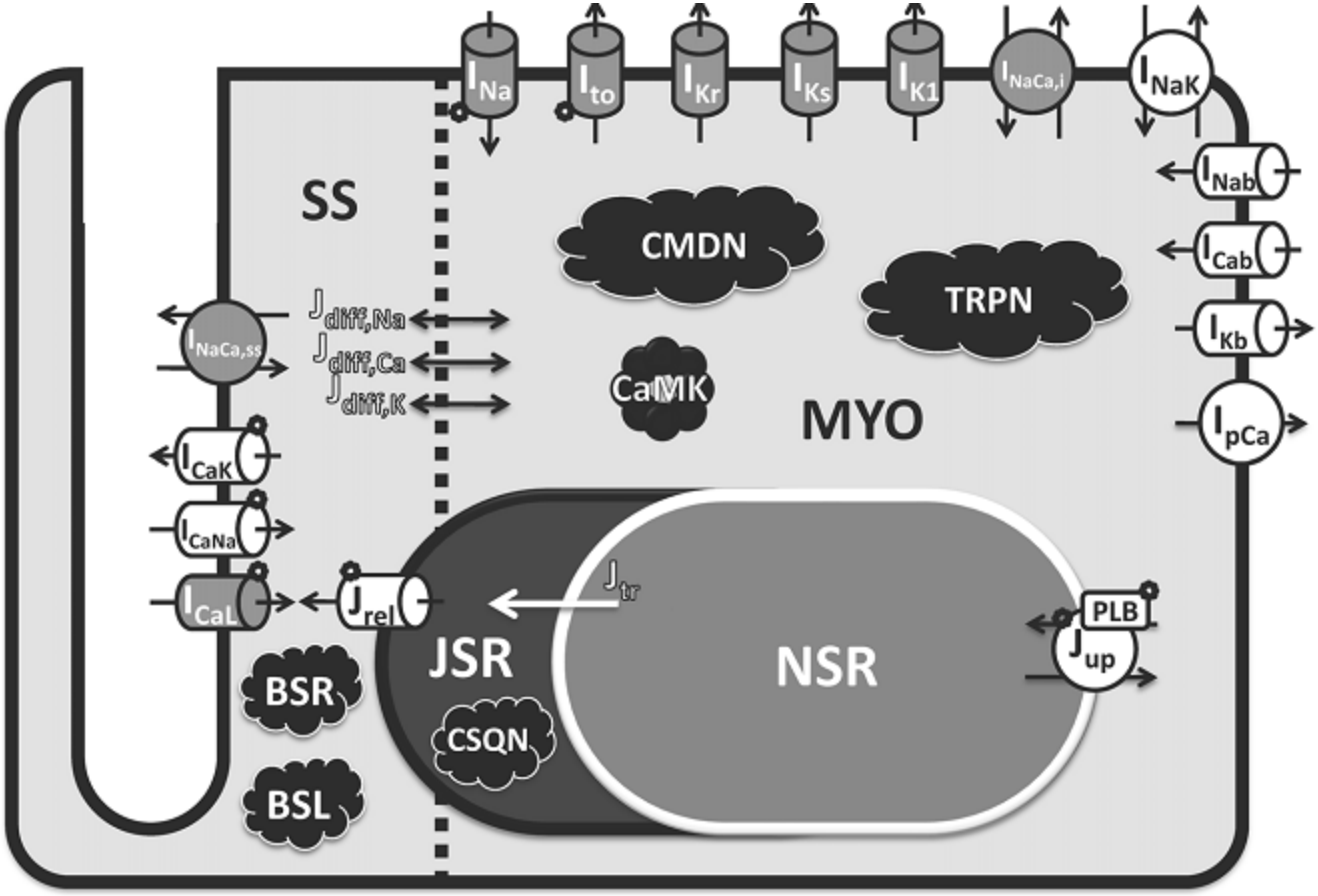
Structure of left ventricular cell model

- molecular structure ——> QTc prolongation/TdP
  - mechanistic/physiological

$$\frac{dV}{dt} = \frac{I_{ion} + I_{stim}}{C_m}$$

HUMAN HEART LEFT VENTRICULAR CELL MODEL



O'Hara and Rudy *PLoS computational Biology* 7, 2011
Ten Tusscher et al. *AmJPhys-HeartPhys* 286, 2004

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Variability matters

- Clinical evidence

Group	Parameter	Influence on ECG	Reference
Demography	age	↑ age - ↑ QT/QTc	Pham 2002
	gender	Females have longer QT/QTc as compared to males.	James 2007
Anatomy/ physiology	plasma ions concentration (K^+, Ca^{2+})	↑ K^+ - ↓ QT/QTc ↑ Ca^{2+} - ↓ QT/QTc	Etheridge 2003 Covis 2002
	cardiomyocyte size (volume, area)	↑ size - ↑ QT/QTc	Pacifico 2003
	heart wall thickness	↑ thickness - ↑ QT/QTc	Jouven 2002
	cells heterogeneity across heart wall	M cells presence influence the T wave and ECG in general.	Antzelevitch 2010
	heart rate	↑ RR - ↑ QT	Harris 2003 Malik 2002
	sex hormones	↑ testosterone - ↓ QT/QTc ↑ progesterone - ↓ QT/QTc	Pham 2002 Sedlak 2012
Genetics	common polymorphisms (ion channels)	Usually slight modification of ECG, may act as a genetic modifier (with different mutation both protective effect and QTc prolongation were observed).	Crotti 2005
	mutations (ion channels)	↑ QT/QTc	Etheridge 2003 McPate 2005

Polak 2013 DDT accepted

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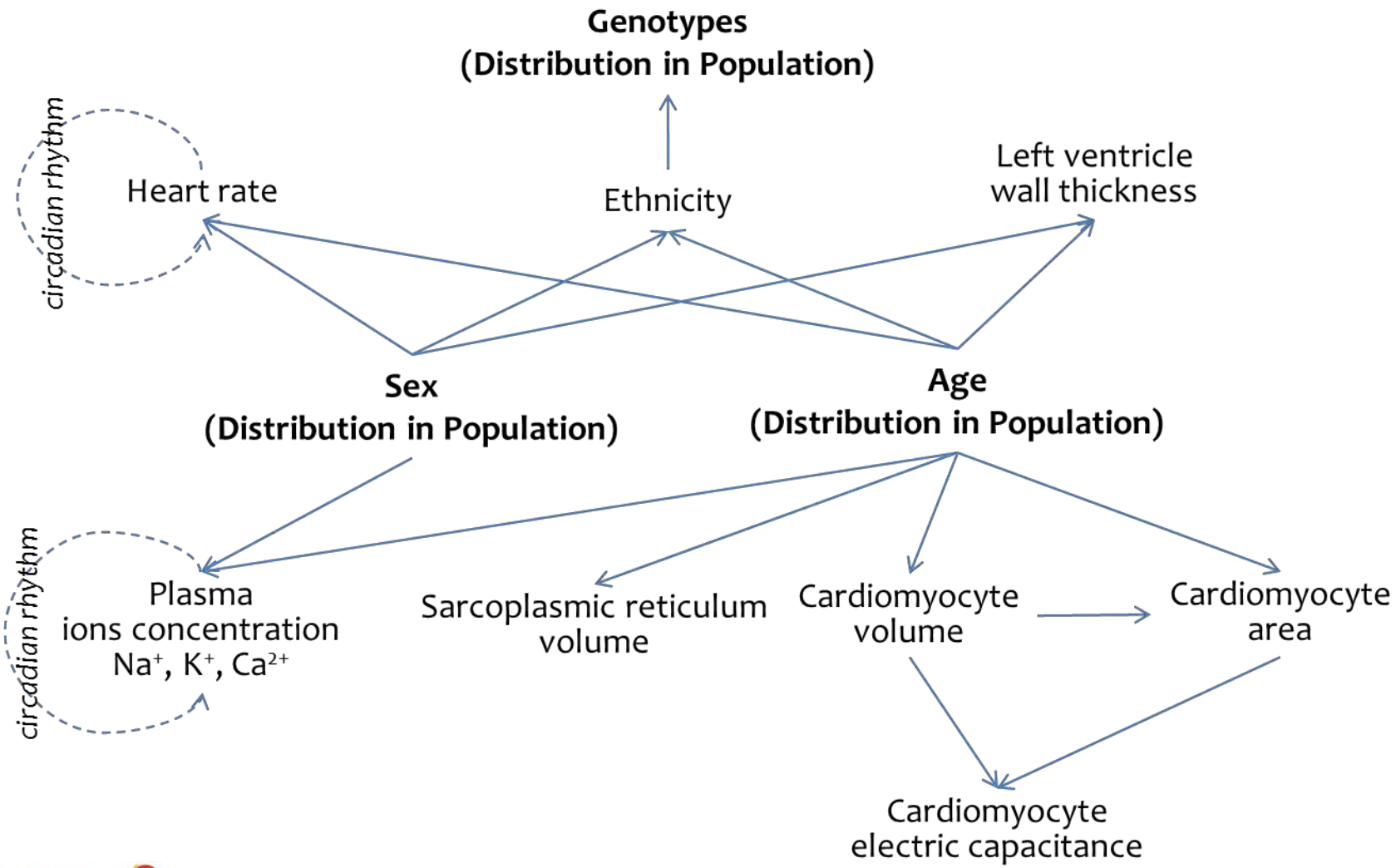
Building virtual populations – cardiac safety assessment



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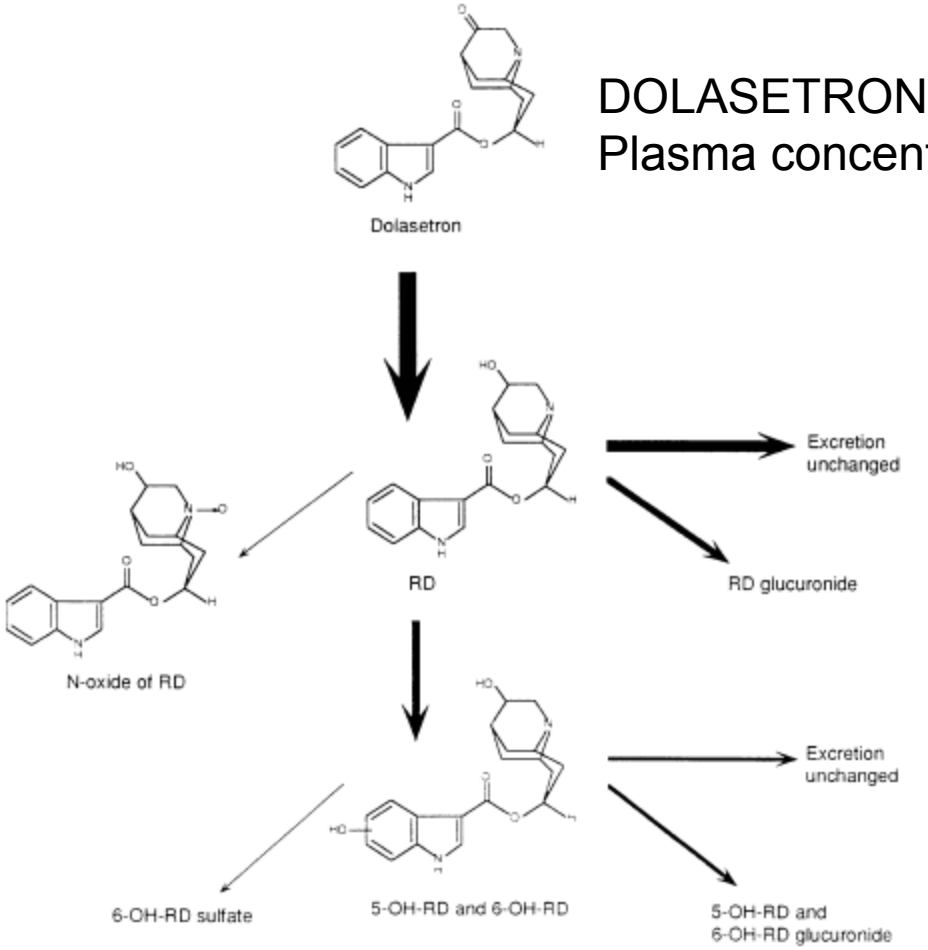
Example 1: Dolasetron – formulation dependent effect



DOLASETRON – CARDIOLOGICALLY ACTIVE
Plasma concentration negligible after po dosing

iv formulations – withdrawn from the market due to the TdP reports

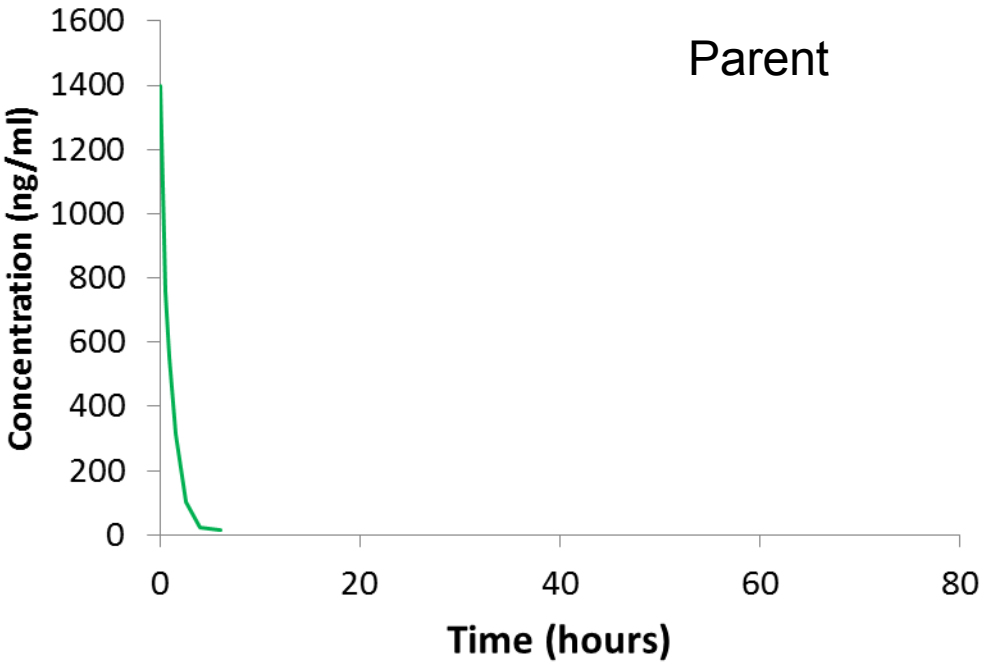
po formulation – considered as safe

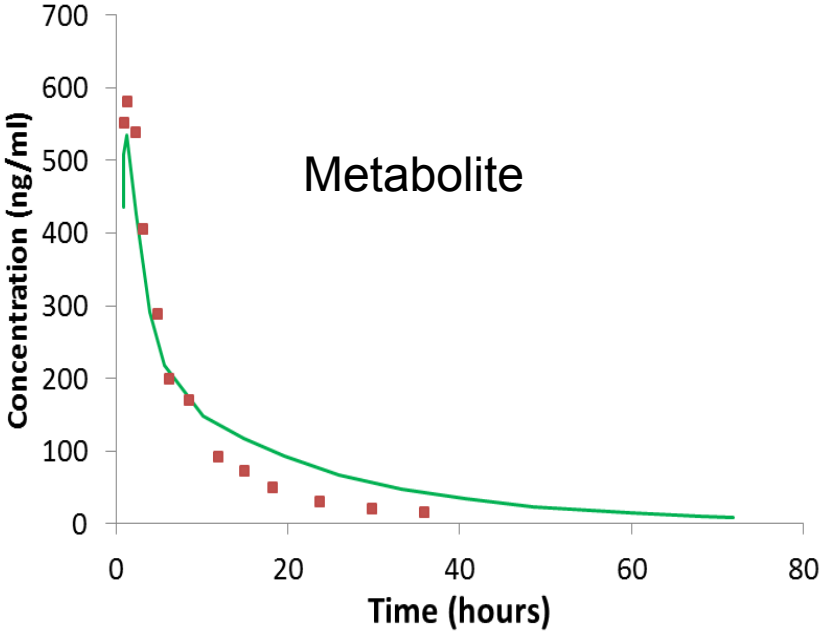
Example 1: Dolasetron – Simcyp PK prediction

iv 2.4 mg/kg

Dolasetron

Hydrodolasetron





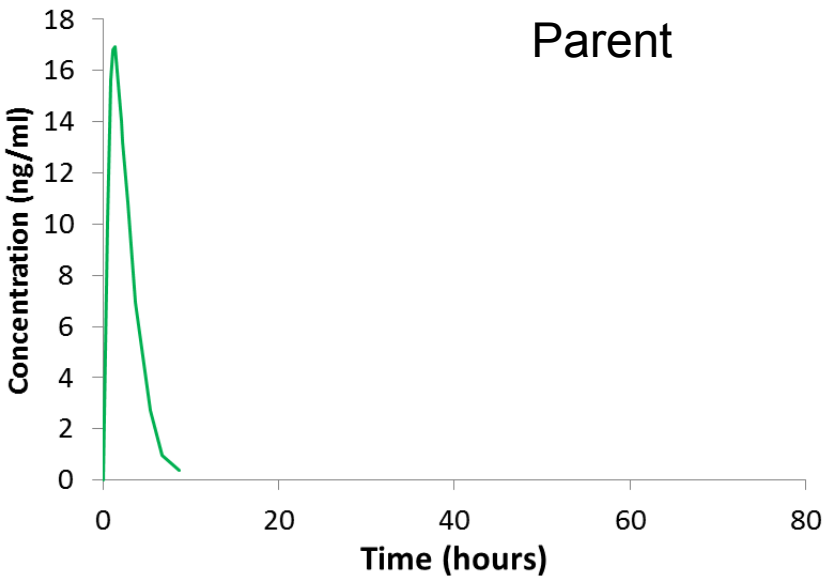
Dempsey 1996

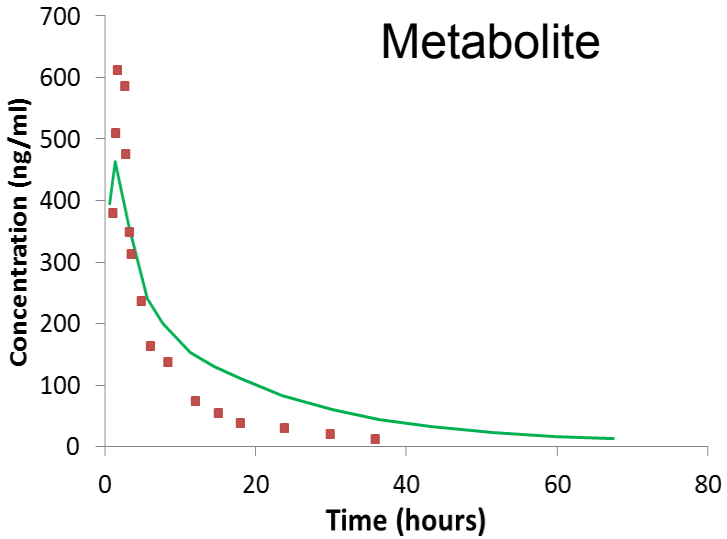
Example 1: Dolasetron – Simcyp PK prediction

po 2.4 mg/kg

Dolasetron

Hydrodolasetron

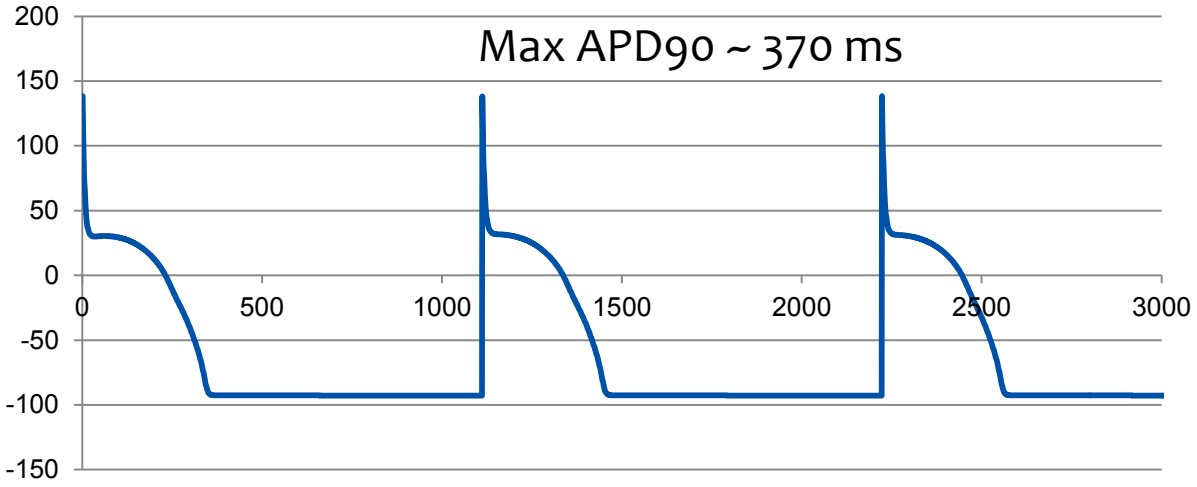




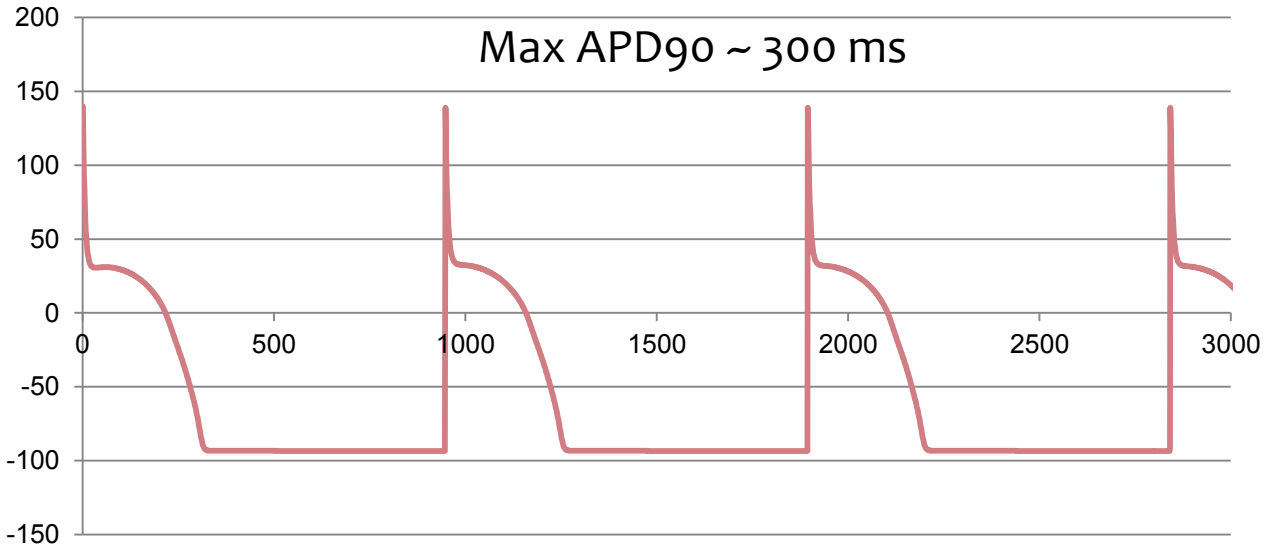
Dempsey 1996

Example 1: Dolasetron – CSS PD effect prediction

iv 2.4 mg/kg

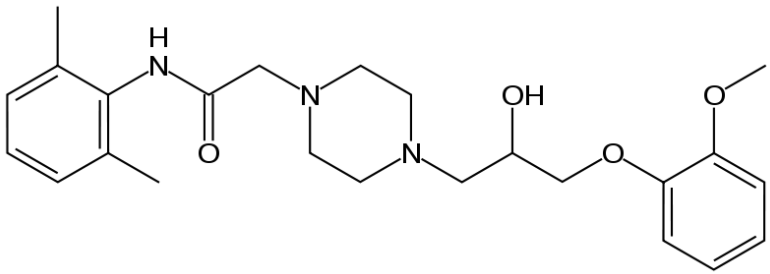


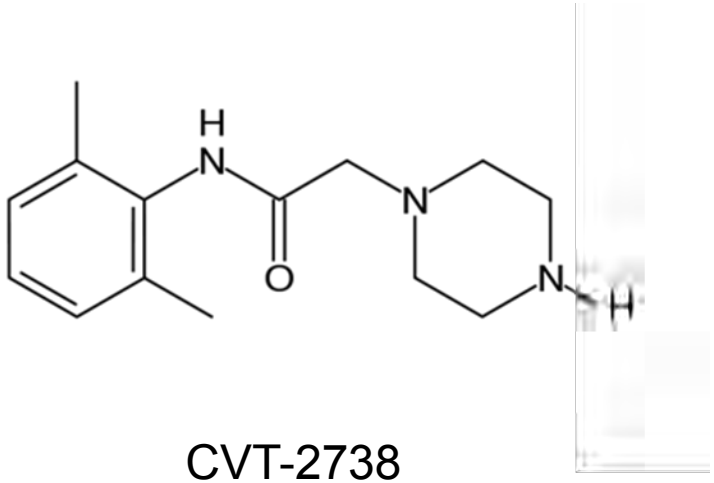
po 2.4 mg/kg



Dempsey 1996

Example 2 – Ranolazine: IVIVE at the population level





CVT-2738

Ranolazine

- I_{Kr} inhibitor (*in vitro*)
- multiple other ionic currents inhibition (*in vitro*)
- pharmacologically/electrically active metabolites
- clinically – large variability

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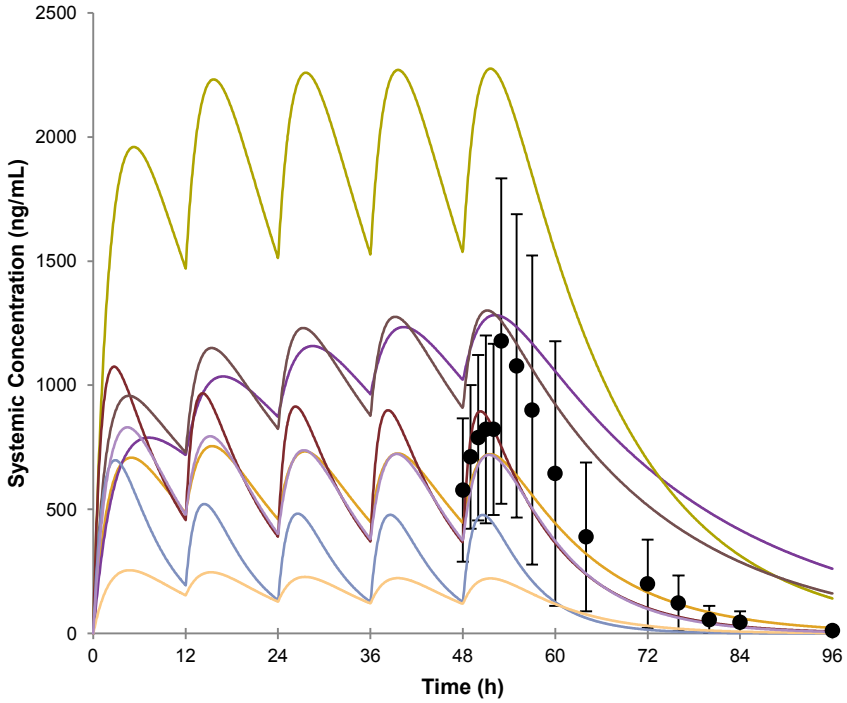
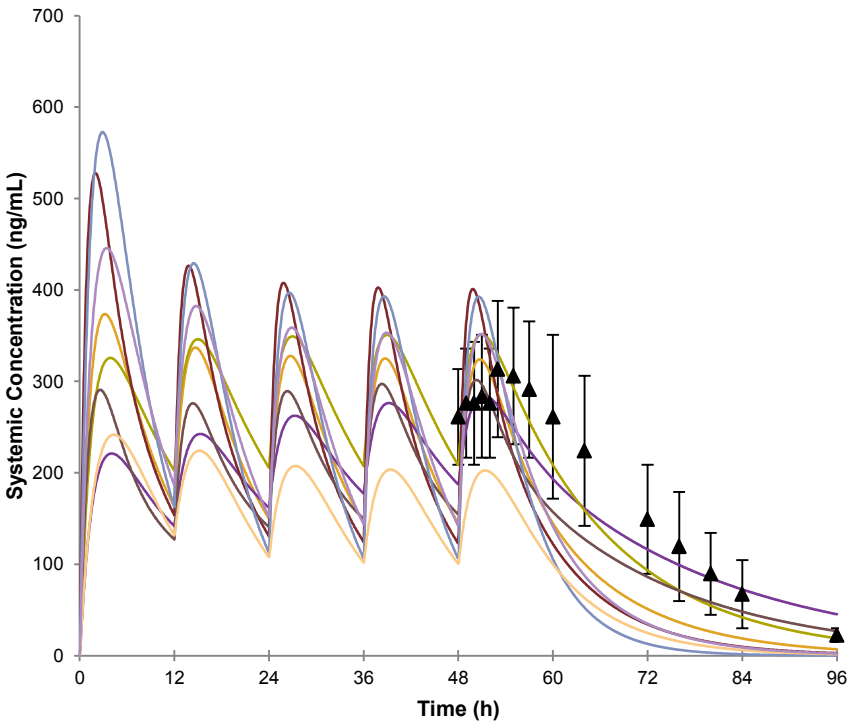
Ranolazine and CVT-2738 plasma concentrations

Ranolazine



CVT-2738



Reasonable description of the plasma concentrations after multiple dosing

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Electrophysiology inputs to the model

Ionic current	Ranolazine [IC_{50}]/n	Source	CVT-2738 [IC_{50}]	Source
I_{Kr}	12/1	Measured	1.19	QSAR predicted
I_{Ks}	1900/1	Measured	-	
I_{Ca}	311/1	Measured	26.38	QSAR predicted
$I_{Na\ peak}$	428/1.63	Measured	-	-
$I_{Na\ late}$	6.86/0.71	Measured		

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PRO-ARRHYTHMIC POTENCY - IVIVE at the population level - RESULTS

OBSERVED

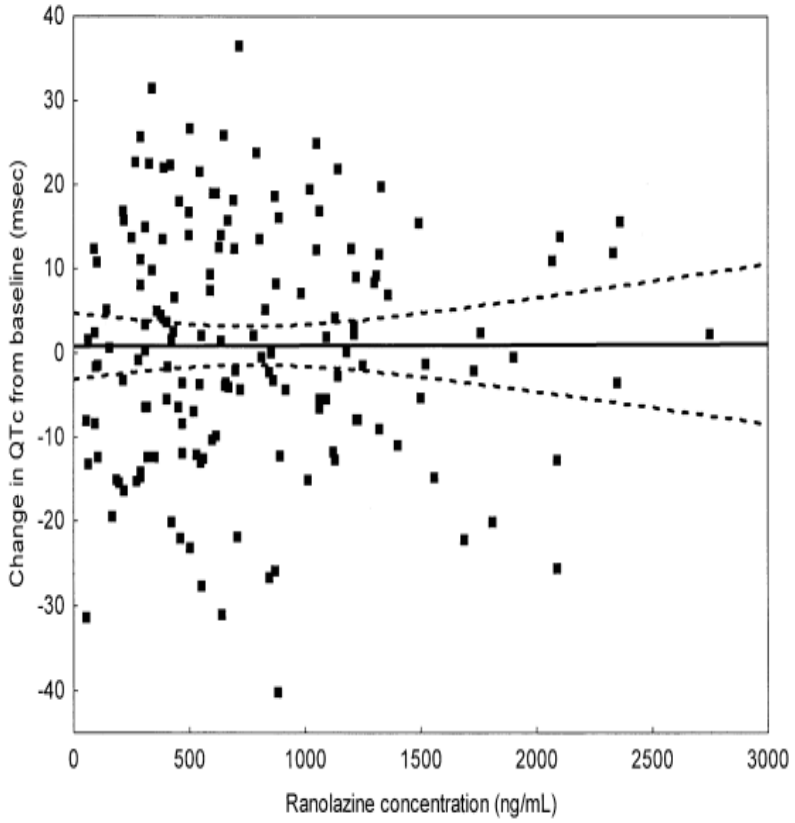
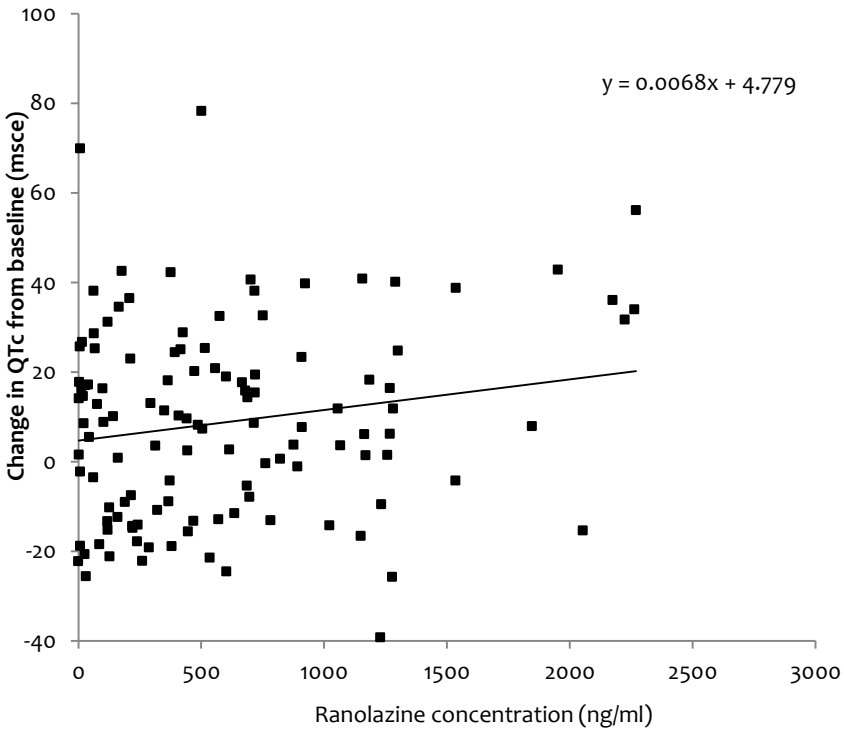


Fig 4. Change in QTc from time-matched baseline values versus ranolazine plasma concentration in healthy control subjects. Linear regression with 95% CI was as follows: $\Delta QTc = 0.82 + 8 \times 10^{-5} \times$ Ranolazine concentration ($R^2 < 0.001$, $P = 0.97$ for slope [95% CI, −0.004 to 0.004]).

PREDICTED



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Summary

- Using extrapolated *in vitro* data coupled with PBPK models it is possible to simulate the pharmacokinetics of many drugs
- By incorporating known physiological co-variates it is possible to make simulations in virtual populations rather than an “average” individual
- Concentrations of drugs in tissue compartments of the PBPK model can be linked to mechanistic models to predict side effects/toxicity
- Physiological variability can also be included within the toxicity models

- Acknowledgements
  - Sebastian Polak, Amin Rostami

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