Mechanistic Modeling and Simulation of Oral Drug Absorption: *Opportunities and Challenges*

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Outline

IVIV_E-Linked PBPK absorption modelling

Physiologically-based IVIVC (PB-IVIVC)

Bioequivalence and PBPK modelling

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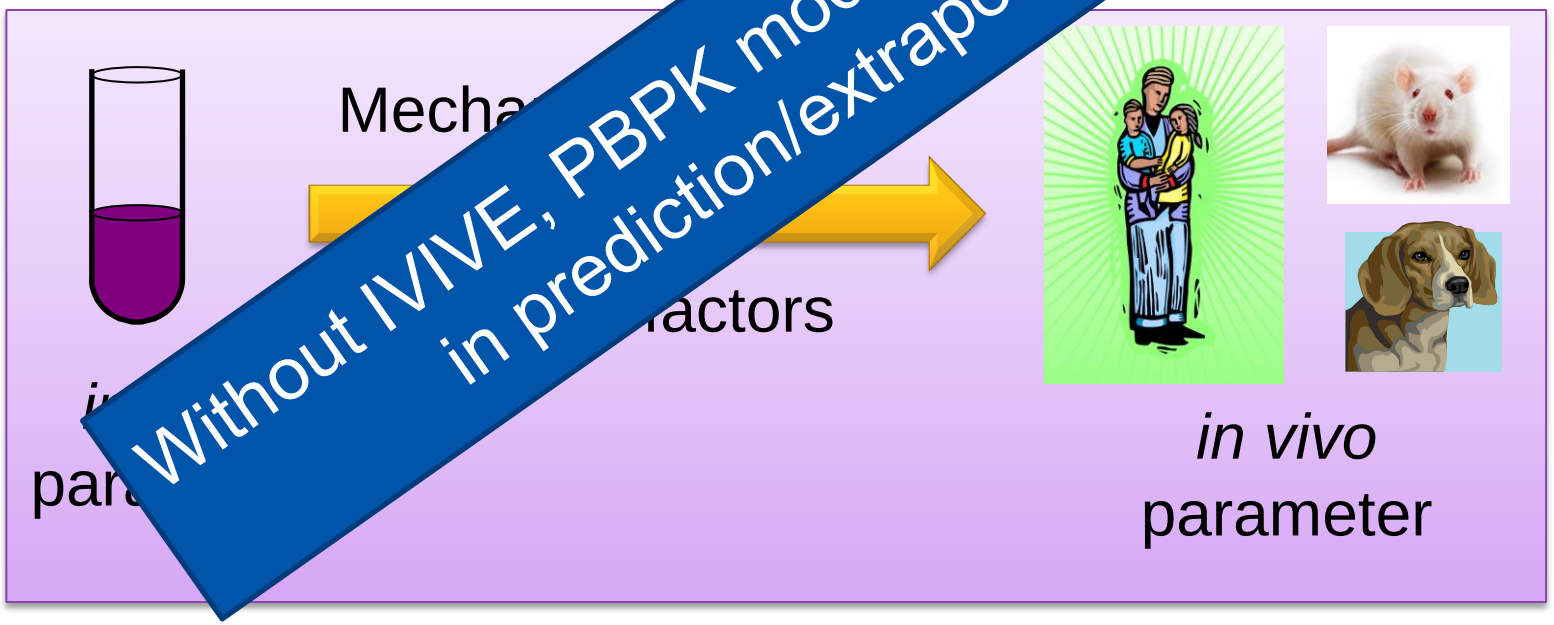
IVIVE-Linked PBPK approach

STATE OF THE ART

Physiologically Based Pharmacokine
Joined With *In Vitro–In Vivo* Extrap
ADME: A Marriage Under the A
Pharmacology

A Rostami-Hodjegan[1,2]

Without IVIVE, PBPK models are very limited in prediction/extrapolation!

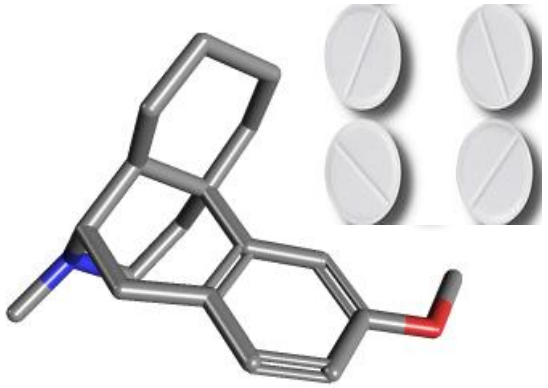


Rostami-Hodjegan, CPT, 2012

Systems pharmacology paradigm – Separation of system/drug data

Systems Data | Trial Design | Drug Data

Dose
Administration route
Frequency
Co-administered drugs
Populations
No of male/female



Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

Jamei, Current Pharmacology Reports, (in press)

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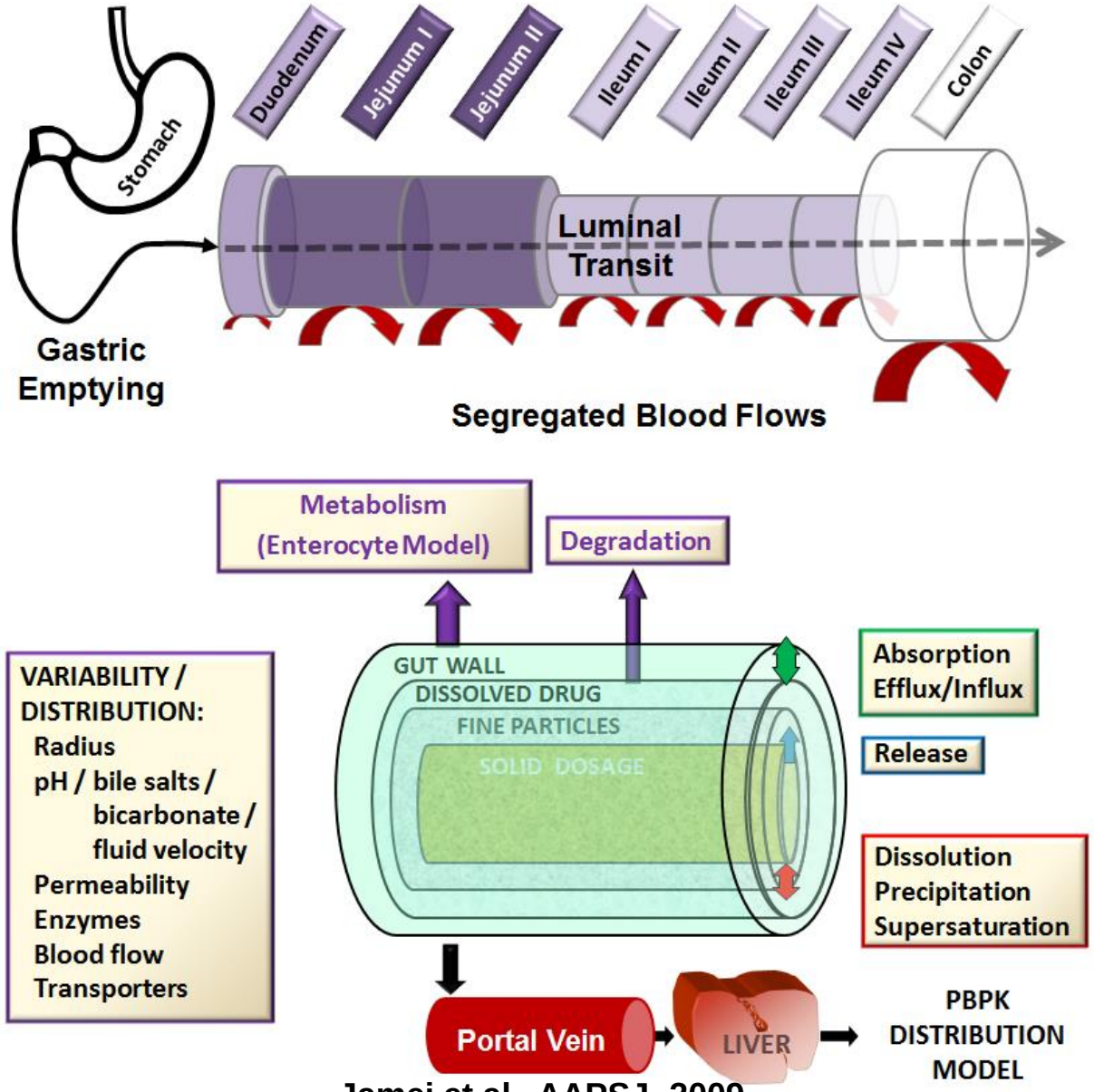
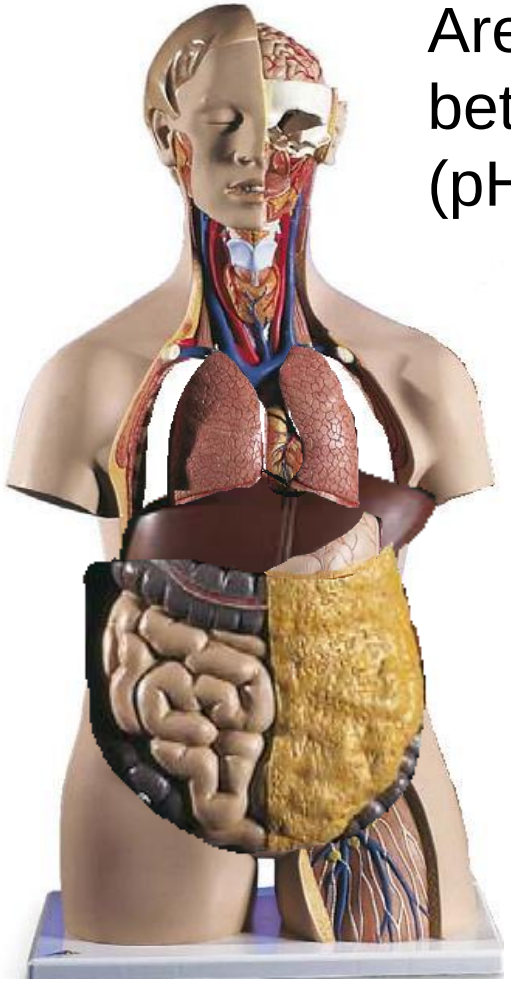
A mechanistic absorption framework (ADAM model)



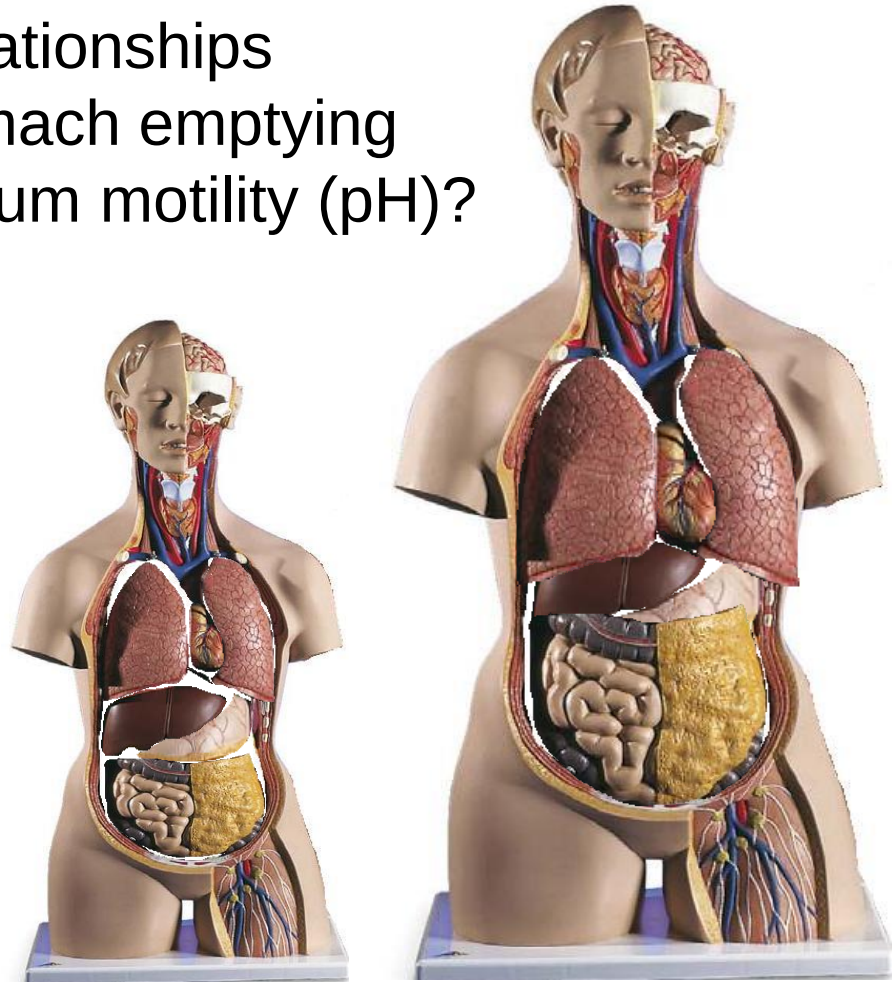
Jamei et al., AAPSJ, 2009

Monte Carlo (MC) *vs.* Correlated Monte Carlo (CMC)

Are there any relationships between the stomach emptying (pH) and duodenum motility (pH)?



A randomly generated subject using MC sampling



Randomly generated subjects using CMC sampling

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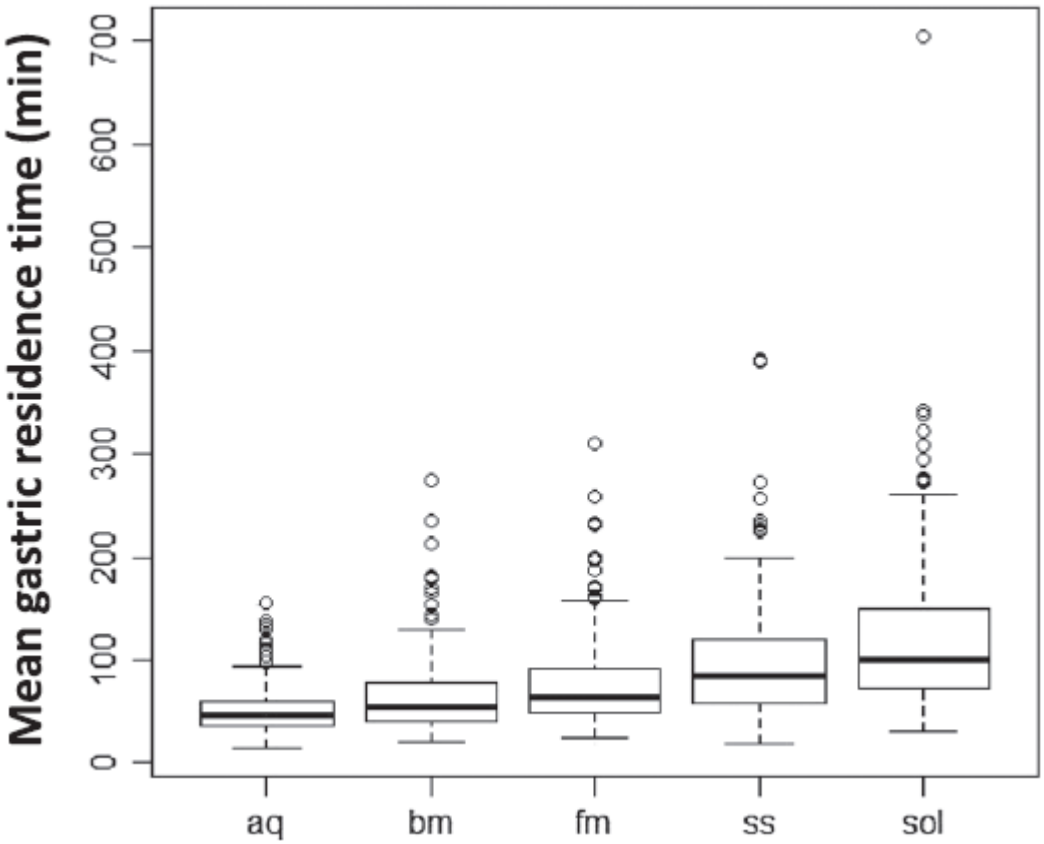
Gastric emptying changes with age?



Bonner et al., BDD, 2015

aq: aqueous solution
bm: breast milk
fm: formula
ss: semi-solid meal
sol: solid meal

Age was not a significant covariate for gastric emptying but meal type was. Aqueous solutions were associated with the fastest emptying time (mean simulated gastric residence time of 45min) and solid food was associated with the slowest (98 min).

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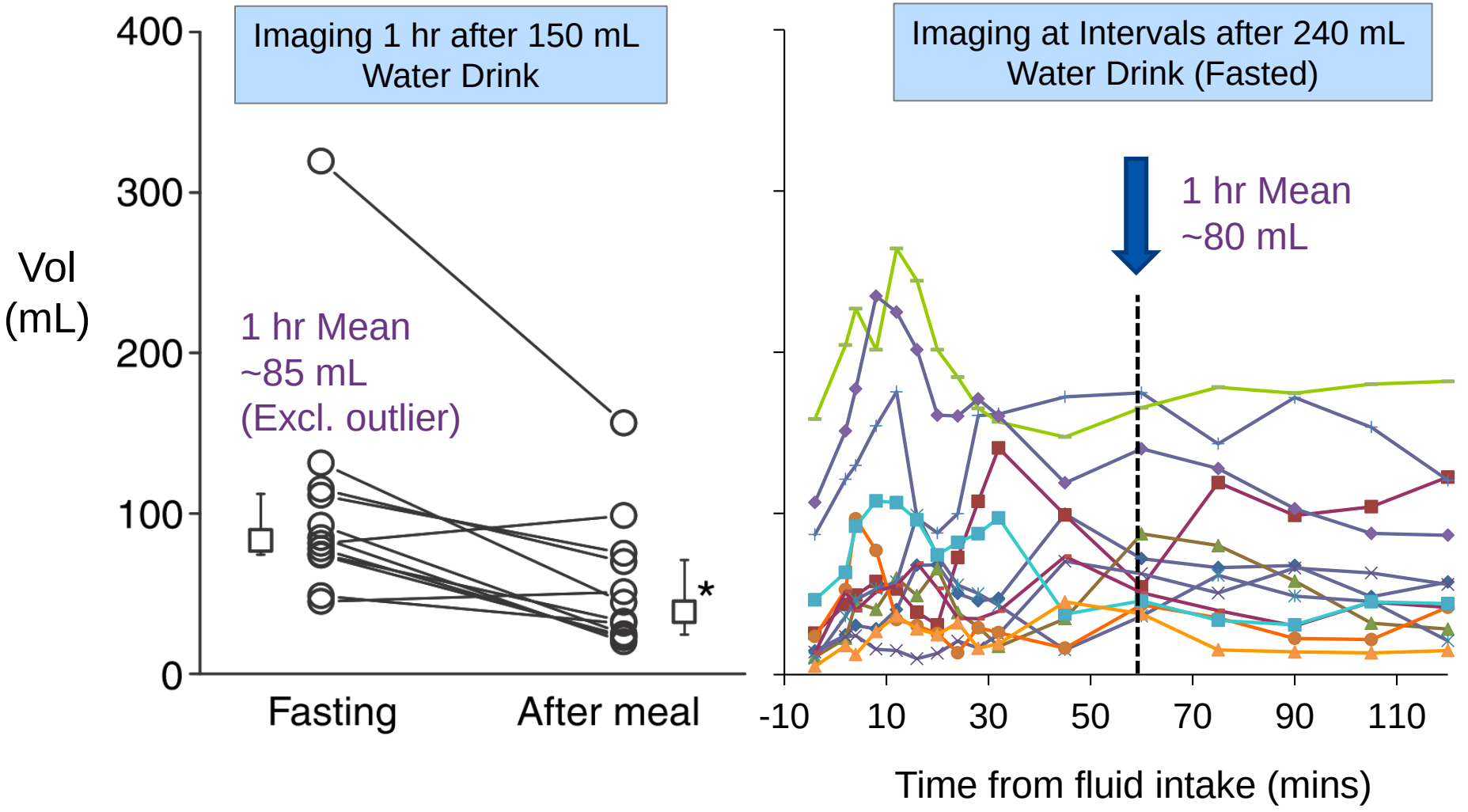
Luminal fluid volumes and dynamics from MRI studies

Total Small Bowel Water Volumes



* Schiller, Weitschies et al. 2005

* Mudie, Marciani et al. 2014 with permission

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Luminal water fluid dynamics

- In reality luminal water fluid is dynamically changing
- Considering this dynamic assists with:
  - Handling variability in water taken with dose
  - Dynamic dilution of food and viscosity
  - Accounting for molecular/micellar diffusivity
  - Particle dissolution
  - Disintegration
  - Supersaturation / Precipitation

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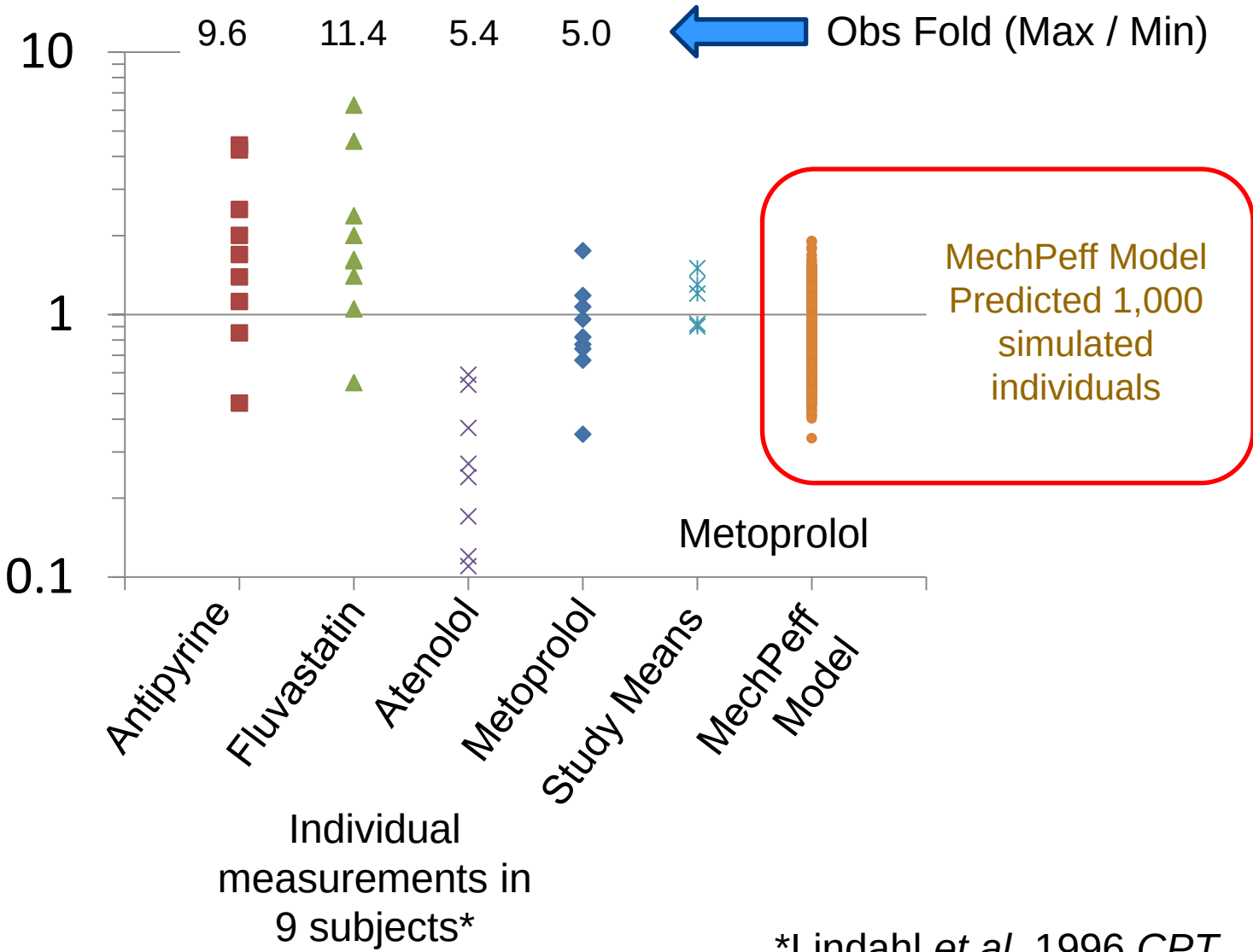
Embracing Variability: Gut Wall Permeability

Exp. Loc-I-gut Human Jejunal P_{eff} *(10^{-4} cm/s)*

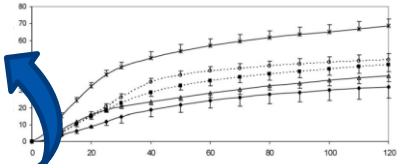


*Lindahl *et al.* 1996 *CPT*

In vitro in vivo extrapolation (IVIV_E) – clinically relevant specifications

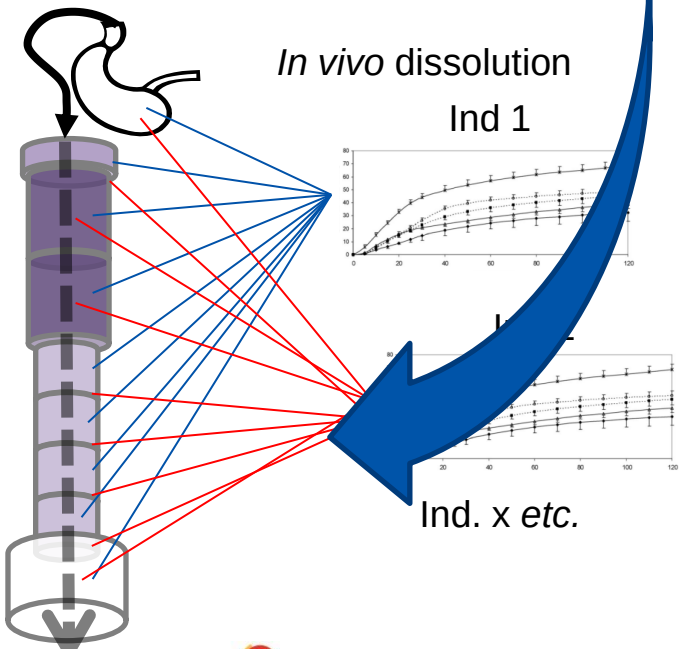
$$\frac{dA_{lumen}}{dt} = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi a(t)(a(t)+h_{eff}(t))(S_{surf}(t)-C_b(t))$$

In vitro dissolution



***In vitro* System parameters**
- RPM (Fluid velocity)
- Buffer (e.g., Phosphate)
- Media (pH, [Bile Salts] …)

API Parameters
- S_0, pKa, SR, PRC
- $LogK_{m:w}$
- Particle size *etc.*
- DLM scalar (*S*)



In vivo dissolution

Ind 1

Ind. x *etc.*

***In vivo* System parameters + variability**
- Fluid dynamics
- Luminal fluid velocities
- Buffer (bicarbonate)
- Luminal pH, [Bile Salts]
- …

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Summary of Sequential Modelling Approach

Aqueous Solubility Modelling

$$S_{(BS)Tot} = \left([BS] \cdot \frac{S_0}{C_{H_2O}} \cdot K_{m:w,unionised} + S_0\right) + \left([BS] \cdot \frac{S_i}{C_{H_2O}} \cdot K_{m:w,ionised} + S_i\right)$$

Confirmed Intrinsic Solubility & Solubility Factors

Biorelevant Solubility Modelling

$$S_{(BS)Tot} = \left([BS] \cdot \frac{S_0}{C_{H_2O}} \cdot K_{m:w,unionised} + S_0\right) + \left([BS] \cdot \frac{S_i}{C_{H_2O}} \cdot K_{m:w,ionised} + S_i\right)$$

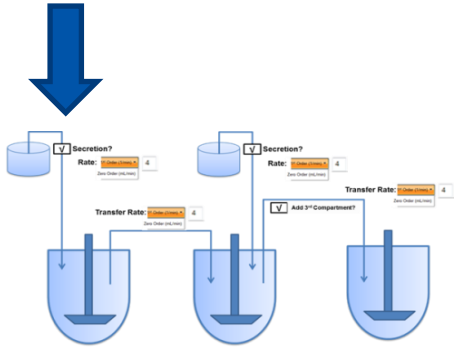
Confirmed Bile Micelle Partition Coefficients

USP- 2 Dissolution Modelling

$$DR(t) = -NS\frac{D_{eff}}{h_{eff}(t)}4\pi a(t)\left(a(t)+h_{eff}(t)\right)\left(S_{surface}(t)-C_{bulk}(t)\right)$$

Confirmed Disintegration & other Parameters

Transfer Experiment Modelling



Confirmed Precipitation Parameters

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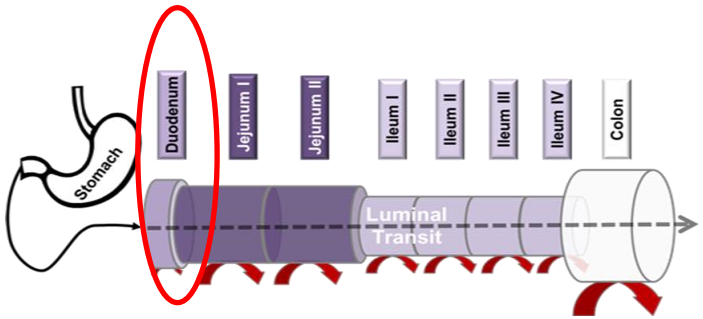
Simulating *in vivo* dissolution using analysed *in vitro* dissolution data

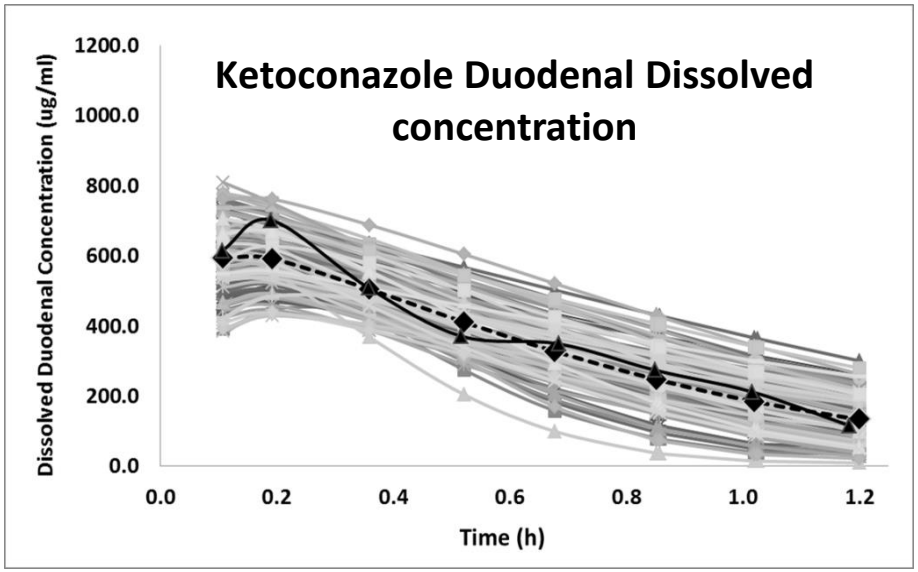
SIVA Toolkit

Solubility, DLM and Precipitation Parameters from in vitro experiments

Virtual Population Simulating Clinical Trial as in Psachoulias et al. 2011



Duodenal Precipitation

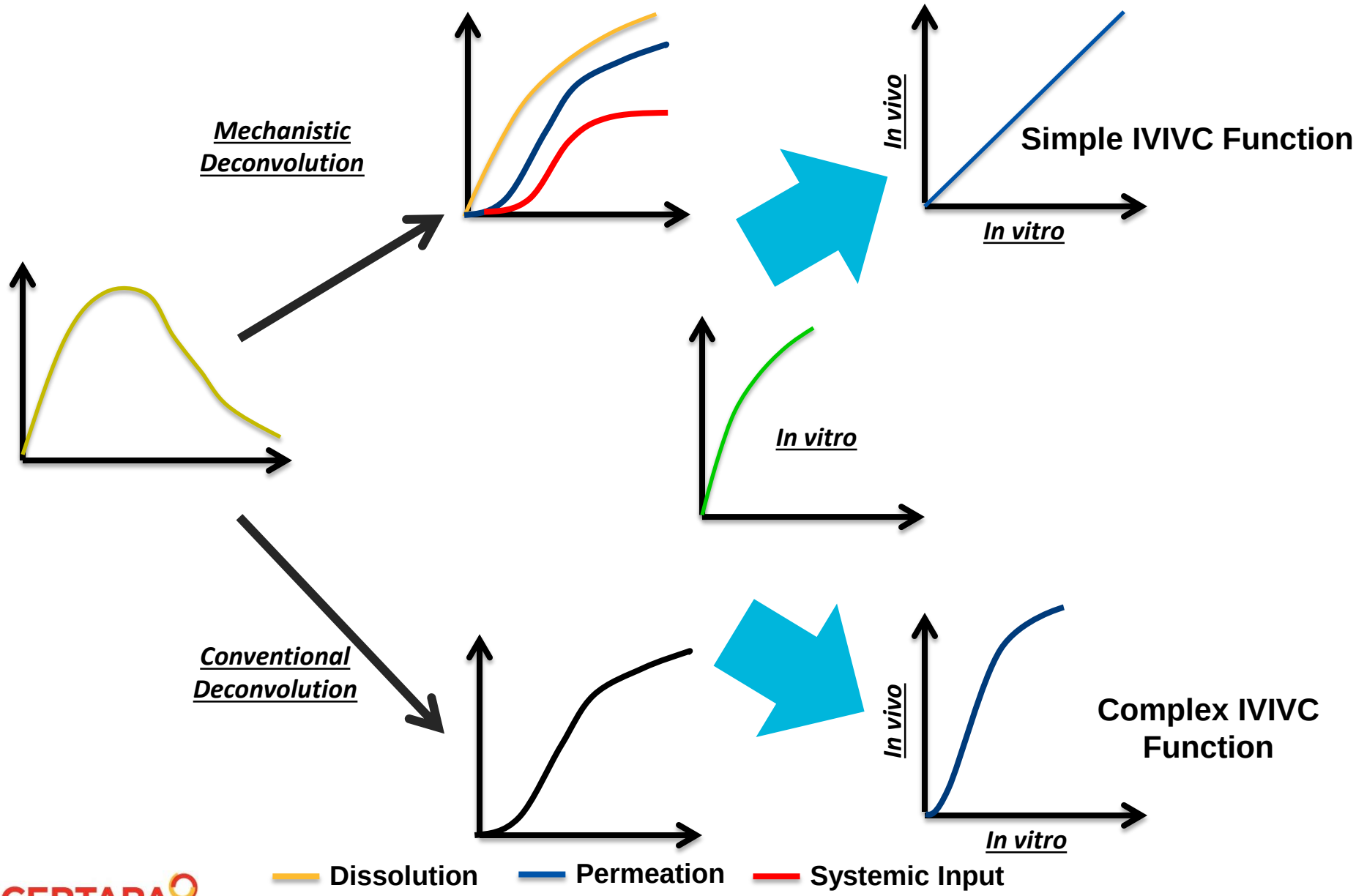


DLM: Diffusion Layer Model

Pathak et al. 2016 PBP Meeting

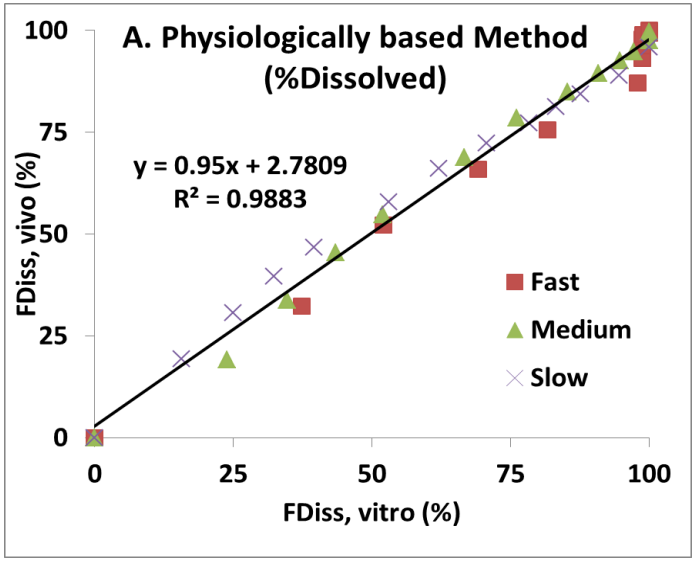
Luminal Data- Psachoulias et al. 2011

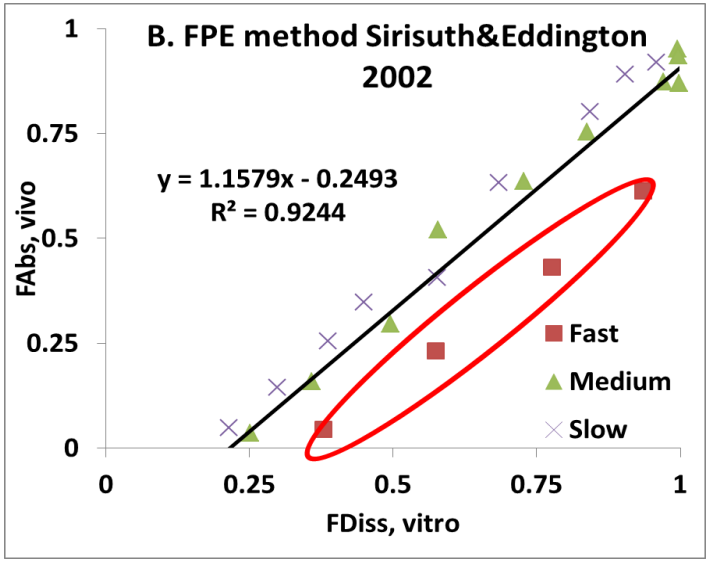
Physiologically-based IVIVC

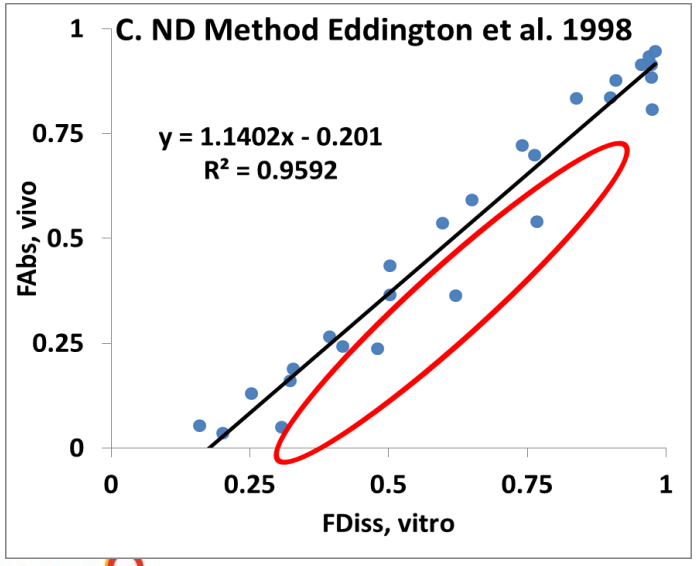


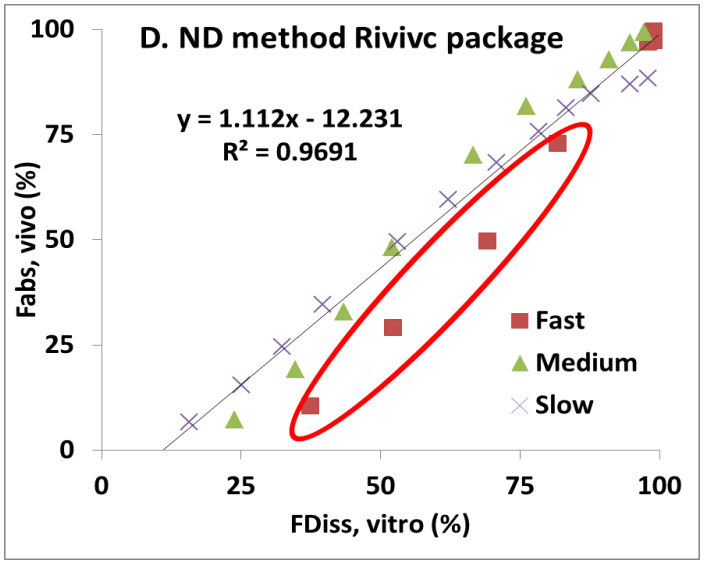
PB-IVIVC deconvolutes to dissolution rather than absorption

IVIVC of Metoprolol CR products









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Population level PB-IVIVC and extrapolation to unseen scenarios

Examining the Use of a Mechanistic Model to Generate an In Vivo/In Vitro Correlation: Journey Through a Thought Process ***Accepted, AAPS J, 2016***

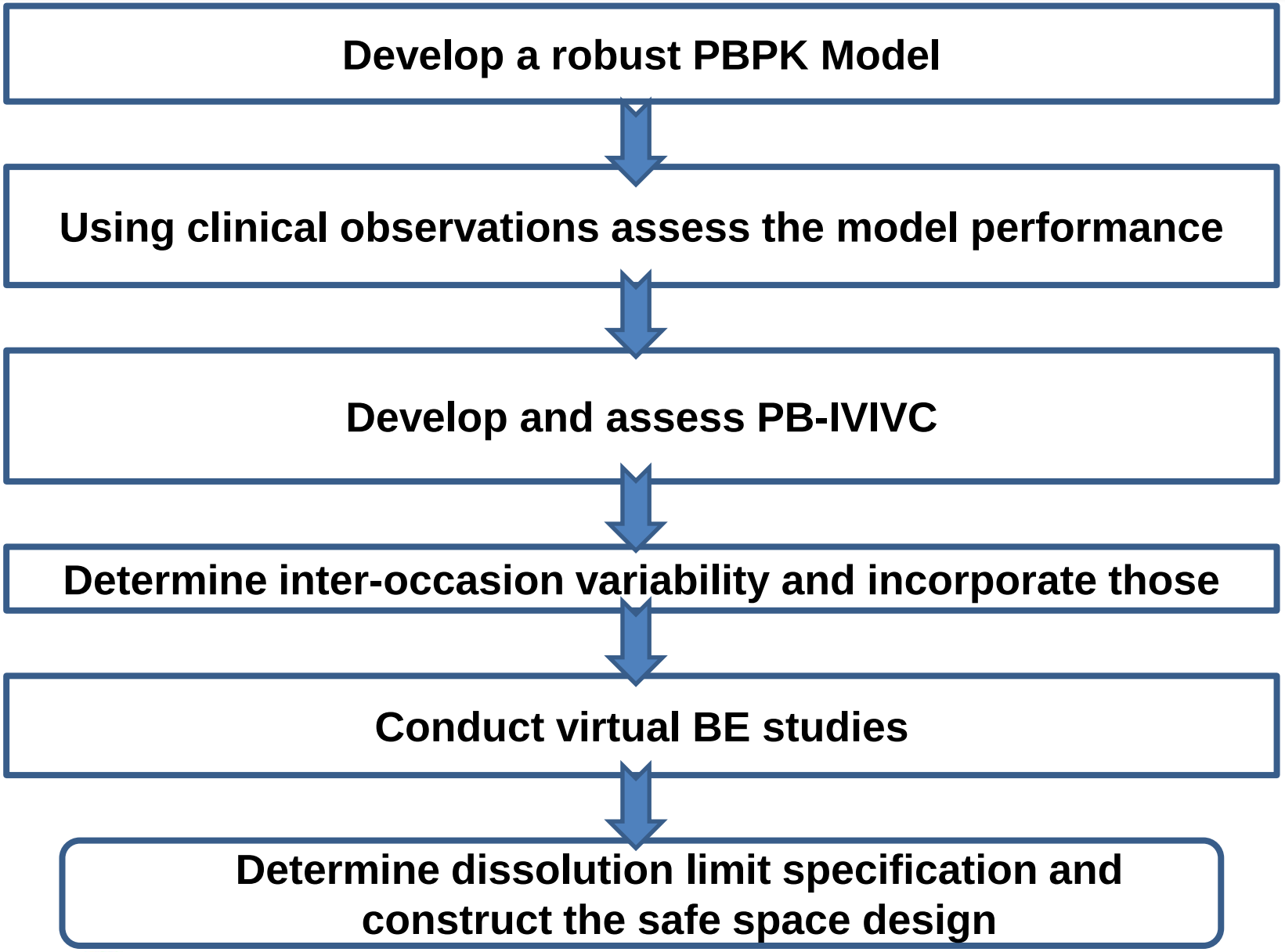
Bipin Mistry[1], Nikunjkumar Patel[2], 'Masoud Jamei[2], Amin Rostami-Hodjegan[2,3], Marilyn N. Martinez[1*]

PB-IVIVC for metoprolol was established and the consequences of following were explored:

1) method of fitting a Weibull function to the in vivo dissolution;
2) selection of optimization and weighting schemes;
3) the impact of applying a fixed versus fitted gastric emptying time;
4) The importance of factoring population variability into the IVIVC estimation and profile re-convolution.

Model then applied to predict formulation performance in CYP2D6 PM subjects.

A virtual bioequivalence workflow



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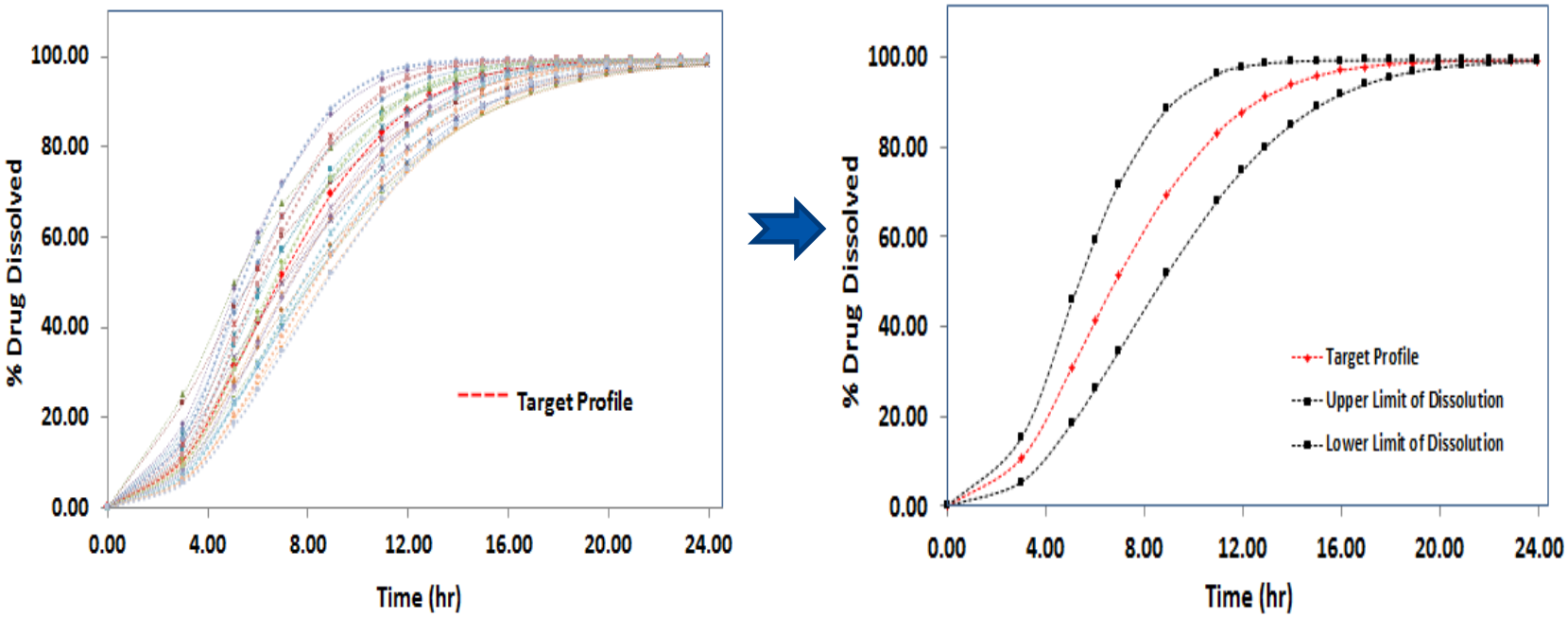
Determining dissolution specifications for a Tramadol ER



Dissolution profiles obtained using optimum α and β Weibull parameters and used to define upper and lower bounds of dissolution specifications.

Pathak et al., CRS meeting, UK, 2015

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Fitting/assuming model parameters

Some absorption processes are poorly understood or are yet to be fully characterised.

Hence, the “bottom-up” approach may not work well and observed data may be used to improve predictions.

When fitting/assuming parameters then assumptions should be clearly stated.

Sensitivity Analysis can help to assess/justify assumptions.

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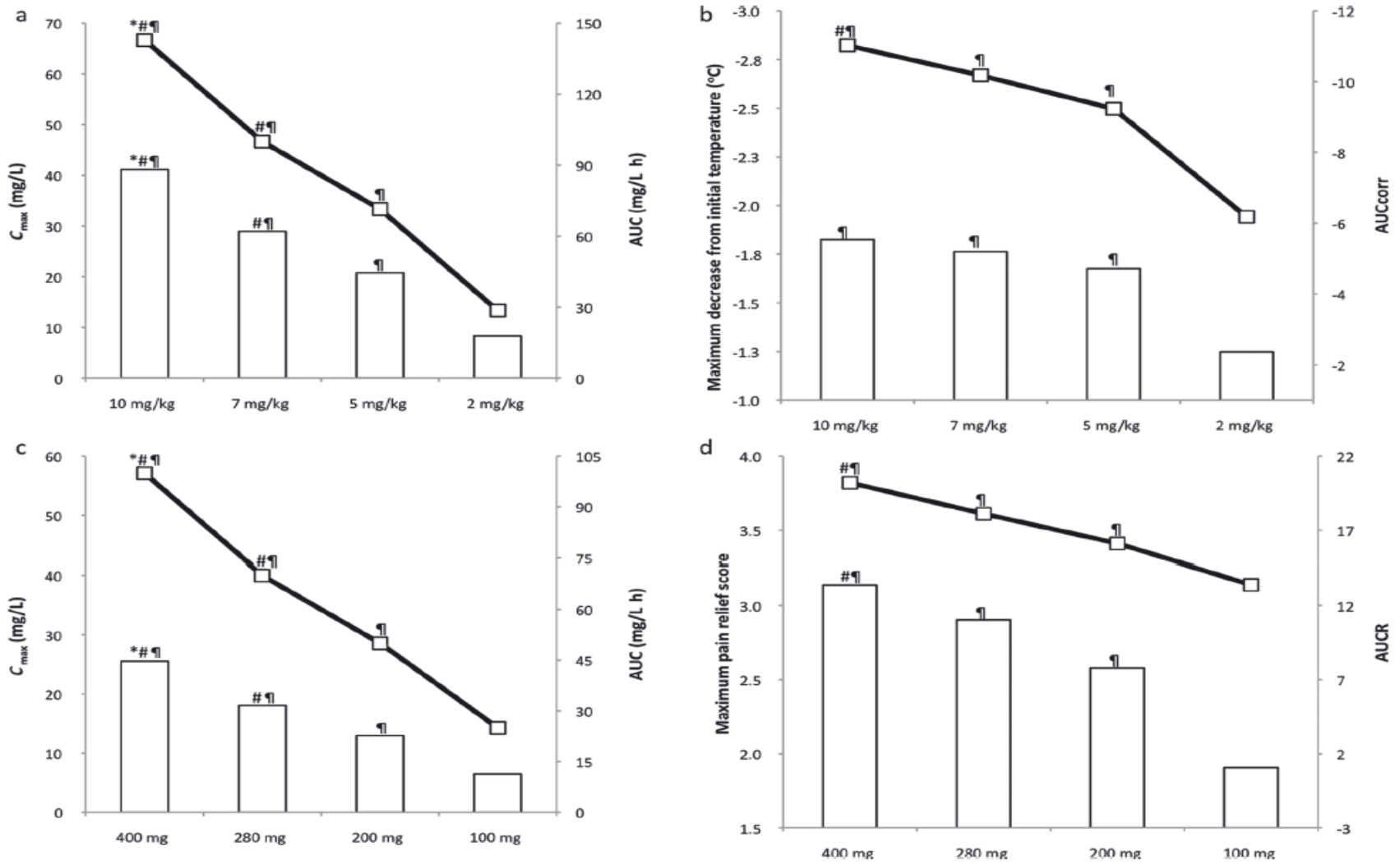
Therapeutic Equivalence Assessment using PBPK Simulations

Ibuprofen IR products PK and PD differences with dose



Cristofoletti & Dressman 2014, J Pharm Sci, 103 (10), 3263-75

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Extrapolating Formulation Assessment from Adult to Paediatric

Exploratory Investigation of the Limiting Steps of Oral Absorption of Fluconazole and Ketoconazole in Children Using an *In Silico* Pediatric Absorption Model

Rodrigo Cristofoletti [1, 2], Naseem A. Charoo [3, 4], Jennifer B. Dressman [2, *]

Using Physiologically Based Pharmacokinetic (PBPK) Modelling to Gain Insights into the Effect of Physiological Factors on Oral Absorption in Paediatric Populations

Angela Villiger,[1,3] Cordula Stillhart,[1] Neil Parrott,[2] and Martin Kuentz[3,4]

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

Trevor N. Johnson[a], Diansong Zhou[b], and Khanh H. Bui[b,*]

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PBPK models are used to predict/understand food effects

Differences in Food Effects for 2 Weak Bases With Similar BCS Drug-Related Properties: What Is Happening in the Intestinal Lumen?

Rodrigo Cristofoletti [1,2], Nikunjkumar Patel [3], Jennifer B. Dressman [2,*] 2016

Quantitative prediction of formulation-specific food effects and their population variability from *in vitro* data with the physiologically-based ADAM model: A case study using the BCS/BDDCS Class II drug nifedipine

2014

Nikunjkumar Patel [a,*], Sebastian Polak [a,b], Masoud Jamei [a], Amin Rostami-Hodjegan [a,c], David B. Turner [a]

Case Studies for Practical Food Effect Assessments across BCS/BDDCS Class Compounds using *In Silico*, *In Vitro*, and Preclinical *In Vivo* Data

Tycho Heimbach,[1,2] Binfeng Xia,[1] Tsu-han Lin,[1] and Handan He[1] 2013

Opportunities and Challenges!

- Extrapolation (e.g. patient/special populations)
- Better understanding of formulation performance in vivo
- Determining the product critical quality attributes and clinically relevant specifications
- Prediction of food effects
- PB-IVIVC
- Virtual bioequivalence studies
- Knowledge gaps in both systems data and absorption mechanisms
- Advancing our knowledge of inter-occasion variability (BE)
- A collective and multi-disciplinary paradigm
- Education, Education, Education
- Colonic absorption

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Orbito Project

Anette Mullertz, Christel Bergstrom, Xavier Pepin, Christos Reppas, Maria Vertzoni and colleagues

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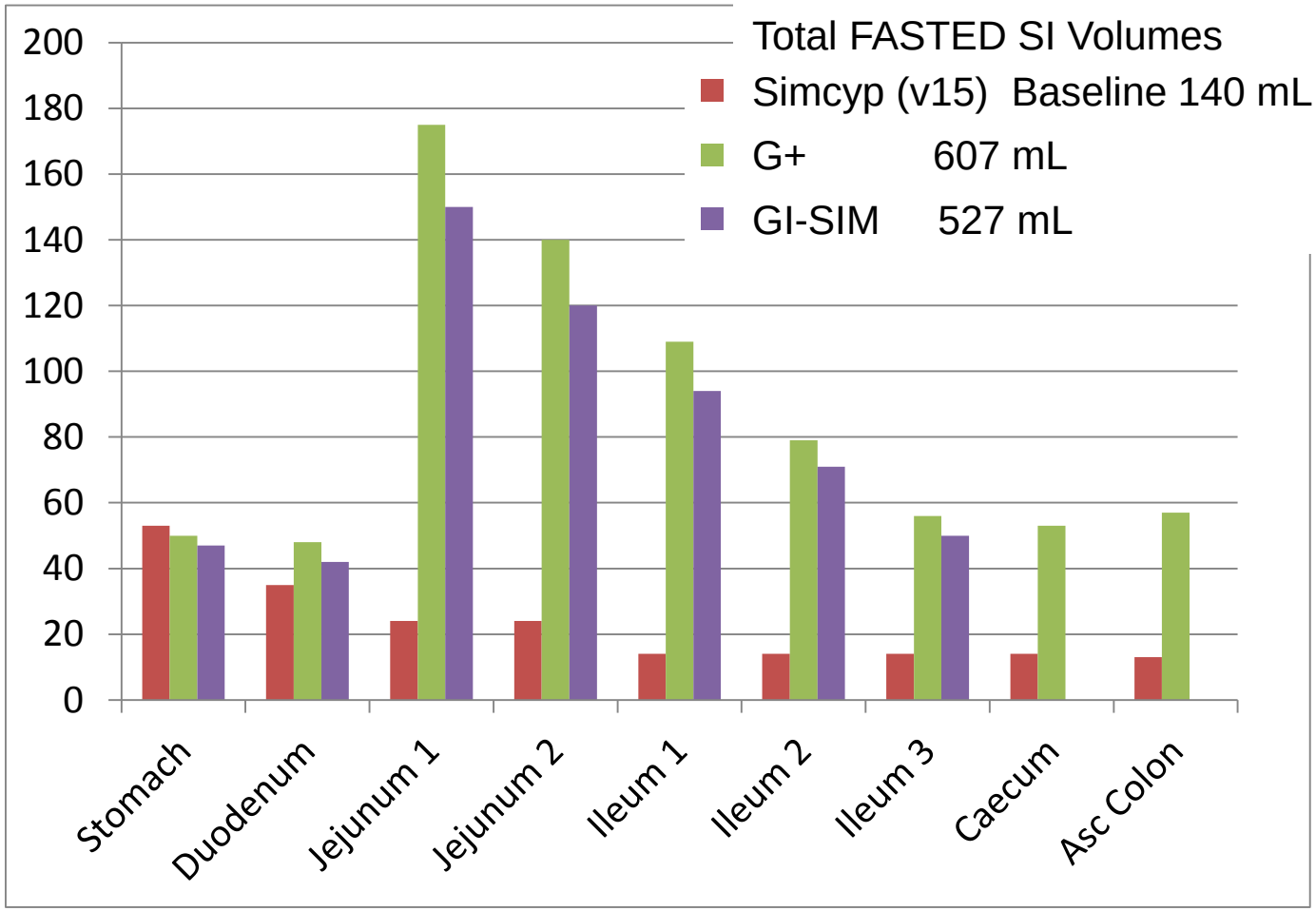
Backup Slides

Simcyp Dynamic vs. GastroPlus and GI-SIM Static Volumes

G+ - Babiskin 2015 FDA; Sjogren et al 2016 40% of anatomical cylindrical volume

GI-SIM - Sjogren et al 2016



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