In silico tools to simulate the regional differences of the human GI tract

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Simcyp Limited (A Certara Company)

Ungap meeting, Leuven, March 2018

Available Tools

CERTARA Simcyp

GastroPlus™

PSE gCOAS oral absorption module

PK-Sim® PBPK modeling & simulation

STELLA®
GI-Sim

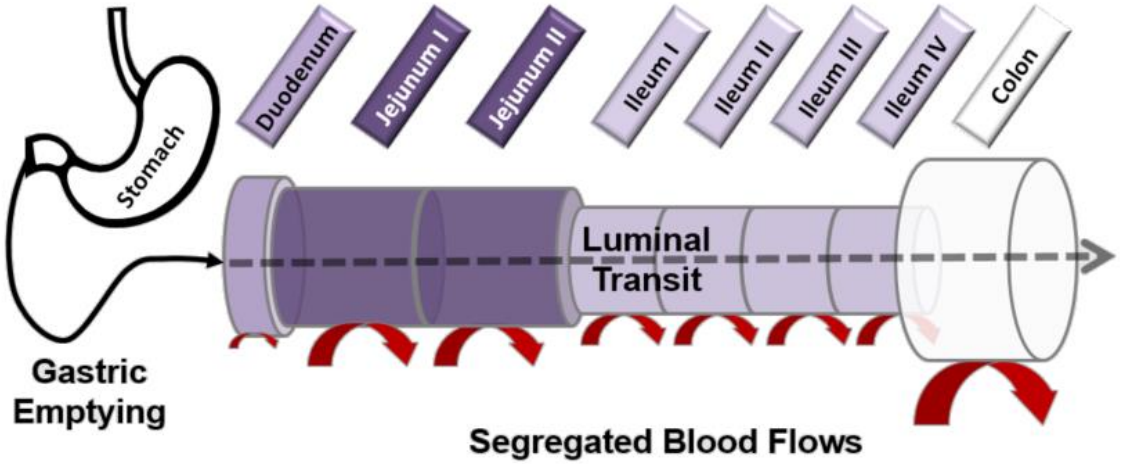
Review

European Journal of Pharmaceutical Sciences 57 (2014) 300–321

PBPK models for the prediction of *in vivo* performance of oral dosage forms

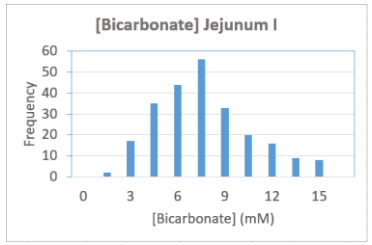
Edmund S. Kostewicz [a,*], Leon Aarons [b], Martin Bergstrand [c], Michael B. Bolger [d], Aleksandra Galetin [b], Oliver Hatley [b], Masoud Jamei [e], Richard Lloyd [f], Xavier Pepin [g], Amin Rostami-Hodjegan [b,e], Erik Sjögren [h], Christer Tannergren [i], David B. Turner [e], Christian Wagner [a], Werner Weitschies [j], Jennifer Dressman [a]

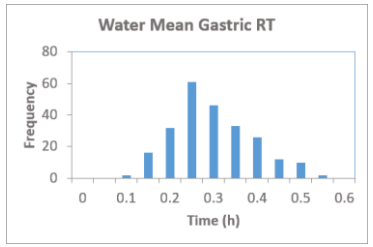
Oral Absorption: ADAM Framework

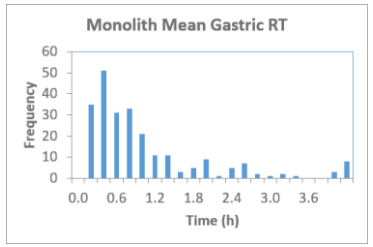


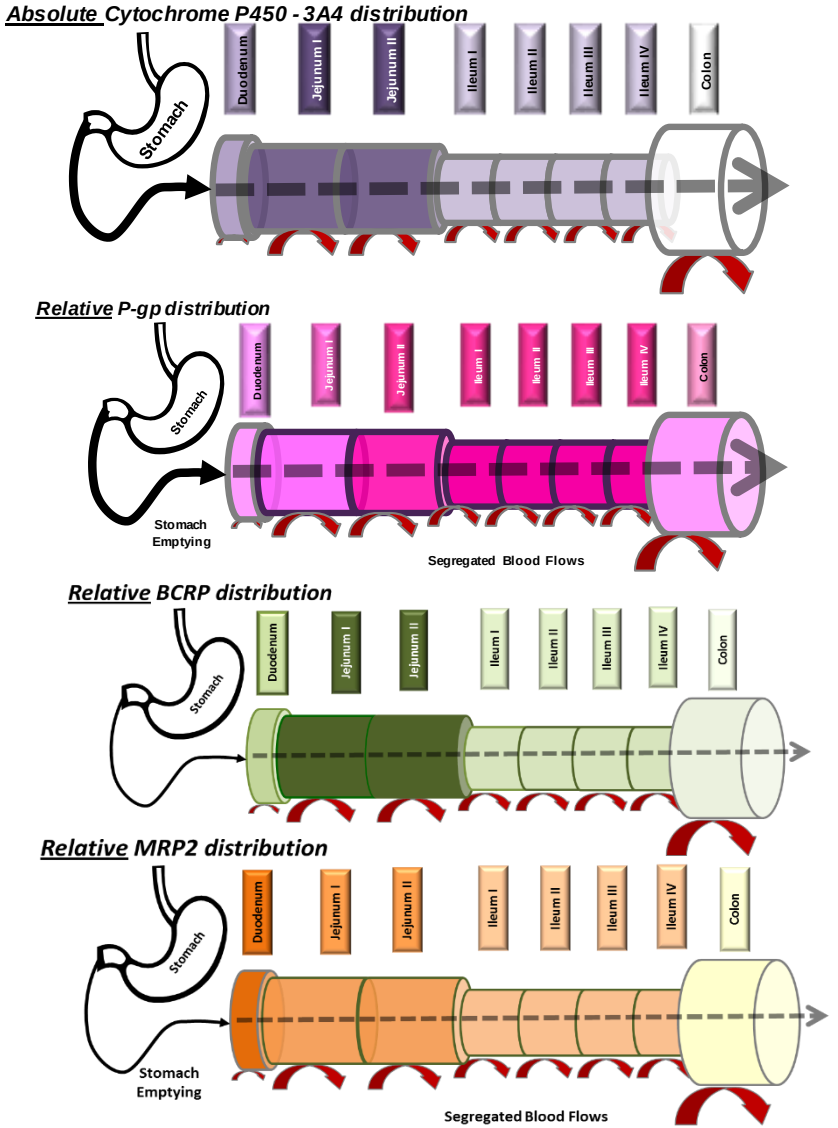
Mean and Regional and Inter-individual Variability of: pH, [bile salts], fluid volumes, viscosity, [bicarbonate], gut wall morphology, enzyme and transporter abundances, blood flow, *etc*.

Regional and Inter-individual Variability of <u>Derived</u> Parameters: Bulk Solubility, surface solubility, free fraction, dissolution rate, permeation rate, metabolism etc.









CAT : Lu et al., 1996; ACAT: Agoram et al., 2001; ADAM: Jamei et al., 2009

Harwood *et al.*, 2013

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Introduction to GI Tract Physiology and its Variability

Outline

- GI Motility
  - Segregated transit time model
- GI Luminal Fluid Volumes and Dynamics
  - Fluid Dynamic model
  - Dynamic secretions (e.g. Biliary outputs)
- Luminal pH
- Inter-subject variability

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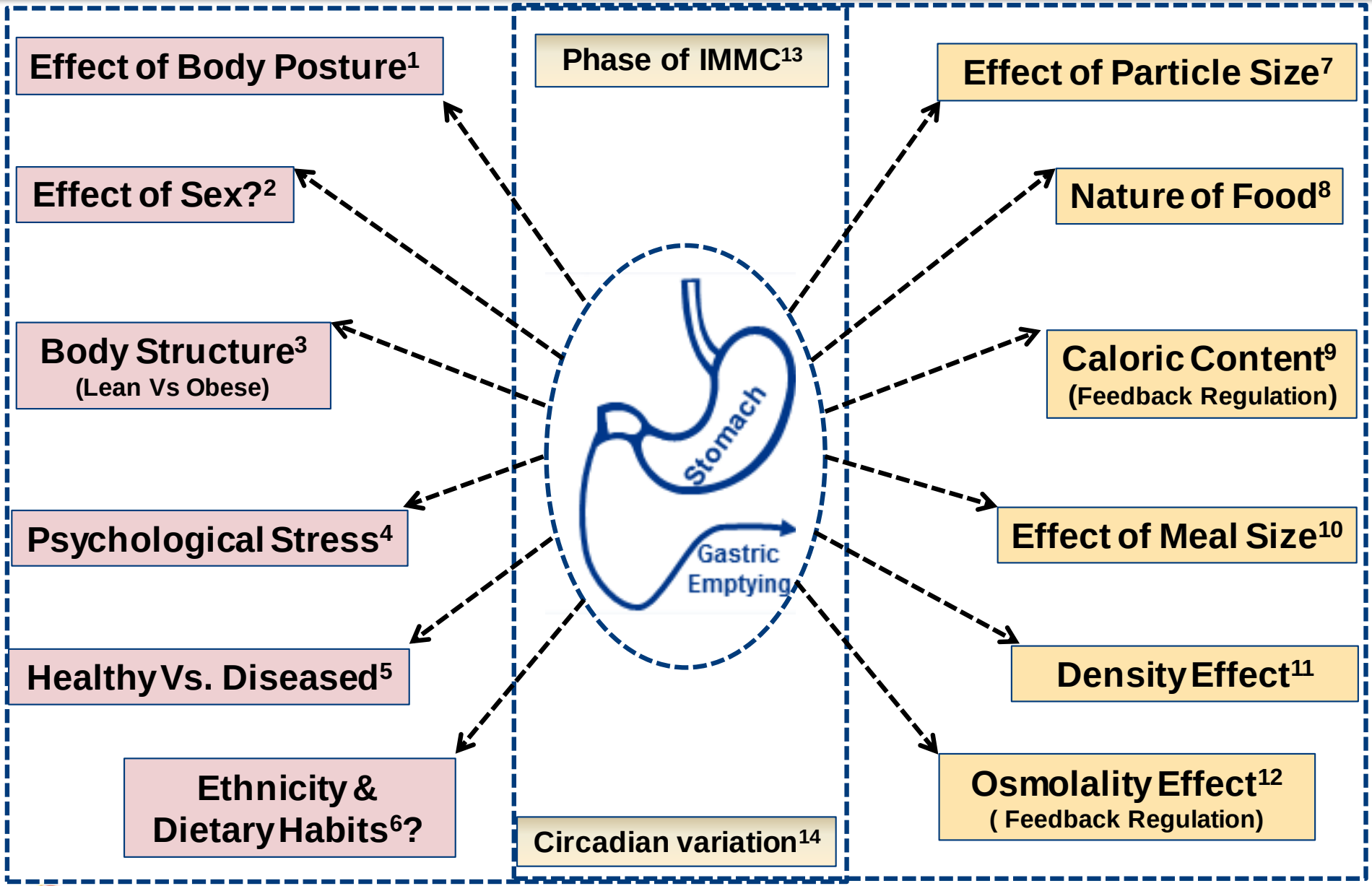
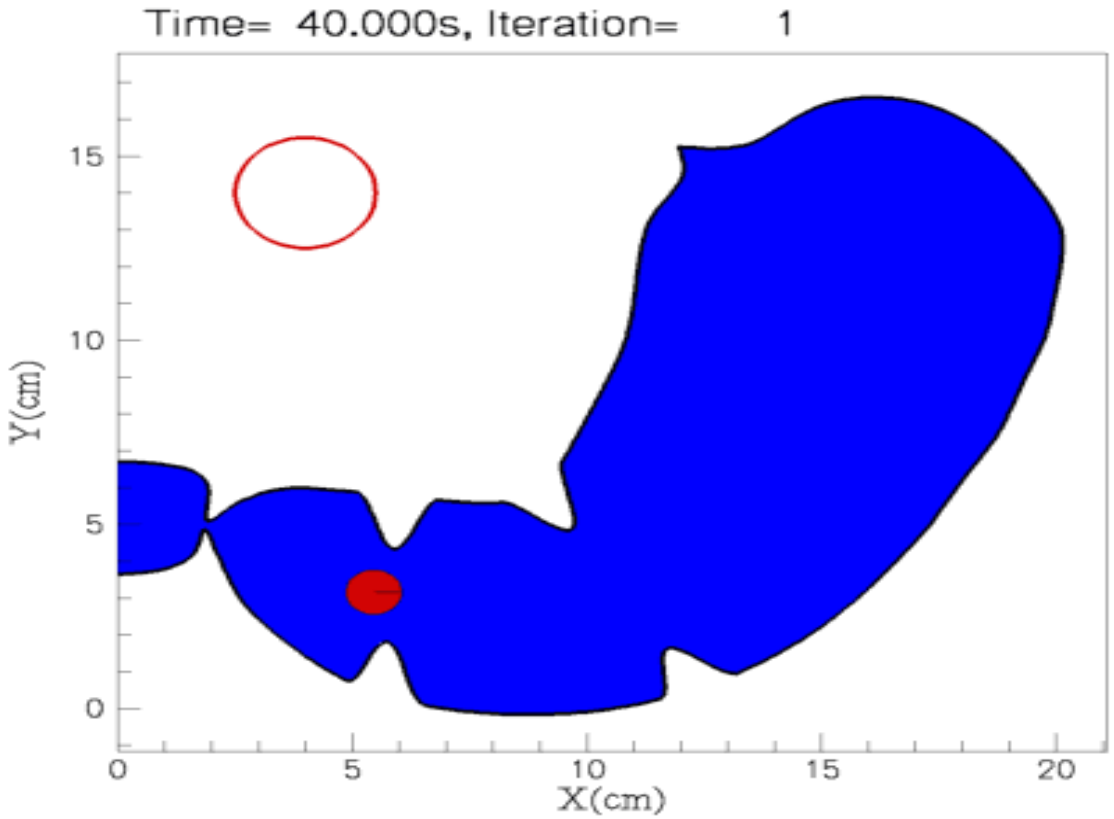
GI motility - Gastric Emptying - The Complexity of Covariate Effects

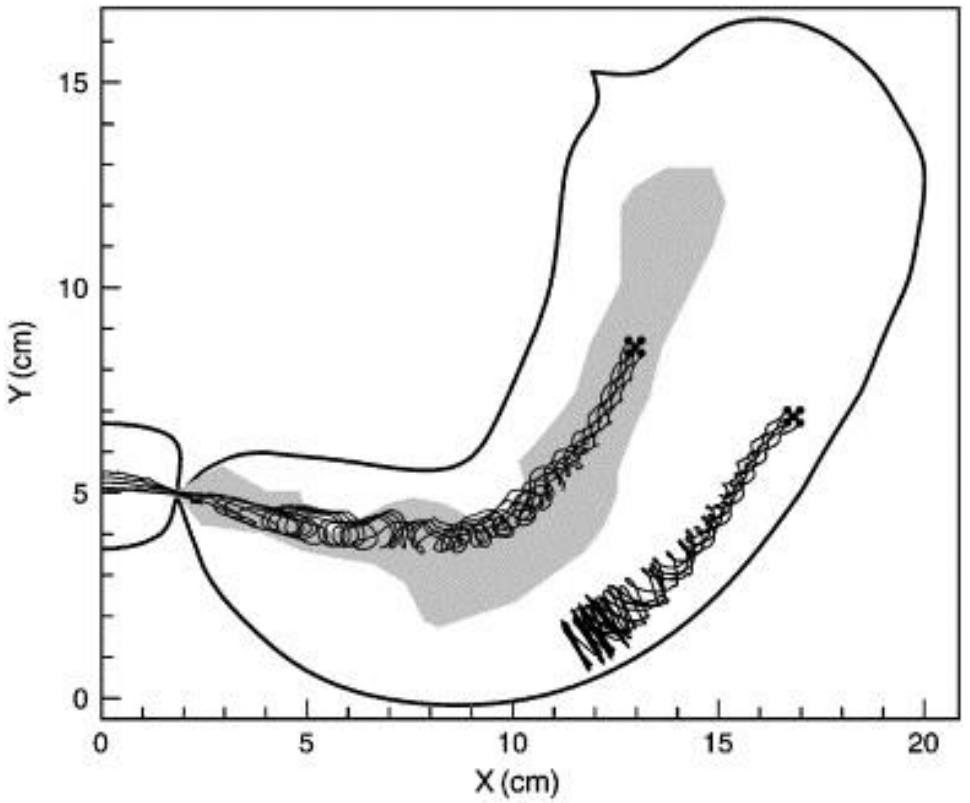


GI motility - Need for Segregated Transit Time Model!

Gastric Emptying



Animation from - Pal et. al. (2004) A two-dimensional computer model of the stomach was developed with the 'lattice-Boltzmann' numerical method from the laws of physics, and stomach geometry modelled from MRI.



Trajectories of 10 particles, 5 on (Rapid emptying) and 5 off (delayed emptying) the Magenstrasse (Pal et al. 2007)

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Methodological Consideration for Different Entities

Fluid/Dissolved Drug

youtube.com

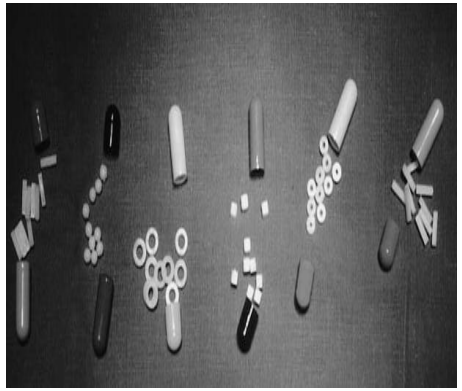
- ^{111}In-DPTA (in water) administered orally
- Scintigraphy monitoring (γ-camera) up to 96h
- Distinguish regions

Particles

Wikipedia.org

- ^{111}In-activated charcoal single dose – capsule
- Capsule is coated for ileo-caecal release
- Scintigraphy monitoring (γ-camera) up to 48h
- Distinguish ascending colon

Pellets



Gutiérrez et al., 2002*

- 20-40 mg; 3-6 mm long
- 10-20 ^{111}In-markers in a methacrylate-coated capsule, oral τ = 24h
- X-ray monitoring up to 7d
- Distinguish regions

* Gutiérrez et al., 2002, JPGN, 35, 31

Monolith

Fallingborg_90'
pH capsule

Buhmann_07'
reaction tube

Becker_14', Koziolek 15' & Soderlind 15
Intellicap

Haase_14'
Electromagnetic pill

- Variety of monolith systems
- Typically 2-3 cm length
- Monitoring up to 3d
- Regions not distinguished

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Total Colon Mean Residence Time (TC-MRT)

- Monoliths possess shorter residence times than other entities

We are generally more than willing to share and discuss the obscured (but as yet unpublished) meta-analysis results so please contact Simcyp if you wish to do so: konstantinos.stamatopoulos@certara.com or david.turner@certara.com

*__Fine particles__ – no TC-MRT studies (proximal colon t½ only)
  - __Fluid-based__ TC-MRT's used as surrogate ◦ __Assumption__: Fine particles transit with fluids

- For all entities females have longer MRT
- Too few studies to assess the impact of age on TC-MRT for adults

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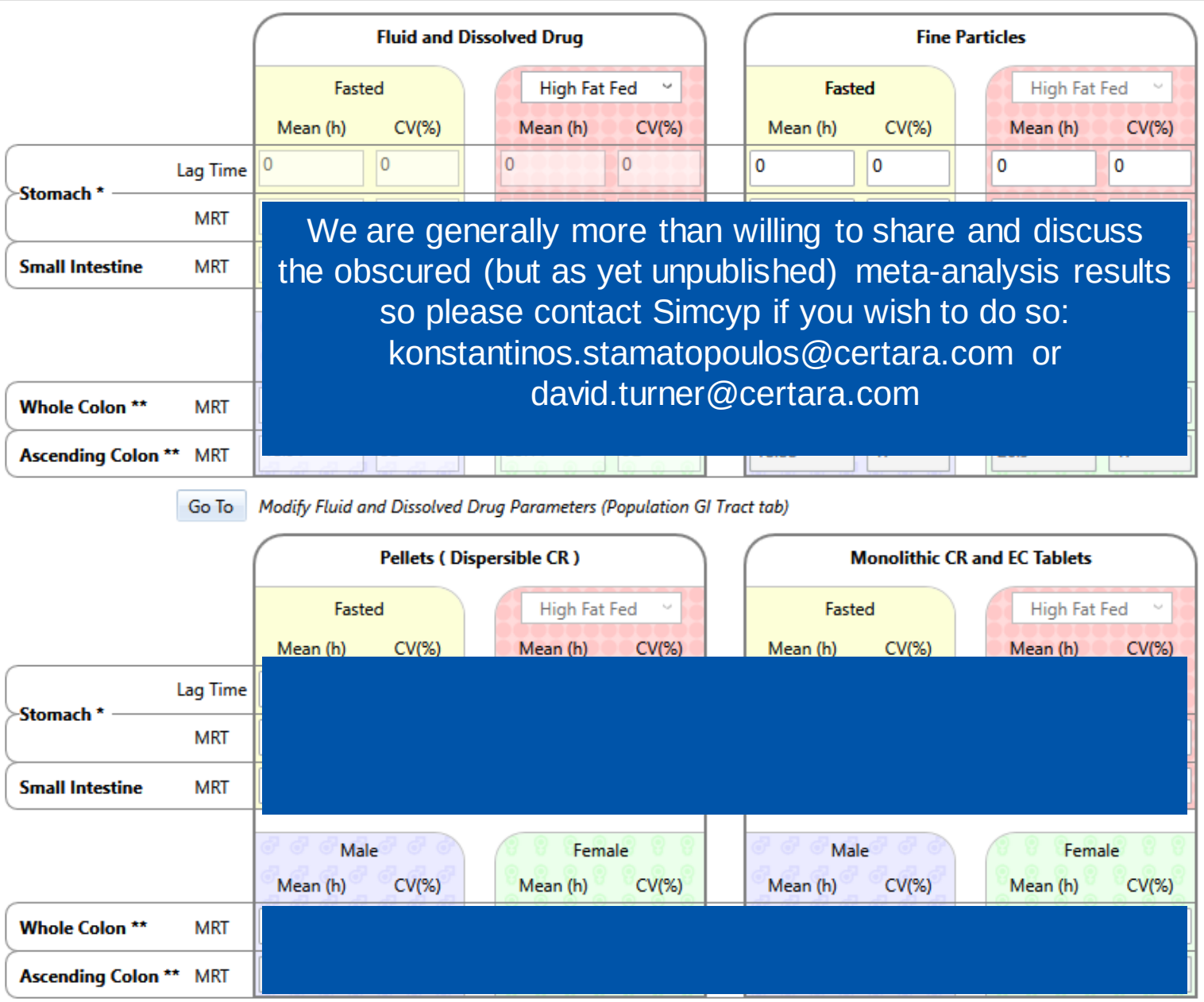
__Unpublished in house meta-analysis__

Segregated Transit Model

B. Simcyp Formulation tab

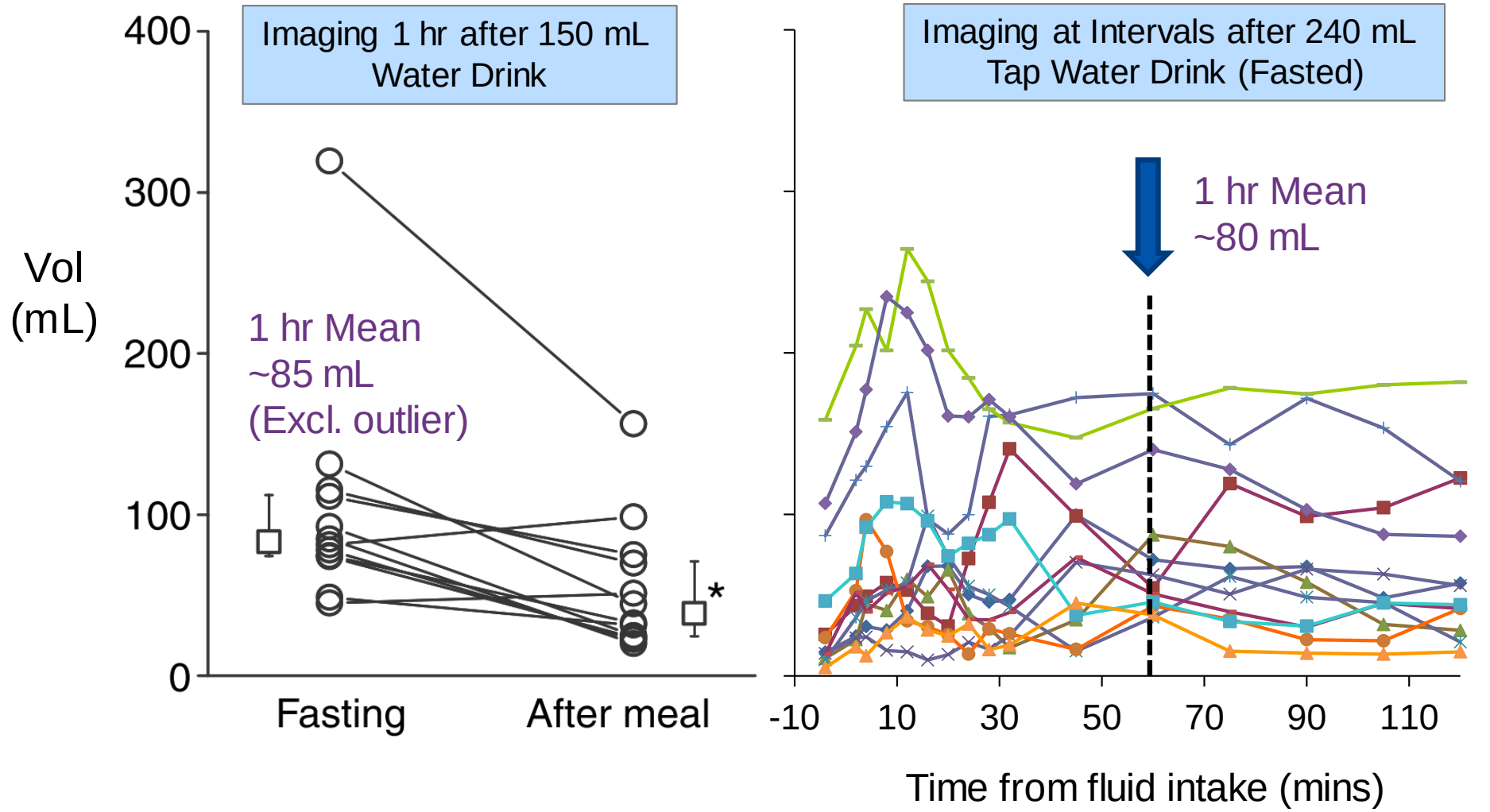
Dispersible material (fluid, particles, Pellets) transits via first order kinetics.



- Permit MRT and lag time of particles and pellets to be less than that of fluid

Luminal Fluid Volumes and Dynamics: MRI Studies

Total Small Bowel Water Volumes



* Schiller, Weitschies et al. 2005

* Mudie, Marciani et al. 2014 with permission

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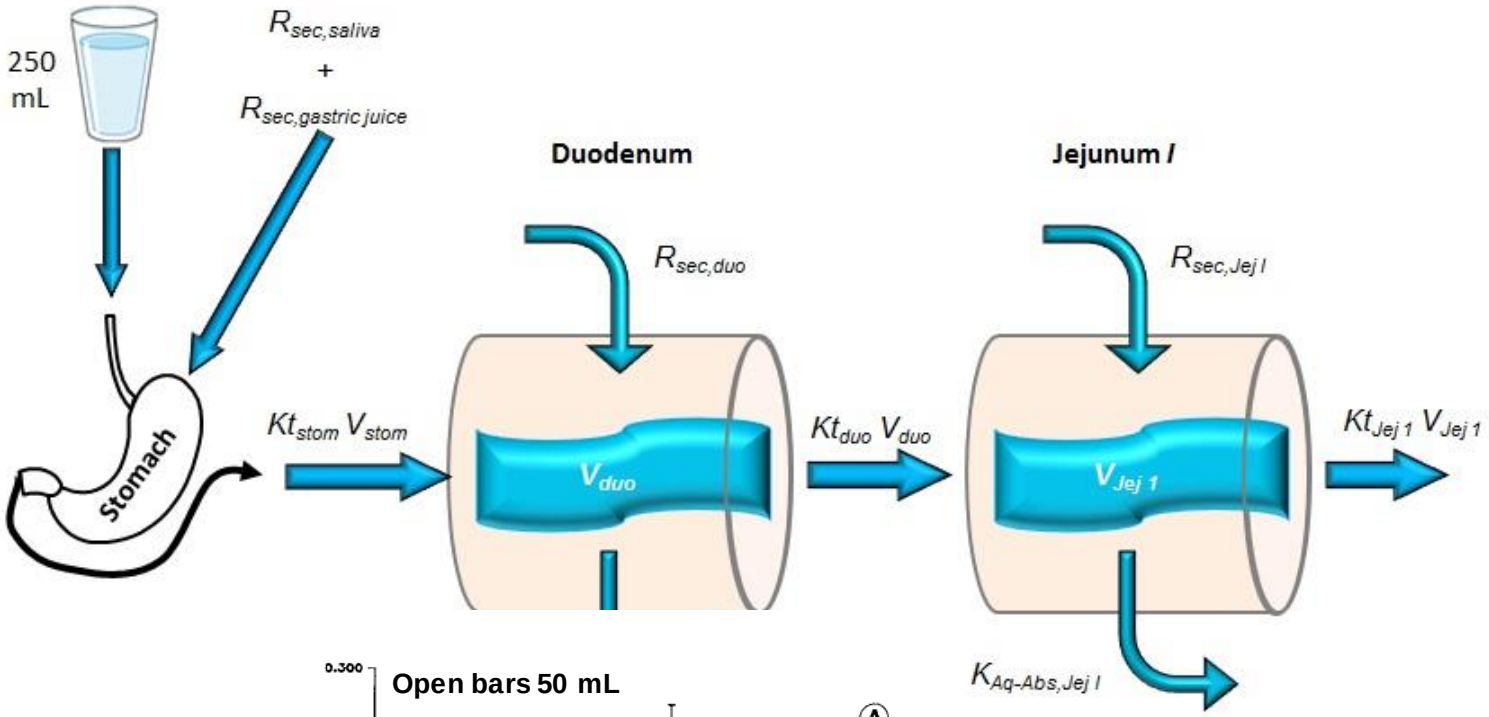
Modelling Fluid Dynamics in the GI-tract – Time-dependent Volumes



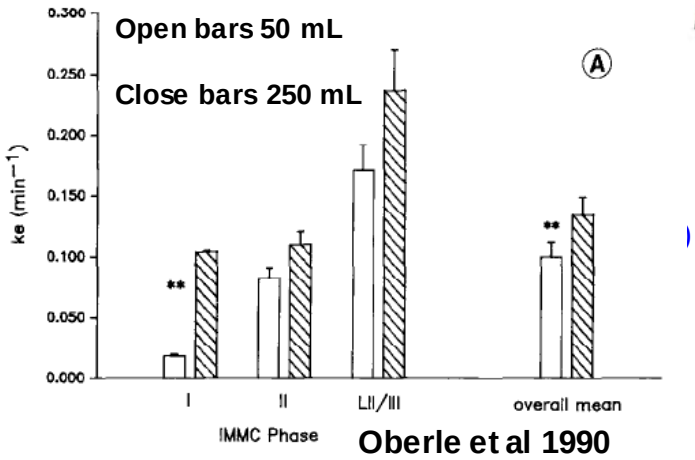
V_j: Volume

$R_{sec,j}$: Fluid se

$K_{Re\text{-}Abs,j}$: Fluid re

Kt_j: Transit

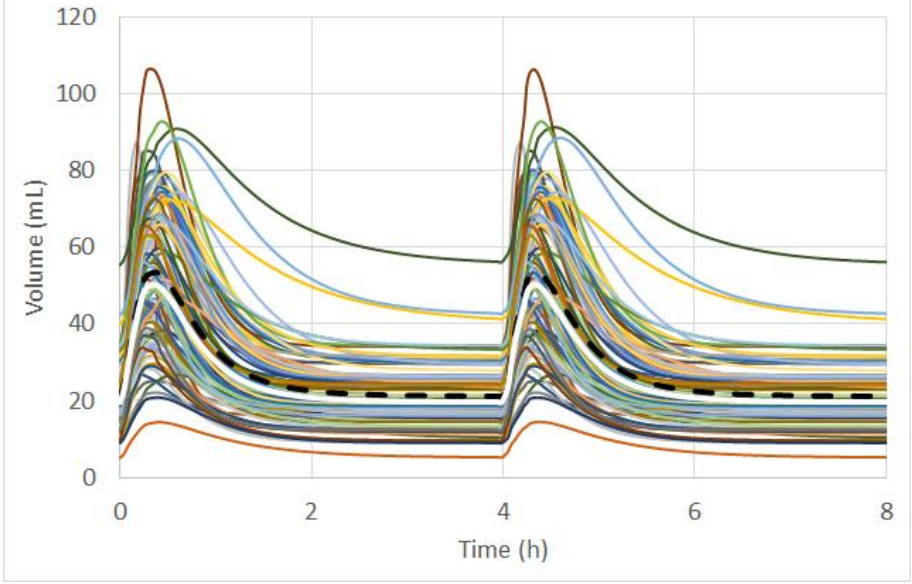
$$\frac{dV_j}{dt} =$$



Oberle et al 1990

Population Variability: 100 subjects

Simulated Time-dependent Water Volumes (Fasted): **Jejunum I**: 2 x 240 mL drinks



Volumes being revised down (v18)

Issues:

- **Water pockets** Schiller *et al*. (2005); Mudie et al. (2014)
- **Link fluid volume dynamics to IMMC** (Oberle et al 1990)

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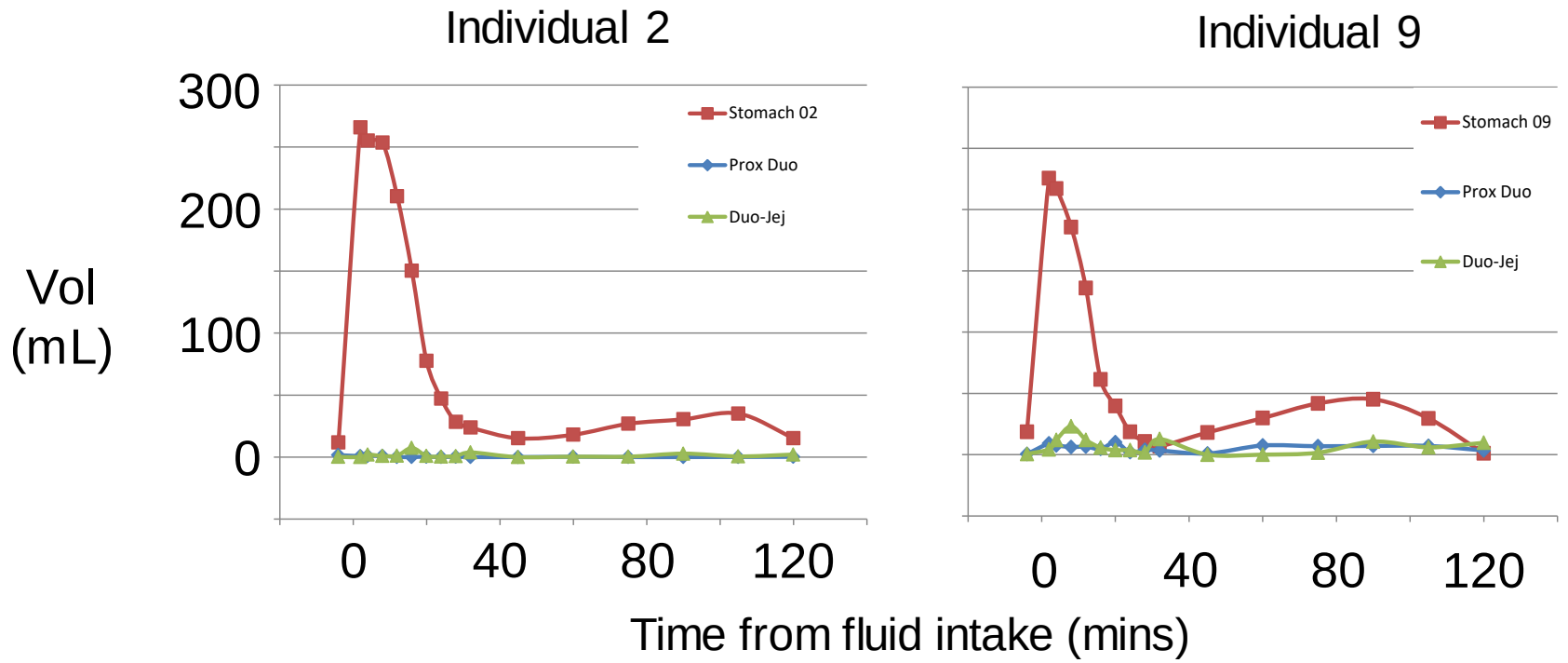
Luminal Fluid Volumes Dynamics: Where is the Water?

Regional Water vs. Time Profiles*



In many individuals water taken with dose appears to be neither in the Proximal duodenum nor Distal Duodenum / Proximal Jejunum

* Mudie, Marciani et al. 2014 with permission

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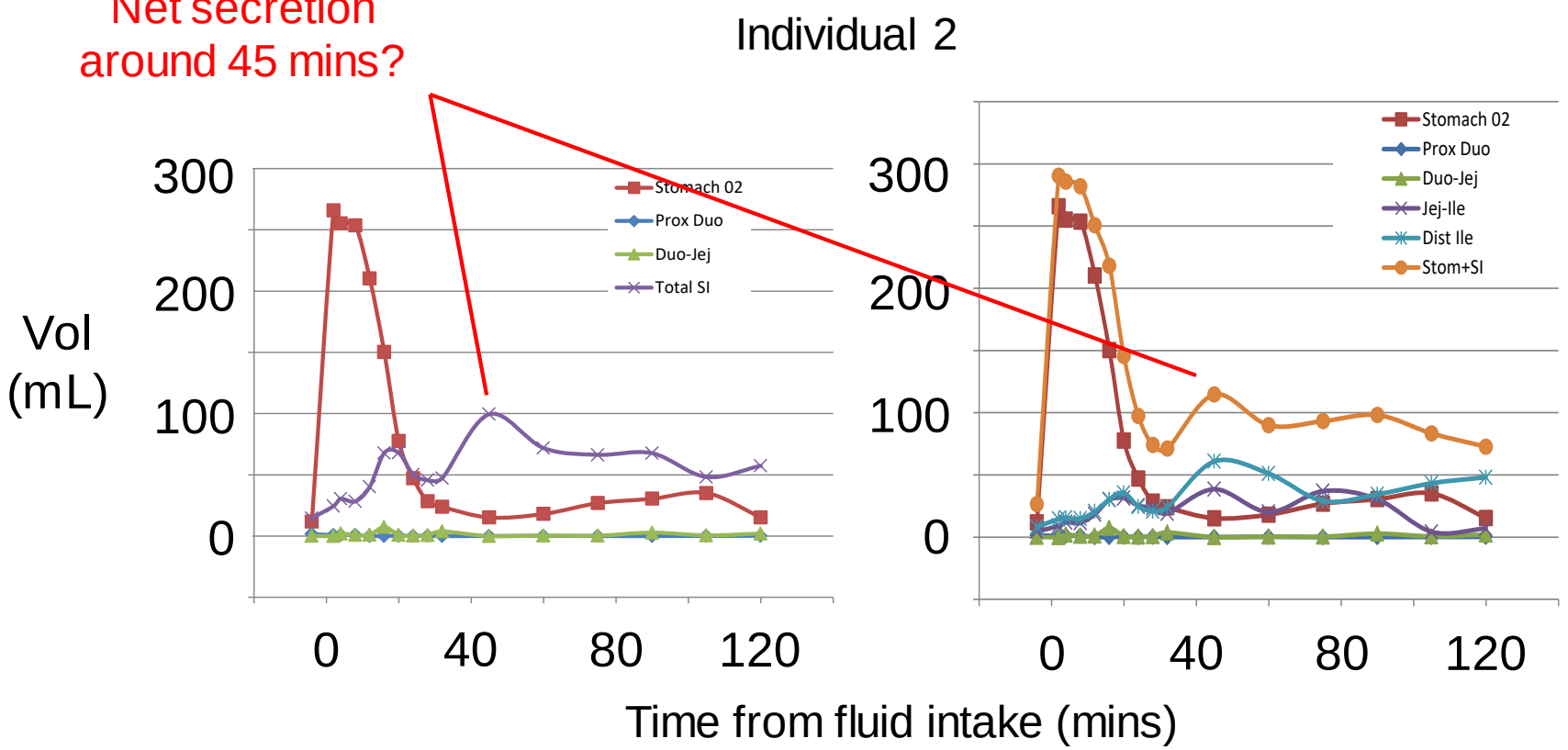
Luminal Fluid Volumes Dynamics: Where is the Water?

Rapid absorption and transit

Tap water is ~30 mOsm vs. plasma 300 mOsm (i.e., hypo-osmotic)

Net secretion around 45 mins?



Required: Regional imaging studies in humans with iso- and hypertonic fluids (e.g., non-absorbable excipients)

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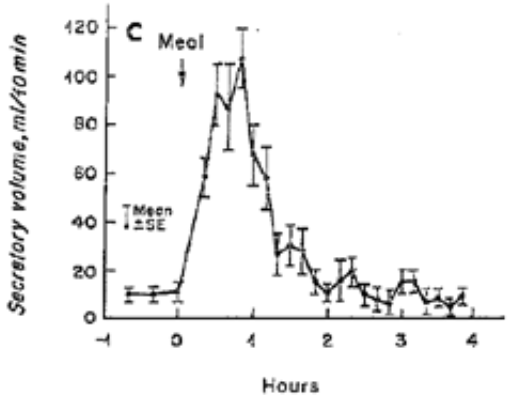
Fluid Volume Dynamics in the GI-tract – Dynamic secretions (in v18)

Gastric juice flow rate (mL/h)



Malagelada 1976

Saliva (mL/h)

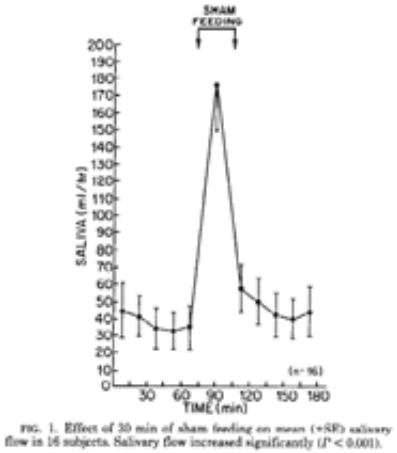


FIG. 1. Effect of 30 min of sham feeding on mean (±SE) salivary flow in 16 subjects. Salivary flow increased significantly ($P < 0.001$).

Richardson 1986

In house meta-analysis (Unpublished)

Parameter	Gastric juice flow rate (ml/h)	subjects	Current value in Simcyp

We are generally more than willing to share and discuss the obscured (but as yet unpublished) meta-analysis results so please contact Simcyp if you wish to do so: konstantinos.stamatopoulos@certara.com or david.turner@certara.com

Lack of data for FDA high fat meal …

* Not being incorporated in the physiology databases

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Pancreatic Juice Fasted state Secretion Rates – Summary (Work in-progress)

Study	Sample/Analytical Method	Sample Size	Value (mL/h)

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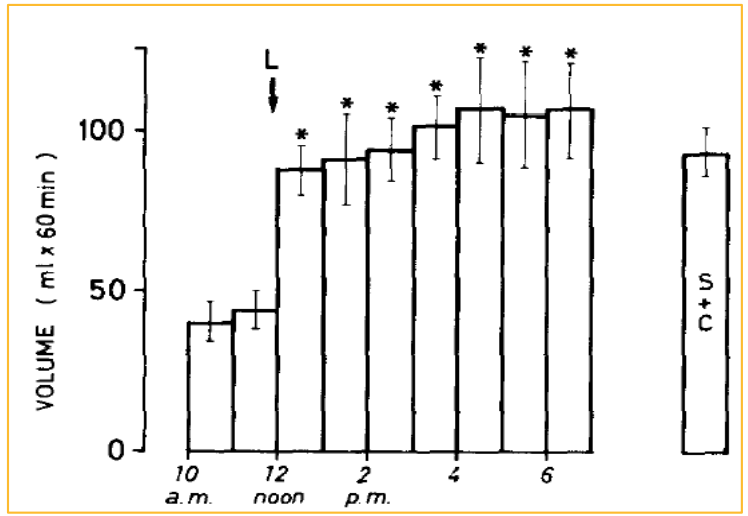

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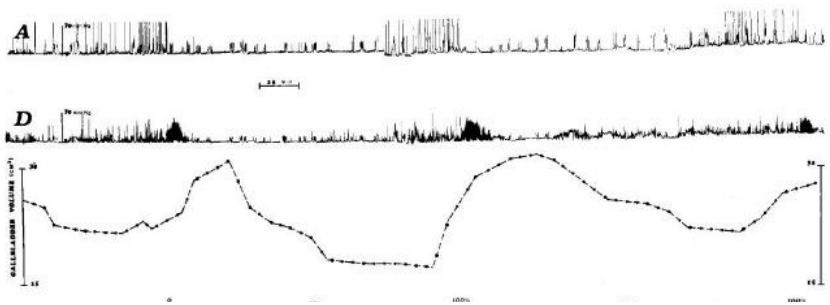
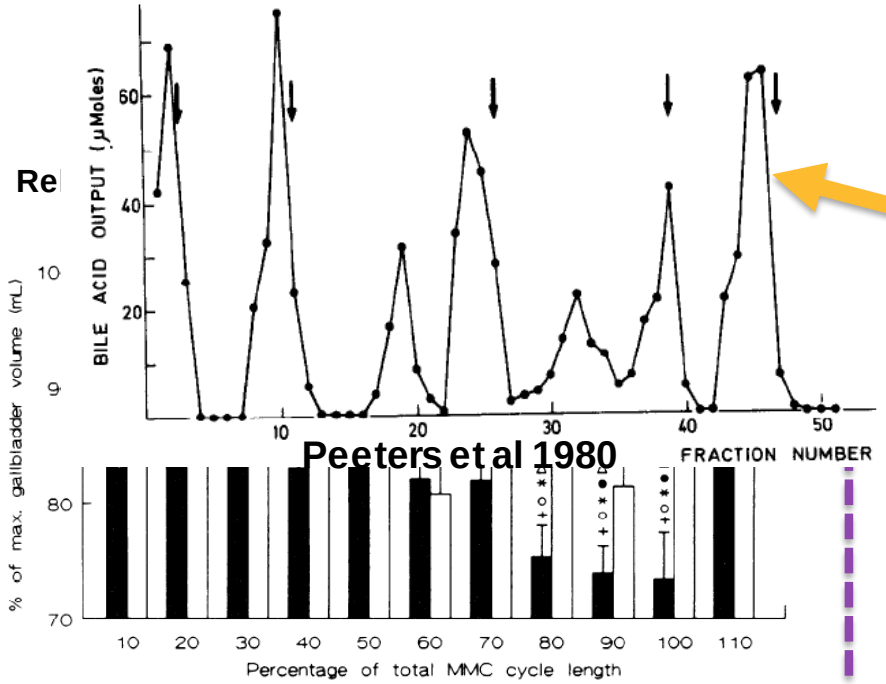
Time-dependent Secretions, Gallbladder, Bile Salts

Biliary Motility

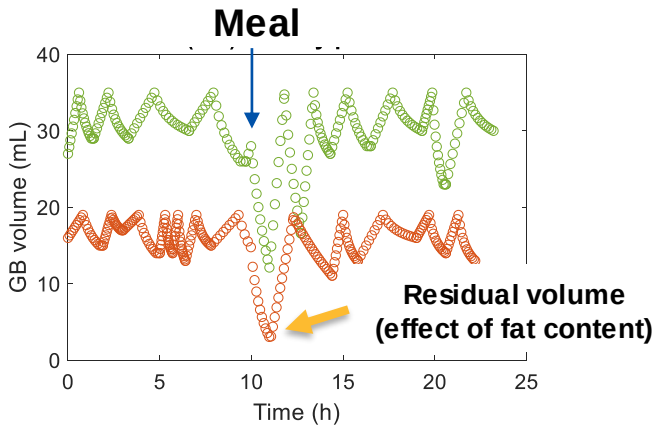
Cyclic gallbladder volume changes & IMMC

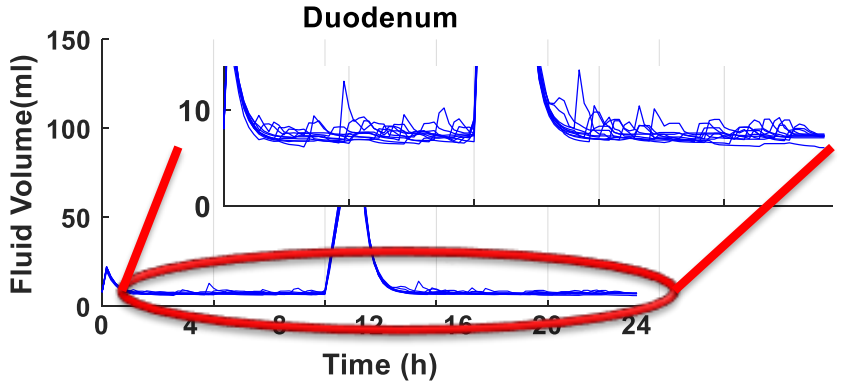




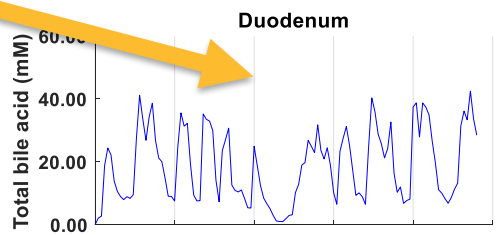
Stolk et al., 1993

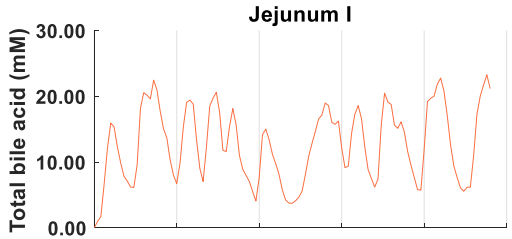
Dynamic Bile salt model coupled to Dynamic Fluid volumes model (work in progress)





Regional Total Bile salts concentration (mM)





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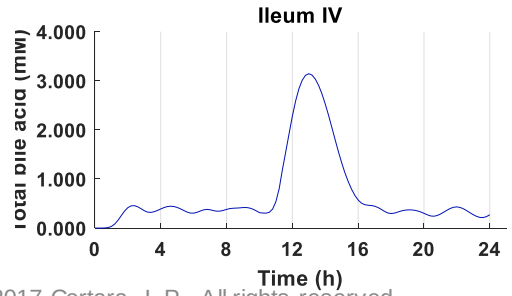

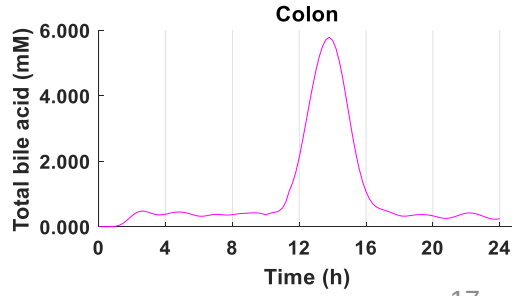

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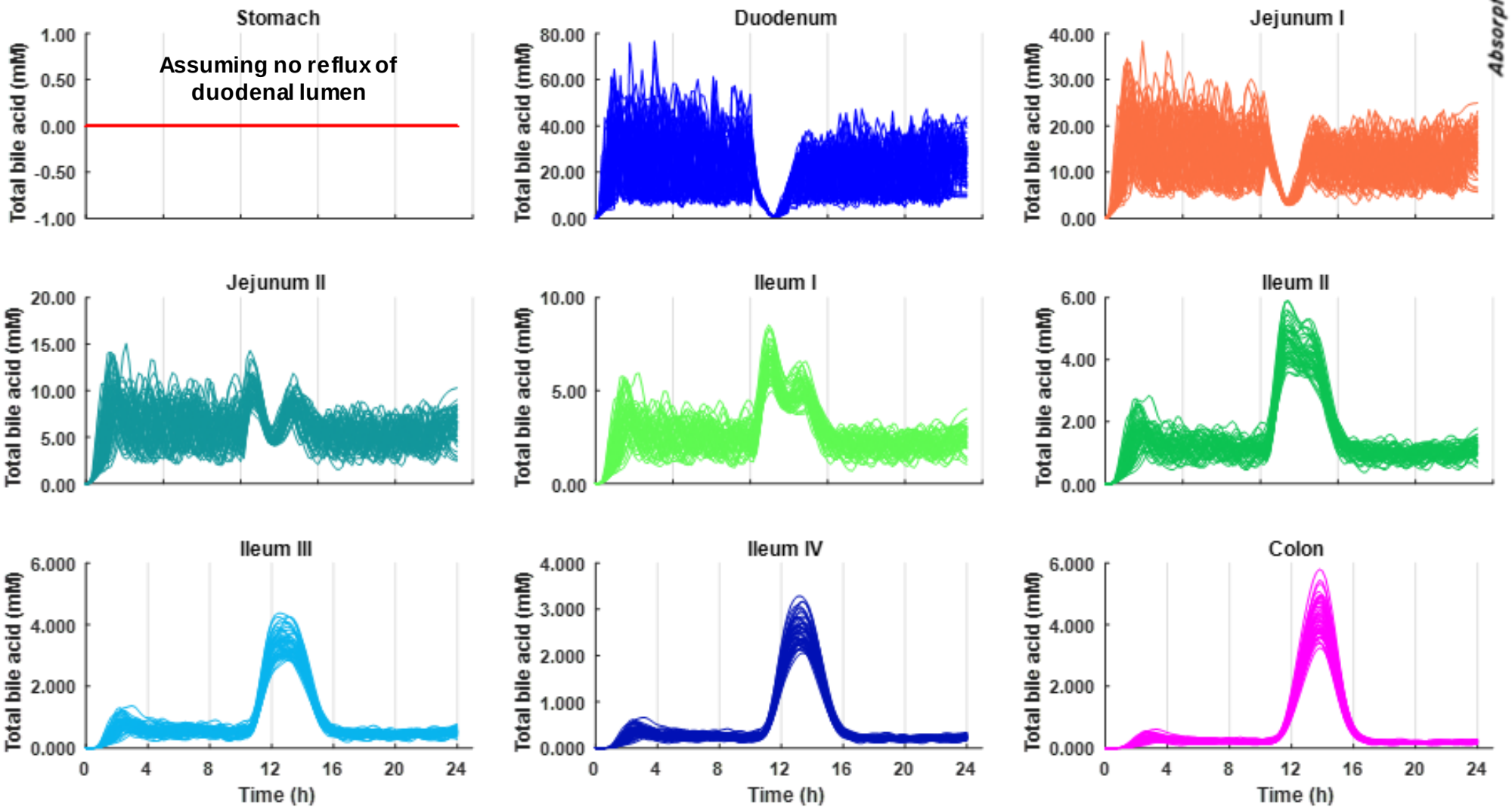
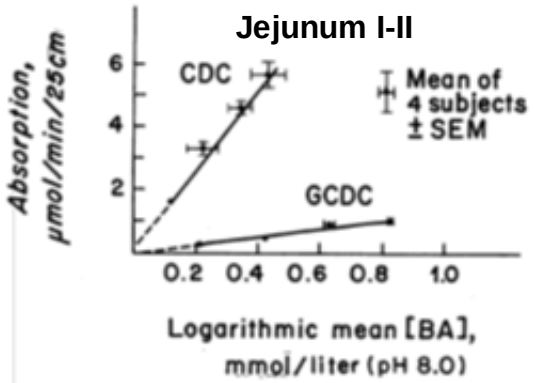
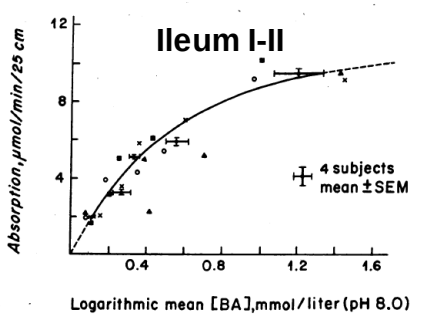
Regional Bile salt concentrations- Applying absorption kinetics (work in progress)

- Predicting regional GI BS concentration (1000 individuals)

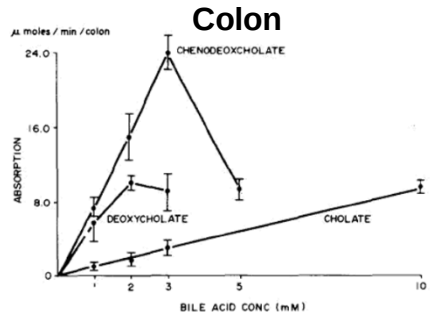




Chenodeoxycholic acid (CDC) & Glycochenodeoxycholic acid absorption kinetics (Krag et al 1974)



Taurocholate absorption kinetics (Krag et al 1974)



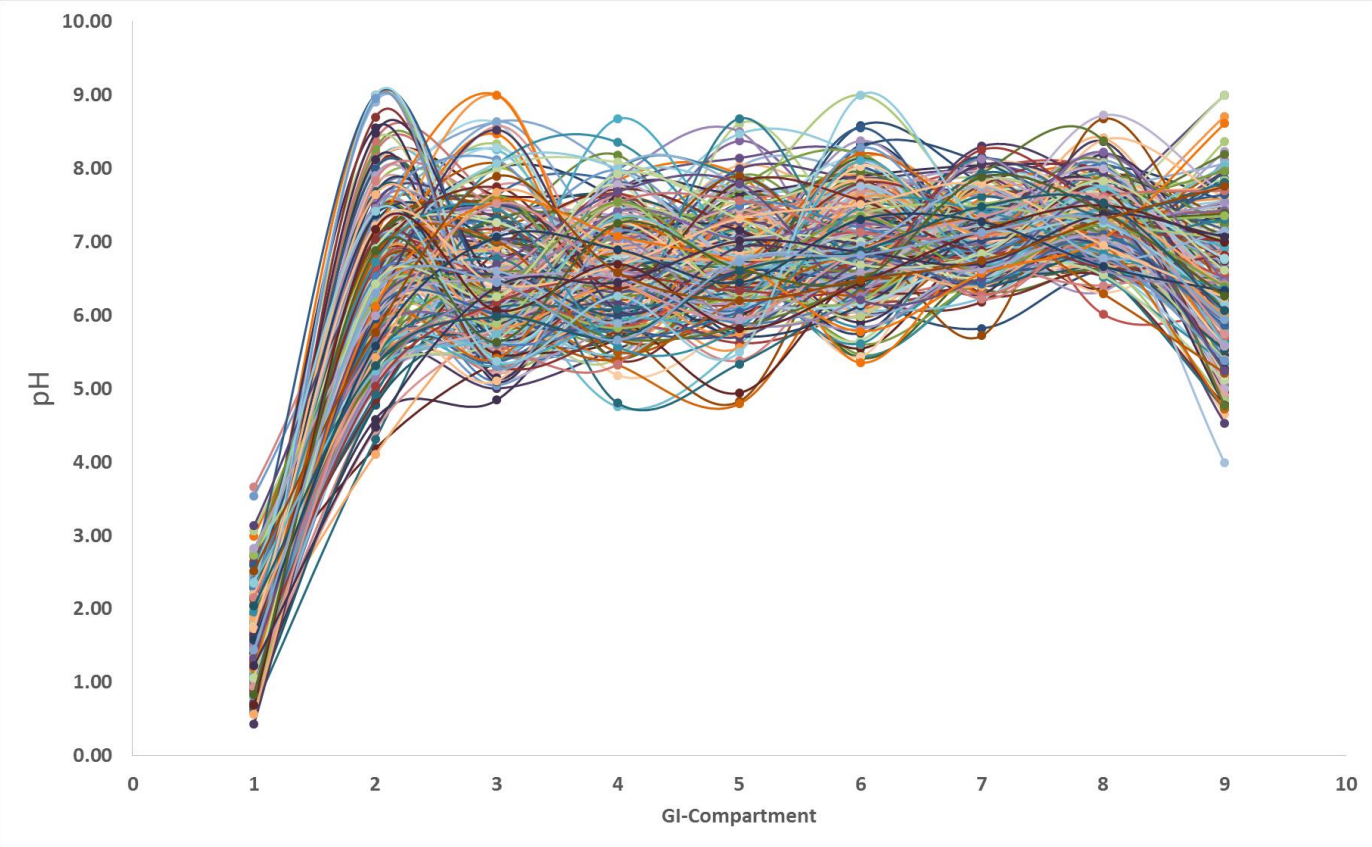
Mekhjian et al 1979

Intestinal pH- Fasted and Fed- Current Scenario

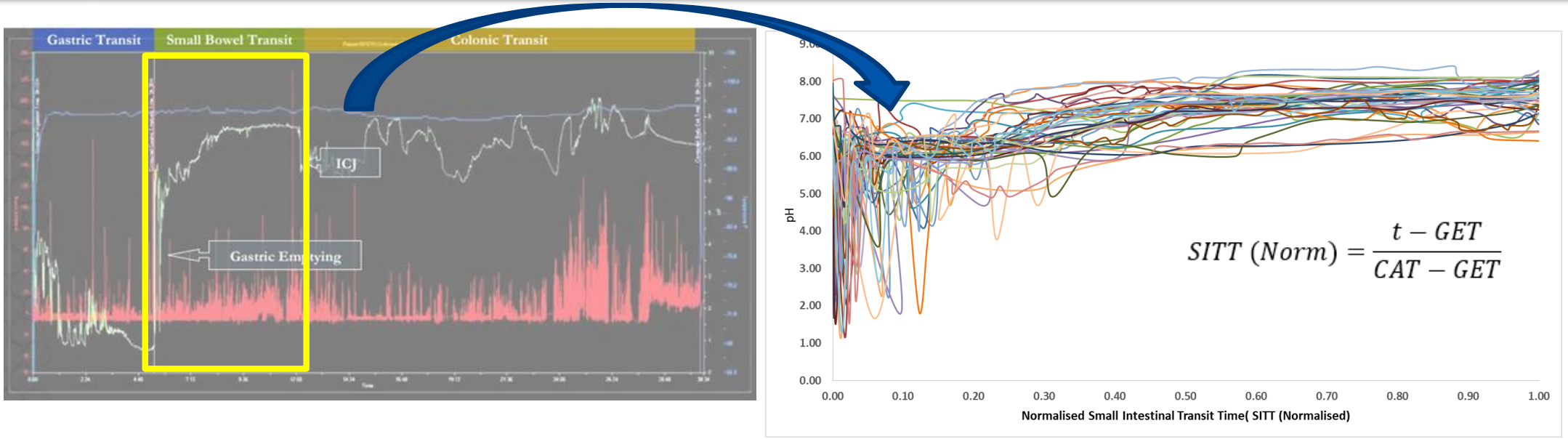
General | Water Physicochemical Properties | Luminal pH | Luminal Bicarbonate | Luminal Fluid Velocity | Luminal Bile Salts | GI Morphology | Luminal Boundary | Viscosity | Luminal Fluid Volume

	Stomach	Duodenum	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
pH Fasted	1.5	6.4	6.5	6.6	6.8	7	7.1	7.3	6.5
CV pH Fasted (%)	38	16	13	11	10	10	7	6	15
pH Fed	5	5.4	6.5	6.6	6.8	7	7.1	7.3	6.5
CV pH Fed (%)	25	11	13	11	10	10	7	6	15

Time-Dependent pH



Gradient Increase in Intestinal pH (work in progress)



GET: Gastric Emptying Time
CAT: Colon Arrival Time

- In proximal parts, pH values indicated strong fluctuations,
- Whereas in distal parts, pH values tend to have a very narrow range & only minor fluctuations
- The emptying of acidic contents from the stomach into the duodenum decreases the intestinal pH value for short time but then pH will increase again due to biliary secretions.

Unpublished in-house meta-analysis (Shriram Pathak 2017-2018)

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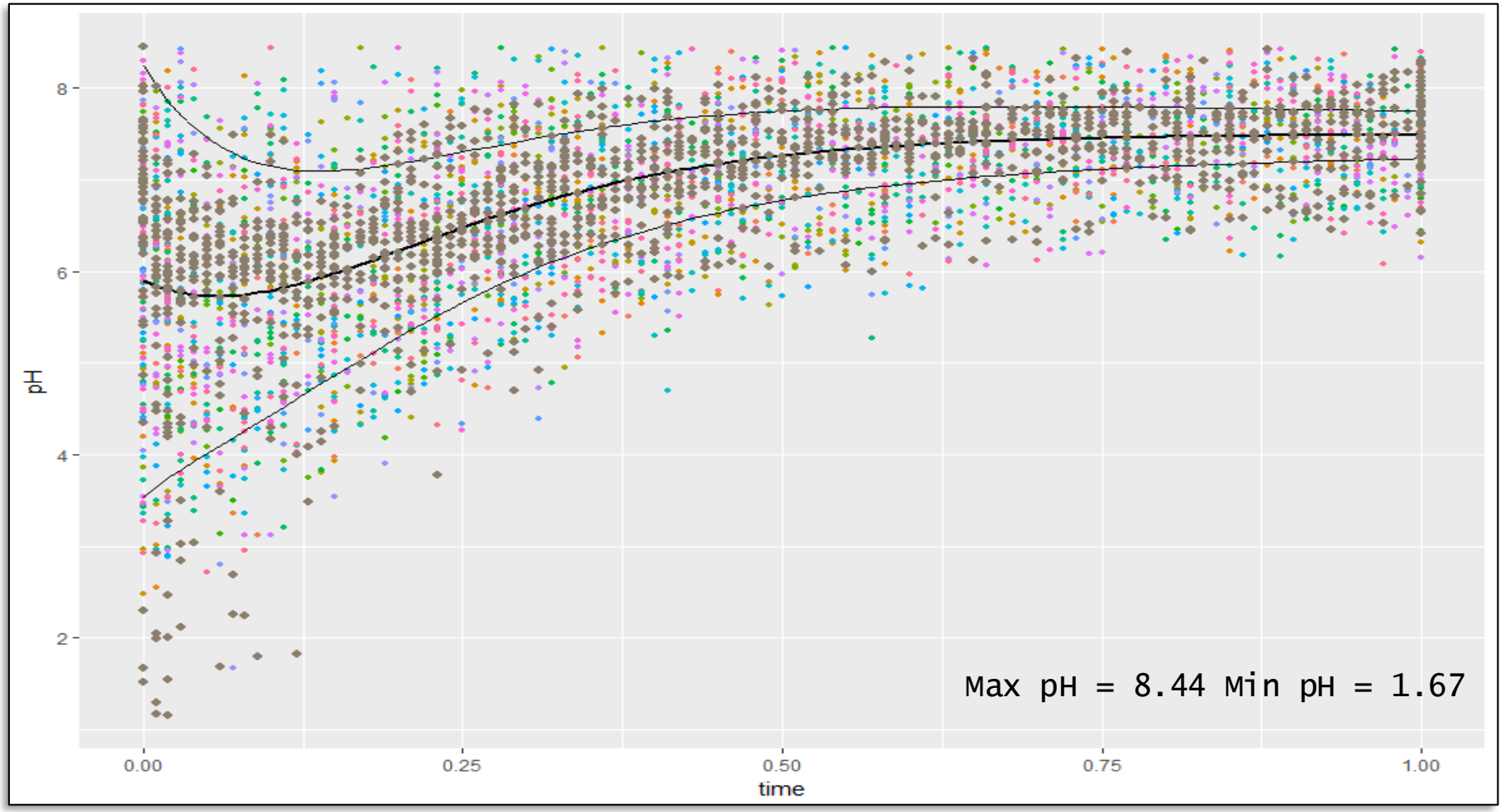
Dynamic pH model-Need for Time-dependent Variance (work in progress)



Observed fasted luminal pH data collected from multiple studies

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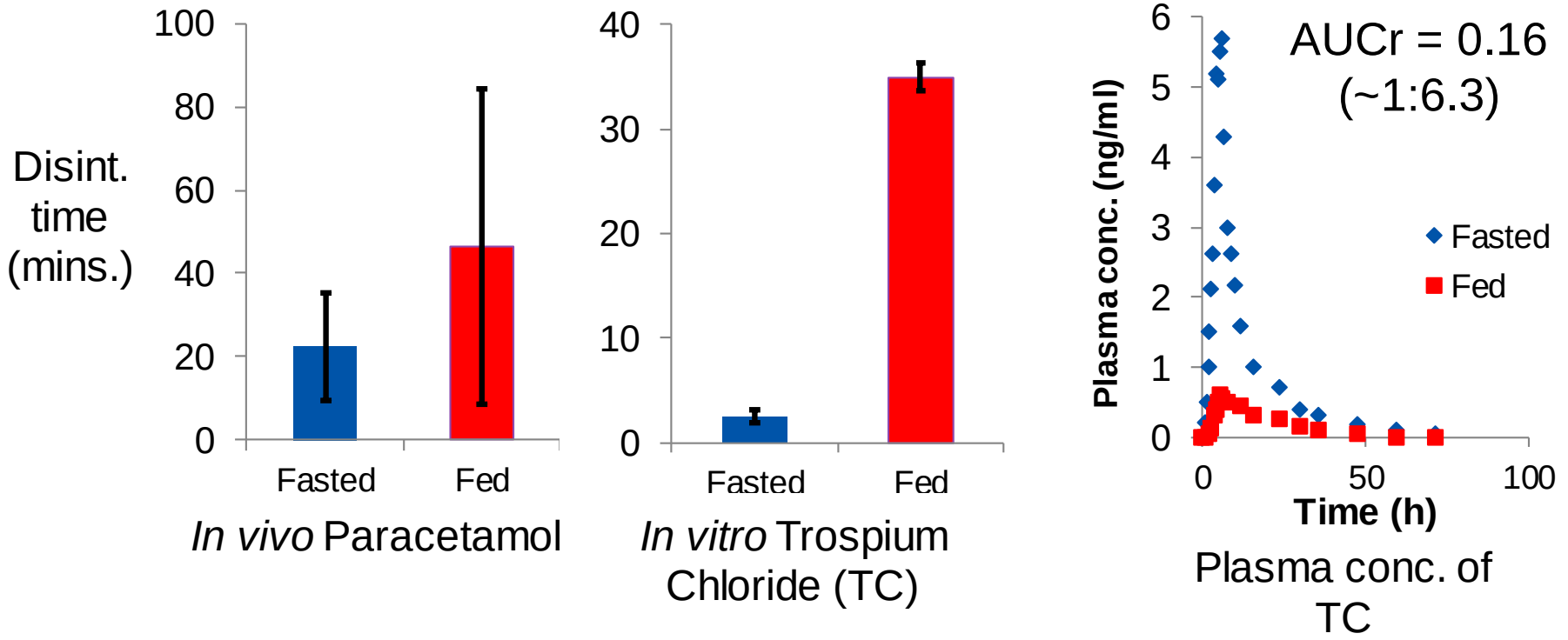
Food/ Viscosity: Disintegration of IR Formulation

- Food Effects: pH, bile salt concs., small intestinal blood flow, viscosity, gut wall metabolism, gastric emptying time, ... *etc*.
- Food can delay formulation disintegration (increasing *in vivo* disintegration time) AND change drug dissolution rate (slower hydration of the dosage form)



In vivo Paracetamol

In vitro Trospium Chloride (TC)

Plasma conc. of TC

Paracetamol: Kelly et al. 2003 *Pharm. Res*; TC: Radwan et al. 2012 *Biopharm Drug Dispos*

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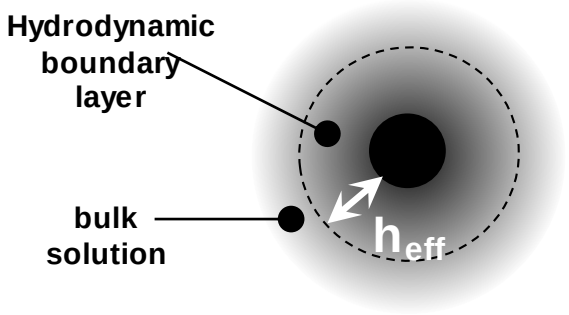
Impact of Viscosity effect on Dissolution



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

Parameters needed:
Lumen pH
Bicarbonate (mM)

a(t) – particle radius; ***C_b*** (t) – bulk concentration; ***S_{surf}*** **(t)** – solubility at particle surface; ***D_{eff}*** – effective diffusion coefficient; ***DR*** – Dissolution rate; ***h_{eff}***(t) – effective diffusion layer thickness; ***N*** – number of particles; ***t*** – time; **S**-Adjustable Scalar (optional)

h_{eff}

$$h_{eff}(t) = \frac{2\cdot a(t)}{Sh} \qquad Sh = 2 + 0.6\cdot Re^{1/2}\cdot Sc^{1/3} \qquad Sc = \frac{\upsilon}{D_{eff}} = \frac{\mu_f}{\rho_f D_{eff}} \qquad Re = \rho_f U_{total}\frac{2\cdot a(t)}{\mu_f} \qquad U_{total} = \left|V_2 - U_p\right|$$

D_{eff}

Inversely proportional to particle radius and viscosity

Apparent Viscosity (fasted-fed differences) (shear?)

(Noyes & Whitney, 1897; Wang & Flanagan, 1999; Further discussion: Sugano, 2010)

Total Relative Velocity (U_{total}) ?

In vitro (e.g., USP II, µDiss axial and tangential) reasonably well characterised

In vivo gut - poorly characterised

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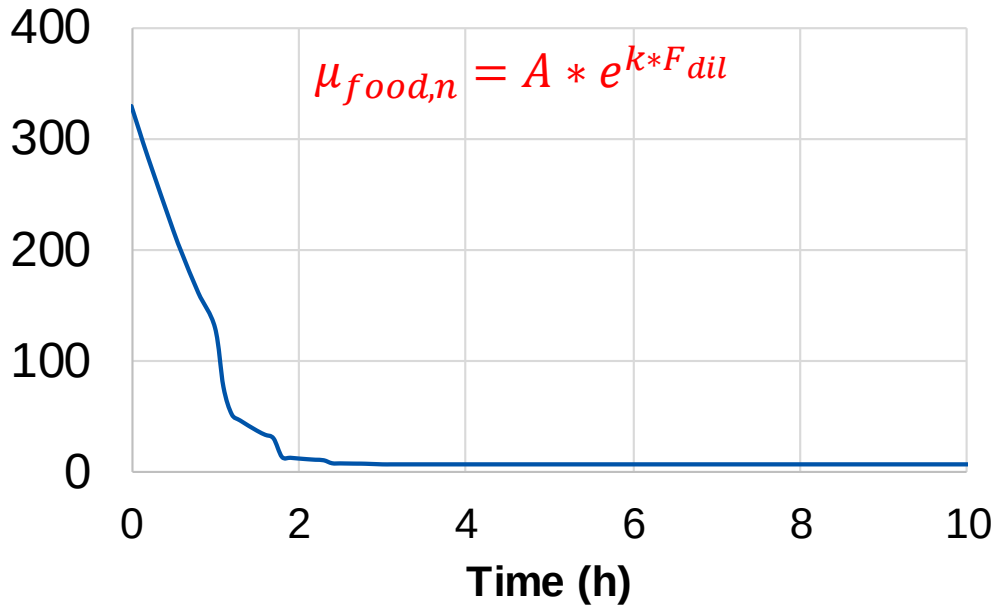
Static vs. Dynamic Viscosity of Luminal Contents

Fed state Radwan et al. (2012) *BiopharmDrugDisp*
FDA Meal (Volume of food 460 mL)

Dynamic dilution (v18)

Apparent Viscosity at shear rate of 50 s^{-1}



Caveat: Model assumes well mixed contents (food, fluid), But

IF the Magenstrasse route is followed (fasted-like gastric emptying rate of fluid drink and drug) then this model does not apply to the stomach
(Magenstrasse: Weitschies and co-workers)

Future work: better characterisation of in vivo shear including it's regional values and variability

Static Model (v17)

General | Water Physicochemical Properties | Luminal pH | Luminal Bicarbonate | Luminal Fluid Velocity | Luminal Bile Salts | GI Morphology | Luminal Boundary | Viscosity | Luminal Fluid Volume

	Stomach	Duodenum	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
Fasted									
Apparent Viscosity Mean (cP)	3	3	3	3	3	3	3	3	3
CV (%)	71	71	71	71	71	71	71	71	71
Fed									
Apparent Viscosity Mean (cP)	232	65	33	12	9	3	3	3	3
CV (%)	32	27	36	14	2	71	71	71	71

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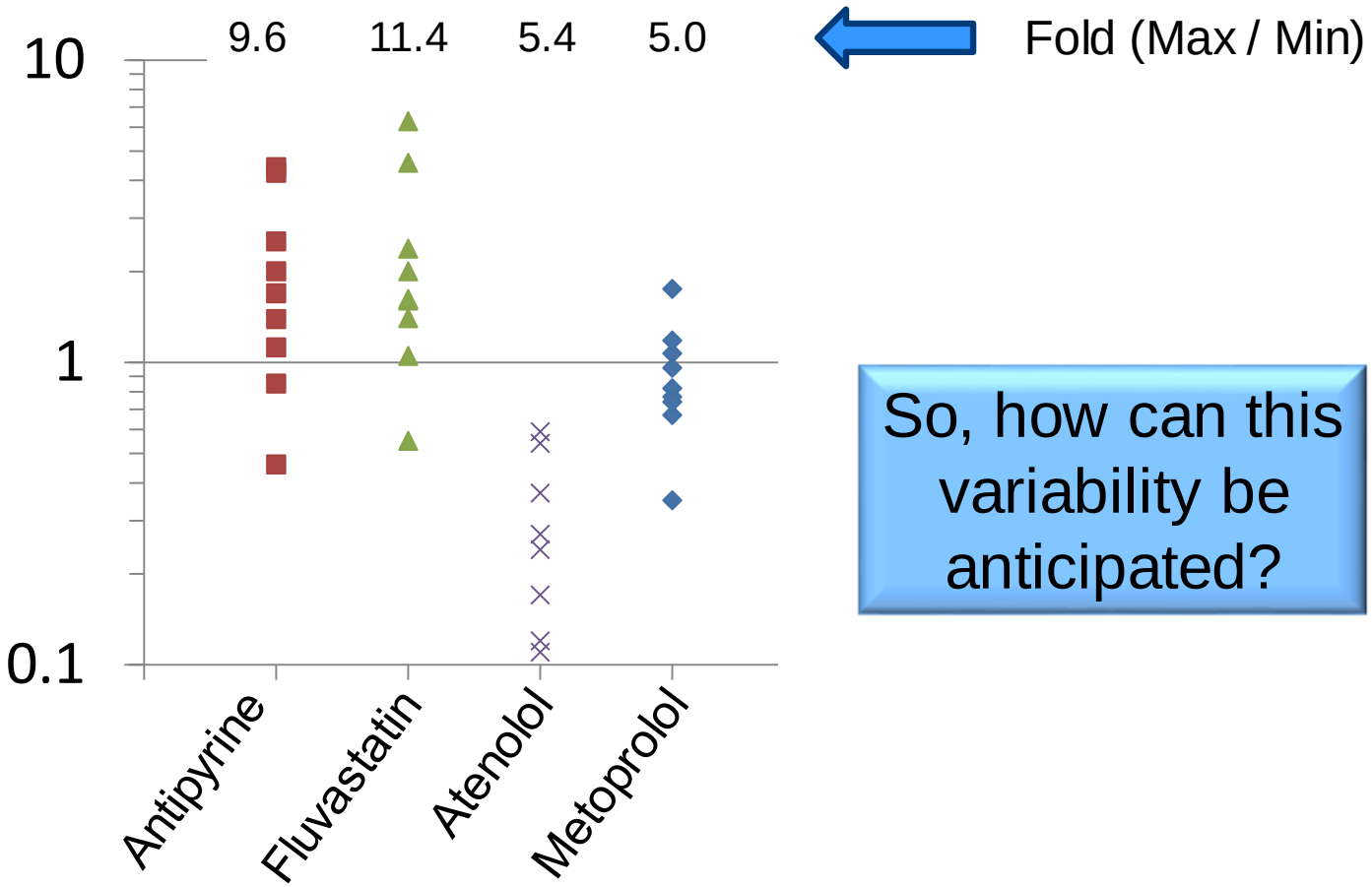
Embracing Between Subject Variability: Gut Wall Permeability

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

$f_{unbound}$ = 1 (non-micellar perfusate)

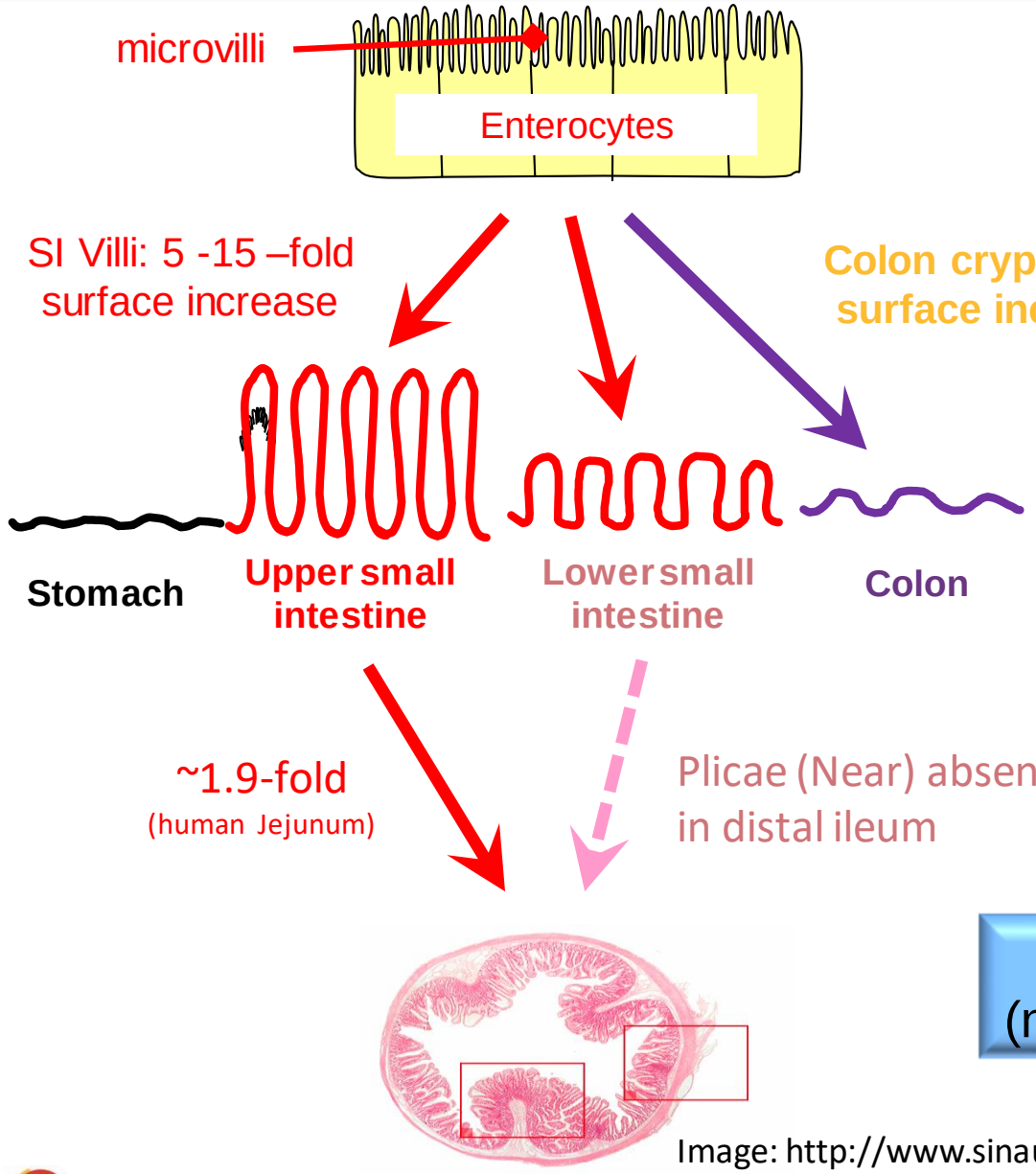


Individual measurements in 9 subjects*

So, how can this variability be anticipated?

*Lindahl *et al.* 1996 *CPT*

Embracing Variability: Sources of P_{eff} Variability (Passive)



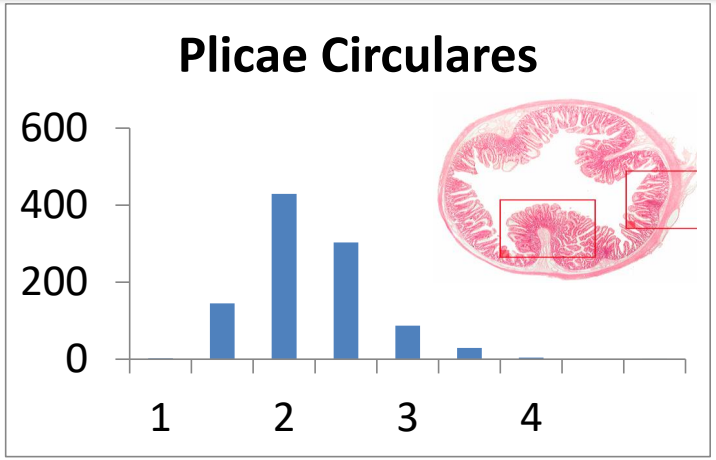
In vivo: Epithelial Surface

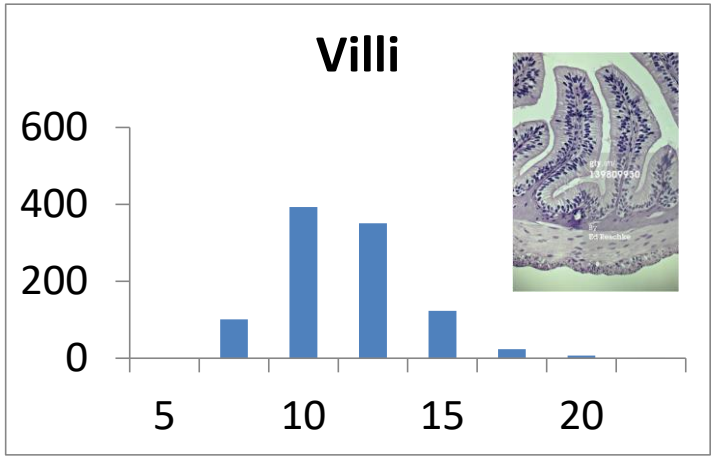
In vivo: Structure of the intestinal mucosa

In vivo: Plicae Circulares (not present in rat / dog / mouse)

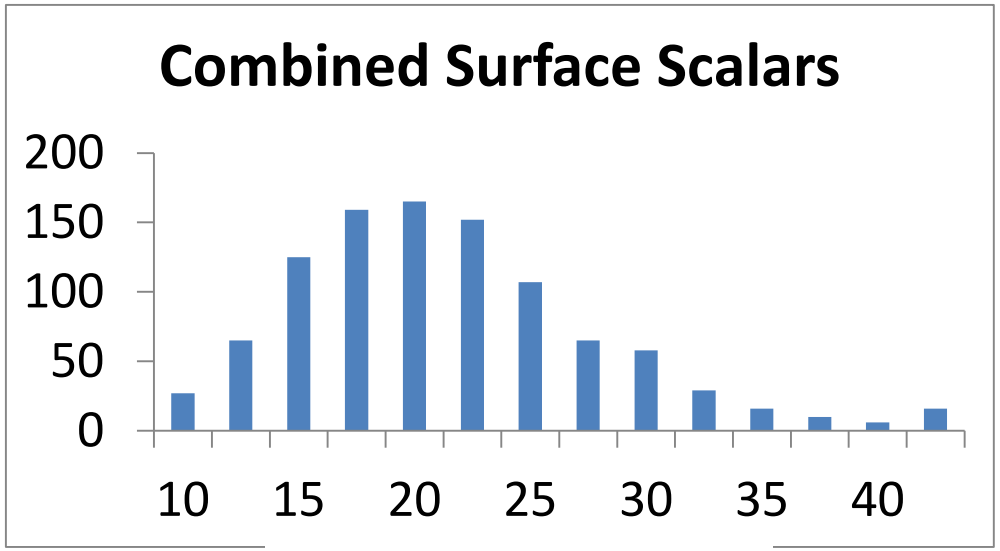
Image: http://www.sinauer.com/wood/Contents/labs/epith/091/91-01.html

Embracing Between Subject Variability: Gut Surface Area Expansion Scalars





Human MechPeff Model*



Combined Surface Area Scalar: Mean (Geomean): 20 (19)

*Posters: Deven Pade W5029 and W5030
Paper with algorithm (rodent):
Pade et al, 2017, *BiopharmDrugDisp* 38 94

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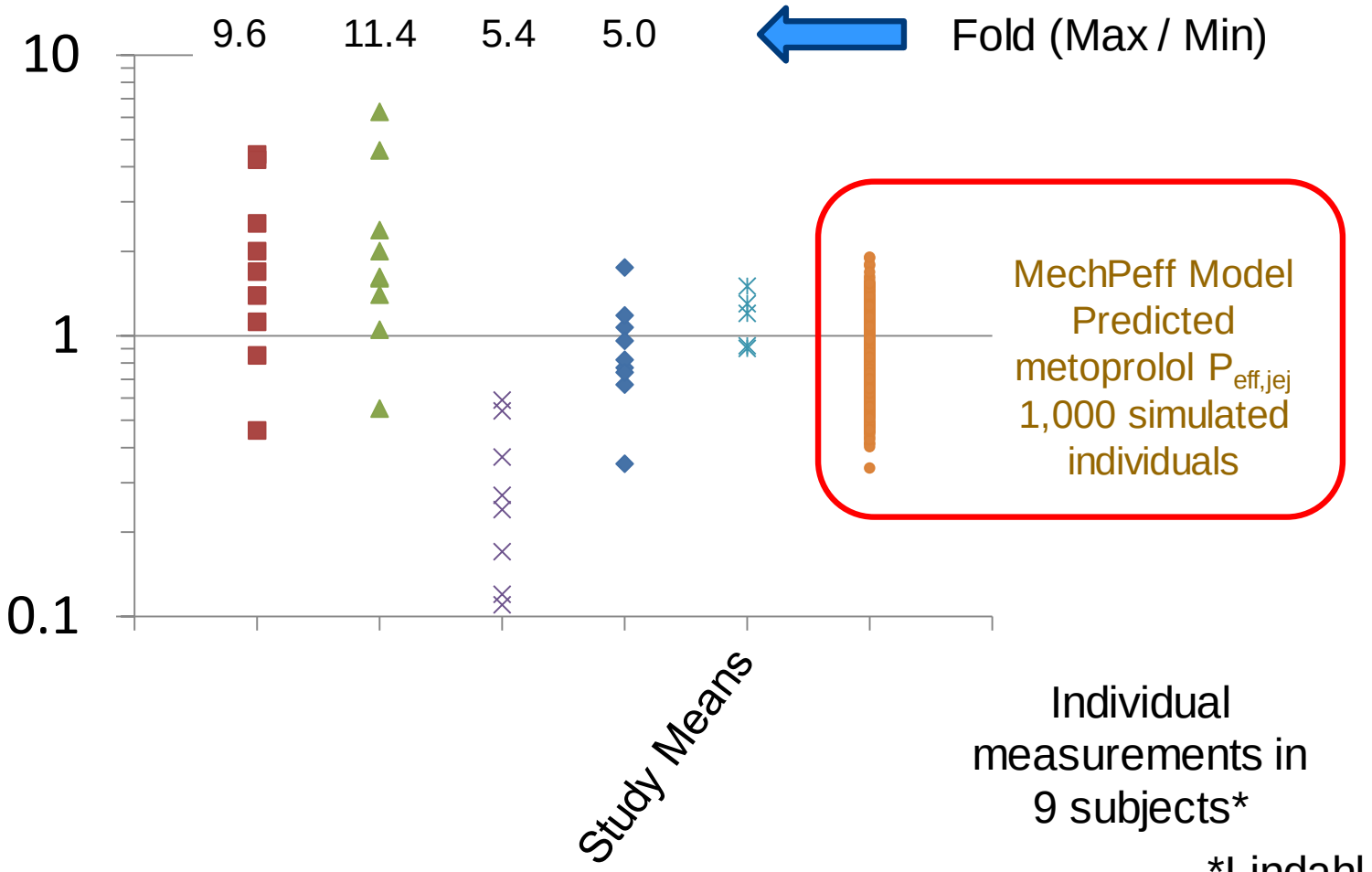
Embracing Between Subject Variability: MechPeff Model (Passive Permeability)

$$P_{eff} = \left(\left(\left(P_{Trans,0} \cdot f_{neutral,pH} + P_{para} \right) \cdot \boldsymbol{ACC} \cdot \boldsymbol{MVE} \cdot fu_{UBL} \right)^{-1} + \left(P_{UBL} \right)^{-1} \right)^{-1} \cdot \boldsymbol{FEp}$$

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



MechPeff allows the prediction of passive regional Peff and its inter-individual variability based on intestinal morphology

Individual measurements in 9 subjects*

*Lindahl *et al.* 1996 *CPT*

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Thank You!