A Dynamic Bile Salt Model to Predict Bile Salt Disposition within the GI Luminal Fluids

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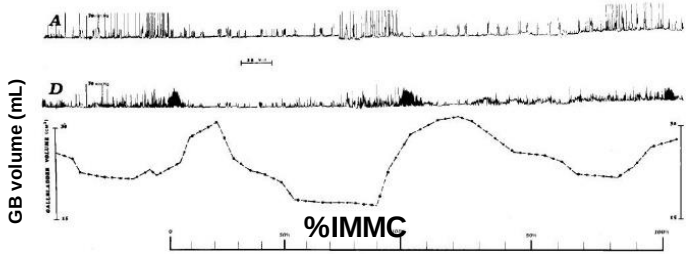
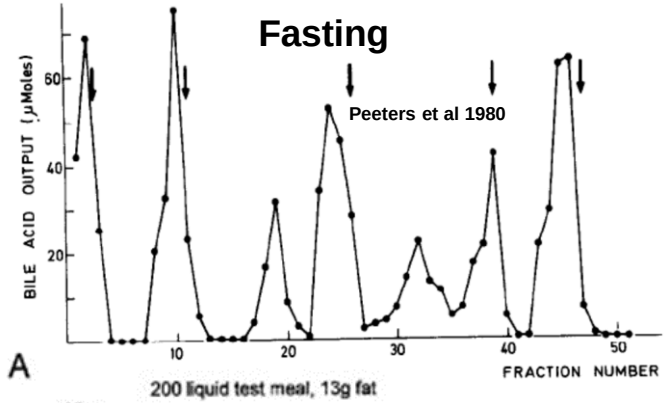
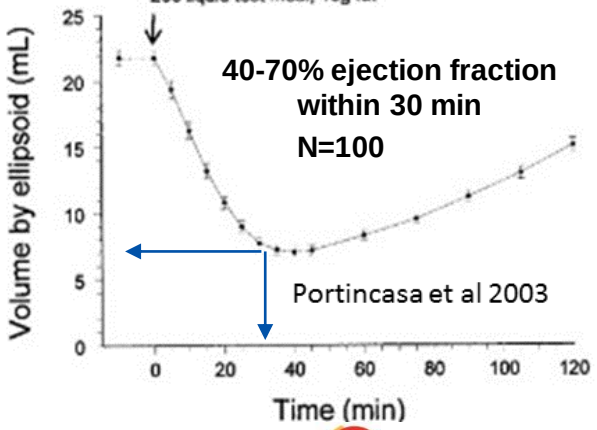
Why we need a Dynamic Bile Salt Model

Human Physiology
coordinated Biliary-GI tract motility

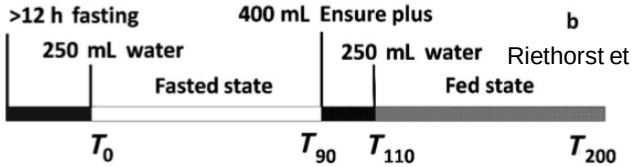


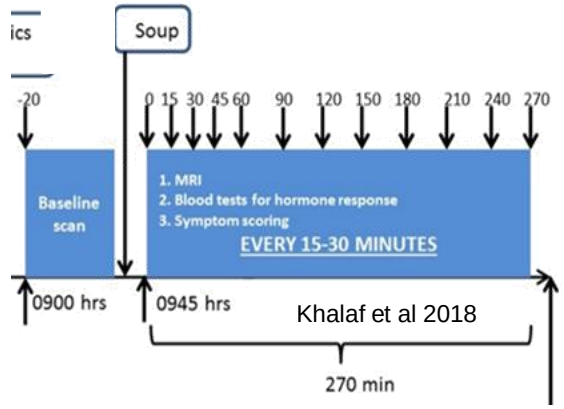




Current situation

In vivo studies





Dynamic Mechanistic modelling

- Benefit for PBPK modelling
- Inform *in vivo* study design-sampling
- Contribute to better understanding of human physiology
- No additional inputs from users

Current PBPK Models

luminal fluid bile salt conc. in a given gut region is FIXED in a given subject

	Stomach	Duodenum	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
CMC Fasted (mM)	1	1	1	1	1	1	1	1	1
[Bile] Fasted (mM)	0.29	3.31	2.3	3.55	1.25	1.25	1.25	1.25	0.6
CV [Bile] Fasted (%)	141	97	100	42	30	30	30	30	50
CMC Fed (mM)	1	1	1	1	1	1	1	1	1
[Bile] Fed (mM)	0.29	8.74	10.03	4.79	5.86	8.61	8.06	5.96	0.6
CV [Bile] Fed (%)	100	79	73	66	84	88	65	65	50

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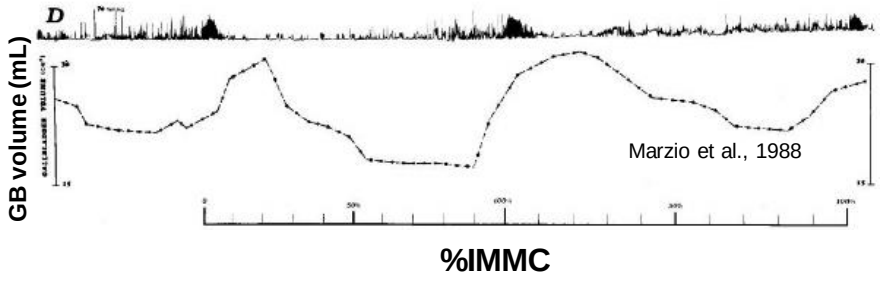
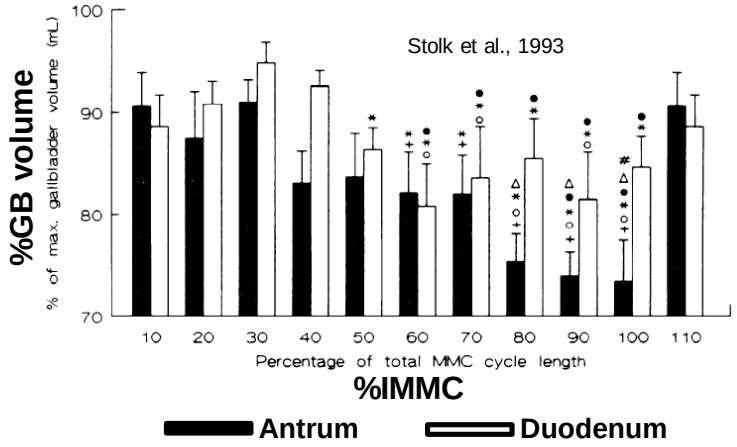
Why we need a Dynamic Bile Salt Model

Gallbladder (GB) motility profiles are not the same per IMMC per individual

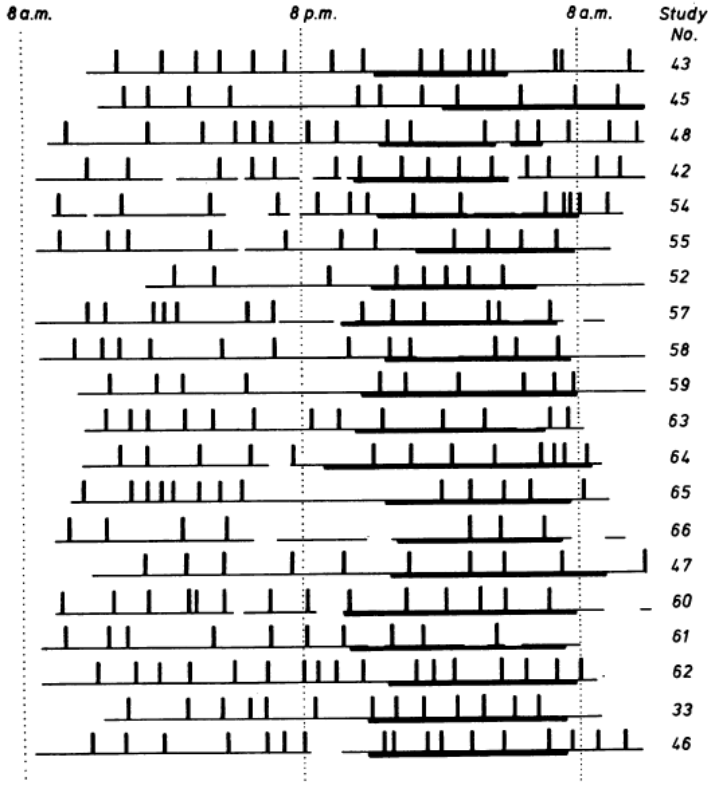


- GB emptying depends on origin of IMMC

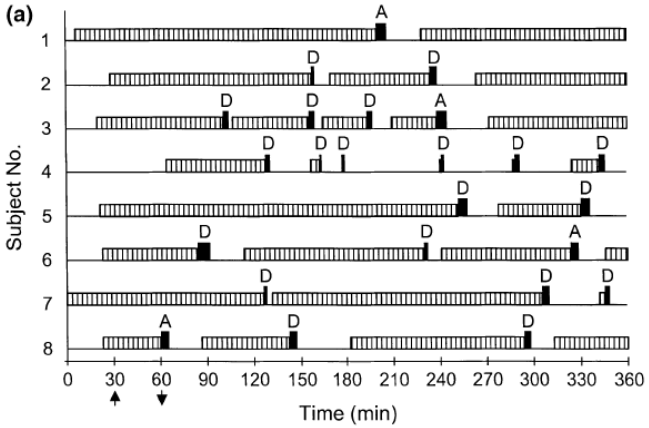


Converting %GBV vs %IMMC to actual GBV (mL) and IMMC (h), **<u>intra- and inter-subject</u>** variability can be obtained

Tompson et al 1980



Luiking et al 2002

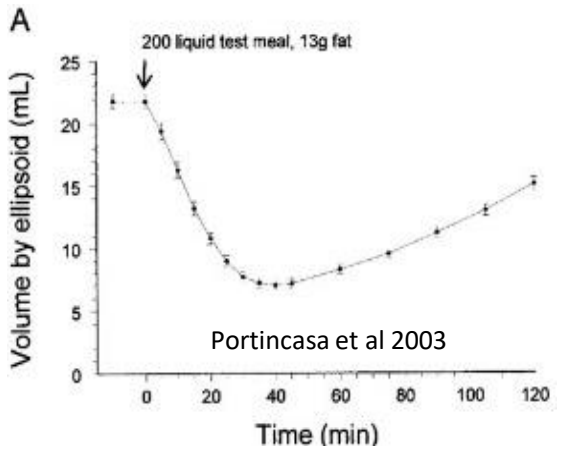


In house meta-analysis (manuscript in preparation)

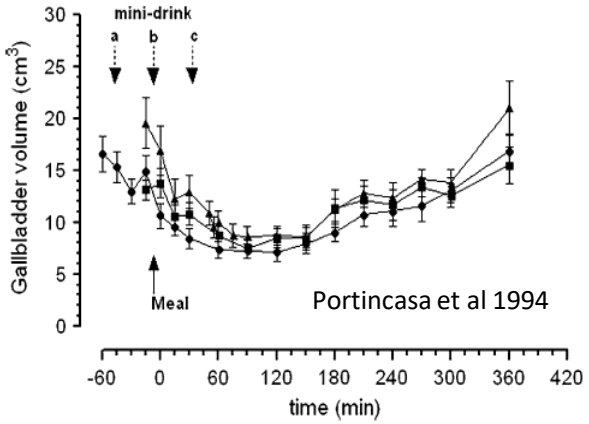
- Mean ±SD for the duration of IMMC based on origin
- Probability of the IMMC starting from different origin

Why we need a Dynamic Bile Salt Model

- Transition from fed to fasted state and vice versa

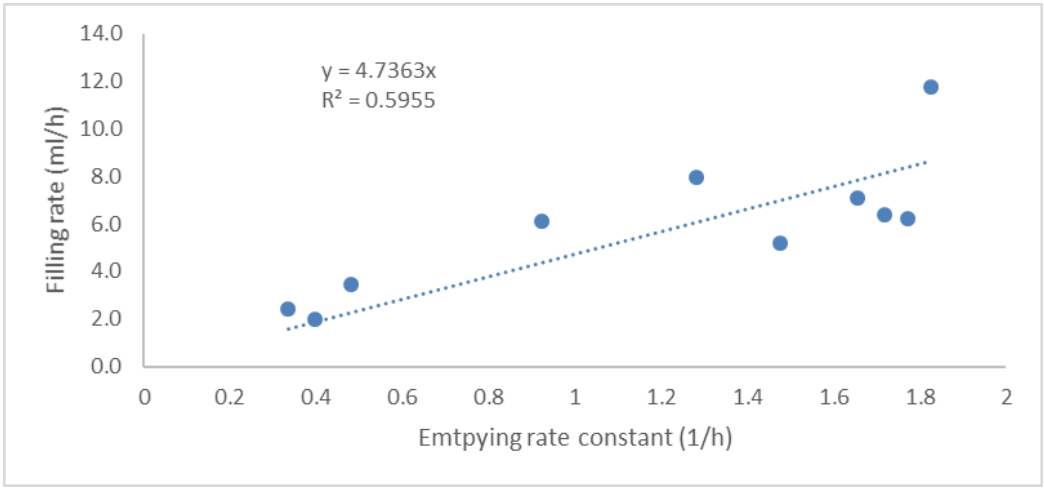


Portincasa et al 2003



Portincasa et al 1994

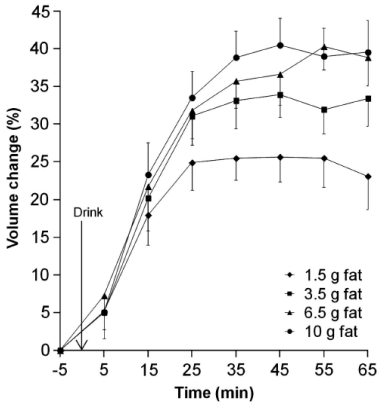
GB Filling Rate vs. Emptying Rate Constant



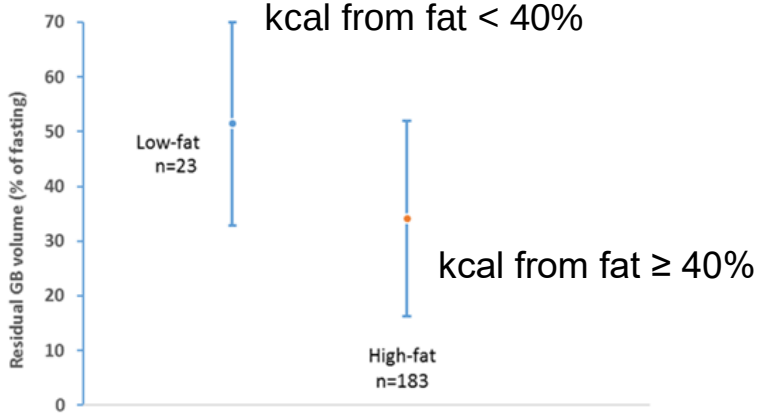
In-house meta-analysis (manuscript in preparation)

- Effect of high and low fat meal on postprandial GB residual volume & the duration of emptying phase should be accounted for

In vivo (an example)



Marciani et al 2013



	Tem (h)	
	Low-fat	High-fat
Total N	23	183
Weighted mean	0.614	1.069

Tem = duration of emptying phase

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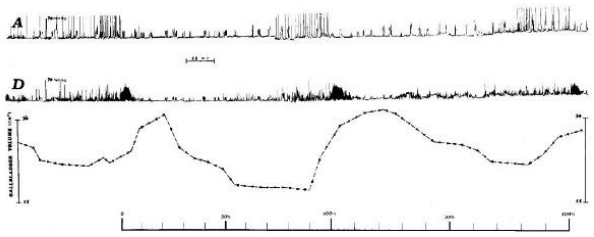
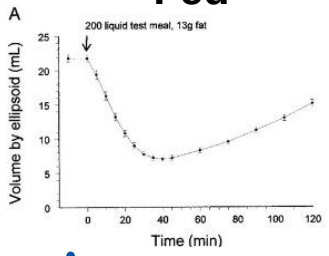
V18- Advanced Dynamic Bile Salt Model (ADBSM)

Fasted



Fed



Gallbladder's time-dependent volume changes linked to IMMC & Fed conditions are generated separately and used to calculate $k_{filling}$, $k_{emptying}$, **hepatic bile flow rate (mL/h)** and **BS mass (mmol) ejected.**

Liver

BS mass rate (mmol/h)
Hepatic bile flow rate (mL/h)

$k_{filling}$ / fr

BS mass rate*fr (mmol/h)

$k_{filling}$ (h^{-1})

BS mass rate*(100-fr) (mmol/h)

Hepatic bile flow (mL/h)

Gallbladder

$k_{emptying}$ (h^{-1})
BS mass ejected (mmol)

Pappcoef, Km, Jmax, favail

Jejunum II

Kt_{Jej1}*BSm_{JejI}

Jejunum I

Kt_{duo}*BSm_{Duo}

Duodenum

Kt_{JejII}*BSm_{JejII}

Ileum I

Kt_{IleumI}*BSm_{IleumI}

Ileum II

$Kt_{IleumII}$*$BSm_{IleumII}$

Ileum III

$Kt_{IleumIII}$*$BSm_{IleumIII}$

Ileum IV

$Kt_{IleumIV}$*$BSm_{IleumIV}$

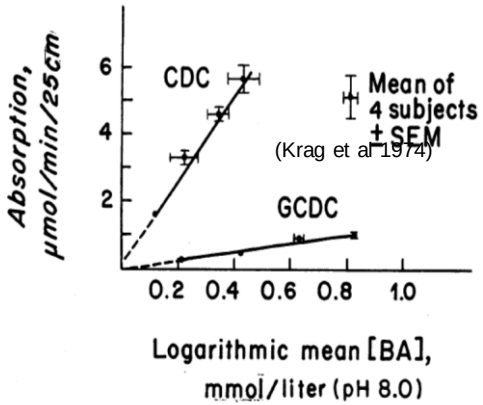
Colon

Kt_{Colon}*BSm_{Colon}

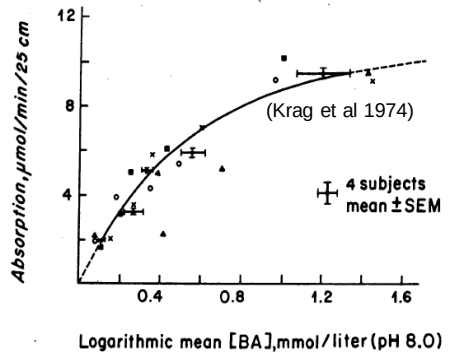
Faeces

Absorption kinetics of Bile Salts
(perfusion studies in humans)

Jejunum I-II



Ileum I-IV

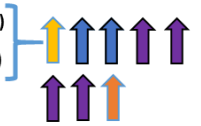


fr= %Hepatic bile entering Gallbladder

$k_{filling}$ (h^{-1}): filling constant rate of Gallbladder

BSm=Mass of Bile Salts (mmol)

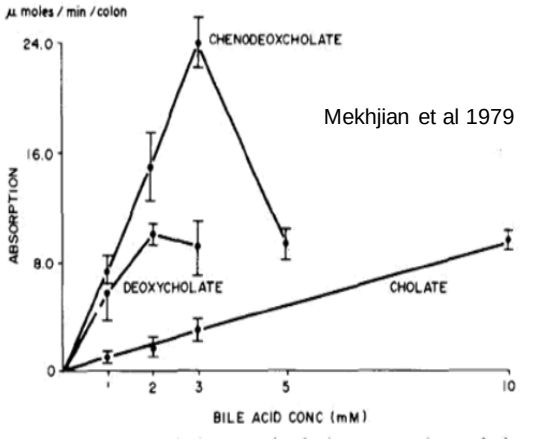
kt= transit rate constants (h^{-1})



Absorption parameters:
Pappcoef: Apparent permeability coefficient (mmol/h/mM)
Km: Apparent Michaelis constant (mmol)
Jmax: Apparent maximal transport velocity (mmol/h)
favail: fraction of BS available for absorption

Other secretions/absorptions rates of intestinal fluids handled by Fluid Dynamic Model

Colon



Mekhjian et al 1979

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V18- ADBSM - On Screen additions

Enterohepatic Recirculation (EHR) ○ Original Model ◉ Advanced Dynamic Bile Salt Model (ADBSM) High Fat Fed

Original Model | ADBSM

IMMC Parameters

		Duration of IMMC Cycle (h)		Probability (%)
Antral Origin	Mean	2.6	CV (%) 30.2	60
Duodenal Origin	Mean	1.3	CV (%) 60.3	40

Gallbladder Parameters

Gallbladder Residual Volume (%)

	Fasted		Fed
	IMMC Antral Origin	IMMC Duodenal Origin	
Mean	74	80.7	32.36
CV (%)	9.8	16.5	49.2

Maximal Gallbladder Volume (ml)
Mean 18.8 CV (%) 53.4

Initial Mass of Total Bile Salts in Gallbladder (mmol)
Mean 3.59 CV (%) 49.91

Duration of Gallbladder Emptying Fed State (h)
Mean 1.14 CV (%) 38.53

Liver Parameters

		Fasted	Fed
Hepatic Total Bile Secretion Rate (mmol/h)	Mean	1.07	1.92
	CV (%)	51.8	28.83
% Hepatic Bile Entering Gallbladder	Mean	70.3	
	CV (%)	32.1	

Bile Acid Absorption

	Active *				Passive **	
	Jmax (mmol/h)	CV (%)	Km (mM)	CV (%)	Abs. Rate (mmol/h/mM)	CV (%)
Jejunum I - II	0	30	0	30	0.42	8.57
Ileum I - IV	2.484	20.29	0.6	33.33	0	30
Colon	0	30	0	30	0.0575	30

	Jejunum I	Jejunum II	Ileum I	Ileum II	Ileum III	Ileum IV	Colon
Bile fraction available for absorption	0.15	0.15	0.25	0.25	0.25	0.25	1

Bile Salt Weighted Mean MWt (g/mol) 400

* Active uptake: J_{max} - maximum rate of transport (mmol/h); K_m - Michaelis Constant

** Passive: derived from linear regression of passive absorption rate (mmol/h) vs perfusate bile salt concentration (GCDC - jejunum, CDCA - colon) (mM)

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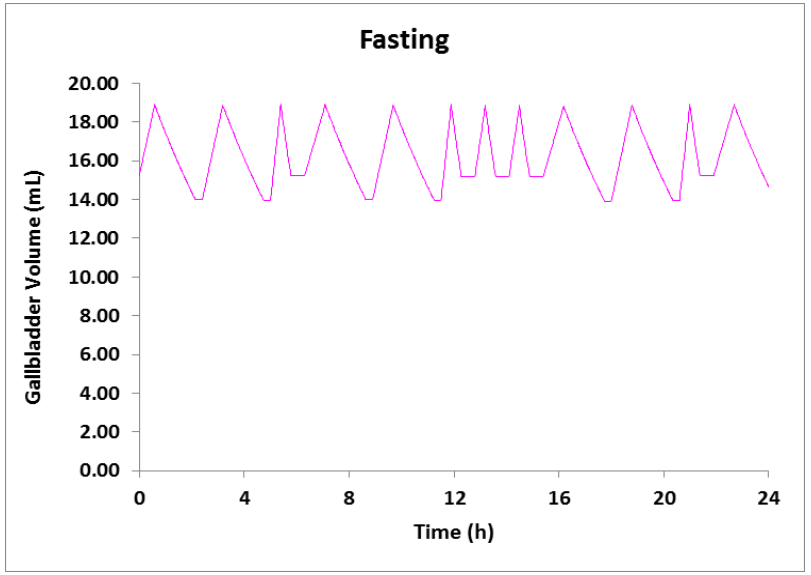
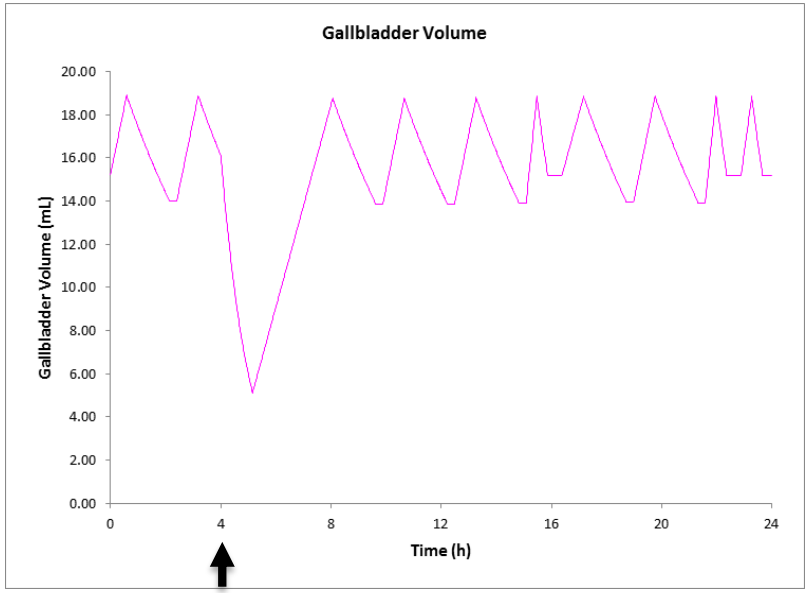
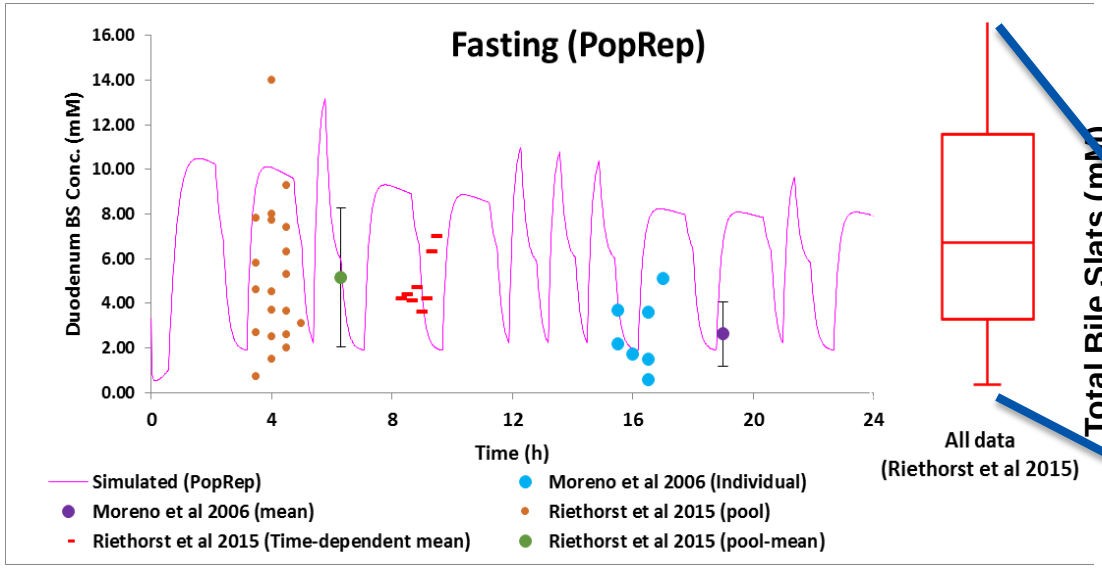
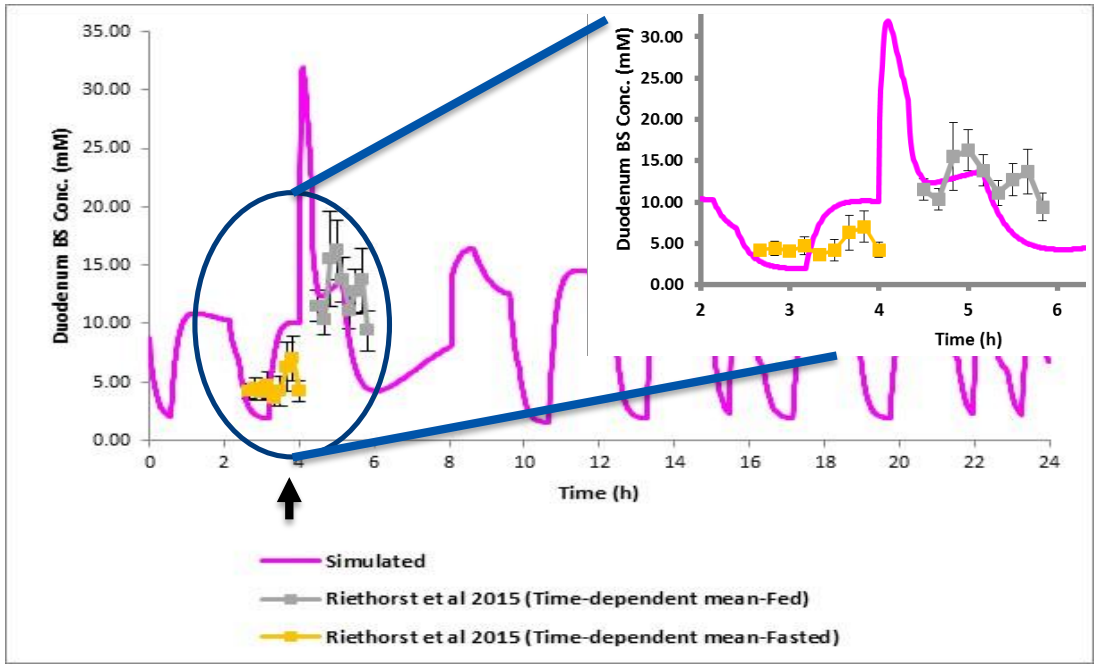
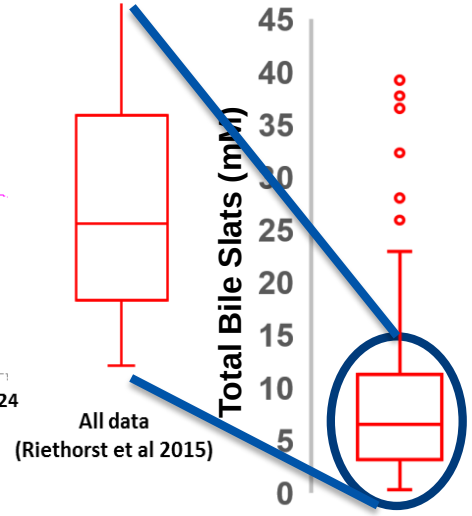
V18- ADBSM-Outputs (Healthy Volunteer Population Representative)











Boxplot of Fig. 2b fasted data in Riethorst et al 2015

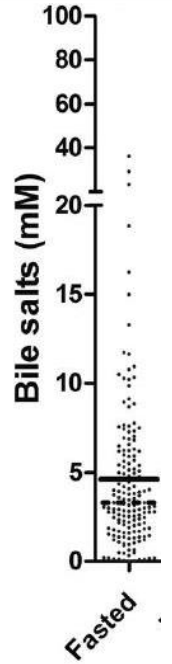


Fig. 2b in Riethorst et al 2015

- ADBSM requires accurate fluid volumes because otherwise the BS concs. won't be correct
- ADBSM is used for EHR of drug(s)
- The impact of the ADBSM for PBPK modelling of oral absorption is under investigation

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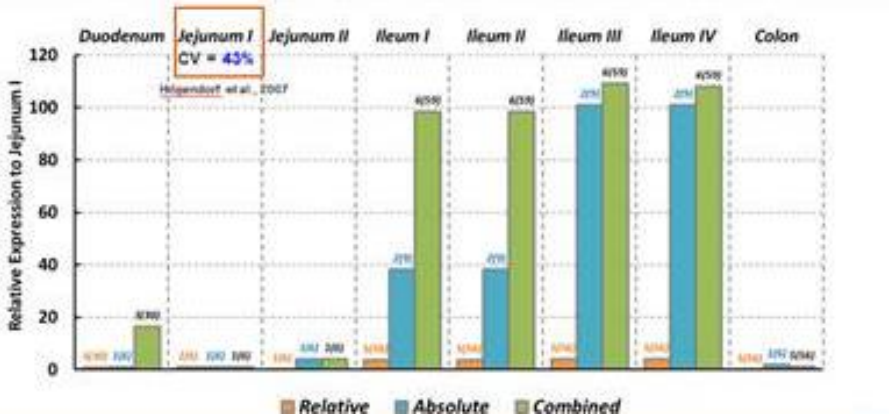
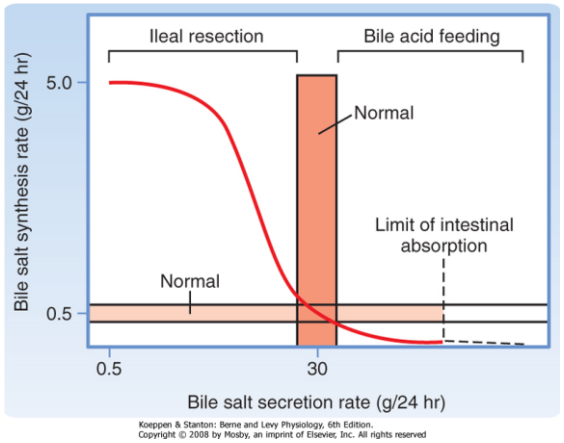
Future Work …

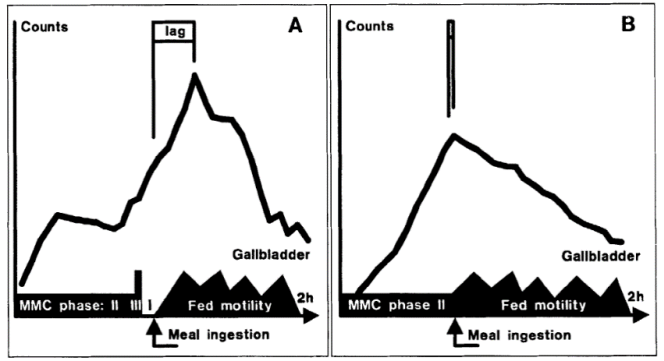
- Add a mechanistic hepatic model for the *de novo* synthesis and secretion of bile salts (Matlab® code is partially developed)
- Exploit the already implemented regional bile salt uptake transporter abundances in the GI tract for individual bile salt uptake kinetics (requires Jmax and Km for each bile salt)



- Negative feedback mechanism linking GI luminal bile salt concentration and hepatic synthesis-secretion rates



- Add a lag time to the Gallbladder emptying phase with respect to the IMMC phase at which a meal is administered



- Fully "connecting" IMMC phase, gastric and intestinal motility, and gallbladder kinetics etc. (covariate model)

E.øster-Jørgensen et al., 1992

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U.S. FOOD & DRUG ADMINISTRATION

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