Mechanism-based modelling of gastric emptying and bile release in response to caloric intake

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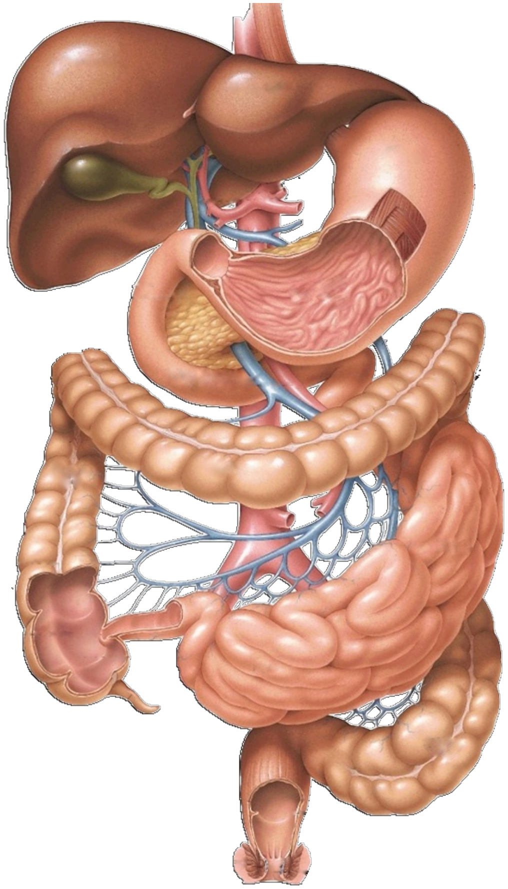
Background

- Majority of drugs administered orally
  - Convenient
  - Flexible
- However
  - Gastrointestinal system complex and not entirely understood
  - Increasing number of poorly soluble drugs*
    - Increased receptor-ligand affinity *(i.e. potency)*
    - Associated with highly variable absorption profiles
    - Absorption affected by intestinal secretions *(e.g. bile)*



*Biopharmaceutics Classification System (BCS) class II and IV

Williams et *al*., Pharmacol Rev. (2013)

Objectives

1. Establish mechanism-based models for:
   a. Gastric emptying *(GE)*
   b. Plasma cholecystokinin *(CCK)* levels
   c. Bile flow patterns to the duodenum
2. Characterize the influence of caloric intake on different system components
3. Explore the effect of Type 2 Diabetes Mellitus *(T2DM)*

Study design and data

Methods

Total 66 subjects

Water study[1]
10 T2DM / 10 HV

Water
100mL of water *(0 kcal)*

Glucose study[2]
8 T2DM / 8 HV

OGTT 25g
25 g of glucose
in 300mL water *(97 kcal)*

OGTT 75g
75 g of glucose
in 300mL water *(290 kcal)*

OGTT 125g
125 g of glucose
in 300mL water *(484 kcal)*

Liquid meals study[3]
15 T2DM / 15 HV

OGTT 75g
75 g of glucose
in 350mL water *(290 kcal)*

Low fat liquid meal
2.5 g fat, 13 g prot., 107 g carb.
Volume of 350mL *(500 kcal)*

Medium fat liquid meal
10 g fat, 11 g prot., 93 g carb.
Volume of 350mL *(500 kcal)*

High fat liquid meal
40 g fat, 3 g prot., 32 g carb.
Volume of 350mL *(500 kcal)*

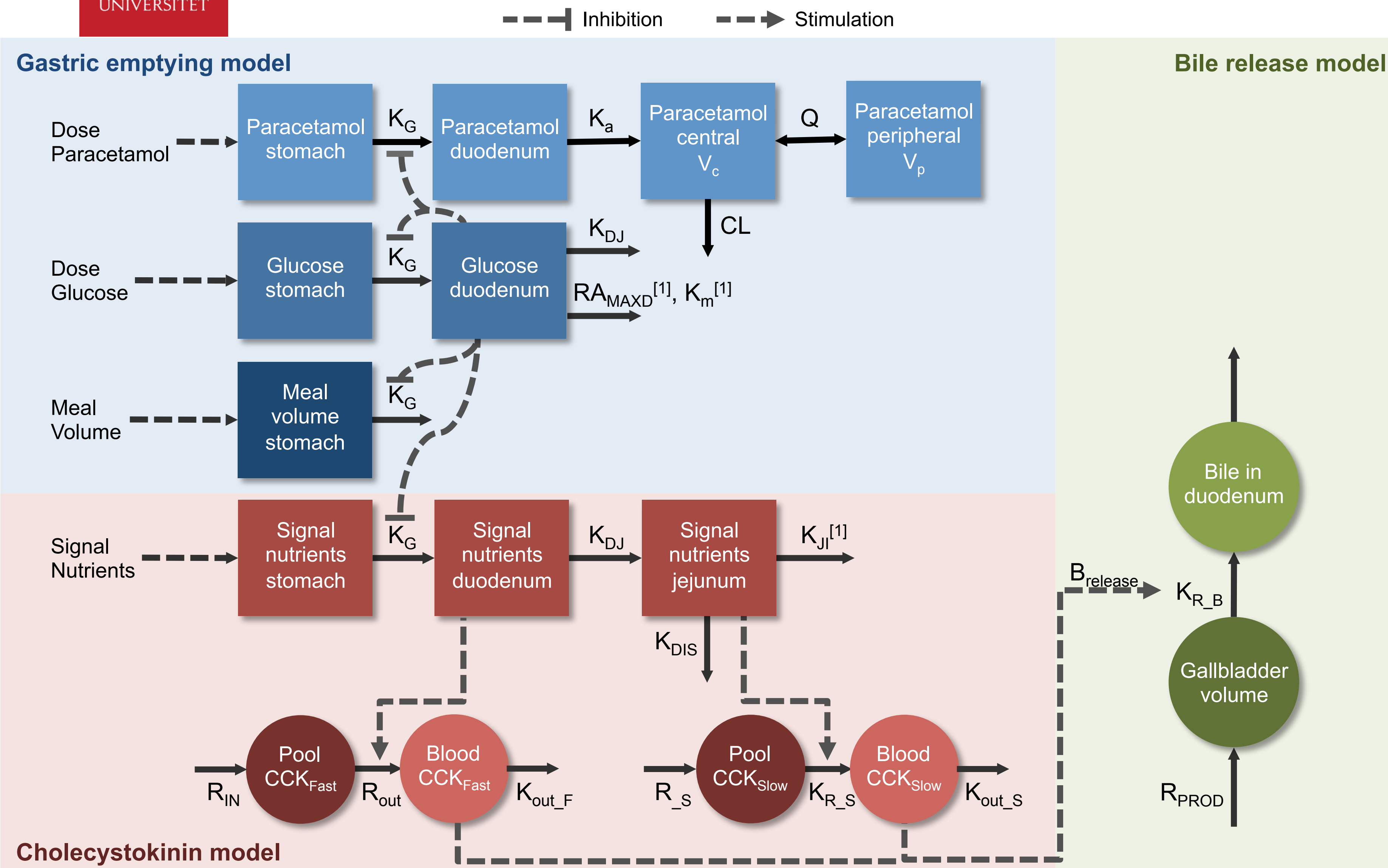
+ Gastric emptying marker
(dissolved paracetamol 1.5 g)

OGTT: Oral Glucose Tolerance Test
T2DM: Type 2 Diabetes Mellitus
HV: Healthy Volunteers *(matched on BMI, gender, age)*

[1] Hansen et *al.*, ClinicalTrials.gov identifier NCT01666223 | [2] Bagger et *al.*, JCEM. (2011) | [3] Sonne. et *al.*, ADA 73 (2013)

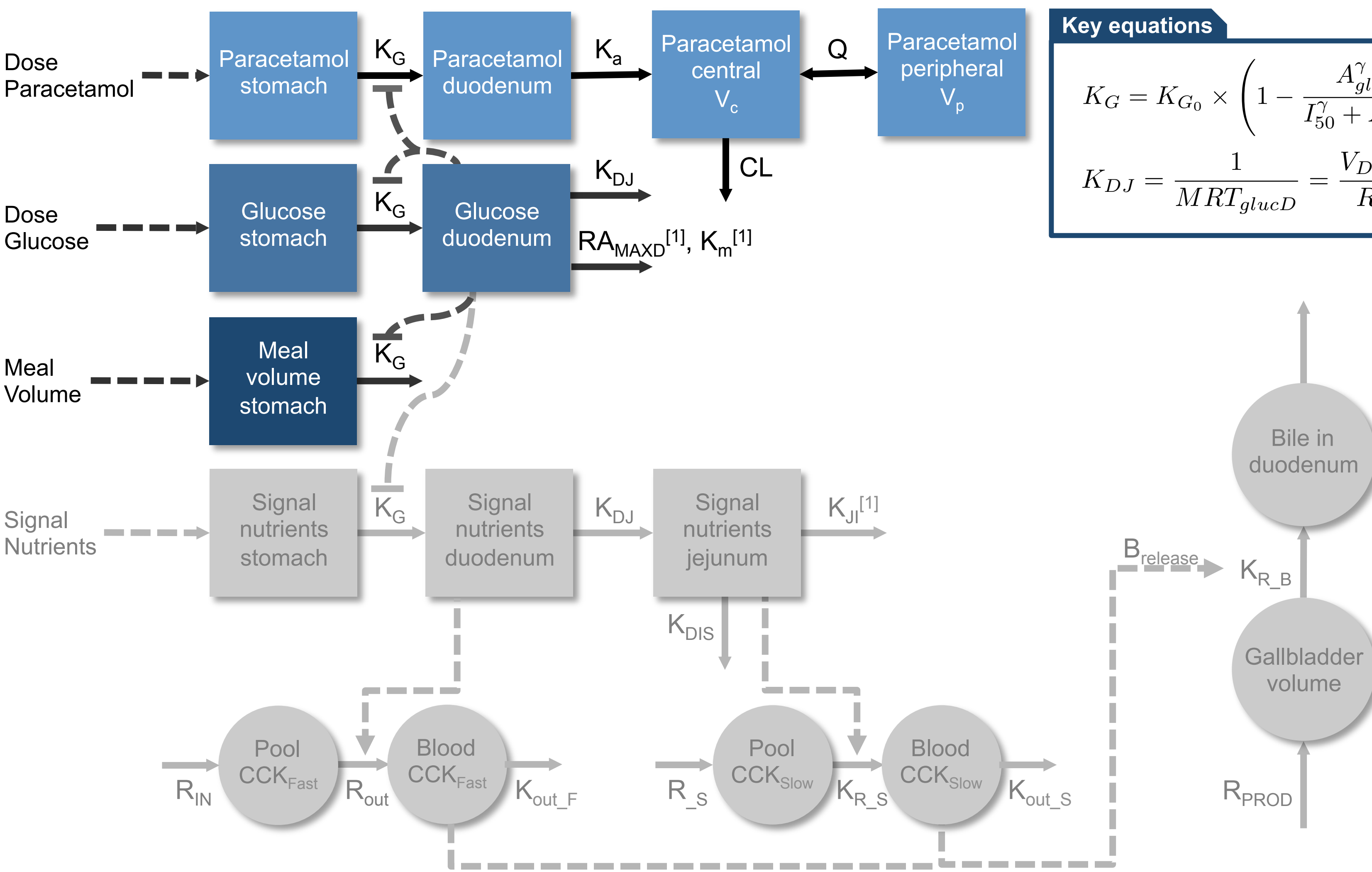
System overview

Methods



Gastric emptying *(GE)* model

Methods



Key equations

$$K_G = K_{G_0} \times \left(1 - \frac{A_{glucD}^{\gamma}}{I_{50}^{\gamma} + A_{glucD}^{\gamma}}\right)$$

$$K_{DJ} = \frac{1}{MRT_{glucD}} = \frac{V_{Duodenum}}{Rate_{GE}}$$

[1] Alskär et *al.* PAGE 22 (2013) Abstr 2897 | [2] Ogungbenro et *al.*, Pharm Res. (2011)

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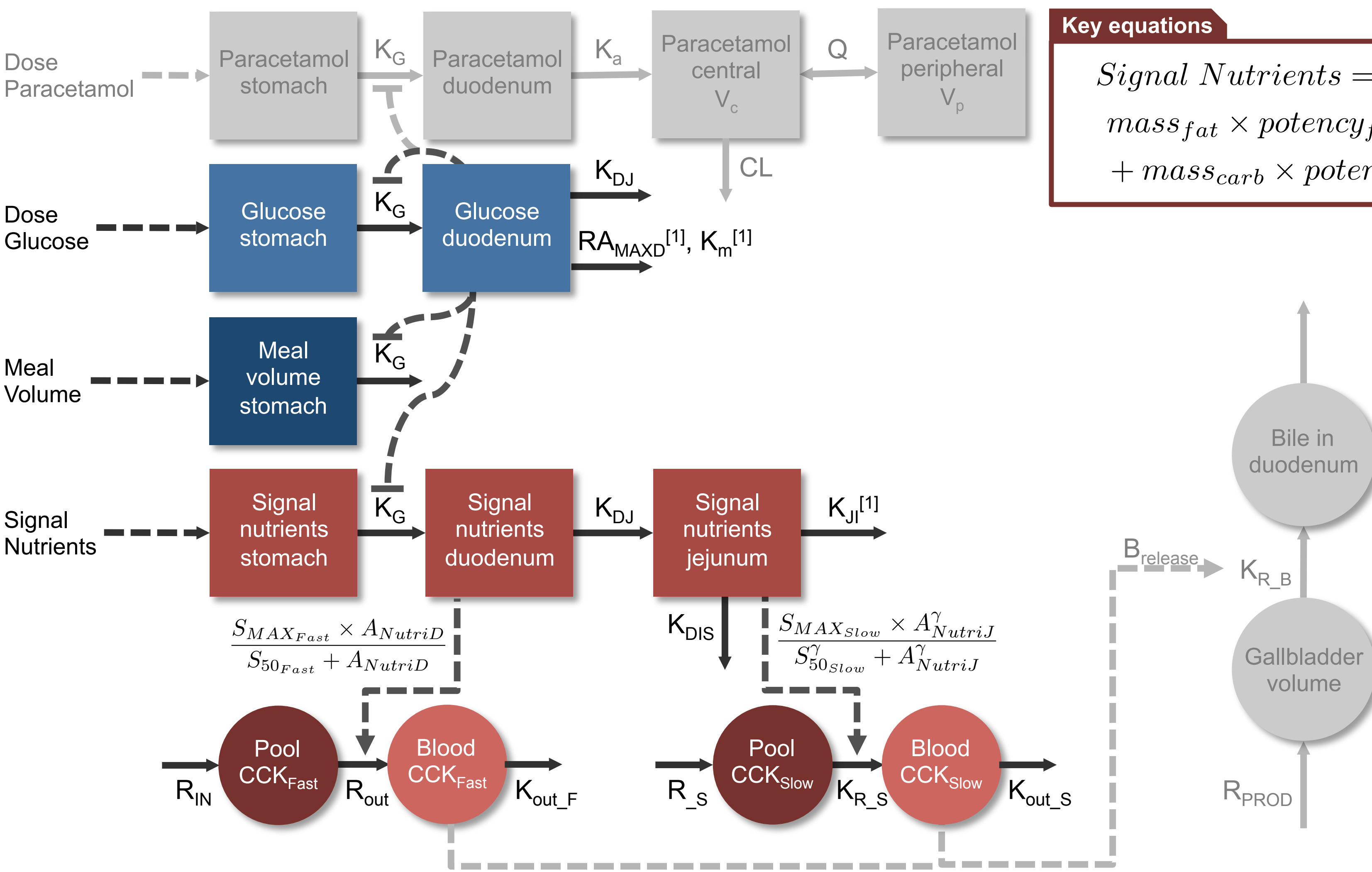
Cholecystokinin *(CCK)* model

Methods



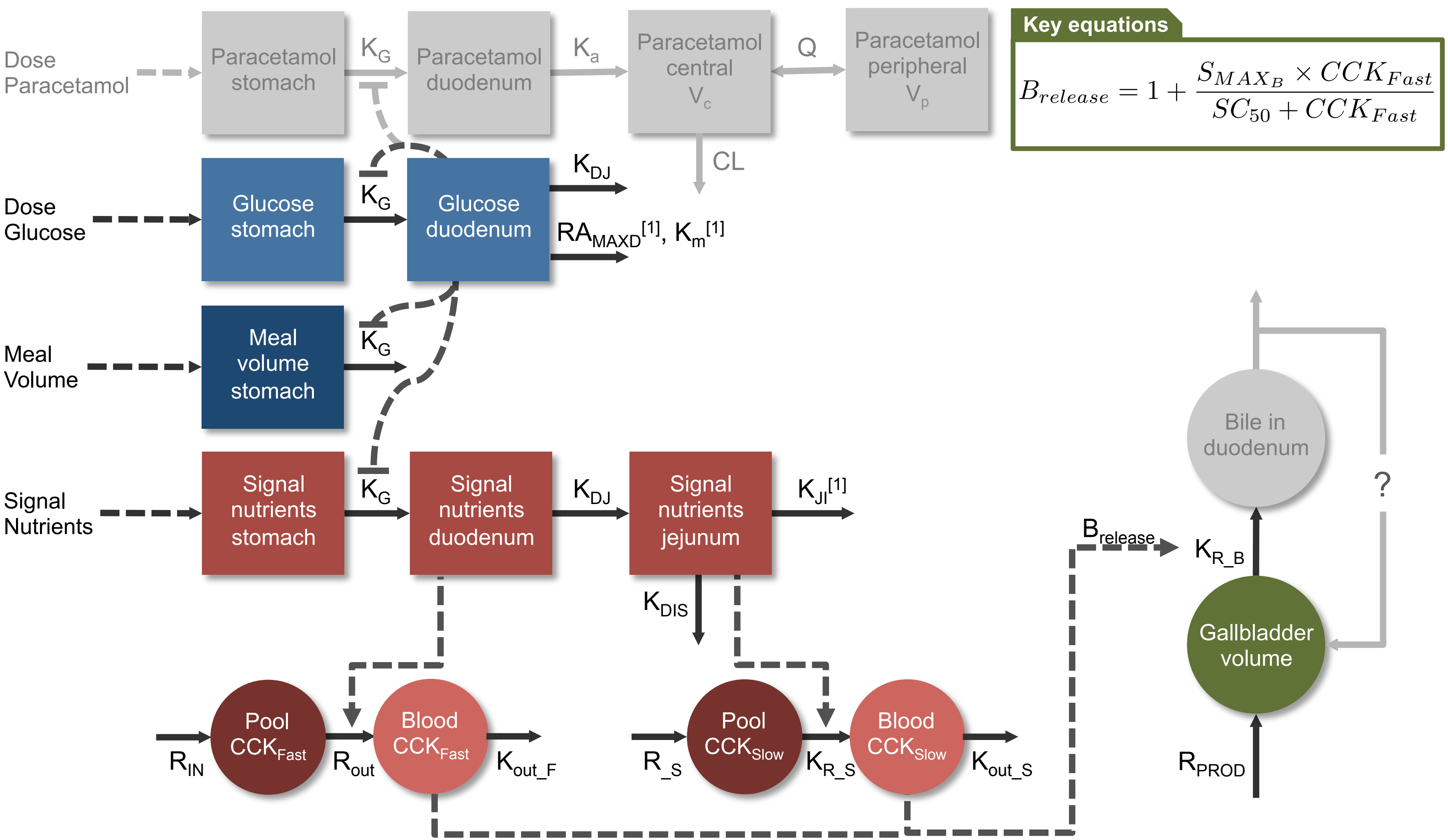
Key equations

$$Signal\ Nutrients = mass_{fat} \times potency_{fat} + mass_{carb} \times potency_{carb}$$

[1] Alskär et *al.* PAGE 22 (2013) Abstr 2897 | [2] Ogungbenro et *al.*, Pharm Res. (2011)

Bile release model

Methods



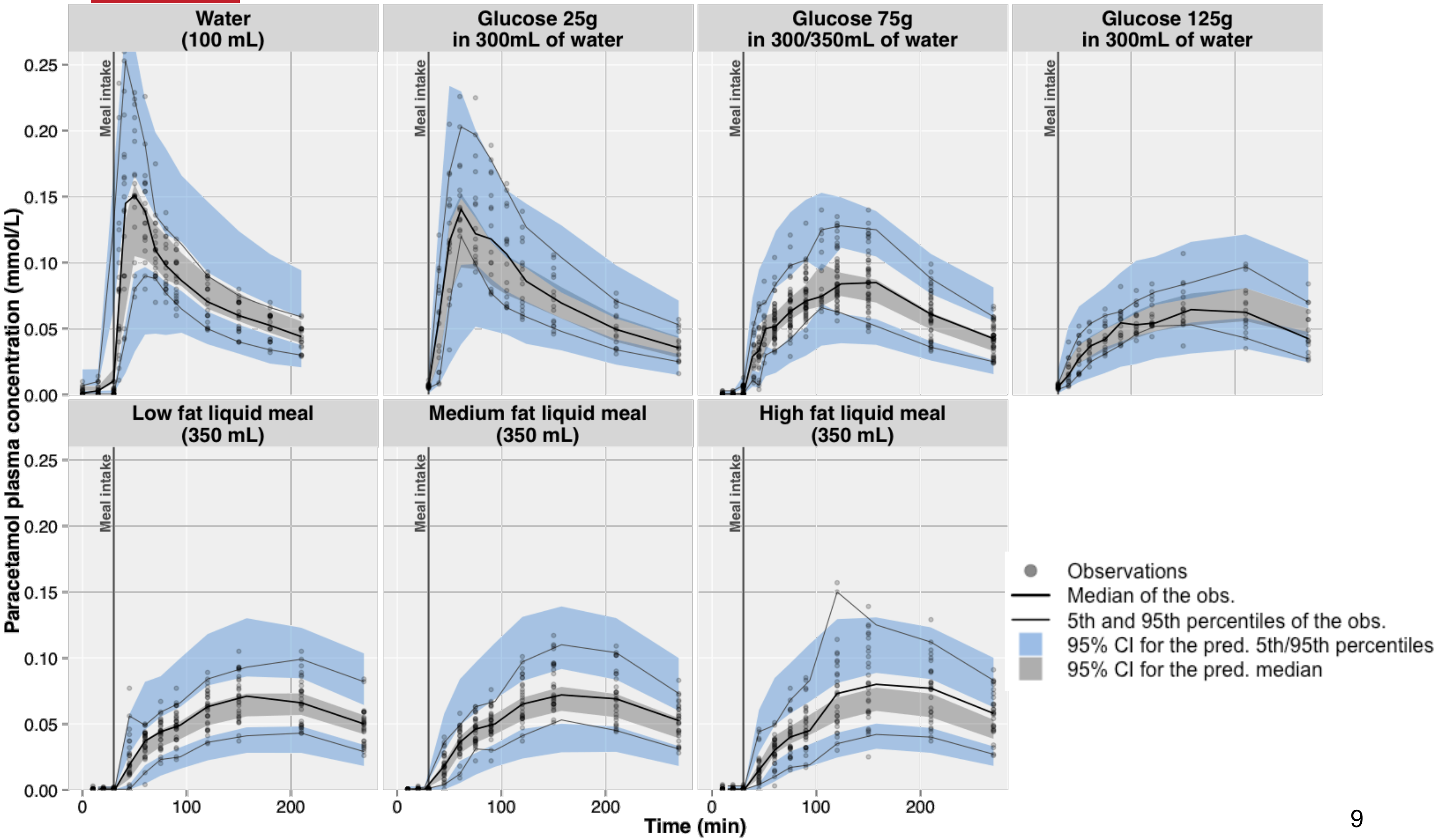
Key equations

$$B_{release} = 1 + \frac{S_{MAX_B} \times CCK_{Fast}}{SC_{50} + CCK_{Fast}}$$

[1] Alskär et *al.* PAGE 22 (2013) Abstr 2897 | [2] Ogungbenro et *al.*, Pharm Res. (2011)

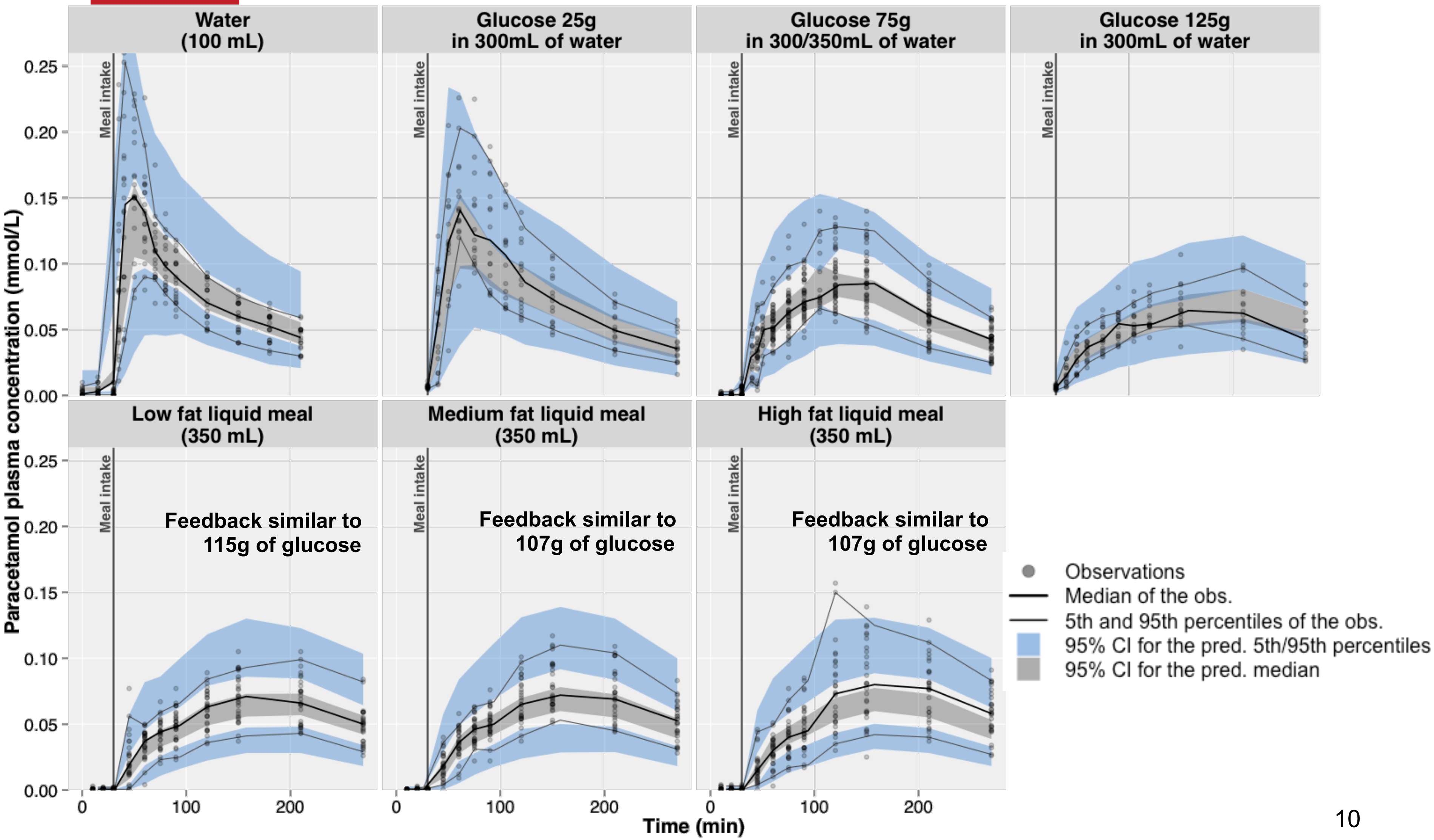
Gastric emptying *(GE)* model VPCs

Results



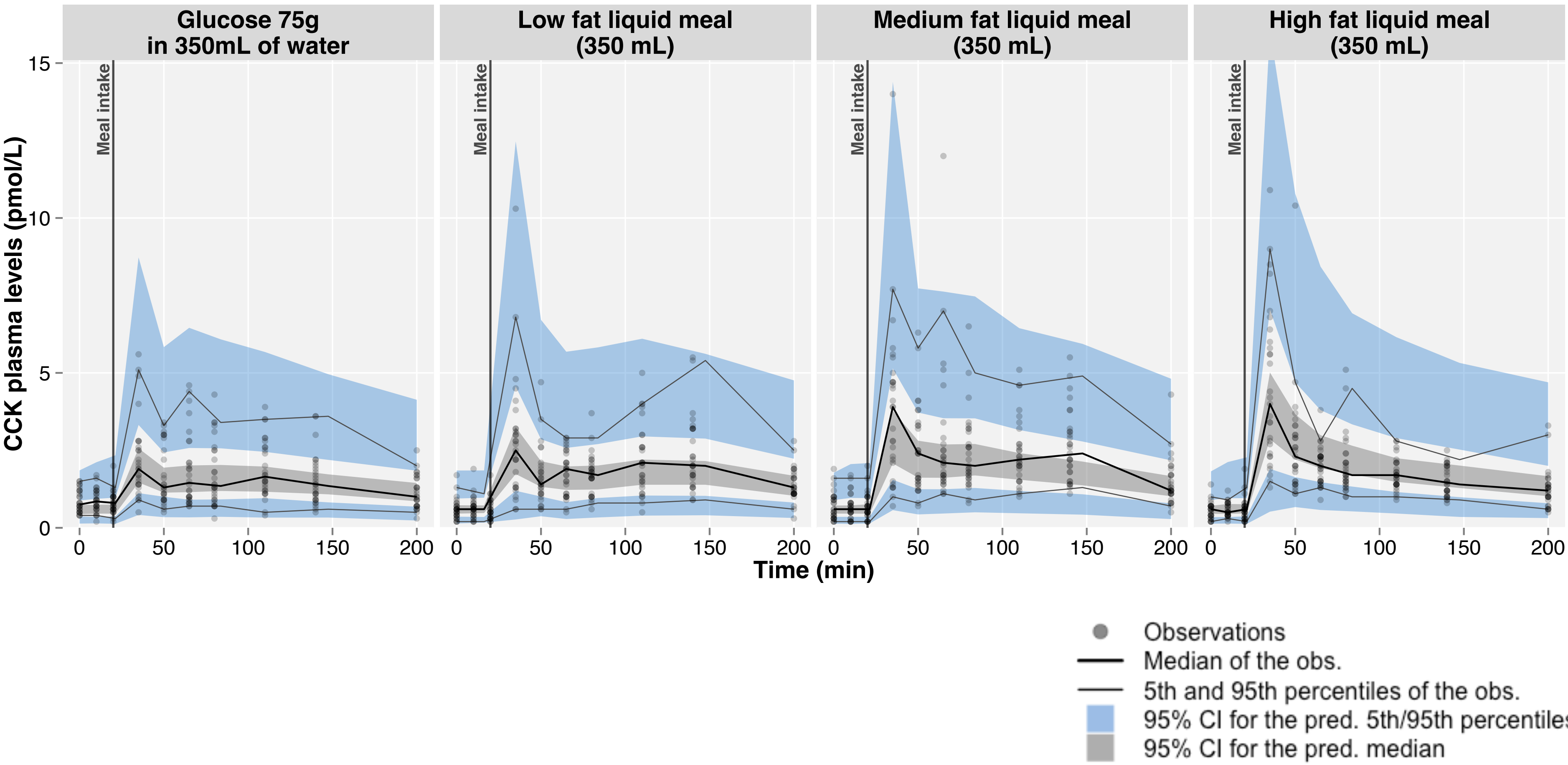
Gastric emptying *(GE)* model VPCs

Results



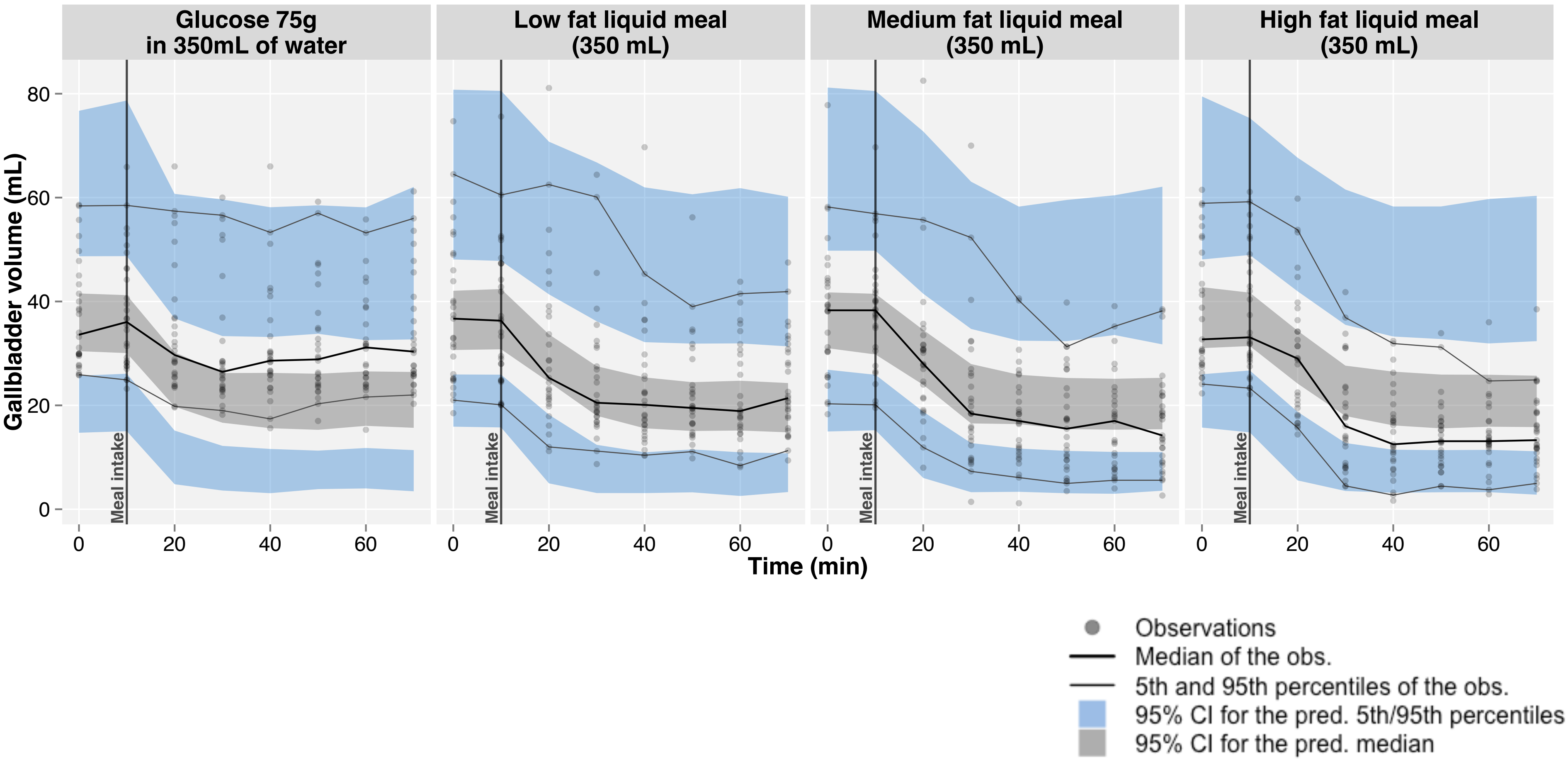
Cholecystokinin *(CCK)* model VPCs

Results



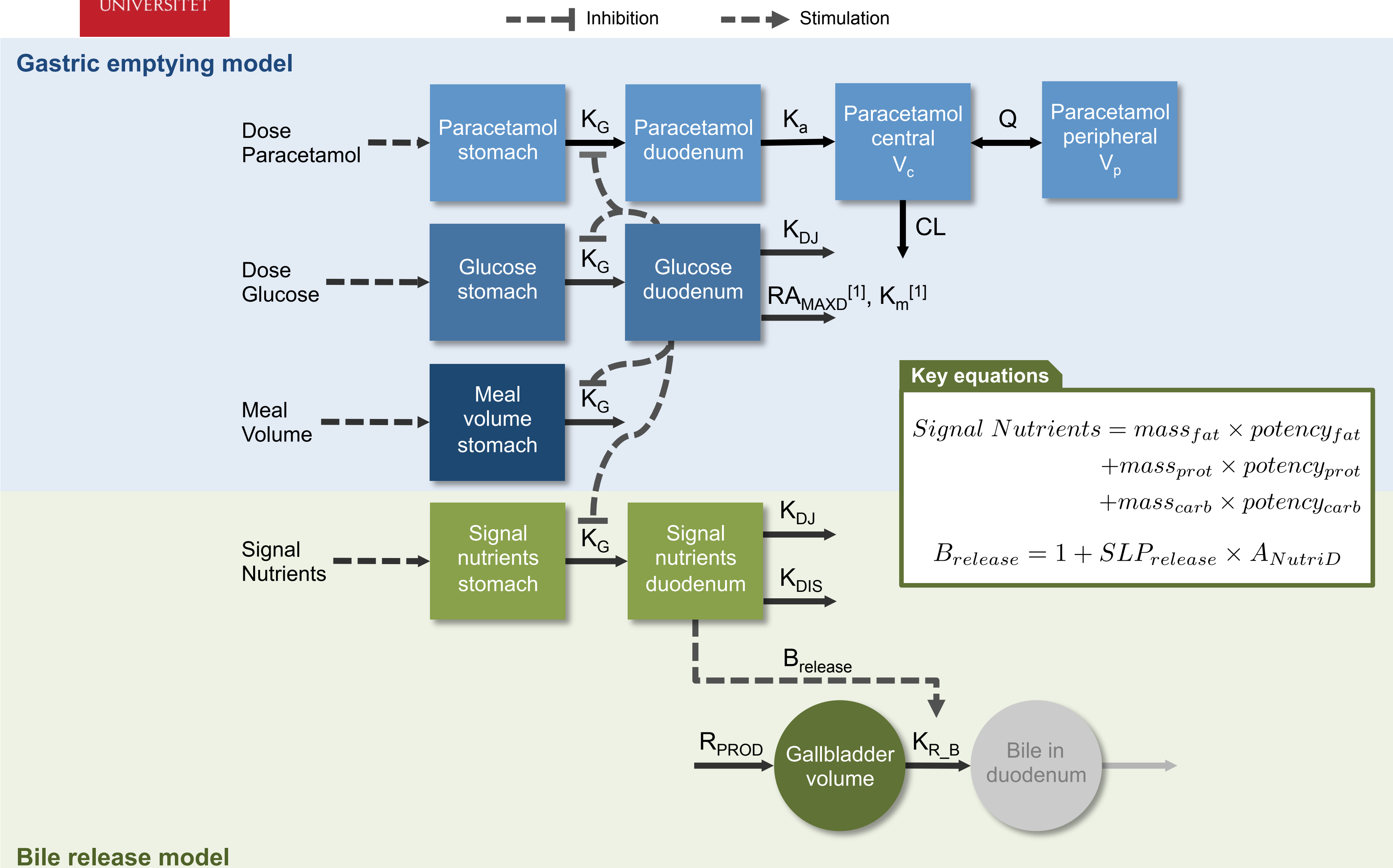
Bile release model VPCs

Results



Final bile release model

Results



Key equations

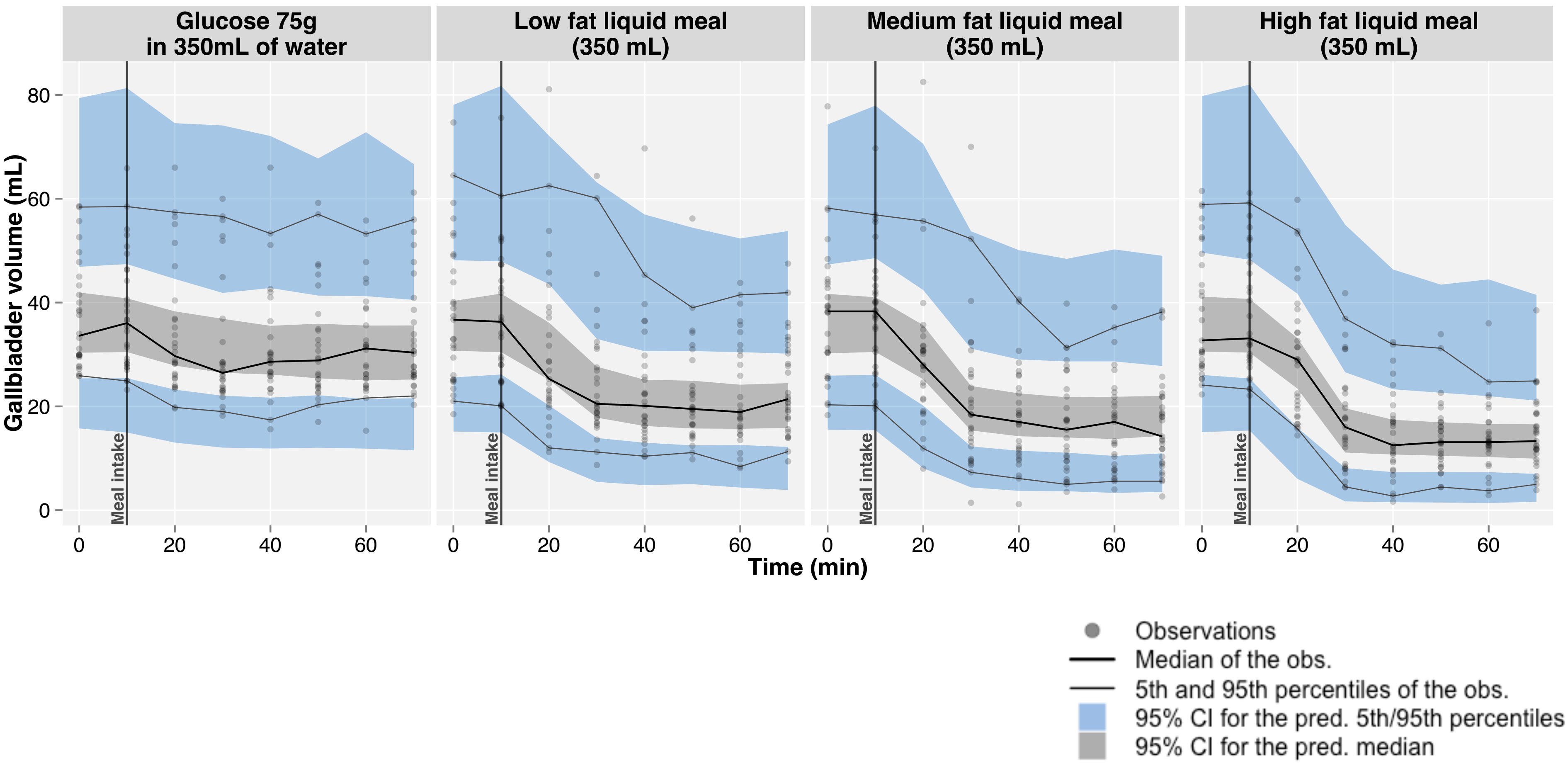
$$Signal\ Nutrients = mass_{fat} \times potency_{fat} + mass_{prot} \times potency_{prot} + mass_{carb} \times potency_{carb}$$

$$B_{release} = 1 + SLP_{release} \times A_{NutriD}$$

[1] Alskär et *al.* PAGE 22 (2013) Abstr 2897 | [2] Ogungbenro et *al.*, Pharm Res. (2011)

Final bile release model VPCs

Results



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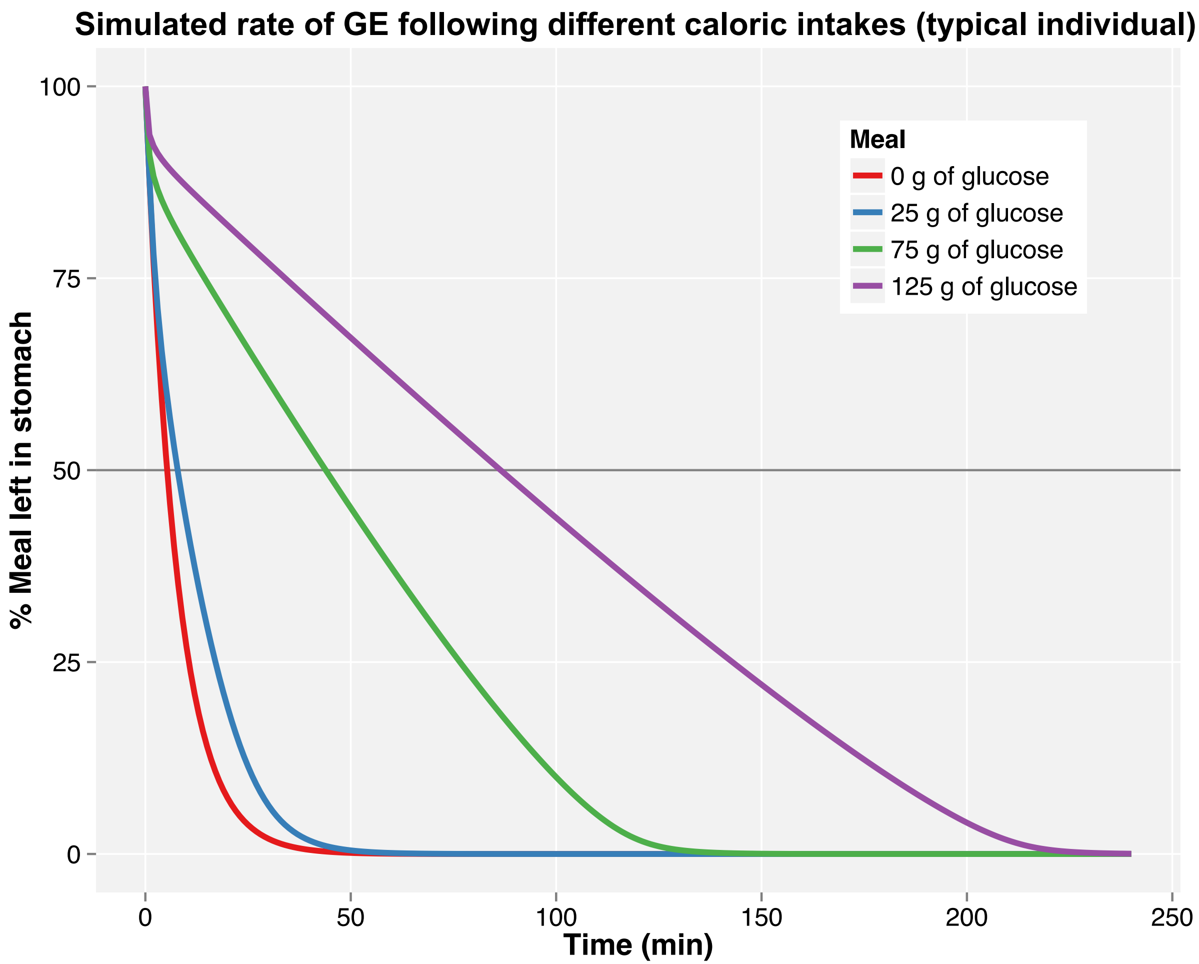
Gastric emptying model predictions

Results



$$K_G = K_{G_0} \times \left(1 - \frac{A_{glucD}^{\gamma}}{I_{50}^{\gamma} + A_{glucD}^{\gamma}}\right)$$

with:

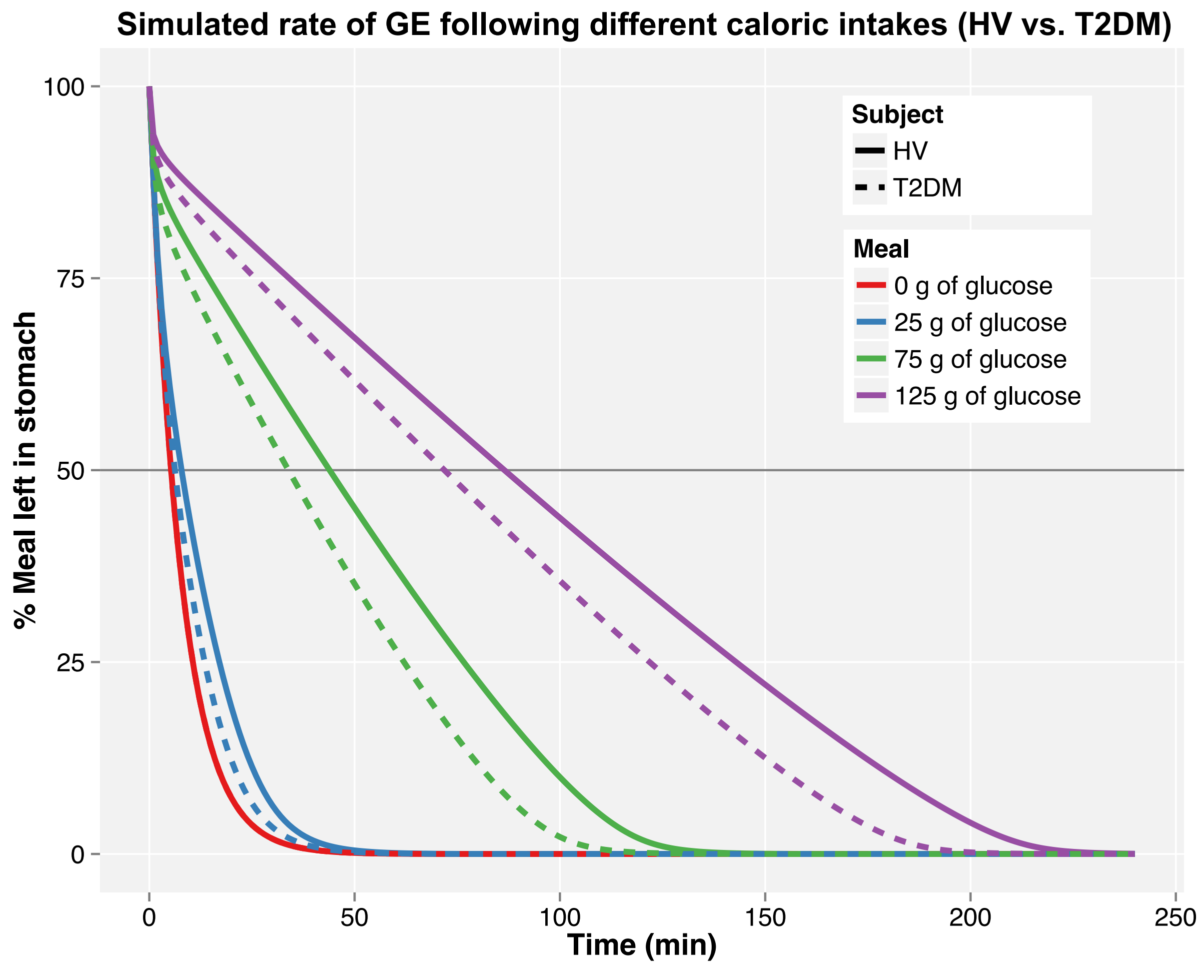
Half-life of K_{G0}	5.3 min
I_{50}	4.9 gluc. gram equivalent
γ	4.8

Meal (g of glucose)	Time to 50% emptying
0	5.3 min
25	8.0 min
75	44 min
125	86 min

*Assuming a meal volume of 300mL

T2DM effects on gastric emptying

Results



$$K_G = K_{G_0} \times \left(1 - \frac{A_{glucD}^{\gamma}}{I_{50}^{\gamma} + A_{glucD}^{\gamma}}\right)$$

with:

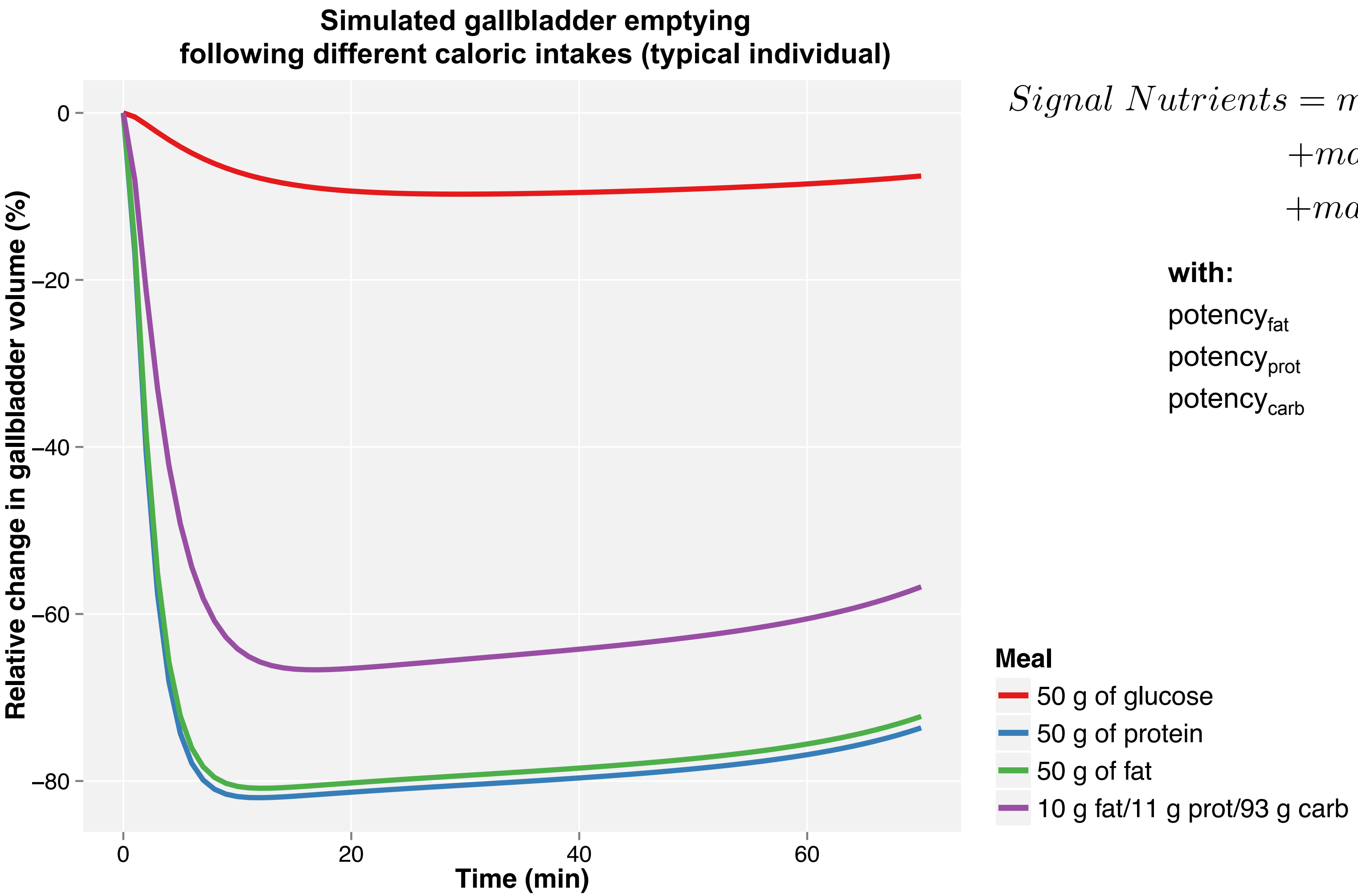
Half-life of K_{G0}	5.3 min
I_{50}	4.9 gluc. gram equivalent
γ	4.8
T2DM on I_{50}	**+29%**

Meal (g of glucose)	Time to 50% emptying (HV)	Time difference (T2DM)
0	5.3 min	0 min
25	8.0 min	-3 min
75	44 min	-10 min
125	86 min	-14 min

T2DM: Type 2 Diabetes Mellitus
HV: Healthy Volunteers *(matched on BMI, gender, age)*

Bile release model predictions

Results



$$Signal\ Nutrients = mass_{fat} \times potency_{fat} + mass_{prot} \times potency_{prot} + mass_{carb} \times potency_{carb}$$

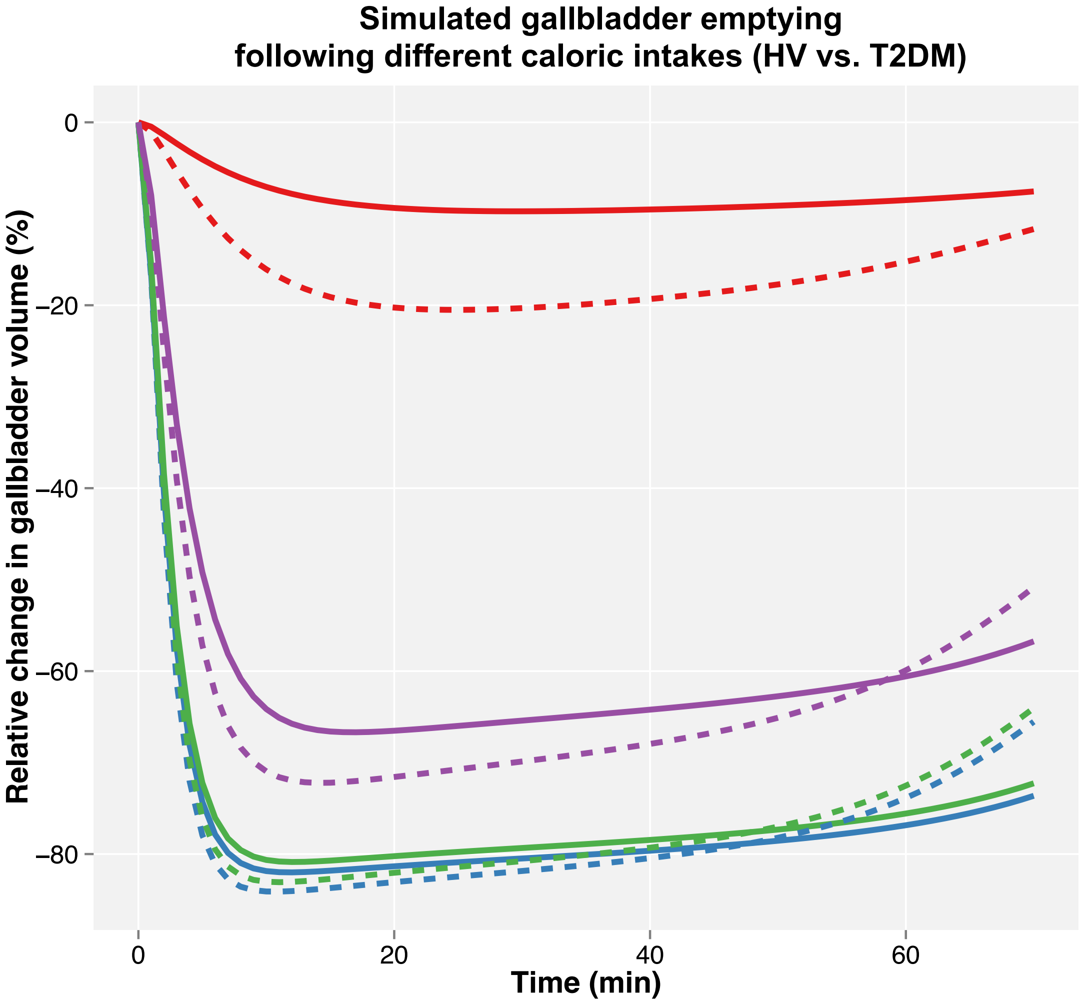
with:

$potency_{fat}$	1.0 fixed
$potency_{prot}$	1.1
$potency_{carb}$	0.028

*Assuming a meal volume of 300mL and the same gastric emptying rate

T2DM effects on bile release

Results



$$Signal\ Nutrients = mass_{fat} \times potency_{fat} + mass_{prot} \times potency_{prot} + mass_{carb} \times potency_{carb}$$

with:

$potency_{fat}$	1.0 fixed
$potency_{prot}$	1.1
$potency_{carb}$	0.028
T2DM on $potency_{carb}$	**+12%**

T2DM: Type 2 Diabetes Mellitus

HV: Healthy Volunteers *(matched on BMI, gender, age)*

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Conclusions

- Gastric emptying was found to be controlled by a feedback mechanism of caloric content in duodenum
- CCK kinetics was not sufficient on its own to describe bile release
- An alternative approach connecting the bile release to nutrients in duodenum was preferred
- T2DM was found to affect gastric emptying and bile release through changes in sensitivity to carbohydrates
- The final model demonstrated to be predictive of gastric emptying, plasma CCK levels and bile release across a wide range of liquid meals

Future Directions

- Use new data to correlate gallbladder volume to bile concentration in duodenum and study recirculation of bile acids
- Explore correlation between plasma biomarkers and bile acid concentration in duodenum
- Integrate findings in systems pharmacology models *(PBPK)* to improve prediction of oral absorption

Acknowledgements

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Innovative Medicines Initiative

Innovative Tools for Oral Biopharmaceutics