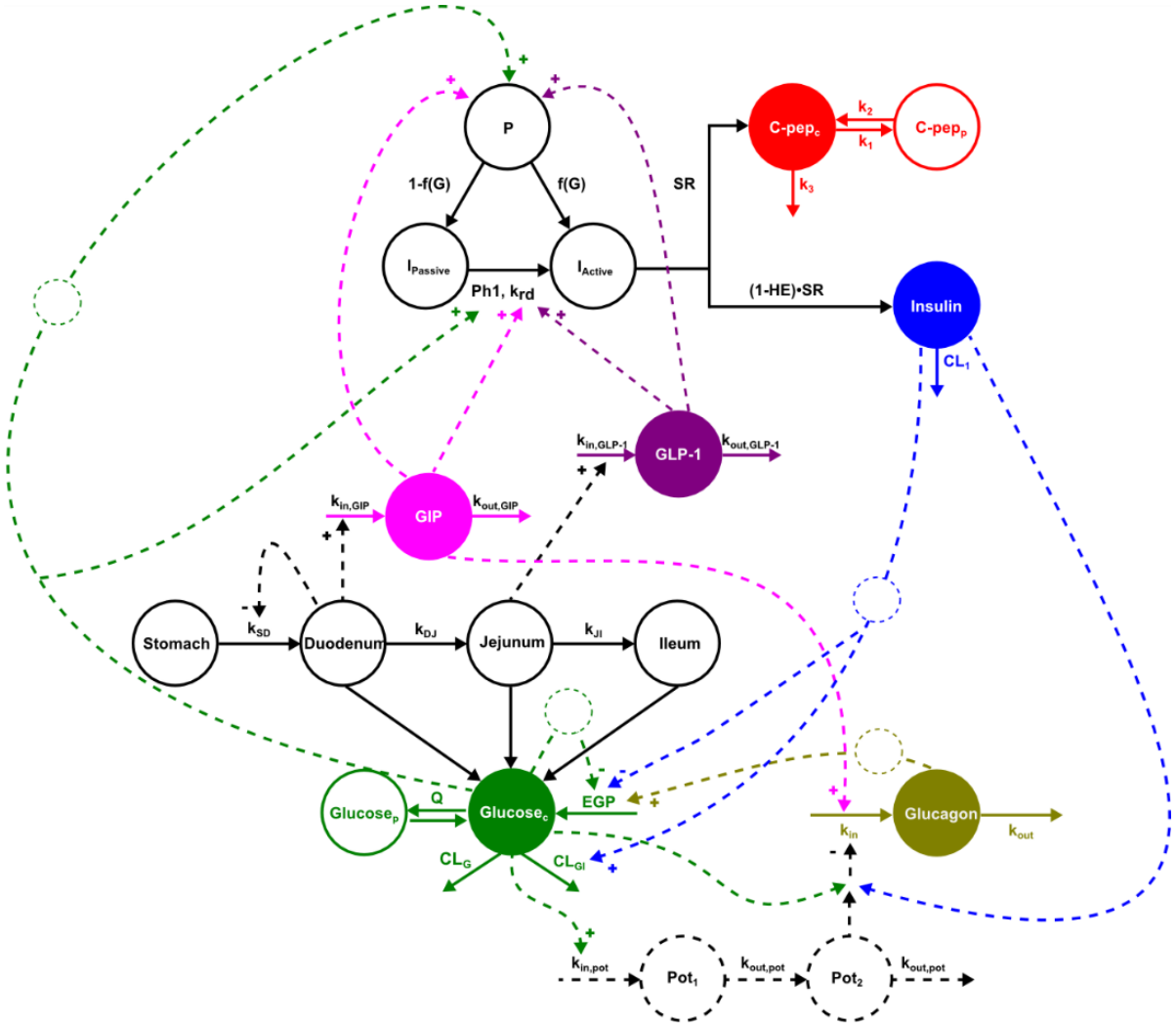
UPPSALA UNIVERSITET

An integrated glucose homeostasis model of glucose, insulin, C-peptide, GLP-1, GIP and glucagon in healthy subjects and patients with type 2 diabetes

Oskar Alskär, Jonatan Bagger, Rikke Røge, Kanji Komatsu, Niels Kristensen, Søren Klim, Steen Ingwersen, Filip Knop, Jens Holst, Tina Vilsbøll, Mats Karlsson, Maria Kjellsson

PAGE meeting
Montreux Switzerland, 30 May 2018


P
1-f(G)
f(G)
$I_{Passive}$
I_{Active}
Ph1, k_{rd}
SR
$C\text{-}pep_c$
$C\text{-}pep_p$
k_2
k_1
k_3
(1-HE)•SR
Insulin
CL_I
GLP-1
$k_{in,GLP\text{-}1}$
$k_{out,GLP\text{-}1}$
GIP
$k_{in,GIP}$
$k_{out,GIP}$
Stomach
Duodenum
Jejunum
Ileum
k_{SD}
k_{DJ}
k_{JI}
$Glucose_p$
$Glucose_c$
Q
EGP
CL_G
CL_{GI}
Glucagon
k_{in}
k_{out}
$k_{in,pot}$
Pot_1
$k_{out,pot}$
Pot_2
$k_{out,pot}$

Pharmacometric models of glucose homeostasis

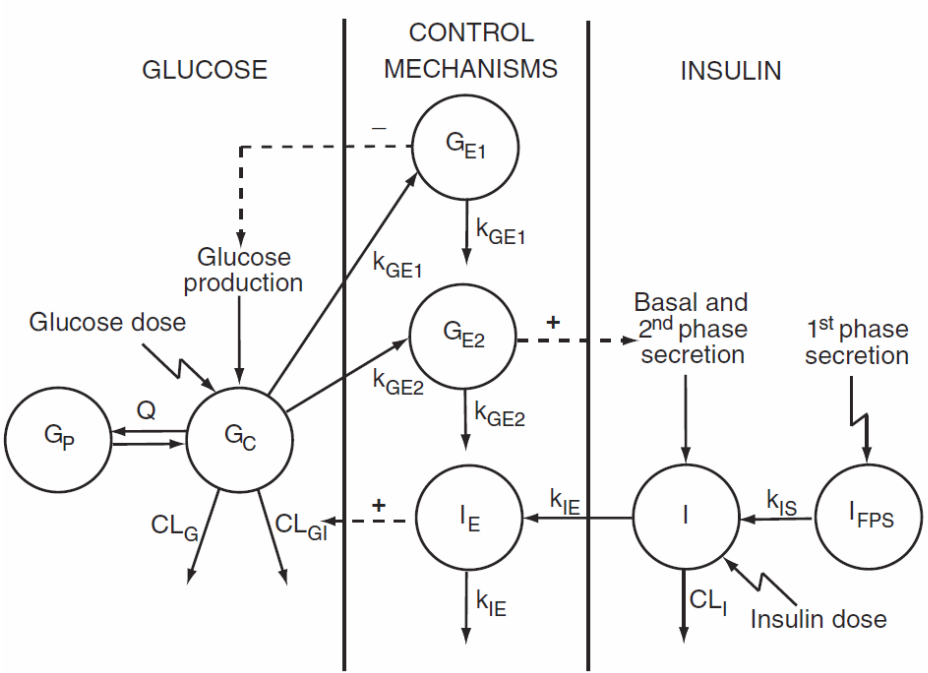
- Glucose homeostasis is a complex process
  - Several organs
  - Many glucoregulatory hormones
- Mathematical models are important tools to understand and quantify these mechanisms

Pharmacometric models of glucose homeostasis

- Glucose homeostasis is a complex process
  - Several organs
  - Many glucoregulatory hormones
- Mathematical models are important tools to understand and quantify these mechanisms
- Integrated glucose insulin (IGI) model[1]
  - Glucose tolerance tests
    - Intravenous
    - Oral

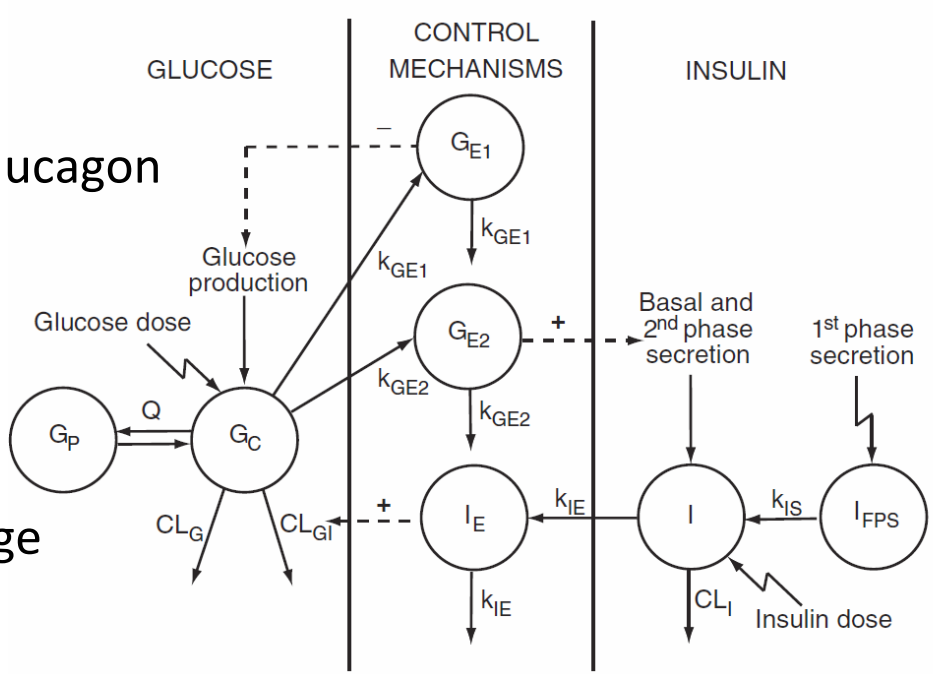
1. Silber et al 2007

Pharmacometric models of glucose homeostasis



Pharmacometric models of glucose homeostasis

- Limitations
  - Only glucose and insulin
    - e.g. incretin hormones, glucagon
  - Empirical elements
    - e.g. first phase secretion, incretin effect
  - Extrapolation properties
    - Narrow glucose dose range



UPPSALA UNIVERSITET

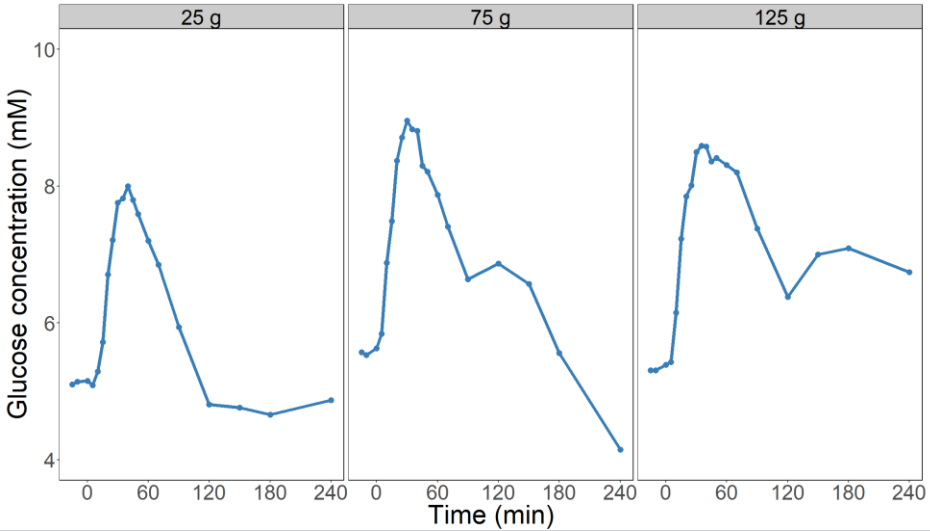
Aim

Develop a mechanism-based model that simultaneously can describe important regulators of glucose homeostasis during glucose tolerance tests

- Healthy subjects and patients with type 2 diabetes (T2D)
- Wide glucose dose range

Analysis data

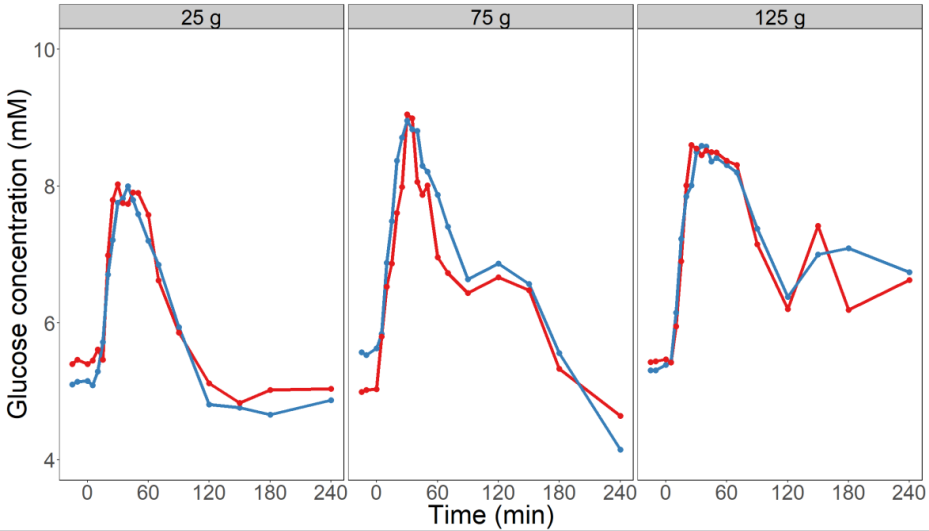
- 8 patients with T2D and 8 matched healthy controls[2]
- 3 oral glucose tolerance tests (OGTT)
  - 25 g, 75 g and 125 g of glucose



2. Bagger et al 2011

Analysis data

- 8 patients with T2D and 8 matched healthy controls
- 3 oral glucose tolerance tests (OGTT)
  - 25 g, 75 g and 125 g of glucose
- 3 isoglycaemic intravenous glucose infusions (IIGI)



Analysis data

- Glucose
- Paracetamol (marker of gastric emptying)
- Incretin hormones
  - Glucose-dependent insulinotropic peptide (GIP)
  - Glucagon-like peptide-1 (GLP-1)
- Pancreatic hormones
  - Insulin, C-peptide
  - Glucagon

Analysis data

- Glucose
- Paracetamol (marker of gastric emptying) } **Submodel 1**
- Incretin hormones
  - Glucose-dependent insulinotropic peptide (GIP) } **Submodel 2**
  - Glucagon-like peptide-1 (GLP-1)
- Pancreatic hormones
  - Insulin, C-peptide **Submodel 3**
  - Glucagon **Submodel 4**

General modeling strategy

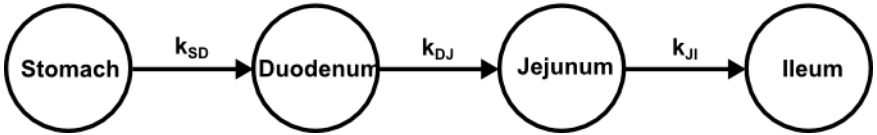
- Observations as time varying covariates (linear interpolation)
  - Shorter run times
  - Simpler interpretation
- Start with healthy controls IV data
  - Differences between healthy and patients with T2D
- Include healthy controls oral data
  - Differences between healthy and patients with T2D

UPPSALA UNIVERSITET

Submodel 1. Gastric emptying and glucose absorption

Stomach and small intestine

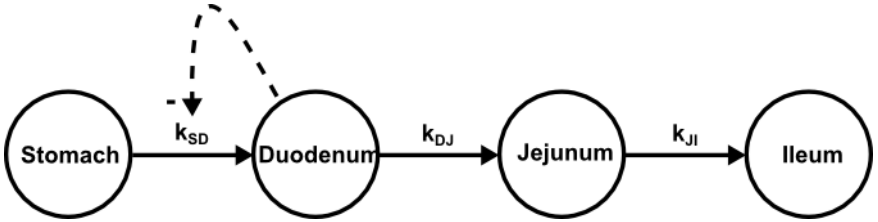
- Assumptions:
  - 4 h small intestine transit time[3]
  - 8% duodenum, 37% jejunum, 55% ileum[4]
  - Gastric emptying half life of non-caloric liquid, 5 min



3. Davis S et al 1986, 4. Snyder WS et al 1975

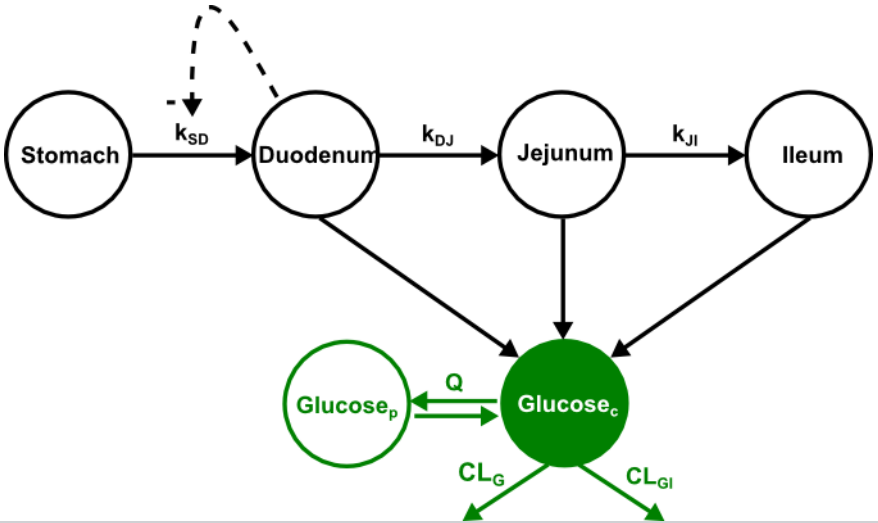
Inhibition of gastric emptying

- Glucose in duodenum inhibit gastric emptying
- 5 min lag before gastric empting starts



Glucose absorption

- Glucose disposition FIX to estimates of the IGI model
  - Insulin dependent glucose clearance estimated
- Glucose absorbed from each intestinal segment



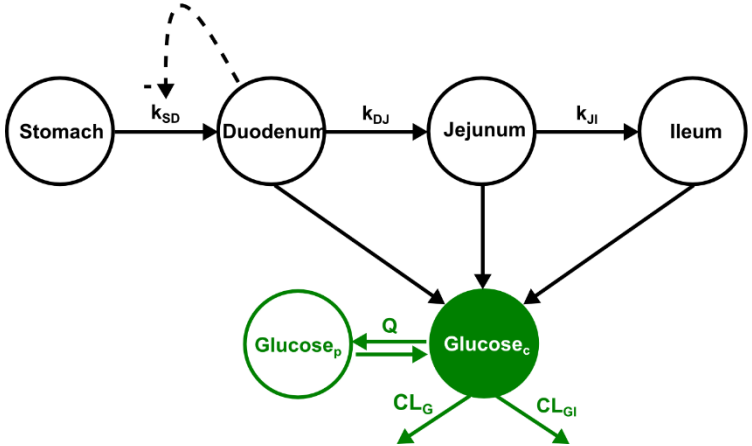
Submodel 2. Incretin hormones

- Half life fixed to literature values
  - GLP-1, 4 min[5]
  - GIP, 6 min[6]

5. Holst et al 1998, 6. Deacon et al 2000

Submodel 2. Incretin hormones

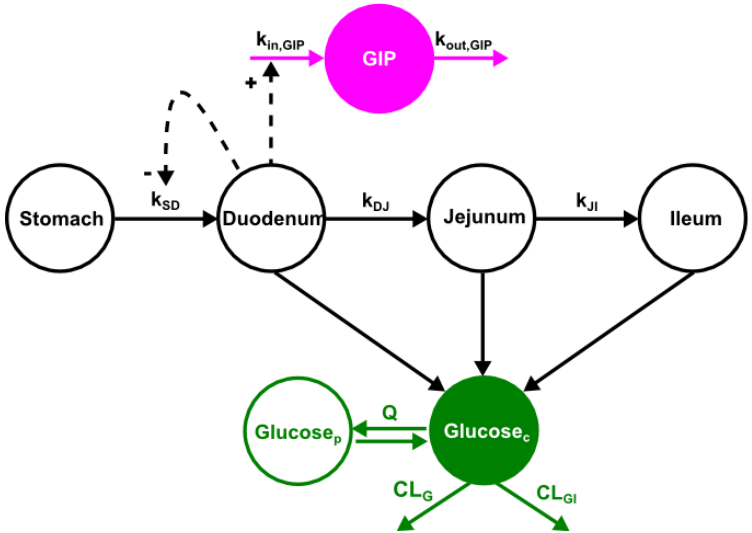
- Half life fixed to literature values
  - GLP-1, 4 min[5]
  - GIP, 6 min[6]
- Investigated stimulation of incretin hormones



5. Holst et al 1998, 6. Deacon et al 2000

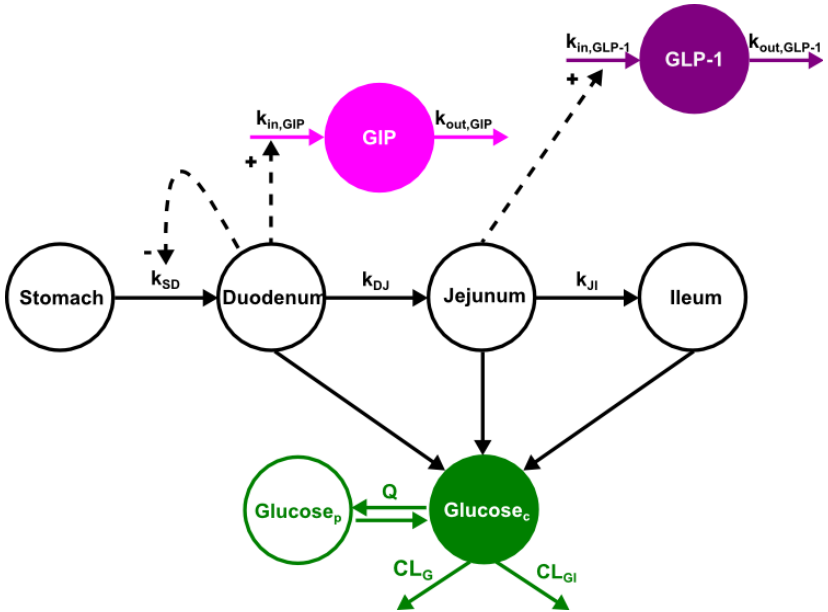
GIP secretion

- GIP secretion stimulated by glucose in duodenum



GLP-1 secretion

- GLP-1 secretion stimulated by glucose in jejunum

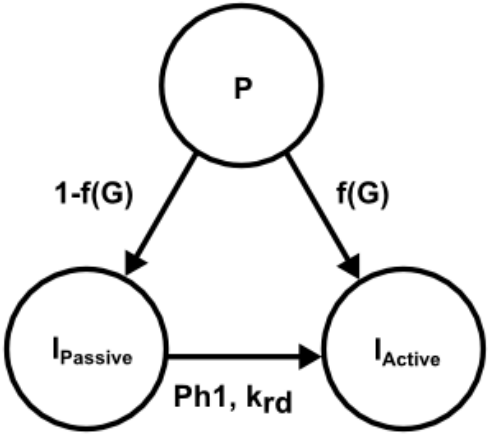


UPPSALA UNIVERSITET

Submodel 3. Incretin effect and hepatic extraction of insulin

Mathematical beta cell model

- Started from a previously published model by Overgaard et al[7]
  - Insulin vesicles have different sensitivity to glucose

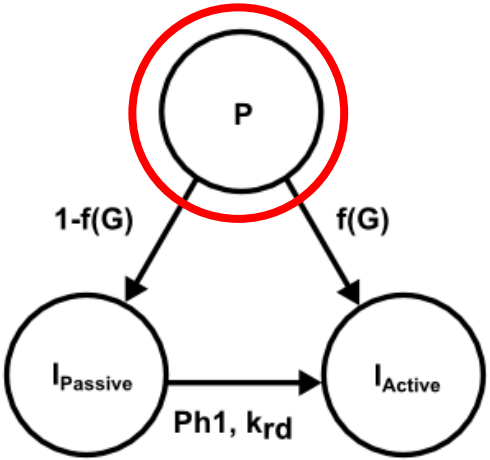


Additional IVGTT insulin data
- Healthy subjects (n=64)
- Patients with T2D (n=42)

7. Overgaard et al 2006

Mathematical beta cell model

- Started from a previously published model by Overgaard et al[7]
  - Insulin vesicles have different sensitivity to glucose

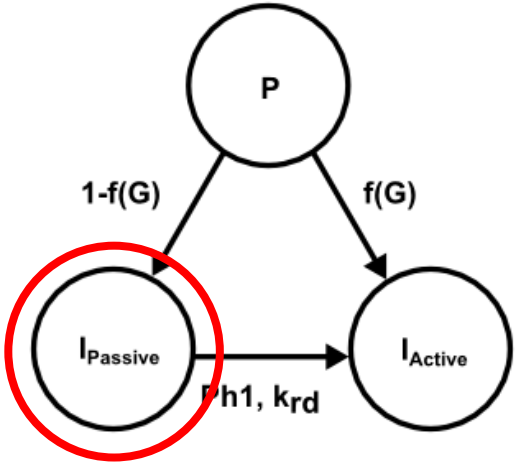


Additional IVGTT insulin data
- Healthy subjects (n=64)
- Patients with T2D (n=42)

7. Overgaard et al 2006

Mathematical beta cell model

- Started from a previously published model by Overgaard et al[7]
  - Insulin vesicles have different sensitivity to glucose

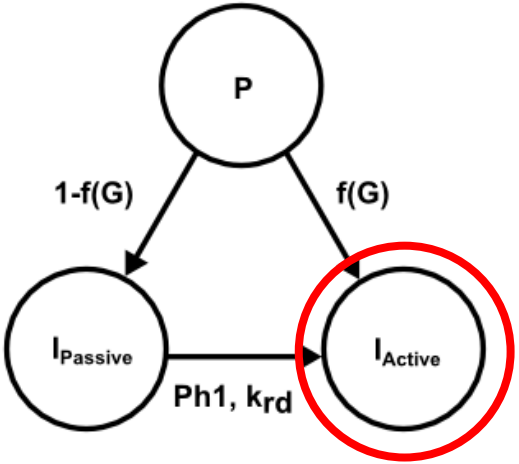


Additional IVGTT insulin data
- Healthy subjects (n=64)
- Patients with T2D (n=42)

7. Overgaard et al 2006

Mathematical beta cell model

- Started from a previously published model by Overgaard et al[7]
  - Insulin vesicles have different sensitivity to glucose

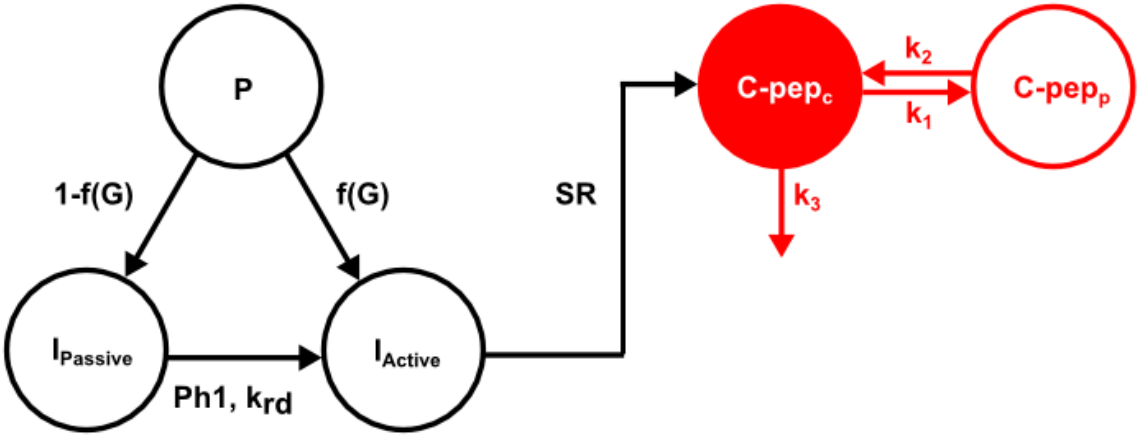


Additional IVGTT insulin data
- Healthy subjects (n=64)
- Patients with T2D (n=42)

7. Overgaard et al 2006

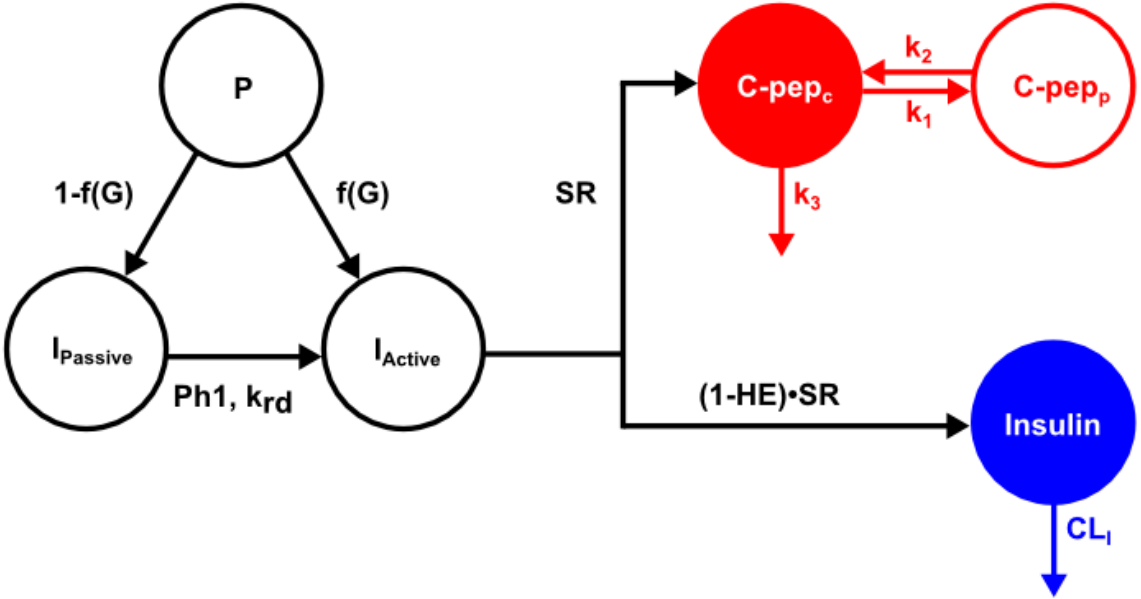
C-peptide model

- C-peptide kinetics described by a two compartment model



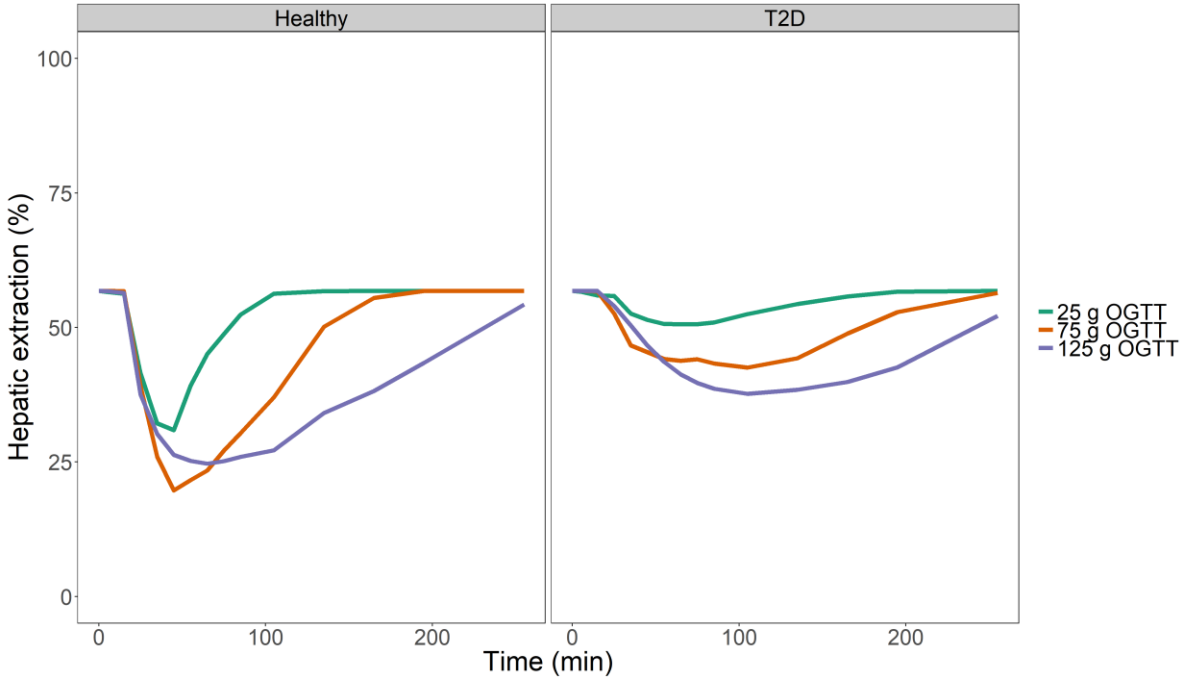
Insulin model

- Insulin kinetics described by a one compartment model



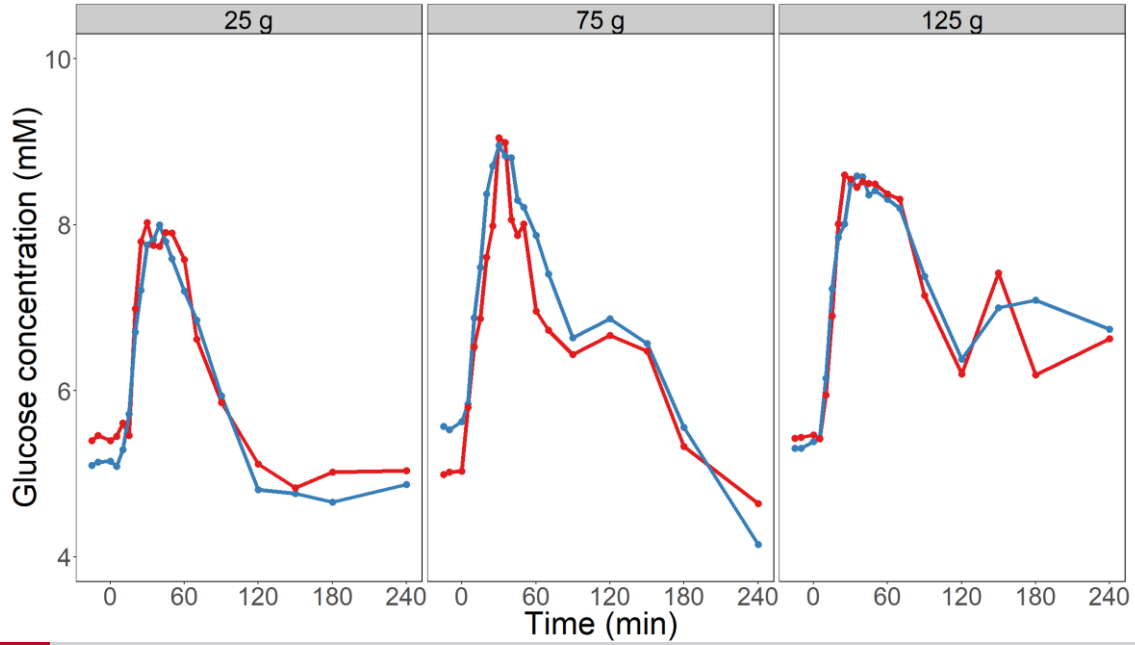
Saturable hepatic extraction of insulin

- Lower hepatic extraction when insulin secretion is high



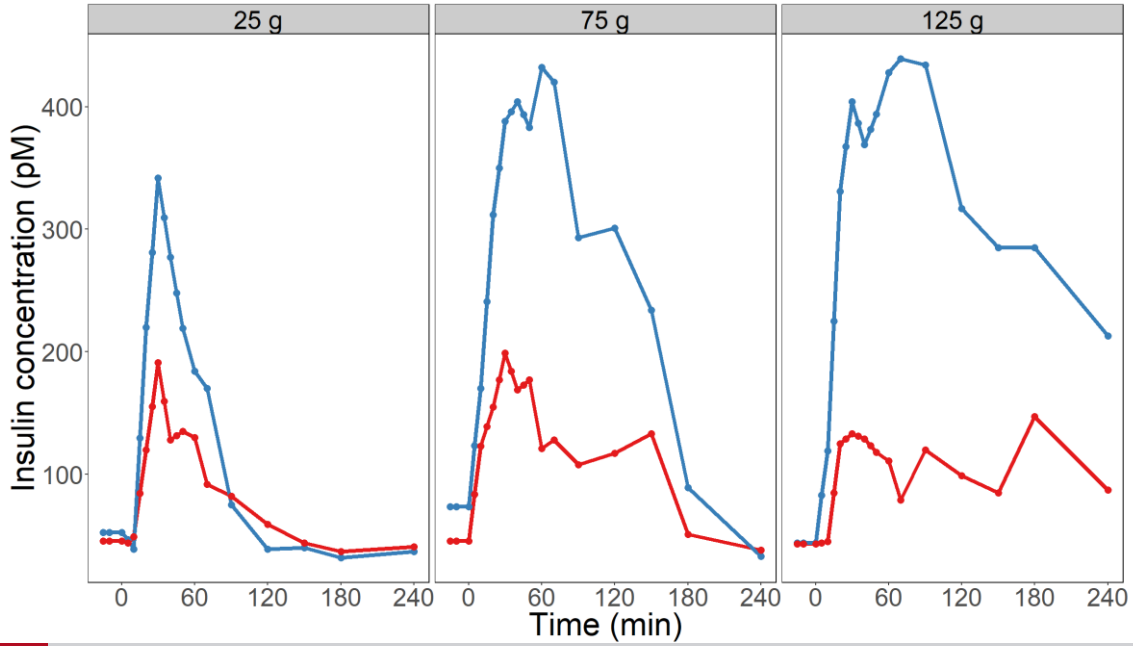
Incretin effect

- Oral and intravenous glucose profiles overlap

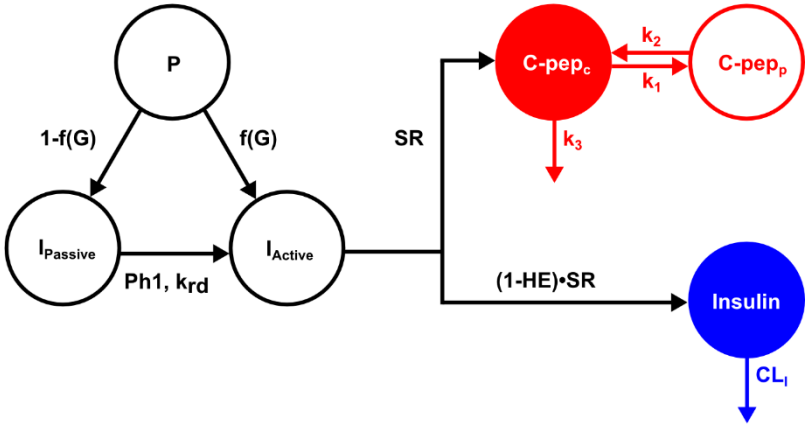


Incretin effect

- Oral glucose gives higher insulin response
- Mediated by GIP and GLP-1

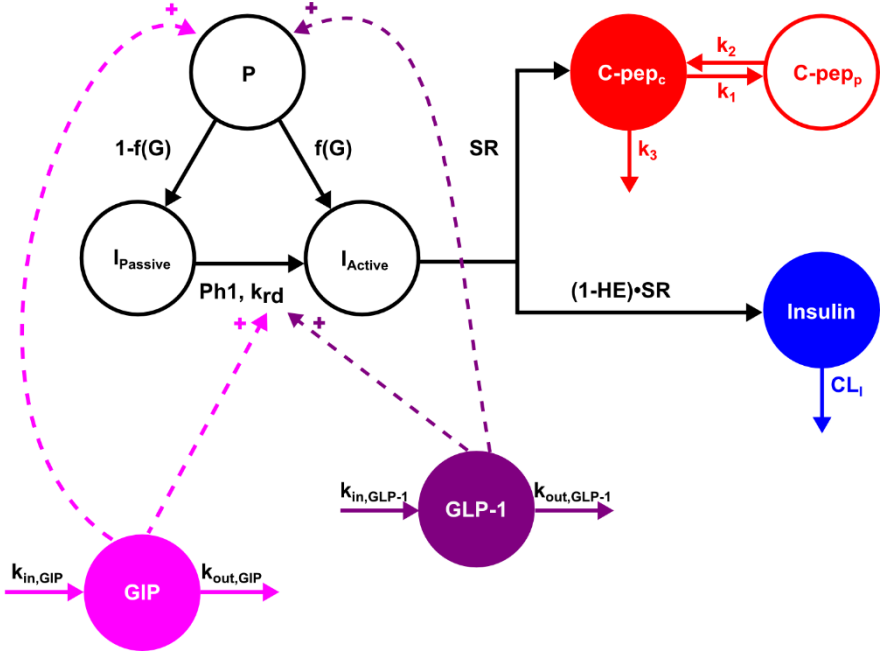


Incretin effect



Incretin effect

- Both hormones increases
  - Production
  - Transfer from passive to active



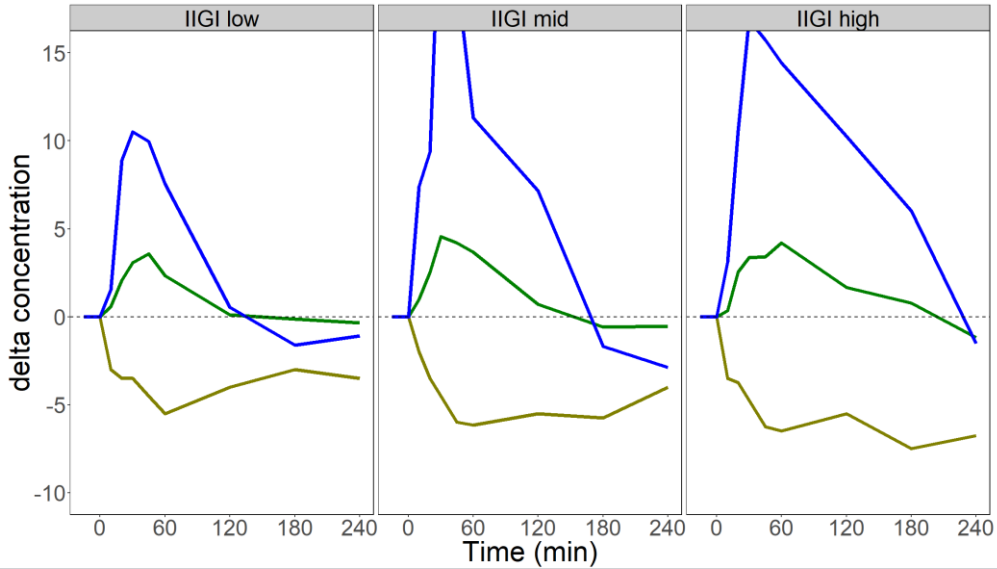
Submodel 4. Glucagon and regulation of endogenous glucose production (EGP)

- Glucagon half life fixed to 7.5 min[8]

8. Pontiroli et al 1993

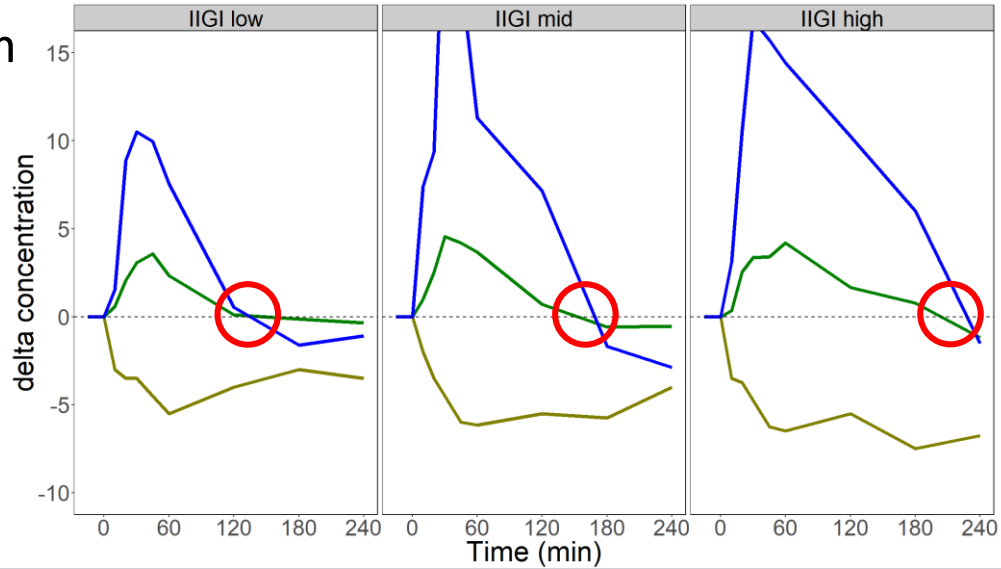
Glucagon secretion

- Glucose and insulin inhibit glucagon secretion



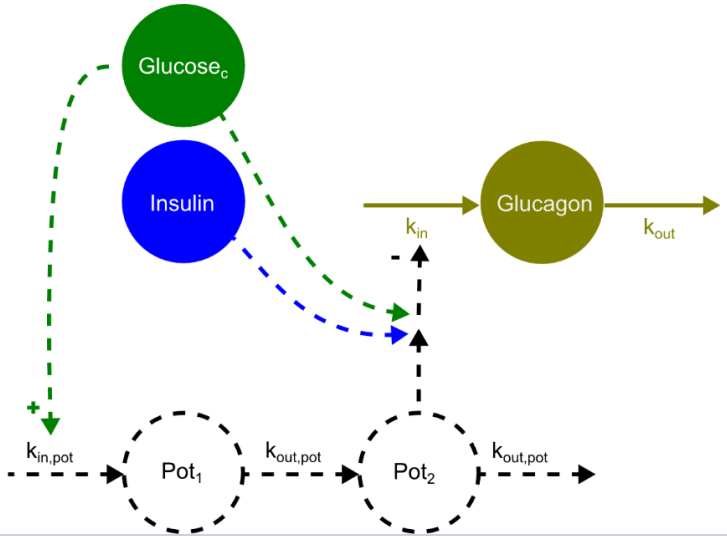
Glucagon prolonged suppression

- Glucose and insulin inhibit glucagon secretion
- Glucagon is rapidly suppressed
- Glucagon stays suppressed after glucose and insulin return to baseline
  - Unknown mechanism

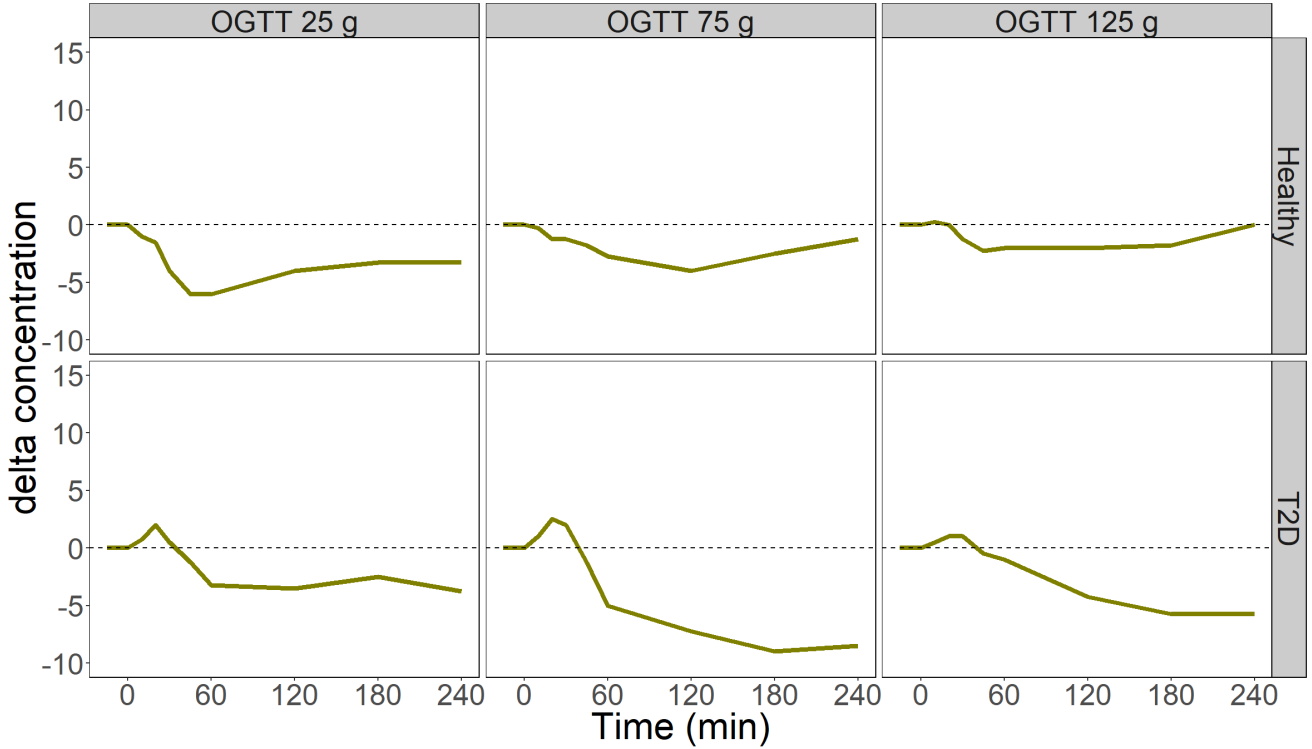


Glucagon suppression potentiated

- Glucagon production inhibited by glucose and insulin
- Inhibition potentiated over time

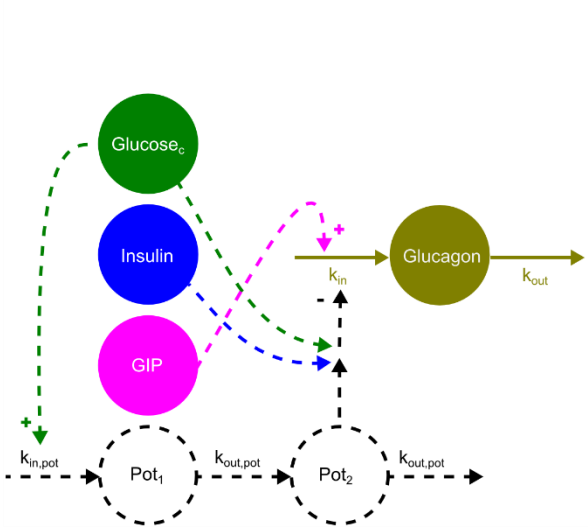


Initial hypersecretion in patients with T2D during OGTT



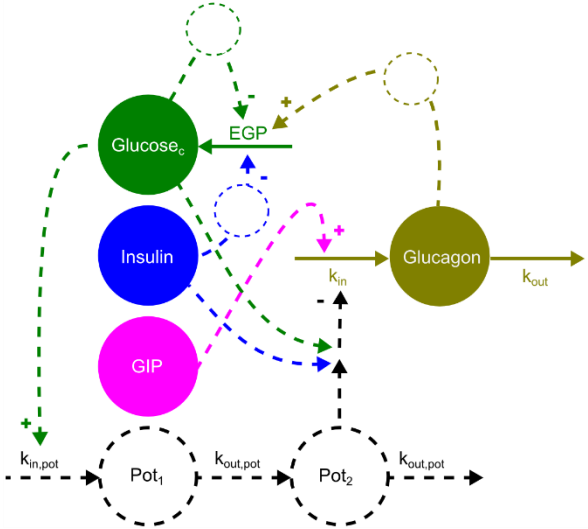
Effect of the incretin hormones

- GIP stimulates glucagon production
  - Stronger effect in patients



Regulation of endogenous glucose production (EGP)

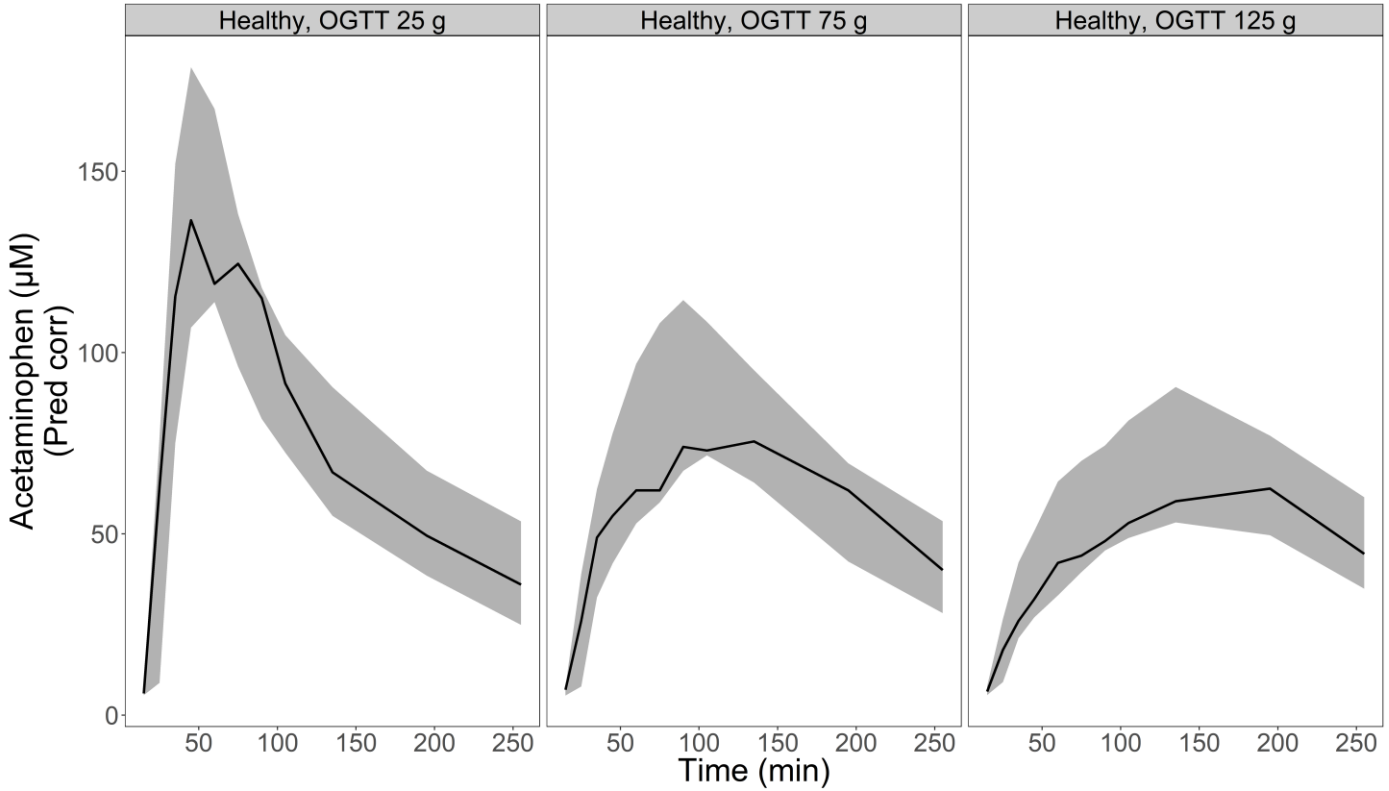
- Glucagon stimulates EGP
- Insulin and Glucose inhibit EGP



Combining the submodels

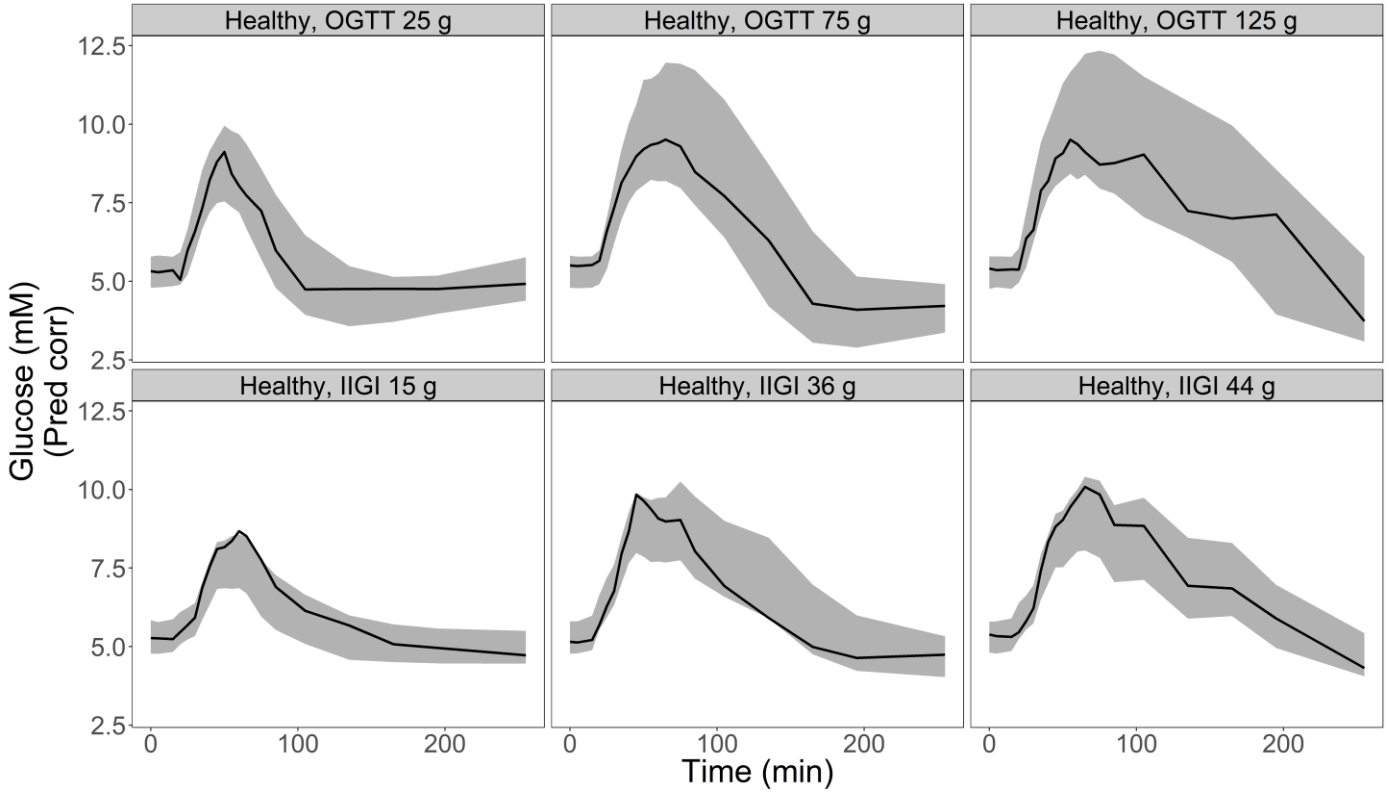
- The submodels were combined into one model
- Evaluation performed
- Predictive performance assessed by prediction-corrected visual predictive checks (pcVPCs)

pcVPC gastric emptying, healthy

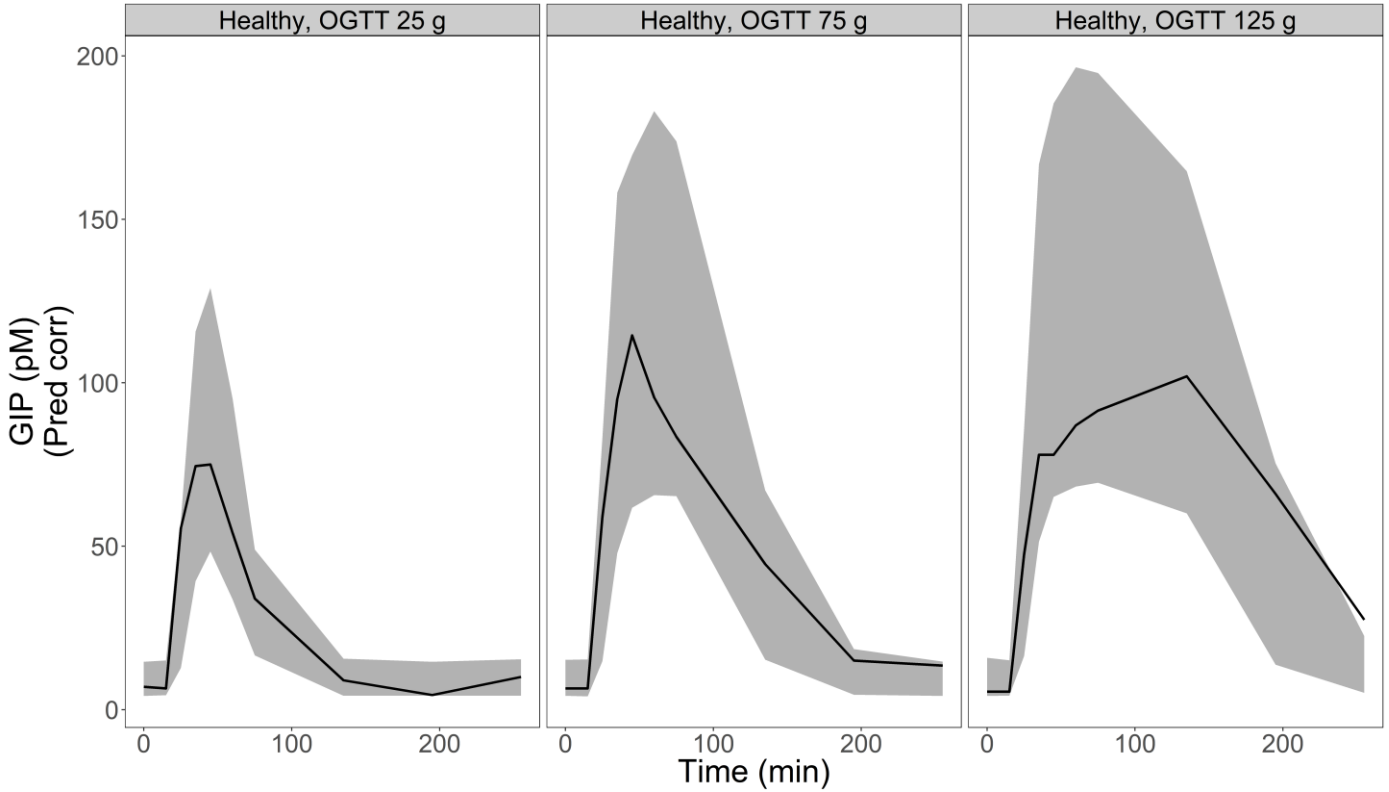


UPPSALA UNIVERSITET

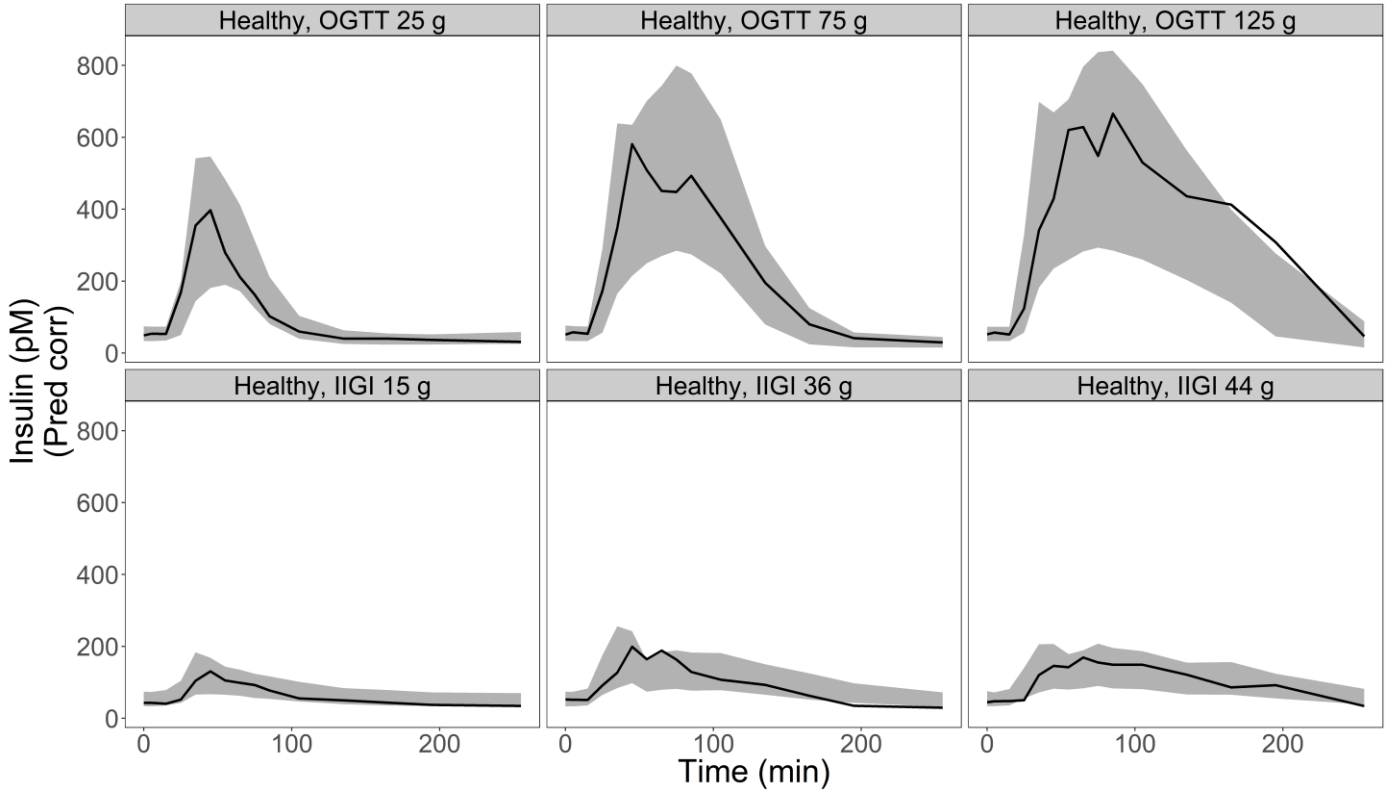
pcVPC glucose, healthy



pcVPC GIP, healthy

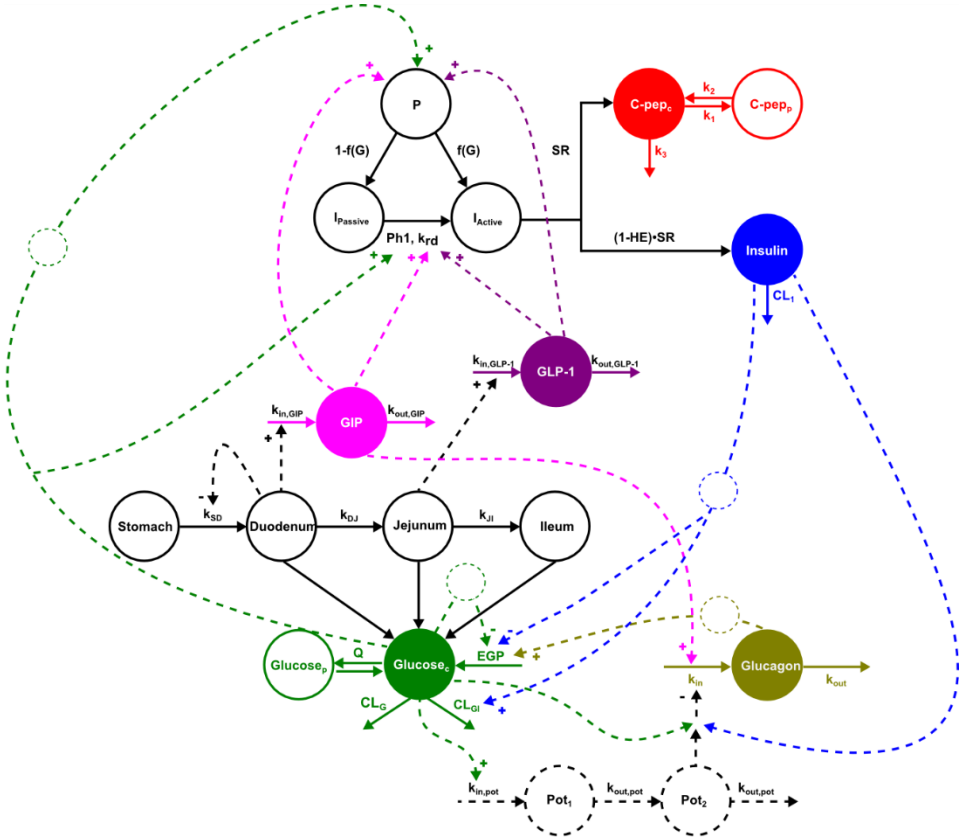


pcVPC insulin, healthy



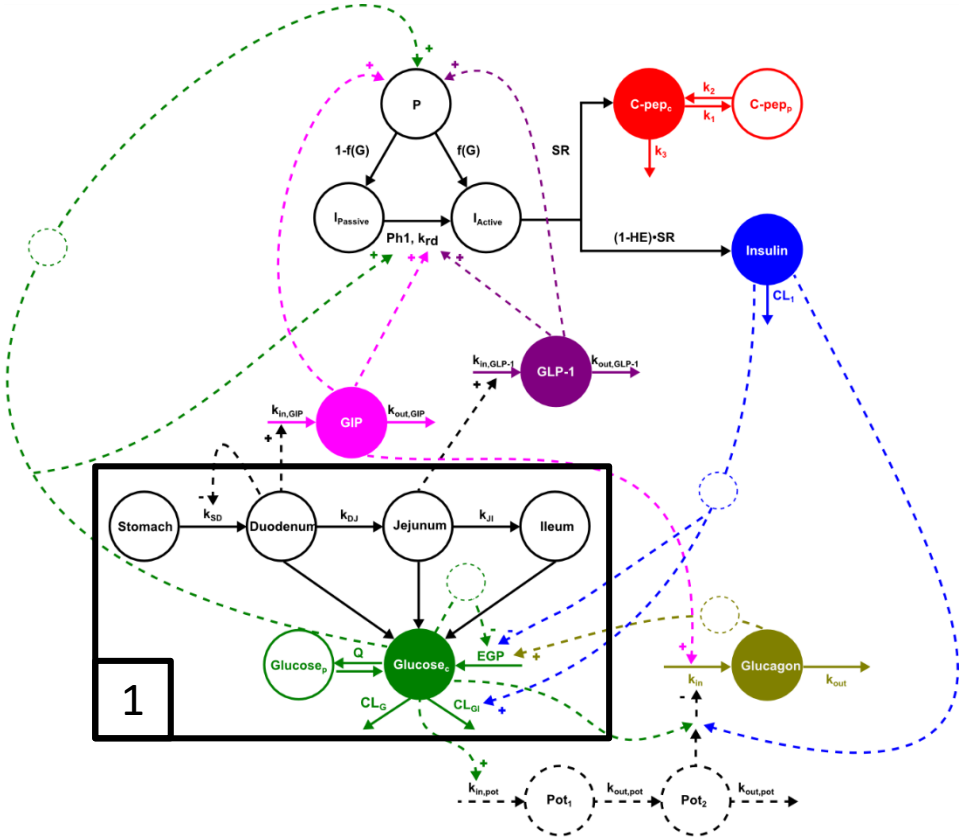
UPPSALA UNIVERSITET

An integrated glucose homeostasis model



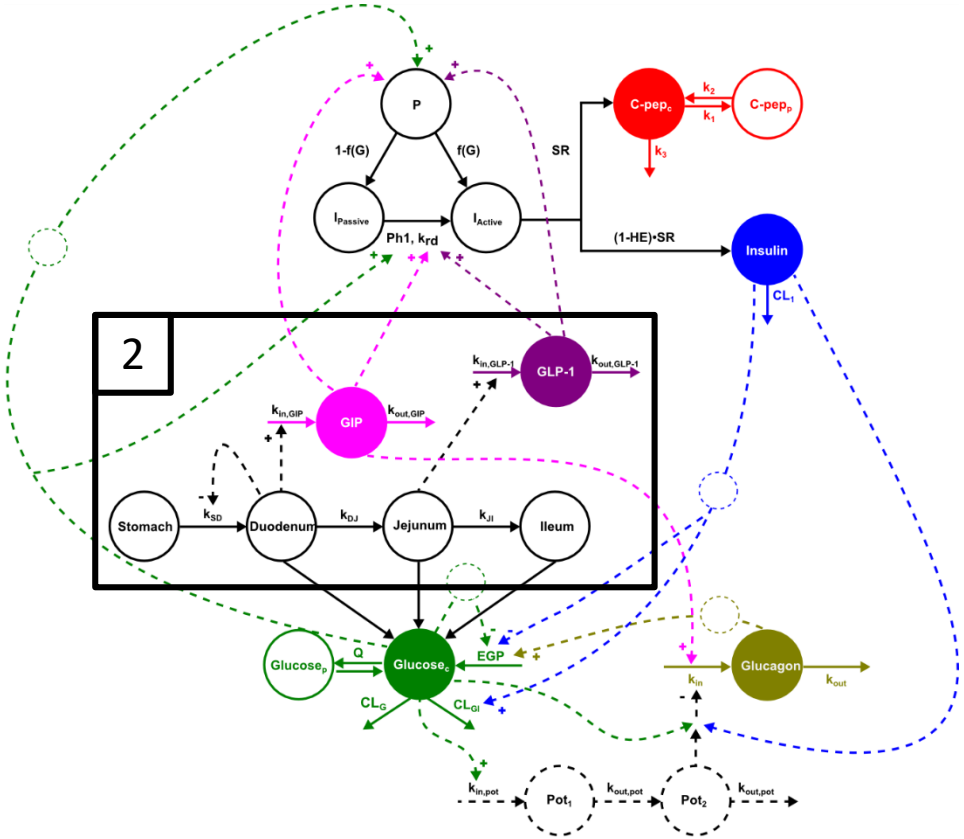
UPPSALA UNIVERSITET

An integrated glucose homeostasis model



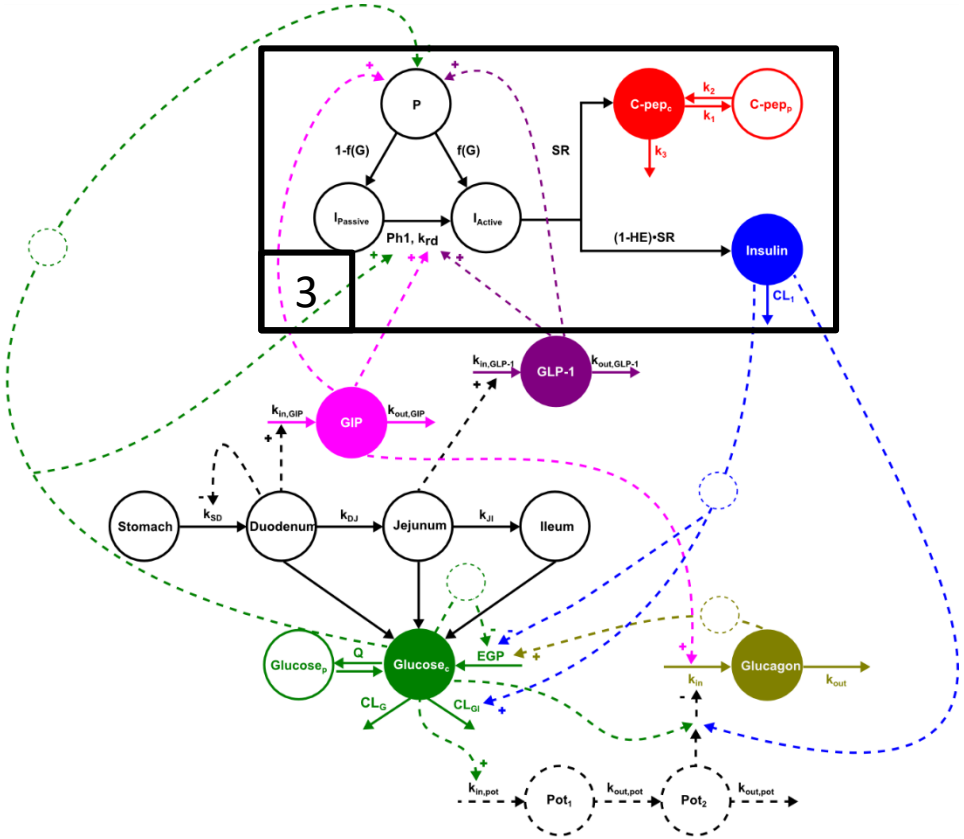
UPPSALA UNIVERSITET

An integrated glucose homeostasis model



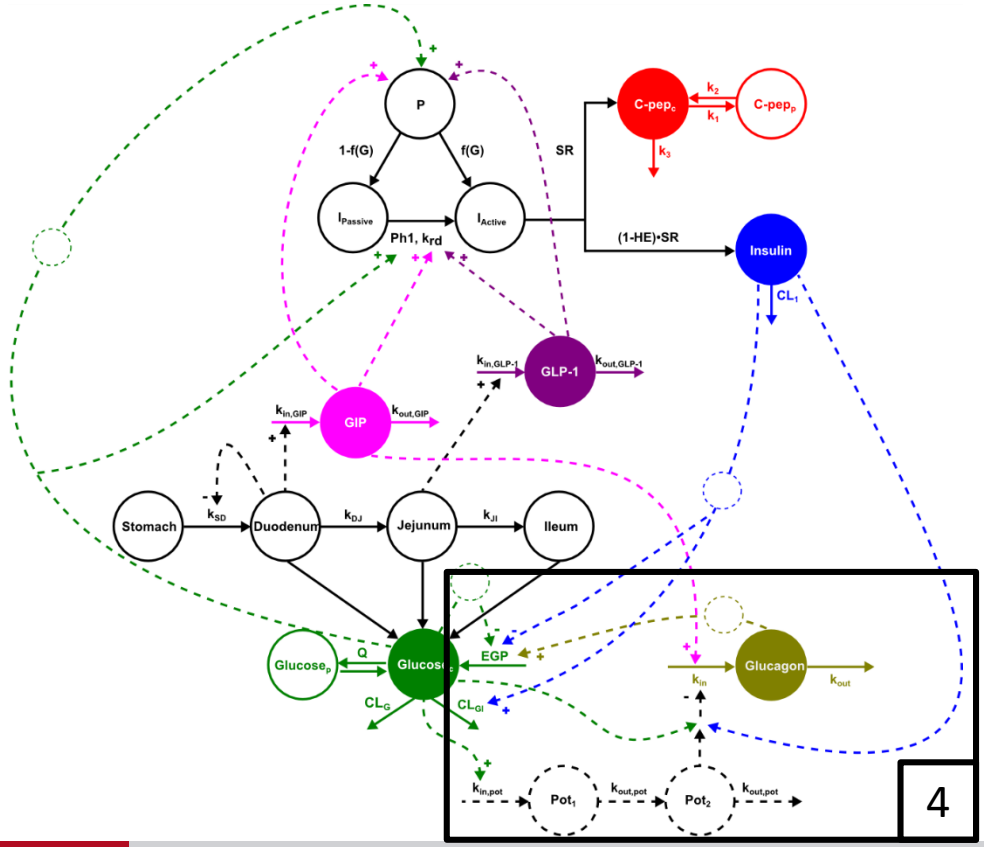
UPPSALA UNIVERSITET

An integrated glucose homeostasis model



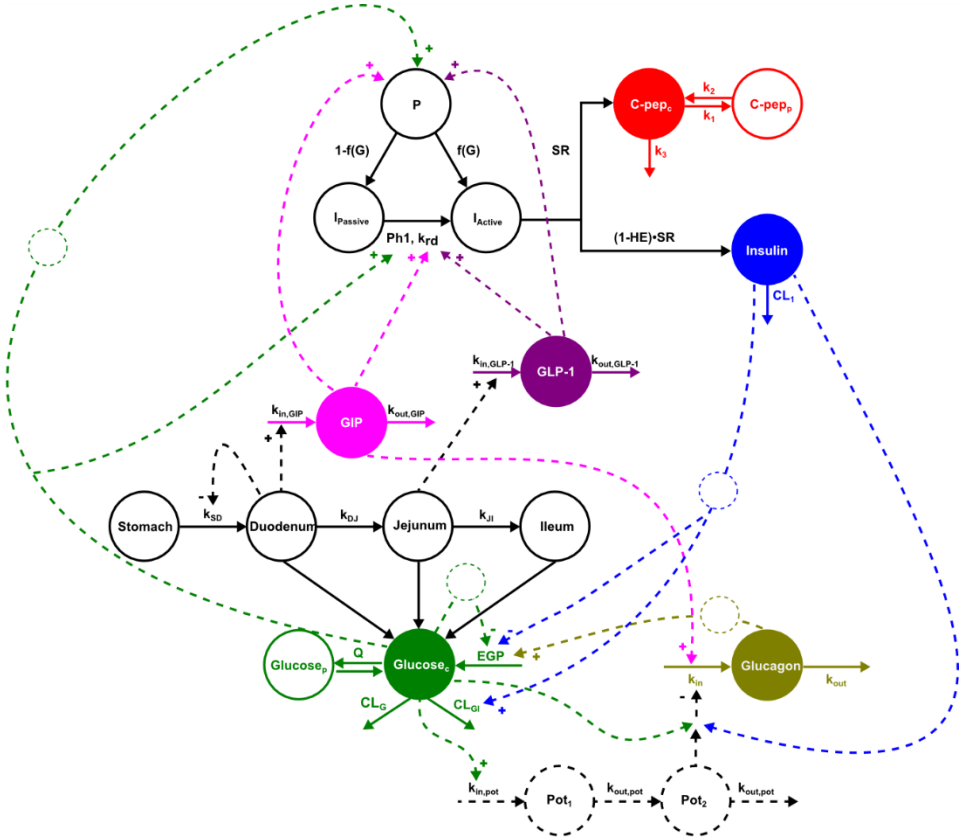
UPPSALA UNIVERSITET

An integrated glucose homeostasis model



UPPSALA UNIVERSITET

An integrated glucose homeostasis model



Conclusions

- The model can simultaneously describe glucose, GLP-1, GIP, Insulin, C-peptide and glucagon
  - Wide dose range
  - Intravenous and oral glucose
  - Healthy controls and patients with T2D

UPPSALA UNIVERSITET

Conclusions

- Enables investigation of
  - Drug effects on multiple sites
  - Combination treatment
- Approach of conditioning on biomarker observations and then combining the submodels was here show-cased to work well

Acknowledgements

- PhD supervisors
  - Mia Kjellsson
  - Mats Karlsson

- Colleagues at Uppsala University