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A Disease Model Describing the Regulation of the Glucose-Insulin System in Diabetic Patients after IVGTT and OGTT

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Modeling &
Simulation

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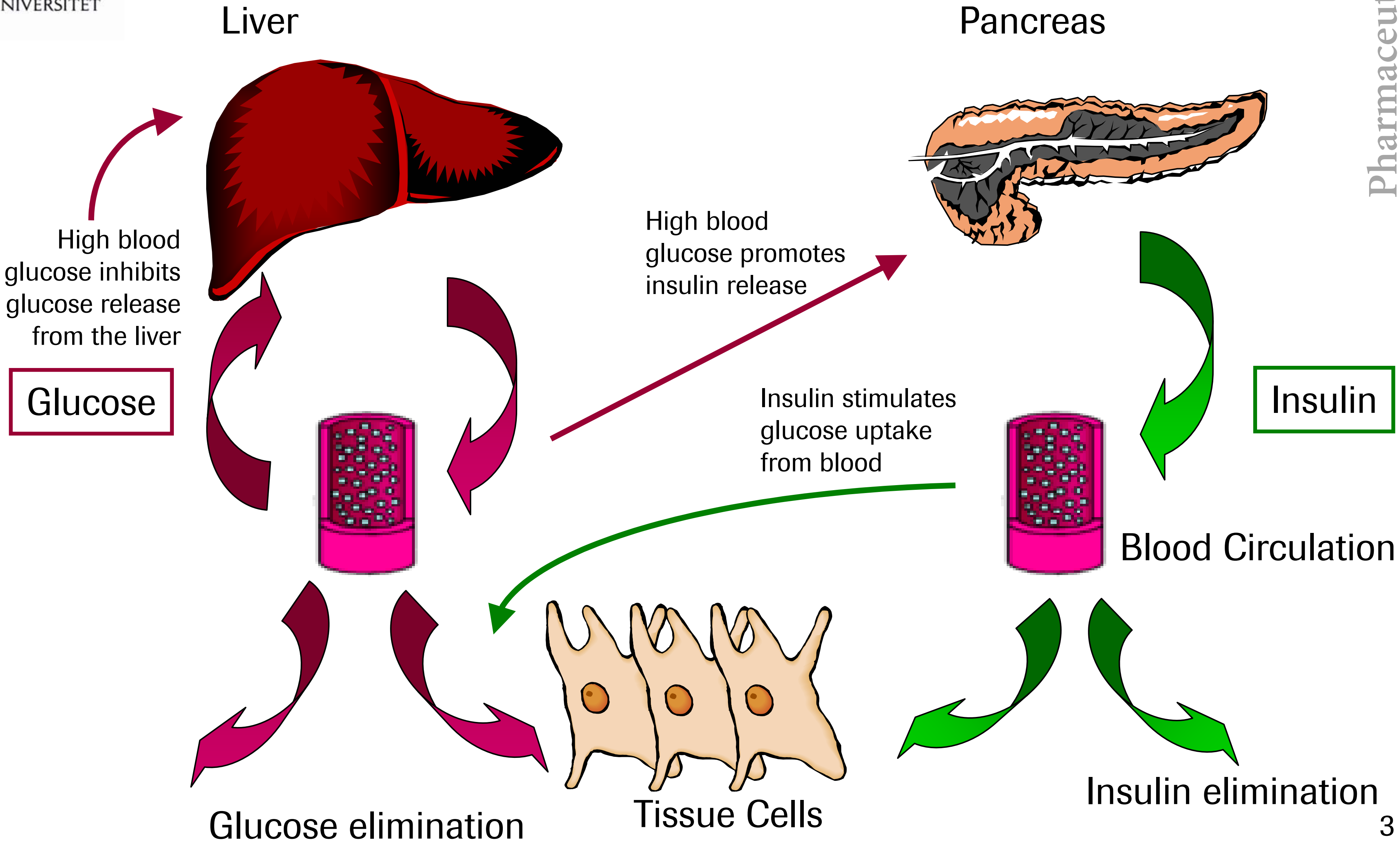
Outline

- Background
  - Glucose-insulin regulation
- Provocation Experiments
  - Intravenous glucose tolerance test (IVGTT)
  - Oral glucose tolerance test (OGTT)
- Model Building
  - ➢ Intravenous Provocation Experiments
  - Overview: Previous modeling of the system (IVGTT)
  - Structural model
  - Feedback loops
  - ➢ Combined IV and Oral Provocation Experiments
  - Glucose absorption (OGTT)
- Results and Discussion
- Conclusion and Future Applications

Glucose–Insulin System



Liver

Pancreas

High blood glucose inhibits glucose release from the liver

Glucose

High blood glucose promotes insulin release

Insulin stimulates glucose uptake from blood

Insulin

Blood Circulation

Glucose elimination

Tissue Cells

Insulin elimination

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IVGTT – Intravenous Glucose Tolerance Test

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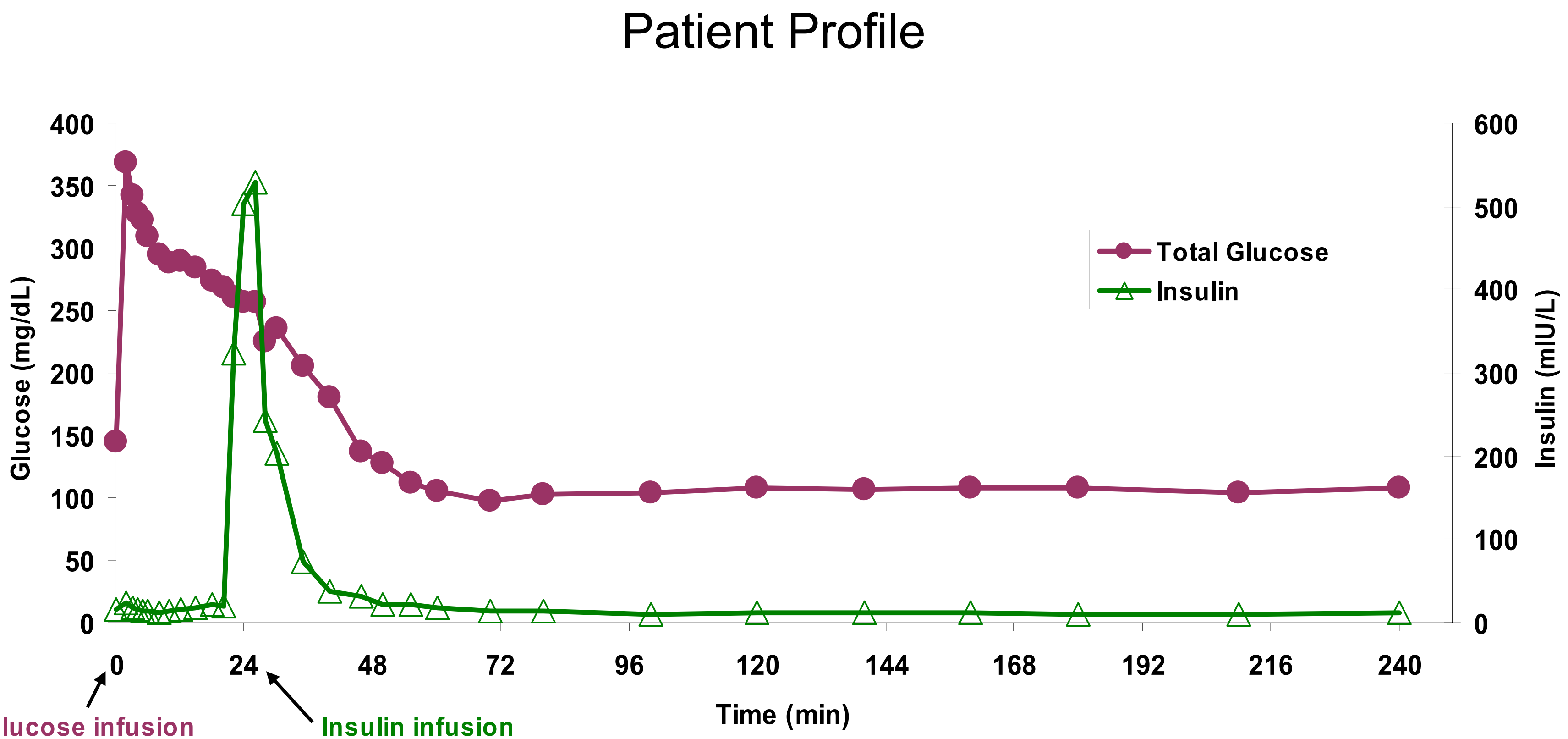
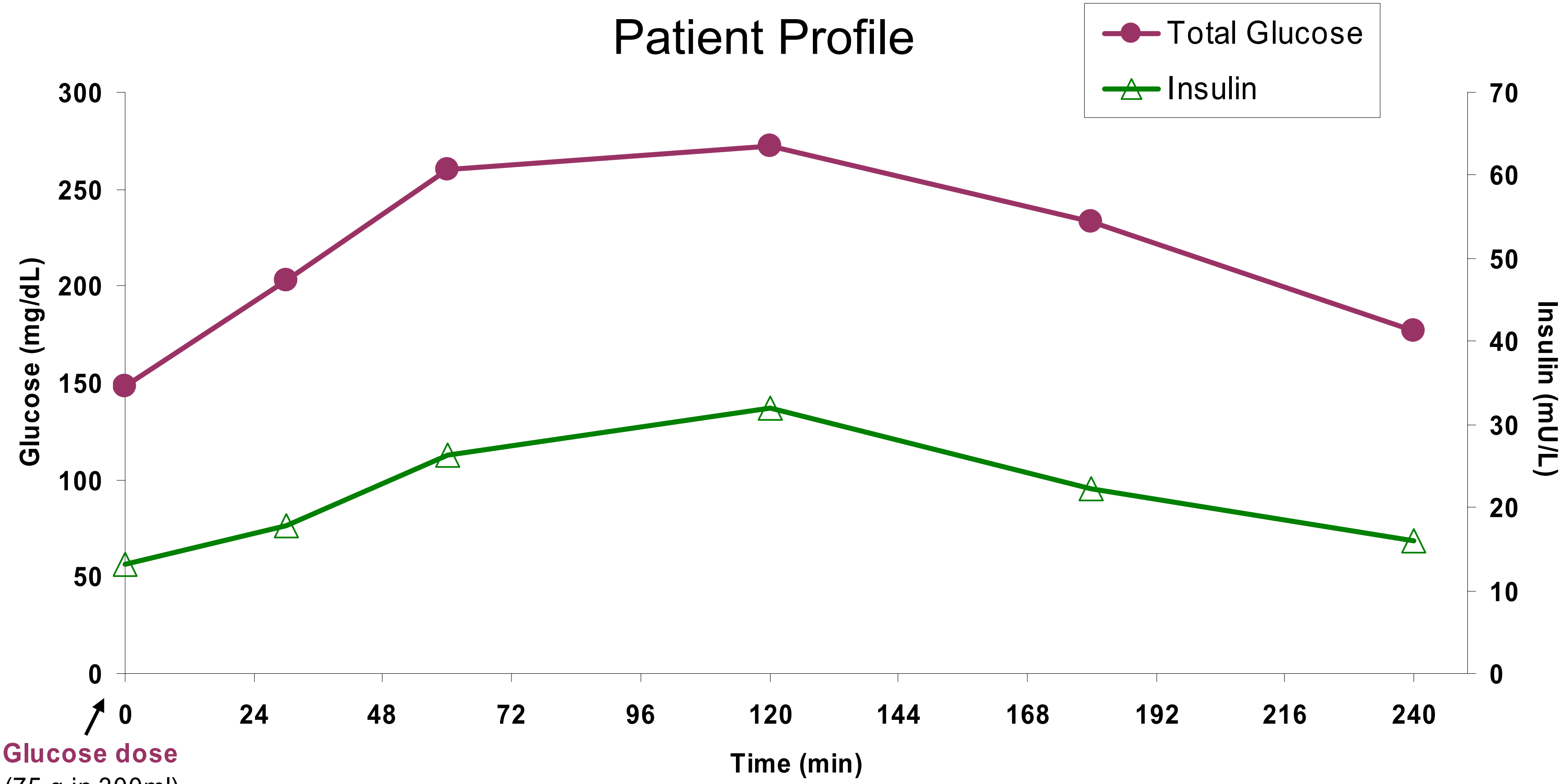


Glucose infusion
(300 mg/kg
in max. 30 secs.)

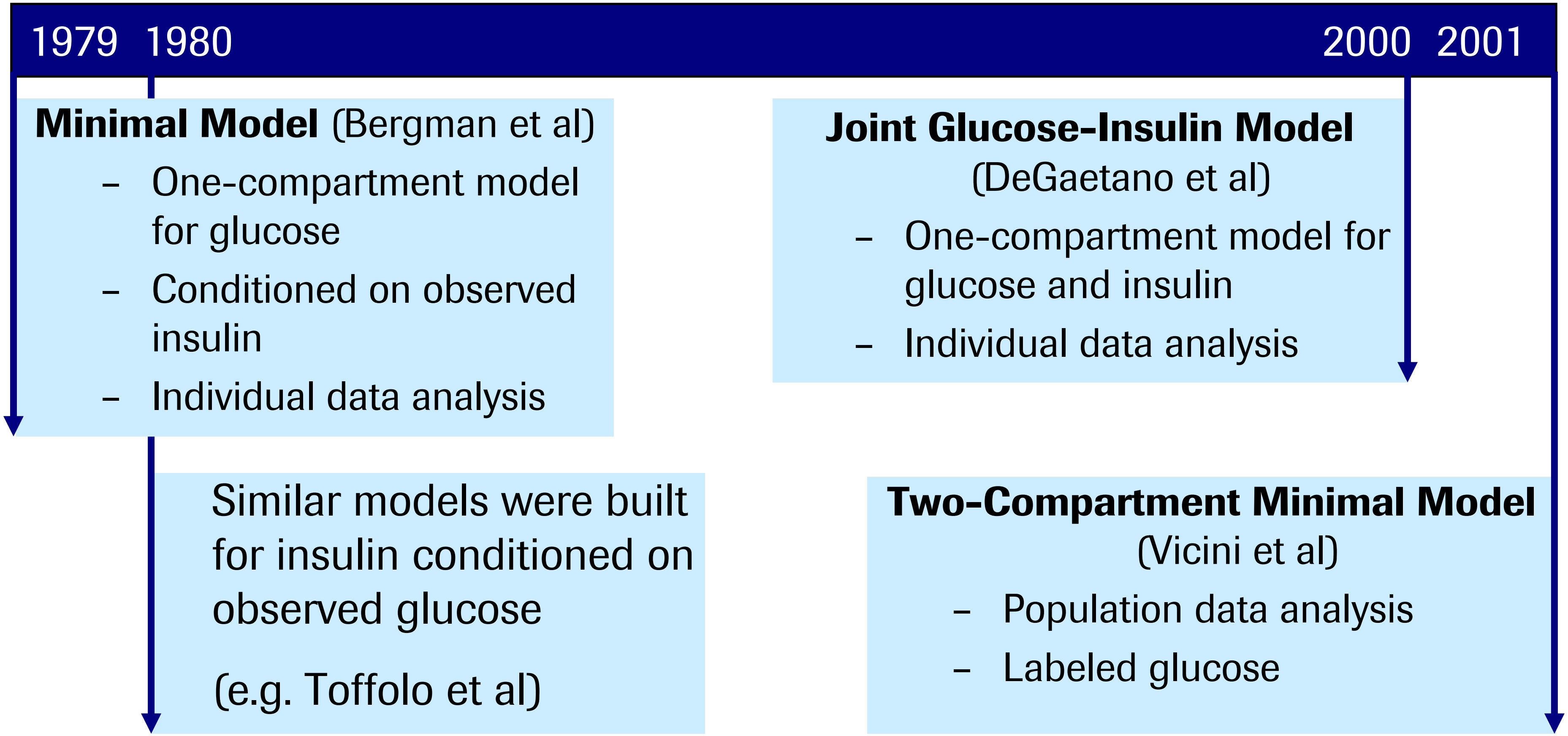
Insulin infusion
(0.05 U/kg, over 5 min,
starting at 20 min.)

OGTT-
Oral Glucose Tolerance Test



Glucose dose
(75 g in 300ml)

Modeling of the Glucose–Insulin System



Minimal Model (Bergman et al)

- One-compartment model for glucose
- Conditioned on observed insulin
- Individual data analysis

Similar models were built for insulin conditioned on observed glucose

(e.g. Toffolo et al)

Joint Glucose-Insulin Model
(DeGaetano et al)

- One-compartment model for glucose and insulin
- Individual data analysis

Two-Compartment Minimal Model
(Vicini et al)

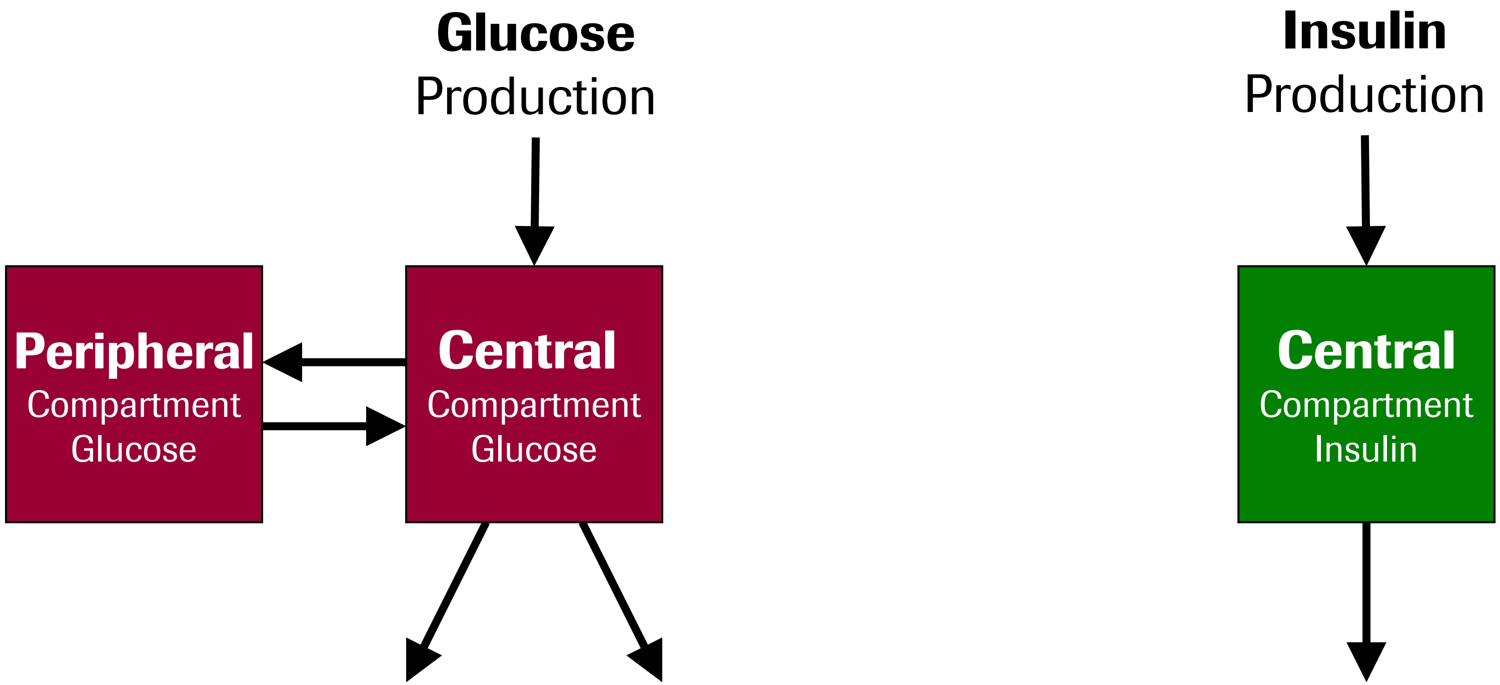
- Population data analysis
- Labeled glucose

A simultaneous model for glucose AND insulin is necessary for adequate simulations. Addressing several types of provocations in healthy volunteers and patients would be desirable.

Study Protocol and Data for the Development of the IV Model

	Type	Subjects	Insulin infusion	Labeled Glucose
Study 1	IVGTT	14 healthy volunteers	-	Yes
Study 2	IVGTT	42 patients	Short infusion at t = 20 min	Yes
Study 3	Clamp	6 healthy volunteers	Continuous	Yes
Study 4	IVGTT	10 healthy volunteers	Short infusion at t = 20 min	Yes

Model Building – First Steps (IV only)



Glucose
Production

Peripheral
Compartment
Glucose

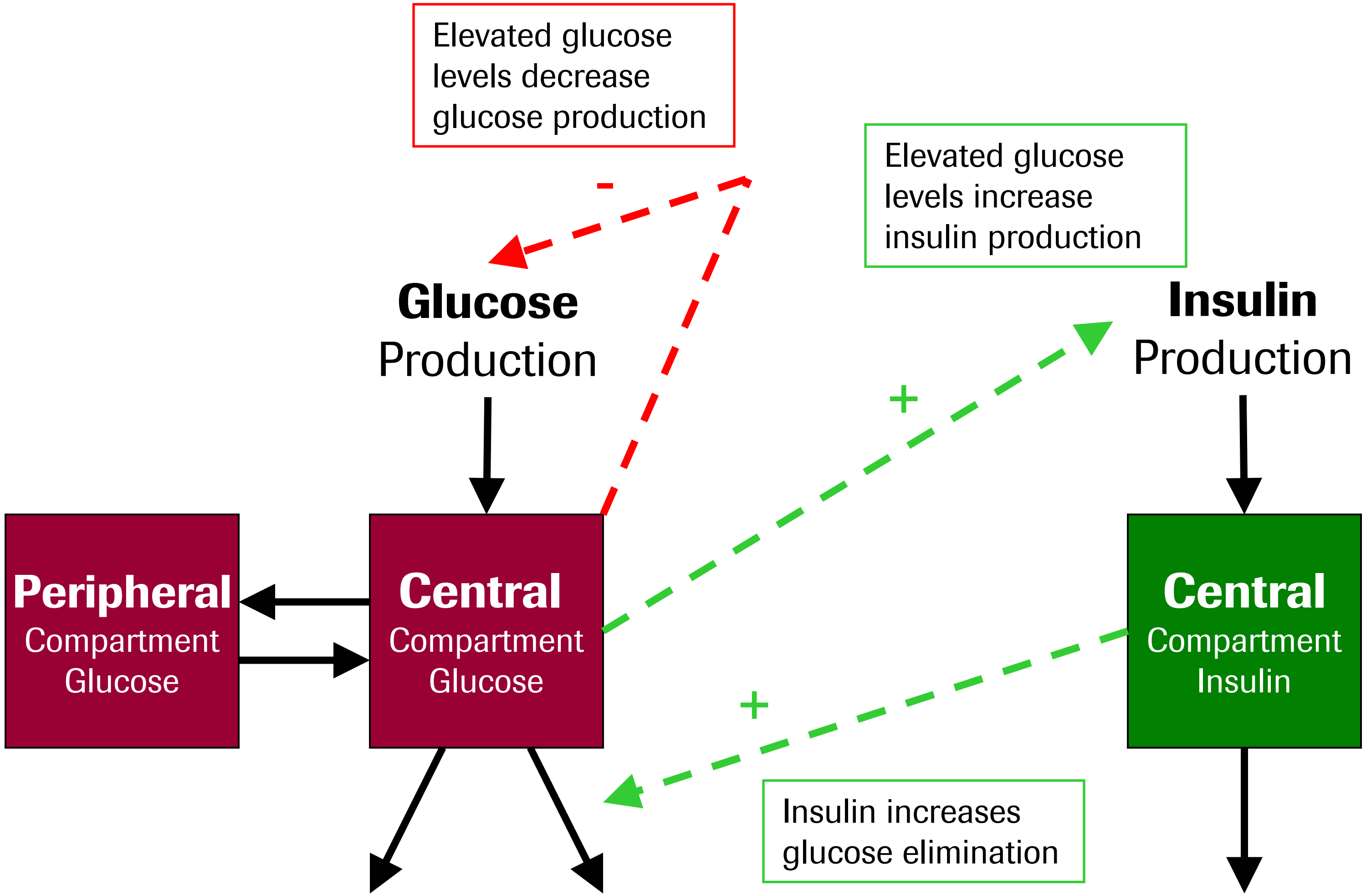
Central
Compartment
Glucose

Insulin
Production

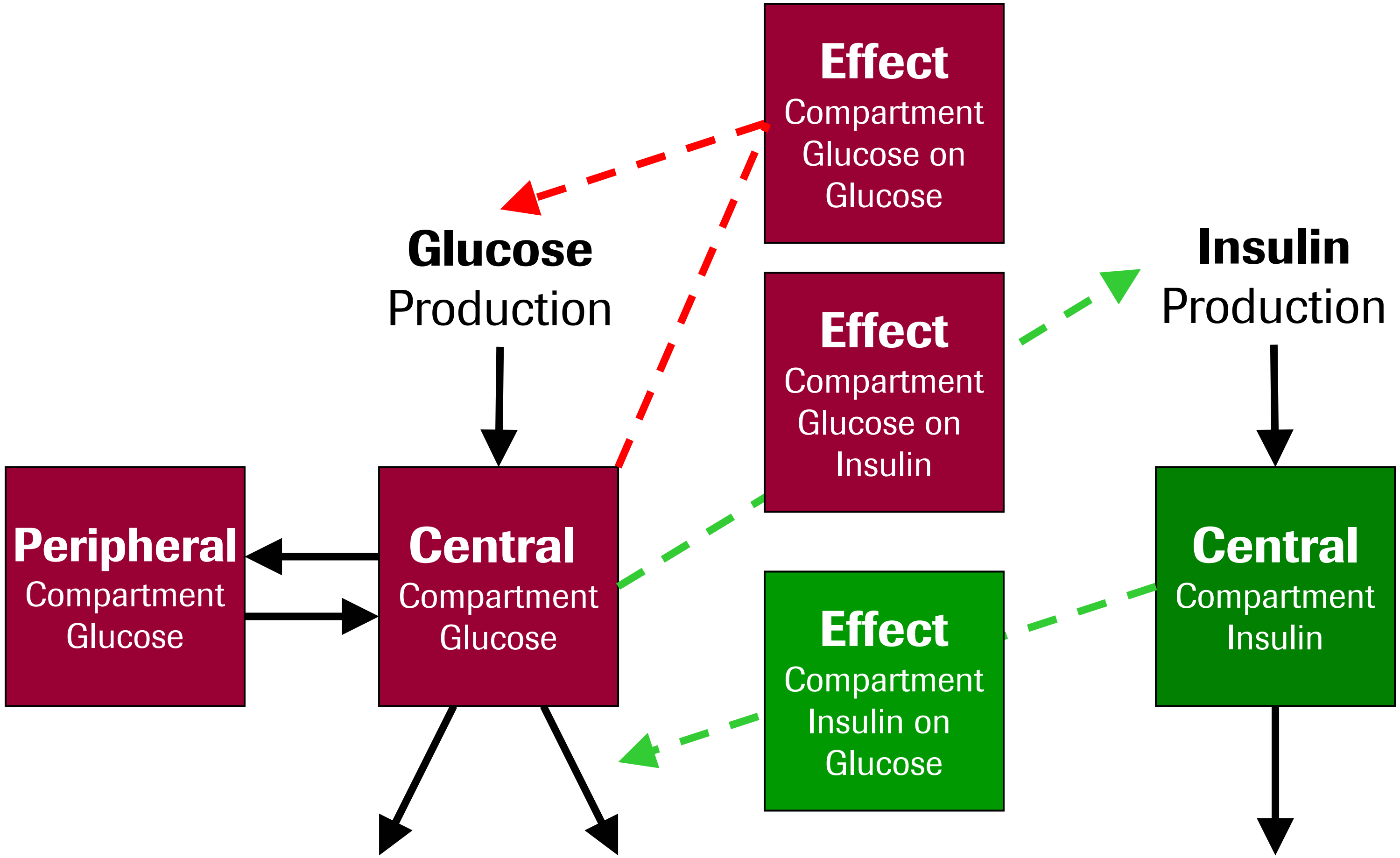
Central
Compartment
Insulin

Feedback Mechanisms and Interactions

Between Glucose and Insulin in Hyperglycemic Condition


Elevated glucose levels decrease glucose production
-
Elevated glucose levels increase insulin production
Glucose Production
Insulin Production
+
Peripheral Compartment Glucose
Central Compartment Glucose
Central Compartment Insulin
+
Insulin increases glucose elimination

Effect Compartments



Effect Compartment Glucose on Glucose

Glucose Production

Effect Compartment Glucose on Insulin

Insulin Production

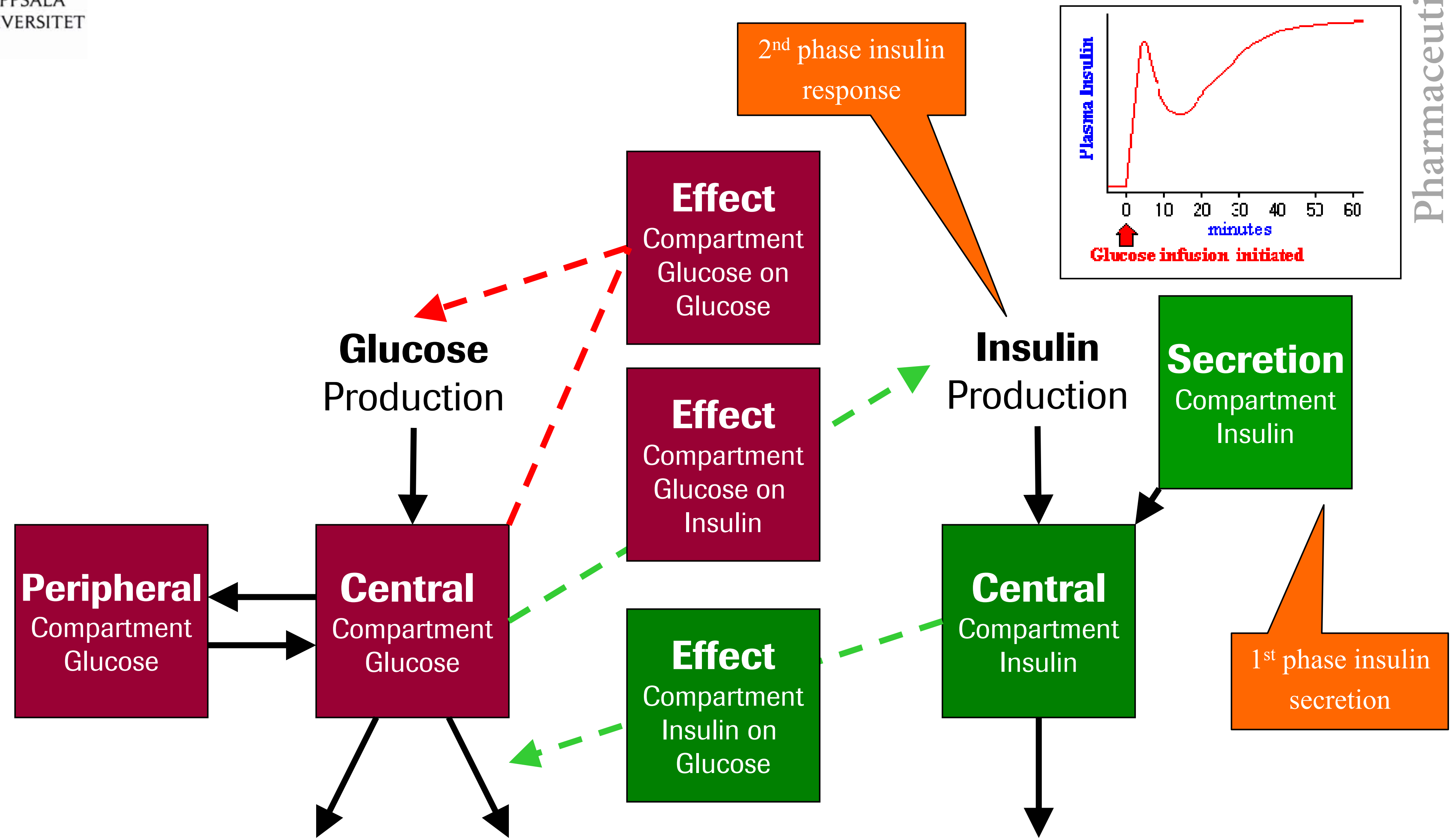
Peripheral Compartment Glucose

Central Compartment Glucose

Effect Compartment Insulin on Glucose

Central Compartment Insulin

Insulin Secretion


Plasma Insulin
0
10
20
30
40
50
60
minutes
Glucose infusion initiated

2nd phase insulin response

Effect Compartment Glucose on Glucose

Glucose Production

Effect Compartment Glucose on Insulin

Insulin Production

Secretion Compartment Insulin

Peripheral Compartment Glucose

Central Compartment Glucose

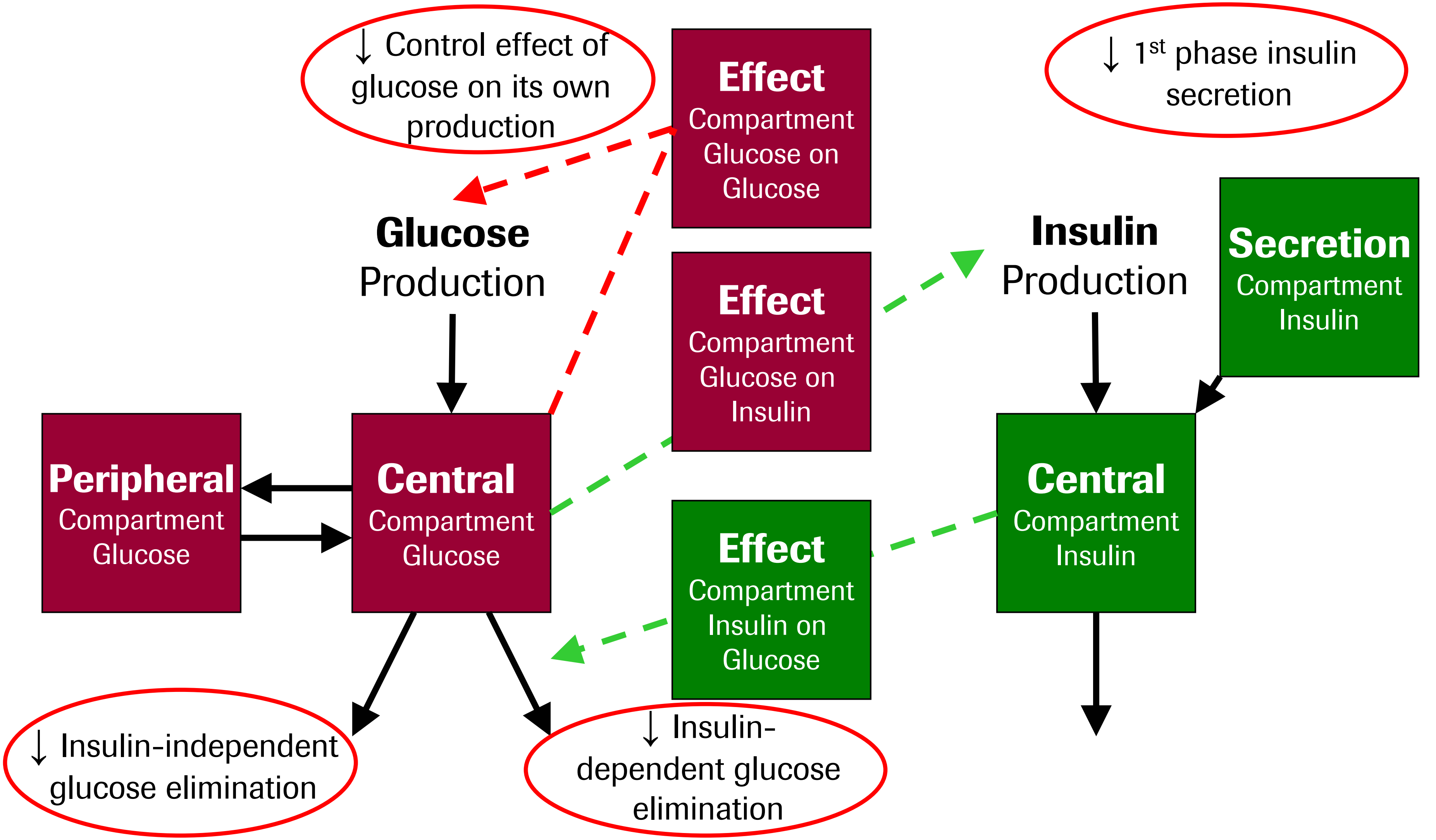
Effect Compartment Insulin on Glucose

Central Compartment Insulin

1st phase insulin secretion

Final IV Model

Parameter Differences in Patients Compared to Healthy Volunteers



↓ Control effect of glucose on its own production

Effect Compartment Glucose on Glucose

↓ 1st phase insulin secretion

Glucose Production

Effect Compartment Glucose on Insulin

Insulin Production

Secretion Compartment Insulin

Peripheral Compartment Glucose

Central Compartment Glucose

Central Compartment Insulin

Effect Compartment Insulin on Glucose

↓ Insulin-independent glucose elimination

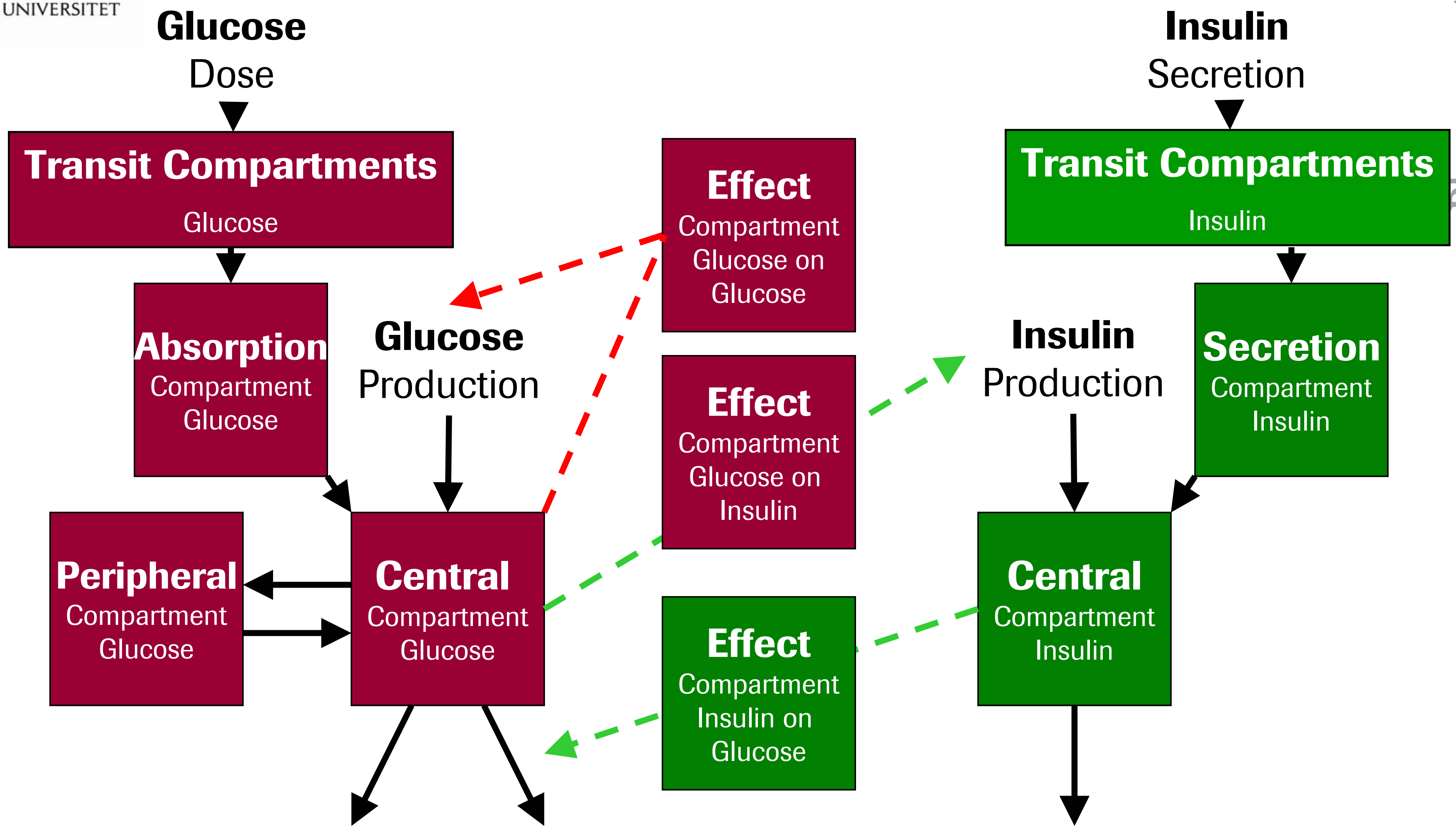
↓ Insulin-dependent glucose elimination

Study Protocol and Data for the Development of the Combined Model

All data from **type 2 diabetic patients**
IVGTT and OGTT performed in the same 42 subjects

Type	Dose	Number of samples	Insulin infusion	Labeled Glucose
IVGTT	300 mg/kg	34 within 4 hours	Short infusion at t = 20 min	Yes
OGTT	75 g	6 within 4 hours	-	No

Model Adaptation to OGTT



Glucose
Dose

Transit Compartments
Glucose

Absorption
Compartment
Glucose

Glucose
Production

Effect
Compartment
Glucose on
Glucose

Effect
Compartment
Glucose on
Insulin

Effect
Compartment
Insulin on
Glucose

Peripheral
Compartment
Glucose

Central
Compartment
Glucose

Insulin
Secretion

Transit Compartments
Insulin

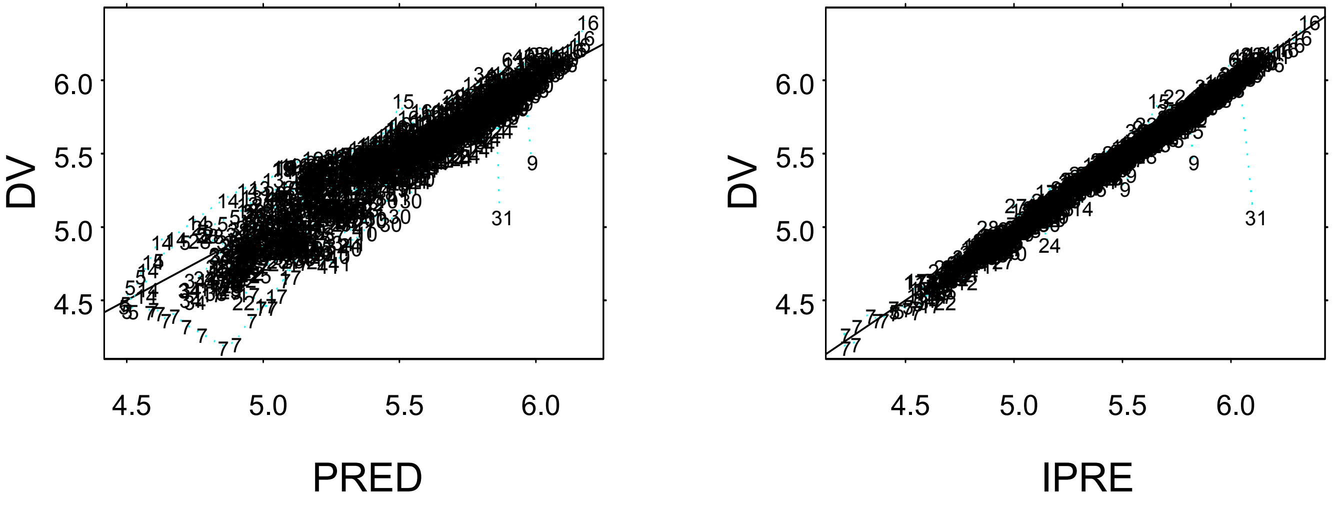
Insulin
Production

Secretion
Compartment
Insulin

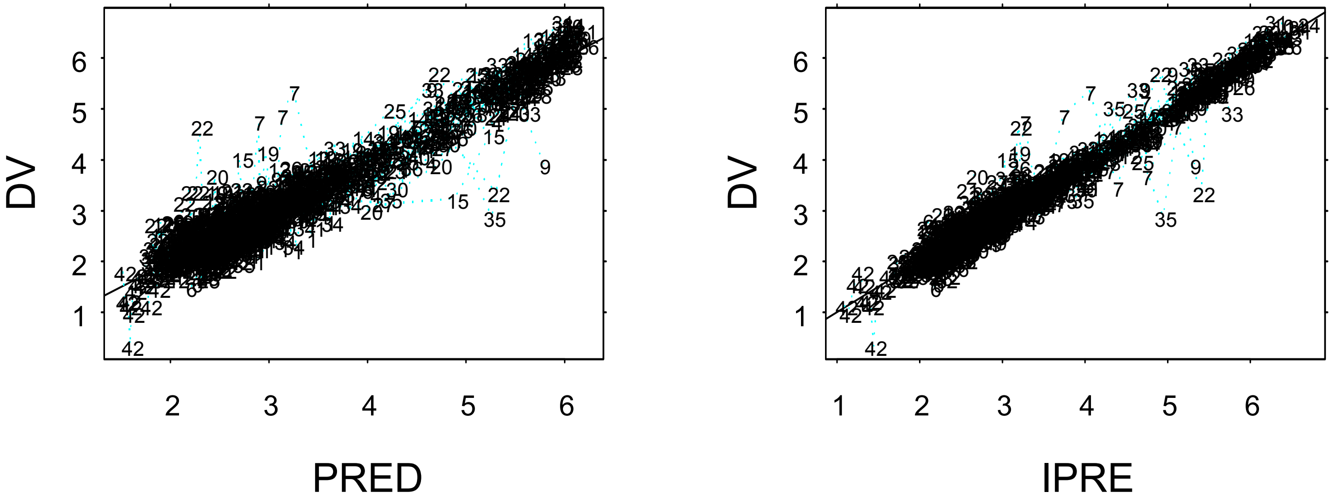
Central
Compartment
Insulin

Goodness of Fit Plots IVGTT

Glucose



Insulin



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Goodness of Fit Plots OGTT

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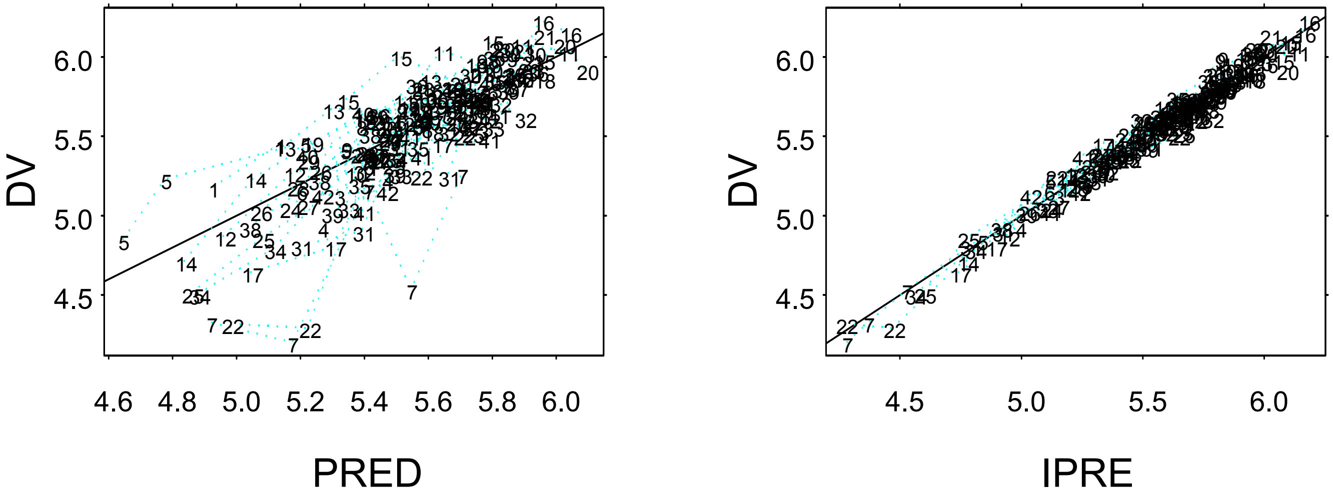
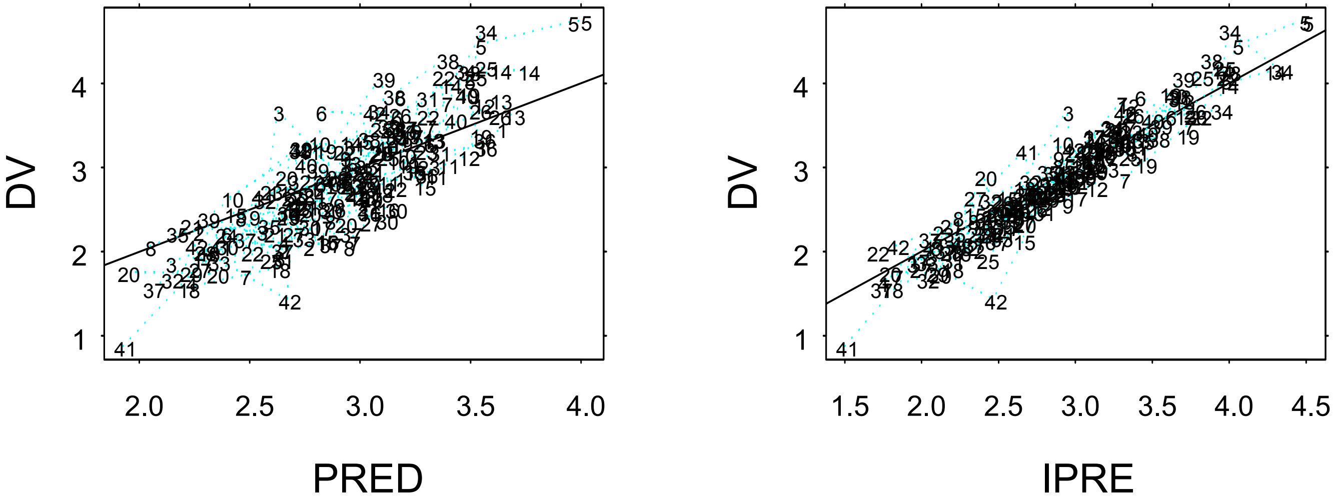
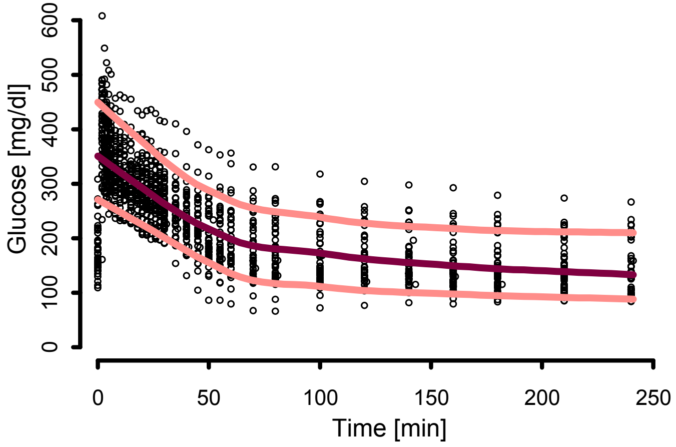
Glucose

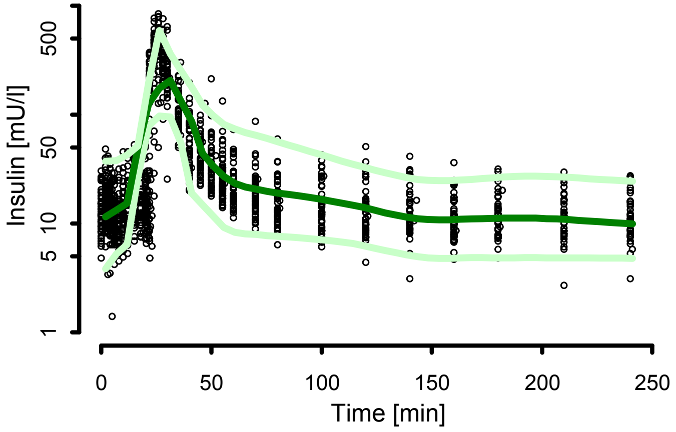


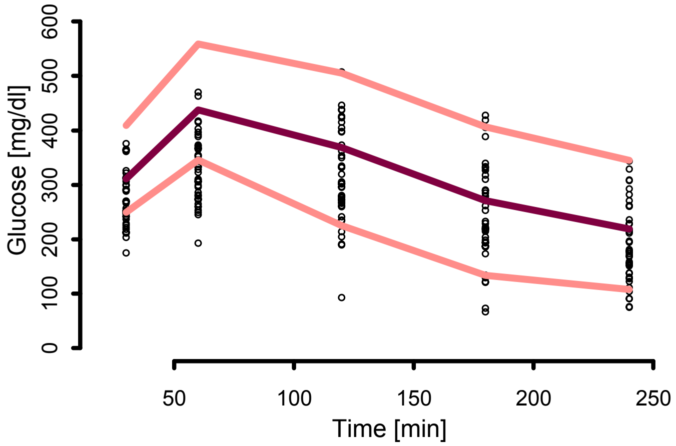
Insulin

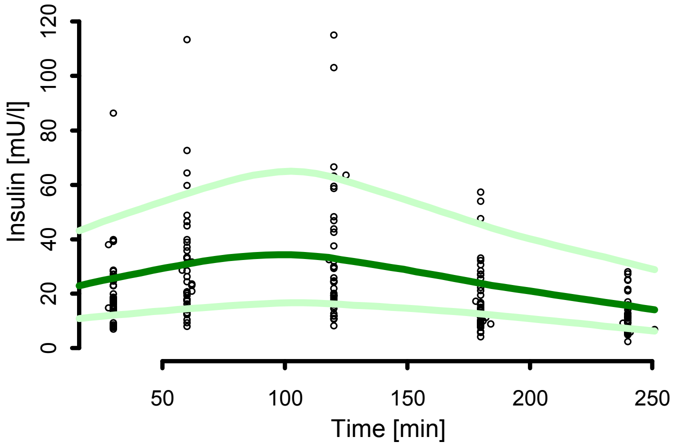


Simulations


Glucose IV


Insulin IV


Glucose ORAL


Insulin ORAL

Result Summary

- Model described OGTT data well

- Absorption phase of glucose adequately described, bioavailability estimated to approximately 80%

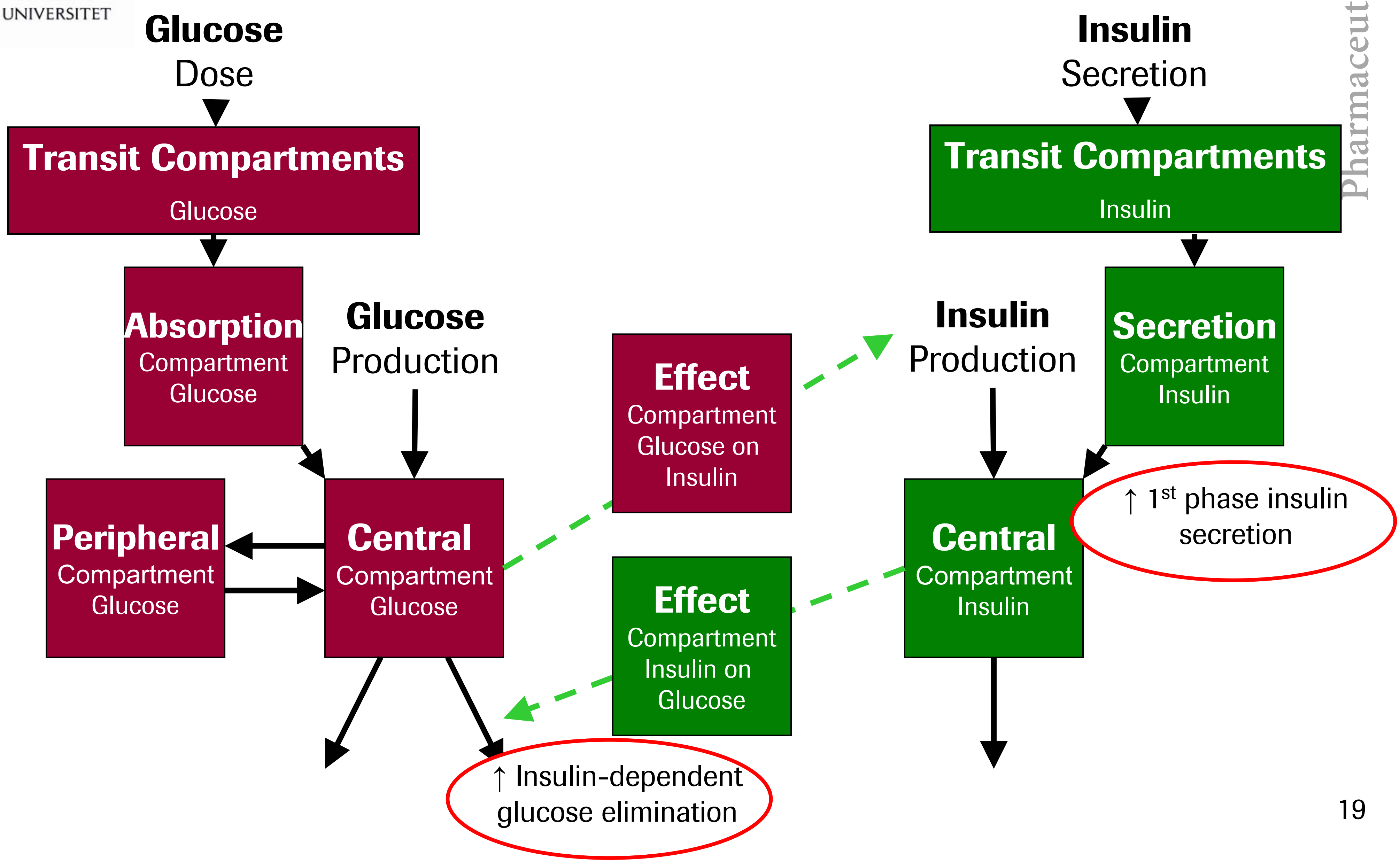
- Parameters well estimated (CV $<$ 15% for all parameters except absorption rate constant)

- Residual errors (multiplicative):
  - Glucose: 5% CV (IVGTT) and 8% CV (OGTT)
  - Insulin: 25% CV (both IVGTT and OGTT)

- Adequate simulations of glucose and insulin concentration-time profiles

Final Combined IV and PO Model

Parameter Differences in OGTT Compared to IVGTT in Patients



Glucose
Dose

Transit Compartments
Glucose

Absorption
Compartment
Glucose

Glucose
Production

Peripheral
Compartment
Glucose

Central
Compartment
Glucose

Effect
Compartment
Glucose on
Insulin

Effect
Compartment
Insulin on
Glucose

↑ Insulin-dependent
glucose elimination

Insulin
Secretion

Transit Compartments
Insulin

Insulin
Production

Secretion
Compartment
Insulin

Central
Compartment
Insulin

↑ 1st phase insulin
secretion

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Percentage of Insulin-Dependent Glucose Elimination in IVGTT and OGTT

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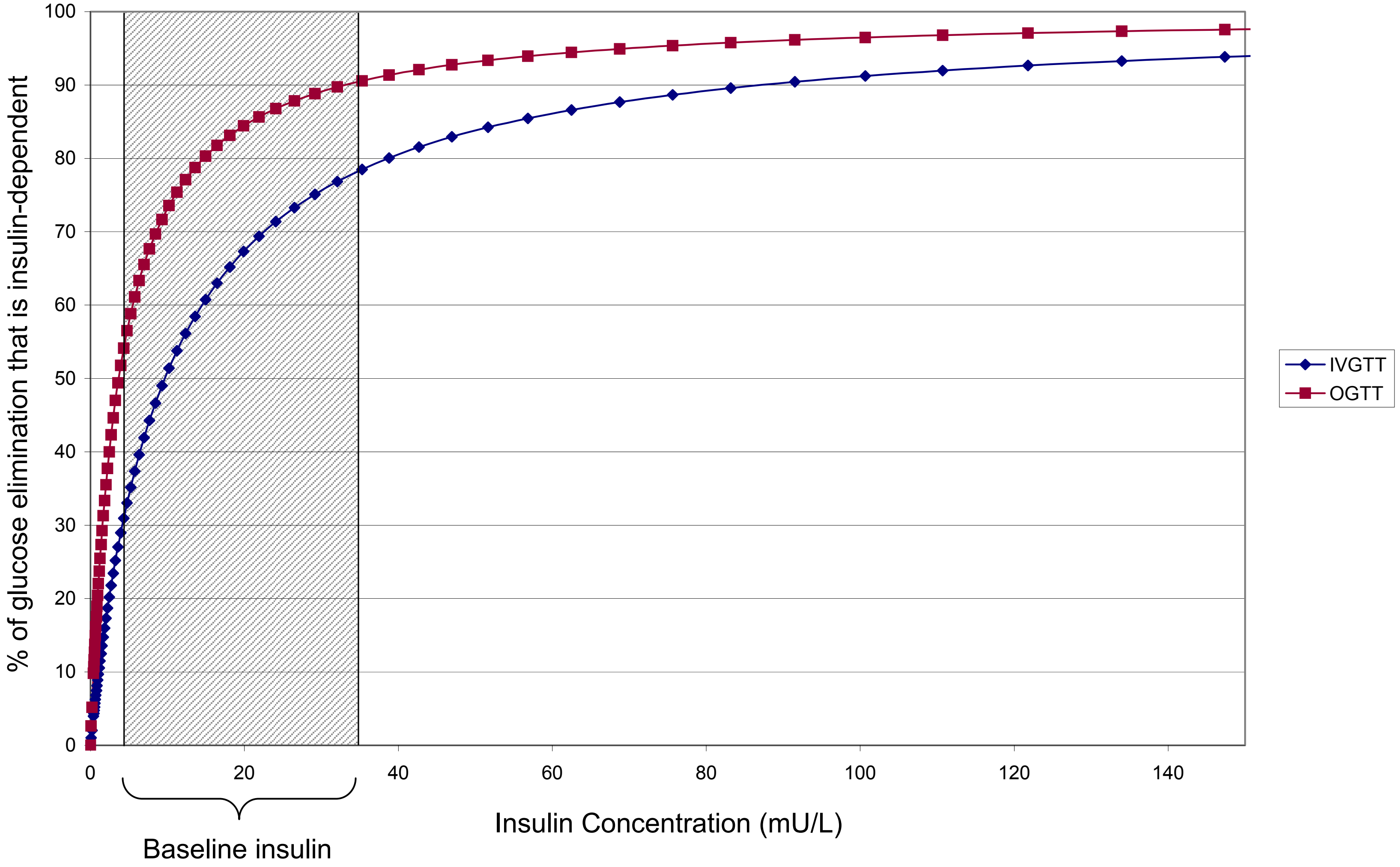

Differences Between IVGTT and OGTT

- Significant first-phase insulin secretion after OGTT
  - Related to the release of the insulin secretagogue GLP-1 (glucagon-like peptide-1) from the gastrointestinal tissues
    → potentiating effect on insulin secretion
  - Higher glucose dose given in the OGTT
- Higher insulin-dependent glucose elimination after OGTT (~3 fold)
  - Similar factor observed for insulin sensitivity in previous works.
    May be due to gastrointestinal or first-pass effects enhancing insulin sensitivity in the liver or the muscle tissue – under debate
  - Impact of the insulin infusion in the IVGTT ?

Conclusion and Future Applications

Achieved: Integrated model for glucose and insulin following OGTT and IVGTT, addresses two different routes of administration simultaneously

Future Aims:

- Evaluation of the model by applying it to a different patient population (more severe disease, Type 1 diabetics etc.)
- Explore possible covariate influence (severity of disease, treatment duration)
- Extension of the model to meal test data
- Study design optimization
- Implementation of drug effects (e.g. PPAR, SU…)