Modelling the Dynamics of Glucose, Insulin, Insulin Sensitivity and Beta-Cells in Subjects with Insulin Resistance and Patients with Type 2 Diabetes

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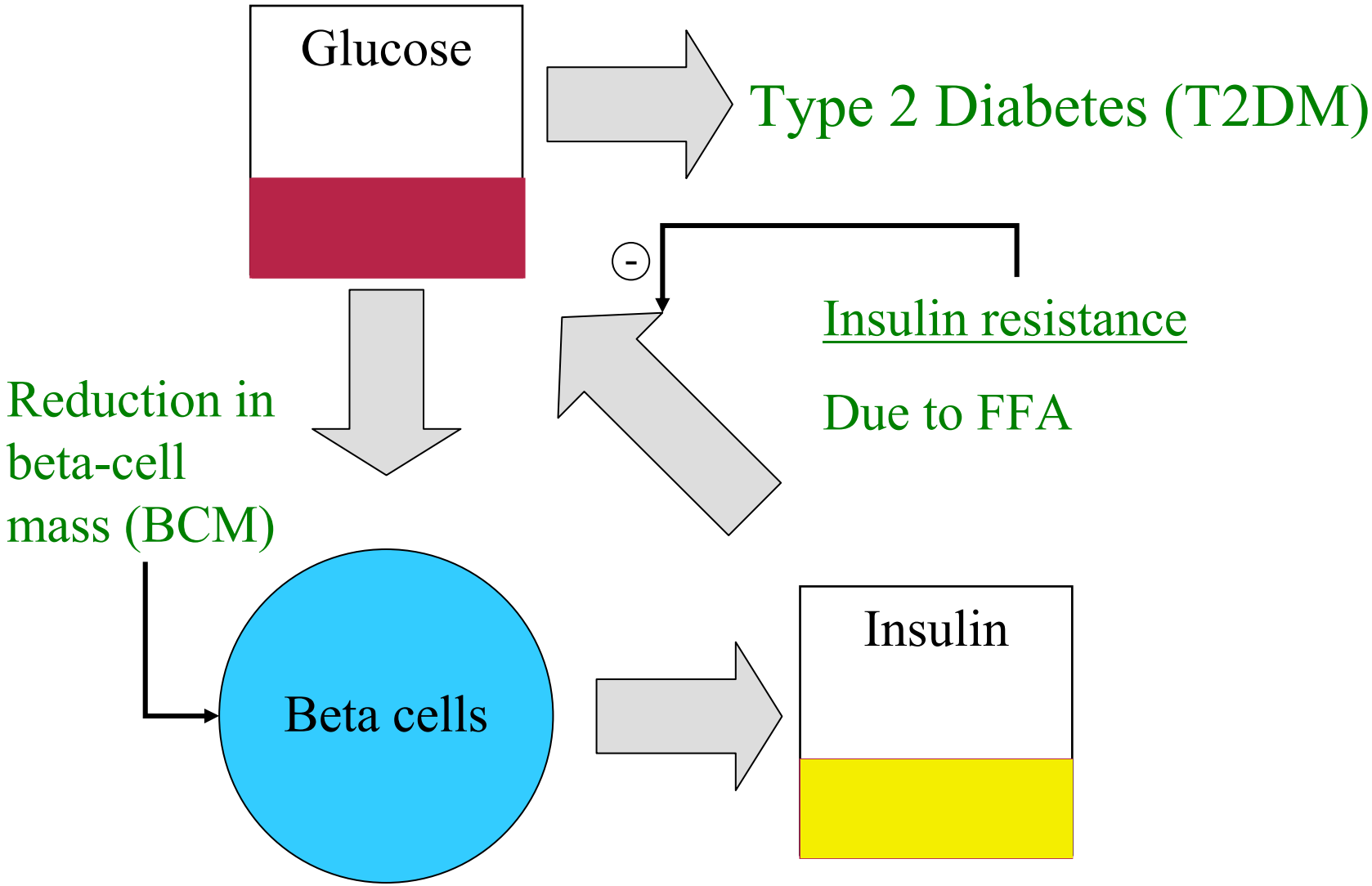
Ribbing J, Hamrén B, Svensson MK, and Karlsson MO A Model for Glucose, Insulin, Beta-Cell and HbA1c Dynamics in Subjects with Insulin Resistance and Patients with Type 2 Diabetes (*Manuscript*)

Scope

- Covered
  - Mechanisms of type 2 diabetes
  - BIG model by Topp et al.
  - The usual suspects: Method, Results and Conclusions
- Not covered
  - Previously developed PK-PD models

Mechanism of Type 2 Diabetes



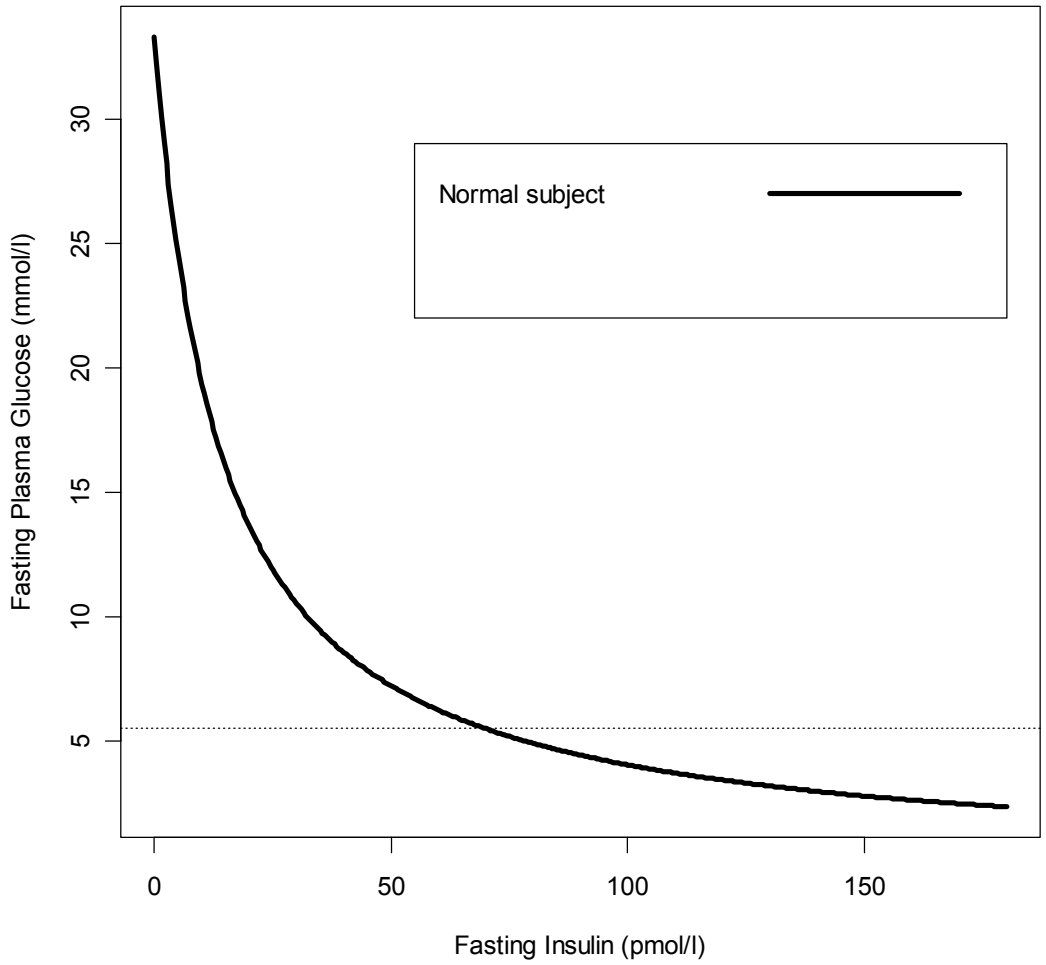
Topp et al. - BIG Model

- **B**eta-cell mass, **I**nsulin and **G**lucose (**BIG**)
- Three differential equations
  - Includes adaptation of beta-cell mass (BCM)
- Not fitted simultaneously
  - Derived from sources in literature
  - Mean parameter values for normal subject
- No pharmacological treatment

Topp B, Promislow K, deVries G, Miura RM, Finegood DT (2000) **A model of beta-cell mass, insulin, and glucose kinetics: pathways to diabetes.** J Theor Biol 206: 605-619

1. Glucose is Regulated by Insulin

$$dFPG/dt = R_0 - \left(E_{GO} + S \cdot FI\right) \cdot FPG$$



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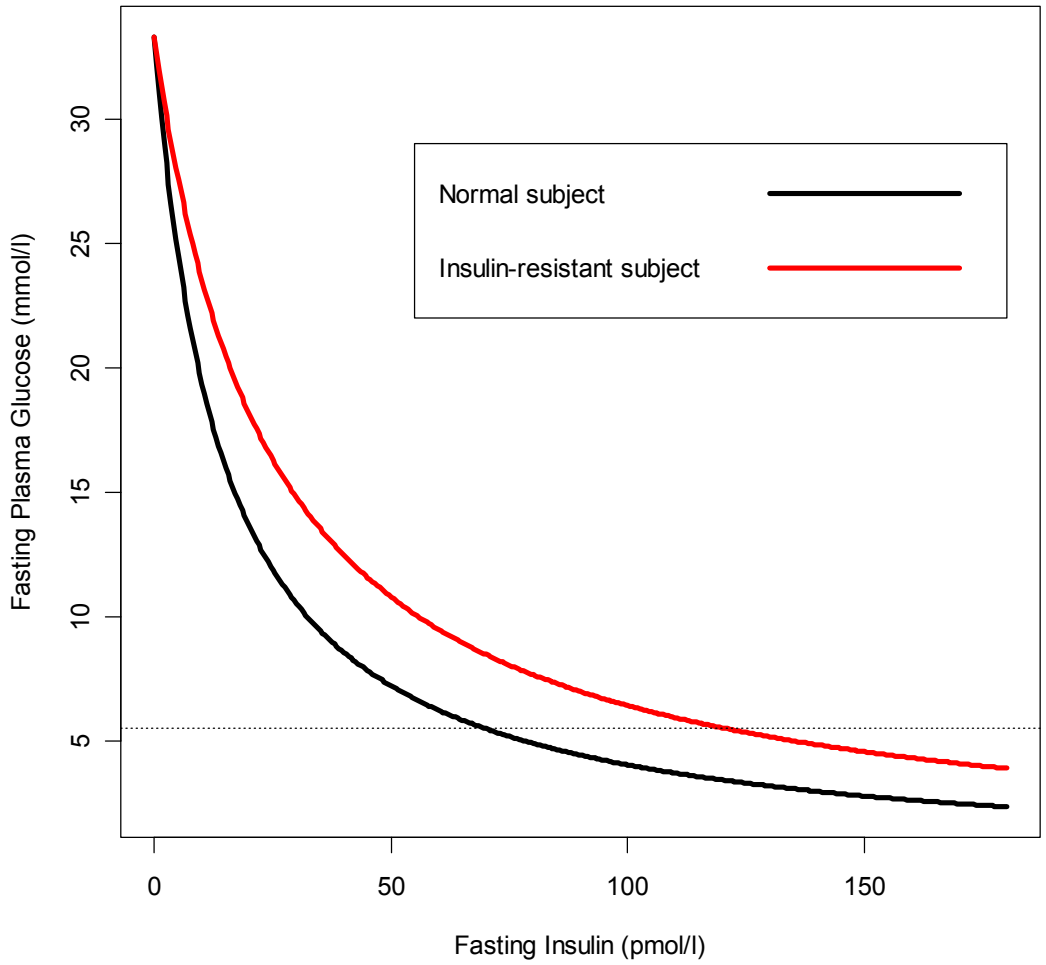
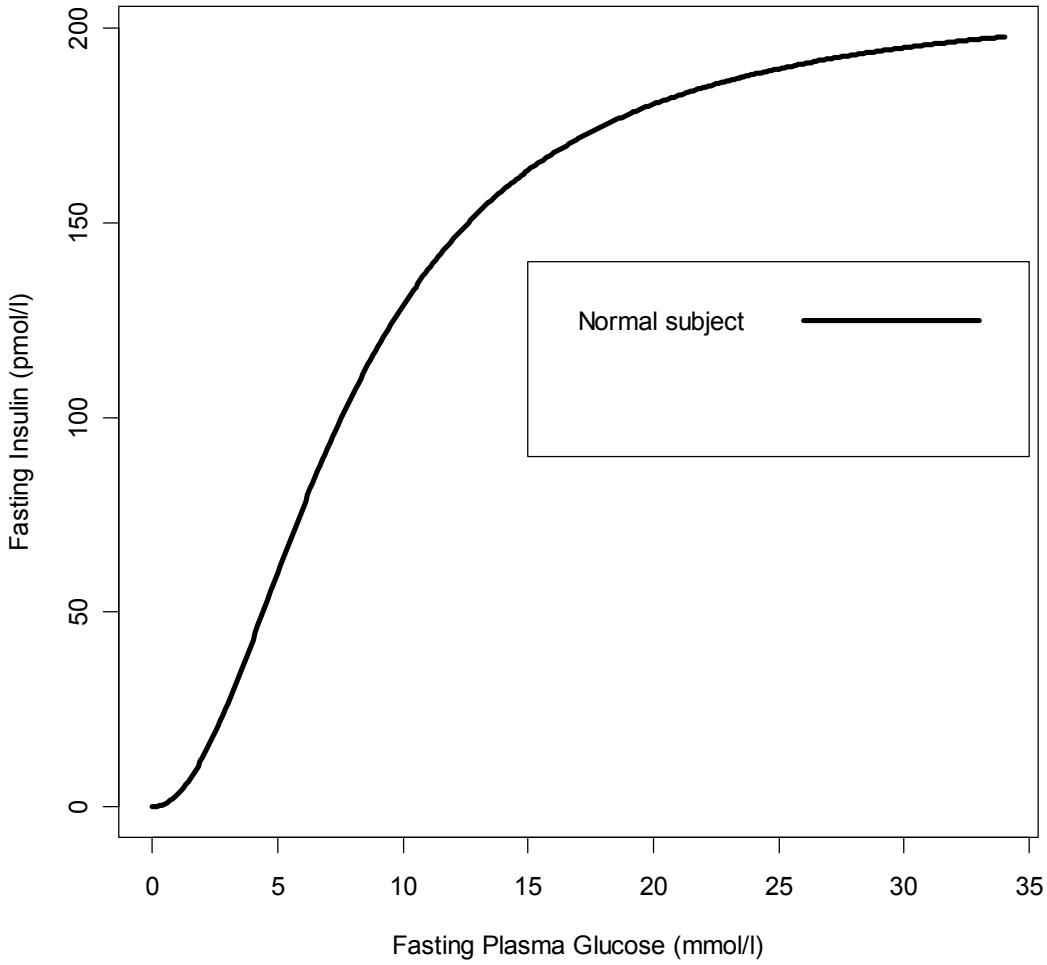


2. Insulin is regulated by Glucose!

$$dFI/dt = BCM \cdot \sigma \cdot FPG^2 \Big/ \left(\alpha^2 + FPG^2\right) - k \cdot FI$$



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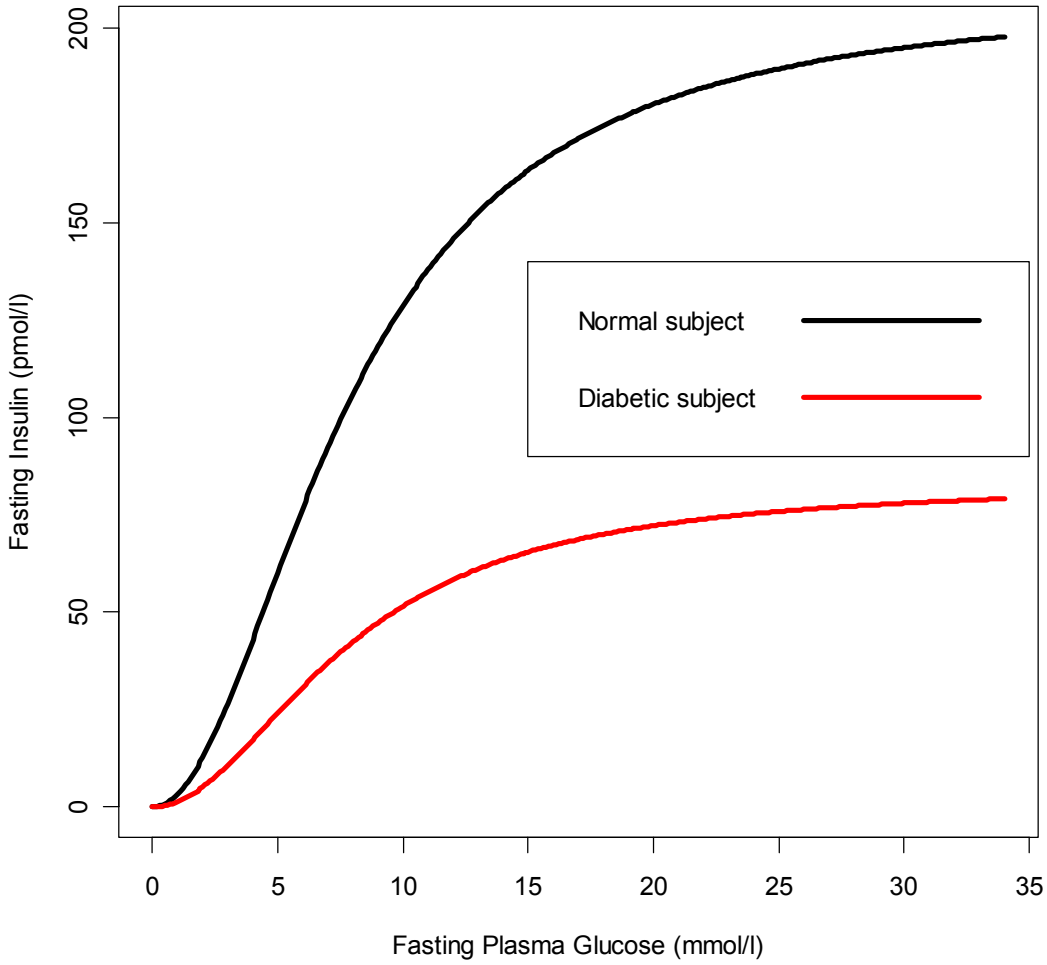
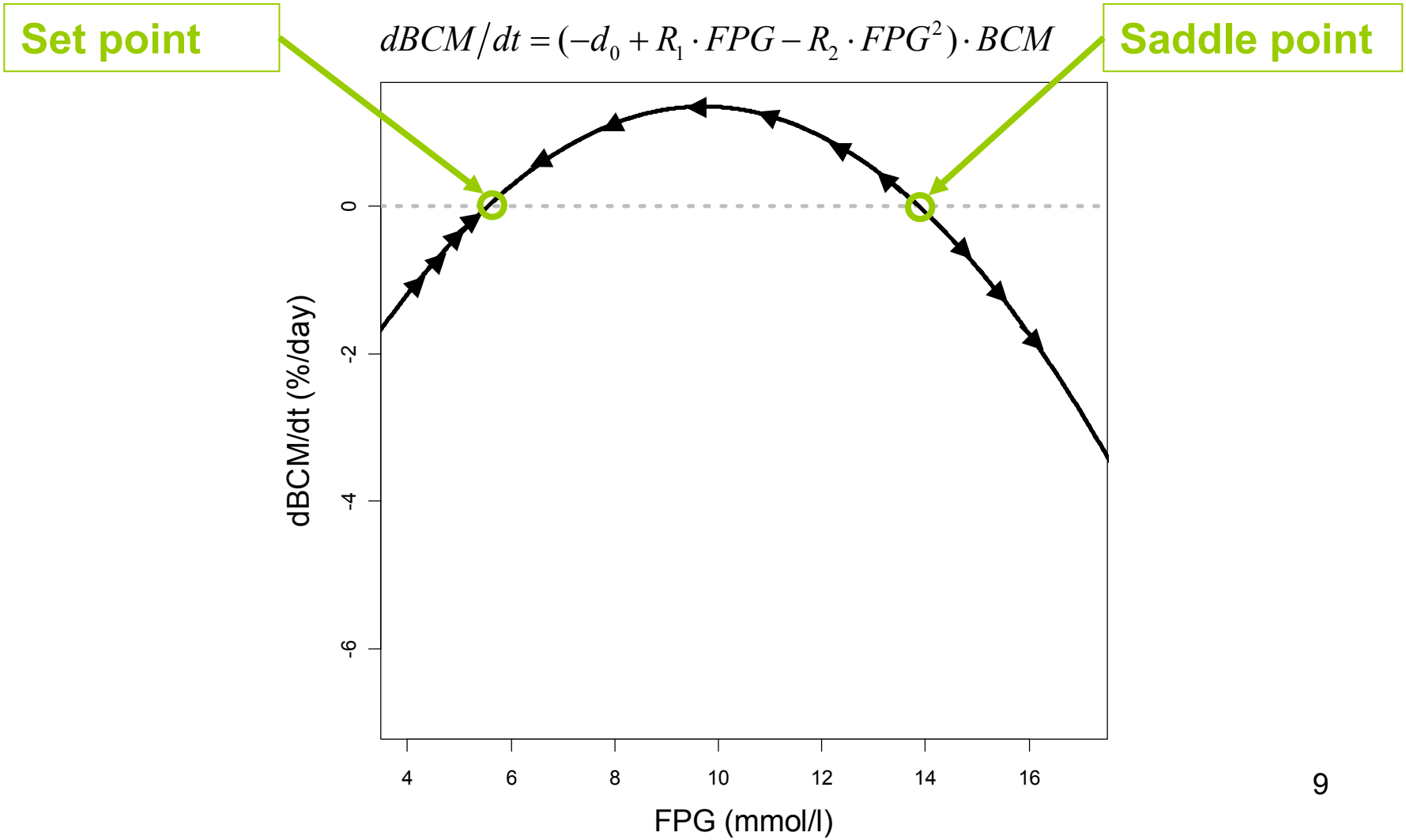
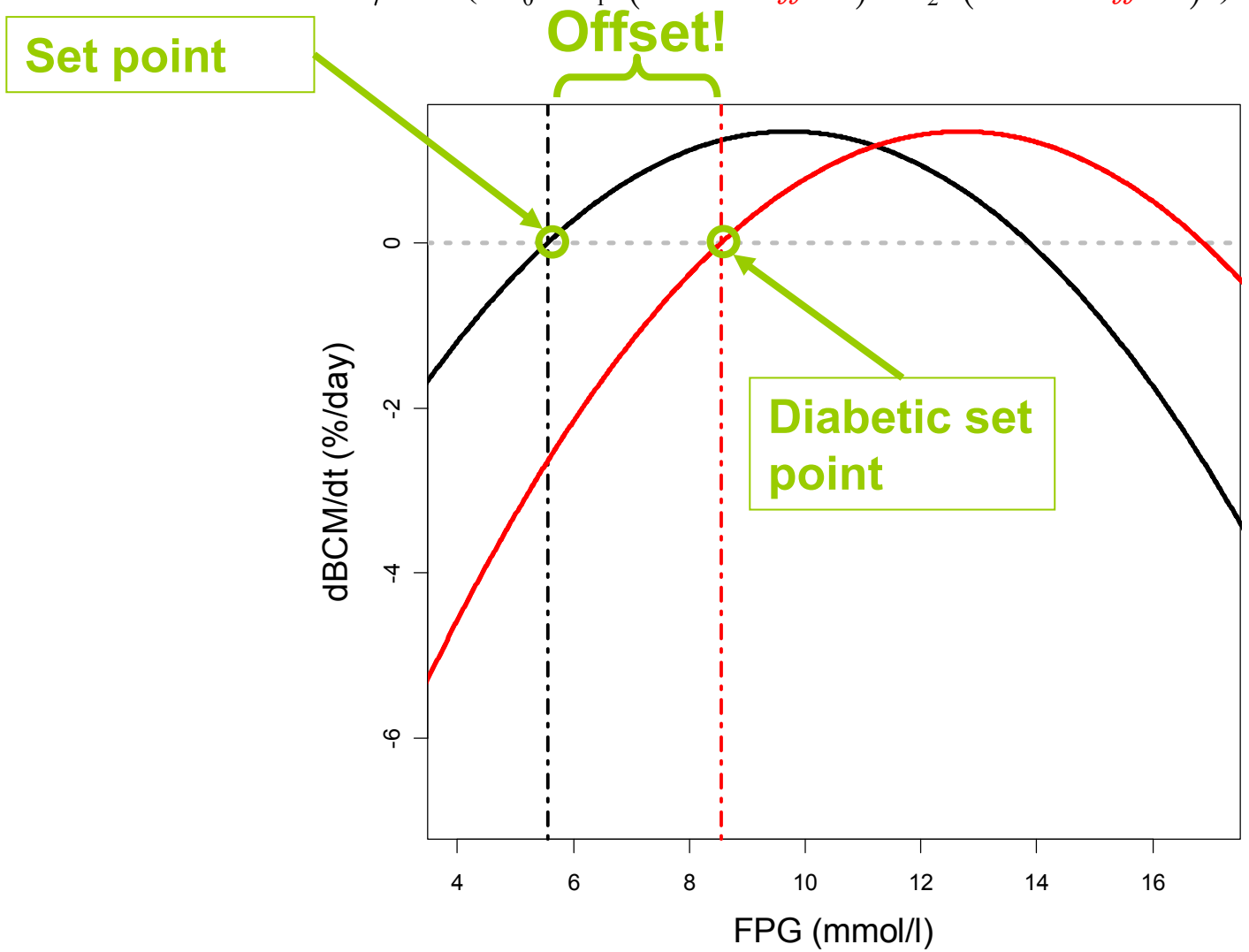


3. Beta-Cell Mass (BCM) Adapting to Glucose Level



3. Beta-Cell Mass (BCM) Adapting to Glucose Level

$$dBCM/dt = (-d_0 + R_1 \cdot (FPG - Offset) - R_2 \cdot (FPG - Offset)^2) \cdot BCM$$



Tesaglitazar – A dual PPAR agonist

- Tesaglitazar PPAR α-γ agonist
- Development discontinued in phase III
  - Reduced renal function
- Anti-diabetic effects similar to γ agonists, pioglitazone and rosiglitazone
  - Increased insulin sensitivity
    - Due to decrease in FFA
  - Increased beta-cell mass?

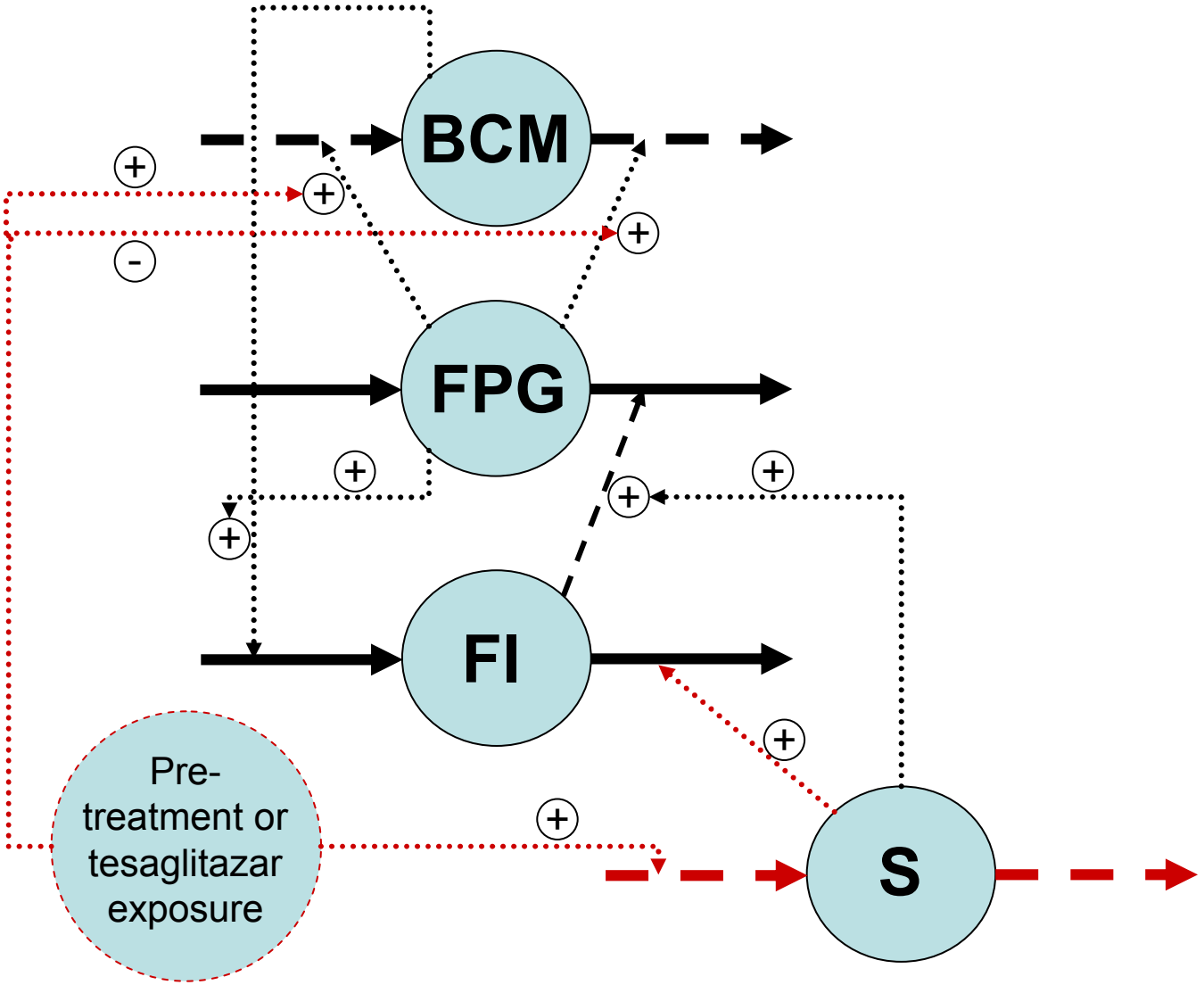
Aim

- Develop an integrated population PK-PD model for glucose, insulin and BCM
  - Treatment effects
    - Tesaglitazar
    - pre-treatment in drug experienced
  - Patient heterogeneity
    - Random IIV
    - Disease stage

Method – Tesaglitazar data

- SIR – Study in Insulin Resistance
  - 3-months, insulin resistant non-diabetics
- GLAD - Glucose and Lipid Assessment in Diabetes
  - 3-months, treatment experienced and naïve
- GALLANT6
  - 6-months, treatment experienced and naïve
- Fasting measurements from 1460 subjects

Method - New Model Structure Based on BIG



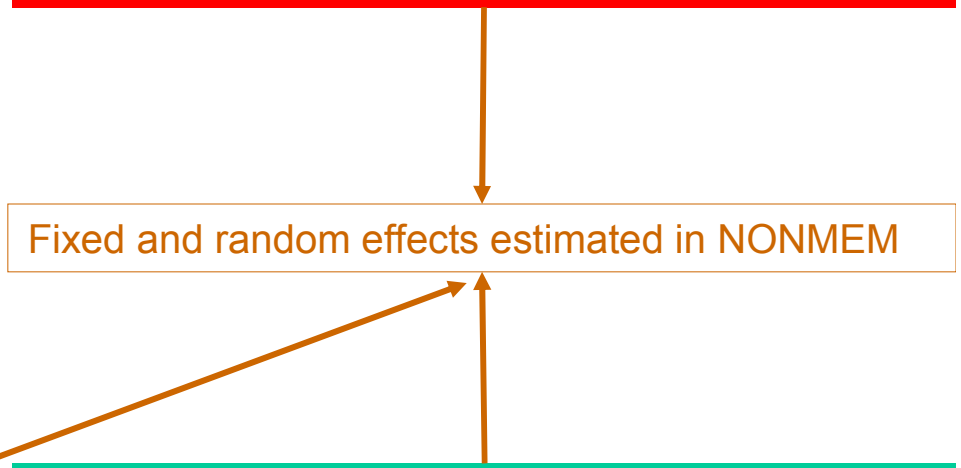
Overview - Drug and System Specific Parameters

Physiological Parameters

- Glucose-dependent growth rate of BCM
- Glucose dependent death rate of BCM
- BCM death rate at zero glucose (extrapol)
- Maximum insulin secretion per unit BCM
- EC_{50}, glucose stimulated insulin secretion
- Hill factor, glucose stimulated insulin secretion
- First order elimination rate of insulin
- Glucose production at zero glucose (extrapol)
- Total glucose effectiveness at zero insulin

Pathophysiological parameters

- OFFSET in BCM adaptation
- Insulin sensitivity



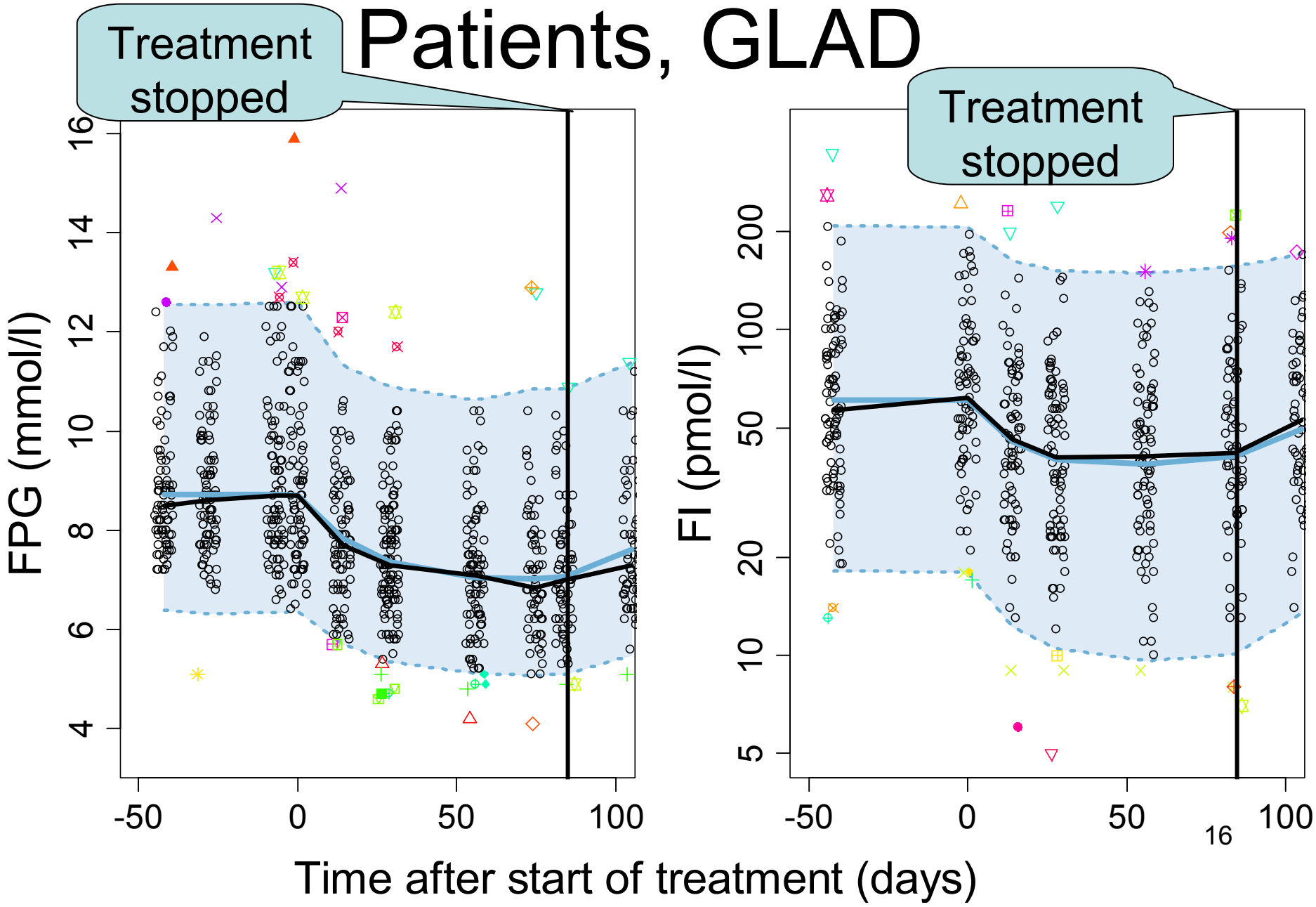
Pharmacology parameters

- E_{max}, insulin sensitivity
- EC_{50}, insulin sensitivity
- EC_{50}, OFFSET
- Hill coefficient, OFFSET
- Pre-treatment effect, insulin sensitivity
- Pre-treatment effect, OFFSET

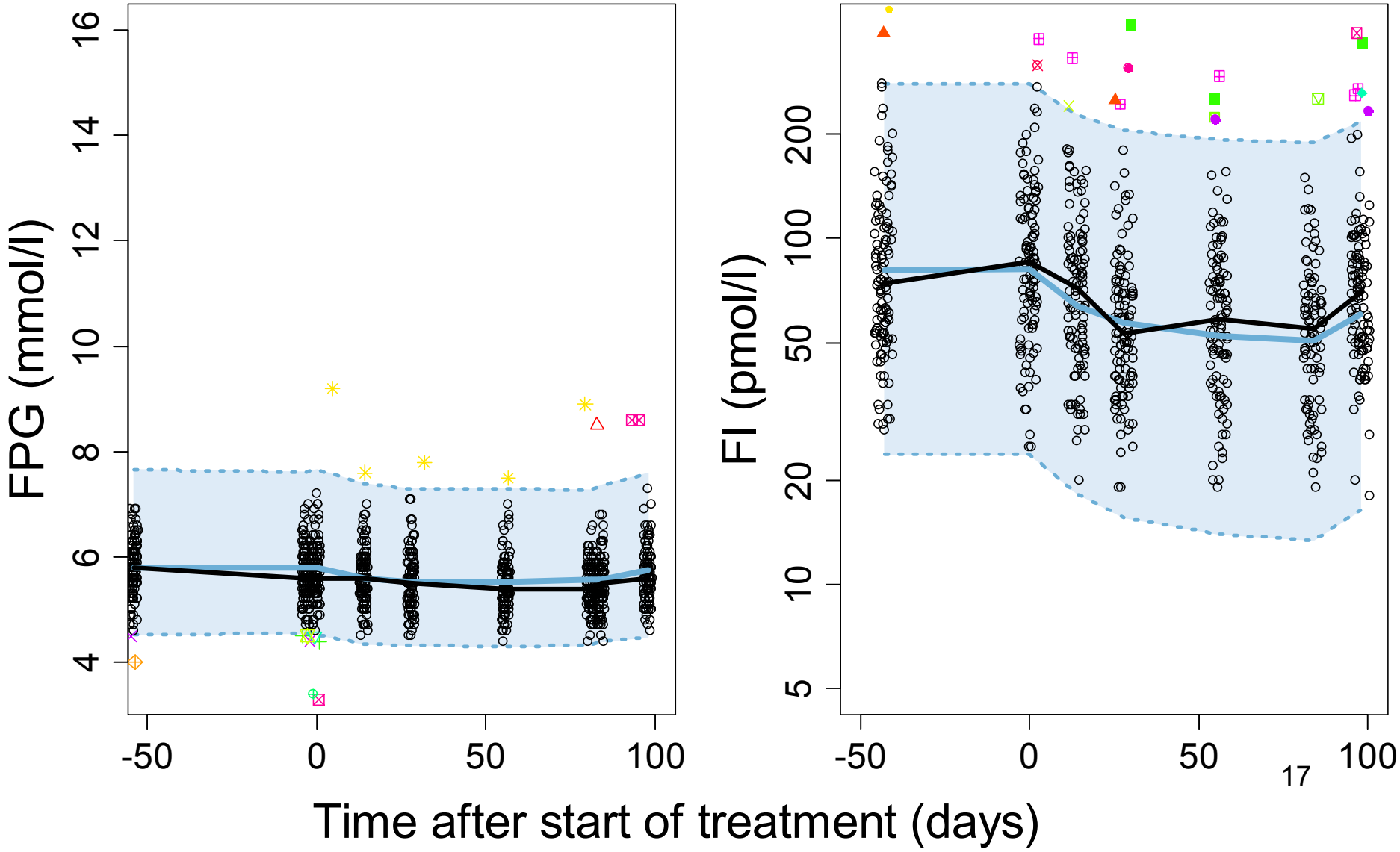
Mixed origin parameters

- K_{out}, insulin sensitivity
- Relation btw insulin elimination & insulin sensitivity

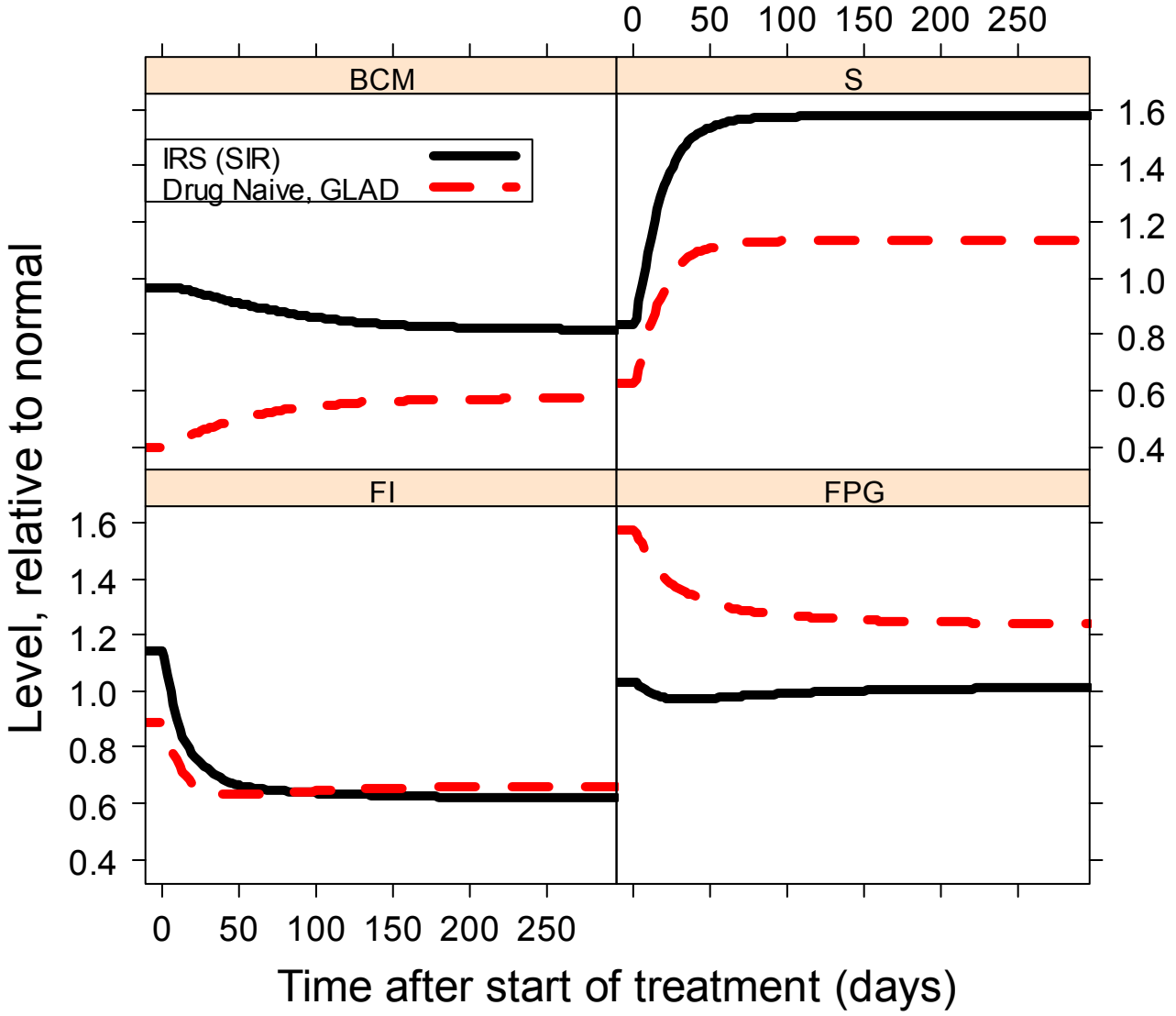
Results - Drug Naïve Diabetic Patients, GLAD



Results - Insulin Resistant Non-Diabetic Subjects



Result – Median Response in IRS Subjects and Naïve Diabetics



Discussion

- Naïve T2DM patients, 40% of normal BCM
  - Well in line with literature
  - Decrease in actual *beta-cell function* mainly decrease in *BCM*
- Strong relation between *insulin elimination* and *insulin sensitivity*
  - Well in line with literature
  - FFA common link
  - Important when assessing beta-cell function!

Conclusions

- Describes FPG, FI and BCM well
  - mechanistic manner
- Allows incorporation of
  - Short-term experiments
  - Observations of FFA
  - Observations of BCM (future)
  - Treatment duration of 1-2 years
    - Long term disease progression
    - Long term disease modifying effects