Artificial pancreas approach based on multi-level model

Winston Garcia-Gabin and Elling W. Jacobsen
Automatic Control Laboratory
KTH Royal Institute of Technology

Outline

- Introduction
  - Artificial pancreas
    - CGMS & insulin pump
    - Closed-loop schemes
    - Meal and fault detection
- Closed-loop glucose control based on multi-level model
- Ongoing results
- Conclusions

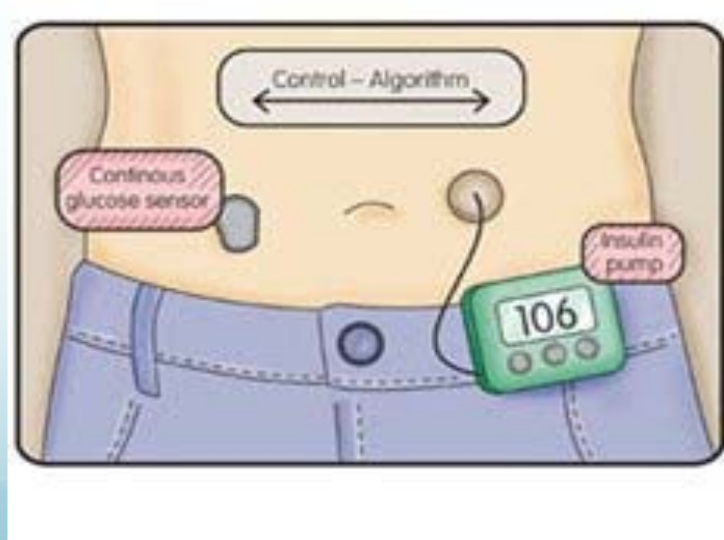
Objectives

- Analyze multi-level models of the glucose regulatory system to identify relevant variables for control
- Develop closed-loop glucose control schemes to achieve homeostasis in T1DM patients using multi-level information

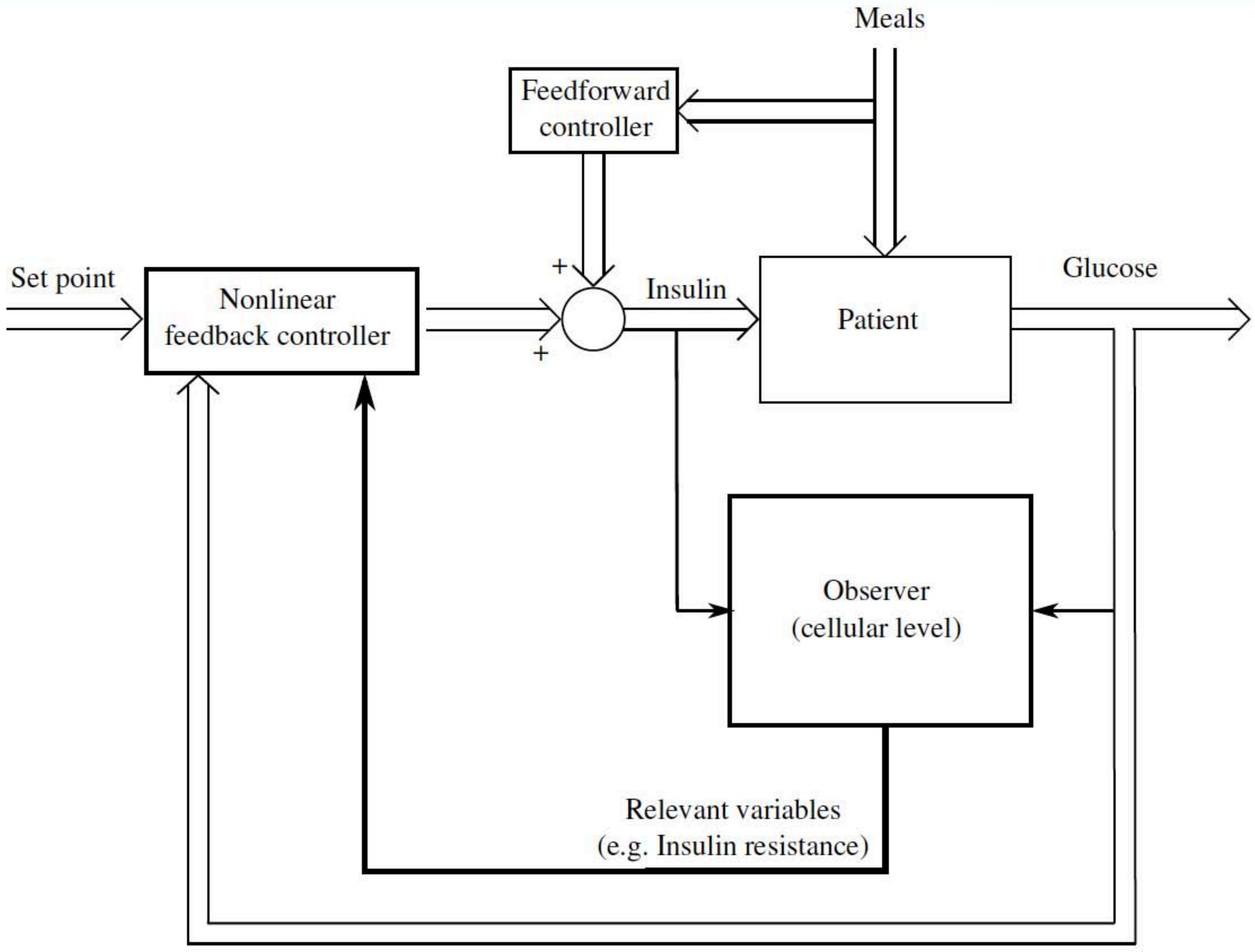
Artificial pancreas

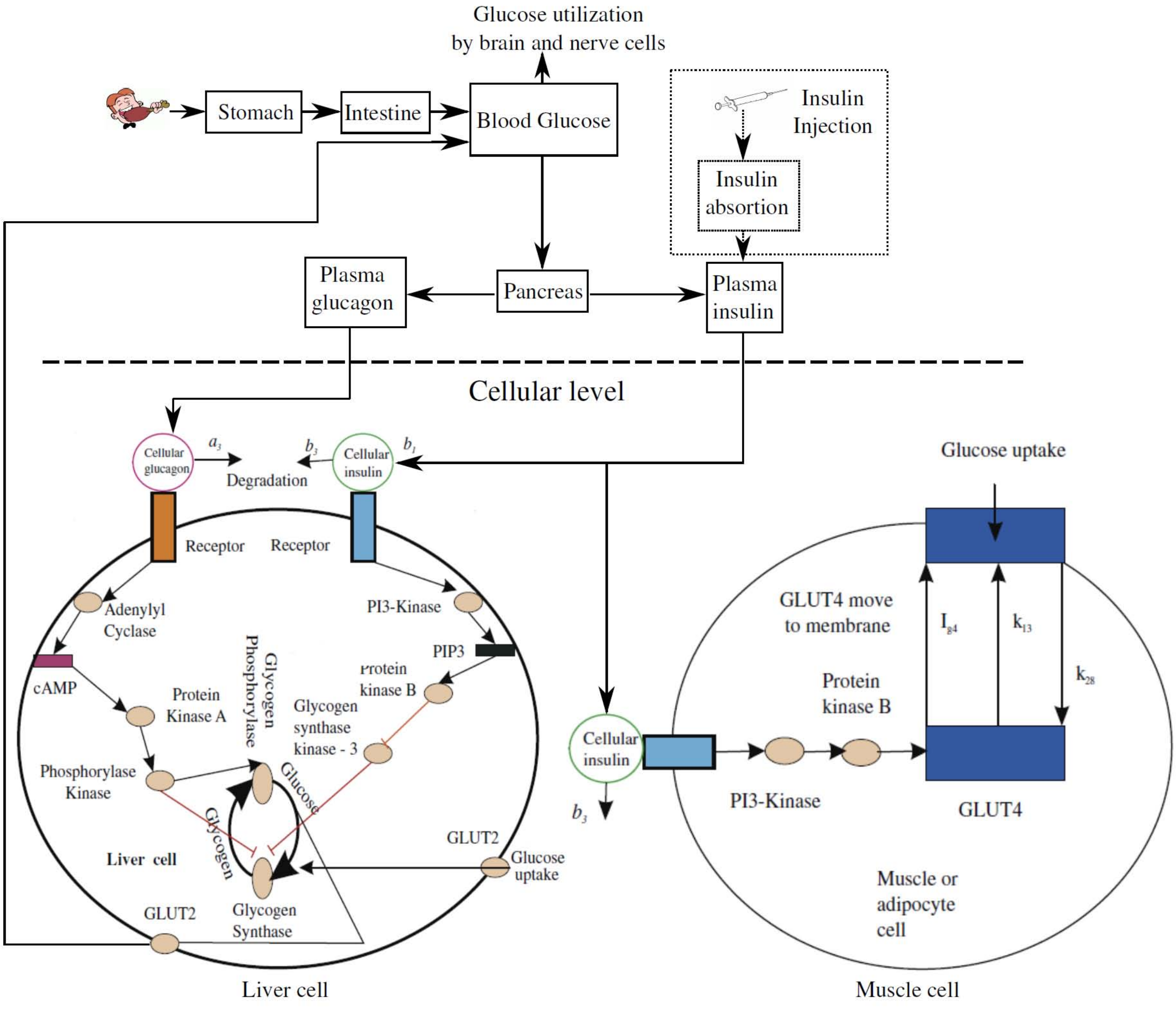
- CGMS can be coupled with CIIP to create a closed-loop artificial pancreas
- Closed-loop control algorithms automatically adjust insulin infusion rates to achieve homeostasis

- Disturbances
  - “Measured” → Meal
  - Non-measured → Stress, physical activities, biological rhythms, medicaments



Artificial pancreas approach based on multi-level model





Glucose utilization
by brain and nerve cells
Stomach
Intestine
Blood Glucose
Insulin Injection
Insulin absorption
Plasma glucagon
Pancreas
Plasma insulin
Cellular level
Cellular glucagon
a_3
Degradation
b_3
Cellular insulin
b_1
Receptor
Receptor
Adenylyl Cyclase
PI3-Kinase
PIP3
cAMP
Protein Kinase A
Glycogen Phosphorylase
Protein kinase B
Glycogen synthase kinase - 3
Phosphorylase Kinase
Glucose
Glycogen
Liver cell
GLUT2
Glucose uptake
GLUT2
Glycogen Synthase
Liver cell
Glucose uptake
GLUT4 move to membrane
I_{g4}
k_{13}
k_{28}
Protein kinase B
Cellular insulin
b_3
PI3-Kinase
GLUT4
Muscle or adipocyte cell
Muscle cell

Multi-level model

ROYAL INSTITUTE OF TECHNOLOGY

- Low level model
  - A physiological based PK-PD model with 50 ordinary differential equations considers:
  - The kinetics of GLUT2, GLUT3, and GLUT4
  - The intracellular conversion of glucose and glycogen in liver
  - The dynamics of the insulin signaling pathway

- High level model
  - The glucose transit through the stomach and intestine
  - Insulin kinetics

Multi-level model

- Model subsystems
  - Insulin and glucagon transition
  - Glucagon signaling pathway
  - Insulin signaling pathway
  - Glucose mobilization in liver
  - Glucose uptake
  - Feedback glucagon and insulin infusion rates

ROYAL INSTITUTE OF TECHNOLOGY

Insulin signaling pathway

$$\frac{dx_1^j}{dt} = -k_1 x_1^j x_2^j - b_3 x_1^j + b_1 V_p h_2^p / V,$$

$$\frac{dx_2^j}{dt} = k_{15} x_3^j + k_{17}[\mathrm{PTP}] x_5^j - k_1 x_1^j x_2^j + k_{18} x_6^j - k_4 x_2^j,$$

$$\frac{dx_3^j}{dt} = -k_{15} x_3^j + k_1 x_1^j x_2^j - k_3 x_3^j,$$

$$\frac{dx_4^j}{dt} = k_2 x_1^j x_5^j - k_{16} x_4^j + k_{20} x_7^j - k_{19} x_4^j,$$

$$\frac{dx_5^j}{dt} = k_3 x_3^j + k_{16} x_4^j - k_2 x_1^j x_5^j - k_{17}[\mathrm{PTP}] x_5^j + k_{20} x_8^j - k_{19} x_5^j,$$

$$\frac{dx_6^j}{dt} = k_5 - k_{21} x_6^j + k_6[\mathrm{PTP}](x_7^j + x_8^j) + k_4 x_2^j - k_{18} x_6^j,$$

$$\frac{dx_7^j}{dt} = k_{19} x_4^j - k_{20} x_7^j - k_6[\mathrm{PTP}] x_7^j,$$

$$\frac{dx_8^j}{dt} = k_{19} x_5^j - k_{20} x_8^j - k_6[\mathrm{PTP}] x_8^j,$$

$$\frac{dx_9^j}{dt} = k_{22}[\mathrm{PTP}] x_{10}^j - k_7 x_9^j (x_4^j + x_5^j)/[IR_p],$$

$$\frac{dx_{10}^j}{dt} = k_7 x_9^j (x_4^j + x_5^j)/[IR_p] + k_{23} x_{12}^j - (k_{22}[\mathrm{PTP}] + k_8 x_{11}^j) x_{10}^j,$$

$$\frac{dx_{11}^j}{dt} = k_{23} x_{12}^j - k_8 x_{11}^j x_{10}^j,$$

$$\frac{dx_{12}^j}{dt} = -k_{23} x_{12}^j + k_8 x_{11}^j x_{10}^j,$$

$$\frac{dx_{13}^j}{dt} = k_9 x_{14}^j + k_{10} x_{15}^j - (k_{24}[\mathrm{PTEN}] + k_{25}[\mathrm{SHIP}]) x_{13}^j,$$

$$\frac{dx_{14}^j}{dt} = k_{24}[\mathrm{PTEN}] x_{13}^j - k_9 x_{14}^j,$$

$$\frac{dx_{15}^j}{dt} = k_{25}[\mathrm{SHIP}] x_{13}^j - k_{10} x_{15}^j,$$

$$\frac{dx_{16}^j}{dt} = k_{26} x_{17}^j - k_{11} x_{16}^j,$$

$$\frac{dx_{17}^j}{dt} = -k_{26} x_{17}^j + k_{11} x_{16}^j,$$

$$\frac{dx_{18}^j}{dt} = k_{27} x_{19}^j - k_{12} x_{18}^j,$$

$$\frac{dx_{19}^j}{dt} = -k_{27} x_{19}^j + k_{12} x_{18}^j,$$

Glucose uptake

The glucose transporter is modelled by

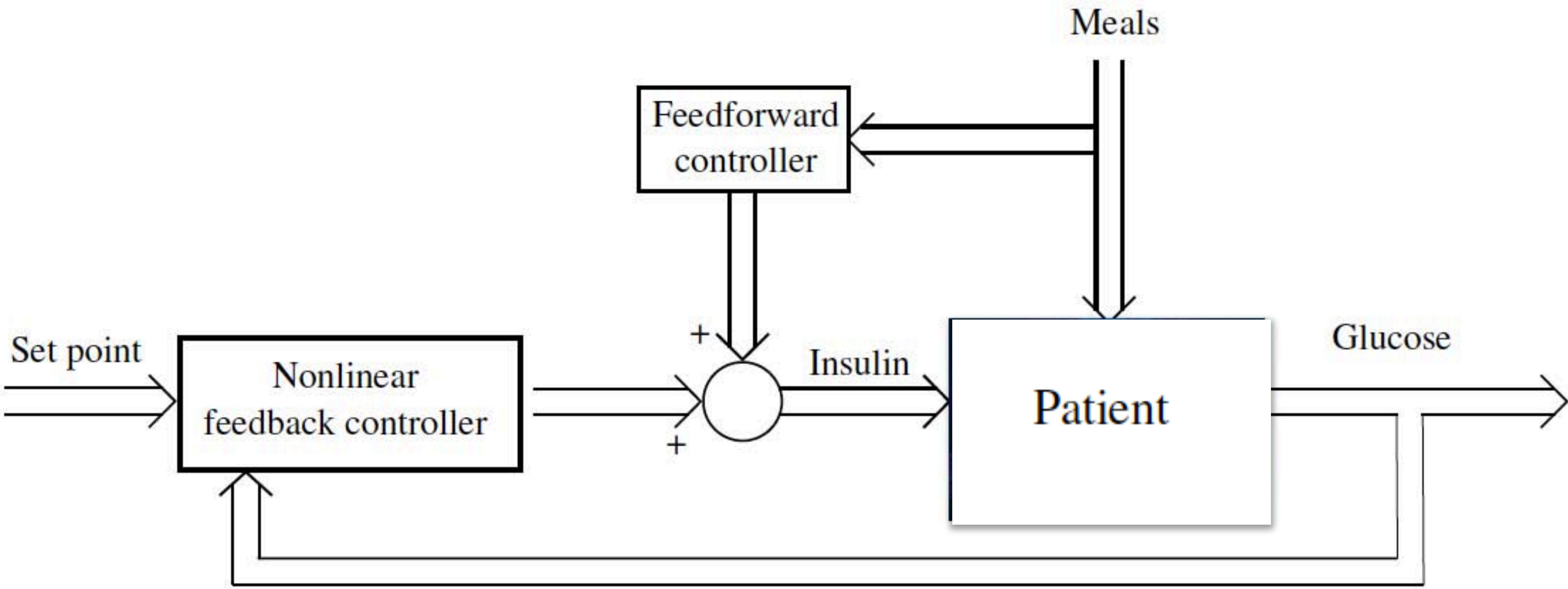
$$\frac{dx_{20}^m}{dt} = k_{28}x_{21}^m - (k_{13} + I_{g4})x_{20}^m - k_{29}x_{20}^m + k_{14},$$
$$\frac{dx_{21}^m}{dt} = -k_{28}x_{21}^m + (k_{13} + I_{g4})x_{20}^m,$$

The insulin effect on the transporter is given by

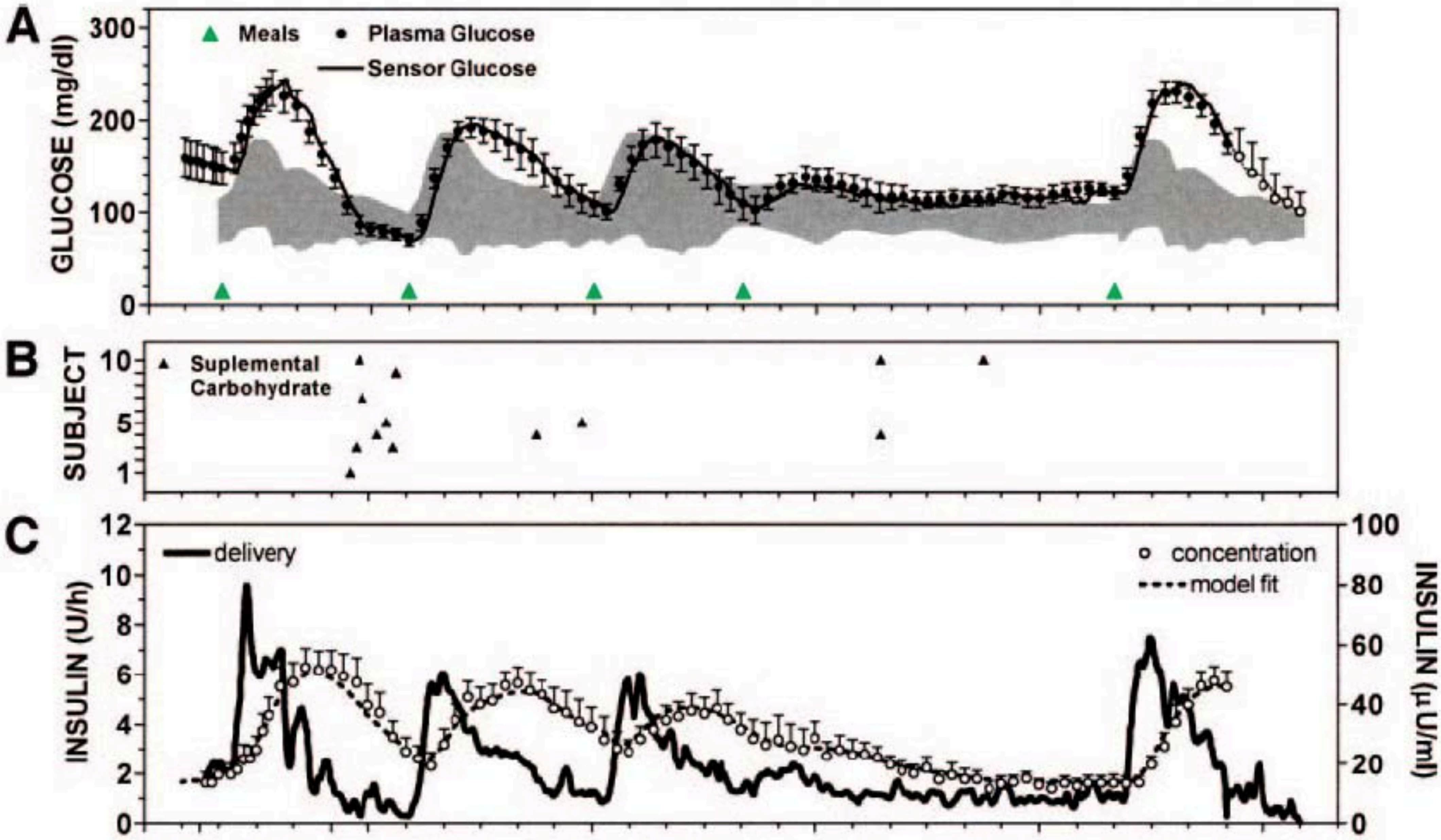
$$\text{effect} = 11(0.2x_{17}^m + 0.8x_{19}^m)/100,$$
$$I_{g4} = \left(\frac{2}{3} - \frac{4}{96}\right)k_{28}[\text{effect}],$$

ROYAL INSTITUTE OF TECHNOLOGY

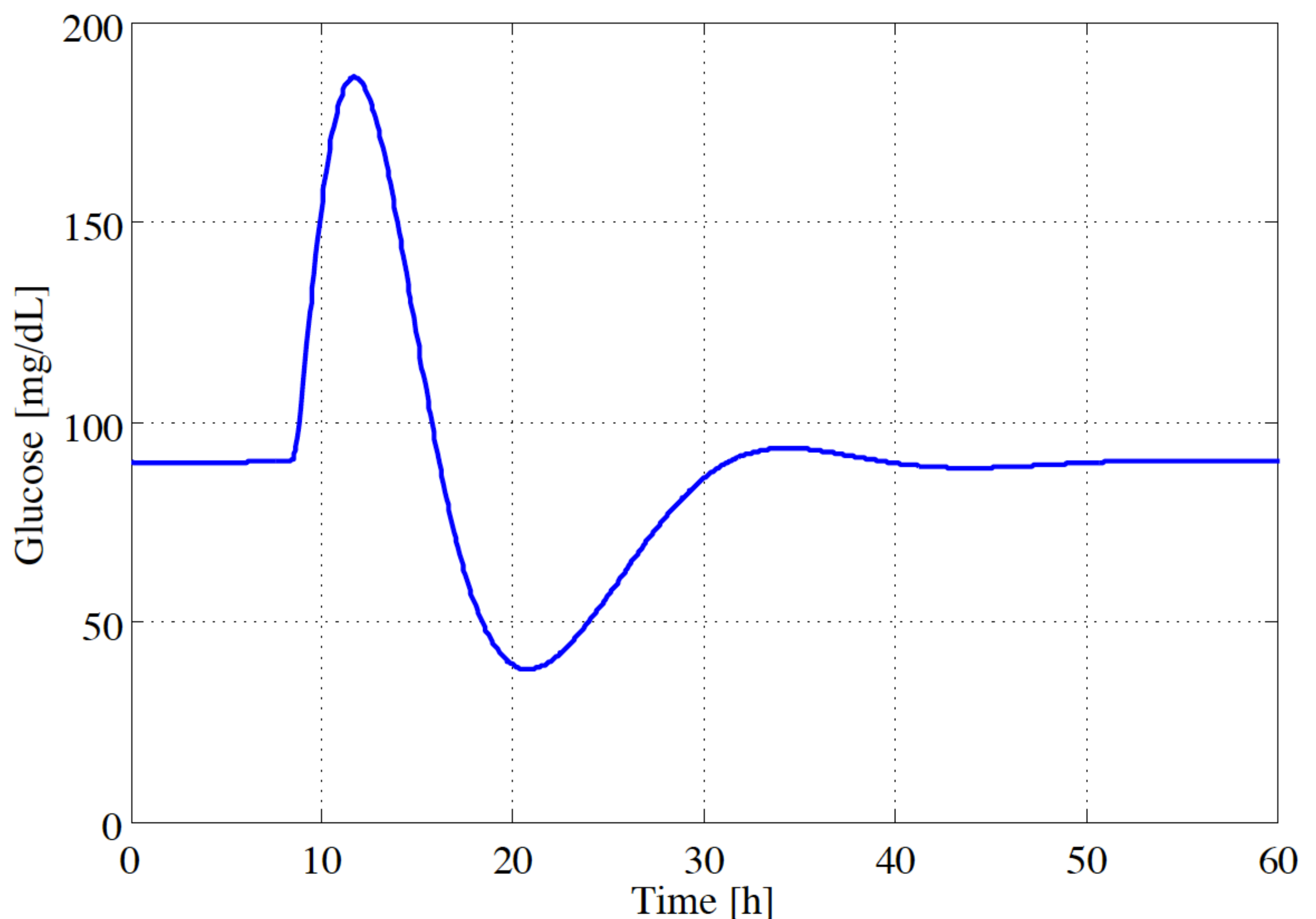
Classic approach



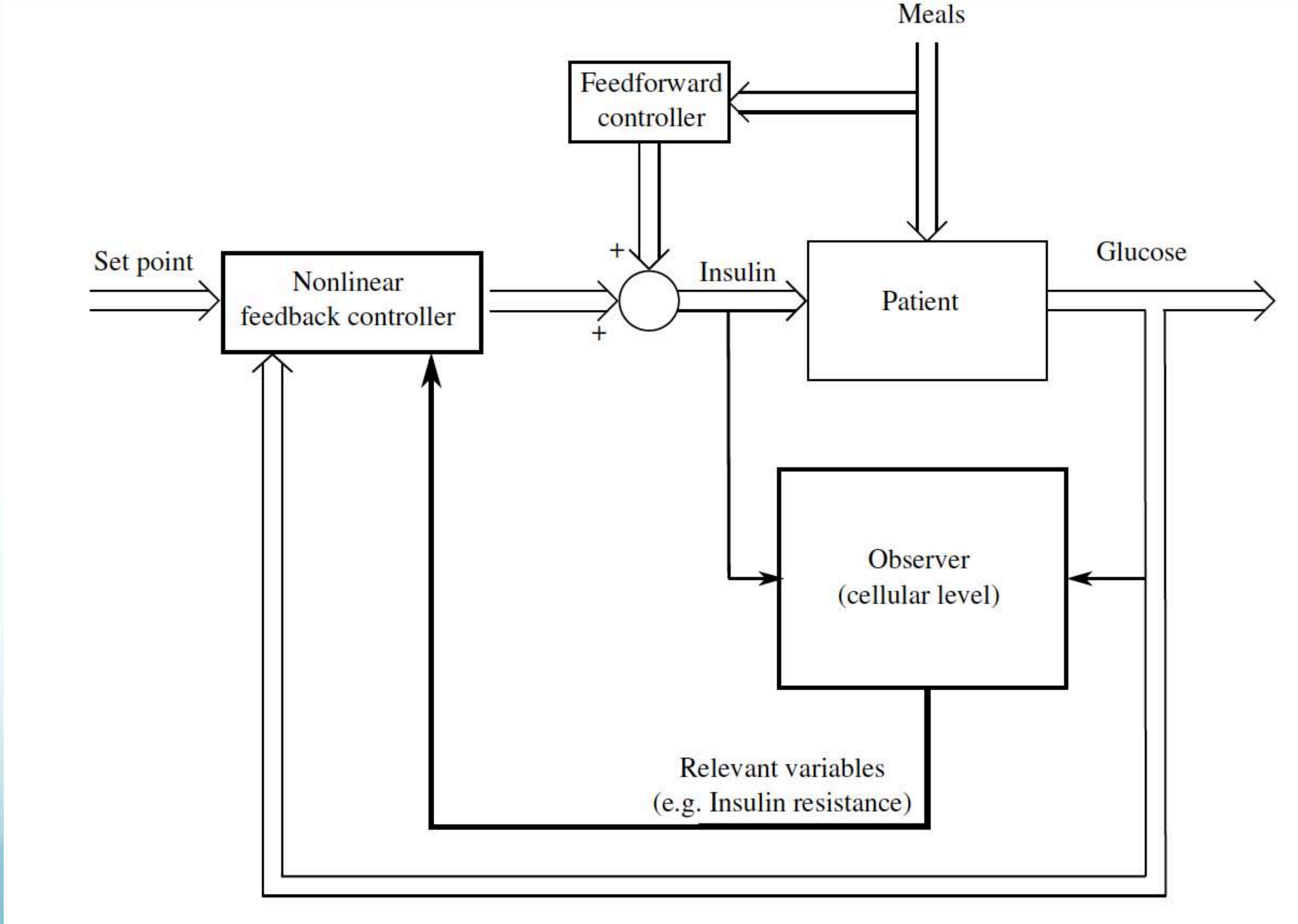
Classic approach



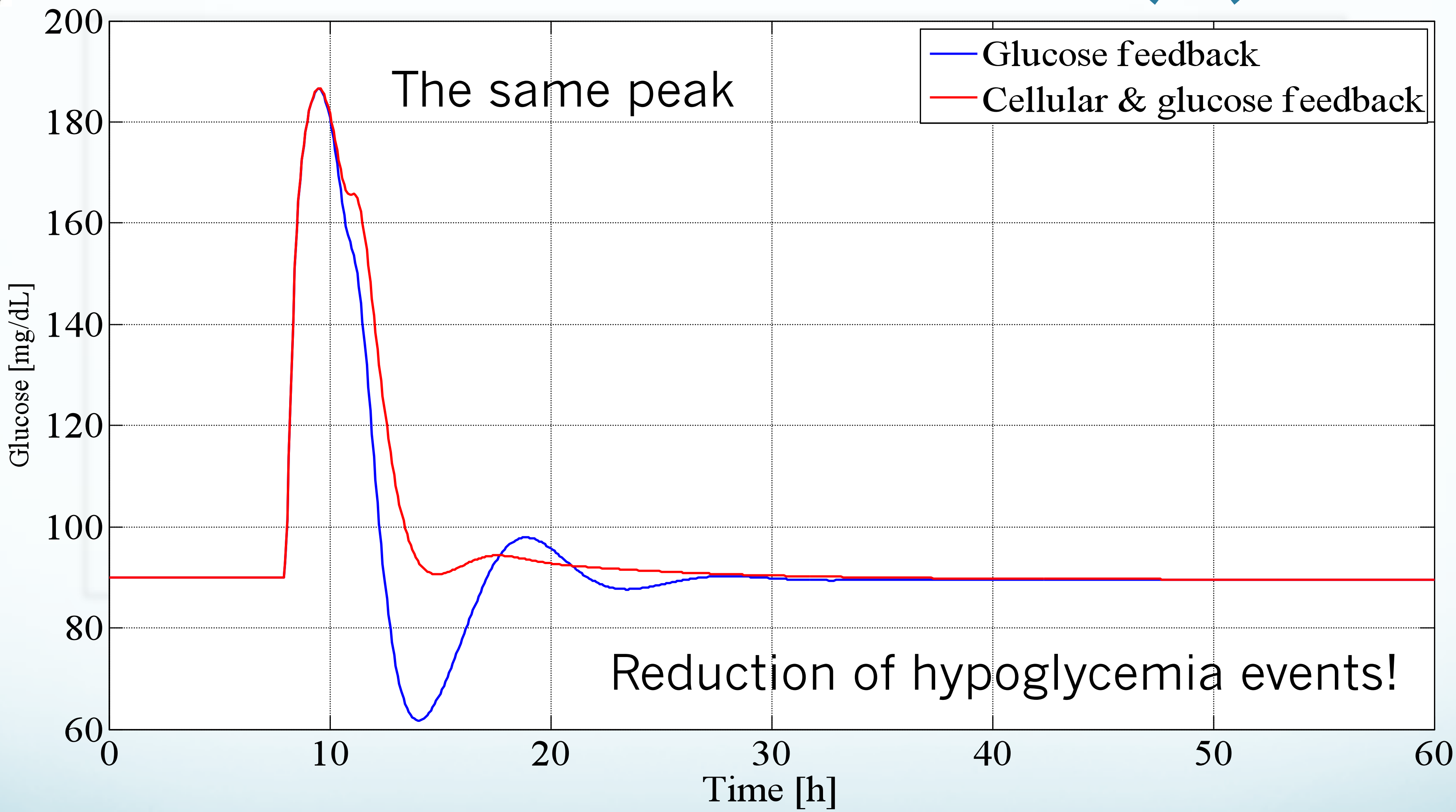
Classic approach



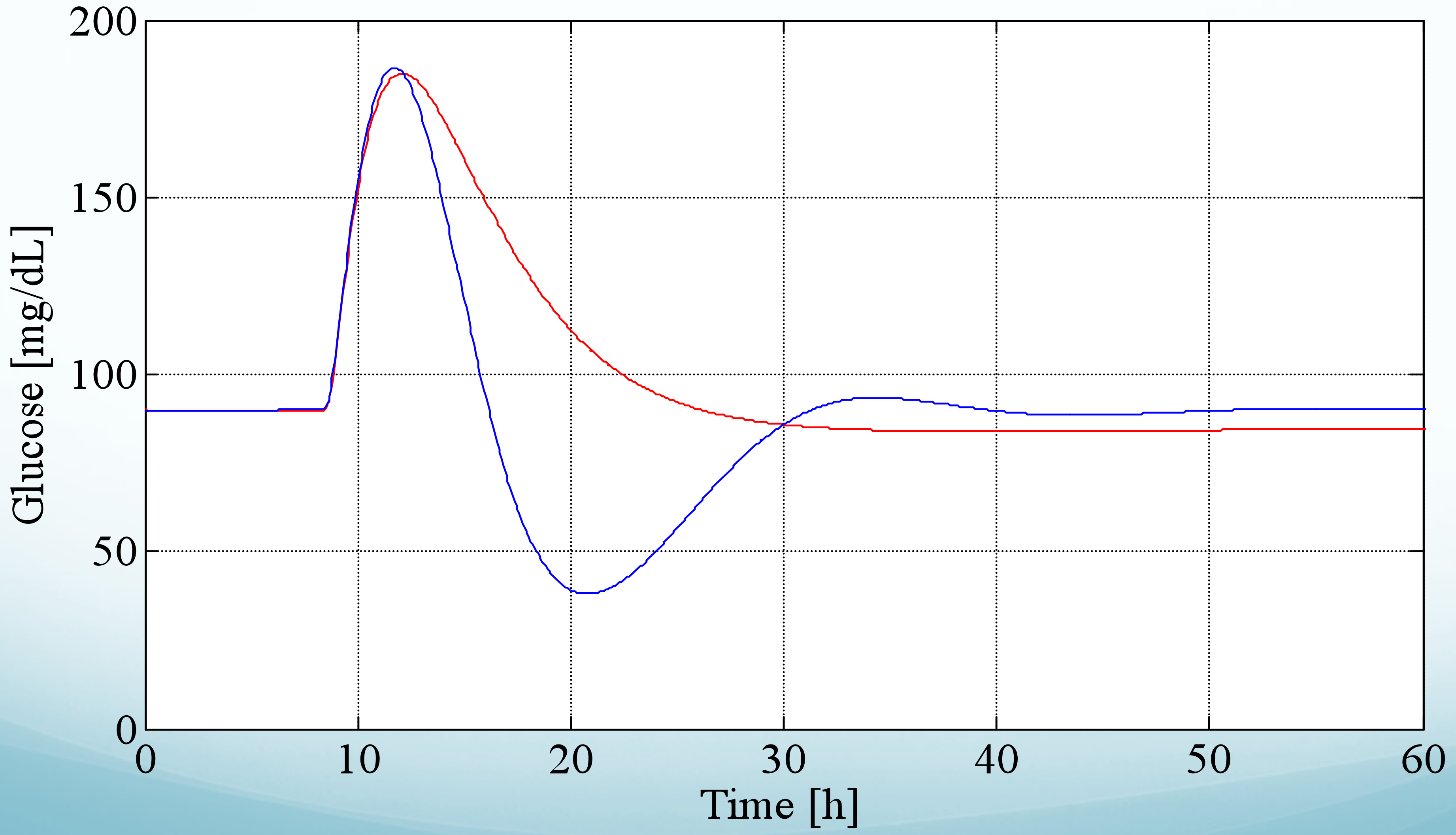
Artificial pancreas approach based on multi-level model



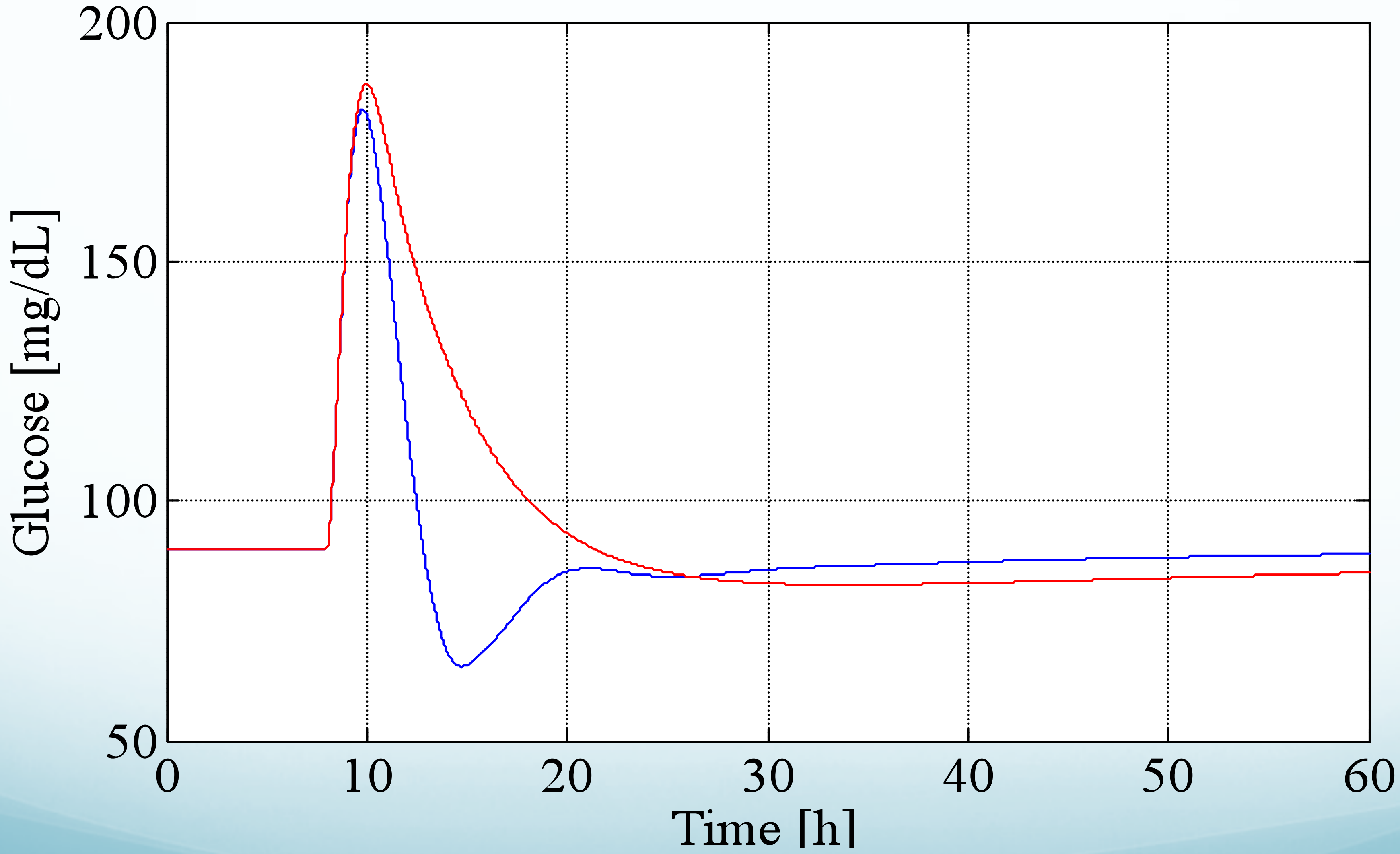
Nonlinear model 1(L)



Nonlinear model 2 (D)



Nonlinear model 3 (H)



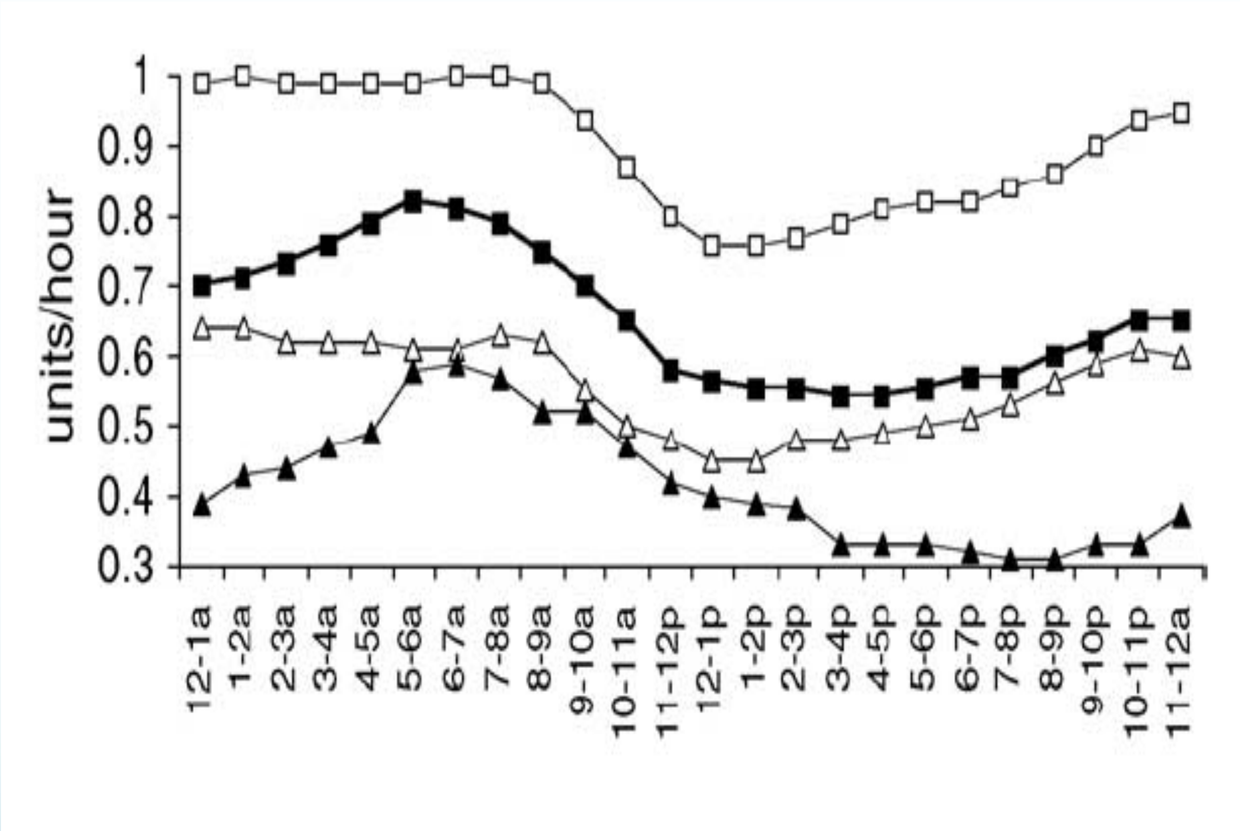
Factors affecting blood glucose regulation

- Nonlinear behaviour
- Meal disturbances
  - Variable composition
  - Estimation errors
- Time-varying dynamics
  - Circadian fluctuation (e.g. Insulin sensitivity)
  - Exercise (different intensity levels)
  - Stress
- Lag in the appearance of insulin in blood
- Time delay in the subcutaneous glucose sensing

Insulin sensitivity

- Are insulin sensitivity changes responsible of this behaviour?
- Can a pre-programmed insulin infusion compensate this behaviour?

Insulin infusion pattern



Legend:

Open triangle = age 3-10

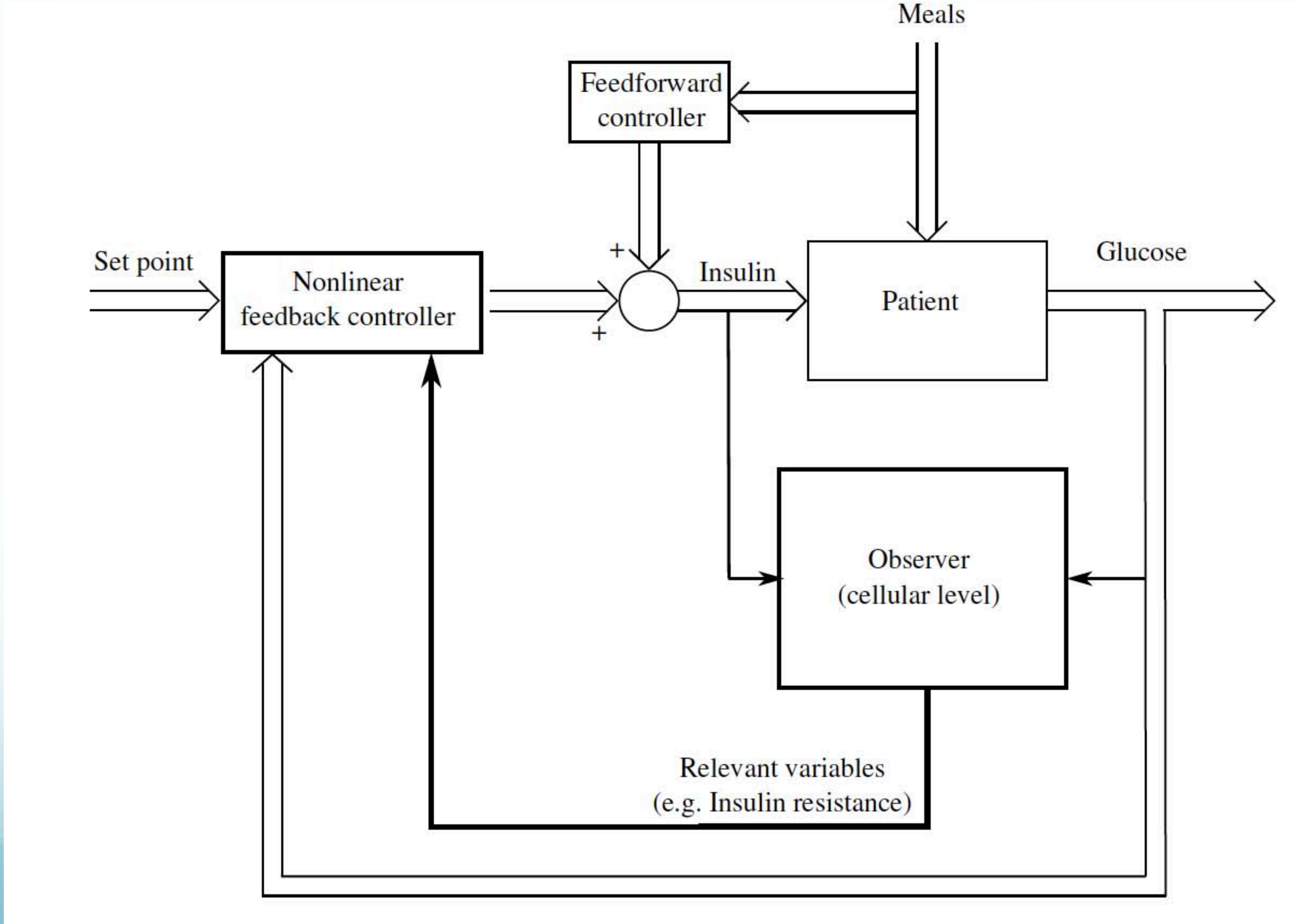
Open square = age 11-20

Solid square = age 21-60

Solid triangle = age >60

(Scheiner, 2005)

Artificial pancreas approach based on multi-level model



ROYAL INSTITUTE
OF TECHNOLOGY

Conclusions

- Estimation of cellular information as feedback signal reduce the hypoglycaemic events.
- Insulin sensitivity changes can be compensated.
- Intracellular information can be used as part of closed-loop glucose control.
- A comprehensive understanding of the causes and mechanisms underlying glucose regulation is the key to develop an artificial pancreas.