Clamp Trainer Based on Physiologically Based Pharmacokinetic Modeling and Machine Learning Methods

Ivan Lunev

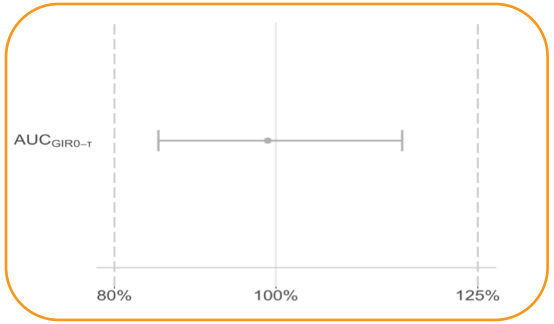
ГЕРОФАРМ

Clinical study

Researchers

Clinical study Data

Statistical analysis



Stress

No time

No Experience

Data variability

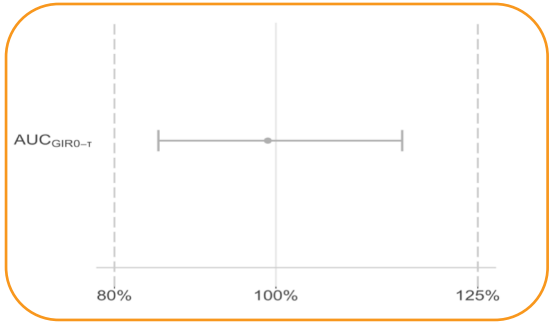
Quality of analysis

Clinical study

Researchers

Clinical study Data

Statistical analysis



Stress

No time

No Experience

Quality of analysis

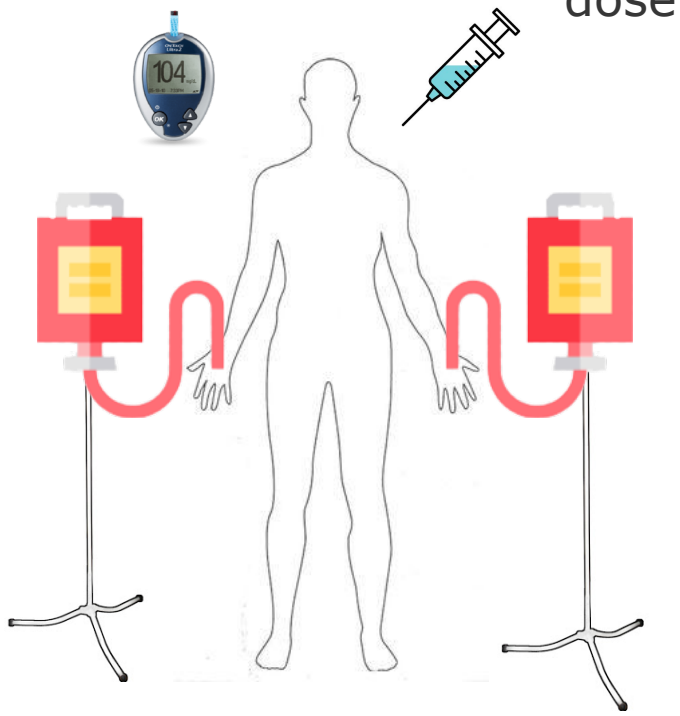
Trainer

Clamp study

PD Data

Glucose concentration

Insulin dose

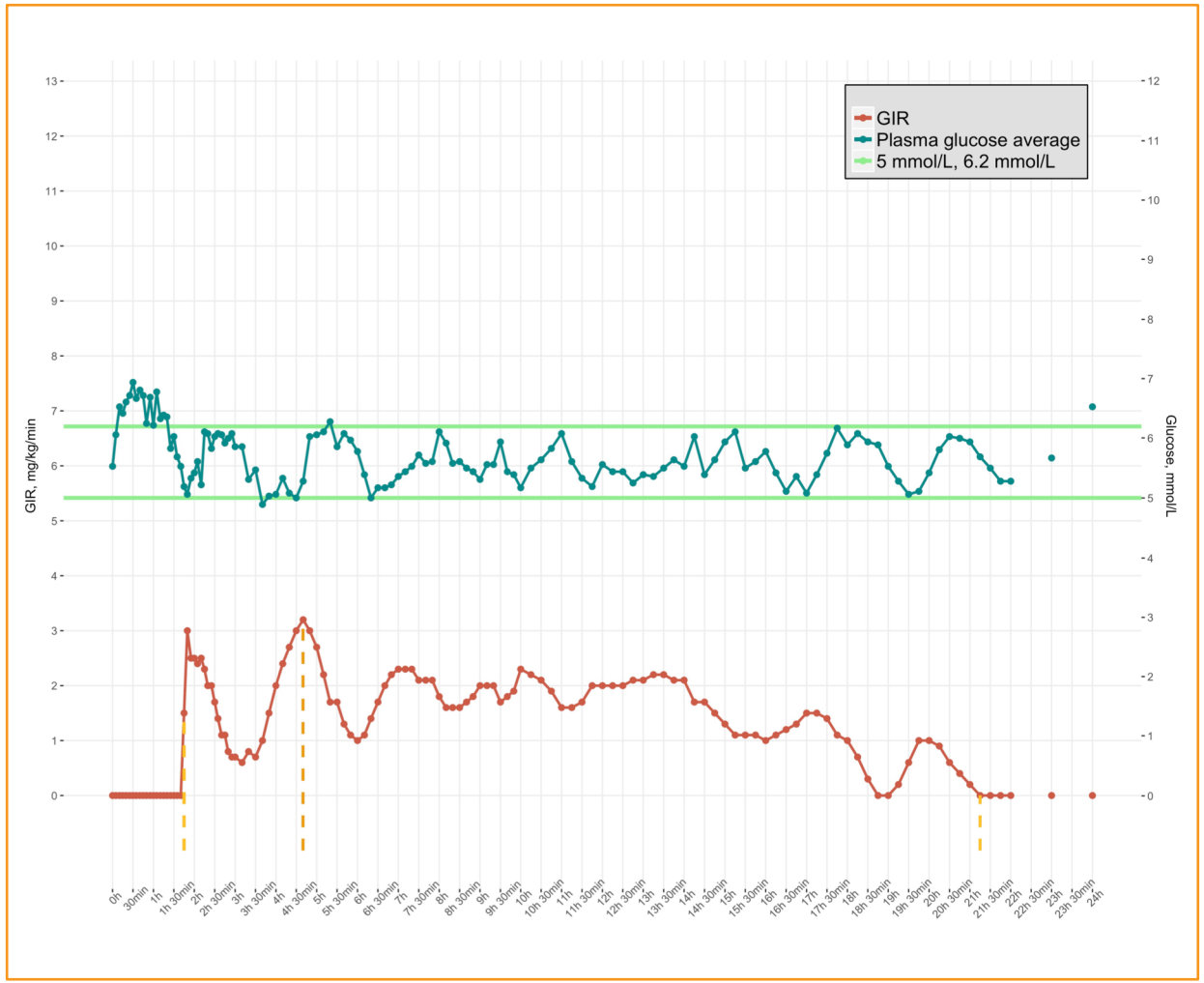


Glucose Infusion Rate

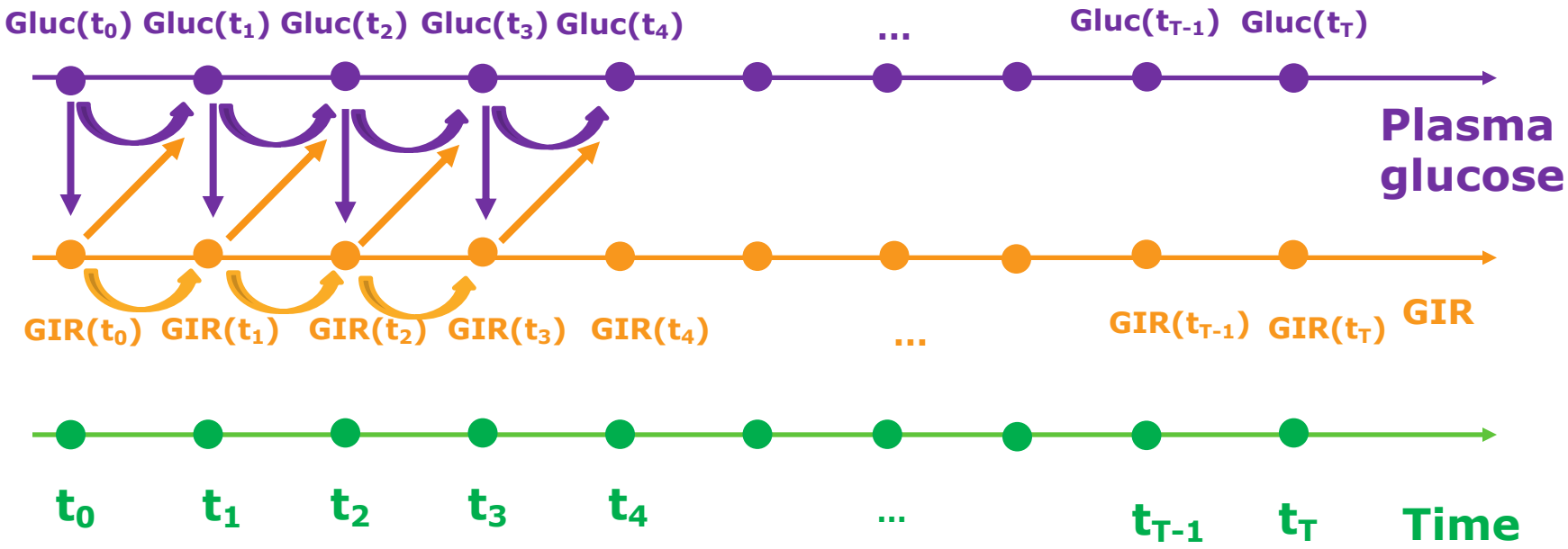
PK Data

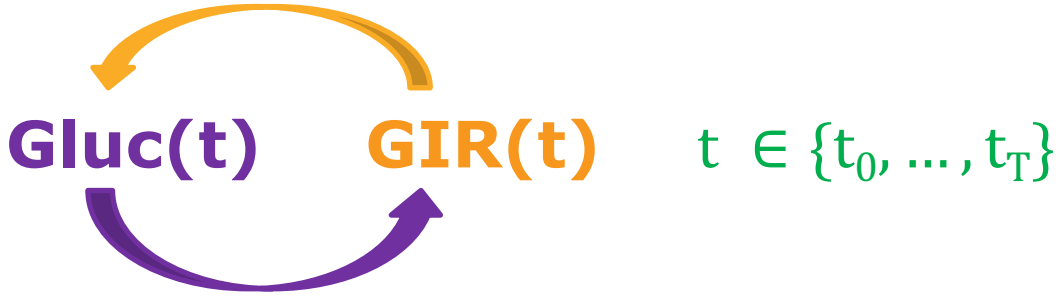
Insulin concentration

Clamp study


GIR
Plasma glucose average
5 mmol/L, 6.2 mmol/L
GIR, mg/kg/min
Glucose, mmol/L

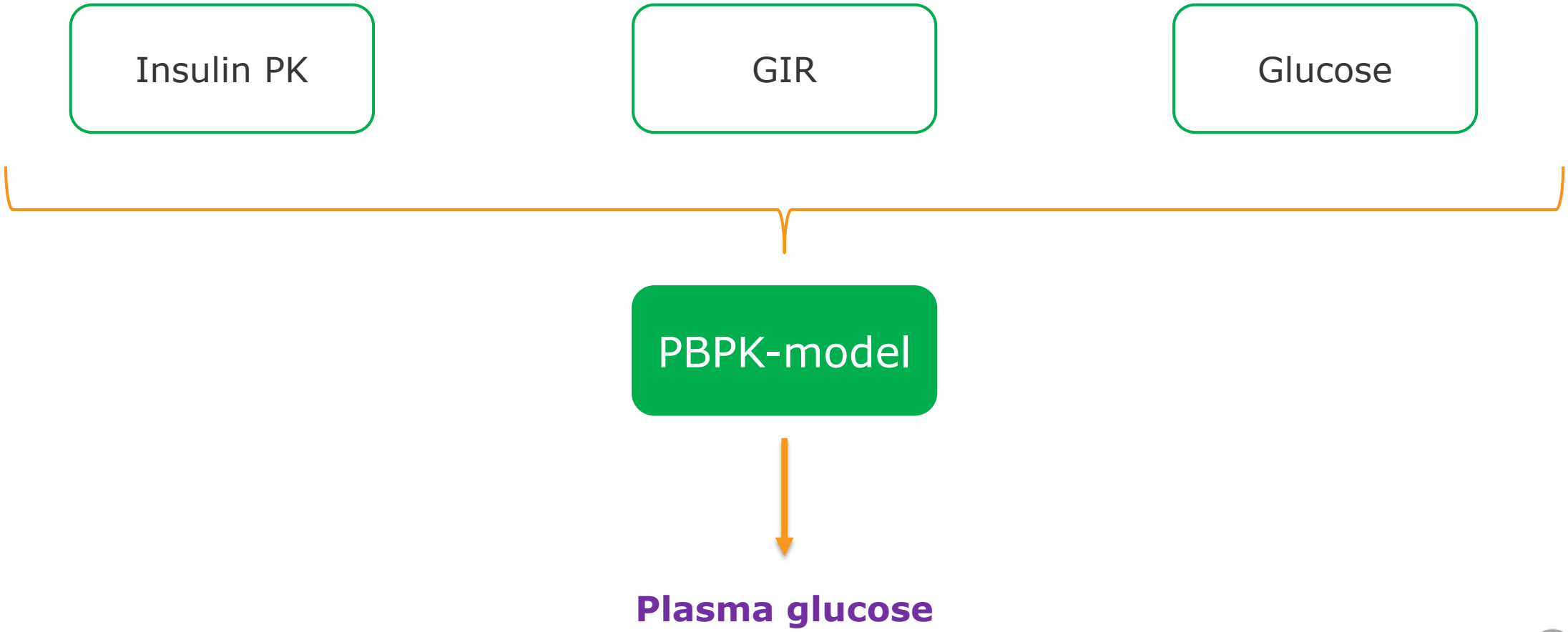
Data flow



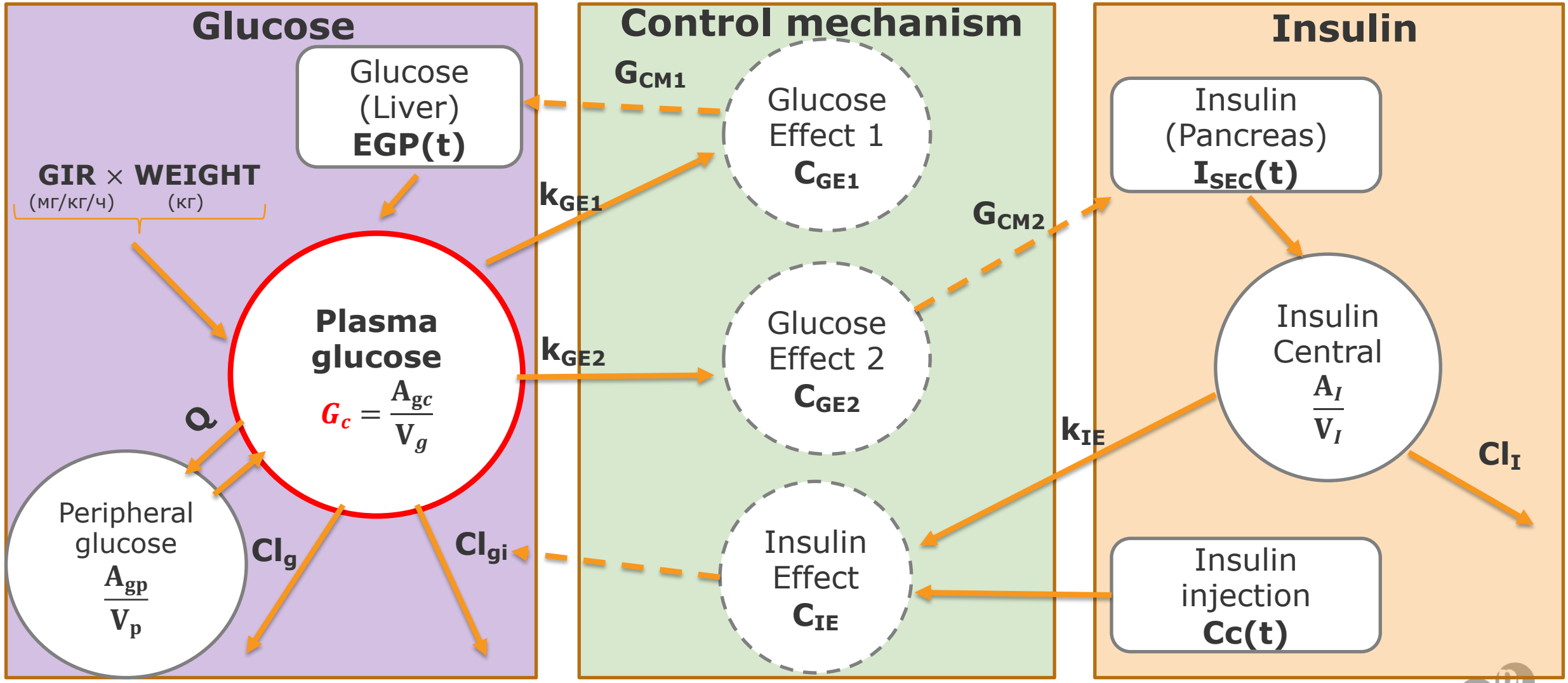


$t \in \{t_0, \ldots, t_T\}$

PBPK-modeling



Model of glucose and insulin behavior in the body



Model scheme from Silber et al., 2007

GIR model

Time	Previous GIR	Glucose	GIR
0	0	5.6	0
0.08	0	5.4	0.5
0.15	0.5	5.3	1.1
0.23	1.1	5.5	1.2
…	…	…	…
23.5	0.3	5.7	0.1
24	0.1	5.6	0

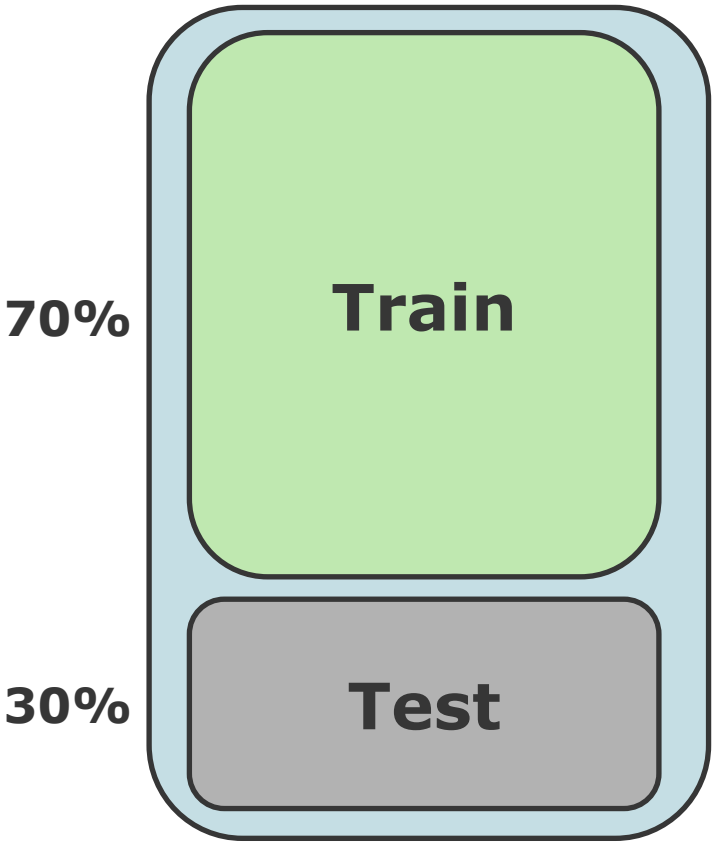
$$\widehat{GIR}: \ \text{MSE} = \sum_{t=t_0}^{t_T} \frac{1}{T} (\widehat{GIR}(t) - GIR(t))^2 \longrightarrow min$$

Decision:

Machine learning

GIR model

Data: 11340 rows



ML Algorithms

- *Random Forest*
- *Adaboost*
- ***Xgboost***
- *Linear Regression*
- *Neural Network*

Parameters tuning

k-fold cross-validation

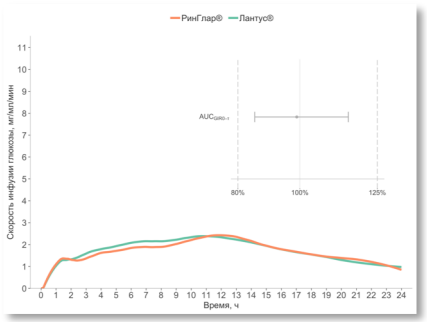
$\widehat{GIR}$

$MSE_{test} \rightarrow min$

- *RF* 0.015
- *Adab* 0.051
- ***Xgb*** **0.013**
- *LR* 0.026
- *NN* 0.016

Development process

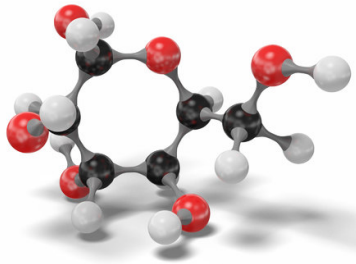
PK Data



PBPK-model

Monolix + R

Glucose prediction model



Predicts the next Glucose value using **the current&previous GIR** and Glucose values.

Model transferring using fitted model weights.

Model coding

import scipy

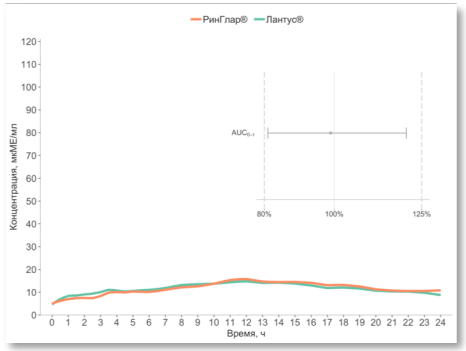
Python

Kivy - a special Python library for applications creating.

Kivy library

import kivy

PD Data

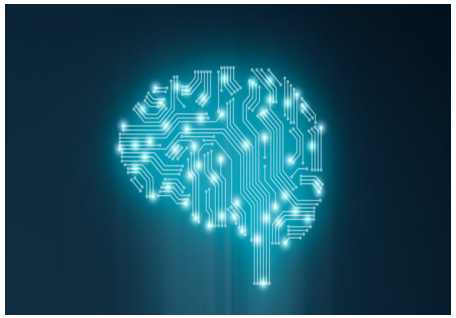


PBPK-model

ML

- Random forest
- Neural network
- **Boosting**
- …

GIR prediction model



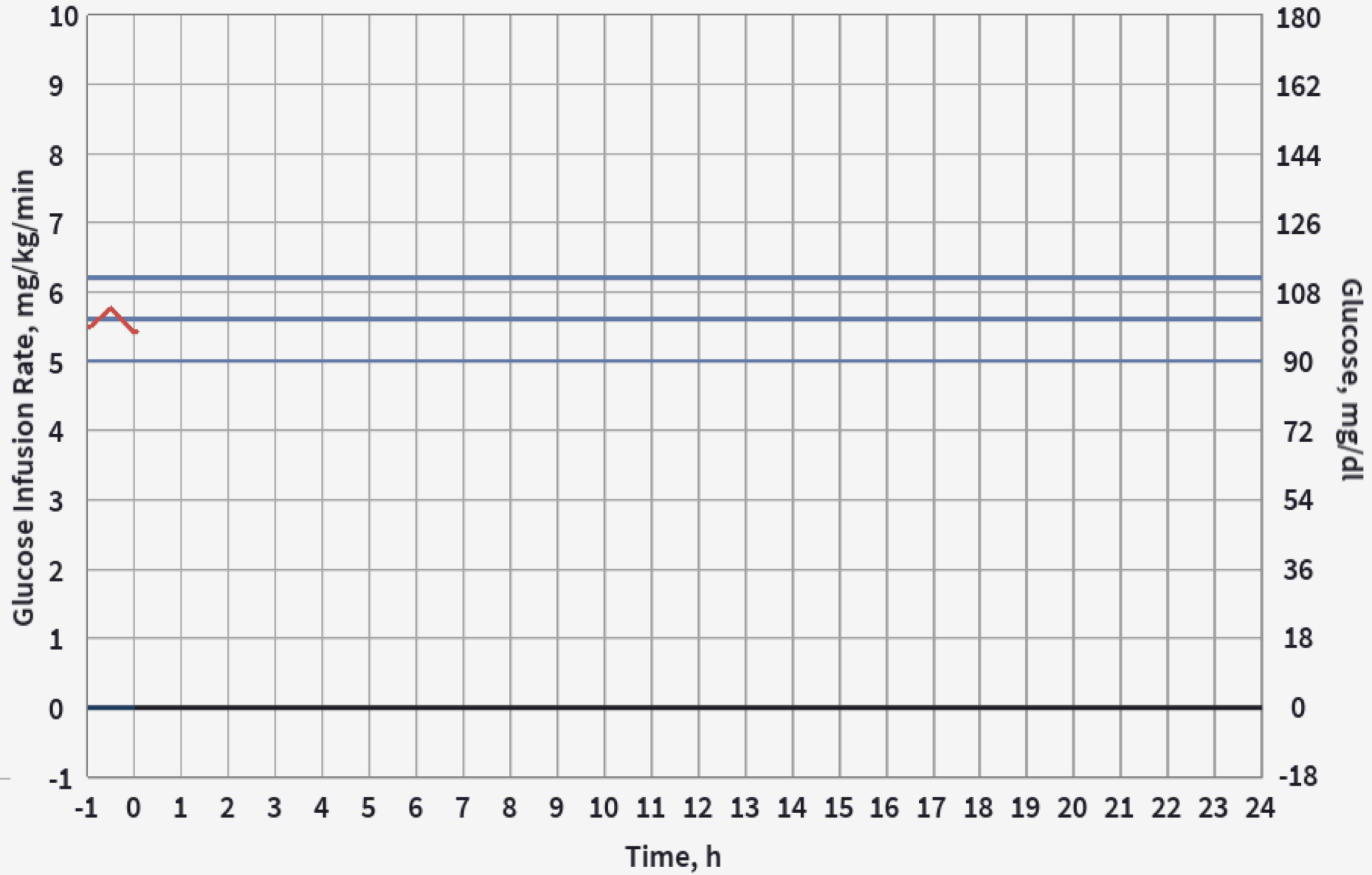
ML libraries

import sklearn
import xgboost
import keras

Predicts GIR value using **current&previous Glucose values** and **previous GIR**. Behaves like an investigator.

Trainer

Timepoint	Glucose	GIR	Predicted GIR
-1 h 0 min	98.42	0.000	0.000
-0 h 30 min	103.78	0.000	0.000
0 h 0 min	97.44	0.000	0.000
0 h 5 min	97.90	---	---



Initials: LIS

Weight: 76.0 **Insulin:** Glargine

BMI: 25.1 **Dose:** 0.2

Current timepoint 0 h 5 min
Current glucose 100.85 mg/dl
Previous GIR 0.000 mg/kg/min

Enter GIR:

My score:
–

Reset

Thanks for your attention

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Backup

IGI-model equations

Glucose:

- $\frac{dA_{gc}}{dt} = EGP(t) + \frac{Q}{V_P} * A_{gp}(t) - \frac{Q}{V_G} * A_{gc}(t) - \left(CL_G + CL_{GI} * C_{IE}(t)\right) * \frac{A_{gc}(t)}{V_G} + GIR(t) * WEIGHT$
- $A_{gc}(0) = G_{SS} * V_G$
- $\frac{dA_{gp}}{dt} = Q * \left(\frac{A_{gc}(t)}{V_G} - \frac{A_{gc}(t)}{V_P}\right),$
- $A_{gp}(0) = G_{SS} * V_P$
- $EGP(t) = EGP(0) * G_{CM1}(t)$
- $EGP(0) = G_{SS} * (CL_G + CL_{GI} * I_{SS});$
- $\frac{dC_{GE1}}{dt} = k_{GE1} * \frac{A_{gc}(t)}{V_G} - k_{GE1} * C_{GE1}(t),$
- $C_{GE1}(0) = G_{SS}$
- $\frac{dC_{GE2}}{dt} = k_{GE2} * \frac{A_{gc}(t)}{V_G} - k_{GE2} * C_{GE2}(t),$
- $C_{GE2}(0) = 0$

Insulin:

- $\frac{dA_i}{dt} = I_{SEC}(t) - \frac{CL_I}{V_I} * A_i(t),$
- $A_i(0) = I_{SS} * V_I$
- $I_{SEC}(t) = I_{SEC}(0) * G_{CM2}(t),$
- $I_{SEC}(0) = I_{SS} * CL_I$
- $G_{CM1}(t) = \left(\frac{C_{GE1}(t)}{G_{SS}}\right)^{GPRG}$
- $G_{CM2}(t) = \left(\frac{C_{GE2}(t)}{G_{SS}}\right)^{IPRG}$
- $\frac{dC_{IE}}{dt} = k_{IE} * \left(\frac{A_i(t)}{V_I} + Cc(t)\right) - k_{IE} * C_{IE}(t),$
- $C_{IE}(0) = I_{SS}$

OUTPUT:

$G_c = A_{gc}(t) / V_G$

IGI-model parameters

Steady-state glucose

Insulin-dependent glucose clearance

Parameter	Value
Gss (mg/L)	1000
Iss (mU/L)	0
Vg (L)	9,33
Vp (L)	8,56
Vi (L)	6,09
Q (L/h)	26,50
Cli (L/h)	73,2
CLg (L/h)	1,72
Clgi (L/h/mU/L)	0,616
kGE1 (1/h)	3,44
kGE2 (1/h)	1,73
kIE (1/h)	0,464
IPRG (-)	1,42
GPRG (-)	-2,79

← Start of clamp study

← Mixed effect model

$$Clgi_i = Clgi_{pop} + \eta_i^{Clgi}\ , \eta_i^{Clgi} \sim N(0, \omega^2_{Clgi})$$

$$\widehat{Gc} = Gc + a\ *\ \varepsilon\ , \varepsilon \sim N(0,1)$$