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DI PADOVA

The Padova Type 2 Diabetes Simulator: In Silico Trials Also Possible in Rare but Not-So-Rare Individuals

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The role of In Silico Medicine in Diabetes
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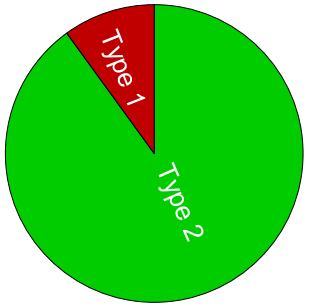
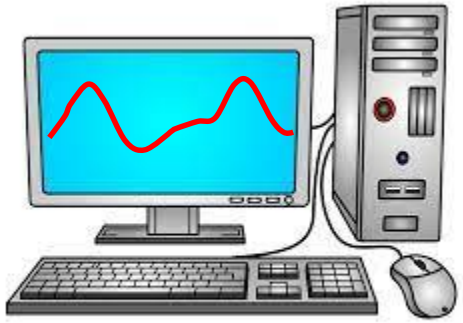
Introduction

- Type 2 diabetes (T2D) is much more widespread than type 1 diabetes (~90% of subjects with diabetes).



- *In silico* trials in T2D would be useful for testing diabetes treatments and accelerating the development of new antidiabetic drugs.



- Here, I will present a T2D simulator able to reproduce the variability observed in a T2D population but also to safely experiment on virtual subjects with severe (and possibly rare) pathological conditions.

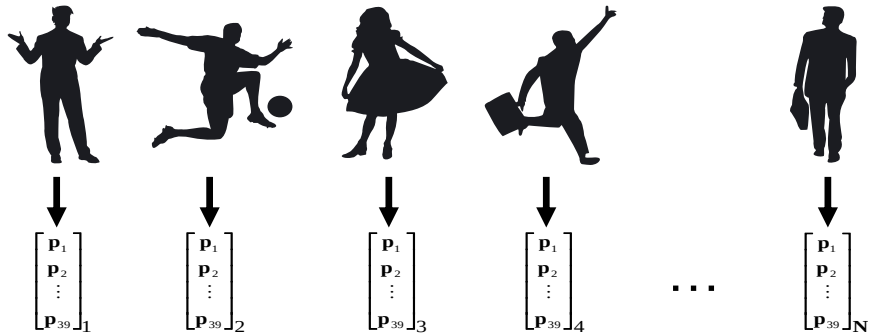
Simulator Structure

- **A set of model** equations

$$\begin{cases} \dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) & G_p(0) = G_{pb} \\ \dot{G}_t(t) = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) & G_t(0) = G_{tb} \\ G(t) = \dfrac{G_p}{V_G} & G(0) = G_b \end{cases}$$

$$\begin{cases} \dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) + R_{ai}(t) & I_p(0) = I_{pb} \\ \dot{I}_l(t) = -(m_1 + m_3) \cdot I_l(t) + m_2 \cdot I_p(t) & I_{pl}(0) = I_{lb} \\ I(t) = \dfrac{I_p(t)}{V_I} \end{cases}$$

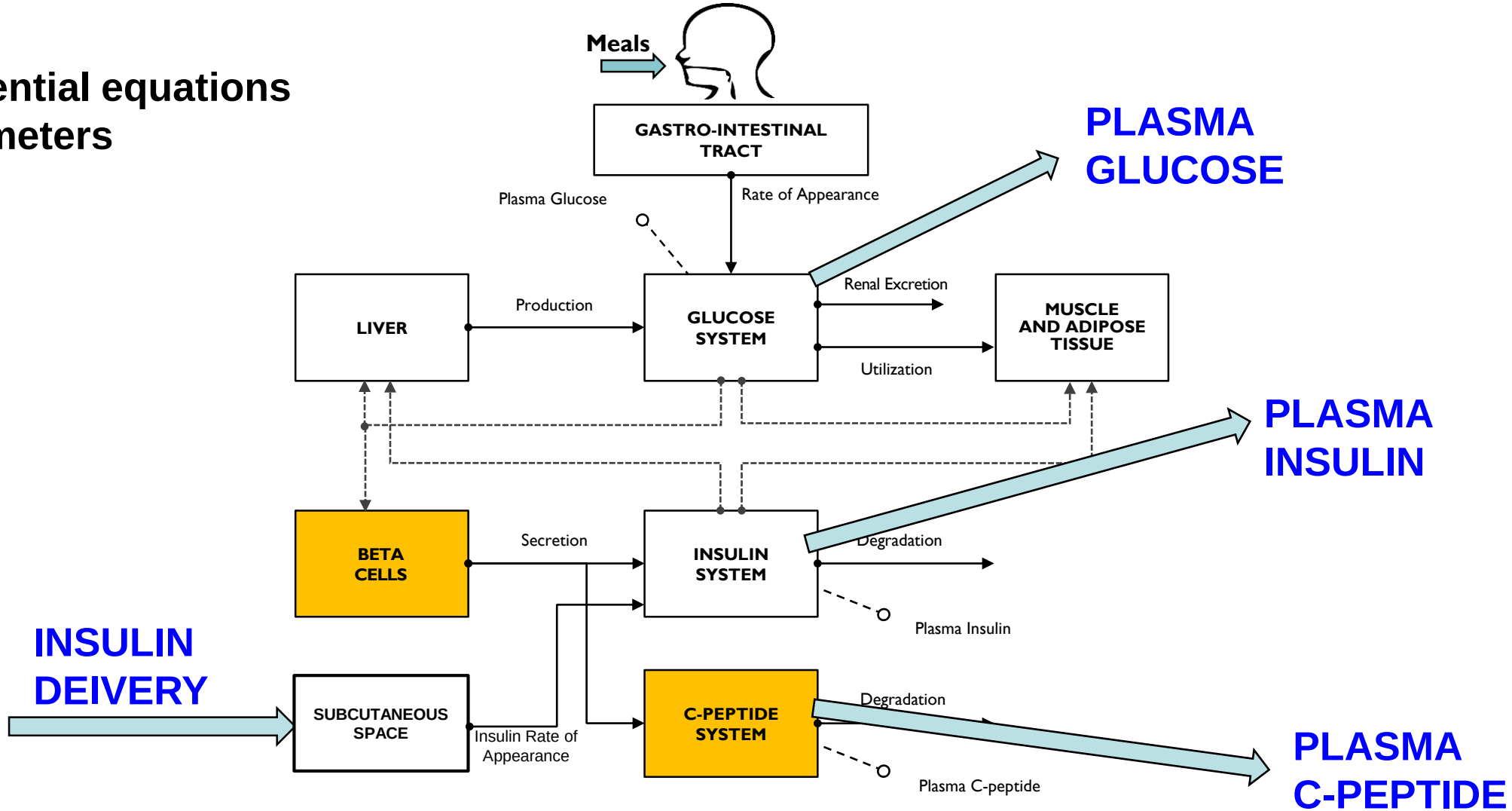
- **A set of virtual subjects,** defining the population on which the user wants to test a given decision support algorithm (each subject being represented by a set of model parameters)



- An infrastructure to set up the **simulation scenarios** (duration of the simulation, time and amount of the meals, hypo-rescue etc).

The Padova Type 2 Diabetes Simulator (T2DS)

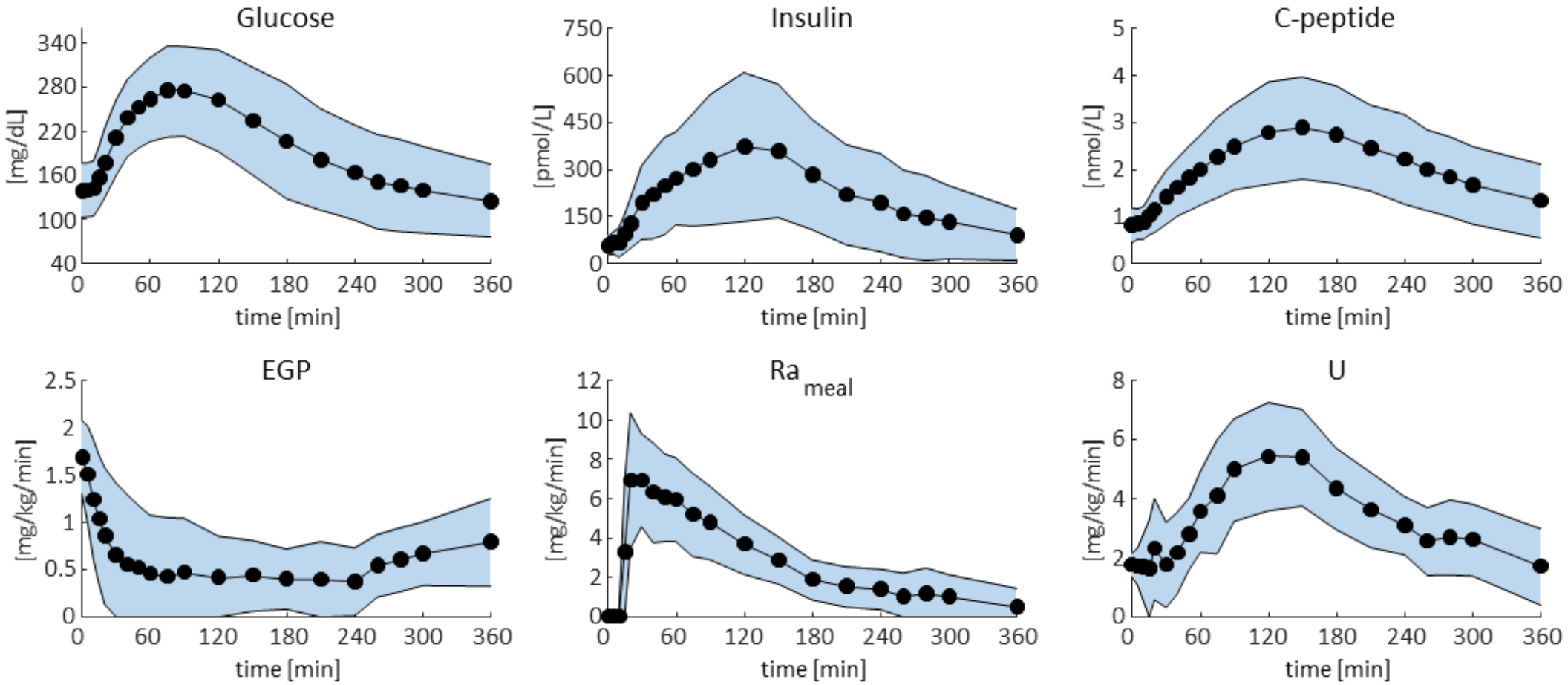
- 14 differential equations
- 39 parameters



(Visentin, *et al.*, *Diabetes Technol. Ther.*, 2020)

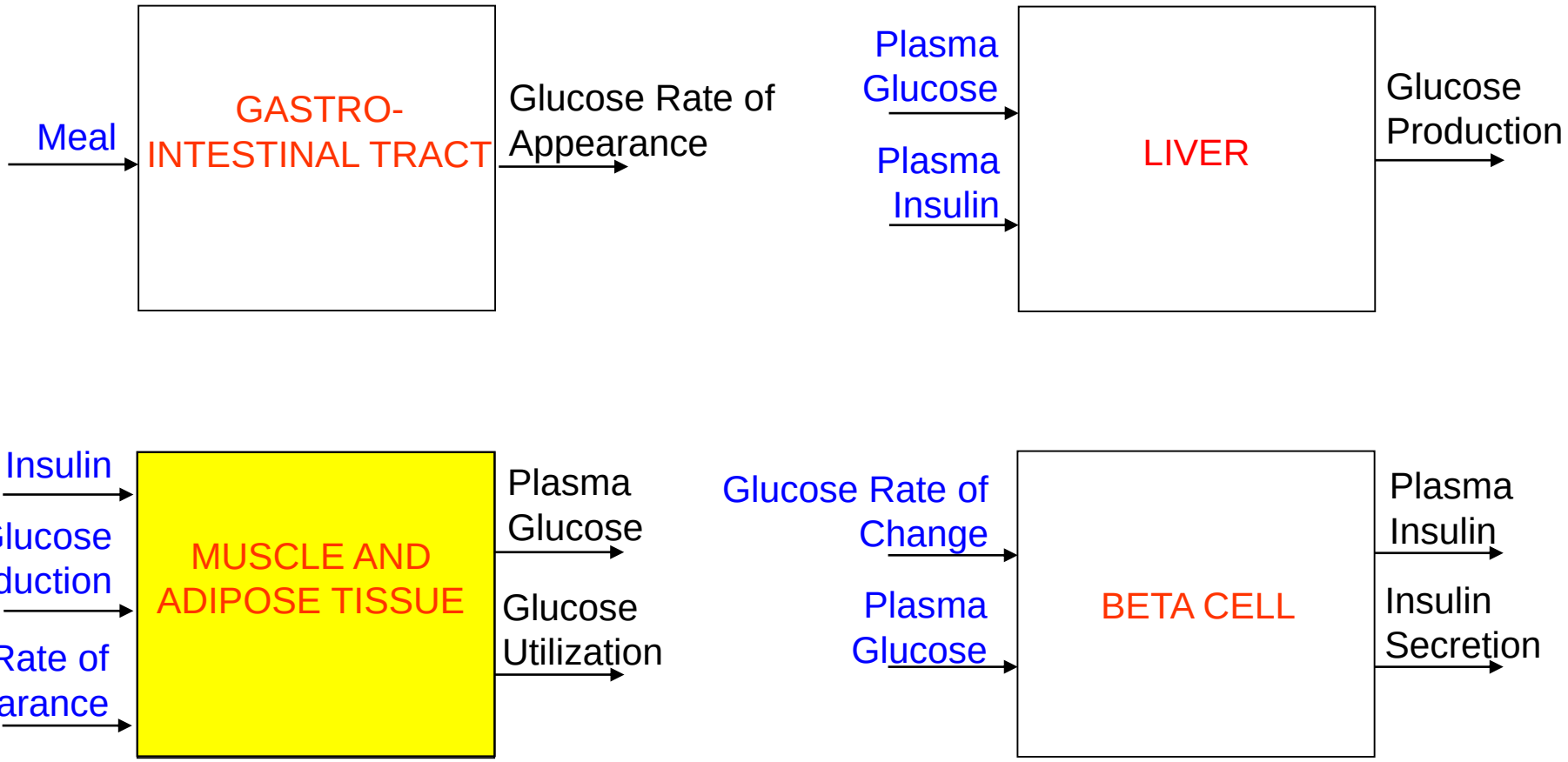
Data

N=51 T2D (Early stage) studied with a Tripe Tracer meal protocol

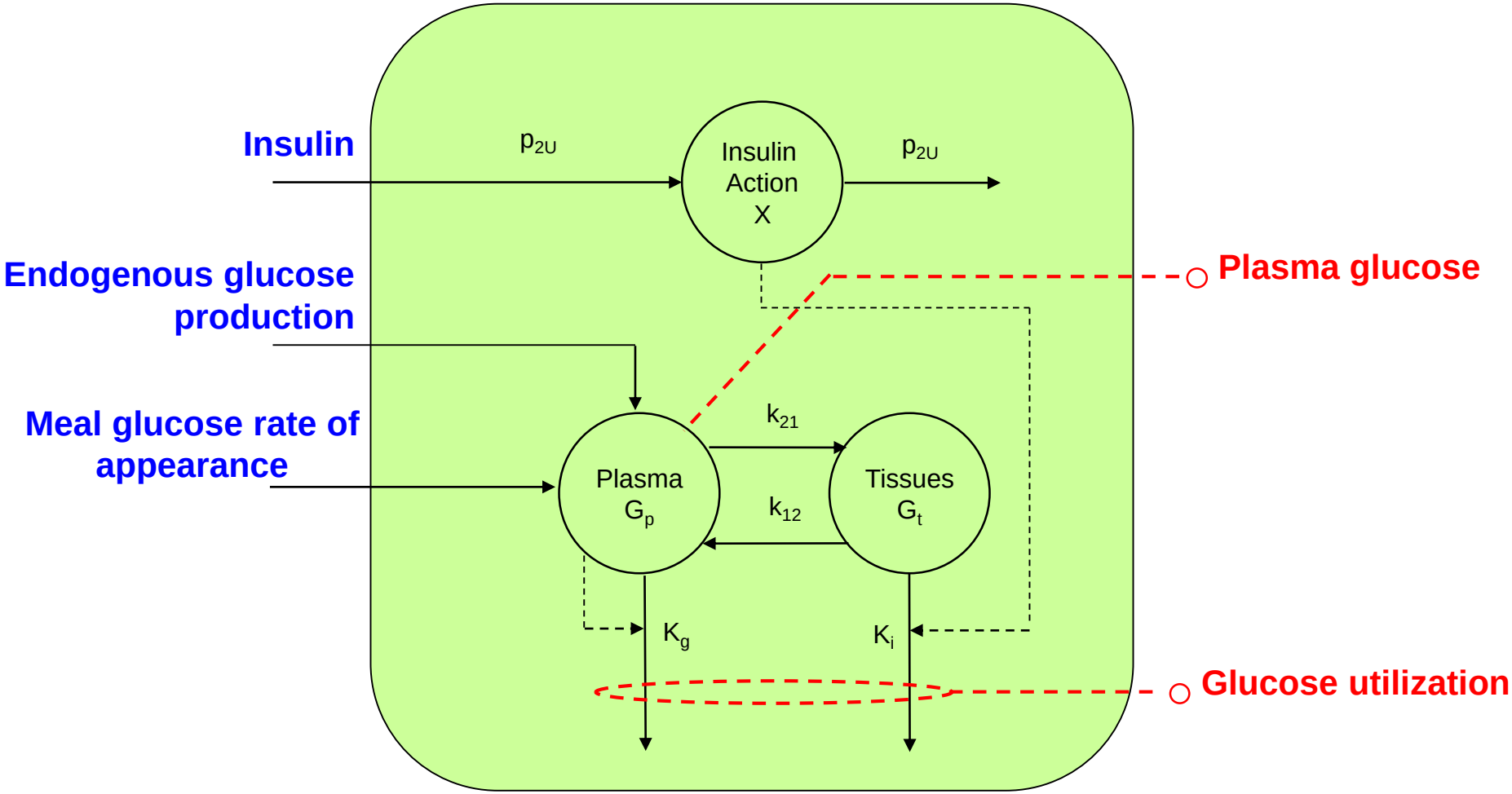


(Basu et al, Diabetes care 2009, Dalla Man et al Diabetes Care 2009)

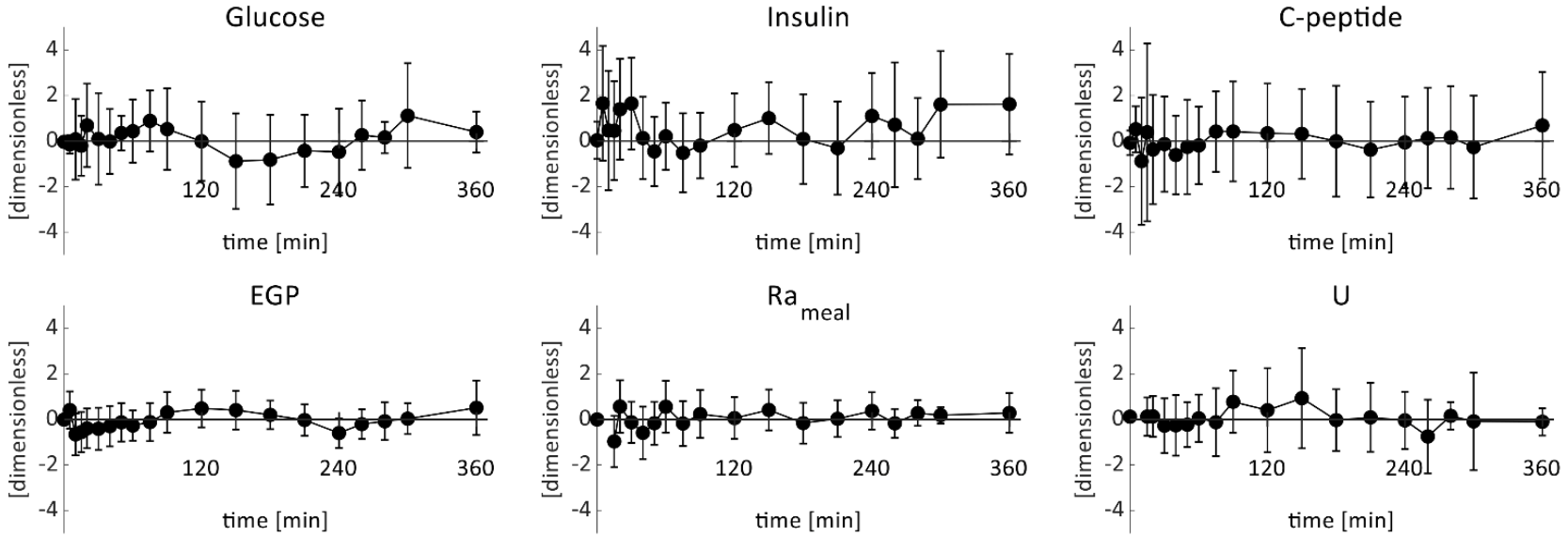
Model Tuning: The Forcing Function Strategy



Model Tuning: The Forcing Function Strategy

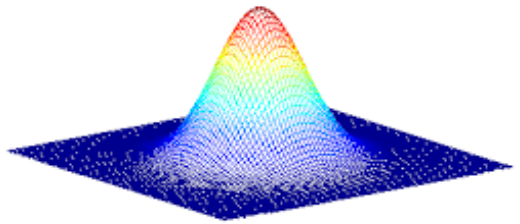


Model Tuning: Results

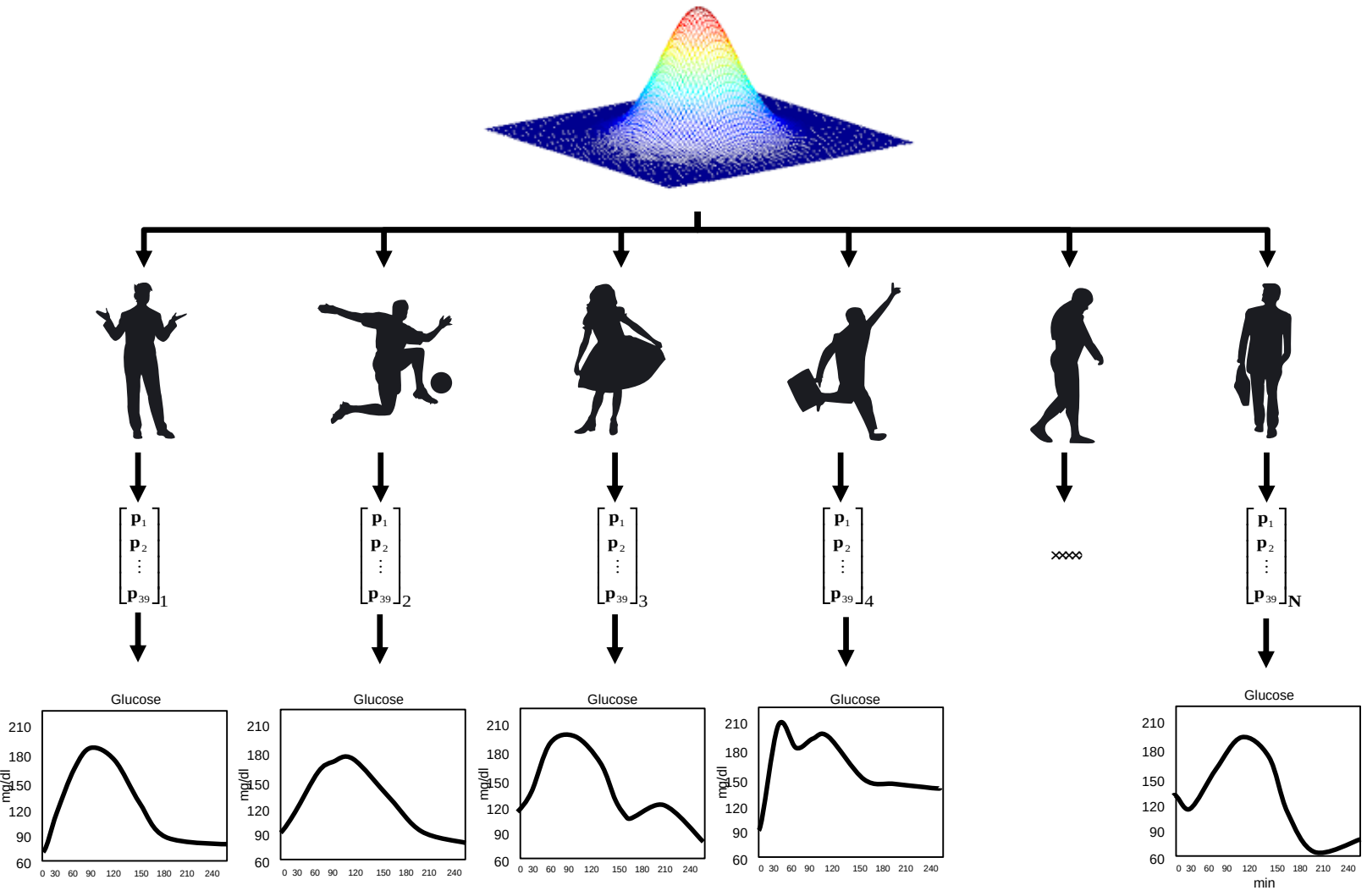


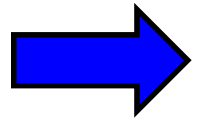
The **n** model parameters available in the 51 T2D subjects

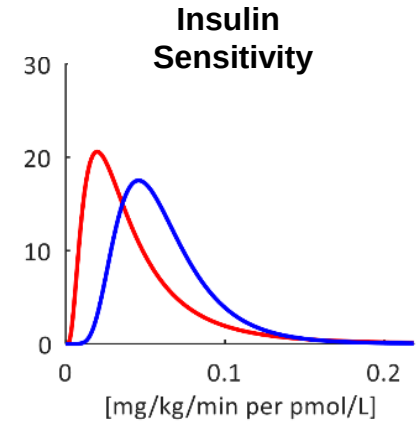
N-dimensional distribution of model parameters

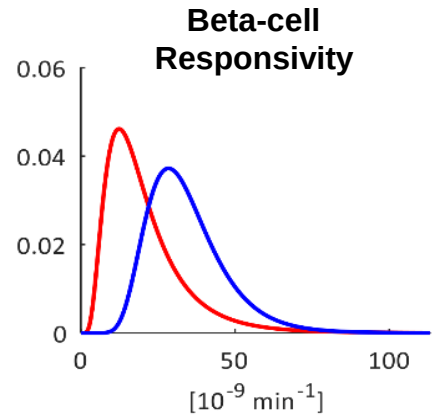


Virtual Subject Generation

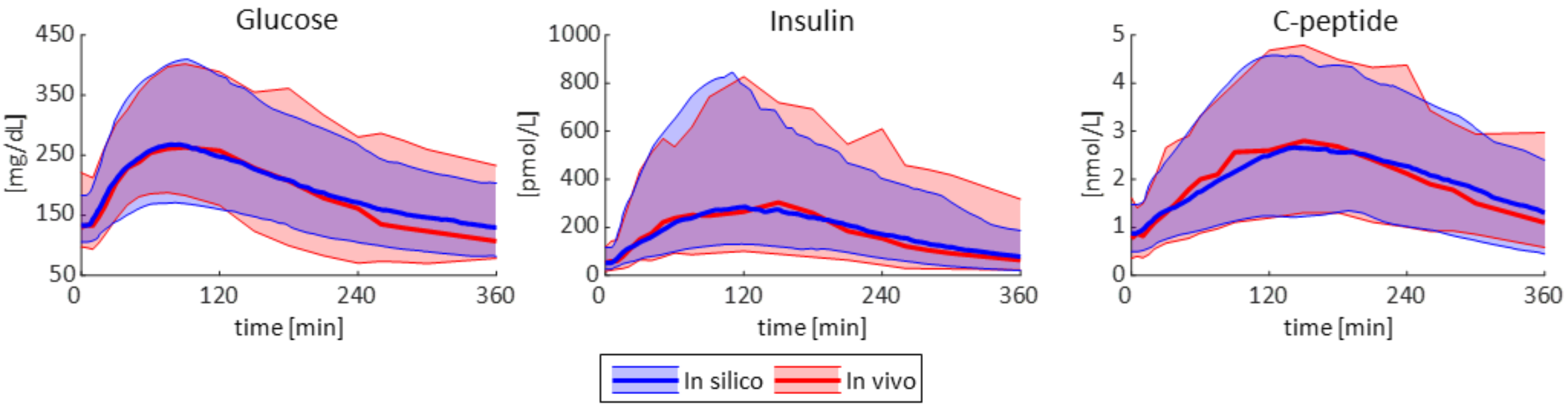








Validation

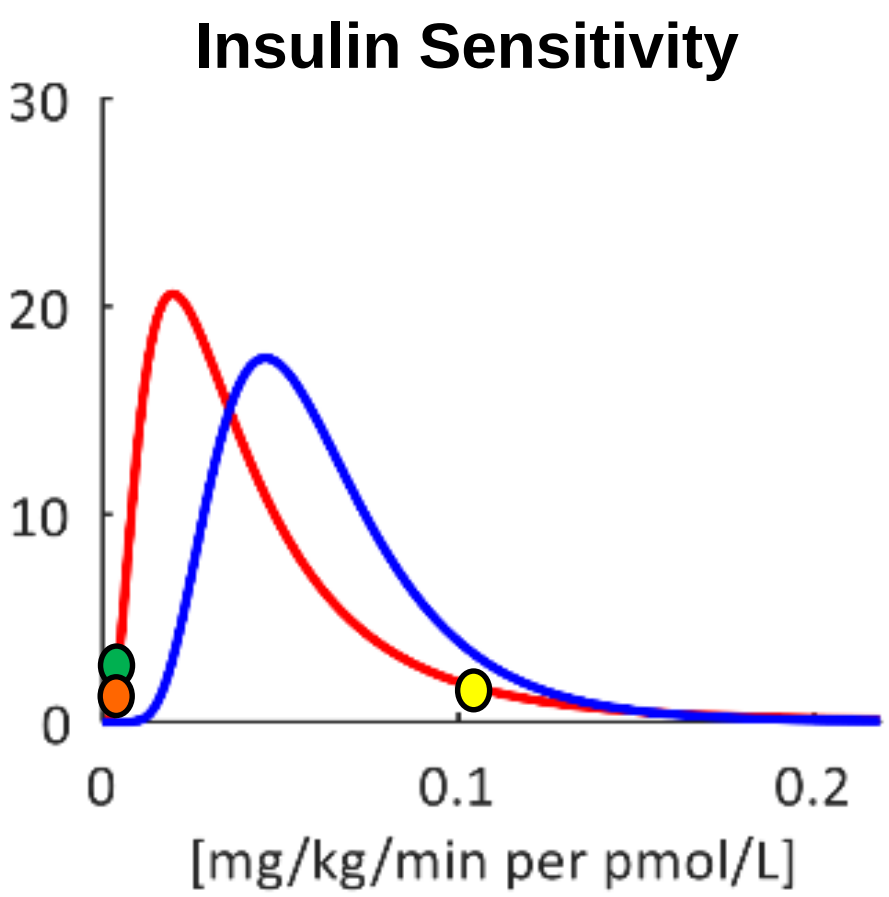


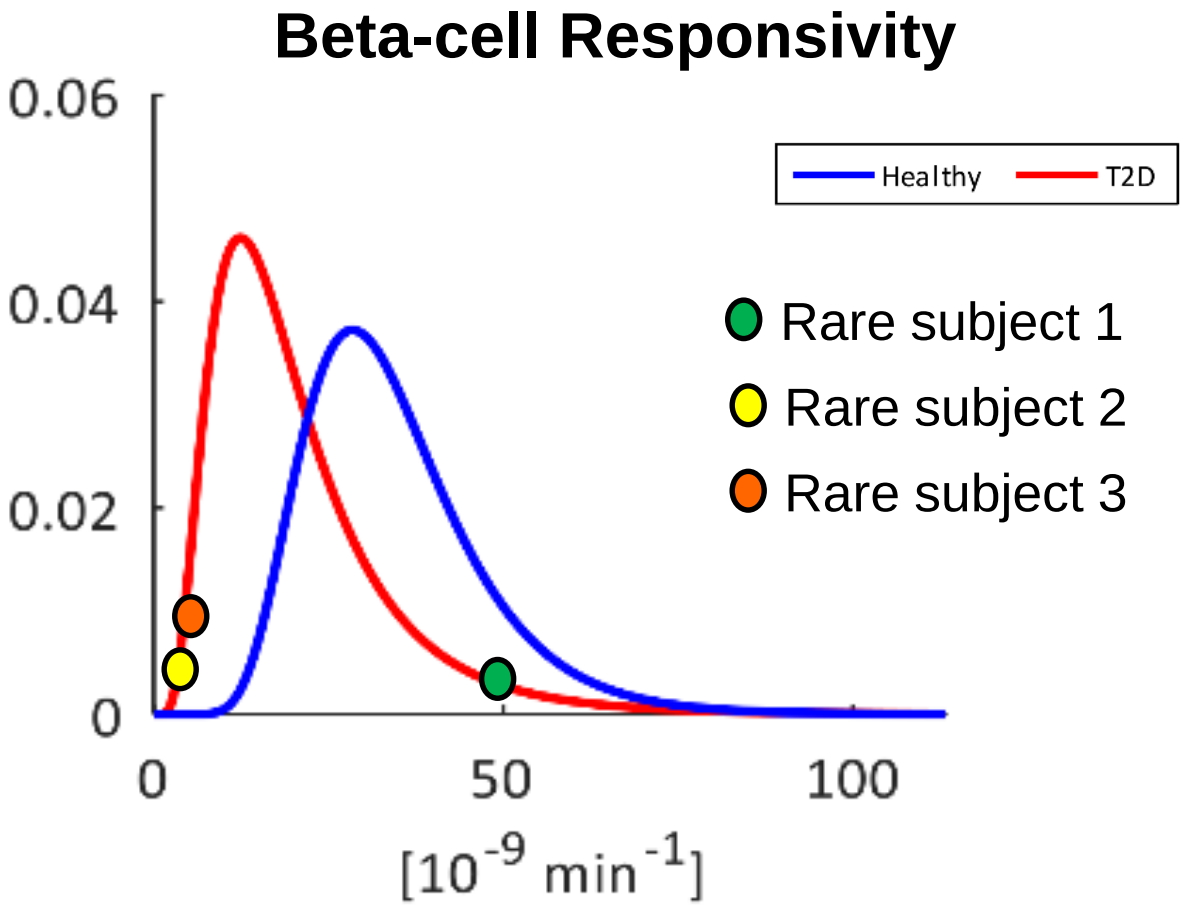
The 100 virtual subjects well cover the average dynamics and the population variability.

But the simulator can be used to evaluate the efficacy of a given treatment **in rare, but not so rare, subjects.**

? What does it mean?

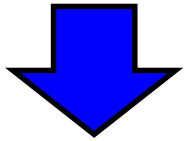
Rare (But Not So Rare) Individuals





Example of In Sicilo Trial in Rare Subjects

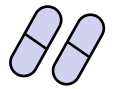
- Selecting N=10 subjects with severe impairment in both insulin action and b-cell function (like rare subject 3).
- The question is if they may benefit from a double vs. a standard (i.e., single) dose of a drug designed to improve both insulin action and b-cell function.



Trial 1: N = 100 treated with and without a **single dose** of the drug;

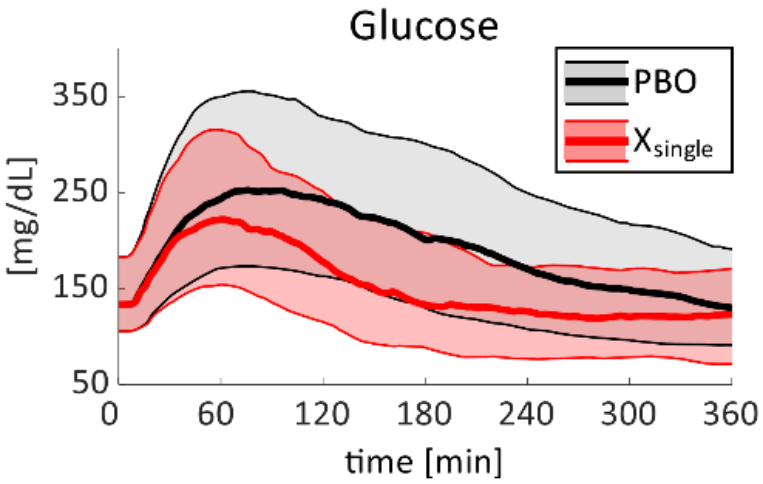
Trial 2: N =10 rare subjects treated with and without a **single dose** of the drug;

Trial 3: N =10 rare subjects treated with and without a **double dose** of the drug.

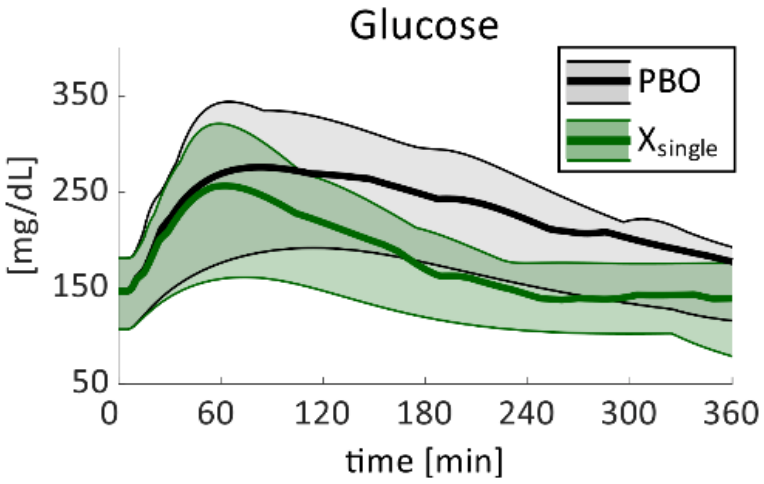


Example of Virtual Trial

N=100
single dose

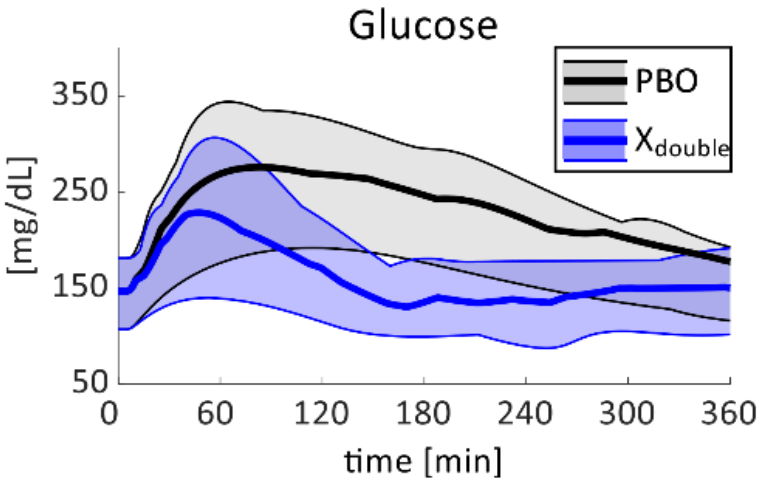


N=10 "rare"
single dose



AUC(G) percent difference
was **+14% (p = 0.028)**
compared to N=100

N=10 "rare"
double dose



AUC(G) percent difference
was **+7% (p = 0.218)**
compared to N=100

Conclusions

- The availability of 100 virtual subjects allows running in silico large-scale trials, as usually occurs in **phase II clinical trials**.
- Given that virtual subjects can undergo the identical experimental scenario several times, one can implement an **ideal crossover design**, where physiological intra-subject variability is minimized (and controlled by the investigator).
- The possibility to **‘‘virtually recruit’’** a subset of subjects with common characteristics permits to extensively study situations characterized by **‘‘extreme’’** parameter vectors, sampled from the distribution tails.
- This could possibly be used for optimizing diabetes therapy also in such ‘‘rare’’ pathological conditions.

Acknowledgements

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Dr. Ananda Basu

Thank you for your attention!

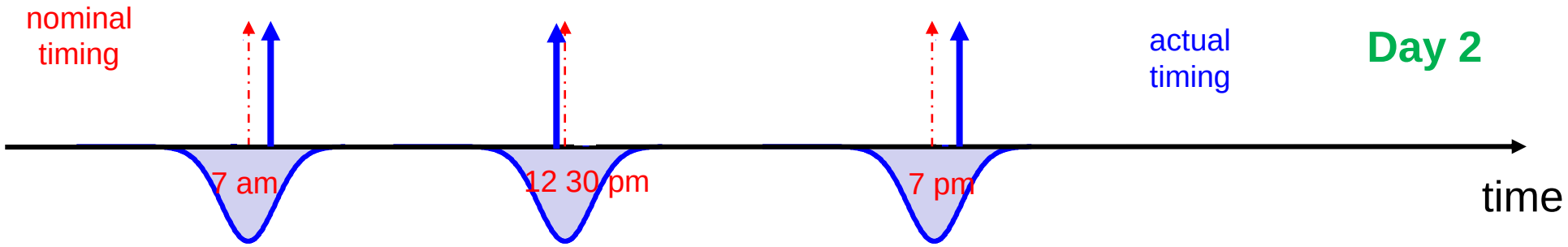
Questions?

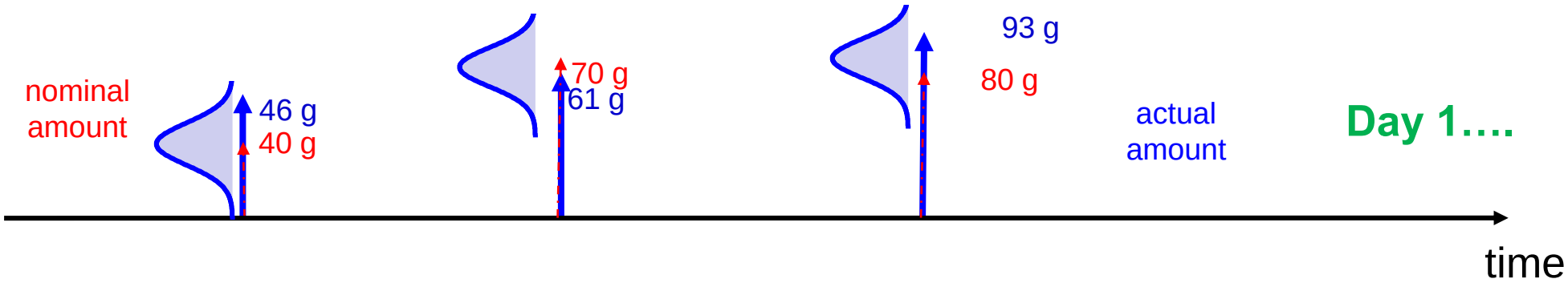
Additional Slides

Setting Up The Simulation Scenario

To set up a realistic simulation, additional sources of variability should be considered:

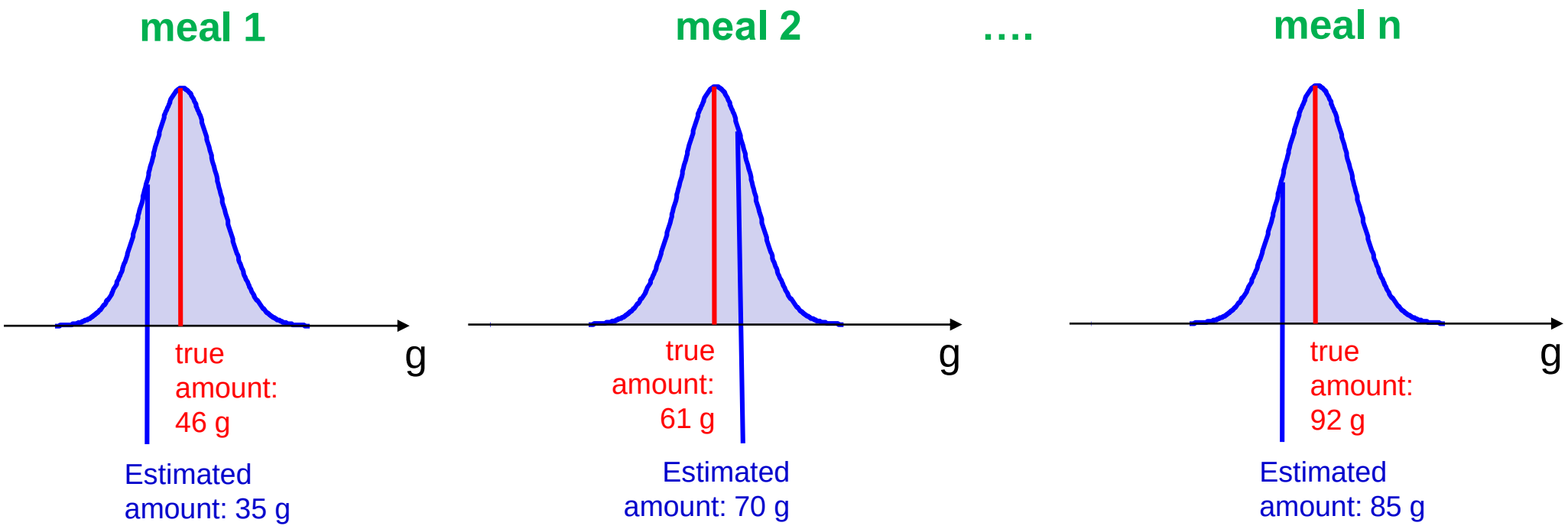
- the difference in the timing and amount of ingested vs nominal meal schedule





Setting Up The Simulation Scenario

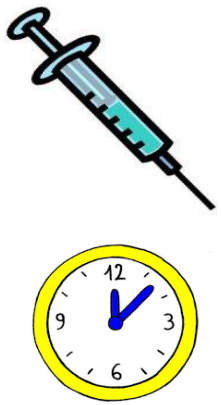
- the possible error in the carbohydrate counting

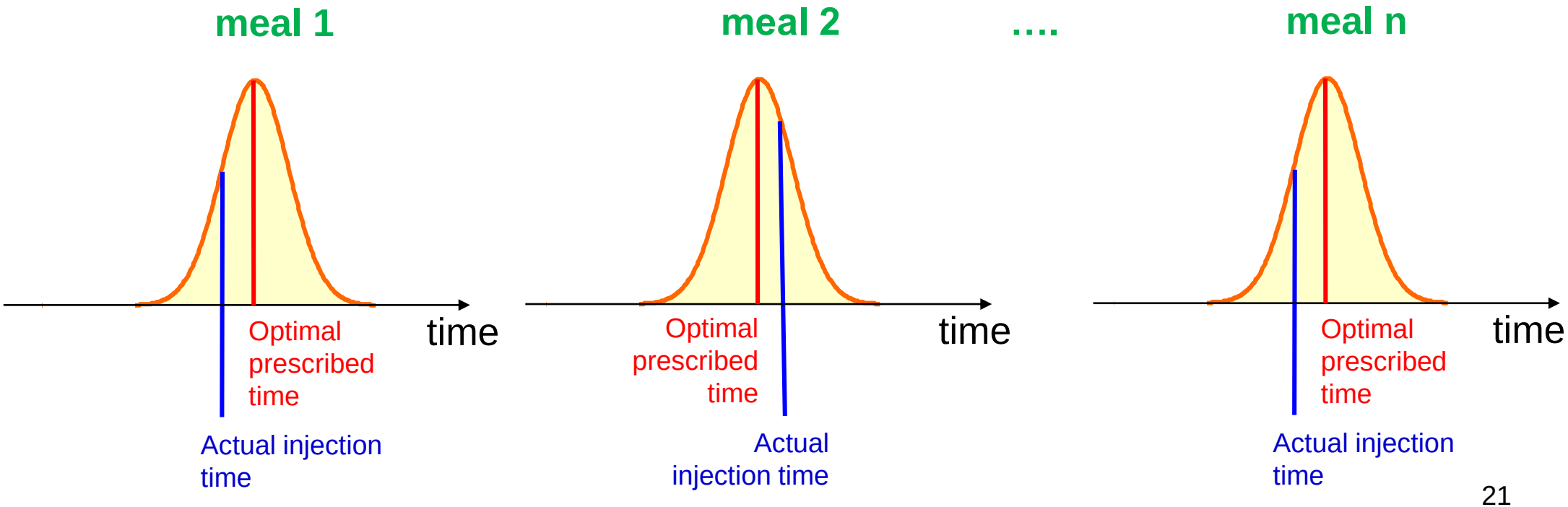


(Vettoretti et al., IEEE *Trans. Biomed Eng.*, 2018)

Setting Up The Simulation Scenario

- the random deviation in the timing of insulin administration from the optimal prescribed one

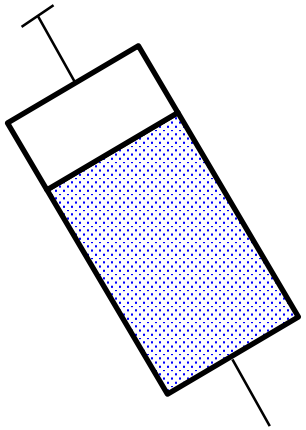




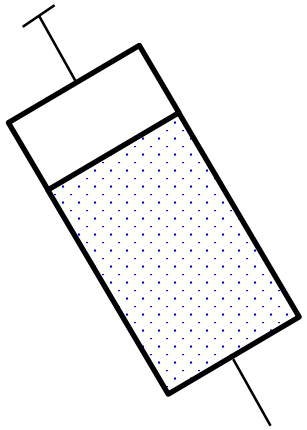
Setting Up The Simulation Scenario

- the interoccasion variability of drug bioavailability, etc.

day 1

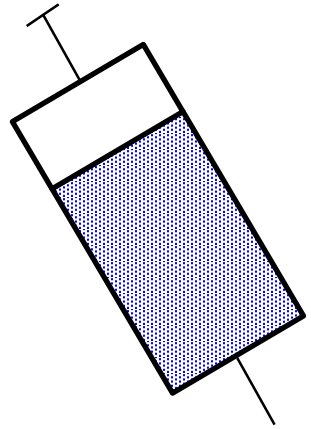


day 2



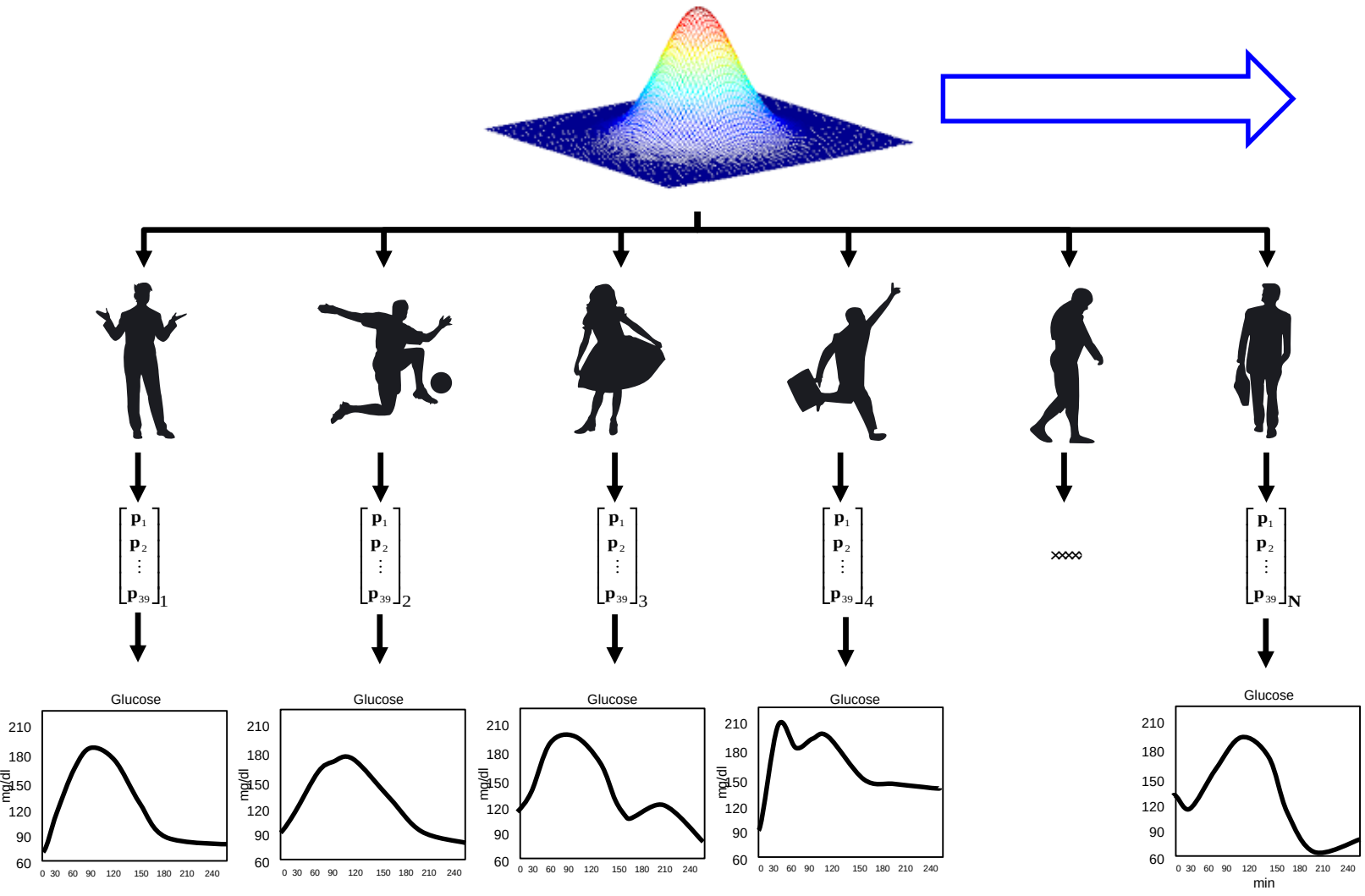
….

day n



(Visentin, *et al.*, *IEEE Trans Biomed Eng.* 2019,
Schiavon et al., *Diab Technol. Ther* 2020)

Virtual Subject Generation



Validated **parameter distribution** derived from multiple tracer experiments performed in Caucasian early-stage type 2 diabetic individuals

WHAT IF ONE NEEDS TO PERFORM SIMULATION ON A DIFFERENT POPULATION (E.G. INSULIN-NAÏVE TYPE 2 DIABETES, ADVANCED-STAGE TYPE 2 DIABETES, OTHER ETHNIC GROUPS…)

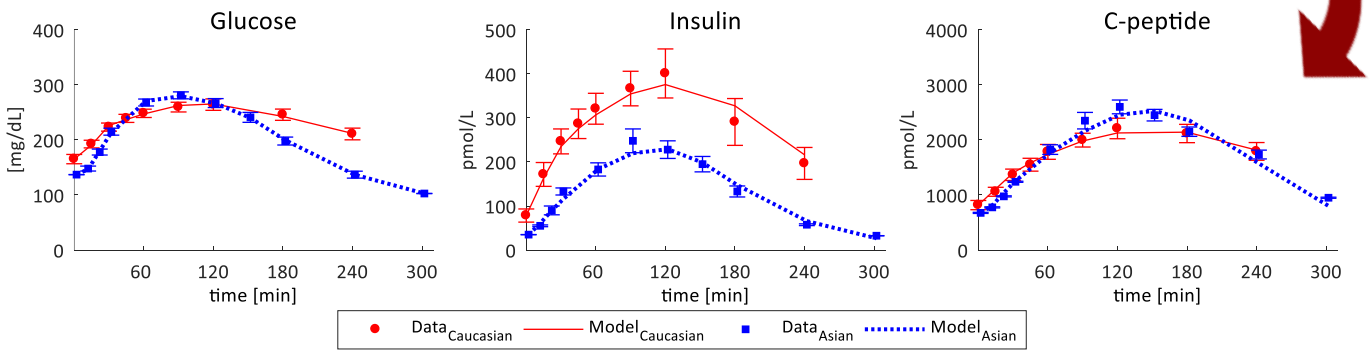
Tailoring The Simulator To A Target Subpopulation

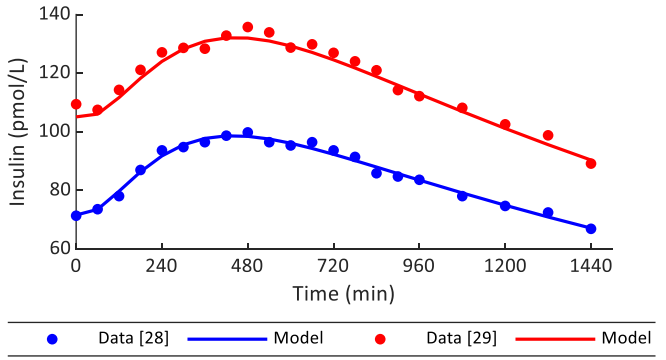
PIPELINE

- Identifying the model using glucose, insulin and possibly C-peptide data (fasting and/or post post-prandial) available from the literature.

$$(p_1, p_2, \ldots p_n)$$

MODEL IDENTIFICATION



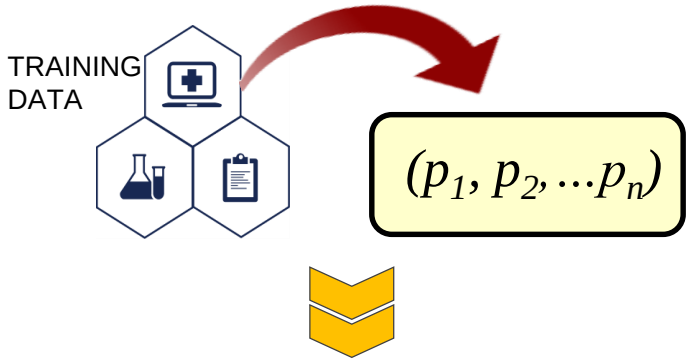


Tailoring The Simulator To A Target Subpopulation

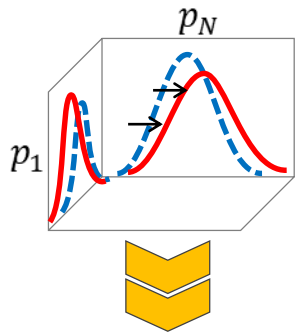
PIPELINE

- Identifying the model using glucose, insulin and possibly C-peptide data (fasting and/or post post-prandial) available from the literature.
- Updating the joint parameter distribution with new model parameter estimates.
- Generating new *in silico* cohort by randomly extracting 100 model parameter sets from the updated joint distribution.

MODEL IDENTIFICATION



UPDATED PARAMETER DISTRIBUTION



IN SILICO SUBJECT GENERATION