UNIVERSITY OF BERN

# Sistema de Apoyo a la Toma de Decisiones Mejorado por Gemelos Digitales en Diabetes Tipo 1 con Terapia MDI

Carlos Builes, Laura Lema, Hernan Alvarez, and

José García-Tirado

Department of Diabetes, Endocrinology, Nutritional Science, and Metabolism (UDEM)

jose.garcia@unibe.ch

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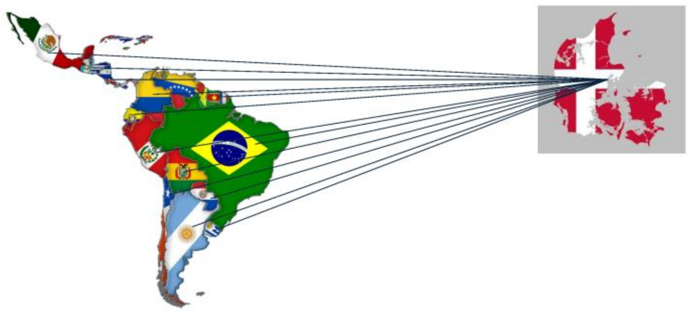
# Thanks

Prof. Jose Omar Silverman- Retana

Internacionalización de la estrategia de investigación del SDCA



# Background

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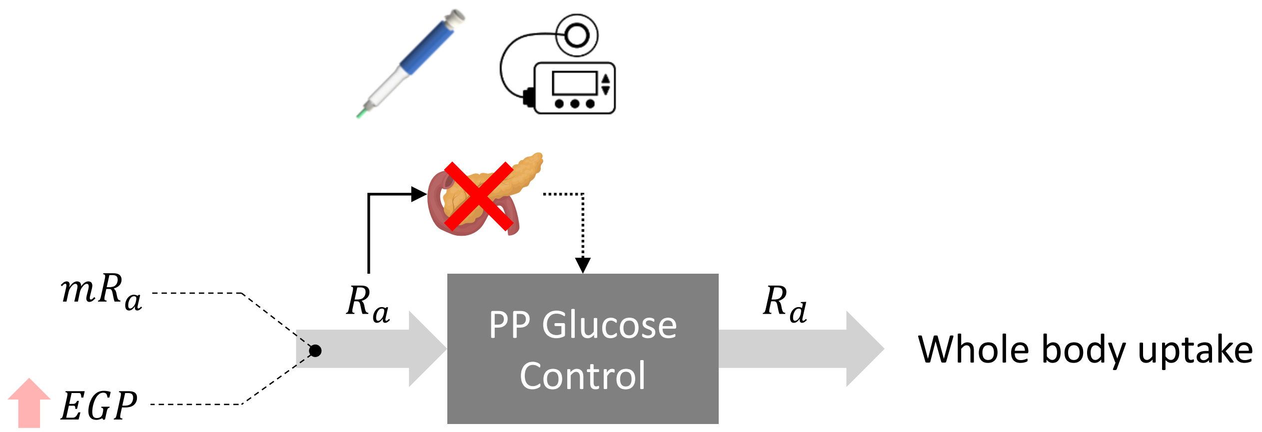
"All models are wrong, but some are useful." *George P. E. Box*

# Background

People with Type 1 Diabetes (PwT1D) need a lifelong insulin replacement (MDI or CSII) to keep glucose levels in the desired range.

\+ Glucose control → − Diabetes-related complications

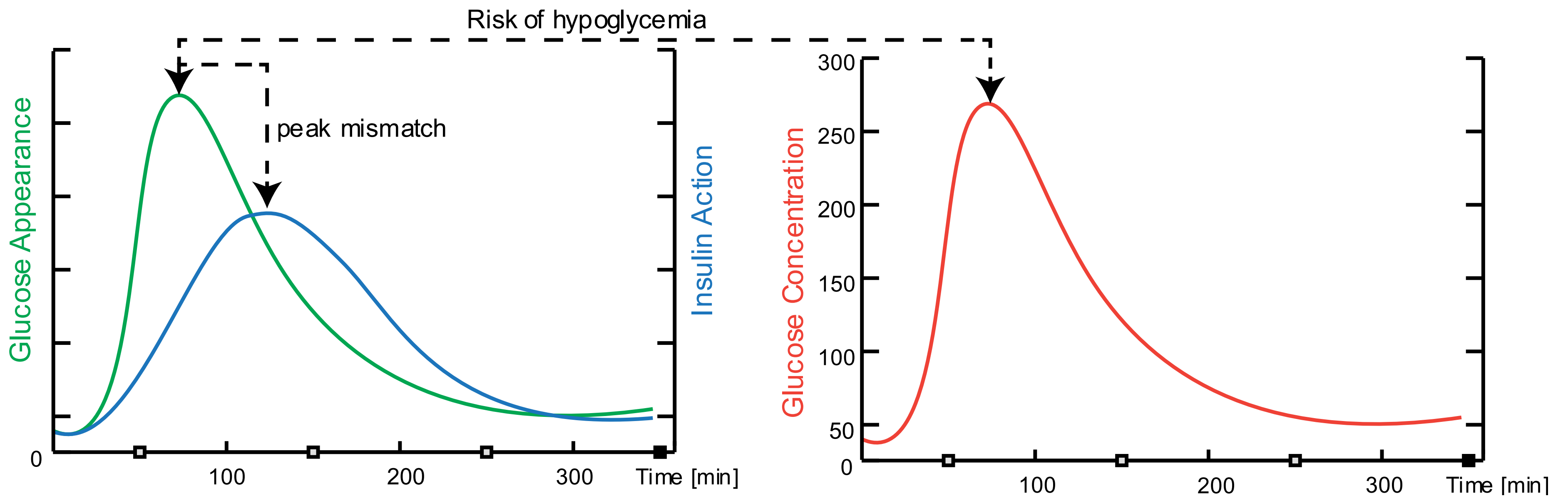


# Background

Diabetes Control and Complication Trial (DCCT) → Intensive Insulin Therapy (IIT) → HbA1c ↓

→ Hypoglycemia ↑


Current insulin preparations



# Background
## Current Landscape

YPSOMED SELFCARE SOLUTIONS


CamAPS/FX

diabeloop


DBLG1

TIDEPOOL

APP

Beta Bionics

iLet (insulin-only)

Medtronic


670G, 770G, 780G

TANDEM DIABETES CARE


Control-IQ

Insulet

Omnipod 5

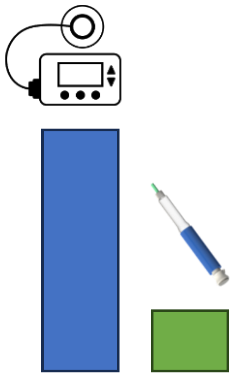
# Background

## Current Landscape

While developed countries are reaching high levels of technology adoption, countries in development are lagging behind:

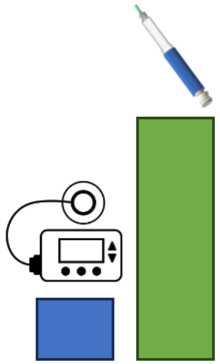
(US and Europe)

**50-70%**



LATAM, Asia, Africa

**10-20%**



# Mathematical Models and the Medical Digital Twin Technology

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# What is a Model?

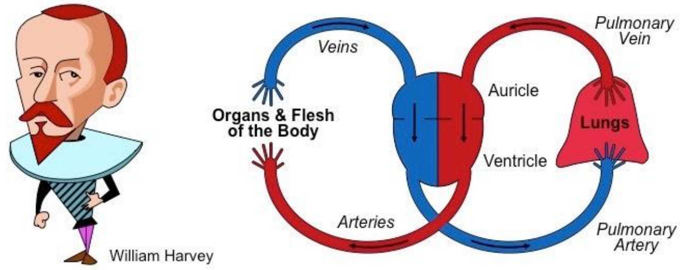
*“A model is an imitation of reality; a representation of a system, entity, phenomenon, or process”* [a]

Subclasses, according to Batzel et al. [b]:

a. Conceptual models

b. Physical models

c. Mathematical models




Harvey’s circulation model (1628) [c]

$$\Sigma: \begin{cases} \dot{x} = f(x, u, d, \theta, t) \\ y = g(x, u) \end{cases}$$

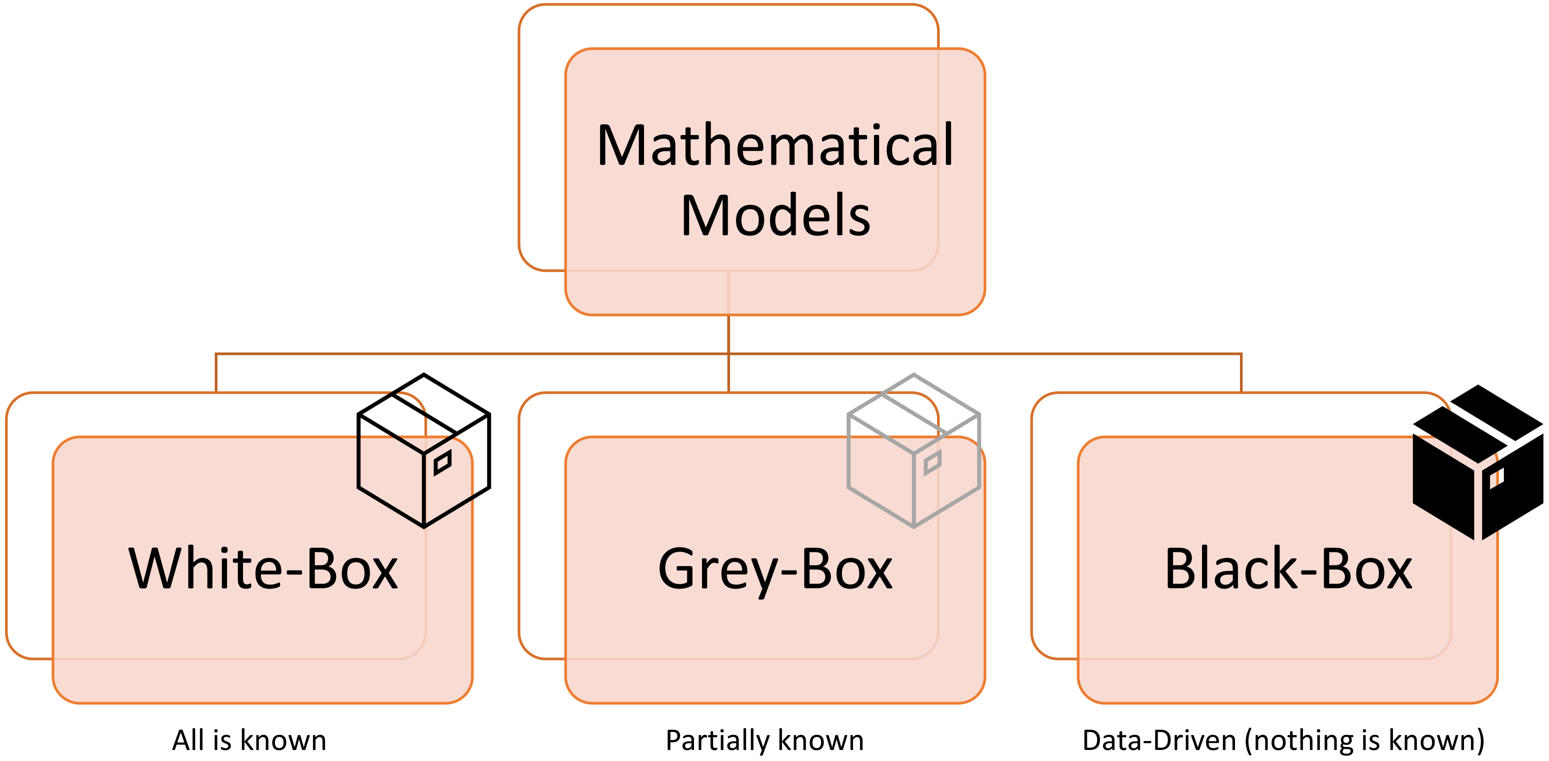
[a] Kaizer JS, Heller AK, Oberkampf WL. 2015. Scientific computer simulation review. *Reliab. Eng. Syst. Saf.* 138:210–18

[b] Batzel J, Bachar M, Karemaker JM, Kappel F. 2012. Merging mathematical and physiological knowledge: dimensions and challenges.

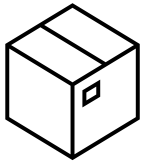
[c] Schultz SG. 2002.William Harvey and the circulation of the blood: the birth of a scientific revolution and modern physiology. *News Physiol. Sci.* 17:175–80

# What is a Model?

According to where the equations come from:



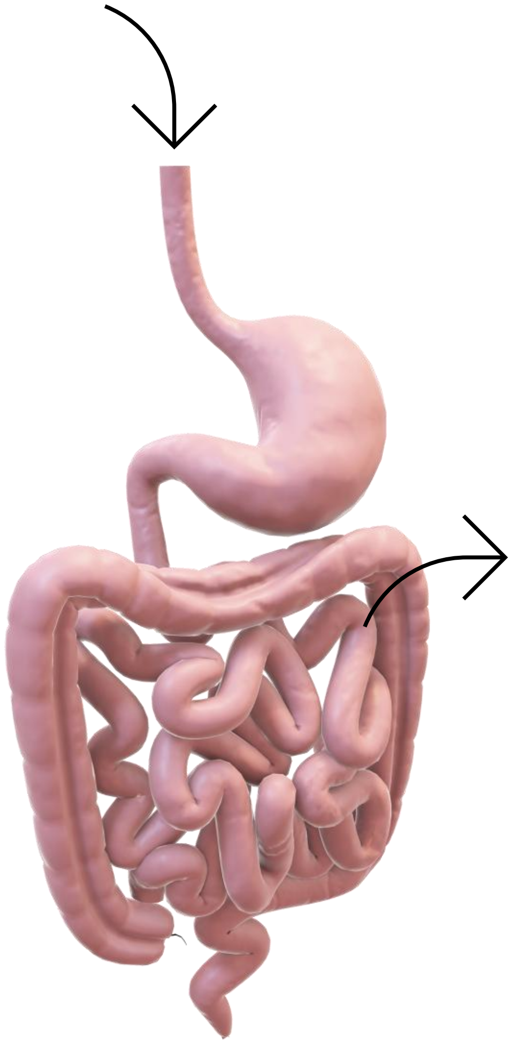
# White-Box Models



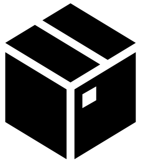
mechanistic – phenomenological – first principles

Their basic derivation comes from system phenomena or mechanisms such as *mass, energy, and momentum transfer*.

$$\left\{\begin{matrix}\text{net change}\\ \text{of quantity in time}\end{matrix}\right\} = \left\{\begin{matrix}\text{flow in}\\ \text{through boundary}\end{matrix}\right\} - \left\{\begin{matrix}\text{flow out}\\ \text{through boundary}\end{matrix}\right\} + \left\{\begin{matrix}\text{net}\\ \text{generation}\end{matrix}\right\} - \left\{\begin{matrix}\text{net}\\ \text{consumption}\end{matrix}\right\}.$$



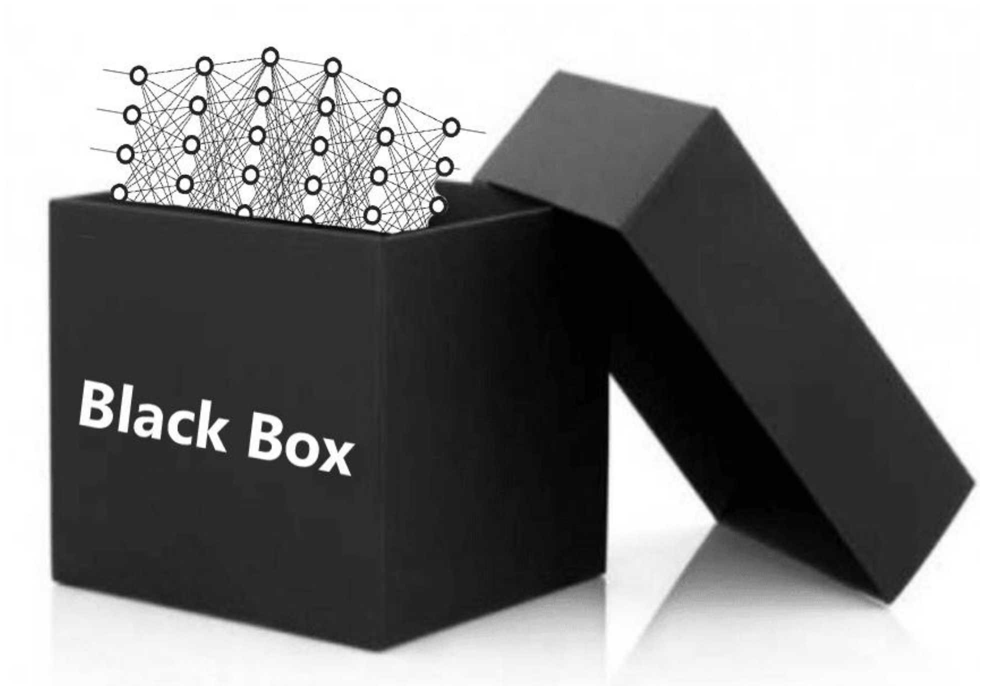
# Black-Box Models



<u>empirical – input/output</u>

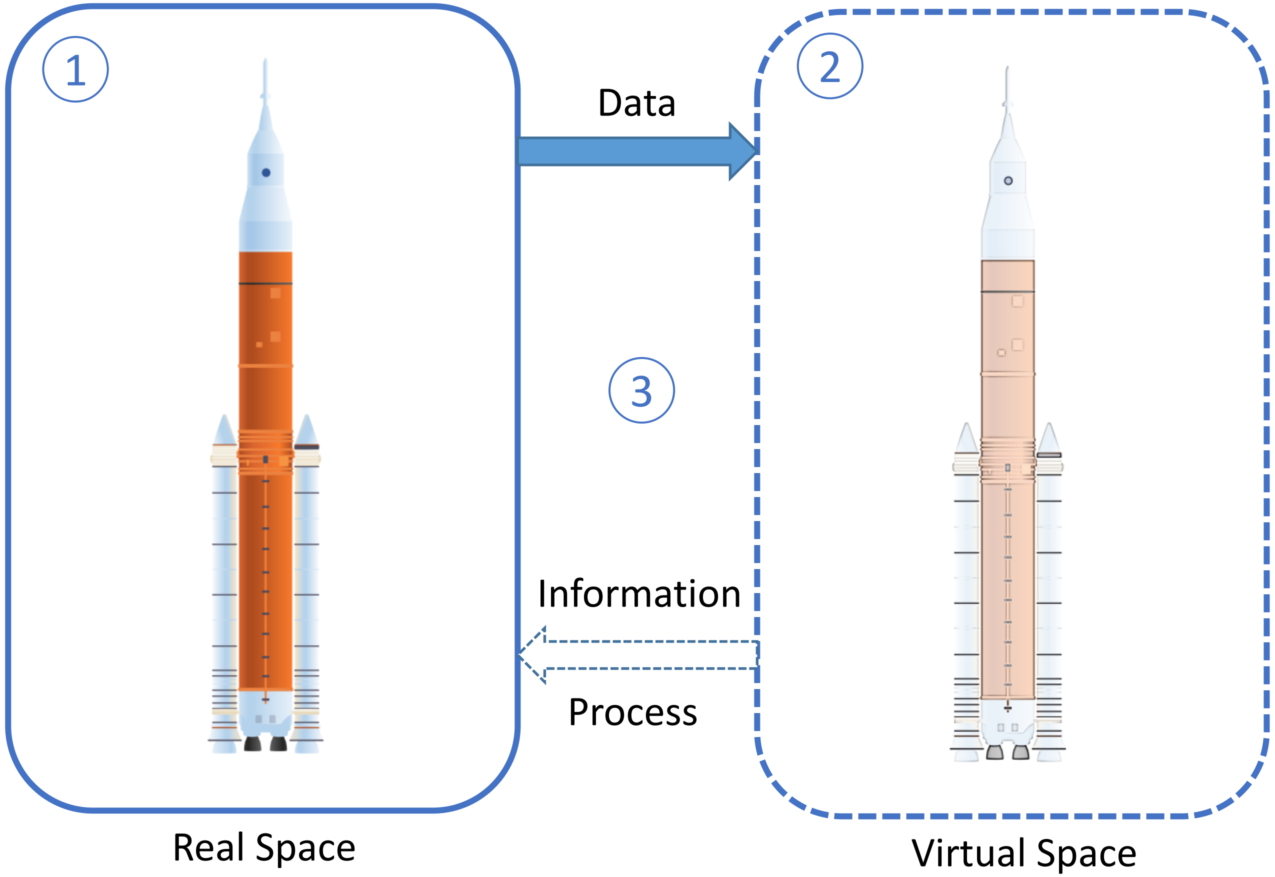
Are the result of experiment and observation (equation fitting where the parameters have little or no physical meaning )

- Time series (lots of…)
- Neural networks
- Transfer functions
- Deep Learning
- Machine Learning
- Recommendation engines
- Predictive analytics
- NLP / Text mining
- Natural language generation
- Etc…



# The Digital Twin

The concept of a virtual, digital equivalent to a physical product, or the Digital Twin (DT) was introduced by M. Grieves in 2003 at the University of Michigan (in a lecture).




Adaptation of Grieves' sketch.

In the following two decades, there has been a tremendous progress in

1. Amount, richness, and quality of the information.

2. Computational capacity.

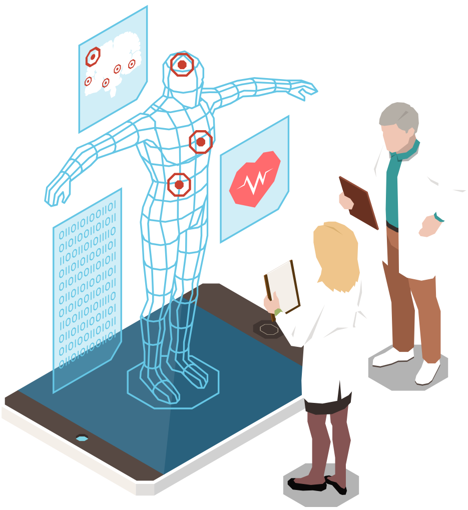
Key enablers of *Precision Medicine*

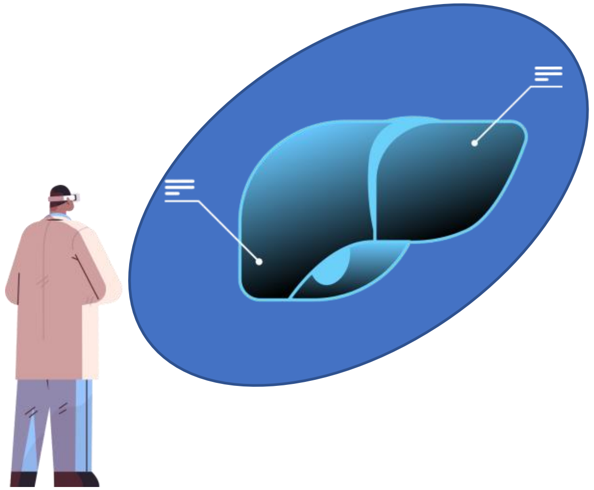
# The Digital Twin (Medicine)

DTs can be defined as (physical and/or virtual) machines or computer-based models that are *simulating, emulating, mirroring, or "twinning"* the life of a physical entity, which may be an object, a process, a human, or a human-related feature [d].

As such, DT in Medicine does not need to be a virtual copy of the entire individual

Whole body | VS | Part of the body





[d] Barricelli, B. et al A Survey on DT: Definitions, Characteristics, Applications, and Design Implications.

# Decision Support System (DSS) to Assist PwT1D with Meal Bolusing

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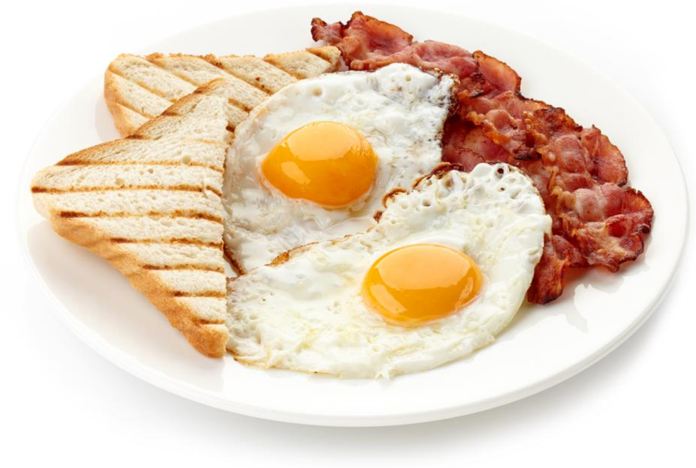
# The Problem

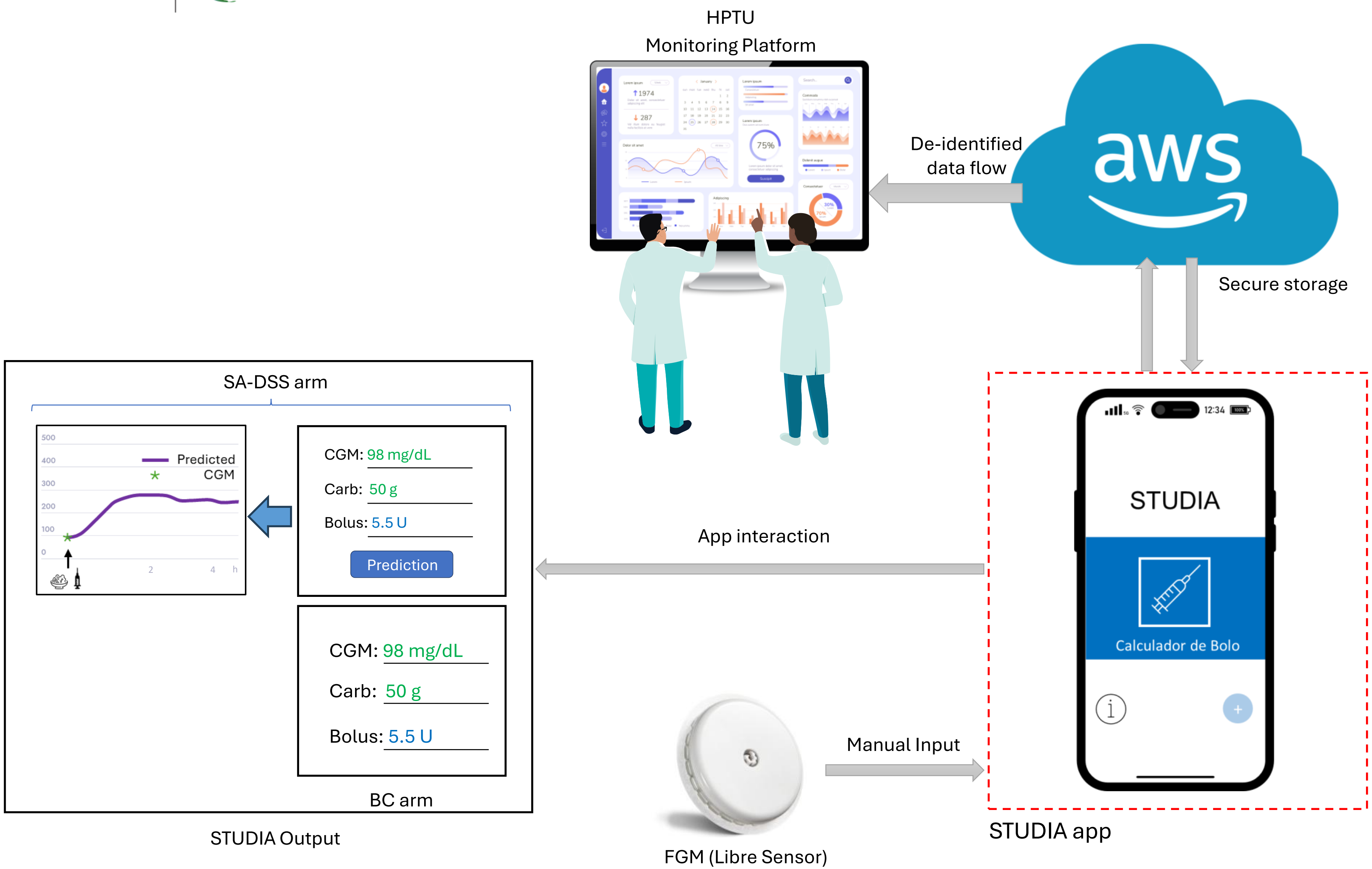
Several times per day, in the mind of a PwT1D:



1. Decide what to eat
2. Monitor the BG level
3. Estimate the carb content
4. Inject insulin as a function of 2. (CF) and 3. (CR)


Some studies have shown systematic estimation errors ~ 20%

# STUDIA App



HPTU
Monitoring Platform
De-identified
data flow
aws
Secure storage
SA-DSS arm
Predicted
CGM
CGM: 98 mg/dL
Carb: 50 g
Bolus: 5.5 U
Prediction
CGM: 98 mg/dL
Carb: 50 g
Bolus: 5.5 U
BC arm
STUDIA Output
App interaction
STUDIA
Calculador de Bolo
Manual Input
FGM (Libre Sensor)
STUDIA app

## Carb counting as a decision-making process

**Challenge**

Glucose will change with food

**A Simulation**

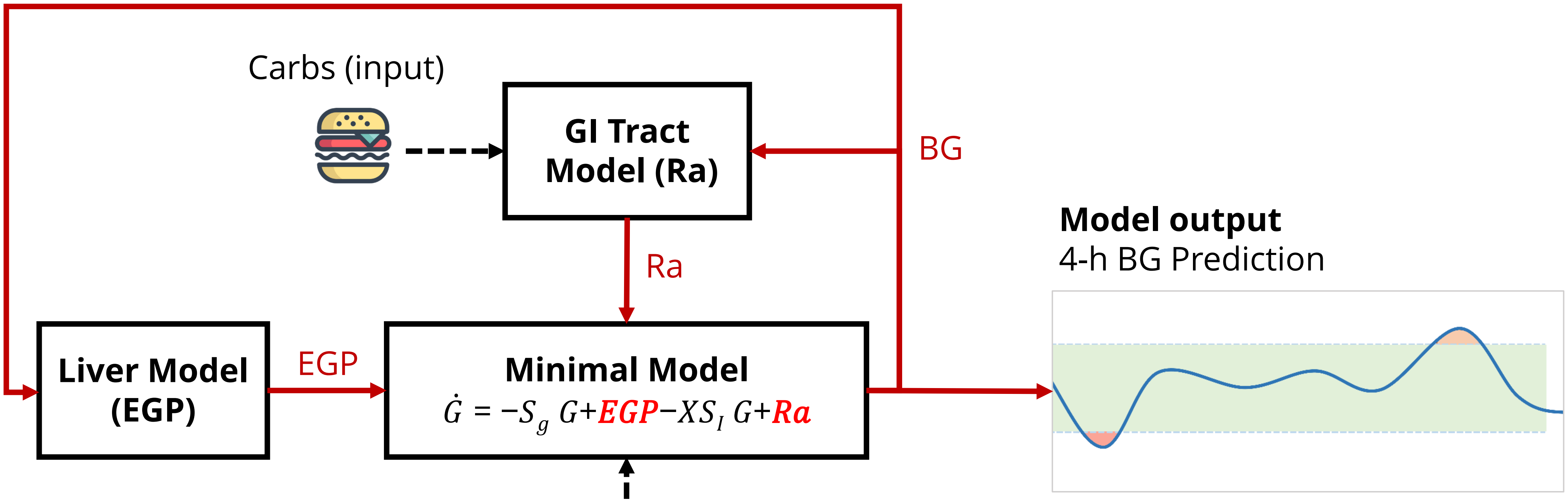
**=**

**What if?**

**Goal**

Keep glucose within the range

# The Model




**Inputs**
- CGM
- Bolus

**Parameters**
- Basal insulin
- BW
- CR, CF

1. Lema-Perez, L. et al., 2019. *Journal of theoretical biology*, *460*, pp.88-100.

2. Builes-Montaño, C.E.et al., 2022. *Computers in Biology and Medicine*, *142*, p.105232.

3. Lema-Perez, L., et al., 2023. *Plos one*, *18*(5), p.e0285849.

# The Study

ClinicalTrials.gov: NCT05181917

Randomized parallel-arm clinical trial

- age 18 – 70 years old, with T1D >1yr
- User of CGM

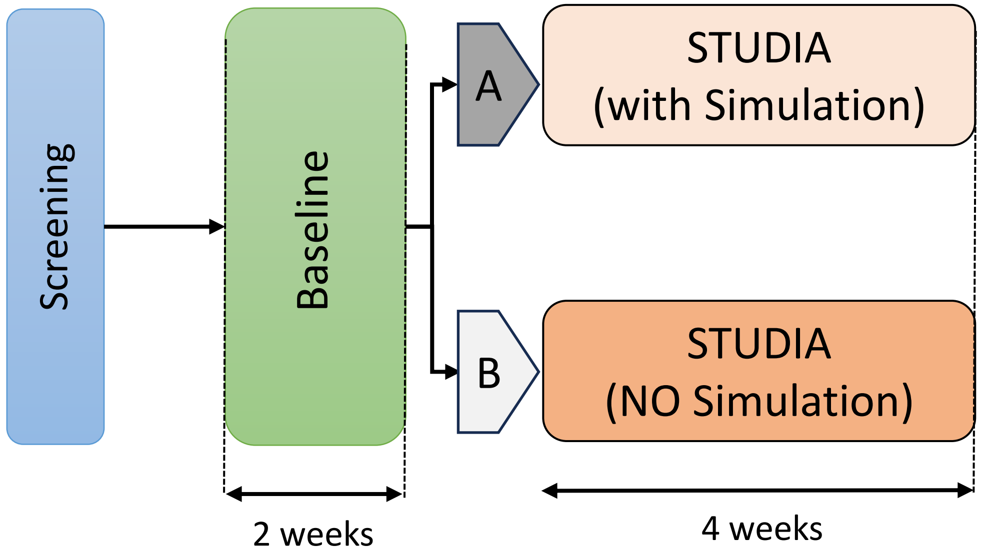
4 weeks data collection (home)

- CGM, insulin, carb estimation

Home portion (four weeks)

At every meal:

- Scan the sensor
- Enter the BG into the app
- Estimate carbs
- Run



# The Study

**Baseline characteristics**

| | Control (N=14) | STUDIA (N=14) |
|---|---|---|
| **Age** | 26.0 (23.0 - 42.5) | 39.5 (32.3 - 54.8) |
| **Sex** | | |
| **Female** | 8 (57.1) | 6 (42.9) |
| **Male** | 6 (42.9) | 8 (57.1) |
| **Timen in range** | 59.9 (20.8) | 63.4 (23.7) |
| **Time counting carbohydrates** | | |
| **Less than a year** | 1 (7.1%) | 2 (14.3) |
| **More than a year** | 13 (92.9%) | 12 (85.7) |
| **Education** | | |
| **Secondary** | 5 (35.7%) | 3 (21.4%) |
| **Post-Secondary** | 9 (64.3%) | 11 (78.6%) |
| **Insulin pump users** | 2 (14.28%) | 1 (7.14%) |
| **Glycated hemoglobin** | 7.29 (1.00) | 7.27 (0.873) |
| **Coefficient of variation** | 36.4 (32.8, 40.2) | 33.6 (28.4, 36.8) |
| **DTSQ** | 28.5 (26.3, 29.8) | 28.5 (23.3, 31.5) |

**Recruitment**

| Phase | # participants |
|---|---|
| Assessed | 68 |
| Withdrew (before) | 32 |
| Screen fail | 8 |
| Randomized | 28 |
| Dropped-off | 0 |
| Finished | 28 |

# Results

**Table 2. Primary and secondary outcomes***

| Outcome | Control (N=14) | STUDIA (N=14) | Estimated Adjusted Difference (95%CI) | P Value |
|---|---|---|---|---|
| **Change in TIR** | -3.71±12 | 7.93±11.3 | 6.95 (3.51 to 10.39) | **<0.001** |
| **Change in TBR level 1** | 1.93±2.89 | -1.64±2.10 | -1.10 (-2.20 to -0.20) | **0.022** |
| **Change in TBR level 2** | 0.71±0.80 | -0.28±0.56 | -0.11 (-0.39 to 0.17 | 0.422 |
| **Change in TAR level 1** | 1.43±13.3 | -3.93±13.6 | -3.21 (-7.67 to 1.25) | 0.396 |
| **Change in TAR level 2** | 2.61±2.5 | 1.78±1.68 | -1.01 (-3.03 to 1.0) | 0.303 |
| **Change in CV** | -1.09±3.4 | 0.0357±7.7 | 0.38 (-2.41 to 3.17) | 0.787 |

*Metrics are computed using all data from the scans.

# Results

We assessed the prediction ability of the model within the control group (the ones who were not 'persuaded' by simulations)

$$RMSE_j = \sqrt{\frac{\sum_{i=1}^{n}\left(\{y_i\}_j - \{\hat{y}_i\}_j\right)^2}{n}}$$

$y_i$: *i-th* CGM measurement

$\hat{y}_i$: *i-th* element of the model prediction

14 participants **(Control Group)**

**Total: 277 meals** → ~ 20 meals per person per 30 days → ~ 22% of the expected use

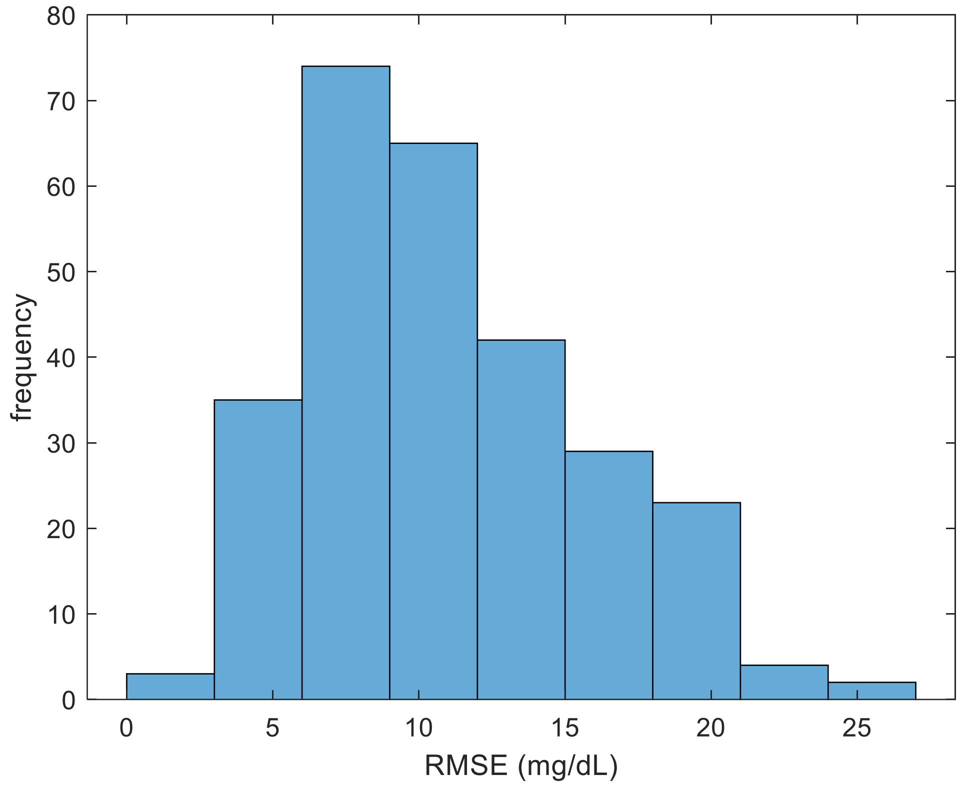
We selected for the analysis 10 participants: >50% of the expected use

# Results

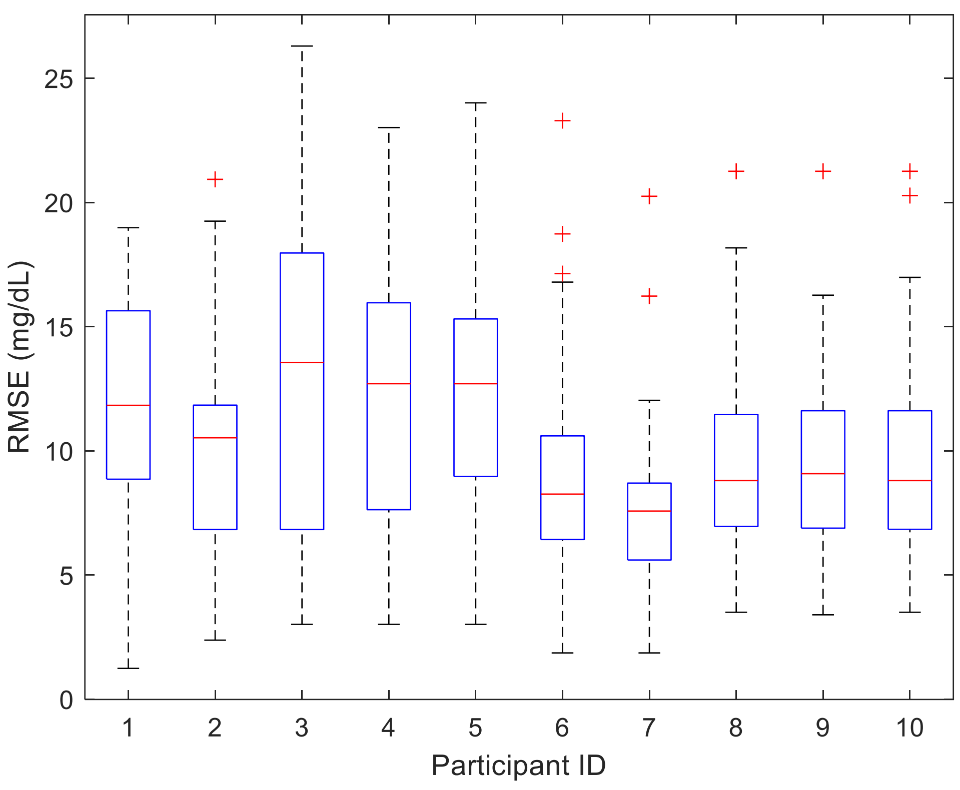
min(RMSE) = 1.24 mg/dL

max(RMSE) = 26.29 mg/dL

All the participants

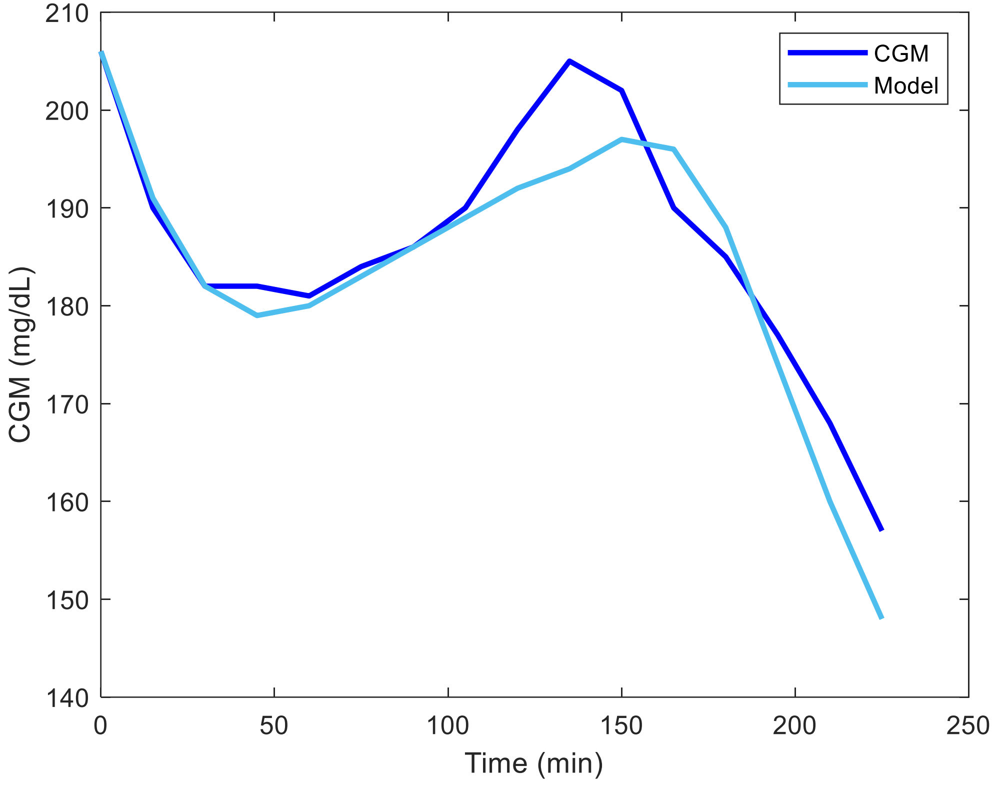



RMSE's Per Participant



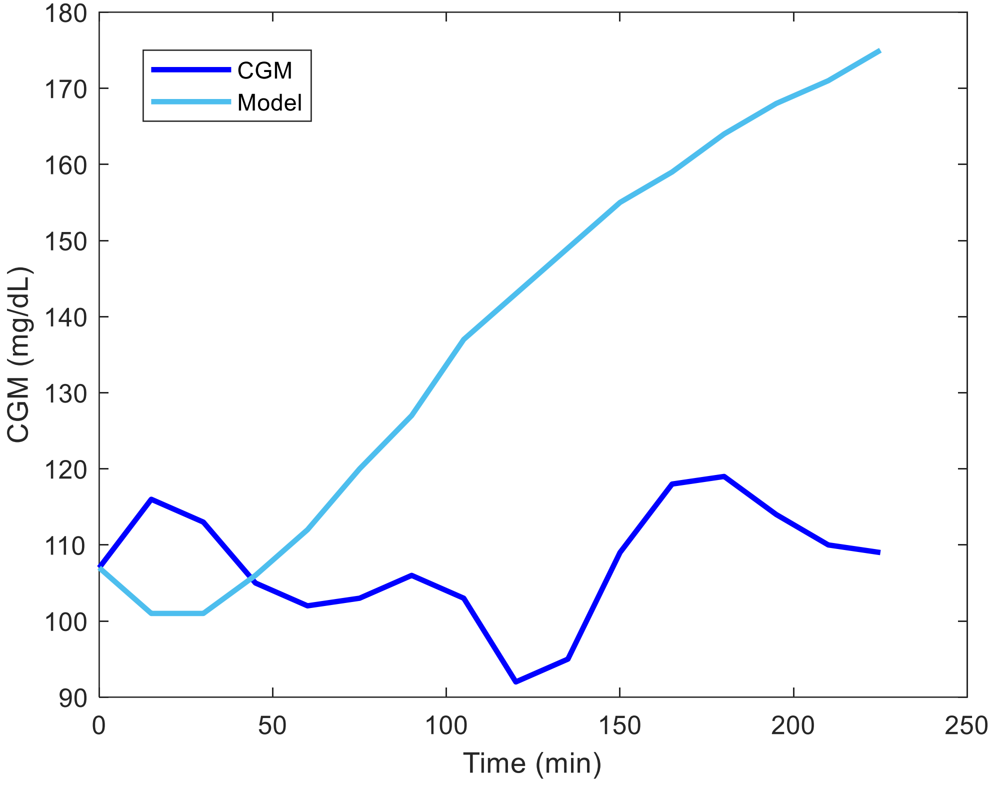
# Results

Best RMSE = 1.24 mg/dL




Participant 1

Worst RMSE: 26.29 mg/dL




Participant 3

# Discussion

- Simulation of meal scenarios appears as a promising tool for conscious decision-making

- Although most CTs using decision-support systems in T1D have shown marginal benefits, our approach reached a clinically significant increase in TIR in a suboptimally controlled population.

- Although simulation accuracy may seem not indispensable in this context, it has the potential to impact user trust

- We achieved an overall median RMSE of 10.5 mg/dL in 277 4-h predictions, which is on the lower side of what's typically observed from the literature 15-30 mg/dL (~2h predictions).

- Future work will include studies with rtCGM and a more established methodology for model calibration/validation

# Thanks!

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Laura Lema, PhD.

Hernan Alvarez, PhD.

Asociación Colombiana de Endocrinología (ACE)

The participants