A one-size-fits-all artificial pancreas for people with type 1 diabetes based on physiological insight and feedback control

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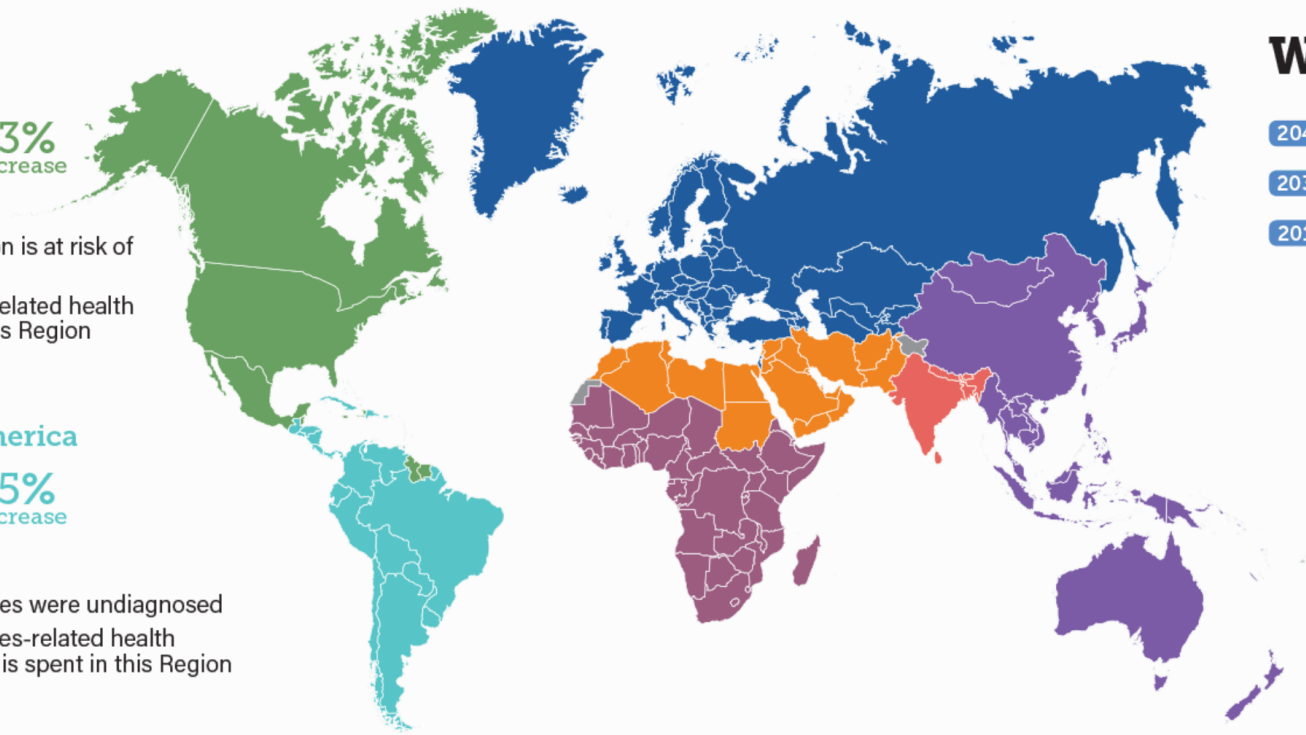
10:50 – 11:10, WeA5.4, June 14, 2023
European Control Conference, Bucharest, Romania

Diabetes in the World

Number of adults (20–79 years) with diabetes worldwide



North America & Caribbean

2045 63 million
2030 56 million
2019 48 million

↑ 33% increase

- 1 in 6 adults in this Region is at risk of type 2 diabetes
- 43% of global diabetes-related health expenditure occurs in this Region

South & Central America

2045 49 million
2030 40 million
2019 32 million

↑ 55% increase

- 2 in 5 people with diabetes were undiagnosed
- Only 9% of global diabetes-related health expenditure for diabetes is spent in this Region

WORLD

2045 700 million
2030 578 million
2019 463 million

↑ 51% increase

Europe

2045 68 million
2030 66 million
2019 59 million

↑ 15% increase

- 1 in 6 live births are affected by hyperglycaemia in pregnancy
- The Region has the highest number of children and adolescents (0–19 years) with type 1 diabetes – 297,000 in total

Africa

2045 47 million
2030 29 million
2019 19 million

↑ 143% increase

- 3 in 5 people with diabetes are undiagnosed
- 3 in 4 deaths due to diabetes were in people under the age of 60

Middle East & North Africa

2045 108 million
2030 76 million
2019 55 million

↑ 96% increase

- 1 in 8 people have diabetes
- 1 in 2 deaths due to diabetes were in people under the age of 60

South-East Asia

2045 153 million
2030 115 million
2019 88 million

↑ 74% increase

- 1 in 5 adults with diabetes lives in this Region
- 1 in 4 live births are affected by hyperglycaemia in pregnancy

Western Pacific

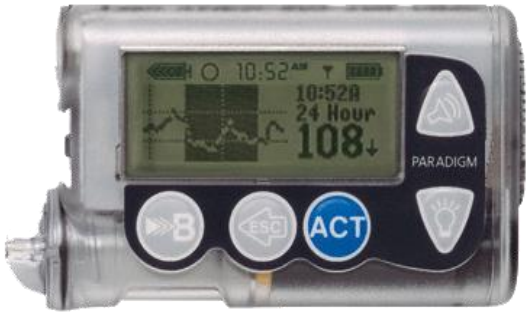
2045 212 million
2030 197 million
2019 163 million

↑ 31% increase

- 1 in 3 adults with diabetes lives in this Region
- 1 in 3 deaths due to diabetes occur in this Region

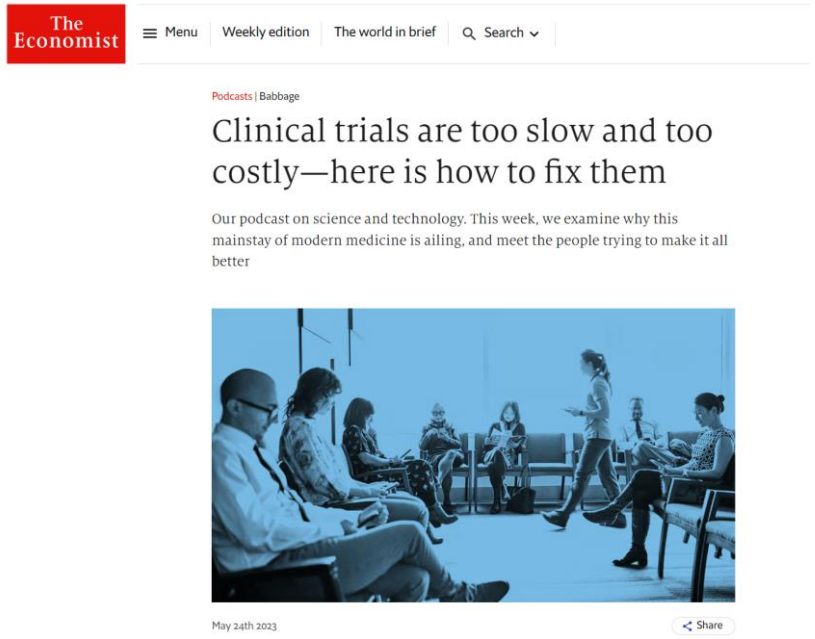
Insulin therapy

+



Objective:

- Develop <u>one</u> controller
- with <u>one</u> set of tuning parameters
- that works for many people ("one-size-fits-all")



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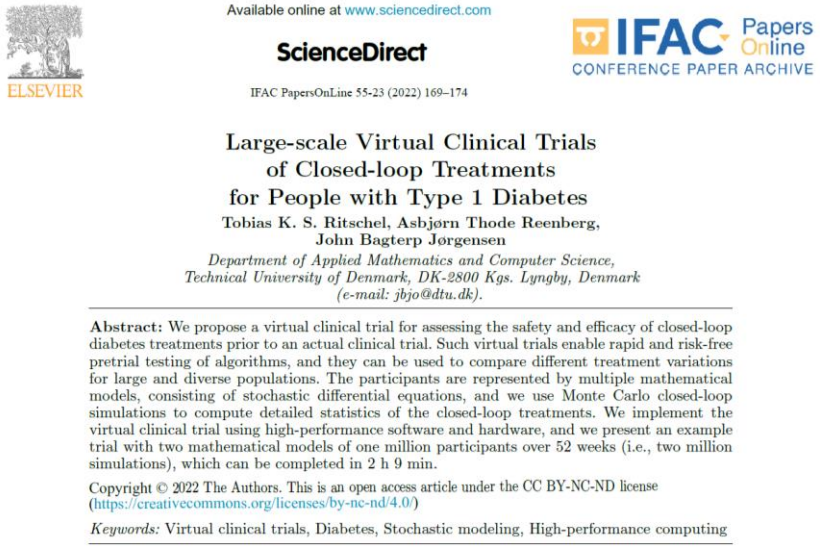

2022 American Control Conference (ACC)
Atlanta, USA, June 8-10, 2022

High-performance Uncertainty Quantification in Large-scale Virtual Clinical Trials of Closed-loop Diabetes Treatment

Asbjørn Thode Reenberg, Tobias K. S. Ritschel, Bernd Dammann, John Bagterp Jørgensen

Abstract— **In this paper, we propose a virtual clinical trial for assessing the performance and identifying risks in closed-loop diabetes treatments. Virtual clinical trials enable fast and risk-free tests of many treatment variations for large populations of fictive patients (represented by mathematical models). We use closed-loop Monte Carlo simulation, implemented in high-performance software and hardware, to quantify the uncertainty in treatment performance as well as to compare the performance in different scenarios or of different closed-loop treatments. Our software can be used for testing a wide variety of control strategies ranging from heuristical approaches to nonlinear model predictive control. We present an example of a virtual clinical trial with one million patients over 52 weeks, and we use high-performance software and hardware to conduct the virtual trial in 1 h and 22 min.**

mated closed-loop diabetes treatment systems. Such systems are referred to as artificial pancreases (APs), and they consist of 1) a continuous glucose monitor (CGM), 2) a control algorithm that determines the insulin dose, and 3) a pump which delivers the insulin to the patient (it is possible to use other hormones, e.g., glucagon or amylin, in addition to insulin). Many AP algorithms have been proposed and the majority is based on heuristics [3], proportional-integral-derivative (PID) control [4], fuzzy logic [5], linear model predictive control (MPC) [6]–[8], or nonlinear MPC [9], [10].

All AP algorithms contain hyperparameters, e.g., the gains in a PID controller, and performance assessment is essential to choosing suitable values for these. There exist both

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Large-scale Virtual Clinical Trials of Closed-loop Treatments for People with Type 1 Diabetes

Tobias K. S. Ritschel, Asbjørn Thode Reenberg, John Bagterp Jørgensen

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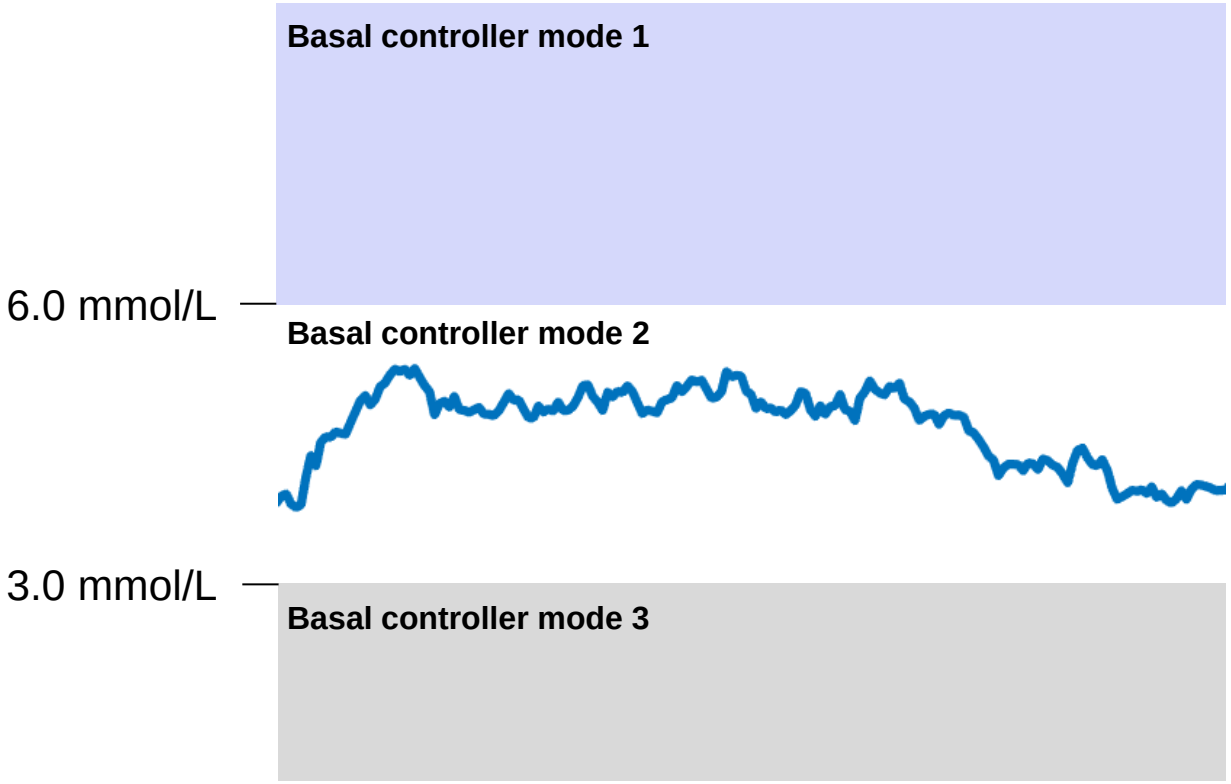
Abstract: We propose a virtual clinical trial for assessing the safety and efficacy of closed-loop diabetes treatments prior to an actual clinical trial. Such virtual trials enable rapid and risk-free pretrial testing of algorithms, and they can be used to compare different treatment variations for large and diverse populations. The participants are represented by multiple mathematical models, consisting of stochastic differential equations, and we use Monte Carlo closed-loop simulations to compute detailed statistics of the closed-loop treatments. We implement the virtual clinical trial using high-performance software and hardware, and we present an example trial with two mathematical models of one million participants over 52 weeks (i.e., two million simulations), which can be completed in 2 h 9 min.

Keywords: Virtual clinical trials, Diabetes, Stochastic modeling, High-performance computing

Basal rate

Basal rate



Estimated Microadjustments

$$u_{ba,k} = \bar{u}_{ba,k} + u_{ma,k}$$

$$u_{ba,k} = \bar{u}_{ba,k} + [u_{ma,k}]^- \qquad [\,\cdot\,]^- = \min\{0,\ \cdot\,\}$$

Only negative microadjustments

$$u_{ba,k} = 0$$

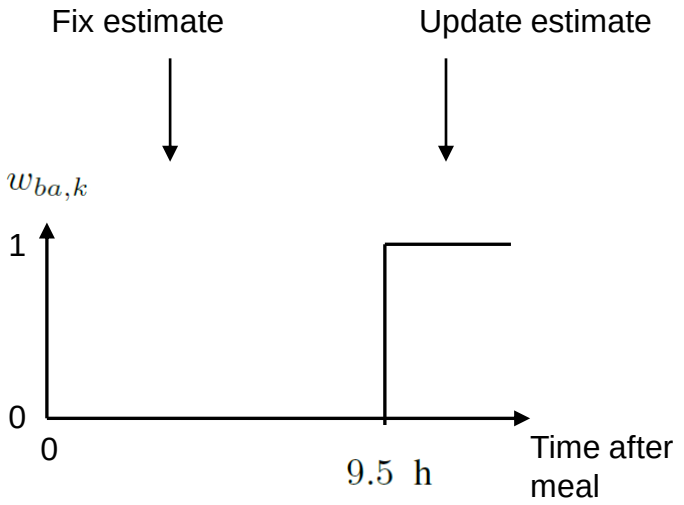
Estimated basal rate

Basal rate estimator

$$\bar{u}_{ba,k} = I_{ba,k} = \max\{0, I_{ba,k-1} + \Delta I_{ba,k}\}$$

$$\Delta I_{ba,k} = w_{ba,k} K_{I,ba} e_{ba,k} T_s$$

$$e_{ba,k} = \begin{cases} y_k - y^u_{ba} & \text{if } y_k > y^u_{ba}, \\ \gamma(y_k - y^\ell_{ba}) & \text{if } y_k < y^\ell_{ba}, \\ 0 & \text{otherwise.} \end{cases}$$



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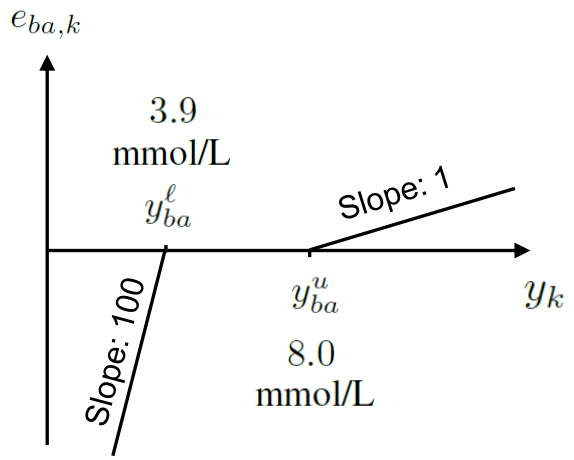


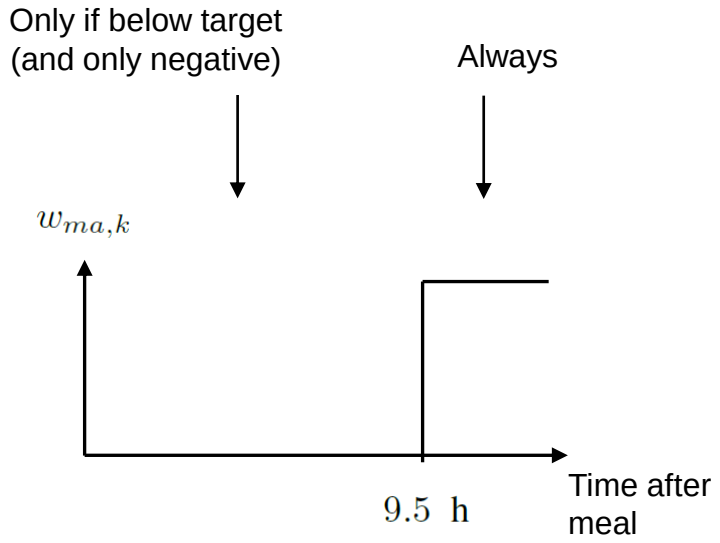
Microadjustments

Microadjustments

$$P_{ma,k} = w_{ma,k} K_{P,ma} e_k,$$

$$D_{ma,k} = w_{ma,k} K_{D,ma} \frac{y_k - y_{k-1}}{T_s}$$

$$e_k = y_k - \bar{y}$$



Bolus calculator

Optimal bolus calculator

Bolus optimization problem

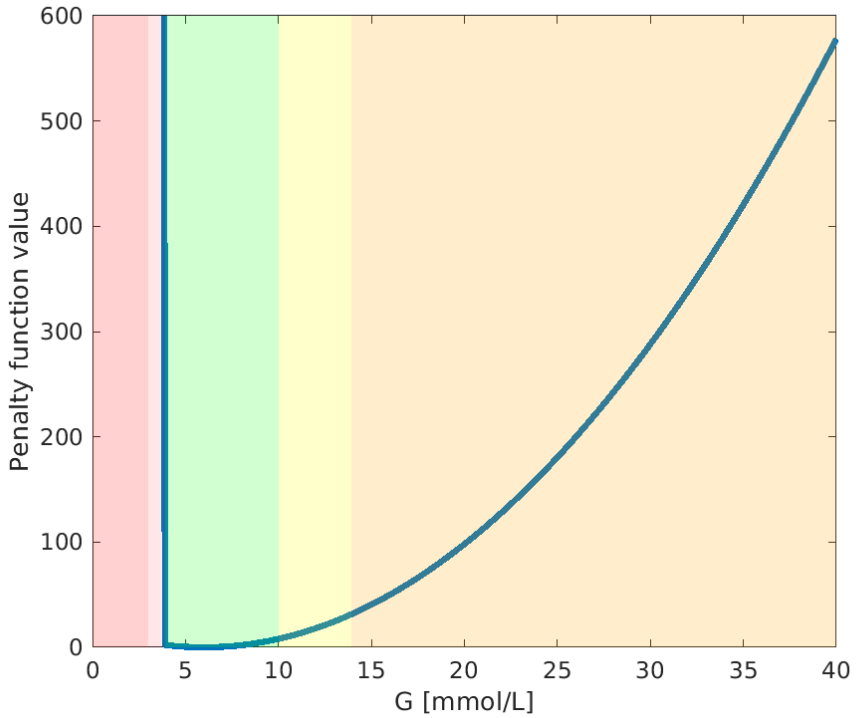
$$\min_{u_0} \quad \phi = \int_{t_0}^{t_f} \rho(z(t))\, dt,$$

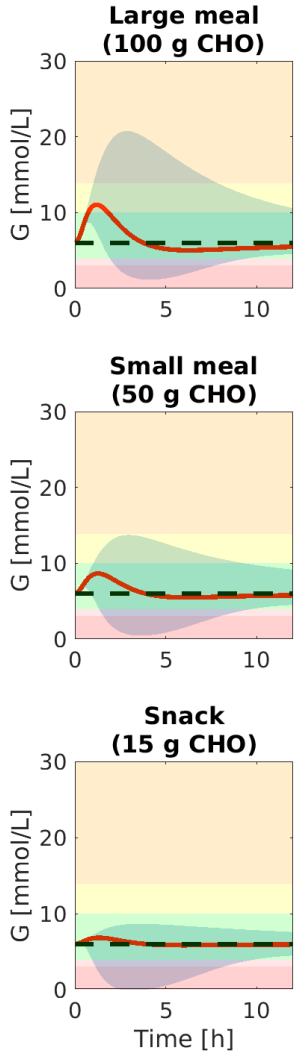
subject to

$$\begin{aligned}
x(t_0) &= x_0, \\
\dot{x}(t) &= f(x(t), u(t), d(t), \theta), \qquad t \in [t_0, t_f], \\
z(t) &= g(x(t), \theta), \qquad t \in [t_0, t_f], \\
u(t) &= u_k, \quad t \in [t_k, t_{k+1}[, \quad k = 0, \ldots, N-1, \\
d(t) &= d_k, \quad t \in [t_k, t_{k+1}[, \quad k = 0, \ldots, N-1, \\
u_{\min} &\leq u_0 \leq u_{\max}.
\end{aligned}$$

Objective function

$$\begin{aligned}
\rho(z(t)) &= \bar{\rho}(z(t)) + \kappa \rho_{\min}(z(t)), && \kappa = 10^6 \\
\bar{\rho}(z(t)) &= \frac{1}{2}(z(t) - \bar{z})^2, && \bar{z} = 6 \text{ mmol/L} \\
\rho_{\min}(z(t)) &= \frac{1}{2} \max\{0, z_{\min} - z(t)\}^2, && z_{\min} = 3.9 \text{ mmol/L}
\end{aligned}$$

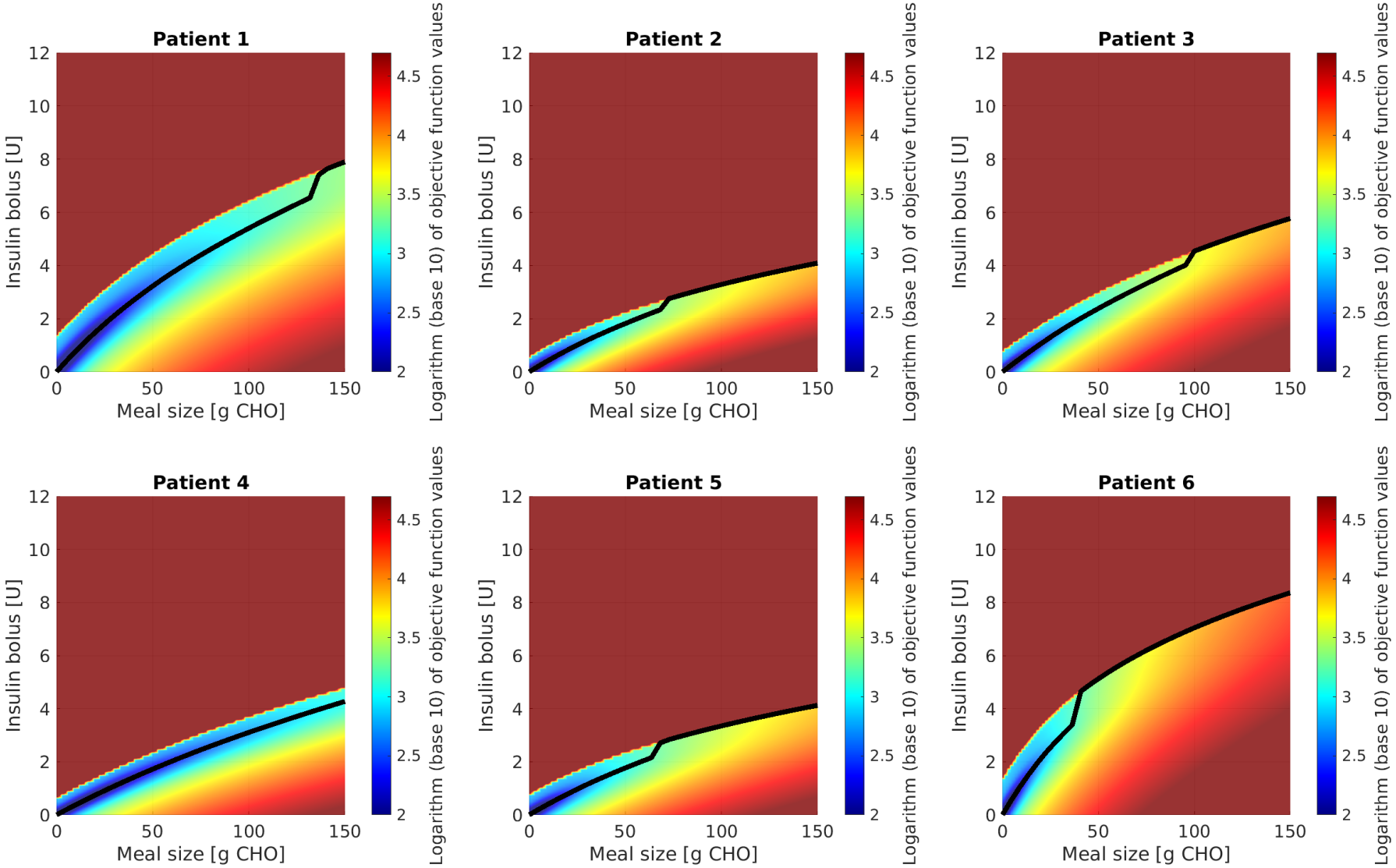


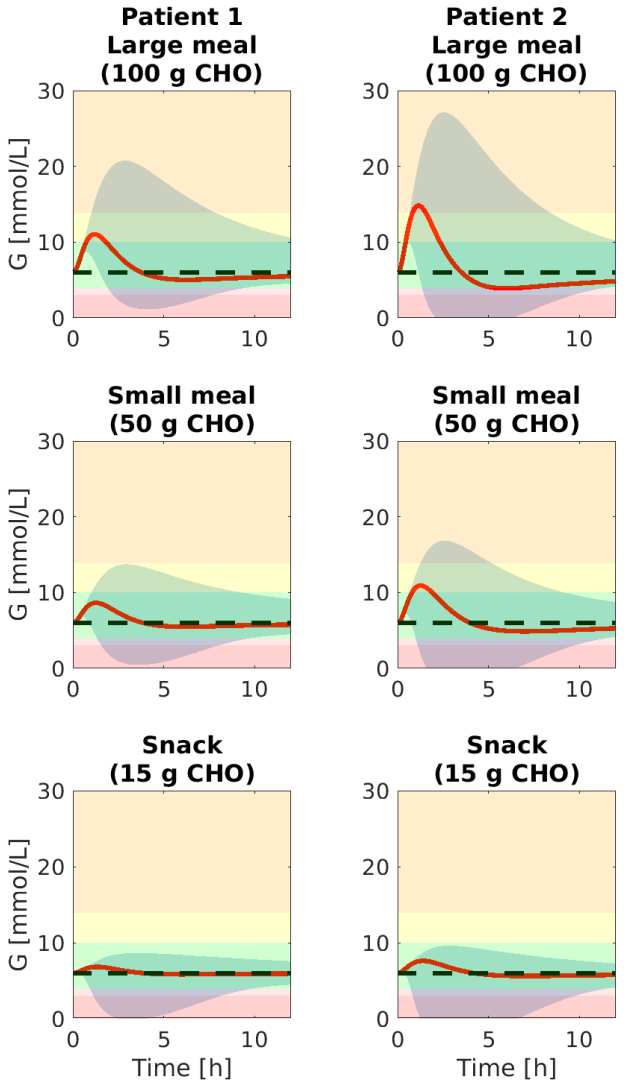


Glycemic ranges

Category	Range [mmol/L]	Color
Level 2 hyperglycemia	]13.9, ∞ [	Orange
Level 1 hyperglycemia	]10.0, 13.9]	Yellow
Normoglycemia	[3.9, 10.0]	Green
Level 1 hypoglycemia	[3.0, 3.9[	Light red
Level 2 hypoglycemia	[0.0, 3.0[	Red

Optimal bolus calculator





Suboptimal bolus calculator

Bolus estimator

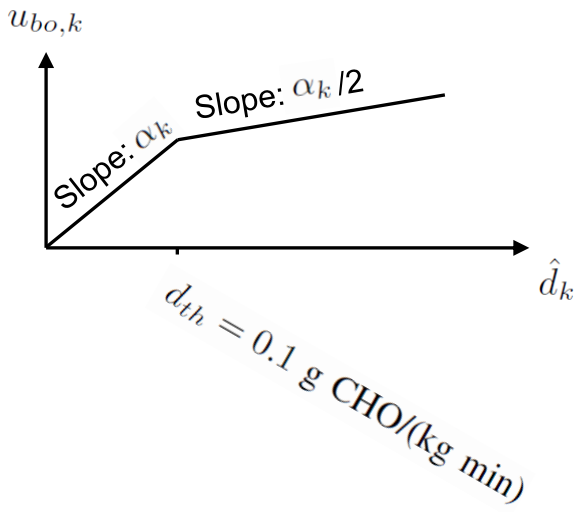
$$u_{bo,k} = \begin{cases} \alpha_k d_{th} + \frac{\alpha_k}{\beta}(\hat{d}_k - d_{th}) & \text{if } \hat{d}_k > d_{th}, \\ \alpha_k \hat{d}_k & \text{otherwise.} \end{cases}$$

$$\alpha_k = I_{bo,k} = \max\{0, I_{bo,k-1} + \Delta I_{bo,k}\}$$

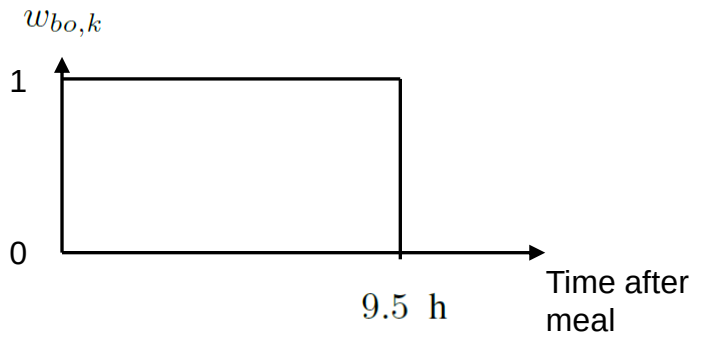
$$\Delta I_{bo,k} = w_{bo,k} K_{I,bo} e_{bo,k} T_s$$

$$e_{bo,k} = \begin{cases} y^{th}_{bo} - y^{u}_{bo} & \text{if } y_k > y^{th}_{bo}, \\ y_k - y^{u}_{bo} & \text{if } y_k \in [y^{u}_{bo}, y^{th}_{bo}], \\ \gamma(y_k - y^{\ell}_{bo}) & \text{if } y_k < y^{\ell}_{bo}, \\ 0 & \text{otherwise.} \end{cases}$$

Bolus curve



Update estimate



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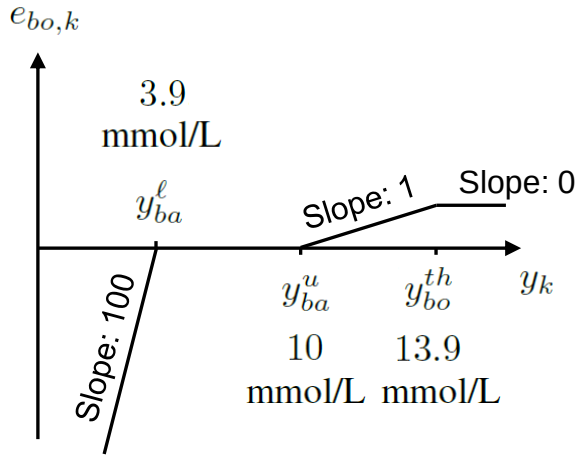


Numerical results

Simulation scenario

Compositions of the seasons

Season	Standard weeks	Active weeks	Vacation weeks
Winter	6	4	3
Spring	6	6	1
Summer	7	3	3
Autumn	9	3	1

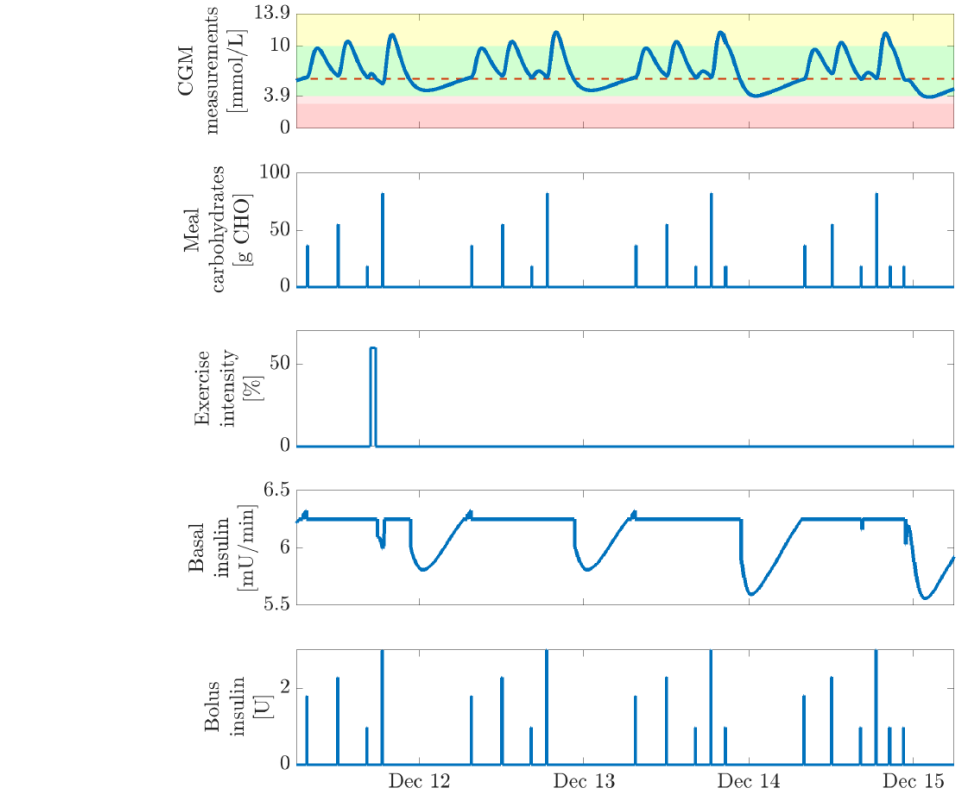
Compositions of the weeks

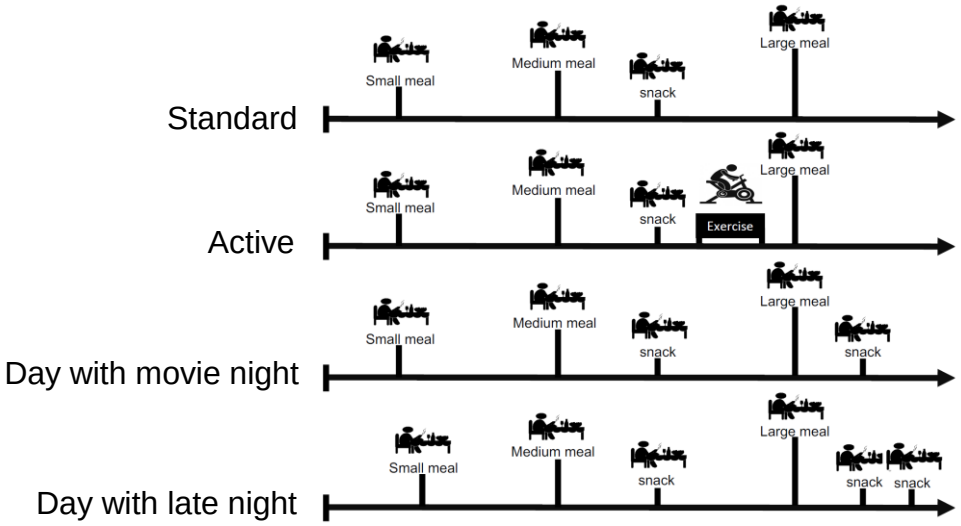
Week type	Standard days	Active days	Movie nights	Late nights
Standard	4	1	1	1
Active	3	3	1	0
Vacation	5	0	0	2

Bodyweight-dependent meal carbohydrate contents

Meal size	Amount of carbohydrates	For a 70 kg person
Large meal	1.29 g CHO/kg	90 g CHO
Medium meal	0.86 g CHO/kg	60 g CHO
Small meal	0.57 g CHO/kg	40 g CHO
Snack	0.29 g CHO/kg	20 g CHO

- We replace parameter sets where any time constant is more than 1 order of magnitude smaller or larger than the mean



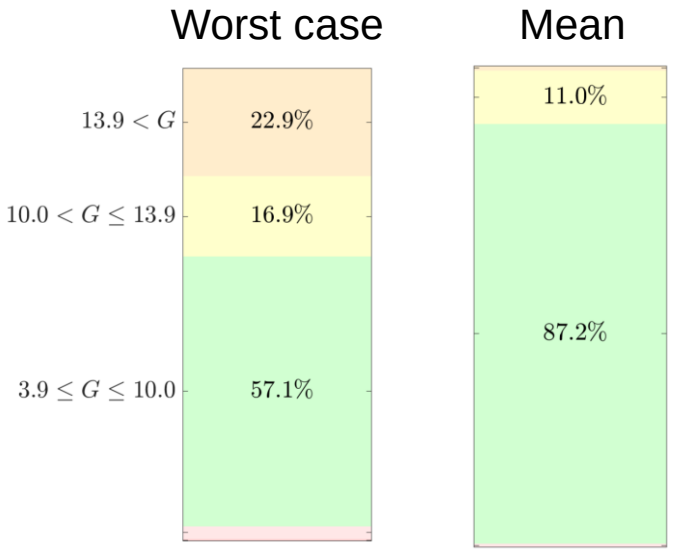


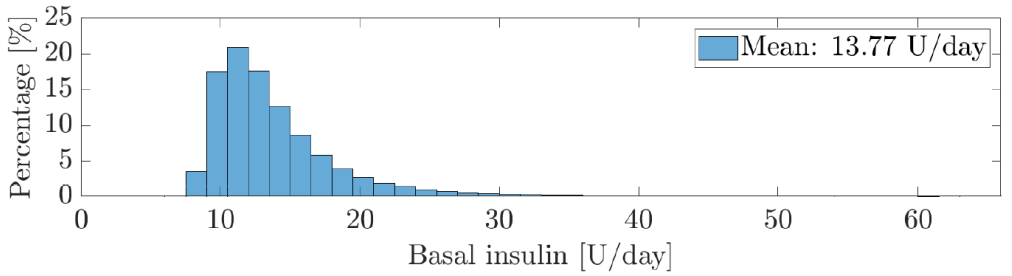
Ritschel, T.K.S., Reenberg, A.T., Jørgensen, J.B., 2022. Large-scale Virtual Clinical Trials of Closed-loop Treatments for People with Type 1 Diabetes. IFAC-PapersOnLine 55(23), pp. 169–174. arXiv: 2205.01332. DOI: 10.1016/j.ifacol.2023.01.037.

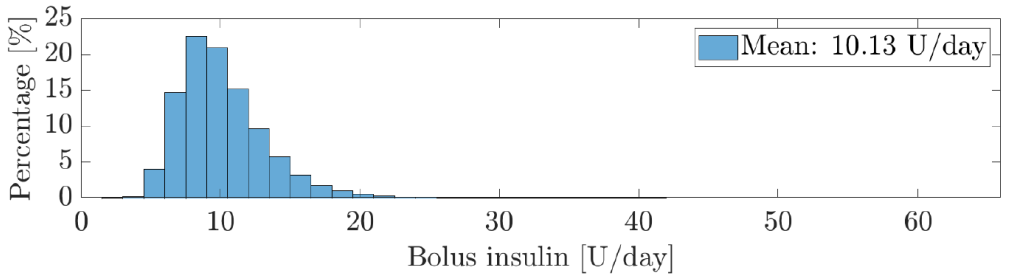
Reenberg, A.T., **Ritschel, T.K.S.**, Dammann, B., Jørgensen, J.B., 2022. High-performance Uncertainty Quantification in Large-scale Virtual Clinical Trials of Closed-loop Diabetes Treatment. **In:** Proceedings of the 2022 American Control Conference (ACC), pp. 1367–1372, Atlanta, Georgia, USA, June 8-10. arXiv: 2202.13927. DOI: ACC53348.2022.9867234.

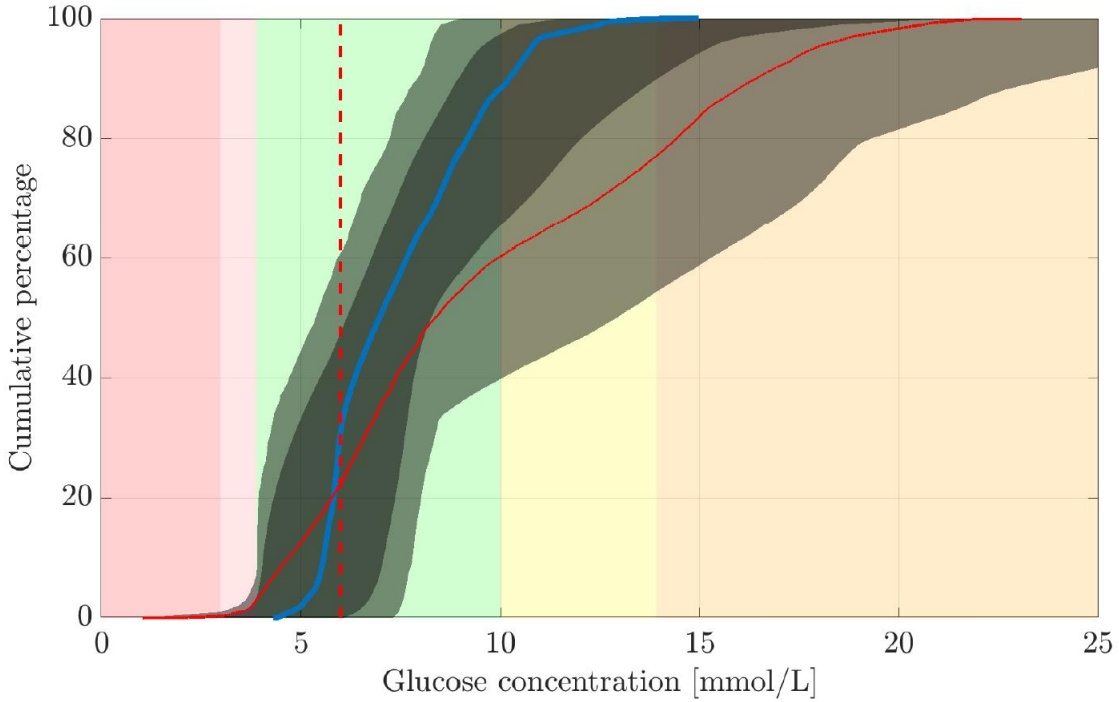
Results

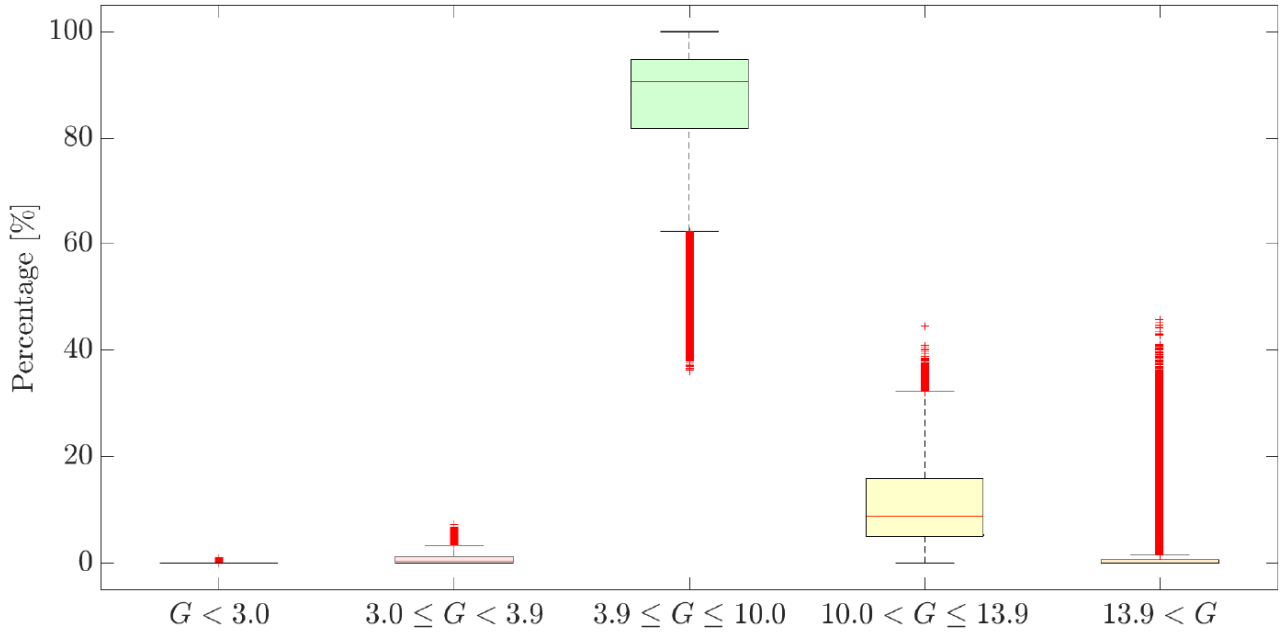
- 1 million participants
- 52-week simulation
- Results based on last 48 weeks (no initial guess for alpha/ICR)
- Time step size: 30 s







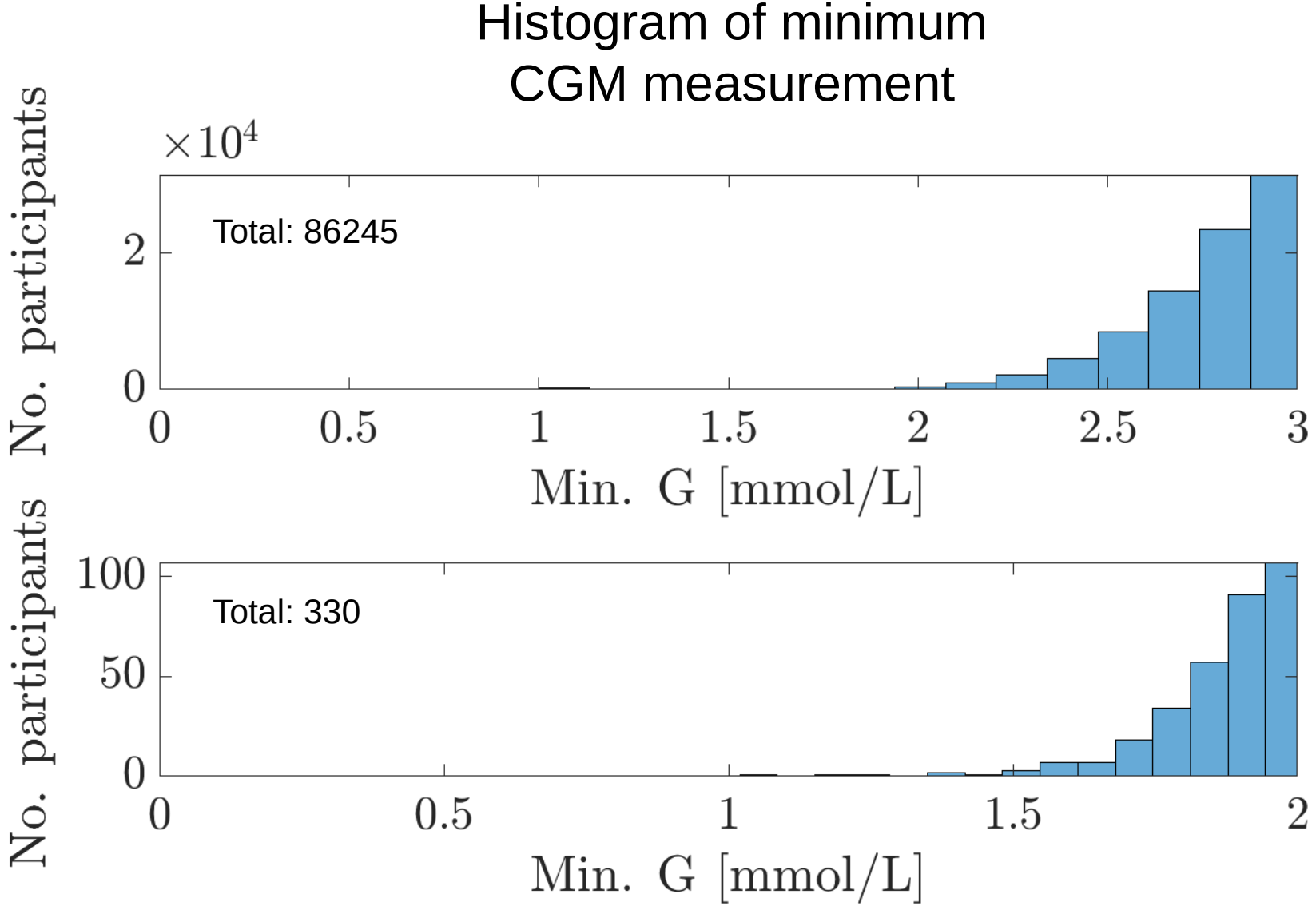




Results

Quantity	Target	Satisfied
Average glucose	< 154 mg/dL	97.69%
GMI	$< 7\%$	97.77%
GV	$\leq 36\%$	82.70%
TAR (level 2 hyperglycemia)	$< 5\%$	93.97%
TAR (level 1 and 2 hyperglycemia)	$< 25\%$	89.06%
TIR (normoglycemia)	$> 70\%$	92.19%
TBR (level 1 and 2 hypoglycemia)	$< 4\%$	98.85%
TBR (level 2 hypoglycemia)	$< 1\%$	100.00%
All TAR, TIR, and TBR targets		88.92%
All targets except the GV target		88.87%
All targets		81.70%

Results


Histogram of minimum CGM measurement
No. participants
×10^4
Total: 86245
0
2
0
0.5
1
1.5
2
2.5
3
Min. G [mmol/L]
No. participants
Total: 330
100
50
0
0
0.5
1
1.5
2
Min. G [mmol/L]

Summary

One controller with one tuning
physiological insight + PID concepts

Tested and developed
in large-scale virtual clinical trial
Computation time: 1 – 2 hours

~89% of 1 mil. satisfy average glucose,
GMI, TAR, TIR, and TBR targets

Thank you