Optimal Continuous Glucose Monitoring Sensor Calibration for Patients with Type 1 Diabetes

Xiaoran Zhang[1], Wan Zhang[2], Yongtong Cao[2], Dawei Shi[1,*], Shi Ling[3]

[1] School of Automation, Beijing Institute of Technology

[2] Clinical Laboratory, China-Japan Friendship Hospital

[3] Department of Electronic and Computer Engineering, HKUST

[*] Corresponding author

北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

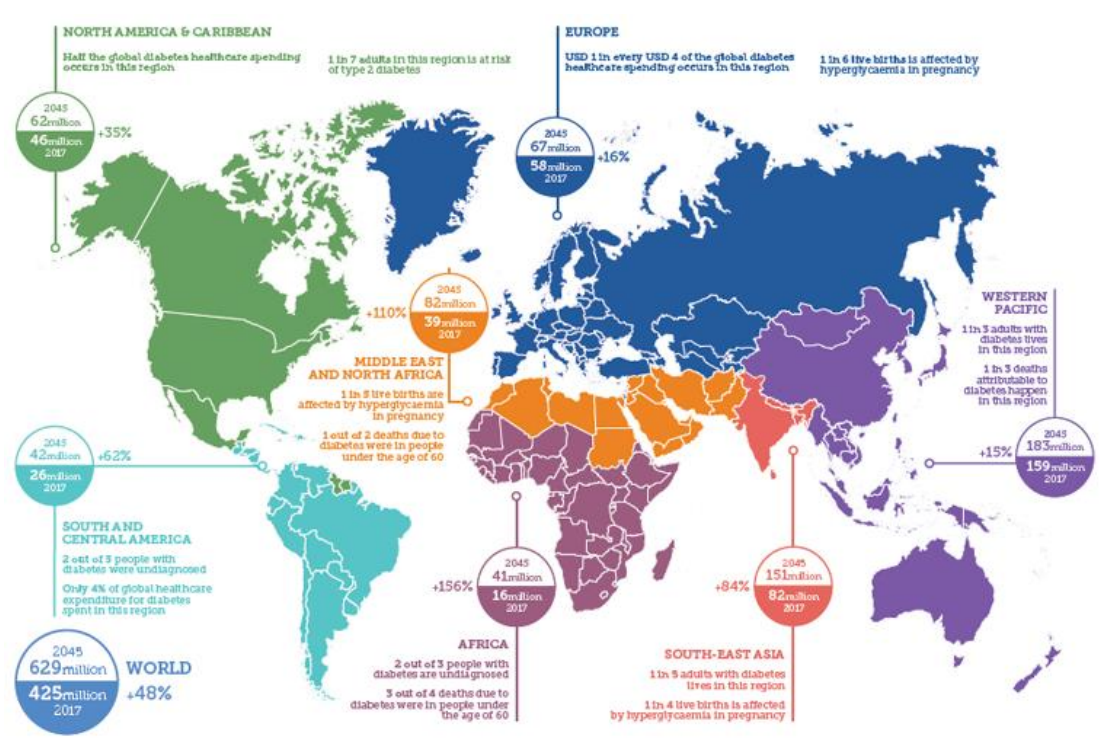
中日友好医院
CHINA-JAPAN FRIENDSHIP HOSPITAL

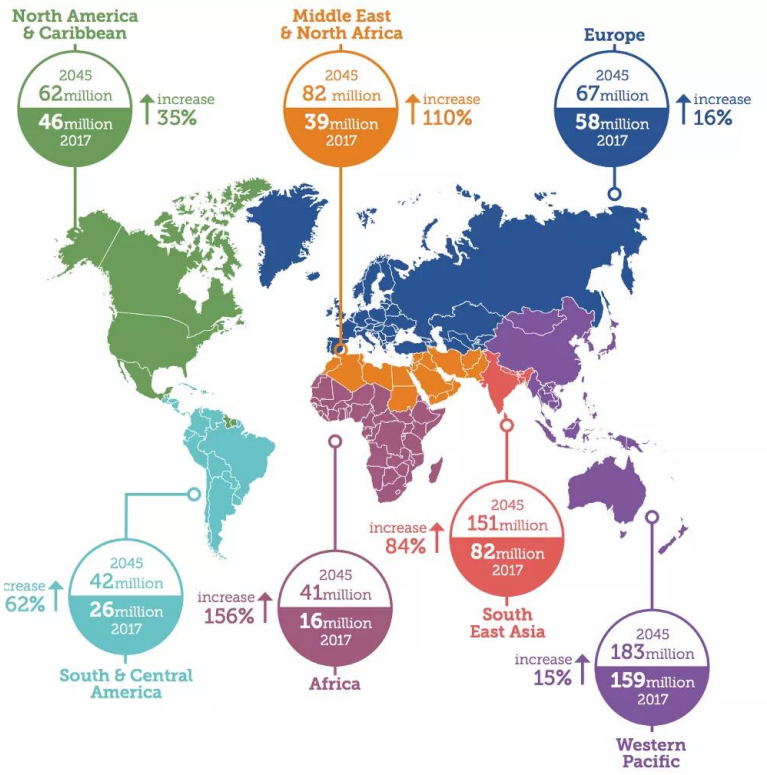
HKUST

1. Background

北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

- **Diabetes is one of the four major chronical diseases in the world with severe complications such as cardiovascular disease and chronic kidney disease.**
- **The World Health Organization (WHO) reports there are more than 400 million adults who are suffering from diabetes**





It is urgent to improve the blood glucose management technology for diabetic patients

2. Objective

北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

Blood Glucose Measuring Approach

Self Monitoring Blood Glucose(SMBG) requires finger prick measurement

Continuous Glucose Monitoring（CGM）

Environmental noise corruption → **Periodic calibration** → **Increase patient discomfort**

Reducing calibration frequency with undiminished accuracy is of great importance

3. Introduction

Guerra et al, **IEEE Trans. Biomed. Eng.,** 2012.

Enhance the calibration signal and possibility to reduce finger prick frequency

F. Barcelo et al, **Diabetes Technol. Ther.,** 2012.

Considered plasma glucose as a static value by ignoring BG-IG dynamics

Acciaroli et al, **Diabetes Technol. Ther.,** 2016.

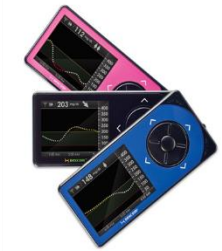
Reduced finger prick frequency but only valid for a limited time interval

Acciaroli et al, **IEEE Trans. Biomed. Eng.,** 2018.

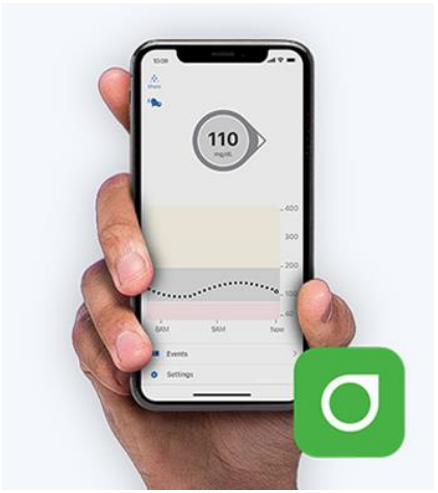
Successfully reduced the finger prick frequency but deconvolution approach is complex

北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Calibration Model



Dexcom G4 Platinum Subcutaneous Sensor



Calibration Model

$$y_i(t) = [u_i(t) + b] \cdot s(t) + v(t)$$

BG-IG Model

$$\tau \frac{d}{dt} u_i(t) = -u_i(t) + u_b(t) + w(t)$$

Time Constant

$$\tau = \frac{1}{k_{02} + k_{12}}$$

Sensitivity Model

$$s(t) = s_1 \alpha(t) + s_2 \beta(t) + s_3$$

Estimation Parameter

$$p = [s_2, s_3, b]$$

北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Dynamic Blood Glucose Model and Discretization

$$\dot{u}_i(t) = -\frac{1}{\tau}u_i(t) + \frac{1}{\tau}u_b(t)$$

$$y_i(t) = s(t)u_i(t) + bs(t) + w(t)$$

Dynamic Blood Glucose Model

$$H(T) = A^{-1}\int_0^T Ae^{A\lambda}d\lambda B = A^{-1}e^{A\lambda}\Big|_{\lambda=0}^{T} B$$

$$= A^{-1}(e^{AT} - I)B = (e^{AT} - I)BA^{-1}$$

$$G(T) = e^{AT}$$

Discretization Model

$$\dot{x}(t) = Ax(t) + Bu(t)$$

$$y(t) = Cx(t) + Du(t)$$

Continuous Dynamic Blood Glucose Model

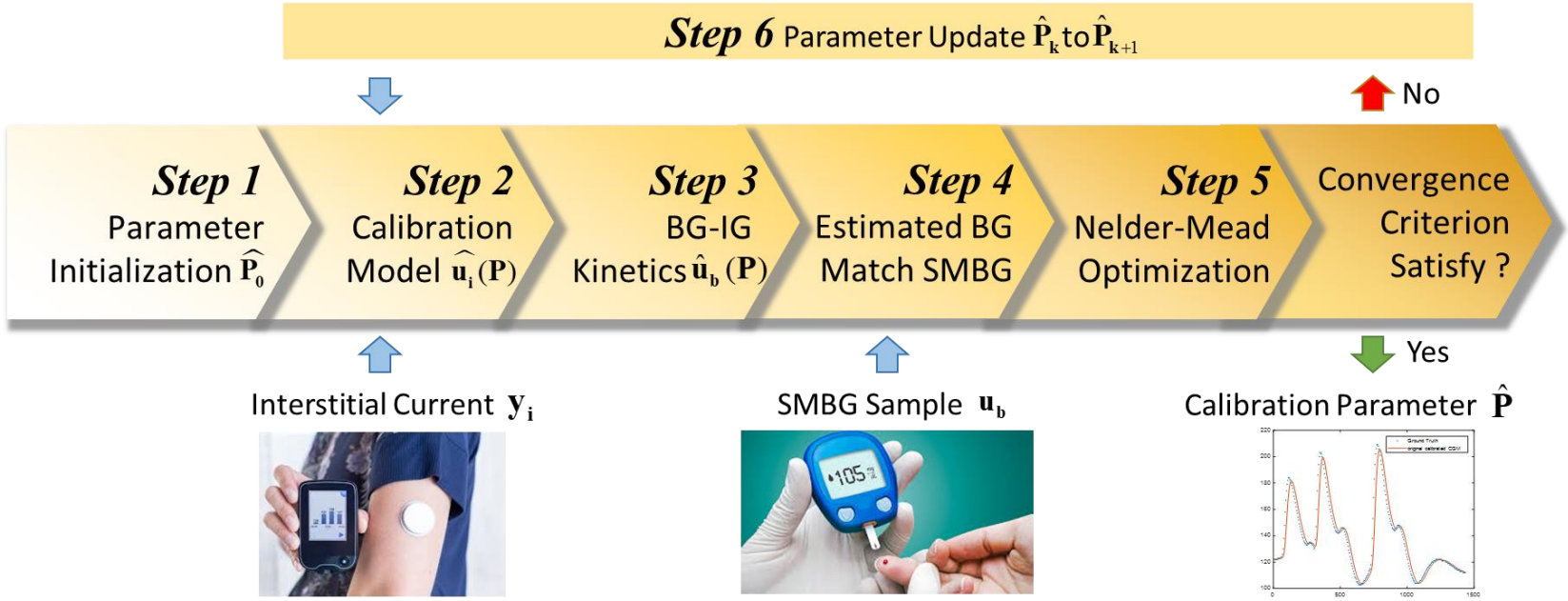
$$x_{k+1} = Gx_k + Hu_{b,k} + w_k$$

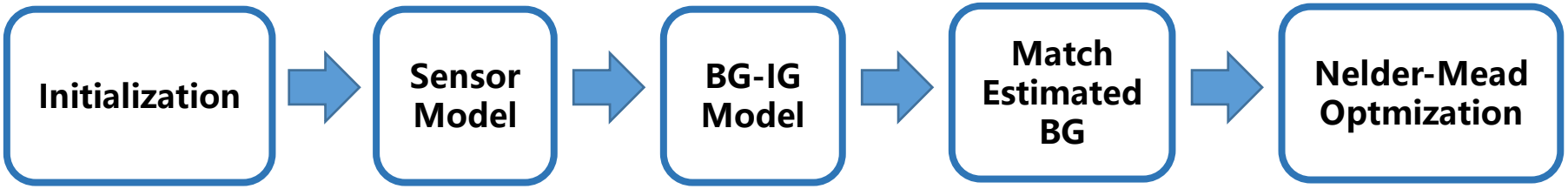
$$y_k = C_k x_k + Du_{b,k} + v_k$$

Discretized Dynamic Blood Glucose Model

北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Algorithm





北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Blood Glucose to Interstitial Glucose Model

Major Challenge

BG-IG model may indicate a complex time relation when given IG profiles inducted by electric current to infer corresponding BG value

Unknown Input Observer

Unknown Input Update: $\hat{u}_{b,k-1} = M_k (y_k - C_k \hat{x}_{k|k-1})$

Time Update: $\hat{x}_{k|k-1} = A\hat{x}_{k-1|k-1} \quad x^*_{k|k} = \hat{x}_{k|k-1} + B\hat{d}_{k-1}$

Measurement Update: $\hat{x}_{k|k} = x^*_{k|k} + K_k (y_k - c_k x^*_{k|k})$

Yong et al, **Automatica,** 2016.

北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Theorem 1

When given state-space representation of glucose model and measurement information $\{y_1 y_2, \ldots, y_k\}$, the estimate of unknown input $\hat{u}_{b,k}$ and state variable $x_{k+1|k+1}$ at time step k

$$\hat{u}_{b,k} = \frac{1}{C_{k+1}B}\left(y_{k+1} - C_{k+1}\frac{Ay_k}{C_k}\right) \qquad x_{k|k} = \frac{y_k}{C_k}$$

Proof:

Base case: when k=1:

$$\hat{u}_{b,1} = M_2(y_2 - c_2\hat{x}_{2|1}) = \frac{1}{C_2 B}\left(y_2 - C_2\frac{Ay_1}{C_1}\right) \qquad x_{2|2} = \hat{x}^*_{2|2} + K_2(y_2 - C_2\hat{x}^*_{2|2}) = \frac{y_2}{C_2}$$

The theorem holds when k=1

Inductive step: from k to k+1

$$u_{b,k+1} = M_{k+1}(y_{k+1} - C_{k+2}x_{k+1|k}) = \frac{1}{C_{k+2}B}\left(y_{k+2} - C_{k+2}\frac{Ay_{k+1}}{C_{k+1}}\right) \qquad x_{k+1|k+1} = x^*_{k+1|k+1} + K_{k+1}(y_{k+1} - C_{k+1}x^*_{k+1|k+1}) = \frac{y_{k+1}}{C_{k+1}}$$

As a result, theorem 1 holds true.

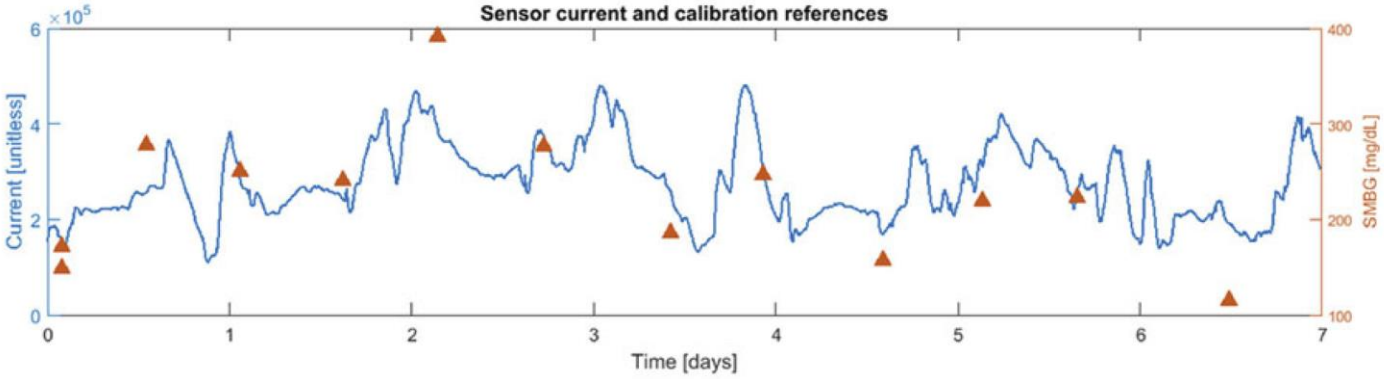
Estimated glucose profile at time k only correlates with interstitial glucose profile at time k and k+1

北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

Match estimated glucose profile

$$\hat{u}_{b,k}(p_k) = [\hat{u}_b(t_1, p_k), \hat{u}_b(t_2, p_k), \ldots, \hat{u}_b(t_k, p_k)]^T$$

We match our estimated glucose profile with SMBG (self-monitoring blood glucose system) sampled patients blood glucose in time axis



Nelder-Mead simplex optimization

$$P = \arg\min_{p_i}\{\frac{1}{N}\sum_{k=1}^{N}(u_{b,k} - u_{b,k}(p_i))^2 + \lambda p_i^T p_i\}$$

北京理工大學 BEIJING INSTITUTE OF TECHNOLOGY

Evaluation metrics

Mean absolute relative deviation (MARD):

$$MARD = \frac{1}{n}\sum_{k=1}^{n}\frac{|z_k - x_k|}{x_k} \times 100\%$$

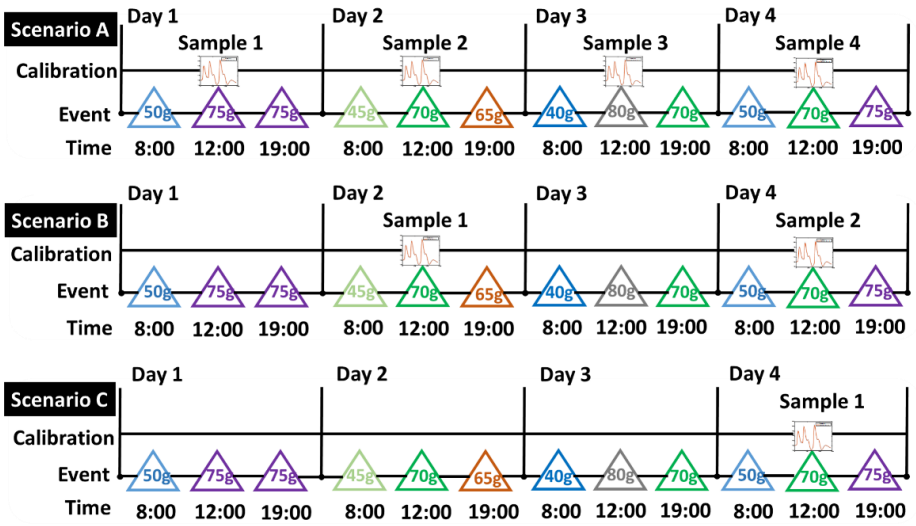
Percentage of accurate glucose estimators (PAGE):

$$d_k = \begin{cases} |x_k - z_k|, & if\ x_k \le 80\dfrac{mg}{dL} \\ \dfrac{|x_k - z_k|}{x_k}, & if\ x_k > 80\dfrac{mg}{dL} \end{cases}$$

Clark error grid lying on "A" zone (CEGA-A):

The CEGA-A approach is used to assess the clinical significance of differences between the glucose measurement technique under test and the venuous blood glucose reference measurements

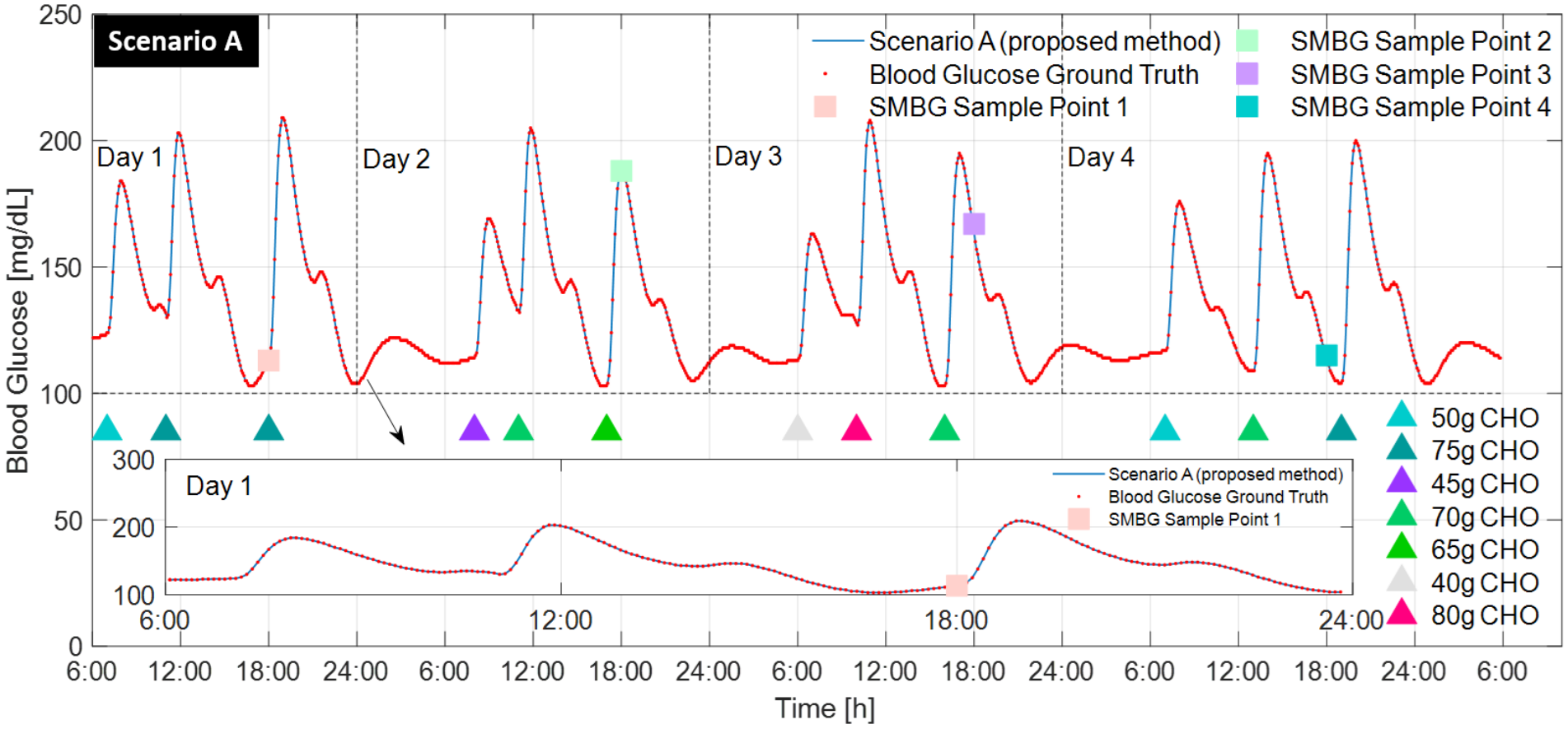
Calibration Scenarios



Scenario A: 1 cal/1 day
Scenario B: 1 cal/2 days
Scenario C: 1 cal/4 days

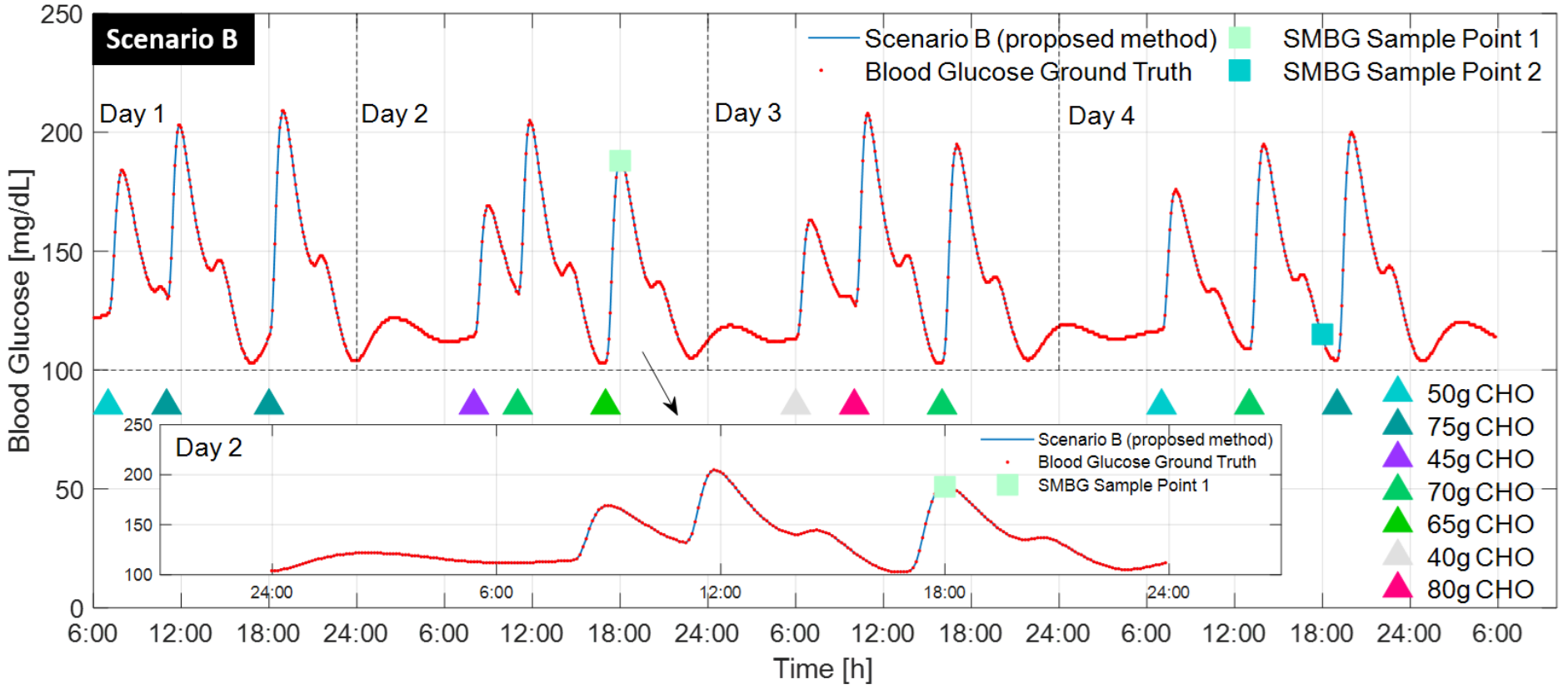
北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

Scenario A: 1 cal/1 day



北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

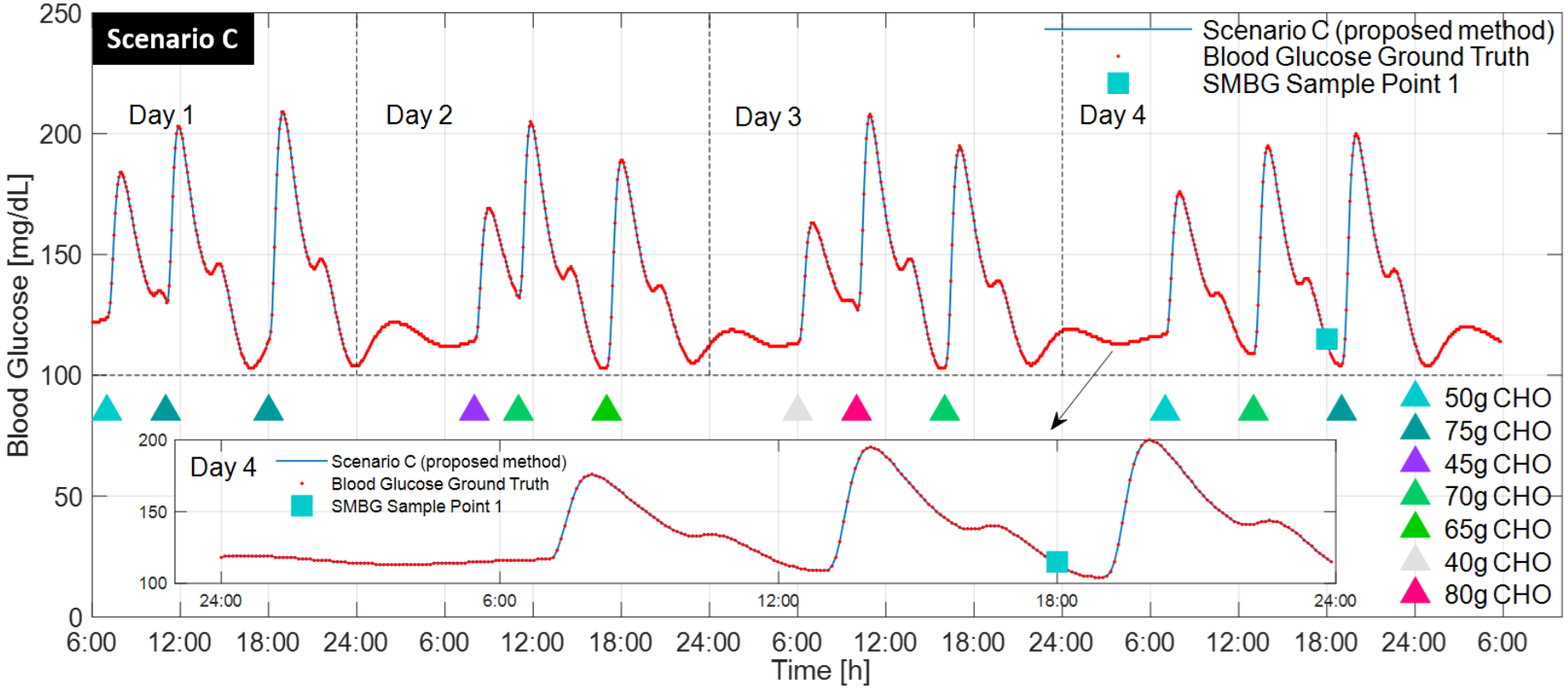
Scenario B: 1 cal/2 days



5. In Silico

北京理工大學
BEIJING INSTITUTE OF TECHNOLOGY

Scenario C: 1 cal/4 days



Evaluation Metrics

Evaluation Metrics	Original Calibration	Scenario A (1 cal/day)	Scenario B (2 cal/day)	Scenario C (3 cal/day)
MARD (%)	3.39	0.1	0.11	0.11
PAGE (%)	94.6	100	100	100
CEGA-A (%)	98.9	100	100	100

The calibration algorithm reaches satisfying frequency and accuracy

Thanks