Modeling Nonlinear Insulin-Glucose Dynamics in Critically-ill Patients

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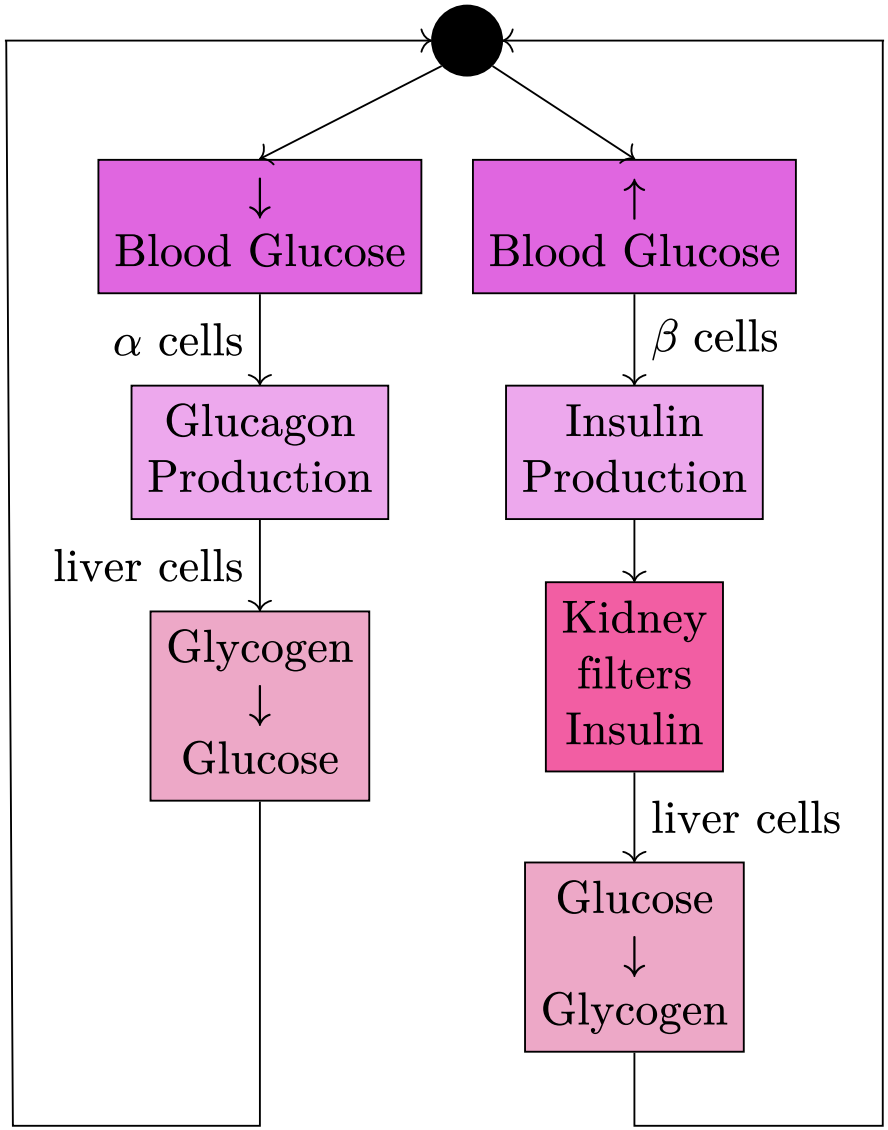
Outline

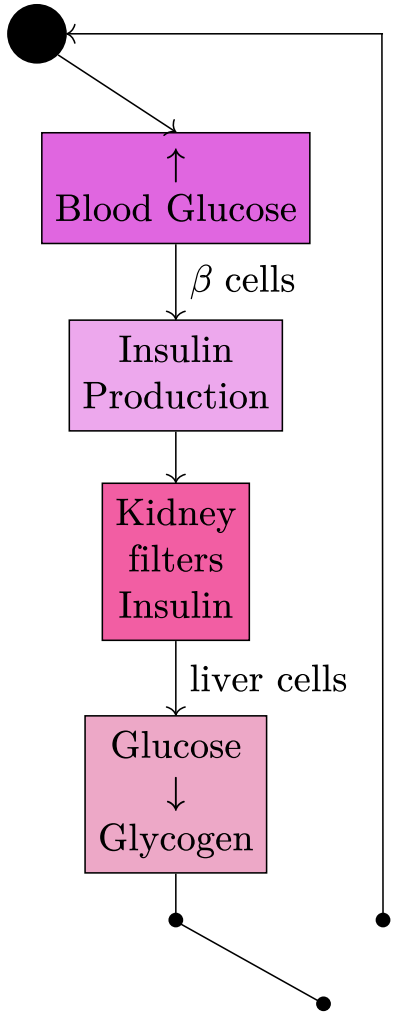
Intensive Insulin Therapy

- **What**: Utilizes insulin infusions and feeding inputs to tightly control blood glucose.
- **Goal**: Prevents an excess of blood glucose (i.e. hyperglycaemia) in patients to reduce mortalities and longer visitation stays [1].
- **How**: Traditionally has relied on ad-hoc sliding protocols.

Fundamentals of Glucoregulation

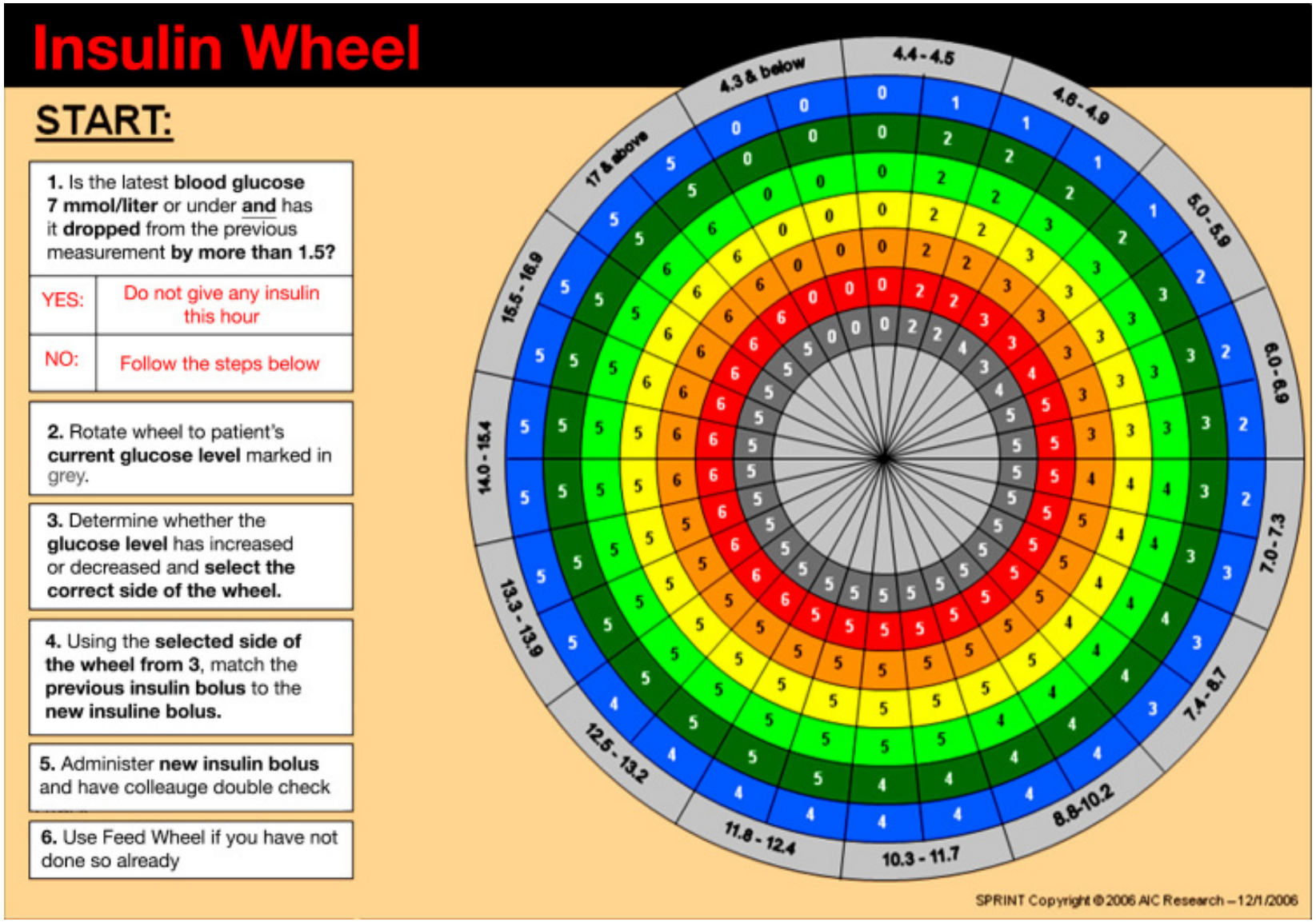


Insulin Resistance in ICU Patients



- Stress-induced insulin resistance has been observed in critically ill patients [2].
- Impaired glycogen production in the liver leads to hyperglycaemia.

Example of an Ad-hoc Sliding Protocol



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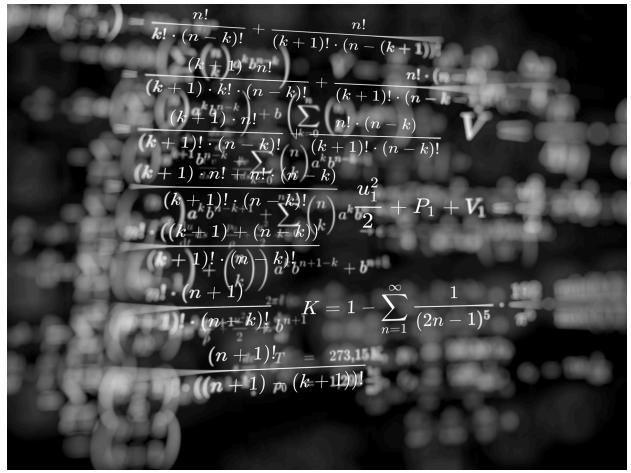
Role of Model-based Glycaemic Control



Physiological models can provide more insight into patients' insulin-glucose dynamics than solely relying on glycaemic measurements.

Intensive Control Insulin-Nutrition-Glucose (ICING) model

Lin et al. has developed a clinically-validated nonlinear insulin-glucose model with the following main components [4]

Dynamic	**Notation**	**Unit**
Blood Glucose	$\dot{G}$	mmol/L
Intersitial Insulin	$\dot{Q}$	mU/L
Plasma Insulin	$\dot{I}$	mU/L
Glucose in the Stomach	$\dot{P}1$	mmol
Glucose in the Gut	$\dot{P}2$	mmol
Endogenous Insulin Production	$u_{en}(t)$	mU/min
Insulin Sensitivity	$S_I(t)$	L/mU/min
Input	**Notation**	**Value**
Exogenous Insulin	$u_{ex}(t)$	mU/min
Enternal Food	$D(t)$	mmol/min
Parenteral Glucose	$P_N(t)$	mmol/min

ICING Model Equations

Insulin Sensitivity

Liver

Kidneys

Blood Glucose Concentration $\dot{G} = -p_G G(t) - S_I(t) G(t) \frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t)+E_G-C_G}{V_G},$

Tissue Insulin Concentration $\dot{Q} = n_I(I(t) - Q(t)) - n_C \frac{Q(t)}{1+\alpha_G Q(t)},$

Blood Insulin Concentration $\dot{I} = -n_K I(t) - n_L \frac{I(t)}{1+\alpha_I I(t)} - n_I(I(t) - Q(t)) + \frac{u_{ex}(t)}{V_I} + \frac{(1-x_L)u_{en}(t)}{V_I}$

Stomach
$$\begin{cases} \dot{P}_1 = -d_1 P_1 + D(t), \\ \dot{P}_2 = -\min\left(d_2 P_2, P_{max}\right) + d_1 P_1, \end{cases}$$

Total External Glucose $P(t) = \min\left(d_2 P_2, P_{max}\right) + P_N(t),$

Pancreas $u_{en}(t) = k_1 \exp\left(-\frac{k_2}{k_3} I(t)\right).$

Bayesian Filtering

The discrete-time dynamic ICING model can be represented in the stochastic state-space.

State-space Representation

$$x_k \sim p(x_k \mid x_{k-1},\, u_{k-1})$$
$$y_k \sim p(y_k \mid x_k)$$

Parameter Description

System Variable	Notation
Dynamics	x_k
Inputs	u_k
Measurements	y_k

There are various methods of optimal filtering, and each has their own assumptions and limitations

Extended Kalman Filter

Approximates nonlinear and Gaussian dynamic and measurement models as a linear transformation [5].

1. *Prediction step*

$$
\begin{aligned}
m_k^- &= f(m_{k-1},\, u_{k-1}),\\
P_k^- &= F_x(m_{k-1})P_{k-1}F_x^{\mathsf{T}}(m_{k-1}) + F_q(m_{k-1})Q_{k-1}F_q^{\mathsf{T}}(m_{k-1}).
\end{aligned}
$$

2. *Update step*

$$
\begin{aligned}
v_k &= y_k - h(m_k^-),\\
S_k &= H_x(m_k^-)P_k^- H_x^{\mathsf{T}}(m_k^-) + H_r(m_k^-)R_k H_r^{\mathsf{T}}(m_k^-),\\
K_k &= P_k^- H_k^{\mathsf{T}}(m_k^-)S_k^{-1},\\
m_k &= m_k^- + K_k v_k,\\
P_k &= P_k^- - K_k S_k K_k^{\mathsf{T}}.
\end{aligned}
$$

Bootstrap Particle Filter

Formulates the posterior of the dynamic function as a Monte Carlo approximation [5].

1. Sample N particles from the dynamic function

$$x_k^{(i)} \sim p(x_k \mid x_{k-1}^{(i)}, u_{k-1}) \quad i = 1, \ldots, N.$$

2. Update weights from the measurement

$$w_k^{*(i)} \propto p(y_k \mid x_k^{(i)}) \quad i = 1, \ldots, N,$$

$$w_k^{(i)} = \frac{w_k^{*(i)}}{\sum_{j=1}^{N} w_k^{*(j)}} \quad i = 1, \ldots, N.$$

3. Systematically resample particles from a distribution proportional to the weights

Parameter Estimation

- There exists unrepresented ICING dynamic $S_{I,k}$.
- Naively assigning either as a general population constant can hinder the performance of the estimators.

State Augmentation

1. Add artificial process noise to the parameters of interest θ_k

$$\theta_k = \theta_{k-1} + \epsilon_{k-1}, \qquad \text{with } \epsilon_{k-1} \sim \mathcal{N}(0,\, W_{k-1}).$$

2. Augment the parameters to the existing dynamics

$$\tilde{x}_k = [x_k, \theta_k]^{\mathsf{T}}.$$

3. Update the state-space representation

$$\tilde{x}_k \sim p(\tilde{x}_k \mid \tilde{x}_{k-1},\, u_{k-1}),$$
$$y_k \sim p(y_k \mid \tilde{x}_k).$$

Formulation of Synthetic Patients

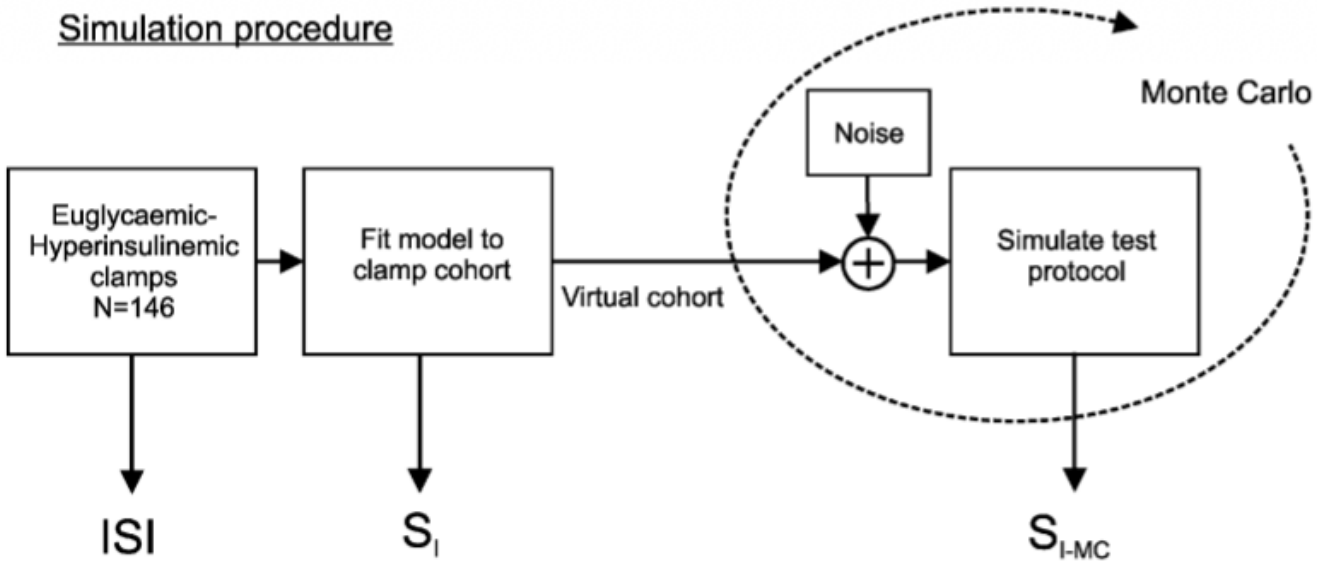


Figure: An example of a simulation procedure [6].

- Synthetic patient trajectories model clinical insulin–glucose dynamics.
- Existing methods typically perturb previously recorded clinical data.

Contribution 1

Creating a reproducible methodology to generate synthetic patient trajectories.

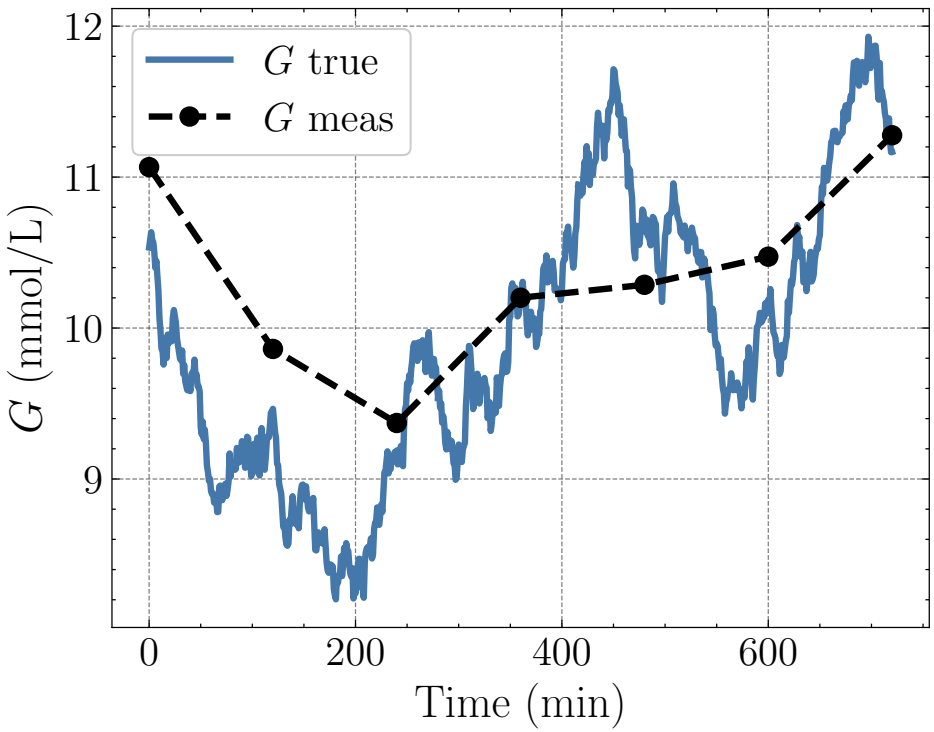
Estimation of Patient Insulin-Glucose Dynamics

- Previous studies have employed Bayesian filtering methods:
  - Extended and unscented Kalman filters
  - Particle filters
- Practical implementation is often insufficiently addressed:
  - Constant nutrition and insulin inputs
  - Known initial insulin–glucose dynamics

Contribution 2

Systematically comparing estimator configurations and performance under realistic situations seen in the ICU.

Estimating Insulin Sensitivity



- Integral-based Parameter Identification method is a nonlinear and nonconvex parameter identification method [7].
- Estimates insulin sensitivity and other parameters as a least squares solution.
- Linearly interpolates between glucose measurements.

Contribution 3

Evaluating insulin sensitivity estimation without relying on interpolated blood glucose measurements.

Outline

Design of Synthetic Patient Trajectories

Data Description (Karolinska Hospital)

- **27,113** ICU patients
- **39.5%** received insulin
- **100M** mins feeding data
- **80M** mins insulin data

Inputs and Parameters

- **Inputs:** Periodic exponential ramps for glucose/insulin.
- **Feeding:** Held constant.
- **Insulin Sensitivity:** Constant or Piecewise-linear function.

ICING Model Configuration

Time Resolution

- Discrete time steps of $\Delta t = 1$ minute.
- Blood-glucose measurements are available every 120 minutes.

Parameters

- Measurement Noise: $r_k \sim \mathcal{N}(0, 0.25^2)$
- Process Noise: $q_k \sim \mathcal{N}(\mathbf{0}, \mathrm{diag}(\boldsymbol{\sigma}^2))$ (10% of initial variance)

Insulin Sensitivity (S_I)

Modeled as log-normal:

$$\log S_{I,k+1} = \log S_{I,k} + q_{S_I,k}.$$

Evaluation Procedures

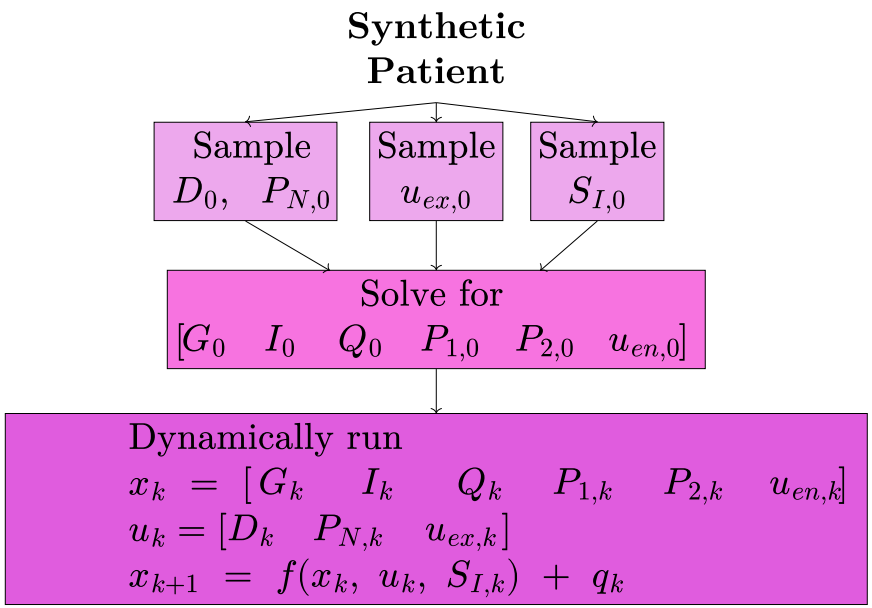
- **Common Setup:** $N = 250$ unique synthetic patients.

Feature	State Estimation	Parameter Estimation
Duration	12 Hours (Convergence)	60 Hours (Slow S_I changes)
Estimators	EKF & PF (100 – 5000 particles)	Augmented EKF & PF 2000
Scenarios	General Accuracy & Runtime	Constant vs. Time-varying S_I
Metric	Avg/SD MSE across patients	Time-step MSE ($\mathrm{MSE}_{S_{I,k}}$)

Performance Metric (MSE)

$$\text{Avg MSE} = \frac{1}{NT}\sum_{i=1}^{N}\sum_{j=1}^{T}(G_i[j] - \hat{G}_i[j])^2$$
$$\mathrm{MSE}_{S_{I,k}} = \frac{1}{N}\sum_{i=1}^{N}(S_{I,i}[k] - \hat{S}_{I,i}[k])^2$$

The Framework Generates Diverse Synthetic Patient Trajectories



- Sampled patient inputs from observed distributions
- Sampled insulin sensitivity from a predefined distribution [8].
- Generated diverse initial insulin–glucose states across synthetic patients.
- Simulated unique trajectories over time without manual interventions.

The Synthetic Patients Captures Patient Variability

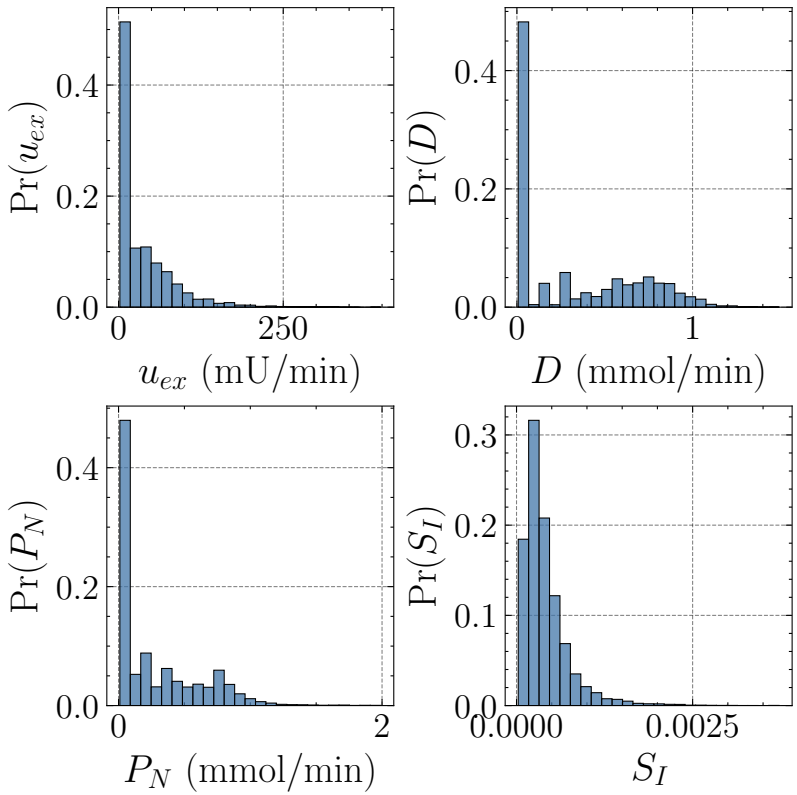


Figure: Initial inputs and insulin sensitivity.

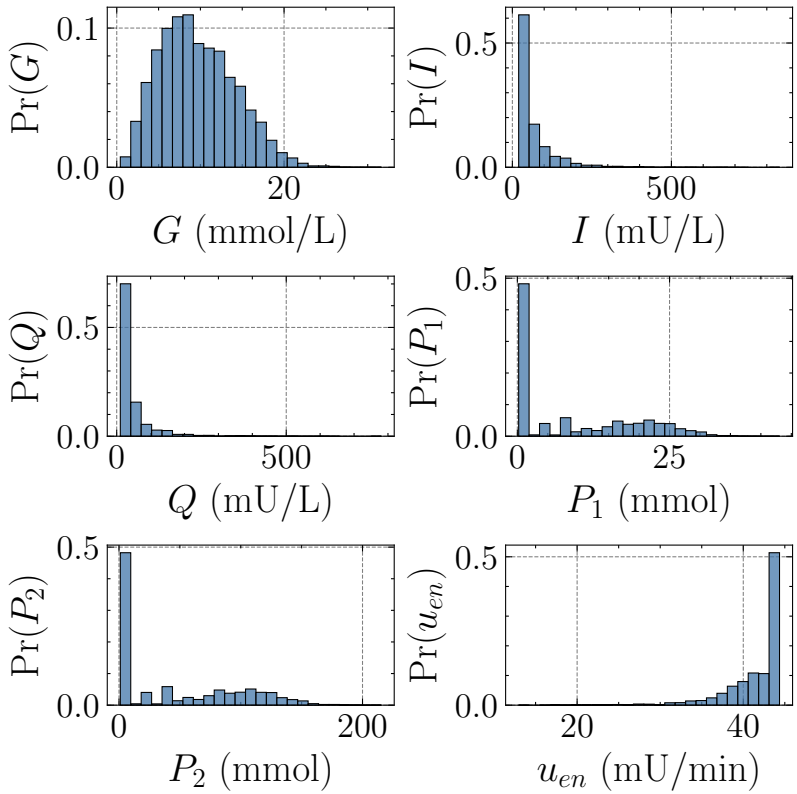
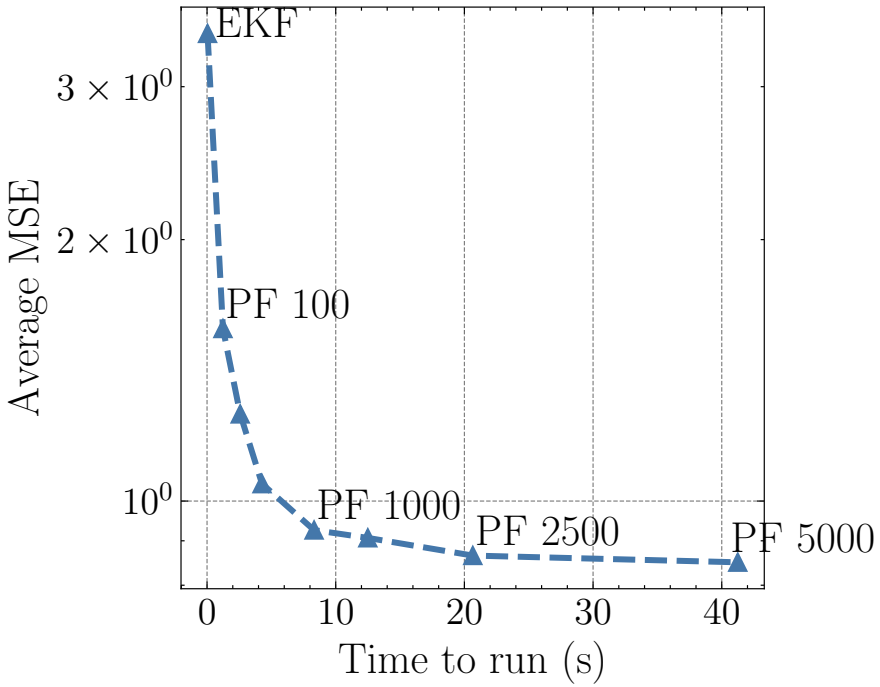


Figure: Initial insulin-glucose states.

- The empirical histograms reflect variability in baseline insulin-glucose dynamics.

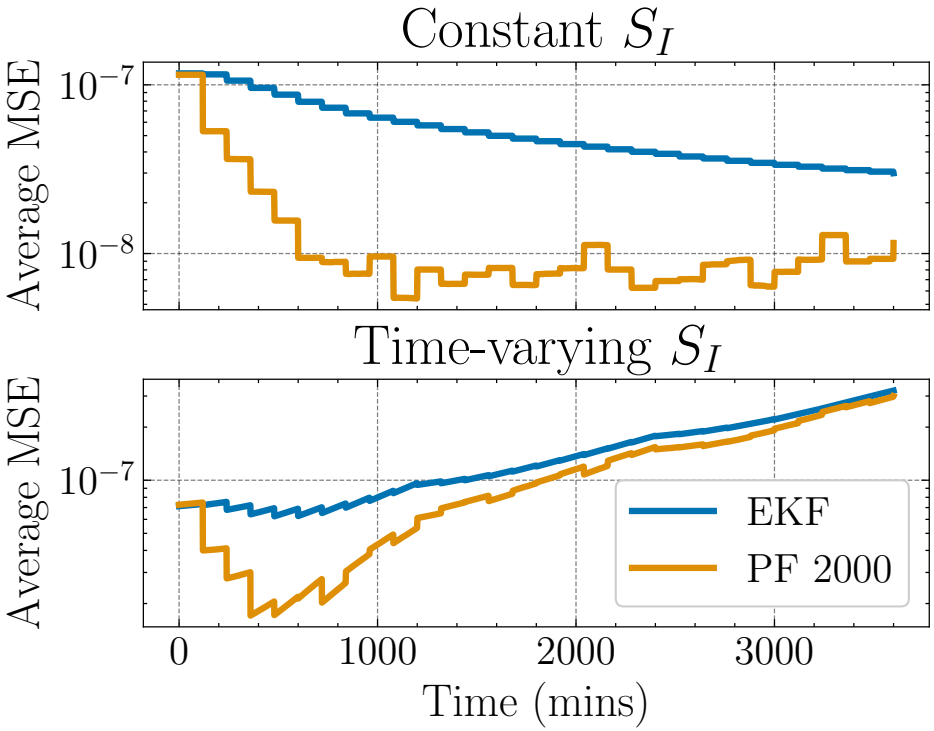
Particle Filters Improve Blood-Glucose Estimation When S_I Is Known



Estimator	Avg MSE	SD MSE
EKF	3.46	9.64
PF 100	1.58	5.28
PF 1000	0.926	2.55
PF 2500	0.865	2.33
PF 5000	0.850	2.26

- Particle filters achieve lower blood-glucose estimation error than the EKF.
  - Increasing the particle count further reduces both the mean MSE and the between-patient variability.
- PF 1000 provides most of the accuracy improvement at a lower computational cost than PF 2500 and PF 5000.

Estimating Time-Varying S_I Remains Challenging



- For constant S_I, PF 2000 reduces the estimation MSE substantially faster than the EKF and achieves a lower steady-state error.
- For time-varying S_I, both methods show increasing MSE, indicating difficulty tracking changes in insulin sensitivity.

Conclusions

Contribution

Evaluated nonlinear state estimators using a new, reproducible framework for synthetic patient trajectories based on Karolinska University Hospital data.

Key Findings

- Particle Filter performance stabilizes at 1,000–5,000 particles.
- Accurately modeled constant insulin sensitivity as an additional state in the ICING model.

Future Work

Transition to recorded blood glucose states and explore data-driven parameter estimation.

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[1] G. V. d. Berghe et al., "Intensive insulin therapy in critically ill patients,", Nov. 2001, DOI: 10.1056/NEJMoa011300

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[6] T. F. Lotz et al., "Monte carlo analysis of a new model-based method for insulin sensitivity testing.", Mar. 2008, DOI: 10.1016/j.cmpb.2007.03.007

[7] C. E. Hann, J. G. Chase, J. Lin, T. Lotz, C. V. Doran, and G. M. Shaw, "Integral-based parameter identification for long-term dynamic verification of a glucose–insulin system model.", Mar. 2005, DOI: 10.1016/j.cmpb.2004.10.006

[8] S. Davidson, C. Pretty, V. Uyttendaele, J. Knopp, T. Desaive, and J. G. Chase, "Multi-input stochastic prediction of insulin sensitivity for tight glycaemic control using insulin sensitivity and blood glucose data.", Dec. 2019, DOI: 10.1016/j.cmpb.2019.105043

Thank you for your attention!