Comprehensive Results: Structural and Practical Identifiability Analysis of the Dalla Man Glucose-Insulin Model

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Contents

Executive Summary

This report consolidates all results from the structural and practical identifiability analysis of the Dalla Man (2007) glucose-insulin model. The analysis spans four complementary methodologies: (1) Sensitivity Analysis, (2) Fisher Information Matrix Analysis, (3) Profile Likelihood Analysis, and (4) Structural Identifiability Analysis using GenSSI. The consistent finding across all methods is that the model exhibits significant non-identifiability when only plasma glucose or CGM measurements are available, necessitating model reduction, parameter fixing, or enriched experimental designs.

1 Sensitivity Analysis Results

1.1 Methodology

Local parametric sensitivity analysis was performed using finite-difference perturbations. The normalized sensitivity of plasma glucose $G(t)$ for parameter p_j was computed as:

$$S_j(t) = \frac{p_j}{G(t)} \frac{\partial G(t)}{\partial p_j}$$

Integrated sensitivity index: $S_j^{\text{int}} = \int_0^T |S_j(t)| dt$.

1.2 Parameter Set Analyzed

The following parameters were analyzed:

$$\{k_1, k_2, V_G, k_{\text{abs}}, k_{\text{gri}}, k_{p1}, k_{p2}, k_{p3}, k_i, k_{\max}, k_{\min}, k_{e1}\}$$

1.3 Key Findings

1.3.1 Sensitivity Correlation Analysis

Strong correlations observed among parameters associated with glucose absorption and insulin action:

- Highly correlated groups: k_{abs}, k_{gri}, $k_{\max}$, k_{p3}, k_i
- Distinct sensitivity patterns: V_G and k_1

High correlation indicates potential identifiability challenges when estimating these parameters simultaneously.

1.3.2 Basal (Fasting) Sensitivity Analysis

Table 1: Basal sensitivity ranking (fasting conditions)

Parameter	S_j^{int}
V_G	4.54×10^2
k_{p1}	2.50×10^2
k_1	6.84×10^1
k_2	6.35×10^1
k_{p2}	3.48×10^1
k_{p3}	2.40×10^1
k_i	1.88×10^0
Others	≈ 0

1.3.3 Post-Prandial Sensitivity Analysis

Table 2: Post-prandial sensitivity ranking

Parameter	S_j^{int}
V_G	2.48×10^2
k_{p1}	6.15×10^1
k_1	3.36×10^1
k_{min}	3.03×10^1
k_2	3.02×10^1
k_{p3}	1.90×10^1
k_{abs}	1.77×10^1
k_{gri}	1.67×10^1

1.3.4 Multi-Excitation Sensitivity and Robust Ranking

Table 3: Multi-excitation sensitivity and robust mean ranking

Parameter	Small Meal	Large Meal	Robust Mean
V_G	217.35	252.59	234.97
k_{p1}	88.90	57.89	73.40
k_1	41.39	32.15	36.77
k_2	37.48	29.07	33.27
k_{min}	14.94	33.54	24.24
k_{p3}	13.43	20.71	17.07

1.3.5 Window-Length Sensitivity Analysis

Table 4: Window-length sensitivity rankings

Parameter	25 min	60 min	120 min
V_G	0.66	7.19	50.09
k_1	6.77	18.26	29.58
k_2	5.82	14.71	23.49
k_{p1}	2.46	8.41	18.72
$k_{\min}$	0.08	2.47	12.21

1.4 Interim Conclusions from Sensitivity Analysis

- V_G and k_{p1} consistently dominate plasma glucose sensitivity across regimes
- Several parameters exhibit strong excitation and time-scale dependence
- Correlated sensitivity patterns suggest potential identifiability challenges

2 Fisher Information Matrix Analysis Results

2.1 Methodology

Fisher Information Matrix (FIM) was constructed from normalized sensitivity matrix:

$$\mathcal{I}(\theta) = \int_0^T S(t)^\top S(t) dt$$

where $S(t)$ is the sensitivity matrix.

2.2 Parameter Subset

Based on sensitivity correlation analysis, reduced subset selected:

$$\theta = \{V_G, k_1, k_{p1}, k_{\text{abs}}, k_i\}$$

2.3 Experimental Regime

Post-prandial excitation with large meal:

- Meal size $D = 90,000$
- Simulation horizon: 120 minutes
- Fasting initial conditions with gastric loading

2.4 Computed Fisher Information Matrix

$$\mathcal{I} = \begin{bmatrix} 34.73 & -9.66 & 8.47 & -0.45 & -0.88 \\ -9.66 & 8.15 & -4.68 & -2.32 & 0.19 \\ 8.47 & -4.68 & 3.07 & 0.94 & -0.19 \\ -0.45 & -2.32 & 0.94 & 1.22 & 0.03 \\ -0.88 & 0.19 & -0.19 & 0.03 & 0.02 \end{bmatrix}$$

2.5 Eigenvalue Analysis

Table 5: Eigenvalues of the Fisher Information Matrix

Mode	Eigenvalue
Mode 1	40.32
Mode 2	6.76
Mode 3	9.4×10^{-2}
Mode 4	1.8×10^{-2}
Mode 5	9.0×10^{-5}

2.6 Interpretation

- First two eigenvalues dominate, indicating majority of information lies in 2D subspace
- Remaining eigenvalues are orders of magnitude smaller, revealing near-unidentifiable parameter directions
- FIM is severely ill-conditioned (condition number $\approx 4.5 \times 10^5$)
- Diagonal entries confirm V_G and k_{p1} carry highest individual information content
- Significant off-diagonal terms indicate strong parameter coupling

2.7 Implications

- Only low-dimensional reparameterization can be reliably identified from glucose data
- Simultaneous estimation of all selected parameters is numerically unstable
- Additional excitation, regularization, or parameter fixing required

3 Profile Likelihood Analysis Results

3.1 Methodology

Profile likelihood for parameter θ_i:

$$\chi^2_{\text{PL}}(\theta_i) = \min_{\theta_{j \neq i}} \chi^2(\theta)$$

where $\chi^2(\theta)$ is the weighted least-squares objective function. 95% confidence threshold: $\Delta\chi^2 = 3.84$ for one degree of freedom.

3.2 Synthetic Data Generation

- Generated using Dalla-Man model under large post-prandial excitation
- Meal size $D = 90,000$, simulation horizon $T = 120$ minutes
- Fasting initial conditions with gastric loading
- Heteroscedastic Gaussian noise added: $G_{\text{meas}}(t_k) = G_{\text{true}}(t_k)(1+\varepsilon_k)$, $\varepsilon_k \sim \mathcal{N}(0, 0.1^2)$

3.3 Parameter Subset

$$\theta = \{V_G, k_1, k_{p1}, k_{\text{abs}}, k_i\}$$

All parameters optimized in $\log_{10}$-space.

3.4 Key Findings

3.4.1 Profile Likelihood for k_{abs}

- Asymmetric profile shape
- Lower side of k_{abs}: profile remains below confidence threshold
- Higher side: $\Delta\chi^2$ rises sharply above threshold
- Suggests partial identifiability but requires robust multi-start profiling

3.4.2 Attempted Profile Likelihood for k_i

- Multi-start profiling failed to converge within reasonable time
- Behavior diagnostic of practical non-identifiability
- Indicates flat or weakly increasing profile likelihood
- Changes in k_i can be compensated by other parameters without degrading fit

3.5 Summary of Profile Likelihood Findings

- k_{abs} shows partial identifiability (requires robust multi-start profiling)
- k_i is practically non-identifiable under present data and excitation conditions
- Findings consistent with sensitivity correlations and FIM analysis

4 Structural Identifiability Analysis Results

4.1 Methodology: GenSSI Framework

Generating Series for Structural Identifiability (GenSSI) based on Lie derivatives:

$$\begin{aligned} \dot{y} &= L_f h \\ \ddot{y} &= L_f^2 h \\ \dddot{y} &= L_f^3 h, \quad \text{etc.} \end{aligned}$$

4.2 Model Formulation

4.2.1 State-Space Representation

12 state variables:

$$x(t) = [G_p, G_t, I_l, I_p, Q_{sto1}, Q_{sto2}, Q_{gut}, I_1, I_d, X, I_{po}, Y]^\top$$

4.2.2 Parameter Vector

Includes:

- Glucose transport and distribution parameters (V_G, k_1, k_2)
- Insulin kinetics parameters (m_1, m_2, m_4, m_5, m_6)
- Gastric emptying and absorption parameters ($k_{abs}, k_{gri}, k_{min}, k_{max}$)
- Endogenous glucose production parameters ($k_{p1}, k_{p2}, k_{p3}, k_{p4}$)
- Insulin action and delay parameters (k_i, p_{2U})
- CGM sensor parameters ($\alpha_y, \beta_y, \tau_{cgm}$)

4.2.3 Output Equation

CGM signal with sensor dynamics:

$$\dot{Y} = -\alpha_y(Y - \beta_y(G - G_b)), \quad G = \frac{G_p}{V_G}$$

4.3 GenSSI Results

4.3.1 Full Identifiability Tableau

- Highly structured but exhibits extensive column dependencies
- Many parameters appear together in identical or nearly identical patterns across rows
- Indicates parameters influence output through same algebraic combinations
- Confirms rank deficiency reported by GenSSI

4.3.2 Reduced Identifiability Tableau: Order 1

- Only single independent constraint from first Lie derivative
- Most parameters appear jointly or not at all
- First derivative captures global scaling rather than parameter-specific effects

4.3.3 Reduced Identifiability Tableau: Order 2

- Additional algebraic structure present
- More parameters enter generating series
- Newly introduced information does not break existing parameter couplings
- Parameters continue to appear in coupled groups

4.3.4 Rank Growth Pattern

- Each additional derivative contributes limited new information
- Parameter columns remain linearly dependent
- No parameter becomes uniquely identifiable at higher orders
- Rank increases linearly from 1 to 4 with derivative order

4.4 Algebraic Sources of Structural Non-Identifiability

4.4.1 Parameters Appearing Only Through Composite Expressions

- Examples: $\frac{fk_{\text{abs}}}{BW}$, $\frac{G_p}{V_G}$, $\beta_y(G - G_b)$
- Only composite quantities influence CGM output
- Multiple parameter sets produce identical composite expressions

4.4.2 Coupling Between Parameters and Initial Conditions

- Terms like $k_1 G_{p0}$, $k_{p2} G_{p0}$, $k_{abs} Q_{gut,0}$
- Changes in parameters compensated by changes in initial conditions
- Enlarges space of indistinguishable parameter-state combinations

4.4.3 Hidden Dynamic Cascades and Information Shielding

- Multiple cascaded subsystems between parameters and output
- Parameters act upstream, affect output after multiple unobserved transformations
- Output generating series collapses multiple mechanisms into few algebraic effects

4.4.4 Effect of CGM Sensor Dynamics

- Introduces additional parameters (α_y, β_y)
- Interact multiplicatively with physiological parameters (e.g., V_G)
- Creates additional parameter groupings that cannot be separated
- Smooths and delays observable signal, suppressing high-frequency components

4.4.5 Absence of Independent Algebraic Directions

- Number of independent algebraic directions grows slowly relative to unknowns
- Strong algebraic dependencies among parameters
- Increasing Lie derivative order increases complexity without increasing rank

4.5 Interim Conclusion from Structural Analysis

- Dalla Man model with CGM output is structurally non-identifiable
- Inability to isolate individual parameters is not due to data limitations
- Results from model's algebraic structure and partial observability
- Provides theoretical foundation for model reduction and parameter fixing

5 Synthesis of All Results

5.1 Consistent Patterns Across All Analyses

1. **Parameter Coupling**: All methods reveal strong correlations/dependencies among parameters
2. **Rank Deficiency**: FIM analysis shows only 2 dominant modes; structural analysis shows limited rank growth
3. **Non-identifiability**: Both practical and structural analyses confirm inability to uniquely estimate parameters
4. **Key Problematic Parameters**: k_i consistently identified as non-identifiable; k_{abs} shows partial identifiability issues

5.2 Quantitative Summary

Table 6: Summary of identifiability status across parameters

Parameter	Sensitivity Rank	FIM Info Content	Practical Identifiability	Structural Identifiabil
V_G	High (1)	High	Likely identifiable	Non-identifiable (compo
k_{p1}	High (2)	High	Likely identifiable	Non-identifiable (compo
k_1	Medium (3)	Medium	Uncertain	Non-identifiable
k_2	Medium (4)	Not analyzed	Not analyzed	Non-identifiable
k_{abs}	Medium	Low	Partially identifiable	Non-identifiable (compo
k_i	Low	Very low	Non-identifiable	Non-identifiable

5.3 Theoretical Explanations for Observed Patterns

1. **Structural Non-identifiability**: Parameters appear only in composite expressions; coupling with initial conditions; hidden dynamic cascades
2. **Practical Non-identifiability**: Manifestation of structural issues under noisy, finite data conditions
3. **Numerical Issues**: Ill-conditioned FIM and optimization difficulties stem from underlying structural deficiencies

6 Implications and Recommendations

6.1 For Parameter Estimation

- Full parameter estimation from CGM data alone is theoretically impossible
- Simultaneous estimation of all parameters is numerically ill-posed
- Parameter fixing is necessary and justified for structurally unobservable parameters

6.2 For Model Reduction

- Reduce-order modeling is mathematically and practically justified
- Focus on preserving dominant input-output behavior
- Consider collapsing: fast insulin kinetics, internal insulin action delays, detailed gastric compartment dynamics

6.3 For Experimental Design

- Identifiability could be improved by: measuring additional outputs (plasma insulin), tracer/clamp experiments, reducing initial condition uncertainty, calibrating sensor dynamics
- In practical scenarios where additional measurements are infeasible, model reduction and parameter fixing are appropriate strategies

6.4 For Control-Oriented Modeling

- Reduced-order models align with fundamental limits of CGM-based observability
- Prioritize: predictive accuracy of glucose trajectories, robustness to parameter uncertainty, tractability for real-time control

7 Conclusion

The comprehensive analysis demonstrates that the Dalla Man glucose-insulin model exhibits significant structural and practical non-identifiability when only plasma glucose or CGM measurements are available. This non-identifiability arises from fundamental algebraic properties of the model structure, including parameter coupling, composite parameter expressions, hidden dynamic cascades, and sensor dynamics. These findings provide a rigorous foundation for subsequent model reduction, parameter fixing, and reparameterization strategies essential for developing clinically applicable glucose prediction and control systems.

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