Working Notes on Glucose–Insulin Modeling

Based on the Dalla Man (2007) Meal Simulation Model

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Contents

1 Stage 1B: Fisher Information Matrix (FIM) Notebook

This section documents the Fisher Information Matrix (FIM) analysis performed on the Dalla–Man glucose–insulin model. The purpose of this notebook is to transition from sensitivity-based influence analysis (Stage 1A) to an information-theoretic assessment of parameter identifiability.

All results reported here correspond to plasma glucose concentration as the observed output. The analysis is conducted in a reproducible, experiment-driven manner consistent with the preceding sensitivity notebook.

1.1 Motivation and Relation to Sensitivity Analysis

Local sensitivity analysis quantifies how strongly perturbations in model parameters affect plasma glucose trajectories. However, sensitivity alone does not determine whether parameters can be uniquely and reliably estimated from data.

In particular, parameters with highly correlated sensitivity profiles may exhibit strong individual sensitivities while remaining practically non-identifiable when estimated simultaneously. This limitation was already anticipated in Stage 1A through sensitivity correlation analysis and excitation-dependent rankings.

The Fisher Information Matrix provides a principled framework to:

- quantify parameter identifiability,
- diagnose parameter coupling,
- assess the effective dimensionality of the estimation problem.

This stage therefore represents a natural continuation of the sensitivity experiments, moving from *influence* to *information*.

1.2 Identification Setup

1.2.1 Parameter Selection

Based on the correlation analysis and robust sensitivity rankings obtained in Stage 1A, a reduced subset of parameters was selected to mitigate severe collinearity effects:

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

This subset includes:

- dominant global scaling parameters (V_G),
- insulin-independent glucose dynamics (k_1),
- insulin-mediated action parameters (k_{p1}),
- gastrointestinal absorption dynamics (k_{abs}),
- delayed insulin action dynamics (k_i).

The selection reflects a balance between physiological relevance and numerical tractability.

1.2.2 Experimental Regime

The FIM was constructed under a post-prandial excitation corresponding to a large meal:

- meal size $D = 90{,}000$,
- simulation horizon of 120 minutes,
- fasting initial conditions with gastric loading.

This regime was chosen to maximize excitation of gastrointestinal and insulin-mediated pathways, thereby increasing the information content of the glucose response.

1.3 Sensitivity Matrix Construction

Let $G(t)$ denote plasma glucose concentration. For each parameter θ_j, the normalized local sensitivity was defined as

$$S_j(t) = \frac{\theta_j}{G(t)} \frac{\partial G(t)}{\partial \theta_j}, \tag{1}$$

where partial derivatives were approximated numerically using finite differences.

The time-resolved sensitivity matrix was assembled as

$$S(t) = \begin{bmatrix} S_1(t) & S_2(t) & \cdots & S_n(t) \end{bmatrix}, \tag{2}$$

with one column per parameter and rows indexed by time.

1.4 Fisher Information Matrix Definition

Assuming additive, independent measurement noise with unit variance, the continuous-time Fisher Information Matrix was defined as

$$\mathcal{I}(\theta) = \int_0^T S(t)^\top S(t)\, dt. \tag{3}$$

Numerical integration was performed using the trapezoidal rule over the simulation grid. This formulation assumes:

- uniform measurement confidence across time,
- no prior regularization,
- identifiability driven purely by glucose data.

1.5 Computed Fisher Information Matrix

The resulting Fisher Information Matrix is:

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

Observations. The diagonal entries confirm that V_G and k_{p1} carry the highest individual information content. Significant off-diagonal terms indicate strong parameter coupling, consistent with the sensitivity correlation patterns observed in Stage 1A. The extremely small diagonal entry associated with k_i already suggests weak practical identifiability.

1.6 Eigenvalue Analysis of the FIM

To assess the effective dimensionality of the estimation problem, an eigenvalue decomposition was performed:

$$\mathcal{I} = Q\Lambda Q^\top.$$

The eigenvalues, sorted in descending order, are reported in Table 1.

Table 1: 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}

Interpretation. The first two eigenvalues dominate the spectrum, indicating that the majority of the information lies in a two-dimensional subspace of the five-parameter space. The remaining eigenvalues are several orders of magnitude smaller, revealing near-unidentifiable parameter directions and a severely ill-conditioned estimation problem.

1.7 Connection to Sensitivity Results

The FIM analysis provides a quantitative confirmation of the qualitative observations made during sensitivity analysis:

- correlated sensitivity trajectories generate aligned columns in $S(t)$,
- aligned sensitivities lead to low-rank or near-singular FIMs,
- high sensitivity does not imply identifiability when parameters act along the same dynamic pathways.

In particular, V_G, k_1, and k_{p1} dominate the same information modes, while k_{abs} and k_i contribute weakly and redundantly.

1.8 Implications for Parameter Estimation and ROM

From an estimation perspective, these results imply that:

- only a 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 is required.

For reduced-order model development, the FIM provides direct guidance: parameters associated with low-information modes are candidates for fixing or lumping, whereas dominant parameters must be preserved explicitly.

1.9 Interim Summary

The Fisher Information Matrix analysis conducted in Stage 1B demonstrates that:

- the Dalla–Man model exhibits strong practical non-identifiability under realistic postprandial excitation,
- sensitivity correlation observed in Stage 1A directly translates into FIM degeneracy,
- only a small number of parameter combinations are supported by glucose data alone.

These findings motivate subsequent stages focused on profile likelihood analysis, structured parameter fixing, and optimal experiment design.