Working Notes on Glucose–Insulin Modeling

Based on the Dalla Man (2007) Meal Simulation Model

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Contents

1 Step 2A: Practical Identifiability Analysis via Profile Likelihood

This section documents the first stage of identifiability analysis performed using the *profile likelihood* approach. The goal of Step 2A is to assess whether parameters identified as influential (Stage 1A) and information-bearing (Stage 1B) can, in practice, be uniquely estimated from noisy plasma glucose measurements.

Unlike sensitivity analysis or Fisher Information Matrix (FIM) analysis, which rely on local linear approximations, the profile likelihood explicitly explores the nonlinear likelihood landscape and therefore provides a direct numerical test of *practical identifiability*.

1.1 Conceptual Background

A parameter is said to be *practically identifiable* if its confidence interval, derived from finite and noisy data, is bounded. Even structurally identifiable parameters may be practically non-identifiable if the data lack sufficient information content.

Raue et al. [1] formalized this distinction and showed that practical non-identifiability manifests as flat or weakly increasing profile likelihoods that fail to cross statistical confidence thresholds. The profile likelihood therefore serves as a bridge between identifiability analysis and confidence interval construction.

1.2 Relation to Previous Steps

- **Stage 1A (Sensitivity Analysis)** revealed strong parameter influence but also significant correlations among parameters.
- **Stage 1B (FIM Analysis)** demonstrated that these correlations lead to a severely ill-conditioned Fisher Information Matrix with low effective rank.

Step 2A tests whether these issues translate into *unbounded or weakly bounded* confidence intervals when realistic measurement noise is present.

1.3 Synthetic Data Generation

To perform identifiability analysis in a controlled setting, synthetic glucose data were generated using the Dalla–Man model under a large post-prandial excitation.

The experimental configuration was chosen to match the most informative regime identified in the sensitivity and FIM analyses:

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

The model was simulated using the nominal parameter set, yielding the "true" plasma glucose trajectory $G_{\text{true}}(t)$. To emulate experimental conditions, heteroscedastic Gaussian noise was added:

$$G_{\text{meas}}(t_k) = G_{\text{true}}(t_k)\,(1 + \varepsilon_k)\,, \qquad \varepsilon_k \sim \mathcal{N}(0,\, 0.1^2).$$

Figure 1 shows the resulting synthetic dataset.

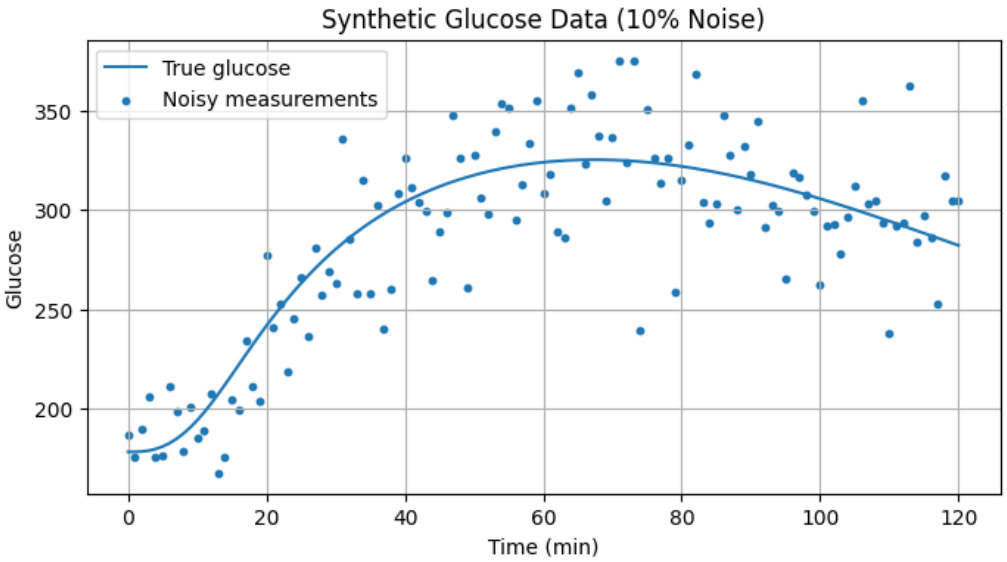

Figure 1: Synthetic plasma glucose data with 10% relative Gaussian noise.

Rationale. Using synthetic data allows identifiability properties to be studied independently of experimental artifacts while retaining realistic noise levels and nonlinear dynamics.

1.4 Likelihood and Objective Function

Assuming independent Gaussian measurement errors, parameter estimation was formulated as a weighted least-squares problem. The chi-square objective function was defined as

$$\chi^2(\theta) = \sum_{k=1}^{N_t} \left(\frac{G_{\text{meas}}(t_k) - G_{\text{sim}}(t_k;\theta)}{\sigma(t_k)} \right)^2, \tag{1}$$

with heteroscedastic standard deviation

$$\sigma(t_k) = 0.1\, G_{\text{meas}}(t_k).$$

Under Gaussian noise assumptions, minimizing $\chi^2(\theta)$ corresponds to maximum likelihood estimation.

The parameter subset analyzed was

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

consistent with the reduced set selected in Stage 1B.

All parameters were optimized in $\log_{10}$-space to ensure positivity and to improve numerical conditioning, as recommended in [1].

1.5 Profile Likelihood Definition

For a parameter θ_i, the profile likelihood is defined as

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

i.e. for each fixed value of θ_i, the remaining parameters are re-optimized to minimize χ^2.

Confidence intervals are determined by the likelihood-ratio criterion:

$$\Delta\chi^2(\theta_i) = \chi^2_{\mathrm{PL}}(\theta_i) - \chi^2_{\mathrm{min}}.$$

For one degree of freedom, the 95% confidence threshold is $\Delta\chi^2 = 3.84$.

1.6 Profile Likelihood for k_{abs}

A profile likelihood was computed for the gastric absorption parameter k_{abs} over a $\log_{10}$ range of ± 2 orders of magnitude around its nominal value. For computational efficiency, a single-start local optimizer was used.

The resulting profile likelihood is shown in Figure 2.

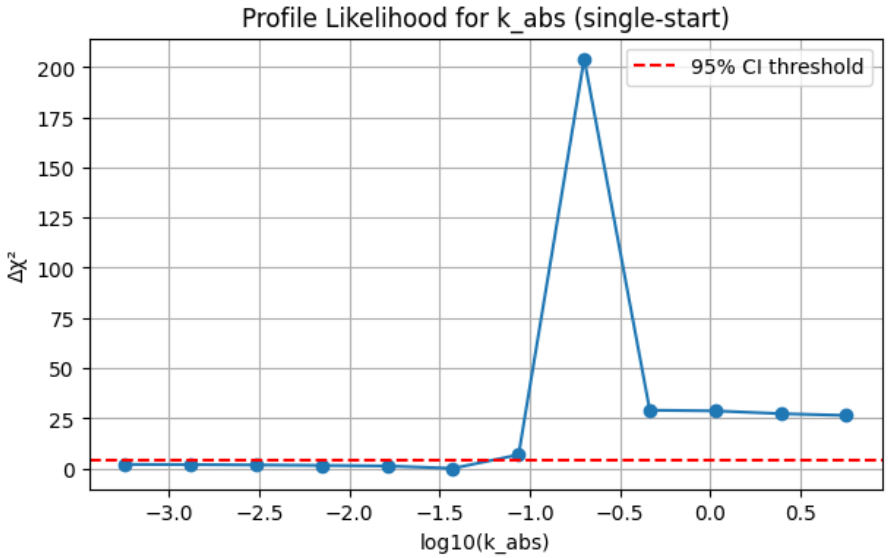

Figure 2: Profile likelihood for k_{abs} (single-start). The dashed red line indicates the 95% confidence threshold $\Delta\chi^2 = 3.84$.

Interpretation. The profile exhibits an asymmetric shape:

- On the lower side of k_{abs}, the profile remains below the confidence threshold, indicating that a range of smaller values is statistically compatible with the data.
- On the higher side, $\Delta\chi^2$ rises sharply and remains well above the threshold.

Because this profile was computed using a single-start optimizer, the steep rise at high values may reflect either true loss of fit or convergence to suboptimal local minima. Consequently, while the result suggests partial identifiability of k_{abs}, robust multi-start profiling is required before drawing quantitative confidence bounds.

1.7 Attempted Profile Likelihood for k_i

A multi-start profile likelihood was attempted for the insulin action delay parameter k_i, using the same $\log_{10}$ range and repeated re-optimization of the remaining parameters.

However, the procedure failed to converge within reasonable computational time and continued running for over one hour without producing a stable profile.

Interpretation of the Failure. Following the framework of Raue et al. [1], this behavior is itself diagnostic:

- A flat or weakly increasing profile likelihood indicates *practical non-identifiability*, where changes in k_i can be compensated by other parameters without significantly degrading the fit.
- The severe ill-conditioning identified in the FIM (Stage 1B) suggests that k_i lies predominantly in a low-information parameter direction.
- The optimizer struggles because the likelihood landscape contains long, shallow valleys rather than a well-defined curvature.

Thus, the failure to obtain a bounded profile likelihood for k_i provides strong evidence that k_i is practically non-identifiable from glucose-only data under the current experimental design.

1.8 Summary of Step 2A Findings

The profile likelihood analysis leads to the following conclusions:

- The gastric absorption parameter k_{abs} shows partial identifiability, but quantitative confidence intervals require robust multi-start profiling.
- The insulin action delay parameter k_i is practically non-identifiable under the present data and excitation conditions.
- These findings are fully consistent with the sensitivity correlations observed in Stage 1A and the low effective information rank revealed by the FIM in Stage 1B.

Step 2A therefore confirms that certain parameters of the Dalla–Man model cannot be reliably estimated from plasma glucose measurements alone, motivating either parameter fixing, model reduction, or enriched experimental design in subsequent steps.

References

[1] A. Raue, C. Kreutz, T. Maiwald, J. Bachmann, M. Schilling, U. Klingmüller, and J. Timmer, *Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood*, Bioinformatics, 25(15), 1923–1929, 2009.

[2] C. Cobelli and J. DiStefano III, *Parameter and structural identifiability concepts and ambiguities*, American Journal of Physiology, 239, R7–R24, 1980.