Working Notes on Glucose–Insulin Modeling

Based on the Dalla Man (2007) Meal Simulation Model

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Contents

1 Sensitivity Analysis Notebook

This section documents the sensitivity analysis experiments performed on the Dalla–Man glucose–insulin model. The purpose of this notebook is to track the methodology, numerical experiments, and observations in a chronological and reproducible manner.

All sensitivities reported here correspond to plasma glucose concentration as the observed output.

1.1 Sensitivity Analysis Setup

Local parametric sensitivity analysis was performed using finite-difference perturbations of model parameters. For a given parameter p_j, the normalized sensitivity of plasma glucose $G(t)$ was computed as

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

where the partial derivative was approximated numerically using a small relative perturbation of the parameter.

The scalar sensitivity index used for ranking parameters was defined as

$$S_j^{\text{int}} = \int_0^T |S_j(t)| \, dt, \tag{2}$$

representing the time-integrated magnitude of sensitivity over the simulation horizon.

The following parameters were analyzed:

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

1.2 Relation to Existing Sensitivity Analyses

The use of normalized local sensitivities follows the formulation originally adopted in the Dalla–Man meal simulation model, where parameter influence is assessed relative to both the state magnitude and parameter scale [1]. Such normalization enables comparison across parameters with heterogeneous units and magnitudes.

Similar sensitivity-based investigations have been employed in subsequent studies, including the work of Sánchez et al., who used time-dependent sensitivity profiles to guide parameter selection and identifiability analysis in glucose–insulin models [2]. The present analysis builds upon this foundation by extending sensitivity evaluation across multiple excitation magnitudes and time scales.

1.3 Stage 1A: Sensitivity Correlation Analysis

To assess potential collinearity among parameters, sensitivity trajectories were collected for a representative post-prandial excitation and assembled into a sensitivity matrix.

Each sensitivity vector was normalized by its Euclidean norm, and a cosine-similarity correlation matrix was computed.

Figure 1 shows the resulting sensitivity correlation matrix.

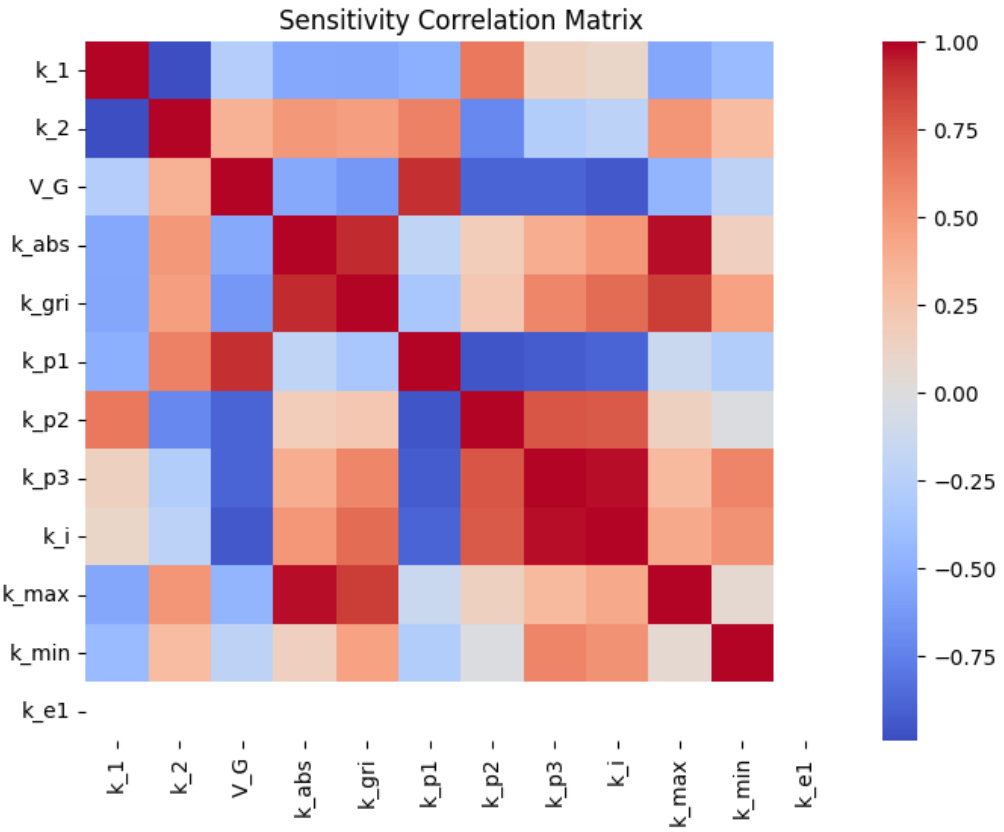

Figure 1: Sensitivity correlation matrix based on normalized sensitivity trajectories.

Observations. Strong correlations are observed among groups of parameters associated with glucose absorption and insulin action (e.g. k_{abs}, k_{gri}, $k_{\max}$, k_{p3}, k_i). This suggests potential identifiability challenges when estimating these parameters simultaneously. Conversely, parameters such as V_G and k_1 exhibit more distinct sensitivity patterns.

Extended Interpretation. Highly correlated sensitivity profiles indicate that perturbations in certain parameters produce nearly indistinguishable effects on plasma glucose. From an estimation perspective, such parameters are difficult to disentangle using glucose-only measurements, as multiple parameter combinations may yield similar outputs. This observation is consistent with prior identifiability studies of the Dalla–Man model, where clusters of insulin action and absorption parameters were shown to be weakly identifiable from plasma glucose alone [2].

Importantly, sensitivity correlation does not constitute a formal proof of non-identifiability, but it provides a practical diagnostic for anticipating estimation difficulties.

1.4 Stage 1A: Basal (Fasting) Sensitivity Analysis

Sensitivity analysis was first conducted under fasting (basal) conditions, with no meal intake. The simulation horizon was extended to 600 minutes to capture slow glucose–insulin dynamics.

Table 1 reports the ranking of parameters based on the integrated sensitivity index.

Figure 2 shows the time evolution of the dominant basal sensitivities.

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

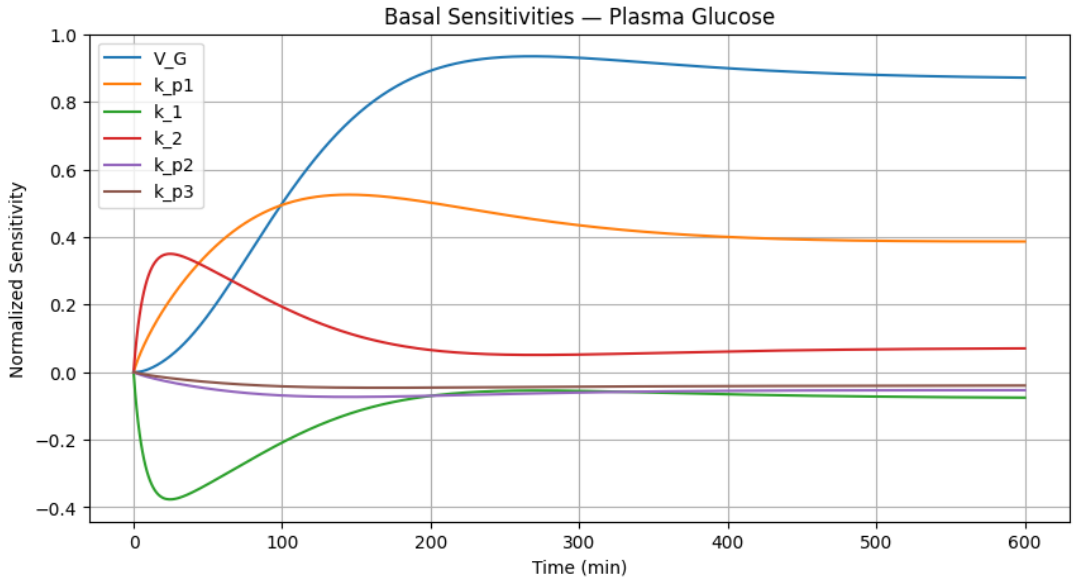

Figure 2: Basal sensitivity trajectories for dominant parameters.

Observations. Under fasting conditions, plasma glucose is most sensitive to the glucose distribution volume V_G and the insulin action parameter k_{p1}. Sensitivity magnitudes are generally smooth and slowly varying, reflecting the dominance of basal glucose turnover mechanisms. Parameters related to gastrointestinal absorption exhibit negligible influence in the absence of a meal.

1.5 Stage 1A: Post-Prandial Sensitivity Analysis

Sensitivity analysis was repeated under post-prandial conditions, with a finite meal input introduced via the stomach compartment. The simulation horizon was set to 300 minutes.

Table 2 summarizes the sensitivity ranking in the meal condition.

Figure 3 shows the corresponding sensitivity trajectories.

Observations. Following a meal, additional parameters associated with gastric emptying and insulin saturation dynamics become influential. While V_G remains the dominant parameter, the relative importance of k_{min}, k_{abs}, and k_{gri} increases compared to the basal case. This indicates a clear regime dependence of sensitivity structure.

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

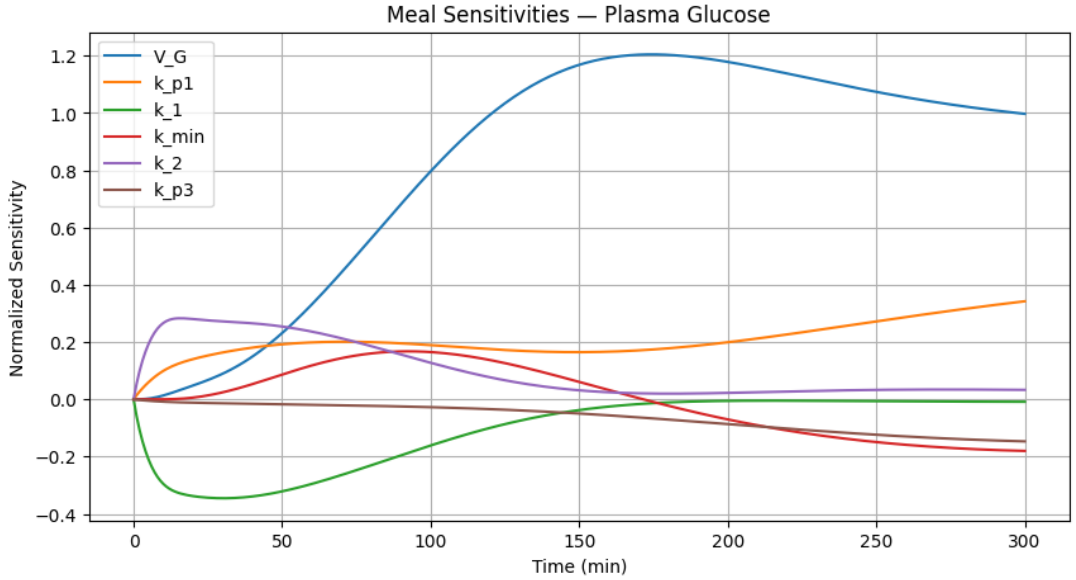

Figure 3: Post-prandial sensitivity trajectories for dominant parameters.

Physiological Interpretation. The dominance of V_G under both basal and post-prandial conditions reflects its role as a scaling factor relating glucose mass to concentration. Changes in V_G affect the entire glucose trajectory uniformly, explaining its consistently high sensitivity.

Under fasting conditions, insulin-mediated glucose uptake parameters (k_{p1}, k_1, k_2) govern the slow regulation of plasma glucose. In contrast, post-prandial dynamics activate additional pathways related to gastric emptying and insulin saturation, leading to increased sensitivity of parameters such as $k_{\min}$, k_{abs}, and k_{gri}. This regime-dependent activation highlights the importance of excitation design when performing sensitivity and identifiability analyses.

1.6 Stage 1A: Multi-Excitation Sensitivity and Robust Ranking

To assess robustness across physiologically distinct conditions, sensitivity analysis was performed for two meal sizes (small and large). A robust sensitivity score was defined as the mean of the integrated sensitivities across both excitations.

Table 3 reports the resulting rankings.

Observations. The robust ranking highlights parameters whose influence persists across excitation magnitudes. The glucose distribution volume V_G and insulin action parameter k_{p1}

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

consistently dominate sensitivity rankings, indicating structural importance. Parameters such as $k_{\min}$ exhibit strong excitation dependence, suggesting their relevance is context-specific.

1.7 Stage 1A: Window-Length Sensitivity Analysis

Finally, sensitivity rankings were examined over multiple time windows (25, 60, and 120 minutes) to distinguish fast and slow dynamics.

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

Observations. Short time windows emphasize rapid insulin-mediated effects, whereas longer windows reveal the increasing dominance of glucose distribution and clearance parameters. This confirms that parameter importance is strongly time-scale dependent.

Time-Scale Dependence. The strong dependence of sensitivity rankings on the observation window demonstrates that parameter influence is inherently time-scale specific. Short windows emphasize rapid insulin signaling and early glucose excursions, while longer windows capture slower distribution and clearance mechanisms.

This observation suggests that parameter estimation strategies should align estimation windows with the dominant dynamics of interest. Failure to do so may bias parameter estimates toward fast or slow processes depending on the chosen data horizon.

1.8 Methodological Limitations

The sensitivity analysis performed here is local in nature and is therefore valid only in the vicinity of the nominal parameter set. Nonlinear interactions between parameters beyond first-order effects are not captured.

Additionally, sensitivity correlation analysis provides only a heuristic indication of identifiability challenges. Formal structural identifiability analysis is required to rigorously determine which parameters can be uniquely inferred from plasma glucose measurements.

Despite these limitations, local sensitivity analysis remains a valuable first step for parameter screening and experimental design.

1.9 Interim Summary

The sensitivity experiments conducted in Stage 1A demonstrate that:

- 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.

These results motivate subsequent analysis stages focused on identifiability assessment and parameter estimation.

References

References

[1] C. Dalla Man, R. A. Rizza, and C. Cobelli, "Meal simulation model of the glucose–insulin system," *IEEE Transactions on Biomedical Engineering*, vol. 54, no. 10, pp. 1740–1749, Oct. 2007.

[2] O. D. Sánchez, E. Ruiz-Velázquez, A. Y. Alanís, G. Quiroz, and L. Torres-Treviño, "Parameter estimation of a meal glucose–insulin model for T1DM patients from therapy historical data," *IET Systems Biology*, vol. 13, no. 1, pp. 8–15, 2019.