A translational mathematical model linking systemic biomarkers to disease recurrence in diabetic macular edema: a proof-of-concept analysis

Tan Aik Kah

Eye Clinic, Normah Medical Specialist Centre, Kuching, Sarawak, Malaysia

Appendix D. Sensitivity Analysis

Sensitivity analysis was performed to characterize the internal behavior of Model 2 and to verify that its output responds to input variables in a manner consistent with its intended design and underlying biological hypotheses. This is essential for confirming the model's logical consistency and interpreting the relative influence of its parameters.

Model 2:

$$I_{model} = \frac{I_{max}}{1 + \alpha \cdot max(H - H_{target}, 0) + \beta \cdot max(B - B_{target}, 0) + \gamma \cdot \Delta G \cdot 1_A}$$

where:

- I_{model} is the Interval between injections (weeks)
- I_{max} is the maximum interval when $H \leq H_{target}$, $B \leq B_{target}$, $G = 0$
- H is the HbA1c level (%),
- B is the systolic blood pressure (mm Hg),
- G is a measure of glycemic variability (%),
- H_{target} and B_{target} are clinical target values (e.g., 7% and 140 mm Hg, respectively).
- $\Delta G = max(G - G_{target}, 0) \cdot \left(\frac{\textit{average glucose (mg/dL)}}{100}\right)$ scales the glycemic variability penalty.
- 1_A is an indicator function where $1_A = 1$ if $H \leq H_{target}$ and $B \leq B_{target}$, and 0 otherwise. This encodes the conditional activation of the glycemic variability penalty.
- α, β, γ are empirical penalty coefficients, with preliminary values set at, α = 0.54 per %, β = 0.015 per mm Hg, and γ = 0.01 per mg/dL.

D.1 Local Sensitivity Analysis [Figure D1]

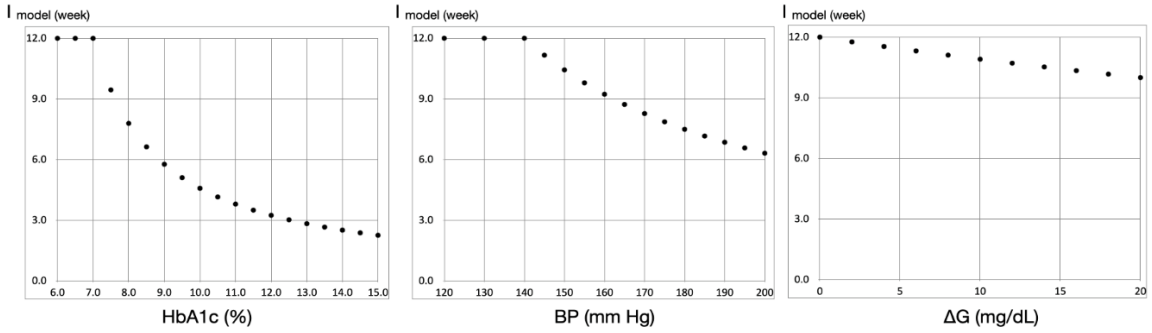
Local sensitivity analysis was performed to evaluate the influence of individual input variables on the I_{model} output. Following a one-at-a-time approach, each input variable was systematically varied across a relevant range while the other variables were held constant at specific values

Sensitivity to H: H was varied from 6.0 to 15.0 (table 1, figure D1A). During this analysis, variable B was fixed at 140, and variable G was fixed at 33 (its target value).

Sensitivity to B: Variable B was varied from 120 to 200 (table 2, figure D1B). During this analysis, H was fixed at its target value of 7, and variable G was fixed at 33 (its target value).

Sensitivity to G (conditional effect): Variable ΔG was varied from 0 to 20 (table 3, figure D1C). To allow for the activation of its conditional term, H was fixed at its target value of 7, and variable B was fixed at its target value of 140.

The scatter plots indicated that I_{model} exhibited the highest sensitivity to changes in H, followed by changes in B, then G.



A B C

Figure D1. Local sensitivity analysis

Table 1. Local Sensitivity to H

H (%)	I_{model} (week)
6.0	12.0
6.5	12.0
7.0	12.0
7.5	9.4
8.0	7.8
8.5	6.6
9.0	5.8
9.5	5.1
10.0	4.6
10.5	4.2
11.0	3.8
11.5	3.5
12.0	3.2
12.5	3.0
13.0	2.8
13.5	2.7
14.0	2.5
14.5	2.4
15.0	2.3

Table 2. Local Sensitivity to B

B (mm Hg)	I_{model} (week)
120	12.0
130	12.0
140	12.0
145	11.2
150	10.4
155	9.8
160	9.2
165	8.7
170	8.3
175	7.9
180	7.5
185	7.2
190	6.9
195	6.6
200	6.3

Table 3. Local Sensitivity to ΔG

ΔG (mg/dL)	I_{model} (week)
0	12.0
2	11.8
4	11.5
6	11.3
8	11.1
10	10.9
12	10.7
14	10.5
16	10.3
18	10.2
20	10.0

D.2 Global Sensitivity Analysis [Figure D2]

A three-dimensional surface plot was generated to visualize the model's internal function across the combined parameter space of HbA1c (x-axis: 6.0% to 14.5%) and systolic blood pressure (y-axis: 120 to 200 mm Hg), with the model-derived interval (I_{model}) on the z-axis.

The surface plot (Figure D2) visually demonstrates the model's built-in hierarchical sensitivity, which is determined by the coefficients α and β. The steep curvature along the HbA1c axis shows that I_{model} decreases rapidly as HbA1c increases, even with

constant BP. In contrast, the gentler slope along the BP axis confirms the model's weaker sensitivity to this parameter. The region where both HbA1c and BP are at or below their clinical targets (conceptually labeled 'Glycemic Variability Zone' in the figure) represents the state where the model's conditional glycemic variability term ($\gamma \cdot \Delta G \cdot 1_A$) would become active, illustrating the designed logic for incorporating residual risk in otherwise well-controlled patients.

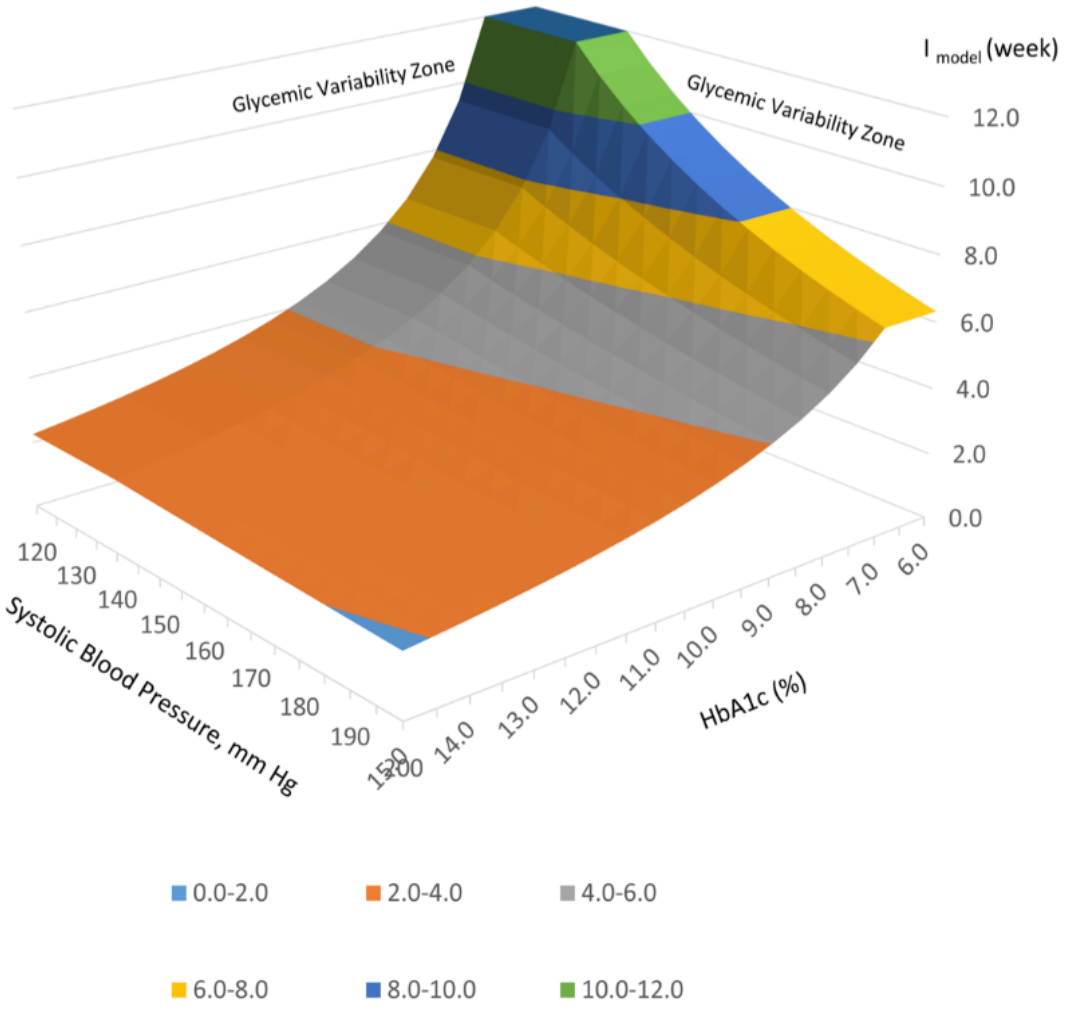


Figure D2. Three-dimensional surface plot providing visual demonstration of the model's built-in hierarchical sensitivity

D.3 Interpretation and Clinical Correlation

The global sensitivity analysis demonstrates the internal behavior encoded in the model: I_{model} is far more responsive to variations in HbA1c than to blood pressure, as dictated by the coefficient ratio. Specifically, the model's weighting of HbA1c (coefficient = 0.54) exerts approximately 36:1 ratio in the coefficient (0.54 for HbA1c vs 0.015 for BP) quantifies this disparity in influence. This modeled differential sensitivity is consistent with the observation that several clinical epidemiological studies have failed to demonstrate a strong association between systemic blood pressure control and anti-VEGF injection frequency.[1,2]

From a mechanistic perspective, the model implies that while blood pressure does contribute to the systemic milieu affecting retinal vascular leakage, it must exceed a relatively higher threshold before impacting re-injecting timing. In contrast, even modest elevations in HbA1c can substantially shorten I_{model}, suggesting that glycemic control remains the dominant systemic factor influencing treatment interval planning.

D.4 Model-Generated Hypothesis Regarding Clinical Observations

The model's structure, with its 36:1 weighting ratio, generates a specific hypothesis: that in a clinical population, the effect of HbA1c on anti-VEGF treatment demand will dominate that of BP, potentially obscuring the detection of a BP signal in conventional statistical analyses. This is not a contradiction of epidemiological findings but a quantitative hypothesis derived from the model's prioritized pathophysiology that could be tested in future studies designed to isolate these effects.

D.4.1 Difference in Analytical Frameworks

Conventional clinical studies assess associations between discrete groupings (e.g., high vs low BP) and outcomes (e.g., injection frequency). These analyses tend to obscure smaller or nonlinear effects, especially in the presence of dominant systemic variables. In contrast, the mathematical model expresses I_{model} as a continuous function of systemic parameters:

$$I_{model} = \frac{I_{max}}{1 + \alpha \cdot max(H - H_{target}, 0) + \beta \cdot max(B - B_{target}, 0) + \gamma \cdot \Delta G \cdot 1_A}$$

where:

$$\Delta G = max(G - G_{target}, 0) \cdot \left(\frac{average\ glucose\ (mg/dL)}{100}\right)$$

This formulation captures nuanced, graded relationships rather than dichotomous outcomes.

D.4.2 Quantification of Sensitivity

This model incorporates different weights for systemic factors, specifically HbA1c coefficient (0.54) and systolic BP coefficient (0.015). This 36:1 ratio mathematically formalizes the model's relative sensitivity to these variables. Holding other parameters constant, a 1% increase in HbA1c has the same effect on shortening I_{model} as a 36 mm Hg increases in systolic BP, a physiologically rare scenario. Therefore, within the model's framework, BP changes with common clinical ranges (e.g., 130-150 mm Hg) exert minimal influence on I_{model} compared to even modest elevations in HbA1c.
This sensitivity difference is further illustrated by examining the partial derivatives:

$$\partial I/\partial H \approx - I_{max} \bullet 0.54 / [1 + \ldots]^2$$

$$\partial I/\partial B \approx - I_{max} \bullet 0.015 / [1 + \ldots]^2$$

These derivatives show that for the same magnitude of increase, HbA1c produces a much steep decline in the injection interval.

D.4.3 Mechanistic Plausibility

The model encodes a hierarchical systemic control mechanism, in which HbA1c directly reflects chronic metabolic load and is strongly linked to endothelial dysfunction and VEGF up-regulation, while BP contributes more modestly to vascular stress and leakage, requiring higher thresholds to become clinically relevant.
From a pathophysiological standpoint, this matches current understanding: glycemic control is the dominant modifiable systemic factor in the progression and treatment responsiveness of DME, while hypertension may act as a secondary or amplifying factor.

References

1. Wong WM, Chee C, Bhargava M, et al. Systemic factors associated with treatment response in diabetic macular edema. *J Ophthalmol*. 2020;2020:1875860. doi:10.1155/2020/1875860
2. Matsuda S, Tam T, Singh RP, et al. The impact of metabolic parameters on clinical response to VEGF inhibitors for diabetic macular edema. *J Diabetes Complications*. 2014;28:166-70. doi:10.1016/j.jdiacomp.2013.11.009