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 B: Model 2 (Empirical Model): Reconciling Mechanistic Dynamics with Clinical Feasibility.

B.1 Defining priorities

An empirical penalty model is derived to operationalize the systemic risk hierarchy into a tractable clinical framework. The model structure is designed to test the hypothesis that anti-VEGF injection intervals should be inversely proportional to the magnitude by which HbA1c (H) and systolic blood pressure (B) exceed clinical targets, with glycemic variability (G) acting as a conditional, secondary modulator.

B.2 Variables

- I_{model} is Interval between injections (weeks)
- H is the HbA1c level (%),
- B is the systolic blood pressure (mm Hg),
- G is a measure of glycemic variability (percent coefficient of variation, %CV),
- $\Delta G = max(G - G_{target}, 0) \cdot \left(\frac{average\ glucose\ (mg/dL)}{100}\right)$ scales the glycemic variability penalty.
- H_{target}, B_{target} and G_{target} are clinical target values (e.g., 7%, 140 mm Hg, and 36% respectively)[1-3]
- I_{max} is the maximum interval when $H \leq H_{target}$, $B \leq B_{target}$, $G = 0$ (12 weeks was used for the calculation of illustrative example cases)[4]
- 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.

The coefficients α, β, γ are preliminary scaling parameters, derived from published epidemiological data as detailed below, which translate biomarker deviations into interval adjustments within the model's structure.

B.3 Step-By-Step Derivation of Empirical Model 2

B.3.1 Initial: If all parameters are at target levels ($H \leq H_{target}$, $B \leq B_{target}$, $G = 0$), the interval between injections should be at its maximum (I_{max}).

Baseline state (all parameters at target):

$$I_{model} = \frac{I_{max}}{1+0+0+0} = I_{max} \qquad \text{(no penalties)}$$

B.3.2 Penalize Elevated HbA1c and Blood Pressure. If H or B exceed their targets, the interval shortens proportionally to their excess. A linear relationship was assumed for this initial model, translating excess biomarker levels directly into interval penalties.

$$\text{Penalty for } H = \alpha \cdot \max(H - H_{target}, 0), \text{ and}$$

$$\text{Penalty for } B = \beta \cdot \max(B - B_{target}, 0),$$

max (…) ensures only excess above the target is penalized. Coefficients α and β determine how much H and B affect the interval.

B.3.3 Adding Glycemic Variability (G) as a Secondary Factor. The model encodes the hypothesis that G exerts a significant influence on recurrence risk primarily after H and B are controlled. In order to enforce this conditional activation, an indication function (1_A) is employed.

Glycemic variability can be characterized through both relative and absolute metrics. The Coefficient of Variation (CV), a widely used relative measure, quantifies the standard deviation of glucose as a percentage of its mean. Consequently, for a consistent degree of relative variability, such as a fixed CV, individuals with differing average glucose levels will inherently manifest distinct absolute values of glycemic variability, as represented by their standard deviation.

The relationship between standard deviation, SD and CV is given by the formula:

$$SD = \frac{CV \cdot Average\ glucose}{100}$$

For example, a patient with an average glucose of 150 mg/dL and a CV of 35% will demonstrate a greater absolute glucose fluctuation (standard deviation of 52.5 mg/dL) compared to a patient with an average glucose of 100 mg/dL maintaining the same 35% CV (standard deviation of 35 mg/dL). This critical distinction between relative and absolute measures is paramount for the accurate interpretation of glycemic variability. Therefore, in this model, the penalty for G is calculated by converting the percentage difference between G and G_{target} to standard deviation (mg/dL) based on the patient's average glucose.

The penalty for G is given by:

$$\gamma \cdot \Delta G \cdot 1_A$$

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

Indicator function:

- 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.

B.3.4 Combining All Terms into a Single Formula. The interval I is inversely proportional to the total penalty (denominator).

$$I_{model} = \frac{I_{max}}{1 + (Penalty\ for\ H) + (Penalty\ for\ B) + (Penalty\ for\ G)}$$

Substituting the penalties:

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

where

- $\Delta G = max(G - G_{target}, 0) \cdot \left(\frac{\text{average glucose (mg/dL)}}{100}\right)$
- 1_A is an indicator function where $1_A = 1$ if $H \leq H_{target}$ and $B \leq B_{target}$, and 0 otherwise

Rationale for the Denominator. "1" ensures the formula does not divide by zero and represents the baseline (no penalties). **Primary control (HbA1c and blood pressure).** If $H > H_{target}$ or $B > B_{target}$, the interval shortens proportional to the excess of H and B. Coefficient α and β reflect the priority of controlling HbA1c and blood

pressure. **Secondary control (glycemic variability).** Once $H \leq H_{target}$ or $B \leq B_{target}$, G influences the interval. Higher G reduces I_{model}, with sensitivity γ.

The structure of this model formalizes a testable clinical hypothesis: that management priorities follow a hierarchy where HbA1c and BP are addressed first, with glycemic variability considered primarily in the context of good primary control.

B.4 Preliminary Parameterization from Published Data

To move the model from a theoretical structure to a testable form, initial values for the empirical coefficients (α, β, γ) were derived by calibrating the model's penalty terms to published risk ratios from epidemiological studies. This provides a biologically plausible, first-order parameterization for proof-of-concept testing. These coefficients are not final and are intended as a starting point for future data-driven optimization.

B.4.1 Coefficient α .

A value for α was approximated by calibrating the model's HbA1c penalty term to the relative risk of microvascular complications reported in the UKPDS. It was determined that a 1% drop in HbA1c reduced microvascular complications by 30-40%.[5] The relative risk (RR) for a 1% increase in HbA1c:

$$RR = \frac{1}{1 - risk\ reduction}$$

For a 35% midpoint risk reduction:

$$RR = \frac{1}{1 - 0.35} = 1.54$$

This corresponds to a 54% increase in the relative risk of microvascular complications per 1% increase in HbA1c. In the formula, the interval I is inversely proportional to the risk. For a 1% increase in HbA1c:

Risk multiplier = 1 + $\boldsymbol{\alpha}$ ⇒ 1 + $\boldsymbol{\alpha}$ = 1.54 ⇒ $\boldsymbol{\alpha}$ = 0.54 per % HbA1c

B.4.2 Coefficient β .

A value for β was approximated by calibrating the model's BP penalty term to the hazard ratios for DME development reported by Angaramo et al.[6] The coefficient β will be derived using hazard ratios (HR) for developing DME across blood pressure categories. The goal is to map the HRs to BP excess above the target (120 mm Hg systolic) and calculate a sensitivity coefficient β.

Step1: Define BP categories and Excess. Assume systolic BP thresholds and midpoints for simplification:

BP category	Systolic BP range (mm Hg)	Midpoint (mm Hg)	Excess BP (ΔB)
Normotensive	<120	110	0
Pre-hypertension	120-139	130	10
Stage 1 hypertension	140-159	150	30
Stage 2 hypertension	≥160	170	50

Step 2: Relate Hazard Ratios (HR) to Excess BP

The study reports HRs for DME risk relative to the normotensive group:

Pre-hypertension : HR = 1.8 (ΔB = 10 mm Hg)

Stage 1 hypertension: HR = 2.0 (ΔB = 30 mm Hg)

Stage 2 hypertension: HR = 3.3 (ΔB = 50 mm Hg)

Assuming a linear relationship between log (HR) and excess BP:

$$\ln(HR) = \beta \cdot \Delta B$$

Step 3: Solve for β (slope) using linear regression.

$\Delta B(x)$	$\ln(HR)\ (y)$
10	ln(1.8) = 0.5878
30	ln(2.0) = 0.6931
50	ln(3.3) = 1.1939

$$\beta = \frac{n\sum(xy) - \sum(x) \cdot \sum(y)}{n\sum(x^2) - (\sum(x))^2}$$

where :

n = 3, $\sum(x)$ = 90, $\sum(y)$ = 2.4748

$\sum(xy)$ = 86.366, $\sum(x^2)$ = 3500

Thus:

$$\beta = \frac{3 \cdot 86.366 - 90 \cdot 2.4748}{3 \cdot 3500 - 90^2} = 0.015\ per\ mm\ Hg$$

The penalty for $B = \beta \cdot max(B - B_{target}, 0)$ approximates the log-hazard ratio for DME risk.

Thus:

β = 0.015 per mm Hg.

Step 4: Validation. For stage 2 hypertension (ΔB = 50)

$$Penalty = 0.015 \cdot 5 = 0.75 \quad \Rightarrow \quad HR = e^{0.015 \cdot 50} = e^{0.75} = 2.12$$

This slightly underestimates the study HR (3.3), but aligns conservatively given nonlinear risk escalation at extreme blood pressure.

Note on Target Value: The coefficient β was derived using 120 mm Hg as the clinical target (aligned with the study's normotensive reference). For consistency with general diabetes care guidelines, the model applies this coefficient to excess above a B_{target} of 140 mm Hg. This approximation implies the model may conservatively underestimate the interval-shortening effect of BP in the 120-140 mm Hg range, which is acceptable for this preliminary, hierarchical model where HbA1c is the dominant driver.

B.4.3 Coefficient γ.

A value for γ was approximated by calibrating the model's glycemic variability penalty term to the hazard ratio associated with fasting glucose variability reported by Hsieh et al.[7] Study data demonstrated that for DME, each 1 mg/dL increase in fasting glucose standard deviation (SD) was associated with a hazard ratio (HR) of 1.008 (p = 0.038).

Step 1: Relating HR to the Model's Coefficient γ. In survival analysis, the HR for a continuous variable G is modeled as:

$$HR = e^{\gamma \cdot \Delta G}, \qquad \gamma \text{ is the coefficient per unit change in } G.$$

Rearranging to solve for γ:

$$\gamma = \frac{\ln (HR)}{\Delta G}$$

In this model, the interval I is inversely proportional to the penalty term:

$$I_{model} = \frac{I_{max}}{1 + (Penalty\ for\ H) + (Penalty\ for\ B) + (Penalty\ for\ G)}$$

The penalty for G is $\gamma \cdot \Delta G$, which approximates the log-hazard ratio for DME risk:

$$\gamma \cdot \Delta G \approx \ln(HR)$$

Thus:

$$\gamma = \frac{\ln(HR)}{\Delta G}$$

Step 2: Calculation for SD of fasting glucose. Assume ΔG = increase in SD of fasting glucose (in mg/dL):

$$HR = 1.008\ per\ 1\ mg/dL\ increase\ in\ SD$$

$$\ln(1.008) = 0.00797$$

$$\gamma = \frac{\ln(1.008)}{1\ mg/dL} = 0.00797\ per\ \frac{mg}{dL} \approx 0.01\ per\ mg/dL$$

Step 3: Validation in the Model. For a patient with controlled HbA1c and blood pressure, and increased glycemic variability, ΔG of 30 mg/dL

$$\text{Penalty} = 0.01 \cdot 30 = 0.3$$

$$I_{model} = \frac{I_{max}}{1 + 0.3} = 0.77 \cdot I_{max}$$

A 30 mg/dL increase in SD reduces the interval by about 23%. This aligns with the study's $HR \approx 1.008^{30} \approx 1.27$ (27% risk increase).

B.5 Hypothetical case examples with corresponding calculations

Case 1: Poor HbA1c and blood pressure (G is irrelevant).

$H = 8\%$, $B = 150\ mm\ Hg$, $G = 45\%$,

$H_{target} = 7\%$ $B_{target} = 140\ mm\ Hg$, $G_{target} = 36\%$

$\alpha = 0.54$, $\beta = 0.015$, $\gamma = 0.01$,

Average glucose = 183 mg/dL, $I_{max} = 12\ weeks$:

$$I_{model} = \frac{12}{1 + 0.54(8 - 7) + 0.015(150 - 140) + 0} = 7\ weeks$$

Case 2: Controlled HbA1c and blood pressure.

$H = 6.5\%,$	$B = 130\ mm\ Hg,$	$G = 45\%,$
$H_{target} = 7\%$	$B_{target} = 140\ mm\ Hg,$	$G_{target} = 36\%$
$\alpha = 0.54,$	$\beta = 0.015,$	$\gamma = 0.01,$
Average glucose	= 140 mg/dL,	$I_{max} = 12\ weeks$:

$$I_{model} = \frac{12}{1 + 0 + 0 + 0.01(45 - 36)(\frac{140}{100})} = 10.7\ weeks$$

This derived empirical model translates a pathophysiological hierarchy into a quantifiable, testable framework. The preliminary parameterization provides a concrete basis for the proof-of-concept analyses presented in the main manuscript, establishing a transparent link between published population risks and a model for personalized interval estimation.

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