Simulation of Gastrointestinal Adverse Events and Weight Loss under GLP-1 Receptor Agonist Treatment

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1. Introduction

GLP-1 receptor agonists are highly effective for weight management, but nausea remains a significant side-effect. Current clinical practice employs dose titration using a standard schedule to improve tolerability. Optimizing titration schedules requires balancing of two competing objectives: Maximizing weight loss efficacy while minimizing nausea burden.

We present a nausea time-to-event (TTE) simulation framework incorporating tolerance development dynamics. Combined with an established weight loss model, we propose a conceptual optimization framework for personalized dose titration.

2. System and Optimization Problem

One coupled ODE system maps weekly doses to two outcomes:

$$\mathbf{u} \xrightarrow{\text{PK}} c(t) \xrightarrow{\dot{\bar{c}}=\beta(c-\bar{c})} \bar{c}(t) \longrightarrow \begin{cases} \Delta BW\% & \text{(efficacy)} \\ P(\text{nausea}) & \text{(tolerability)} \end{cases}$$

Scalarized multi-objective optimization framework:

$$\min_{\mathbf{u}} \ \alpha \cdot \underbrace{H(T)}_{\text{nausea}} + (1-\alpha) \cdot \underbrace{\Delta BW\%(T)}_{\text{relative weight loss}}$$

$$u_{\min} \leq u_k \leq u_{\max}, \quad k = 1, \ldots, T$$

Absorption

$$\dot{A}(t) = -R_{AC}$$
$$\dot{C}(t) = R_{AC} - R_{CP} - R_e$$
$$\dot{P}(t) = R_{CP}$$

Running Weekly Average Concentration

$$c(t) = \frac{C(t)}{V \cdot M_W}$$
$$\dot{\bar{c}}(t) = \beta(c(t) - \bar{c}(t))$$

R_x: Drug transport rates, V: Volume of distribution, M_W: Molecular mass of drug.

Nausea (TTE)

$$\dot{TOL}(t) = k_{TOL}\left(\alpha_{TOL}\bar{c}(t) - [TOL(t) - 1]\right)$$
$$TOL(0) = 1$$

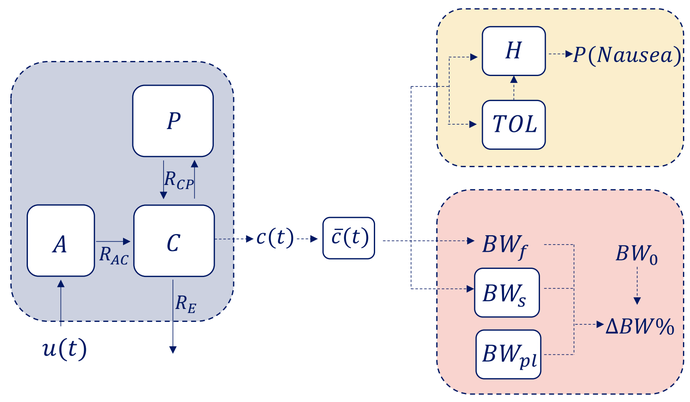
$$EC_{50}(t) = EC_{50,0} \cdot TOL(t)$$
$$\dot{H}(t) = \lambda \cdot \frac{\bar{c}(t)^{Hill}}{EC_{50}(t)^{Hill} + \bar{c}(t)^{Hill}}$$
$$P(nausea) = 1 - \exp(-H)$$

k_{TOL}: Rate of tol. adaptation, α_{TOL}: Magnitude of tol. development, $EC_{50,0}$: Conc. for 50% of maximum effect at baseline, λ: Inst. hazard, $Hill$: Hill coefficient (controls steepness of dose-response).

Body Weight Change [1]

$$BW = BW_0 + BW_s - BW_f + BW_{pl}$$
$$\dot{BW}_s \sim \frac{E_{max,s} \cdot \bar{c}(t)}{EC_{50,BW} + \bar{c}(t)},$$
$$BW_f \propto \frac{E_{max,f} \cdot \bar{c}(t)}{EC_{50,BW} + \bar{c}(t)}$$
$$\Delta BW\% = 100 \cdot \frac{BW - BW_0}{BW_0}$$

BW_0: Baseline body weight, BW_s: Slow drug effect, BW_f: Fast drug effect, BW_{pl}: Placebo effect, E_{max}: Maximum effect, $EC_{50,BW}$: Conc. for 50% of maximum effect. Efficacy parameters have been modified compared to the original model to emulate future GLP-1 variants.



3. Simulations over Different Tolerance Parameters

The proposed nausea TTE model captures exposure- and time-dependent tolerance development, with α_{TOL} controlling the magnitude of the tolerance and k_{TOL} controlling the speed of adaptation, resulting in distinct nausea risk profiles.

Notably, a slow titration schedule does not universally minimize the risk of having a nausea event; under certain tolerance profiles, it may delay the risk rather than prevent it.

Lower exposure may decrease nausea risk, but also yield less or slower weight loss - motivating the dose optimization framework.

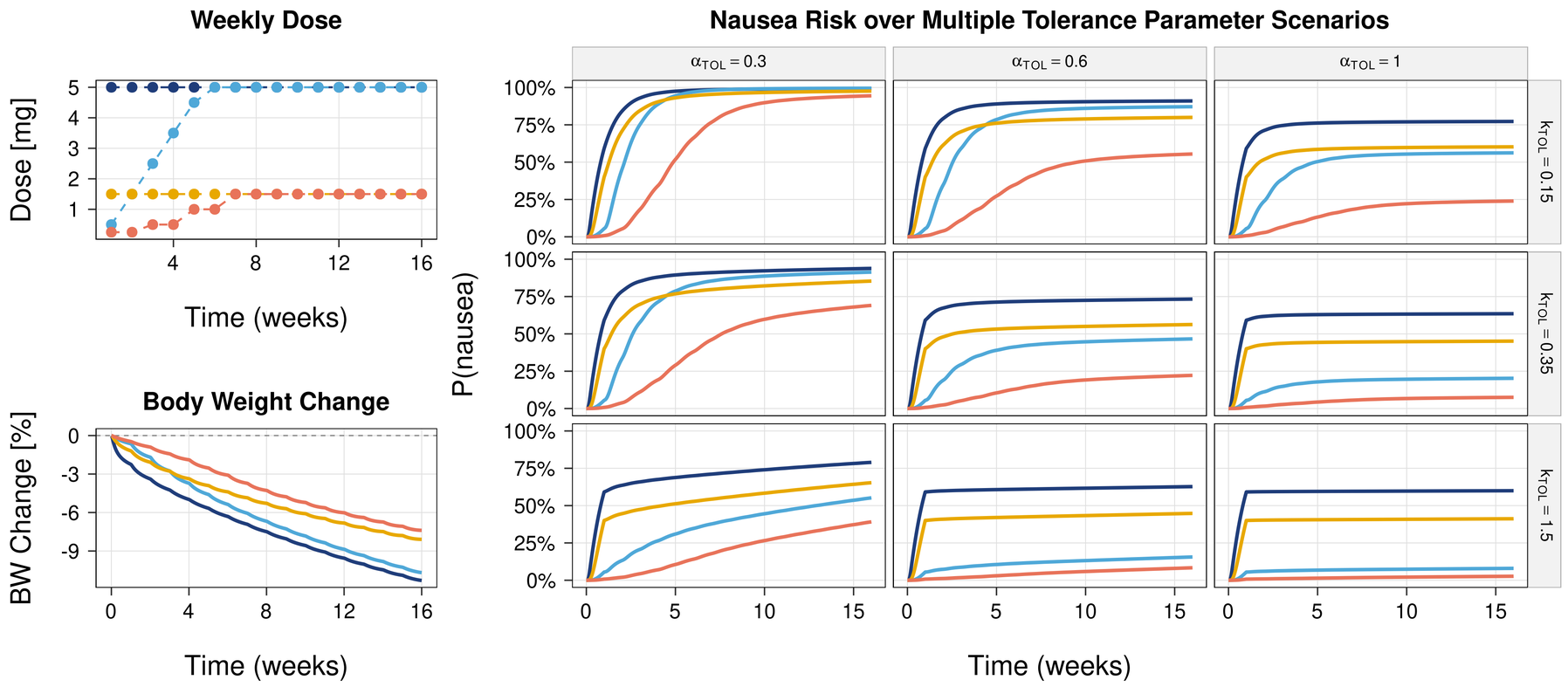


Figure 1: Body weight loss and nausea risk for different dosing schedules.

4. Dosing Optimization Example

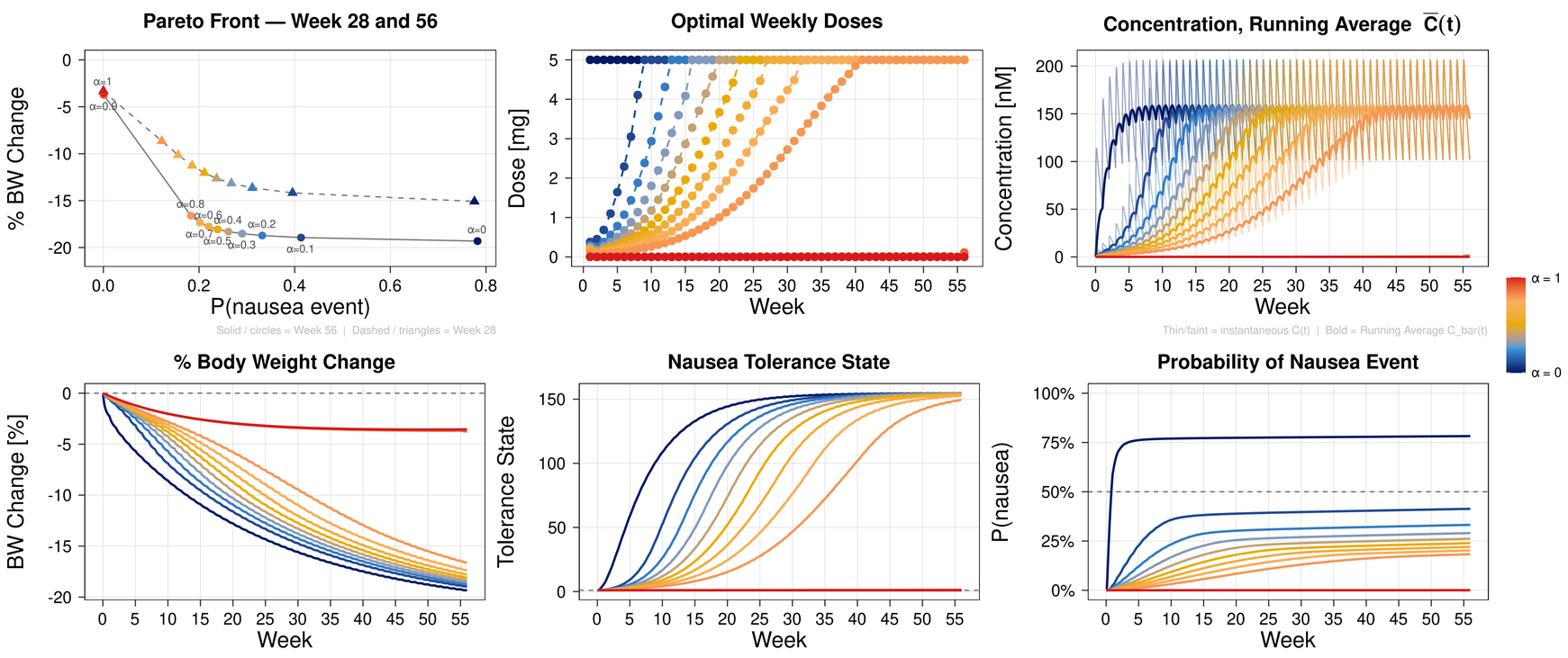


Figure 2: Dosing optimization example with horizon $T = 56$ weeks, and with dosing limits $u_{\min} = 0$ mg, and $u_{\max} = 5$ mg.

Using $k_{TOL} = 0.15$ and $\alpha_{TOL} = 1$, the optimization framework is evaluated on a representative virtual patient over a 56-week titration period, across a range of nausea-weight loss trade-off parameters (α).

For this choice of tolerance parameters, the Pareto front exhibits a nonlinear trade-off: Modest reductions in nausea risk can be achieved with relatively small sacrifices in weight loss efficacy at lower α-values, while $\alpha \to 1$ leads to disproportionately reduced weight loss.

The optimization is open-loop and terminal-objective based, naturally motivating a closed-loop extension with receding horizon control, enabling dynamic dose adjustments as patient response evolves.

5. Conclusion

- By combining the TTE nausea model with a weight loss model, optimal dose titration for future GLP-1 can be planned by an open-loop control framework, with a natural extension to closed-loop receding horizon control.
- Solving the optimization problem repeatedly across varying α approximates the Pareto optimal trade-off between nausea risk and weight loss for a given patient.
- To be clinically relevant, the nausea model requires refinement and parameter estimation from data. Incorporation of covariates would further enable personalized predictions and dose optimization.

Contact: Mathilde Guldbæk Arentsen, mguar@dtu.dk **References:** [1]: Strathe et al. Diabetes. Obes. Metab. 2023;25:3171-3180