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

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Abstract

Obesity is increasing rapidly worldwide, and the global prevalence is projected to reach 20% by 2030 [1]. Glucagon-like peptide-1 (GLP-1) receptor agonists, such as Semaglutide, have demonstrated substantial efficacy in inducing weight loss. However, significant proportions of gastrointestinal (GI) adverse events, such as nausea, remain an important challenge [2]. These events may negatively affect treatment adherence and, consequently, limit the full clinical benefit of therapy.

We present a time-to-event modelling and simulation framework to characterize the risk of GI adverse events during treatment with GLP-1 receptor agonists. The event process is described by an instantaneous risk driven by drug exposure through an Emax relationship. To capture the clinically observed decrease in GI event risk over time, drug tolerance is modelled as a latent dynamic state that increases during treatment, reducing the risk of having an event over time and exposure.

Semaglutide exposure is simulated using a previously published pharmacokinetic model [3] and dosing regimens from a phase 2 clinical trial [4]. Based on these exposure profiles, we explore the risk of developing GI adverse events across multiple parameter scenarios.

Furthermore, we simulate treatment-induced weight loss using the Semaglutide model by Strathe et al. [5] driven by the same simulated exposure profiles. Evaluating both GI adverse events and weight loss under common exposure scenarios enables an exploratory assessment of how alternative dosing and titration regimens may influence both tolerability and efficacy. The framework therefore provides a basis for future model-informed dosing optimization, pending estimation of GI model parameters from observed adverse event data.

We illustrate and discuss that the optimal model-based dosing can be formulated as an optimal control problem. Optimal drug dosing is an important new application of process control involving both the optimal dosing profile, but also a way to incorporate feedback.

References

[1] World Obesity Federation. World obesity atlas 2022. `https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022`, March 2022. Accessed: 2026-05-08.

[2] Melanie Davies, Louise Færch, Ole K Jeppesen, Arash Pakseresht, Sue D Pedersen, Leigh Perreault, Julio Rosenstock, Iichiro Shimomura, Adie Viljoen, Thomas A Wadden, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (step 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *The Lancet*, 397(10278):971–984, 2021.

[3] Rune V Overgaard, Philip H Delff, Kristin CC Petri, Thomas W Anderson, Anne Flint, and Steen H Ingwersen. Population pharmacokinetics of semaglutide for type 2 diabetes. *Diabetes Therapy*, 10(2):649–662, 2019.

[4] Michael A Nauck, John R Petrie, Giorgio Sesti, Edoardo Mannucci, Jean-Pierre Courreges, Marie L Lindegaard, Christine B Jensen, and Stephen L Atkin. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes care*, 39(2):231–241, 2016.

[5] Anders Strathe, Deborah B Horn, Malte Selch Larsen, Domenica Rubino, Rasmus Sørrig, Marie Thi Dao Tran, Sean Wharton, and Rune Viig Overgaard. A model-based approach to predict individual weight loss with semaglutide in people with overweight or obesity. *Diabetes, Obesity and Metabolism*, 25(11):3171–3180, 2023.

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