In silico model and sensitivity analysis of plasma glucose regulation: towards an individualized maximal model for physiology and pathophysiology

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The present study focuses on metabolic hormone regulation of plasma glucose and its role in type 2 diabetes (T2D). We propose an individualized maximal model based on plasma glucose dynamics in healthy individuals, considering key substrates and hormones after oral intake. The model accurately simulates T2D pathophysiology, including effects of free fatty acids, glucagon, GLP-1, ghrelin and leptin on insulin and glucagon levels. Model simulations closely match clinical data from oral glucose tolerance tests in normal and T2D subjects. However, the model's complexity poses challenges for parameter estimation. To address this, we conducted a Sobol sensitivity analysis to identify influential parameters and simplify the model while preserving its dynamic interpretation. This approach reveals critical parameters influencing glucose regulation, aiding in understanding model dynamics and improving computational efficiency.

Keywords: Glucose homeostasis, individualized maximal model, metabolic hormones, Sobol sensitivity analysis, type 2 diabetes.

most determinants of plasma glucose regulation, such as kinetics of glucagon[15,16], FFA[17,18], incretins[19], leptin[20] and ghrelin[21], provides a comprehensive understanding of whole-body glucose regulation. Building a diagnostic tool for T2D is challenging due to uncertainties and physiological complexities. It is, therefore, of utmost significance to measure the control hormones that influence glucose homeostasis.

The Bergman minimal model was the first glucose-insulin dynamics model that used IVGTT to study glucose intolerance. However, it has several limitations, including overestimating glucose effectiveness and underestimating insulin sensitivity[22]. An extended minimal model was developed by Roy *et al.*[17] and Bonet *et al.*[18] with FFA dynamics and is well-suited for estimating plasma FFA dynamics.

Dalla Man *et al.*[23] found that a nonlinear dynamic system model predicts glucose appearance rate accurately in elderly and diabetic patients. The glucose–insulin–glucagon system and their interactions during meals are described in some publications[24,25]. It associates the plasma concentration of glucose, insulin, and glucagon with their fluxes like endogenous glucose production, utilization, renal ex-