A mechanistic model of gastric emptying of caloric liquids and solids

for the use in physiologically-based pharmacokinetic models

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Introduction

The rate of gastric emptying (GE) defines the pharmacokinetic profiles of orally administered drugs and the appearance of ingested glucose in systemic circulation. GE gets slowed down after meal ingestion, whereby the form and composition of the meal defines the emptying rate. Available models of GE used in physiologically-based pharmacokinetic (PBPK) and glucose homeostasis models do not distinguish between the energy sources and describe GE by non-mechanistic functions.

Objectives

Our objective was to develop a mechanistic model of GE for solids and liquids that is able to describe the effects of different meal compositions and integrate it into the PB QSP Diabetes Platform [1, 2].

Methods

The model of GE is based on the standard PBPK model implemented in PK-Sim® and has been extended in MoBi® as part of the Open Systems Pharmacology Suite (OSPS), version 7.3 [3].

Data on either gastric emptying or gastric retention of unabsorbable marker administered together with water, glucose, lipid, or protein solutions, or liquid and solid mixed meals were used to identify model structure and parameter values.

The model was coupled with a mechanistic incretin secretion model [4] developed with intraduodenal glucose perfusion data to assess the predictive performance of incretin secretion following oral glucose administration.

Results I – Gastric emptying of liquids

Schematic representation of the modeled processes is presented in **Figure 1**. The stomach is subdivided into the proximal and the distal parts. After oral ingestion, liquids are immediately distributed with 30% into distal and 70% into the proximal part. Upon entering the duodenum, nutrients slow down the transfer between the stomach parts and the release into duodenum. Carbohydrates (CHO), proteins, and lipids affect the rate of GE into duodenum, while only CHO and proteins affect the transfer between the proximal and distal parts of the stomach.

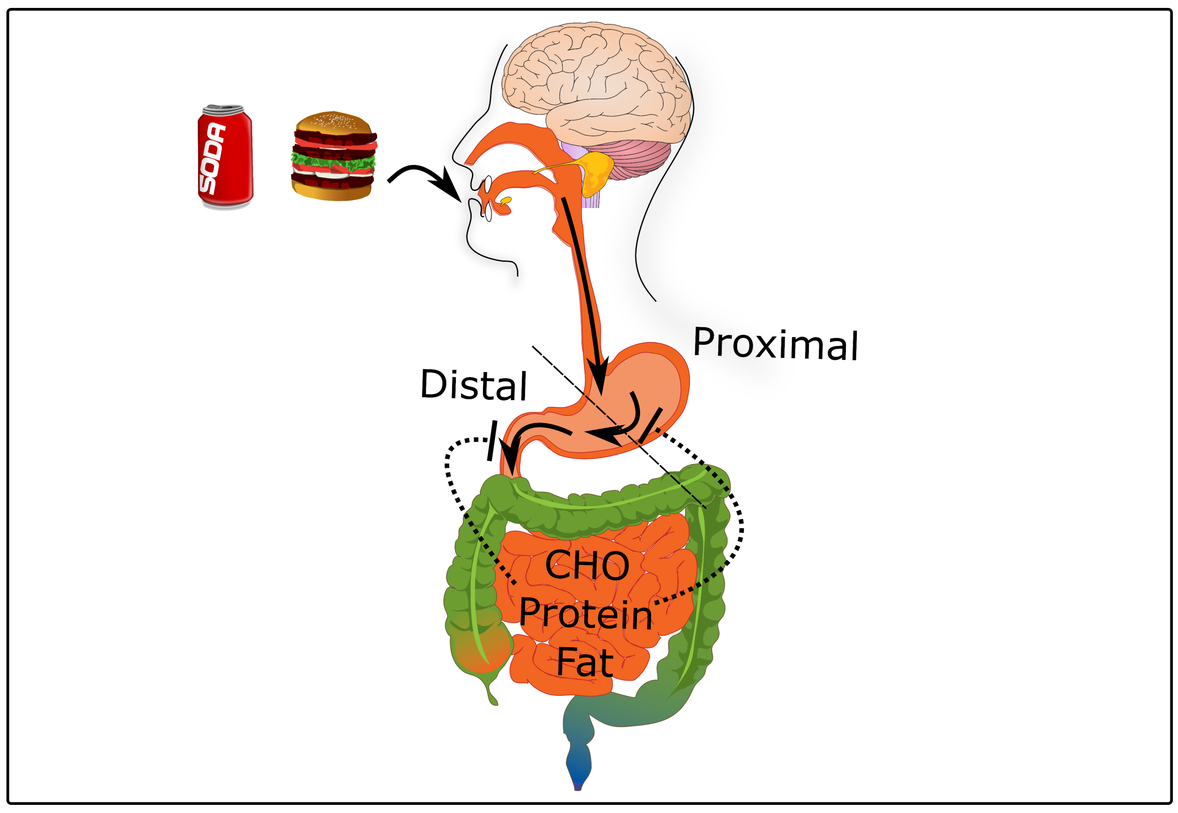

Figure 1: Schematic representation of the modelled stomach structure: The stomach is divided into proximal and distal parts. Ingested meals enter the stomach and are transported from the proximal into the distal parts and then transported into the duodenum. Carbohydrates (CHO), proteins, and lipids in the duodenum slow down the transfer rate between the proximal and the distal stomach parts, and the rate of release of stomach content into duodenum. Only dissolved parts of the meal exert the inhibitory effects.

Exemplary simulated retention of a 75 g glucose solution in the different parts of the stomach is shown in **Figure 2 Panel A**.

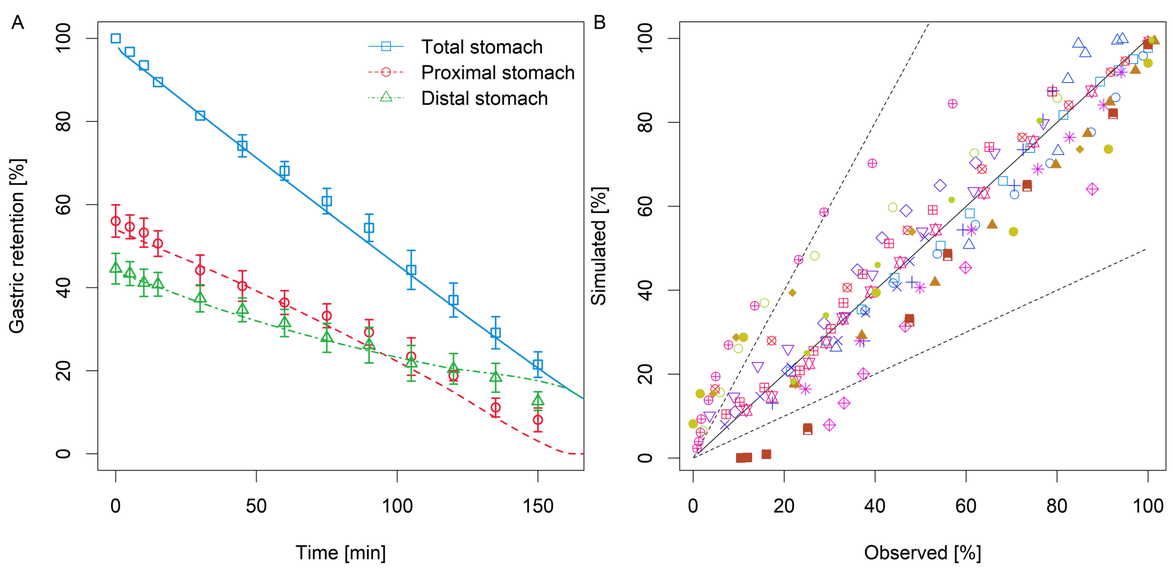

Figure 2: Simulations of gastric retention after administration of liquid meals: Panel A: Simulated (lines) and observed (symbols ±SD) retention of an unabsorbable marker administered together with 75 g glucose. Data from [5] **Panel B**: Simulated (y-axis) vs. observed (x-axis) total gastric retention or emptying values from 25 different sources.

A simulated-versus-observed comparison of the mean model with a total of 25 different data sources, including administrations of water, glucose, fat, and protein solutions, and complex mixed meals, is shown in **Figure 2 Panel B**. Out of 198 compared points, 32 (16%) are outside of the two-fold distance.

Results II – Gastric emptying of solids

Ingested solids have to be grounded to a chyme before being released into the intestine, which is modeled as a transfer from proximal into distal stomach. Nutrients that are in solid and chyme forms cannot be absorbed or exert inhibitory effects on GE. A small fraction of solid nutrients is digested in stomach and duodenum, slowing down the release of both, liquids and solids; changing the digestion rate could reflect the different types of food.

Figure 3 Panel A shows simulated and observed gastric retention of the liquid and solid form of a test meal (scrambled eggs with white bread and a glass of water), **Figure 3 Panel B** presents the comparison of simulated results with observed values from 7 different sources. Emptying of solids is less variable between the datasets compared with the emptying of liquids, and only 5 out of 178 points (2%) are outside of the two-fold distance.

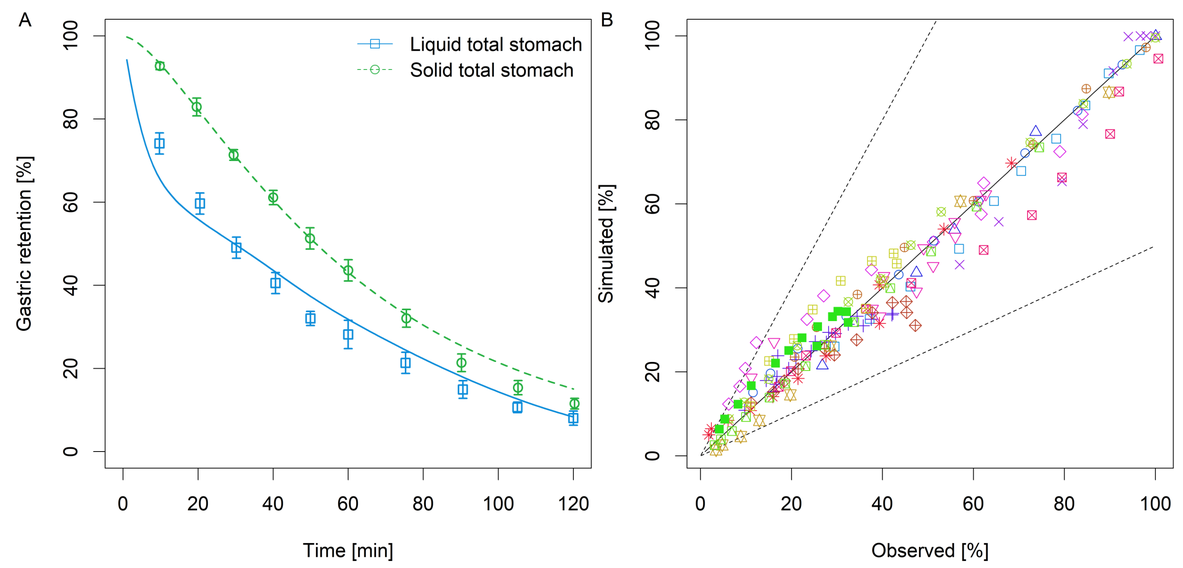

Figure 3: Simulations of gastric retention after administration of mixed solid and liquid meals: Panel A: Simulated (lines) and observed (symbols ±SD) retention of unabsorbable markers administered together a mixed solid and liquid meal. Data from [6] **Panel B**: Simulated (y-axis) vs. observed (x-axis) gastric retention values from 7 different sources.

Results III – Prediction of incretin secretion

The developed model of GE was coupled with the mechanistic model of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) [4] to predict incretin secretion in the response to oral glucose administration. The coupled model shows a good predictive performance for the secretion of GLP-1 and GIP after administration of 50 and 100 g of liquid glucose, as depicted in **Figure 4**.

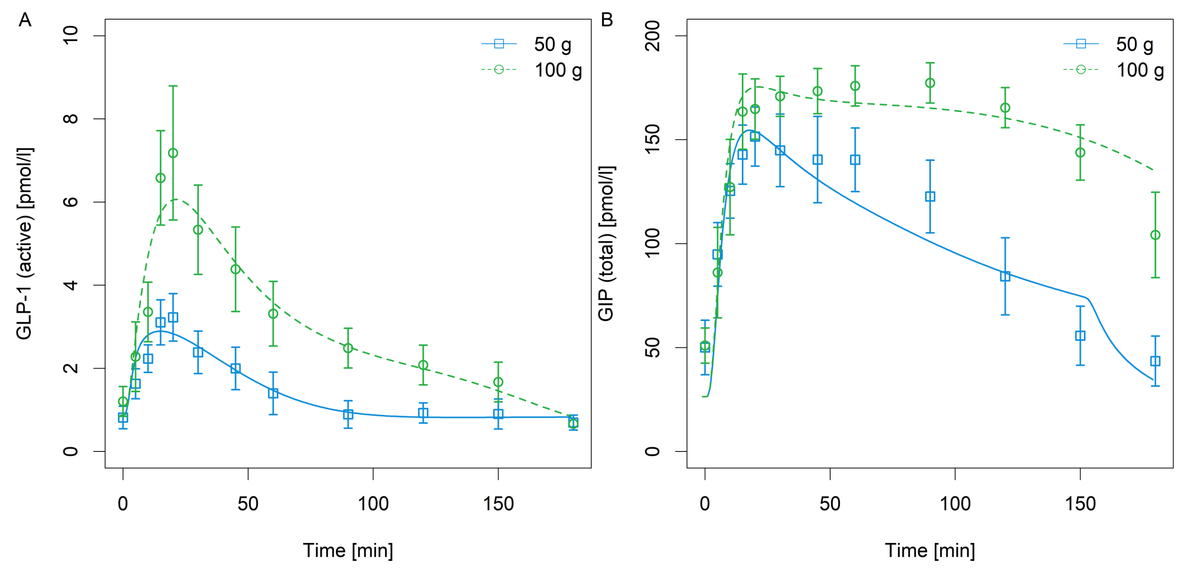

Figure 4: Prediction of incretin response to oral administration of glucose solution: Panel A: Simulated (lines) and observed (symbols ±SD) concentrations of GLP-1 after administration of 50 g and 100 g glucose solution. Data from [7]. **Panel B**: Simulated (lines) and observed (symbols ±SD) concentrations of GIP after administration of 50 g and 100 g glucose solution. Data from [7].

Conclusions

We present a refined mechanistic model of GE that incorporates the distinct effects of CHO, lipids, and proteins and explicitly considers liquid and solid phases of the administered meals. Such a model can improve accuracy drug absorption and bioavailability predictions when the influence of meal composition are investigated with PBPK modeling. Combined with the mechanistic model of incretin metabolism and secretion, the new GE model allows simulation of complex successive meal patterns including a detailed characterization of glucose absorption and the dependent dynamics of incretin hormone secretion. The model is therefore a valuable extension not only to general PBPK modeling, but especially for the application with complex PB-QSP models of glucose homeostasis.

References

[1] Balazki, P. et al. CPT: Pharmacomet Syst Pharmacol. 2018 DOI:10.1002/psp4.12359

[2] Schaller, S. et al. CPT: Pharmacomet Syst Pharmacol. 2013 Aug;2(8):e65

[3] www.open-systems-pharmacology.org

[4] Balazki P et al. Abstracts of the Annual Meeting of the Population Approach Group in Europe (PAGE) (2018)

[5] Horowitz M. et al. Diabetologia. 1993 Sep;36(9):857–62

[6] Bennink R. et al. Eur J Nucl Med. 1998 Sep;25(9):1293-9

[7] Schirra, J. et al. J Clin Invest. 1996 Jan 1;97(1):92-103