A Physiologically Based Pharmacokinetic Model of Dulaglutide

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Background

This Humboldt Internship project develops a physiologically based pharmacokinetic (PBPK) model of dulaglutide, a GLP-1 receptor agonist. The objective of this project is to enhance our understanding of dose-dependency of systemic exposure to dulaglutide, and the different underlying causes of intraindividual variability in efficacy of diabetes treatment with dulaglutide.

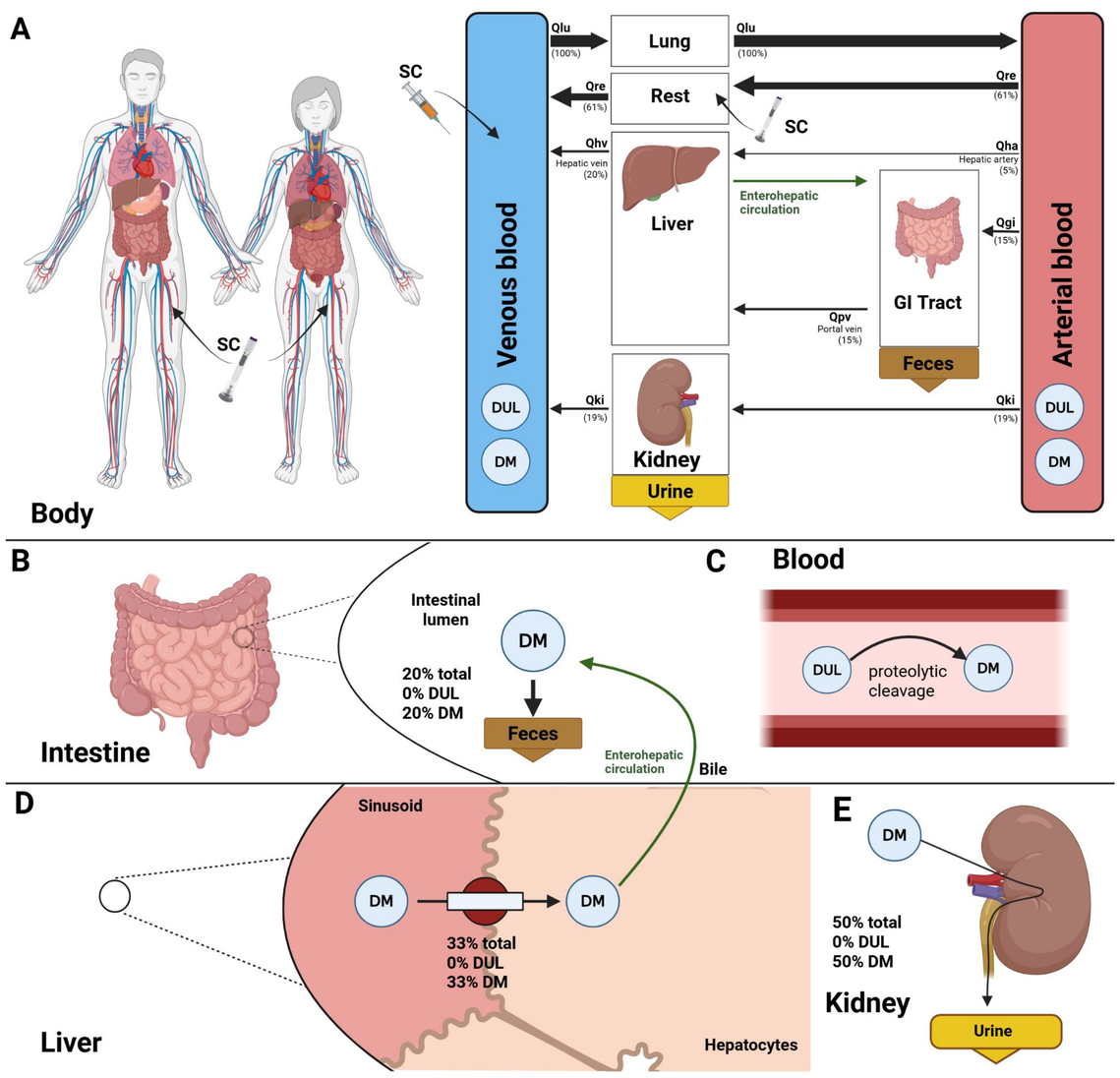

Figure 1. Physiologically-based pharmacokinetic (PBPK) model of dulaglutide. **(A)** The whole-body model illustrates subcutaneous administration of dulaglutide. After administration dulaglutide is distributed throughout the body via blood flow. **(B)** The intestinal model consists of fecal excretion of dulaglutide metabolites (DM). **(C)** Dulaglutide is metabolized into its metabolites in the bloodstream.
(D) The liver model consists of filtration of DM, and its transport to the intestines via enterohepatic circulation. **(E)** The kidney model consists of filtration and excretion of smaller, water-soluble dulaglutide metabolites via urine.

Study identifier	GitHub Issue	Curation status	Priority	Comment	Pharmacokinetics	Pharmacodynamics	PK-DB identifier	Information in Google Docs	Available via repository	upload	simulation	Parameter fitting	healthy	diabetes	overweight	renal impairment	hepatic impairment	plasma/serum dulaglutide	urinary dulaglutide	feces dulaglutide	breath dulaglutide	bodyweight change	blood pressure	heart rate	glucose	insulin	glucagon	HbA1c	C-Peptide	Lipid	eGFR
study	github	status	priority	comment	pk	pd	pkdb	docs	repo	upload	simulation	fitting	healthy	diabetes	overweight	renal	hepatic	plasma/serum dulaglutide	urine	feces	breath	bodyweight	blood pressure	heart rate	glucose	insulin	glucagon	HbA1c	C-Peptide	Lipid	eGFR
Barrington2011	#1903	wip	high		☑	☑		☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	☑	☑	-	-	-	-	-
Barrington2011a	#1904	wip	high		☑	☑		☑	☑	☑	☑	☑	-	☑	☑	-	-	☑	-	-	-	☑	☑	-	☑	☑	☑	☑	☑	-	-
FDA					☑	☑																									
Gao2024	#1905	wip	low		☑	☐		☑	☑	☑	☑	☑	☑	-	-	-	-	☑	-	-	-	-	-	-	-	-	-	-	-	-	-
Liu2025	#1906	wip	low		☑	☑		☑	☑	☑	☑	☑	-	☑	☑	-	-	☑	-	-	-	-	-	-	-	-	-	☑	-	-	-
Xu2022	#1907	wip	high		☑	☑		☑	☑	☑	☑	☑	☑	☑	☑	-	-	☑	-	-	-	-	-	-	☑	-	-	☑	-	-	-
Blonde2015			high		☐	☑		☑	☐	☐	☐	☐	-	☑	☑	-	-	-	-	-	-	☑	-	-	☑	-	-	☑	-	-	-
delaPena2017a			high		☐	☑		☑	☐	☐	☐	☐	☑	☑	☑	-	-	-	-	-	-	-	-	-	-	☑	-	-	☑	-	-
Dungan2014			high		☐	☑		☑	☐	☐	☐	☐	-	☑	☑	-	-	-	-	-	-	☑	-	-	☑	-	-	☑	-	-	-
Dungan2016		wip	high		☐	☑		☑	☑	☑	☐	☐	-	☑	☑	-	-	-	-	-	-	☑	-	-	☑	-	-	☑	-	-	-

Figure 2. Dulaglutide studies & database. Overview of a subset of curated data from dulaglutide trials. A comprehensive literature search was conducted in PubMed and PKPDAI. Pharmacokinetic data were manually curated to include information on subject metadata (e.g., healthy, ill, age, weight, height), dosage, and outcomes measured (e.g., time course, pharmacokinetic data). Time course data from multiple studies reporting plasma concentration of dulaglutide and its metabolites were manually curated and integrated for model building, parameter estimation, and model validation. Studies conducted in subjects with and without type II diabetes were curated to study disease states.

Funding

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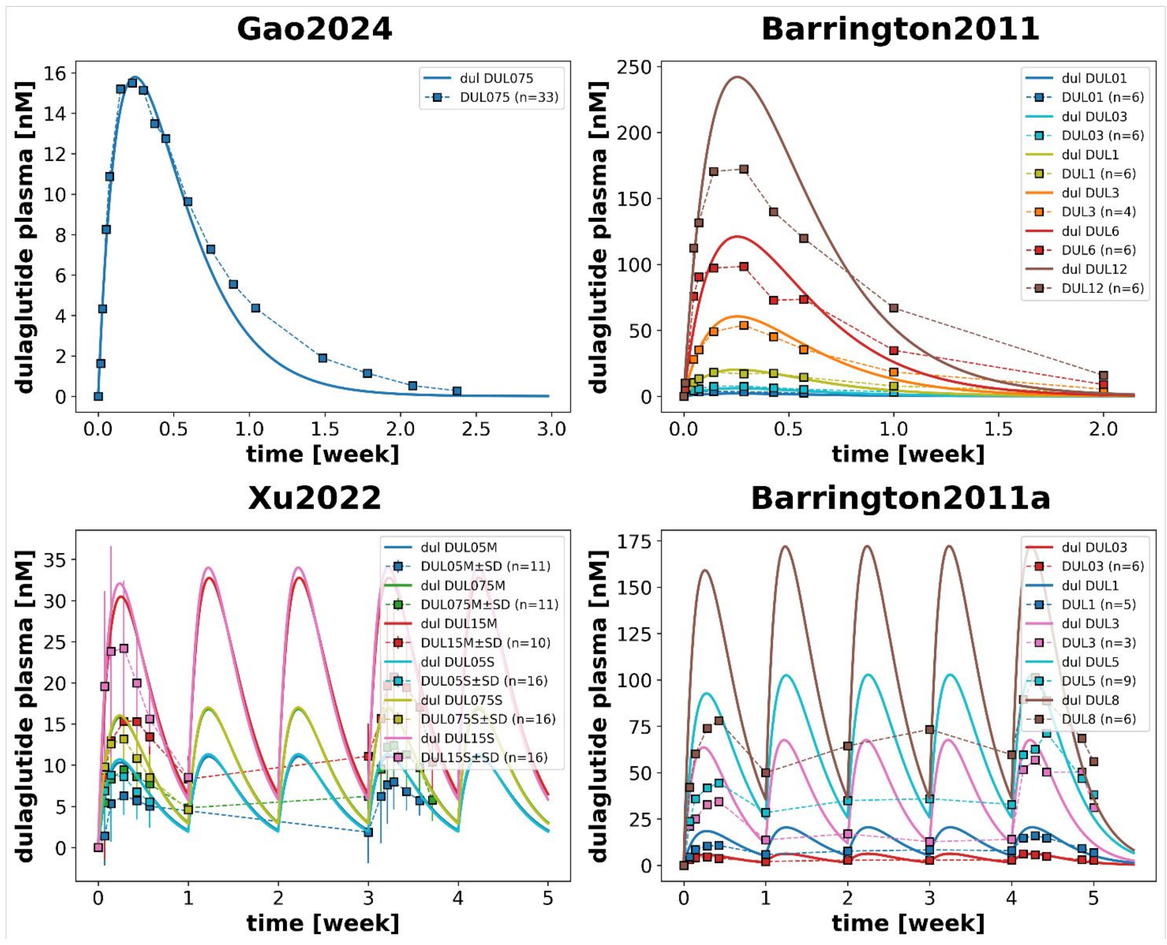

Figure 3. Pharmacokinetic simulations. Gao2024 is a single- dose, single-dose level study, Barrington2011 is a single-dose, multiple-dose levels study, and Xu2022/Barrington2011a is a multiple-dose, multiple-dose levels study. The simulation results (line) was plotted together with curated experimental data (dot) for a concise comparison.

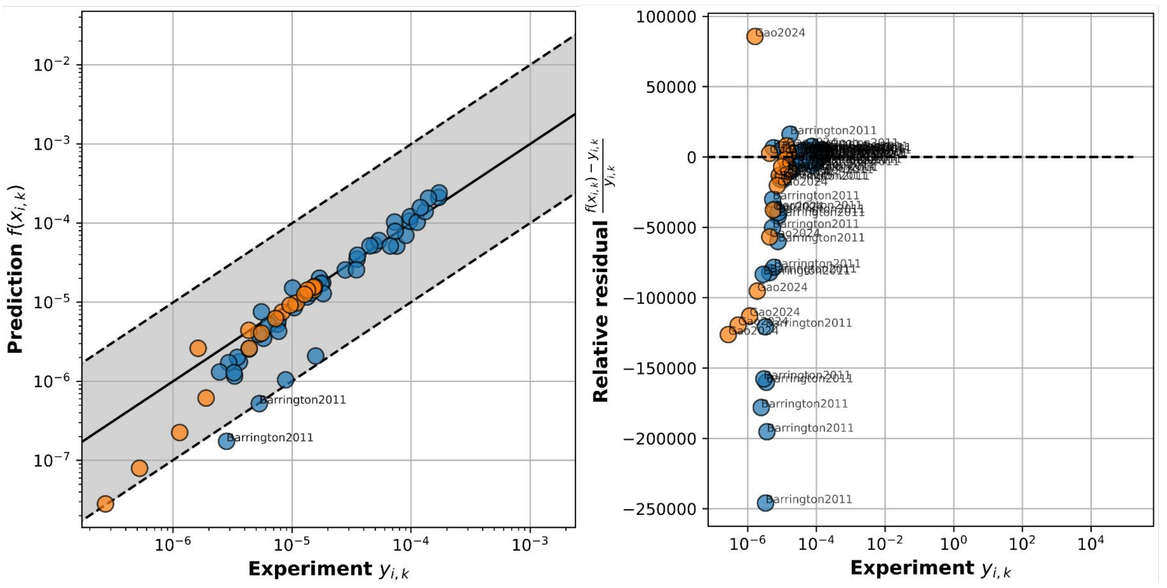

Figure 4. Pharmacokinetic simulations: optimization. Certain simulation parameters that are not specified by the studies were optimized to minimize the squared difference between experimental data. While some systematic errors were observed, especially in higher dosage levels, the model generally performs well in predicting dulaglutide concentration in plasma.

Results

Within the Humboldt Internship Project, a PBPK model of dulaglutide (Fig. 1) was established based on extensive literature searches and data curation (Fig. 2) to simulate the pharmacokinetics of dulaglutide (Fig. 3, Fig. 4).

Next Step

Moving onto pharmacodynamics, The time course data of change in HbA1c levels over time under diabetes treatment with dulaglutide will be curated, and then simulated in a similar manner.
The variables that are at play includes but are not limited to: erythrocyte turnover rate, variance in haemoglobin phenotypes, health conditions such as hepatic and renal impairment.

Humboldt Internship Program (HIP) experience

My experience here at Humboldt University so far has been nothing but enjoyable and fulfilling. This experience allowed me to see how the theoretical foundations from my bachelor's program apply to real-world research and helped me identify areas for further skill development. I would like to express my deepest gratitude to Dr. Matthias König and Mariia Myshkina for their help and guidance throughout this project.