A physiologically based pharmacokinetic model of morphine

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Background

This Humboldt Internship project develops a physiologically based pharmacokinetic (PBPK) model of the pain medication morphine. The objective is to enhance our understanding of how underlying causes of intraindividual variability in morphine treatment, e.g., differences in absorption rates or hepatorenal function.

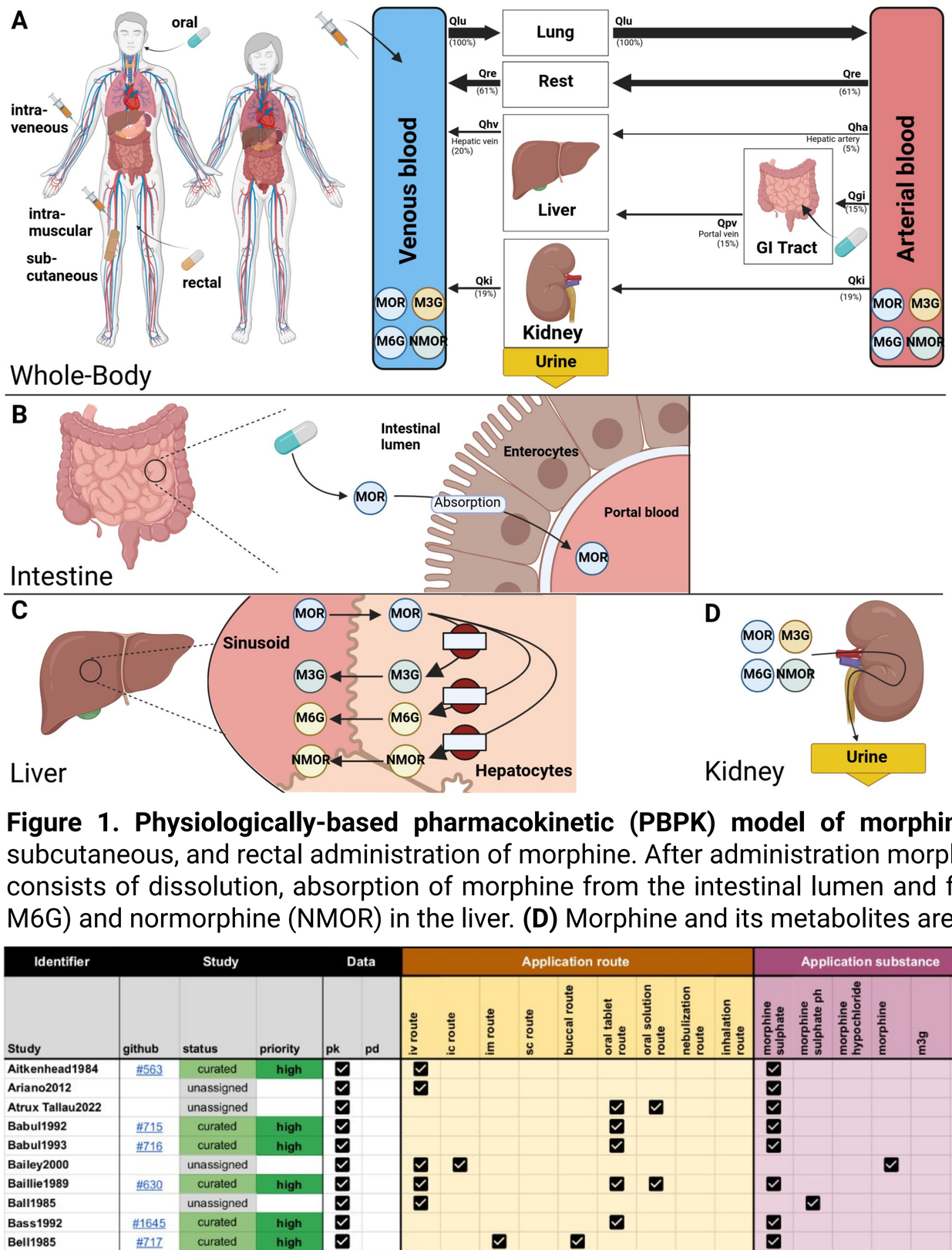
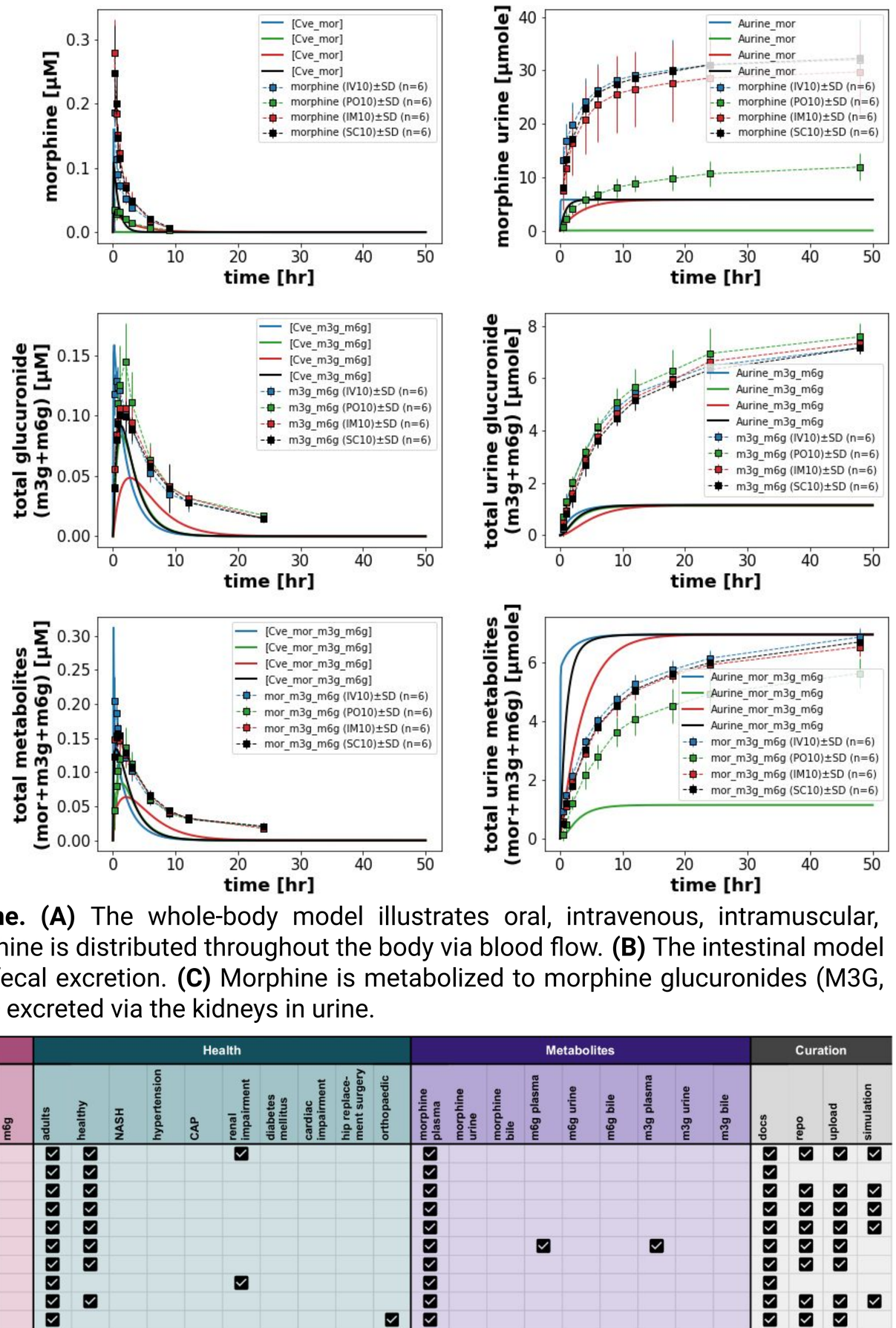


Figure 1. Physiologically-based pharmacokinetic (PBPK) model of morphine. (A) The whole-body model illustrates oral, intravenous, intramuscular, subcutaneous, and rectal administration of morphine. After administration morphine is distributed throughout the body via blood flow. **(B)** The intestinal model consists of dissolution, absorption of morphine from the intestinal lumen and fecal excretion. **(C)** Morphine is metabolized to morphine glucuronides (M3G, M6G) and normorphine (NMOR) in the liver. **(D)** Morphine and its metabolites are excreted via the kidneys in urine.

Identifier		Study		Data		Application route									Application substance						Health										Metabolites									Curation			
Study	github	status	priority	pk	pd	iv route	ic route	im route	sc route	buccal route	oral tablet route	oral solution route	nebulization route	inhalation route	morphine sulphate	morphine sulphate ph	morphine hypochloride	morphine	m3g	m6g	adults	healthy	NASH	hypertension	CAP	renal impairment	diabetes mellitus	cardiac impairment	hip replace-ment surgery	orthopaedic	morphine plasma	morphine urine	morphine bile	m6g plasma	m6g urine	m6g bile	m3g plasma	m3g urine	m3g bile	docs	repo	upload	simulation
Aitkenhead1984	#563	curated	high	✓		✓									✓						✓	✓				✓					✓									✓	✓	✓	✓
Ariano2012		unassigned		✓		✓									✓						✓	✓									✓									✓			
Atrux Tallau2022		unassigned		✓							✓	✓			✓						✓	✓									✓									✓	✓	✓	✓
Babul1992	#715	curated	high	✓							✓				✓						✓	✓									✓									✓	✓	✓	✓
Babul1993	#716	curated	high	✓							✓				✓						✓	✓									✓									✓	✓	✓	✓
Bailey2000		unassigned		✓		✓	✓											✓			✓	✓									✓			✓			✓			✓	✓	✓	
Baillie1989	#630	curated	high	✓		✓					✓	✓			✓						✓	✓									✓									✓	✓	✓	
Ball1985		unassigned		✓		✓										✓					✓					✓					✓									✓			
Bass1992	#1645	curated	high	✓							✓				✓						✓	✓									✓									✓	✓	✓	✓
Bell1985	#717	curated	high	✓				✓		✓					✓						✓									✓	✓									✓	✓	✓	
Berkowitz1975		unassigned		✓		✓									✓						✓										✓												
Bochner1999	#633	curated	high	✓							✓				✓						✓	✓									✓									✓	✓	✓	
Bourget1995	#1579	curated	high	✓							✓				✓						✓	✓									✓			✓			✓			✓			✓
Broomhead1997	#1681	curated	high	✓							✓				✓						✓	✓									✓									✓	✓	✓	
Brunk1974	#1590	curated	high	✓		✓		✓	✓		✓				✓						✓	✓									✓									✓	✓	✓	✓
Chapman1990	#1680	curated	high	✓		✓					✓				✓					✓	✓	✓									✓			✓						✓	✓	✓	
Dayno2017	#1728	curated	high	✓		✓					✓				✓			✓			✓	✓									✓									✓	✓		
Dale2007	#1693	curated	high	✓																																				✓	✓		
Dershwitz2000	#1730	assigned	high	✓		✓								✓	✓						✓	✓									✓									✓			
Drake1996	#1729	curated	high	✓							✓				✓						✓	✓									✓									✓	✓		

Figure 2. Morphine studies & database. Overview of a subset of curated data from morphine trials. A comprehensive literature search was conducted in PubMed and PKPDAI. Pharmacokinetic data were manually curated to include information on the form of drug administered (e.g., tablet, capsule, solution), route of administration (e.g., oral, intravenous, intramuscular, subcutaneous, buccal), subject metadata (e.g., healthy, ill, age, weight, height), and outcomes measured (e.g., time course, pharmacokinetic data). Time course data from multiple studies reporting plasma, serum, and urine concentrations of morphine and its metabolites, glucuronides, were manually curated and integrated for model building, parameter estimation, and model validation. Studies conducted in subjects with liver diseases such as cirrhosis, non-alcoholic steatohepatitis, and renal impairment were curated to study disease states.

Figure 3. Effect of route of administration. Example simulation illustrating the effect of route of administration (intravenous, intramuscular, subcutaneous, and oral) on the level of morphine and and metabolites in plasma and urine. Intravenous (IV) in blue; oral (PO) in green; intramuscular (IM) in red; subcutaneous (SC) in black.



Results

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

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Humboldt Internship Program (HIP) experience

The Humboldt Internship Program has been a truly incredible experience. The research project has been instrumental in developing my expertise in the field of pharmacokinetics research and empowers me to contribute to the design and development of computational models for drug detoxification studies. I would like to express my heartfelt gratitude to my project supervisor, Dr. Matthias König, for his support and guidance throughout the duration of this research. The effort and diligence put into the rigors of research will continue to inspire and motivate me throughout my research career. I've been an online intern and the online meetings organized by the program managers have actively engaged me in the program. It has been an exciting experience to meet the other wonderful participants in the program.