

Use of rapid dosimetry modeling to evaluate the effect of long-term spaceflight on drug disposition



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Background & Purpose

Background

- Spaceflight travel causes physiological changes that can affect drug pharmacokinetics (PK), resulting in reduced efficacy or adverse effects.¹
- The astronaut demographic is shifting towards individuals with a broader age range and increased variability in genetic and environmental factors that could affect drug PK.
- Increased PK variability could impact medical provisions planning for long-haul missions.
- A better understanding of how spaceflight physiology impacts drug PK is necessary to protect human health during spaceflight.

Knowledge Gap

- Few studies have tested individual drug PK in spaceflight or a simulated low gravity environment.
- It is not practical to experimentally investigate the PK of spaceflight stressors on all drugs provided to astronauts.

Objective

- This study develops a computational approach to evaluate low gravity effects on drug disposition for 74 drugs likely to be included in spacecraft medical kits.
- Figure 1 shows the computational model workflow with novel components added to the U.S. Environmental Protection Agency's high-throughput toxicokinetic model, "httk".
- Model output is in terms of fold change of the Oral Equivalent Dose (OED) required for steady state drug concentration.

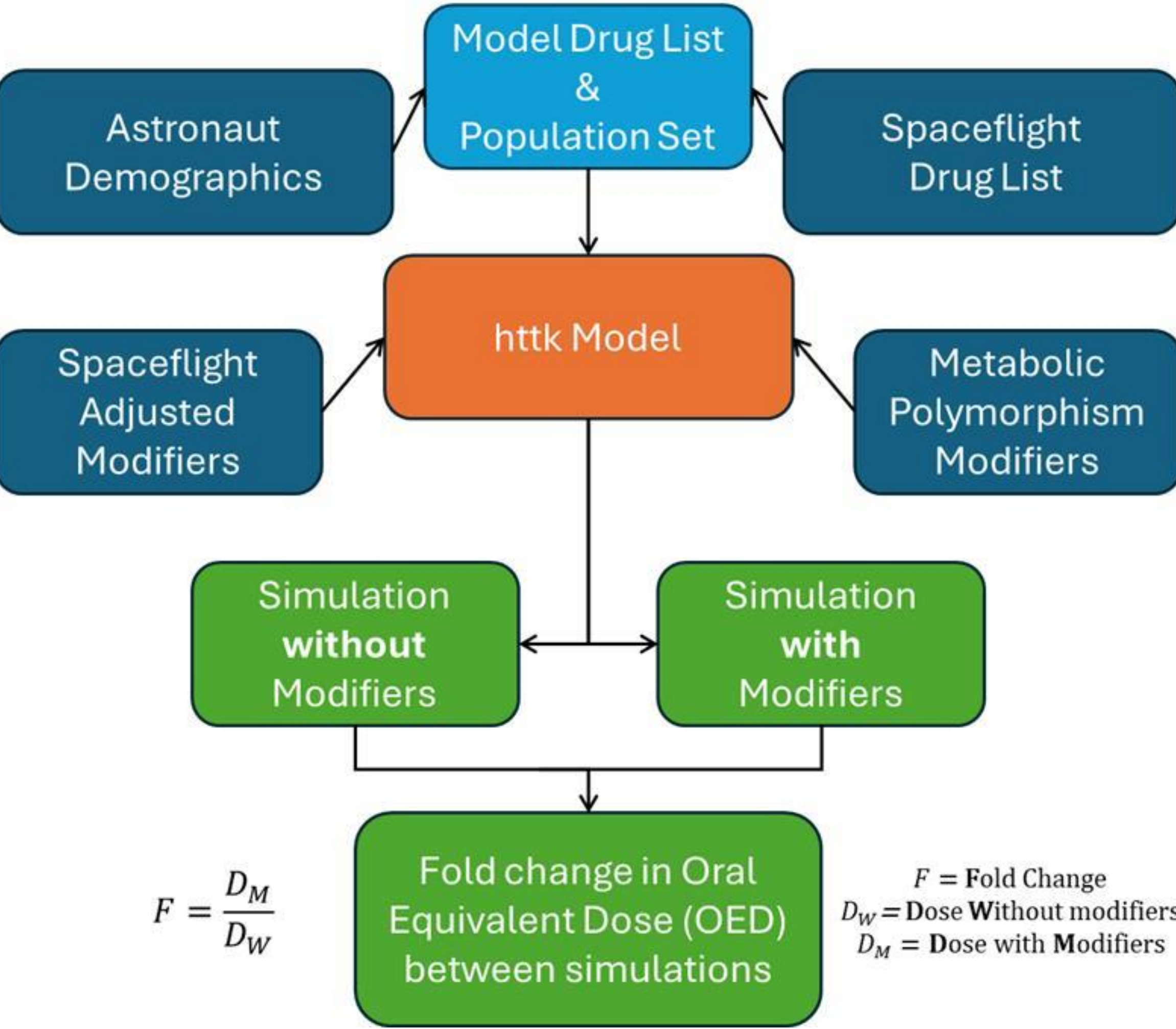


Figure 1. Project workflow of the rapid dosimetry model. Astronaut demographics and spaceflight drugs are input into the httk model. Sensitivity analysis is performed. Metabolic polymorphism and spaceflight adjusted modifiers are calculated. The model is run with and without modifiers. The difference between the two models is calculated as the fold change between OEDs, shown in the equation.

Methods

Sensitivity Analysis

- The pipeline was run in RStudio² on a single compound with an oral dose of 1 mg/kg/day. The steady state concentration was calculated and converted to an OED.
- A one-at-a-time sensitivity analysis was performed by adjusting 33 individual parameters by 10% and then comparing to the baseline.
- A Normalized Sensitivity Coefficient (NSC) was calculated based on the change in model output.
- Table 1 shows the top five most sensitive parameters in the model.

Table 1. Most sensitive model parameters

Parameter	Type	NSC
Plasma drug fraction not protein-bound	Chemical	1.0262
Fraction of oral dose absorbed	Chemical	-0.9117
Glomerular Filtration Rate	Biological	0.646
Hepatic Clearance	Chemical	0.3536
Body Weight	Biological	-0.1554

Metabolic Polymorphism Modifiers

- Cytochrome P450 (CYP) enzymes are a primary mechanism of drug metabolism.³
- Twelve CYPs are involved in metabolism of the 74 spaceflight drugs.
- Table 2 shows a sample of 20 drugs, the CYPs involved in their metabolism, and their Biopharmaceutics Drug Disposition Classification System (BDDCS) labels, which categorize drug metabolism and solubility.⁴
- CYPs are known to have genetic variants or polymorphisms that alter metabolic capacity, causing reduced or absent activity.⁵
- Polymorphism variants were found for 4 relevant CYPs. A total of 41 variants, their frequency per population group, and their effects on metabolism were found in the PharmGKB database.⁶

Table 2. Sample table of spaceflight drugs with CYPs and BDDCS labels

Drug	CYP	BDDCS
Acetaminophen	2E1, 1A2, 3A4	1
Dexamethasone	3A4	1
Fluoxetine	2C19, 2D6, 2C9, 3A4	1
Duloxetine	1A2, 2D6	1
Diazepam	3A4, 2C19, 2B6, 2D6, 2C9	1
Atorvastatin	3A4	2
Ibuprofen	2C19, 3A4	2
Naproxen	1A2, 2C9	2
Phenytoin	2C9, 2C19	2
Clopidogrel	2C19, 3A4, 2B6, 2C8	2
Azithromycin	3A4	3
Fluconazole	3A4	3
Loperamide	2C8, 3A4	3
Metoclopramide	2D6	3
Trimethoprim	3A4, 2C9	3
Acetazolamide		4
Furosemide	2C11, 2E1, 3A1, 3A2	4
Levonorgestrel	3A4	4
Medroxyprogesterone	3A4	4
Ciprofloxacin		4

Spaceflight Adjusted Modifiers

- Based on the sensitivity analysis, literature data for the top five sensitive parameters were used to define spaceflight adjusted modifiers in the model.
- A Body Weight (BW) modifier of 0.976, and a Glomerular Filtration Rate (GFR) modifier of 1.029 was defined.^{7,8}
- Literature data of spaceflight changes for each CYP were used to calculate spaceflight metabolic modifiers. These modifiers ranged from 0.3 to 1.87 times the normal metabolic function.

Simulation Setup

- To test the effects of metabolic polymorphism and spaceflight adjusted modifiers, a four-simulation setup was designed (Table 3).

Table 3. Simulation setup for testing the effects of modifiers on the model

Metabolic Polymorphism Modifiers			
Spaceflight Adjusted Modifiers	Simulation 1		Simulation 2
	No Metabolic Polymorphism Modifiers ✗		Metabolic Polymorphism Modifiers ✓
	No Spaceflight Adjusted Modifiers ✗		No Spaceflight Adjusted Modifiers ✗
	Simulation 3		Simulation 4
No Metabolic Polymorphism Modifiers ✗		Metabolic Polymorphism Modifiers ✓	
Spaceflight Adjusted Modifiers ✓		Spaceflight Adjusted Modifiers ✓	

Results

Modifier Effects

- Simulation comparisons, as shown in Figure 2, were carried out for the sample subset of 20 drugs, grouped based on their BDDCS label.
- The OED output was calculated for the median of the 10,000 person simulations using chemical parameters from multiple databases. A fold change value (Figure 1, equation) was calculated between two simulations and averaged together to represent the fold change for each drug.

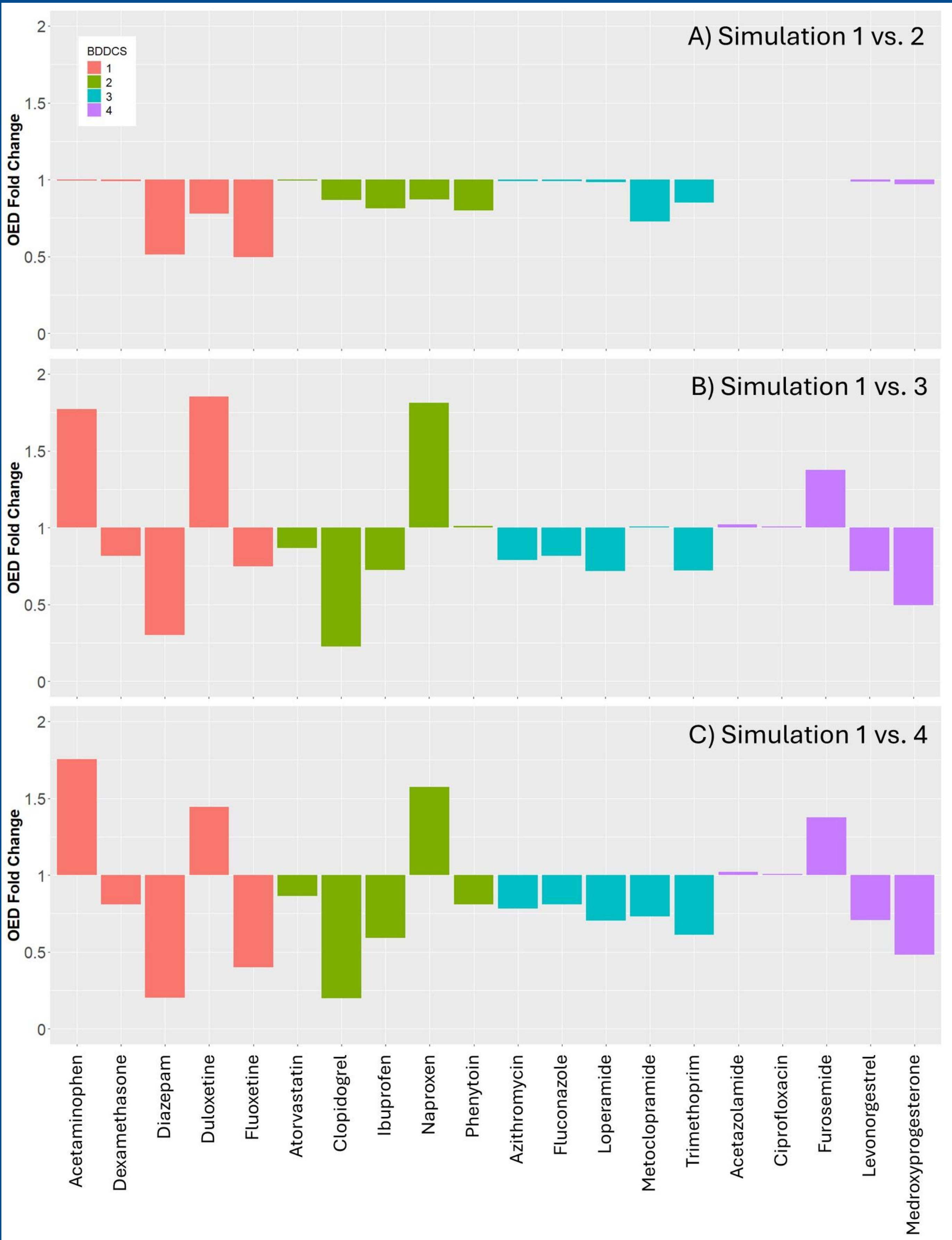


Figure 2. Comparisons between baseline simulation and simulations with modifiers. A) Simulation 2 vs. Simulation 1 compares the effects of Metabolic Polymorphism Modifiers on OED for 20 sample drugs, grouped by BDDCS labels. The y-axis indicates the OED fold change at 50th quantile (no change = 1). B) Simulation 3 vs. Simulation 1 compares the effects of Spaceflight Adjusted Modifiers. C) Simulation 4 vs. Simulation 1 compares the joint effect of Spaceflight Adjusted Modifiers and Metabolic Polymorphism Modifiers on OED.

Results

- OED fold changes were calculated for the full list of 74 spaceflight drugs.
- An average fold change was then calculated for all drugs in each BDDCS category (Table 4.)

Table 4. Fold change between simulations for 74 spaceflight drugs

Average OED Fold Change between Simulations				
BDDCS Label	Total Number of Drugs	Simulation 1 vs Simulation 2	Simulation 1 vs Simulation 3	Simulation 1 vs Simulation 4
1	32	0.870	1.01	0.897
2	16	0.952	0.882	0.841
3	18	0.975	0.962	0.939
4	8	0.995	0.958	0.955

Conclusions

- Metabolic polymorphisms decrease metabolic activity, leading to predicted OED fold change values < 1 (Figure 2).
- Spaceflight adjustments had a larger impact than metabolic polymorphisms on predicted OEDs.
 - Of the spaceflight adjustments, CYP expression had the largest impact on OED predictions.
 - BW and GFR changes during spaceflight had minimal effect on OED predictions.
- Spaceflight and metabolic modifiers had a lesser predicted impact on drugs in categories 3 & 4 when compared to category 1 & 2 drugs.
 - Predictions are consistent with poor metabolism that characterizes BDDCS category 3 & 4 drugs.
- Predicted OEDs can be used to adjust recommended dosing of drugs during spaceflight.**
 - Goal is to ensure that blood concentrations in space are consistent with recommended therapeutic levels.**

Future Directions

- The CYP variant population data currently describe only major NASA population ethnic groups.
 - Next steps would be to expand the description to all ethnicities in the target population.
- The relationship between gene expression and CYP activity is assumed and needs to be validated.

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