AI/ML MODEL TO PREDICT IMPACT OF MICROGRAVITY(SPACE) ON CELL FUNCTION

TEAM MEMBERS

Rahul Raj (BTECH/10307/22)
Shreyansh Gupta (BTECH/10271/22)

AI/ML Model to Predict Impact of Microgravity on Cell Function

Rahul Raj, Shreyansh Gupta, Aditya Ingale, Dr. Abhinav Bhushan

Biomedical Engineering (BME)

ILLINOIS INSTITUTE OF TECHNOLOGY

Introduction

- Microgravity we developed a hybrid pipeline combining RNA-Seq data with a physiologically based pharmacokinetic (PBPK) model to simulate drug behavior in microgravity.
- Gene expression changes were translated into rate adjustments.
- Monte Carlo simulations captured biological variability, predicting concentration-time profiles under spaceflight conditions.

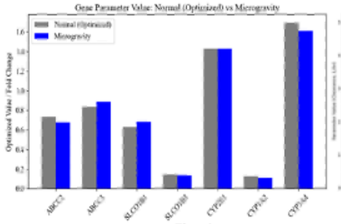


Fig. 1

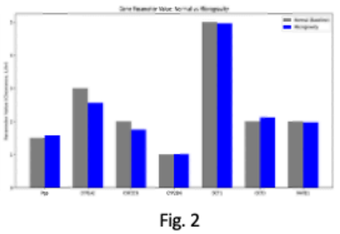


Fig. 2

Methods

- **Data Collection & Preprocessing**
  - We extracted RNA-seq datasets from NASA GeneLab (e.g., OSD 13, 52) which included gene names, Log2 Fold change, p-values, and adjusted p- values.
  - Data preprocessing was performed to remove null or irrelevant entries, focusing only on genes associated with drug transport and metabolism.
- **Pharmacokinetic Modelling**
  - Compartment models were built for acetaminophen and cimetidine, incorporating key metabolic enzymes and transporters.
  - Parameters like enzyme activity and transporter efficiency were adjusted based on gene expression shifts.
- **Model training**
  - Algorithms were trained on these models to predict drug behavior for new compounds with only enzyme level input.
  - Monte Carlo simulations were used to model biological variability in gene expression and enzyme activity, generating a range of predicted concentration-time profiles.
  - Simulated drug concentration-time curves were compared with published experimental data.

- Microgravity caused moderate but meaningful changes in gene expression and drug response, highlighting the need for personalized dosing in space.

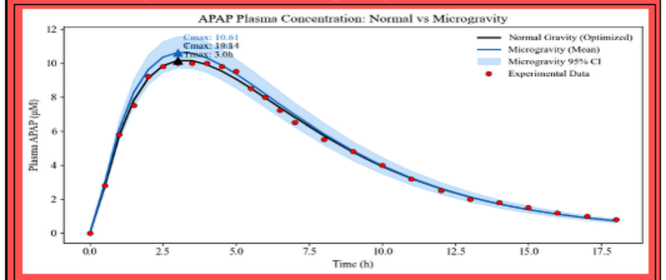


Fig. 4.

A concentration vs. time curve for ***Acetaminophen*** showed a 4.7% increase in Cmax and a 3.1% increase in AUC in microgravity, validating altered drug exposure.

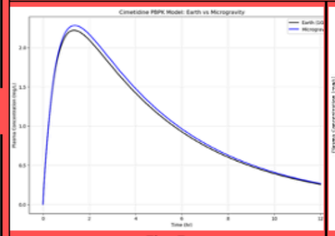


Fig. 5

The graph demonstrates the simulated plasma concentration-time profiles of ***Cimetidine*** under Earth and microgravity conditions, revealing a slightly higher and prolonged peak concentration in microgravity.

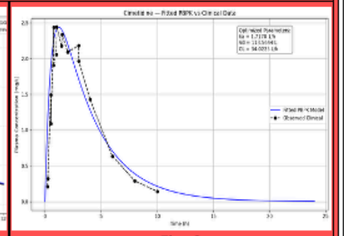


Fig. 6

The PBPK model closely matches the observed clinical data, accurately reflecting the drug's absorption, peak, and elimination trends. This demonstrates the model's reliability in simulating real-world pharmacokinetics.

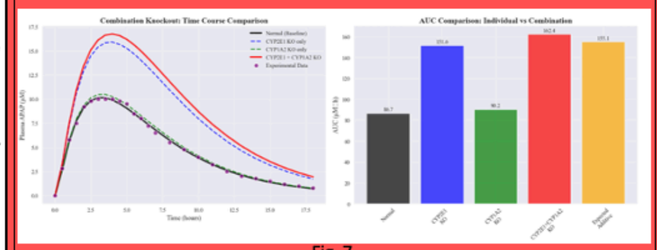


Fig. 7

Deleting both CYP2E1 and CYP1A2 leads to an increase in plasma acetaminophen concentration because the main metabolic pathway for its conversion to the toxic metabolite NAPQI is blocked. This results in higher circulating levels of the parent drug and a much lower risk of toxicity from NAPQI formation.

Results

- Gene - level comparisons revealed both upregulation and downregulation under microgravity, e.g., CYP3A4 activity by 4.2%, ABCC2 by 5.9%.
- A concentration vs. time curve for acetaminophen showed a 4.7% increase in Cmax and 3.1% increase in AUC in microgravity, validating altered drug exposure.
- Simulations showed that knockout of CYP2E1 and CYP1A2 led to increased plasma drug levels, indicating reduced toxic metabolite formation.
- The slight upward shift in the Microgravity curve shows that on average, cimetidine exposure (AUC) and peak concentration (Cmax) are a bit higher in microgravity.

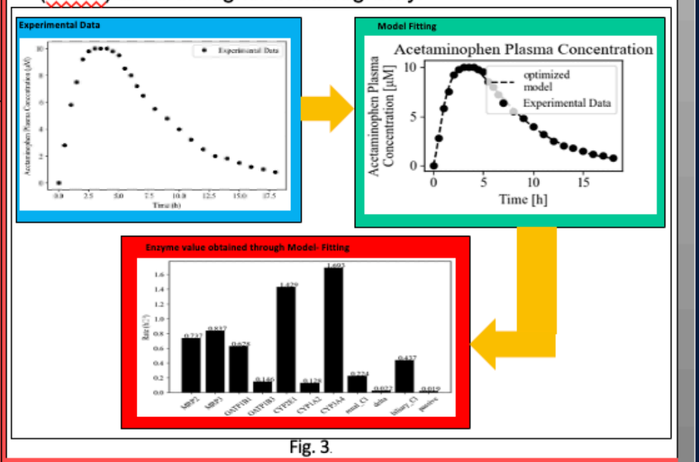


Fig. 3.

Conclusions and Impact

- Microgravity caused measurable shifts in gene expression and drug metabolism, leading to altered pharmacokinetics for drugs like acetaminophen and cimetidine.
- Our model predicted these changes accurately, such as a 4.7% increase in Cmax for acetaminophen and enzyme-driven shifts in cimetidine exposure.

References

- Cooper D.A. et al., "Bacterial Influence on Pharmacokinetics of Tacrolimus and Sulfasalazine through Regulation of Host Metabolism", *Advanced Therapeutics*, v 7, n 8, 2024, pp 1–7.
- Mazaleuskaya LL et al., "PharmGKB summary: Pathways of acetaminophen metabolism at the therapeutic versus toxic doses,"

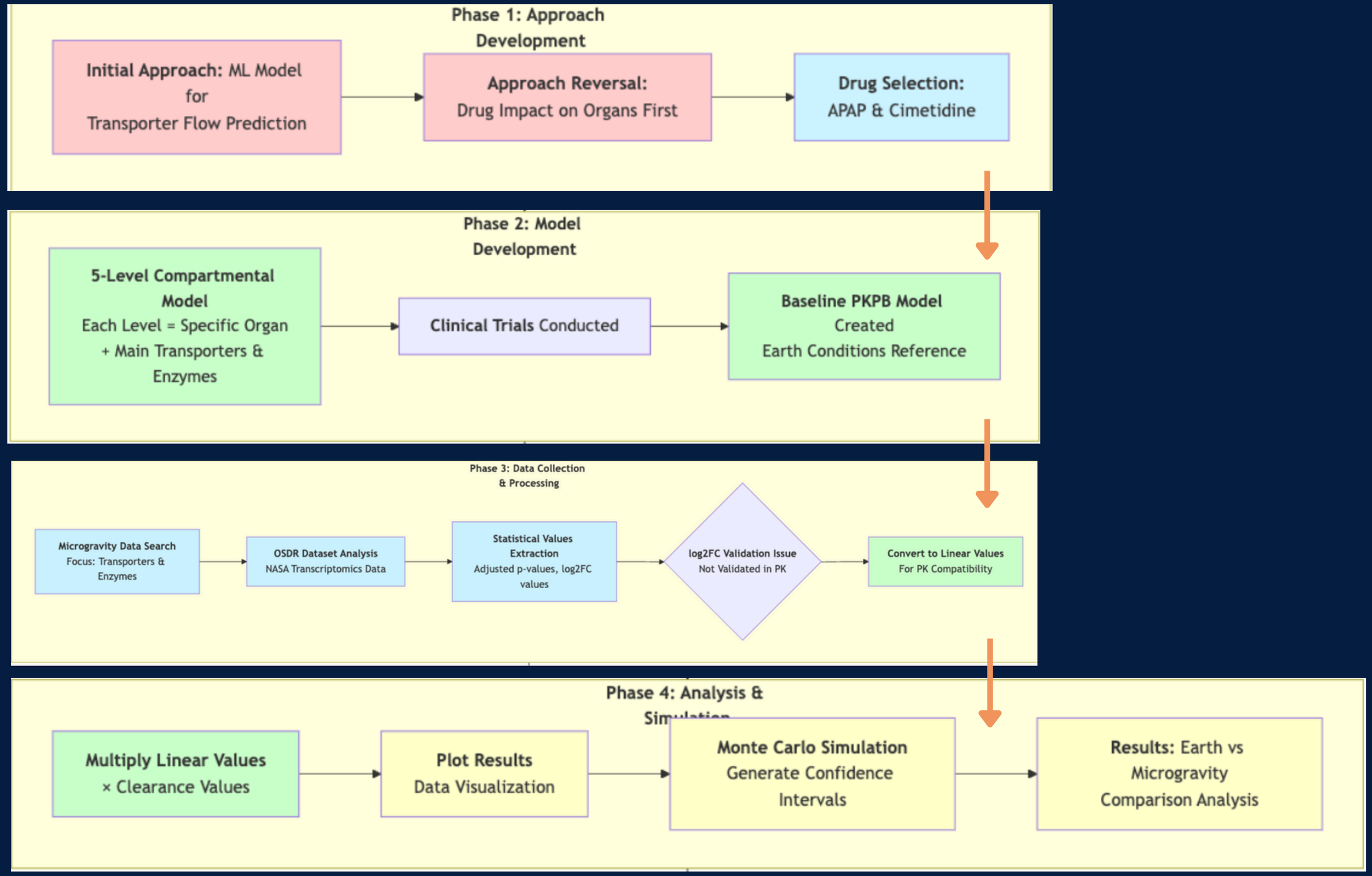
ABOUT THE PROJECT

This project began during our Research internship at the **Illinois Institute of Technology, Chicago (USA)**. under the supervision of **Proff. Abhinav Bhushan**. The research group was working on modeling how changes in biological pathways affect drug pharmacokinetics.

As part of the internship, we were assigned with the task of investigating microgravity conditions, given their significant impact on enzyme and transporter activity as observed in gene expression datasets. This formed the core problem statement for our work.

- **Research objective:** The central aim of this project is to leverage publicly available gene expression data from NASA's GeneLab spaceflight experiments. This data will be integrated into a physiologically-based pharmacokinetic (PBPK) model to build and validate a computational framework capable of predicting how the pharmacokinetics of Acetaminophen, and its interaction with Cimetidine, are altered by spaceflight.

- **Practical relevance:** Space medicine is an emerging area, and understanding drug behavior in such conditions is critical for astronaut health.


Phase 1: Approach Development
Initial Approach: ML Model for Transporter Flow Prediction
Approach Reversal: Drug Impact on Organs First
Drug Selection: APAP & Cimetidine
Phase 2: Model Development
5-Level Compartmental Model
Each Level = Specific Organ + Main Transporters & Enzymes
Clinical Trials Conducted
Baseline PKPB Model Created
Earth Conditions Reference
Phase 3: Data Collection & Processing
Microgravity Data Search
Focus: Transporters & Enzymes
OSDR Dataset Analysis
NASA Transcriptomics Data
Statistical Values Extraction
Adjusted p-values, log2FC values
log2FC Validation Issue
Not Validated in PK
Convert to Linear Values
For PK Compatibility
Phase 4: Analysis & Simulation
Multiply Linear Values
× Clearance Values
Plot Results
Data Visualization
Monte Carlo Simulation
Generate Confidence Intervals
Results: Earth vs Microgravity Comparison Analysis

OVERALL GOAL

01

Comparative Analysis of Pharmacokinetics:

Earth conditions vs. Microgravity Conditions

- **Acetaminophen**
- **Cimetidine**

02

Machine Learning Model

- for Predicting Gene Expression Modulation
- to predict the **%** change in gene expression
- Under microgravity conditions, leveraging **RNA-Seq** and pharmacokinetic data
- Creating a MasterDatabase to predict any known drug pharmokinetics based on its gene fromtthe Databse

03

Personalized drug dosing

- recommendation based on dervied information from predicted model.
- Expected Output from the dosing system is
- For an astronaut with:

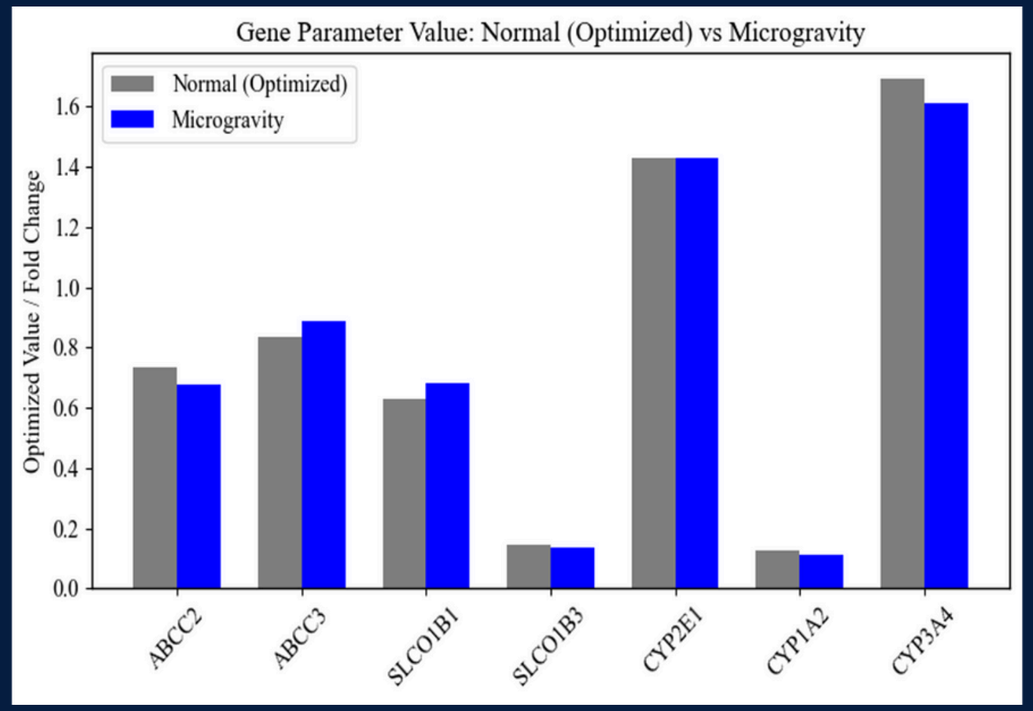
FOS expression ↓60% → Predicted CYP3A4 activity ↓40% → Tacrolimus dose ↑1.7x.

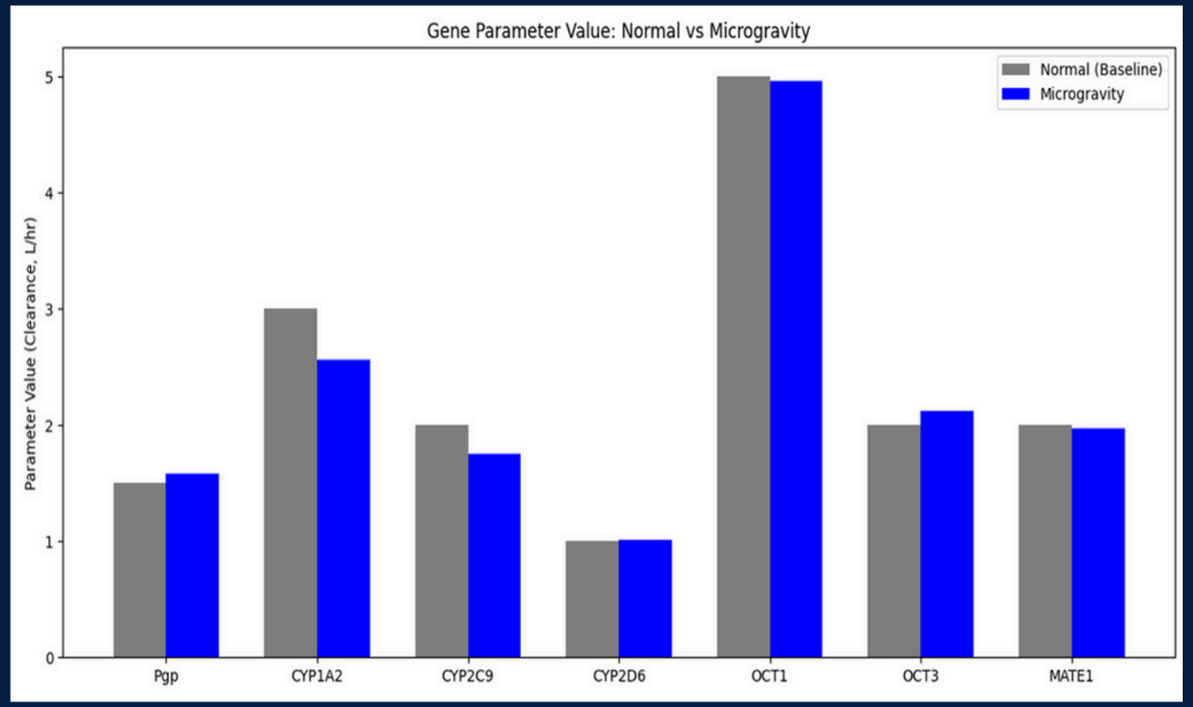
INTRODUCTION

•We developed a hybrid pipeline combining RNA-Seq data with a physiologically based pharmacokinetic (PBPK) model to simulate drug behavior in microgravity.

•Gene expression changes were translated into rate adjustments.

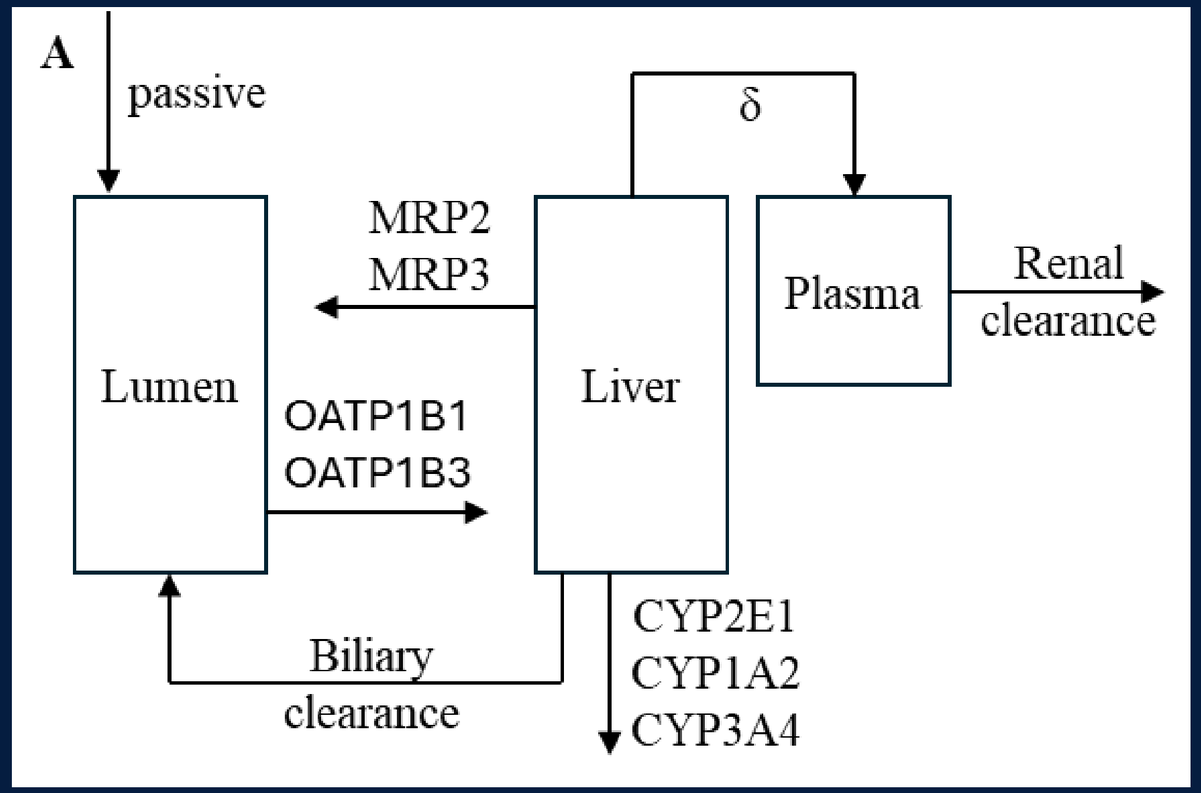
•Monte Carlo simulations captured biological variability, predicting concentration-time profiles under spaceflight conditions.



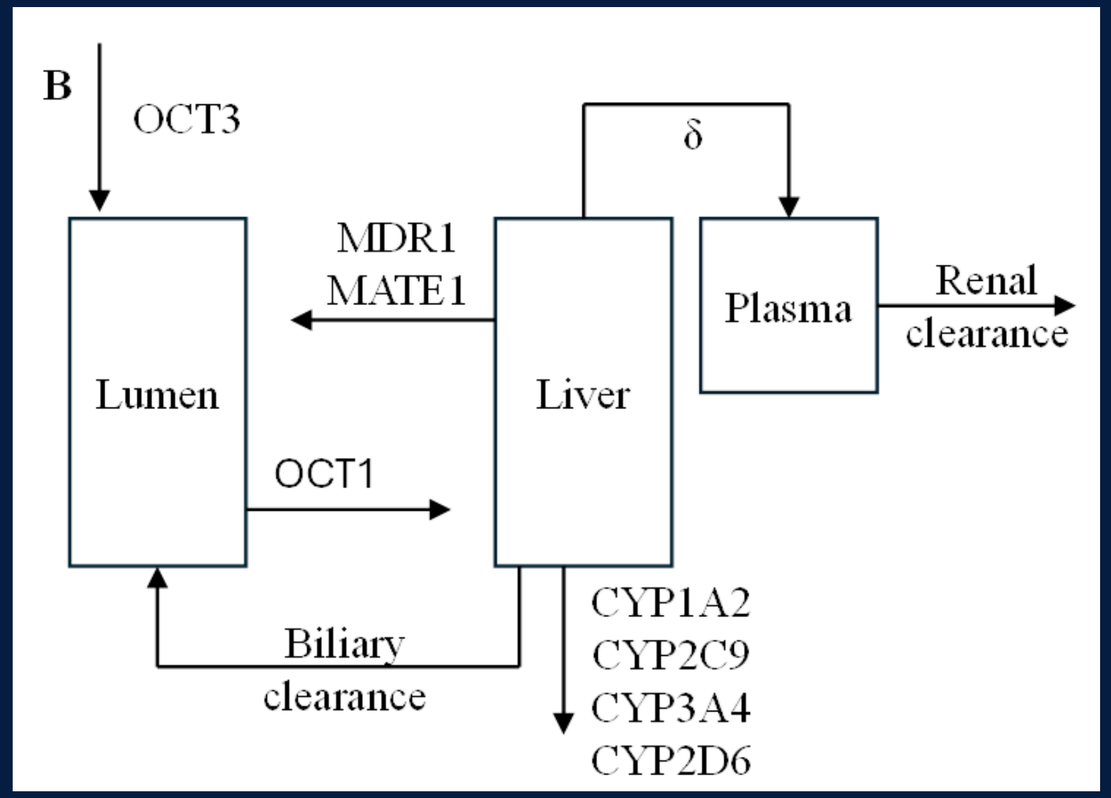


Methods

- **Building Compartment Model**



APAP



Cimetidine

2.) Data Collection & Preprocessing

- We extracted RNA-seq datasets from NASA GeneLab (e.g., OSD 13, 52) which included gene names, Log2 Fold change, p-values, and adjusted p- values.
- Data preprocessing was performed to remove null or irrelevant entries, focusing only on genes associated with drug transport and metabolism.

3.) Pharmacokinetic Modelling

- Compartment models were built for acetaminophen and cimetidine, incorporating key metabolic enzymes and transporters.
- Parameters like enzyme activity and transporter efficiency were adjusted based on gene expression shifts.
- ODE-Based Modelling on how drug flows from one compartment to another

4.) Model training

- Algorithms were trained on these models to predict drug behavior for new compounds with only enzyme level input.
- Monte Carlo simulations were used to model biological variability in gene expression and enzyme activity, generating a range of predicted concentration-time profiles.
- Simulated drug concentration-time curves were compared with published experimental data.

Monte Carlo Simulation

Monte Carlo Simulation is a computational technique that uses repeated random sampling from defined probability distributions to model and analyze the impact of uncertainty and variability in a system's inputs on its outputs. It is widely applied in data science, engineering, finance, and pharmacokinetics to estimate ranges, probabilities, and confidence intervals for outcomes when analytical solutions are difficult or impossible to obtain.

1. p-value

- **Meaning:** The probability of obtaining the observed difference in gene expression (or a more extreme difference) if there is actually no true difference between the conditions.
- Use in our PK model:
  - Helps decide which genes show a statistically significant change in expression between the baseline (Earth) and altered condition (e.g., microgravity).
  - You likely filtered genes with a p-value below a threshold (commonly 0.05) to ensure you only adjusted PK parameters for genes whose expression change is unlikely to be due to random chance.

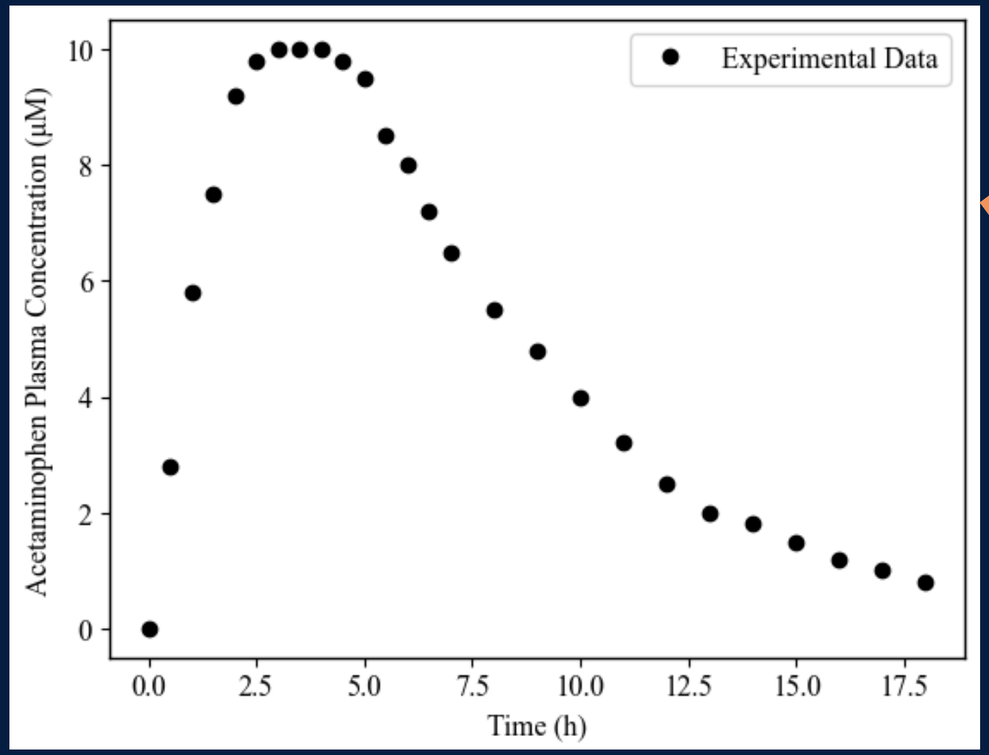
```
n_lumen, n_liver, n_plasma, n_urine, n_metabolites = y

# Unpack parameters
MRP2, MRP3, OATP1B1, OATP1B3, CYP2E1, CYP1A2, CYP3A4, renal_Cl, delta, biliary_Cl, passive = p
```

```
# Total uptake transporters (liver uptake from lumen)
total_uptake = OATP1B1 + OATP1B3

# Total efflux transporters (liver to lumen)
total_efflux = MRP2 + MRP3

# Total metabolism in liver
total_metabolism = CYP2E1 + CYP1A2 + CYP3A4
```

```
# Differential equations based on the APAP model structure:

# Lumen:
dldt = (total_efflux + biliary_Cl) * n_liver - (total_uptake + passive) * n_lumen

# Liver:
drdt = (total_uptake + passive) * n_lumen - (total_efflux + total_metabolism + delta + biliary_Cl) * n_liver

# Plasma:
dpdt = delta*n_liver - renal_Cl*n_plasma

# Urine:
dudt = renal_Cl * n_plasma

# Metabolites: receives from liver metabolism
dmdt = total_metabolism * n_liver
```

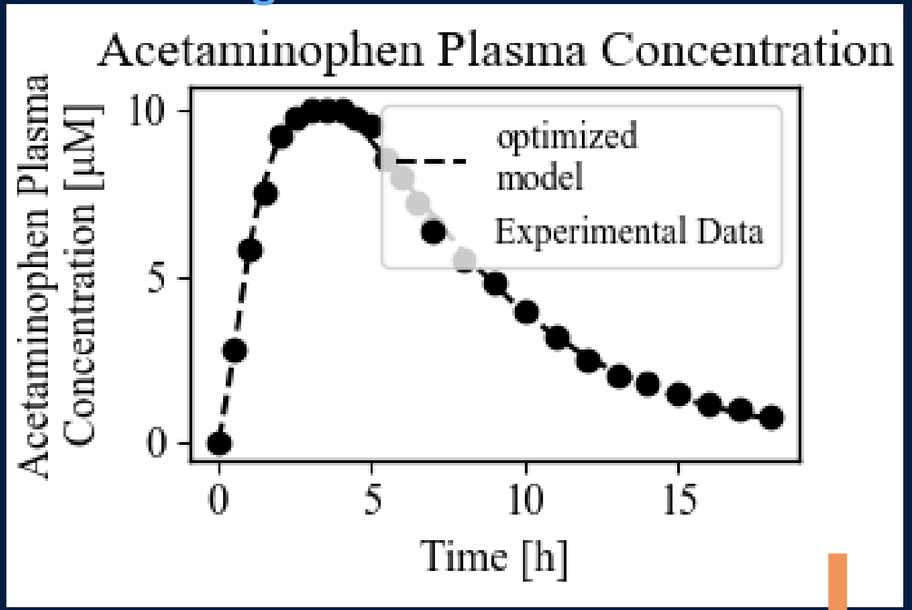
ODE for APAP

RESULTS–Acetaminophen

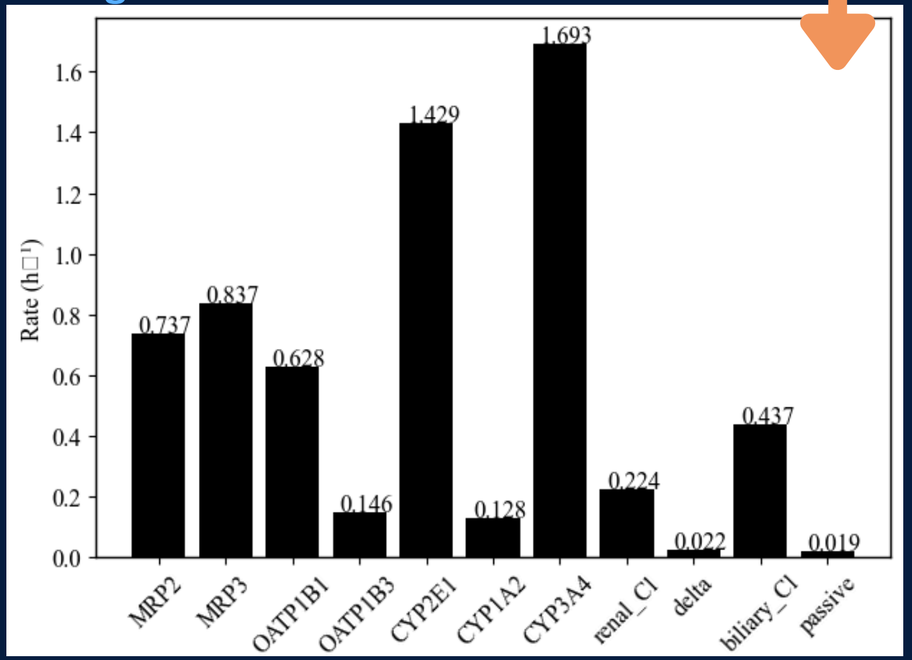


Experimental data Link

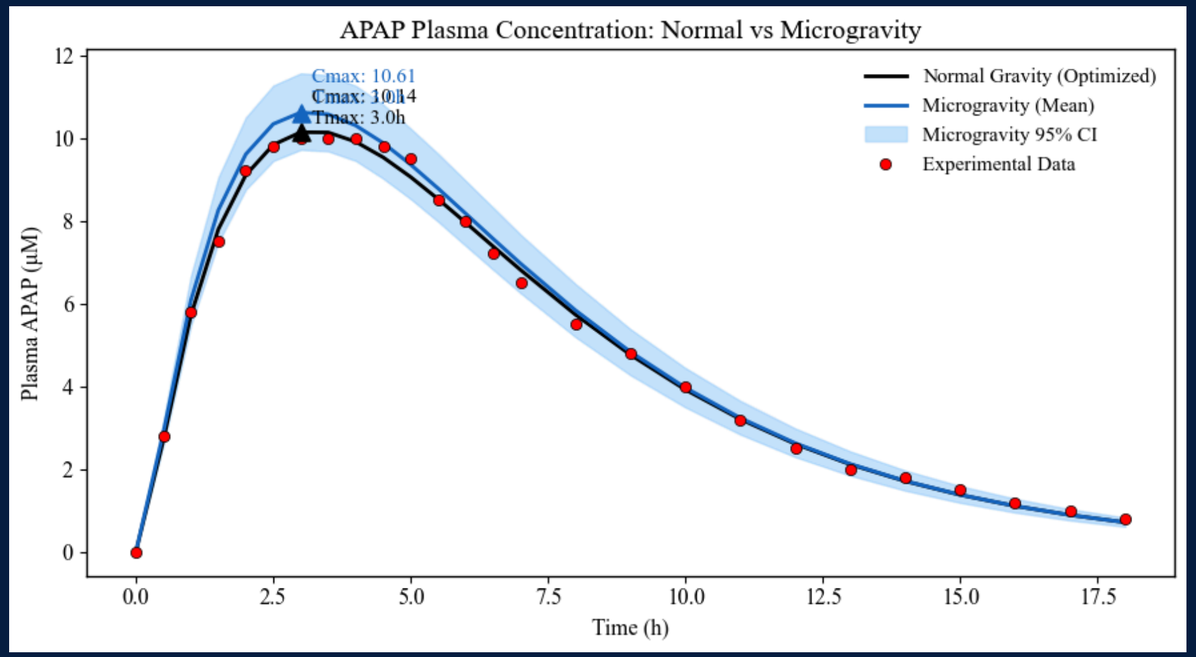
Model Fitting



Enzymes Value obtained through Model Fitting

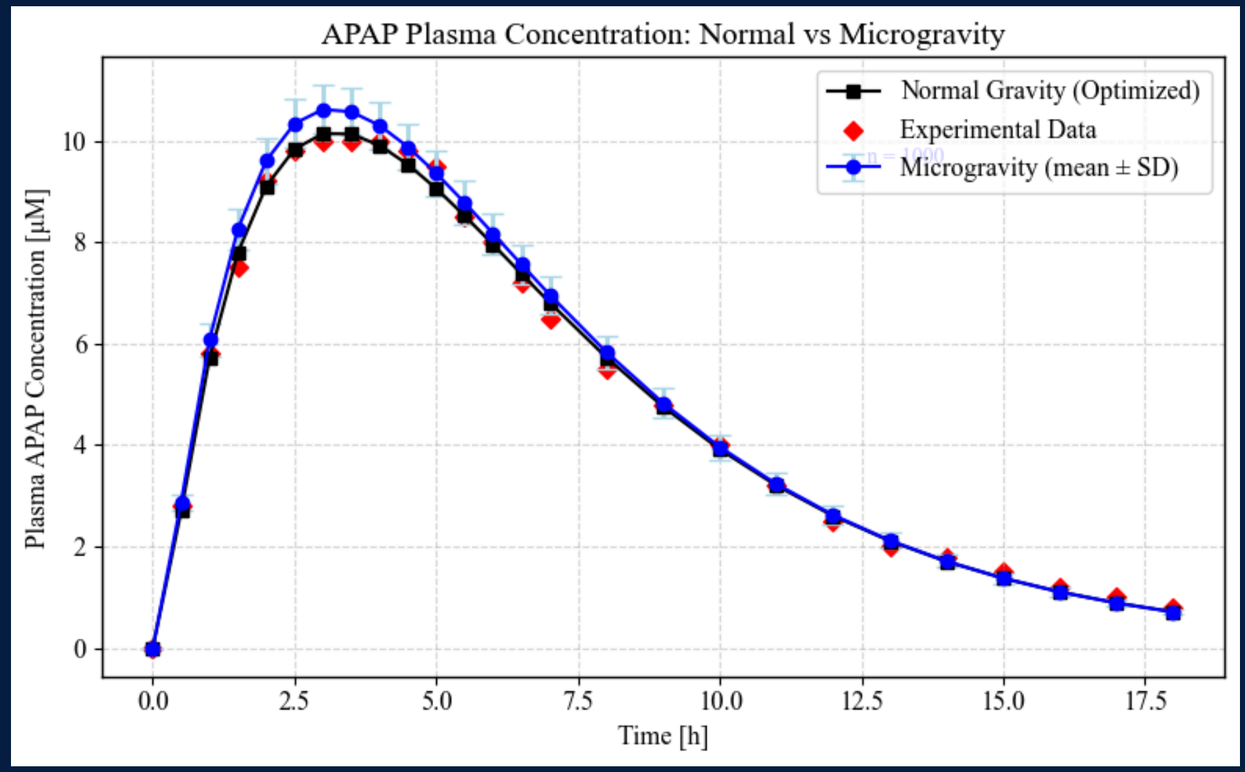


Conc vs Time Graph

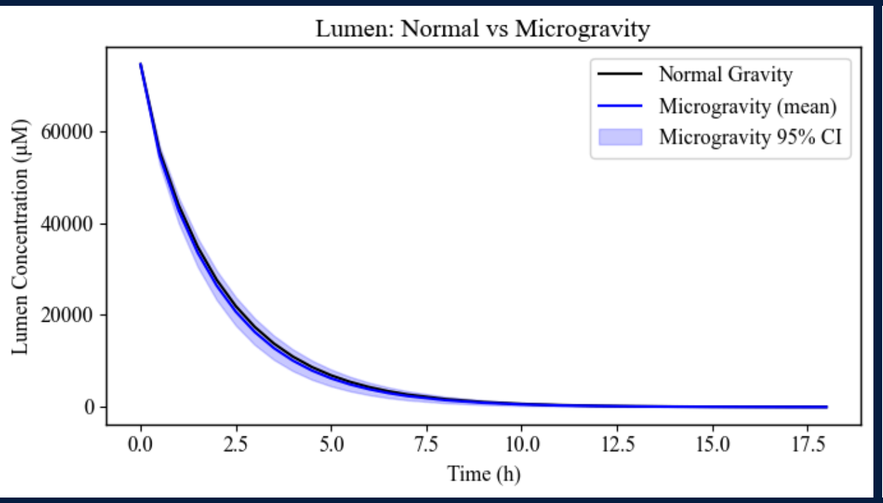


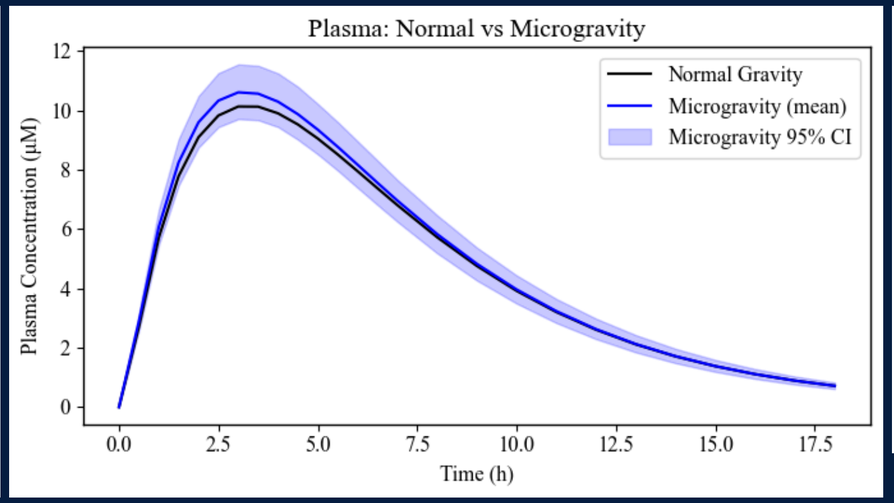
Cmax Normal: 10.14 at 3.0h, Microgravity (mean): 10.61 at 3.0h
AUC Normal: 86.75, Microgravity (mean): 89.47

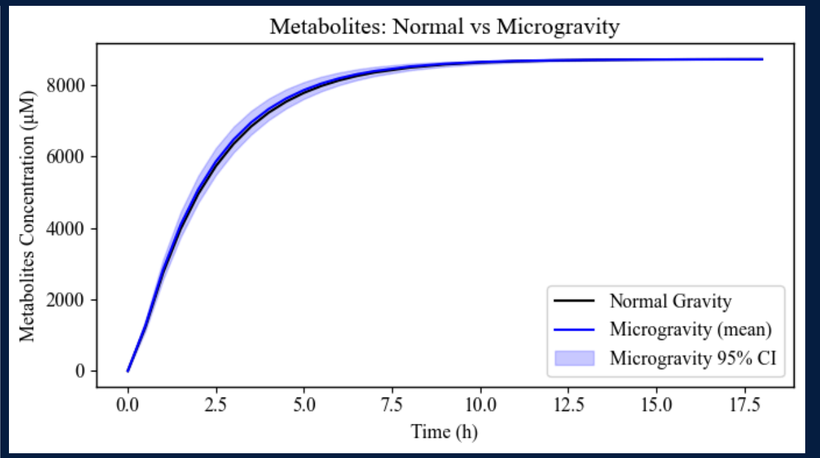
Percent change in Cmax: 4.7%
Percent change in AUC: 3.1%

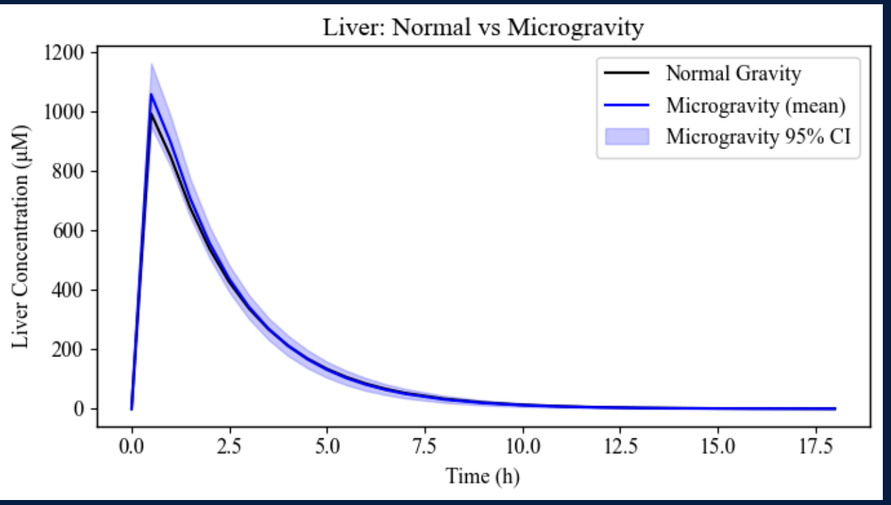


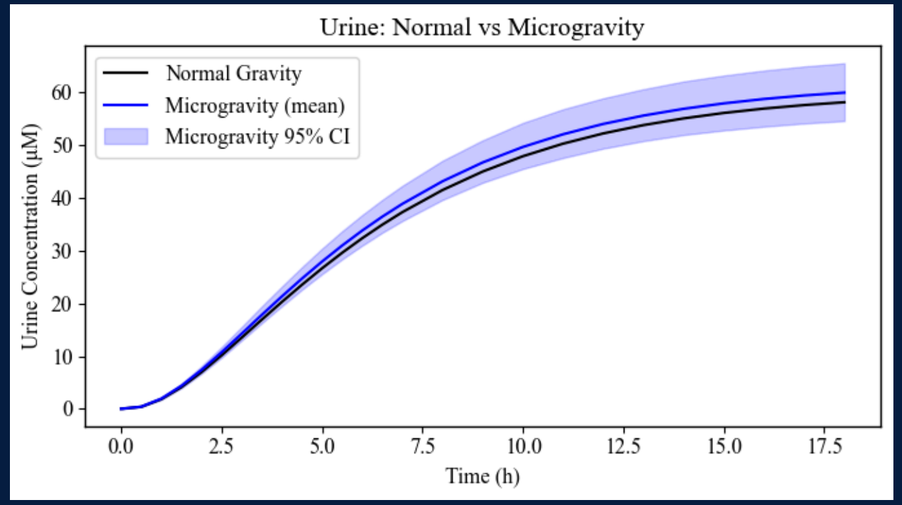
Compartment-Wise Changes



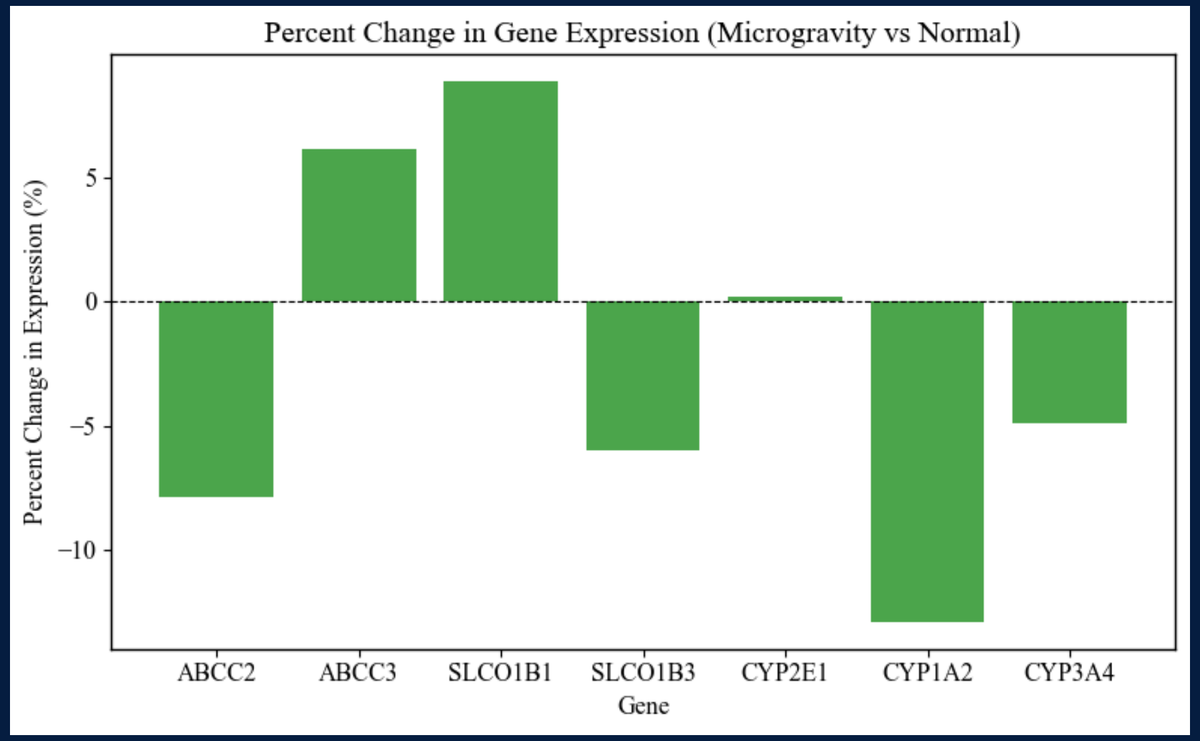


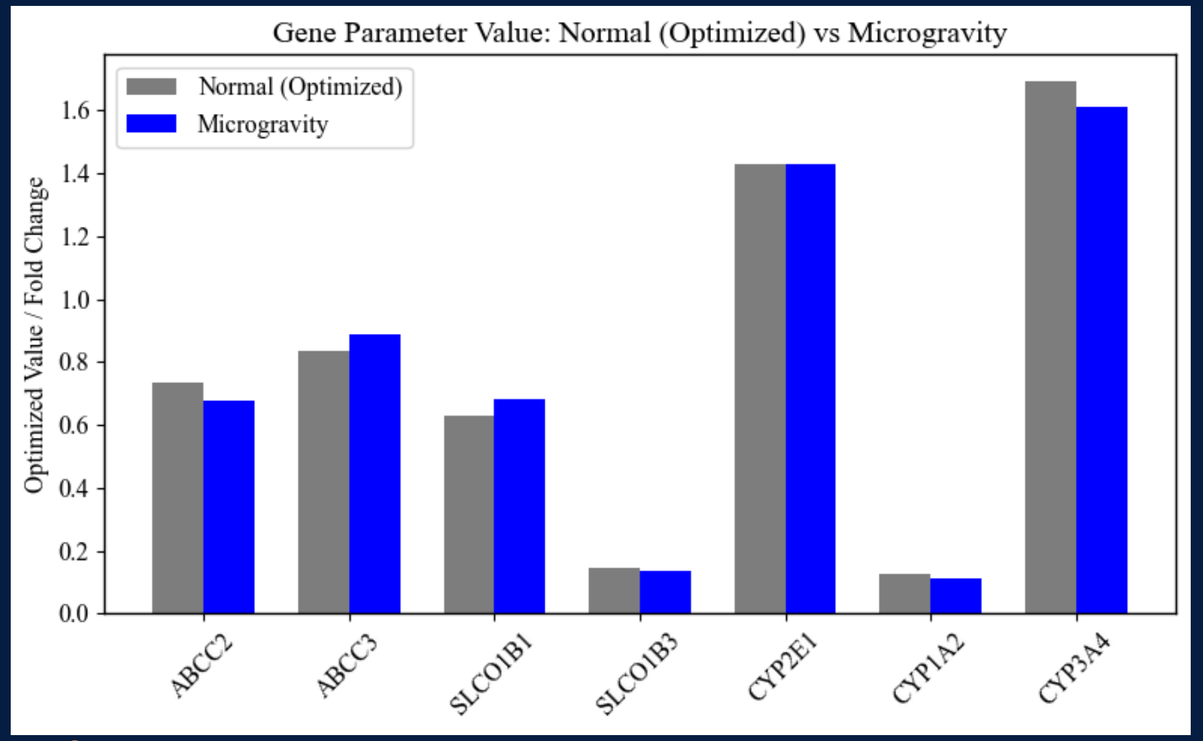






Microgravity Effect





Gene Parameter Value Comparison (Normal vs Microgravity, using optimized rates):

Parameter	Gene	Normal	Microgravity	log2FC
MRP2	ABCC2.	0.736919	0.678917	-0.118272
MRP3	ABCC3	0.836919	0.888415	0.086145
OATP1B1	SLCO1B1	0.628086	0.683617	0.122227
OATP1B3	SLCO1B3	0.146208	0.137485	-0.088750
CYP2E1	CYP2E1	1.428944	1.432057	0.003140
CYP1A2	CYP1A2	0.127525	0.111096	-0.198983
CYP3A4	CYP3A4	1.693195	1.610168	-0.072537

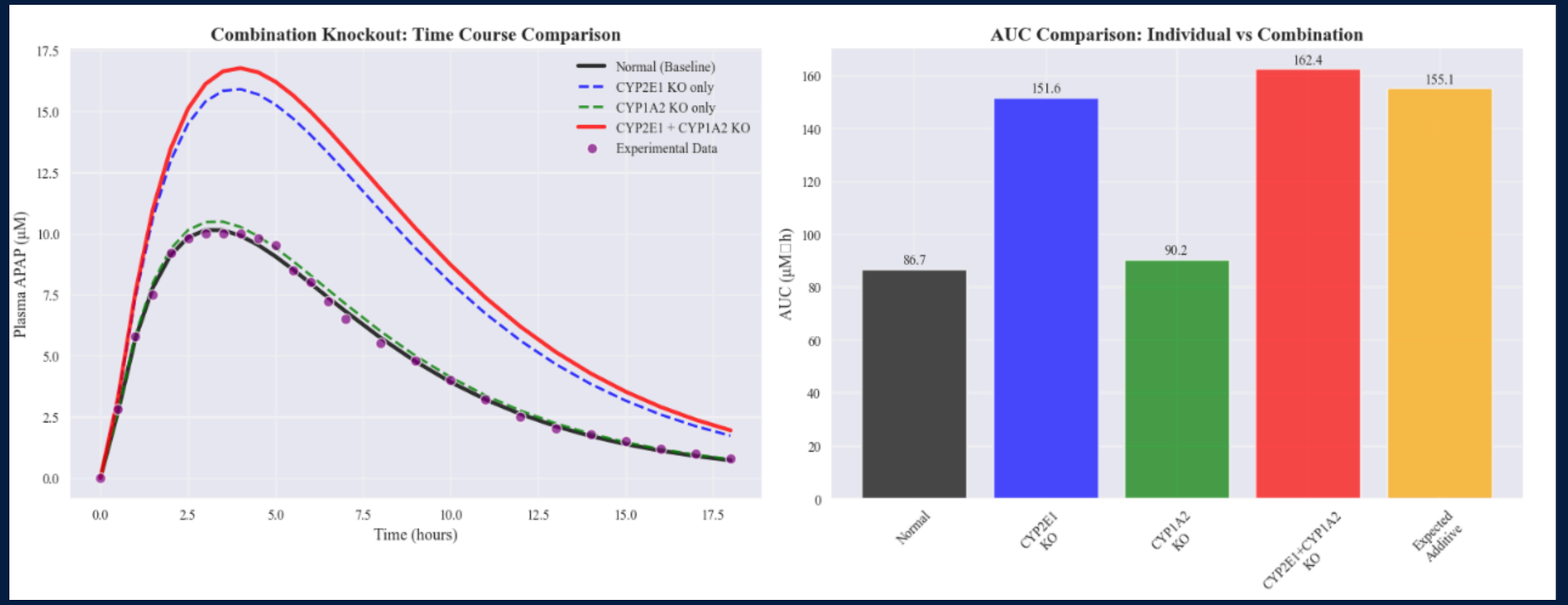
NASA OSDR DATASET

Click Here

MODEL VALIDATION

Knockout Analysis

In pharmacokinetics (PK), knockout validation refers to using gene knockout models (often in animals, sometimes in cell lines) to confirm the role of a specific protein—usually a drug-metabolizing enzyme or transporter—in the absorption, distribution, metabolism, and excretion (ADME) of a drug.



Deleting both CYP2E1 and CYP1A2 leads to an increase in plasma acetaminophen concentration because the main metabolic pathway for its conversion to the toxic metabolite NAPQI is blocked. This results in higher circulating levels of the parent drug and a much lower risk of toxicity from NAPQI formation

link

Results for APAP

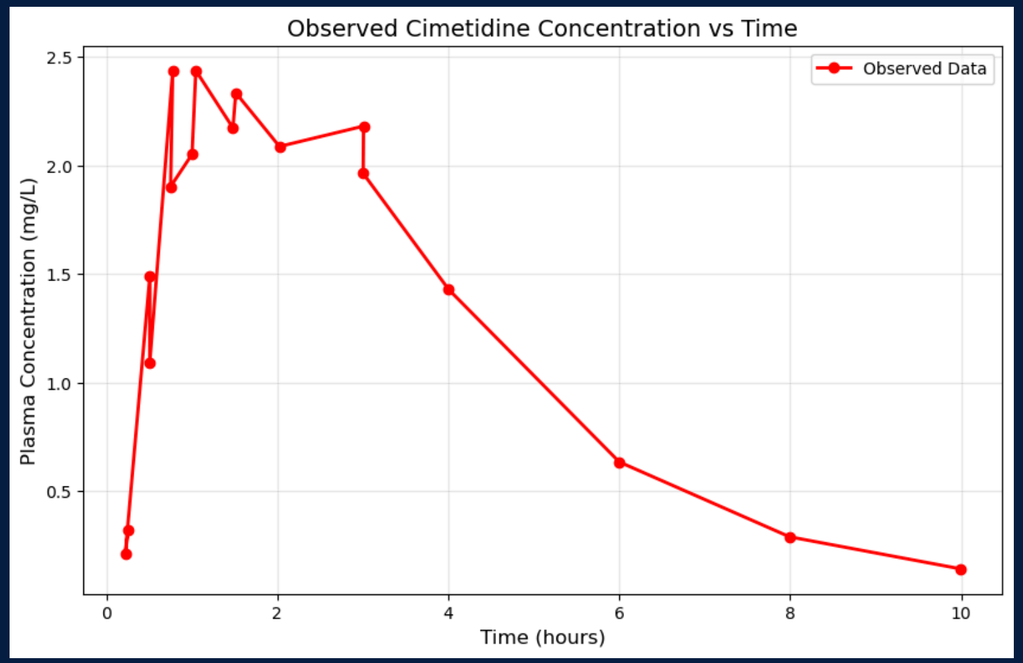
•Gene- level comparisons revealed both upregulation and downregulation under microgravity, e.g., CYP3A4 activity by 4.2%, ABCC2 by 5.9%.

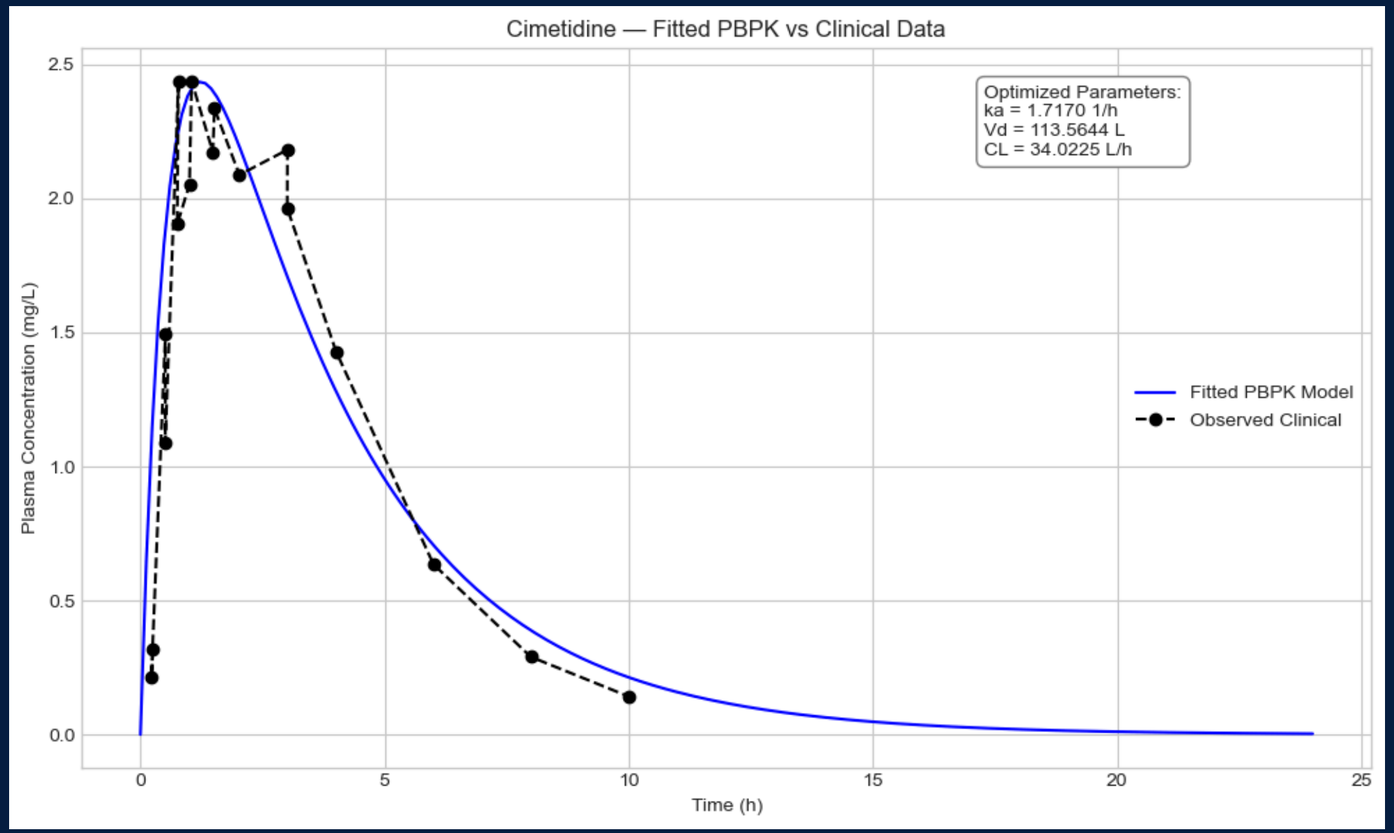
•A concentration vs. time curve for acetaminophen showed a 4.7% increase in Cmax and 3.1% increase in AUC in microgravity, validating altered drug exposure.

•Simulations showed that knockout of CYP2E1 and CYP1A2 led to increased plasma drug levels, indicating reduced toxic metabolite formation.

•The slight upward shift in the Microgravity curve shows that on average, cimetidine exposure (AUC) and peak concentration (Cmax) are a bit higher in microgravity.

Cimetidine





https://pubmed.ncbi.nlm.nih.gov/7479568/

https://pubmed.ncbi.nlm.nih.gov/11777751/

$$\frac{dA_{gut}}{dt} = -k_a \cdot A_{gut}$$

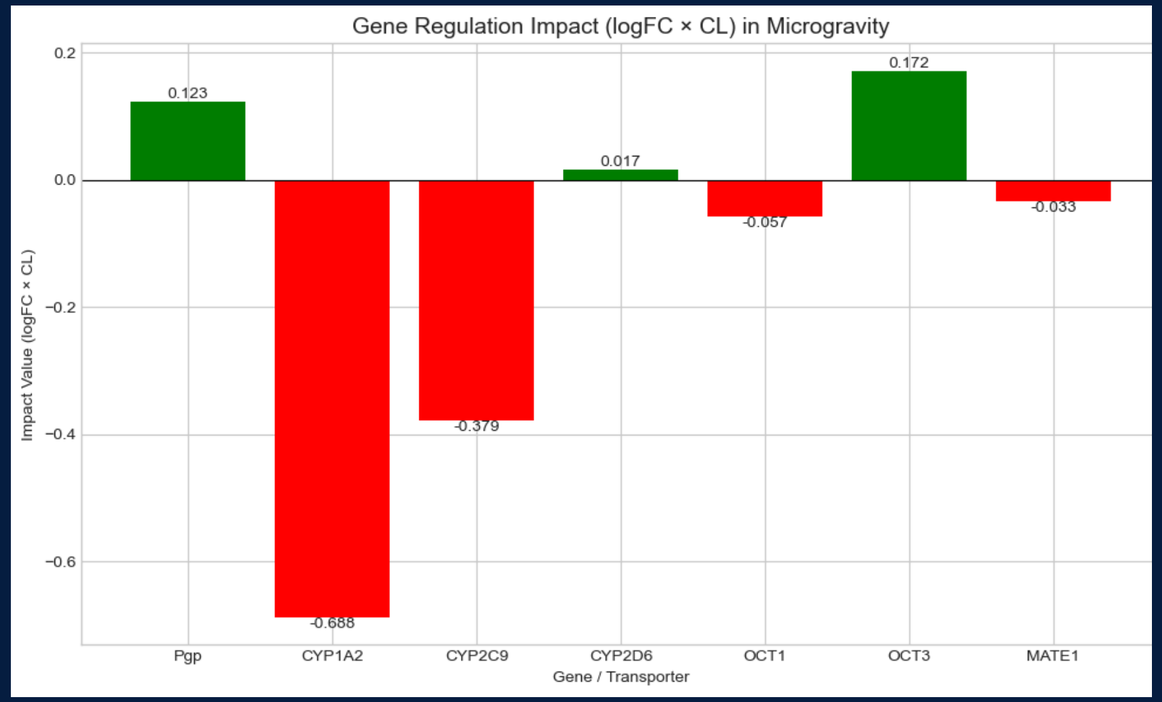
$$\frac{dA_{plasma}}{dt} = F \cdot k_a \cdot A_{gut} - Q_{hepatic} \cdot (C_{plasma} - C_{liver}) - (CL_{OCT1} + CL_{OCT3}) \cdot C_{plasma} + CL_{MATE1} \cdot C_{liver} - (CL_{OCT2} + CL_{renal\_passive}) \cdot C_{plasma}$$

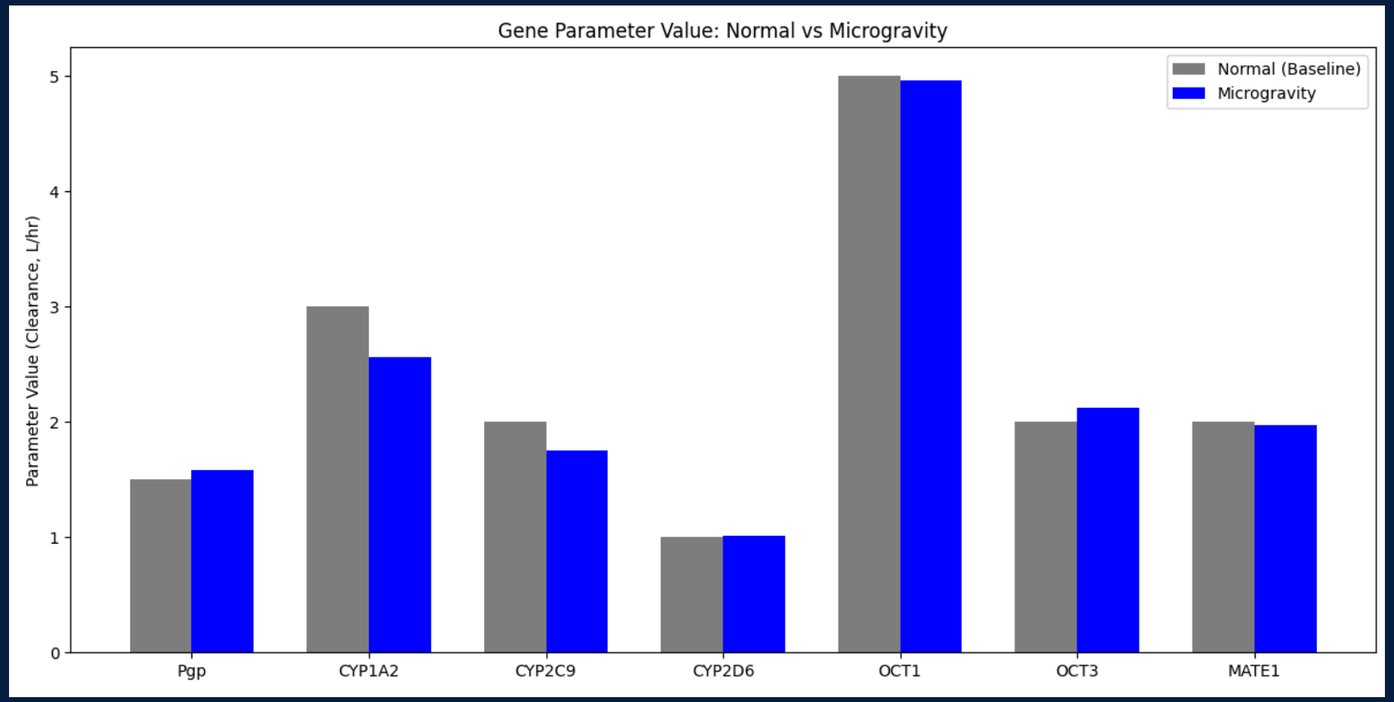
$$\frac{dA_{liver}}{dt} = Q_{hepatic} \cdot (C_{plasma} - C_{liver}) + (CL_{OCT1} + CL_{OCT3}) \cdot C_{plasma} - CL_{MATE1} \cdot C_{liver} - (CL_{CYP1A2} + CL_{CYP2C9} + CL_{CYP2D6}) \cdot C_{liver} - (CL_{biliary} + CL_{Pgp}) \cdot C_{liver}$$

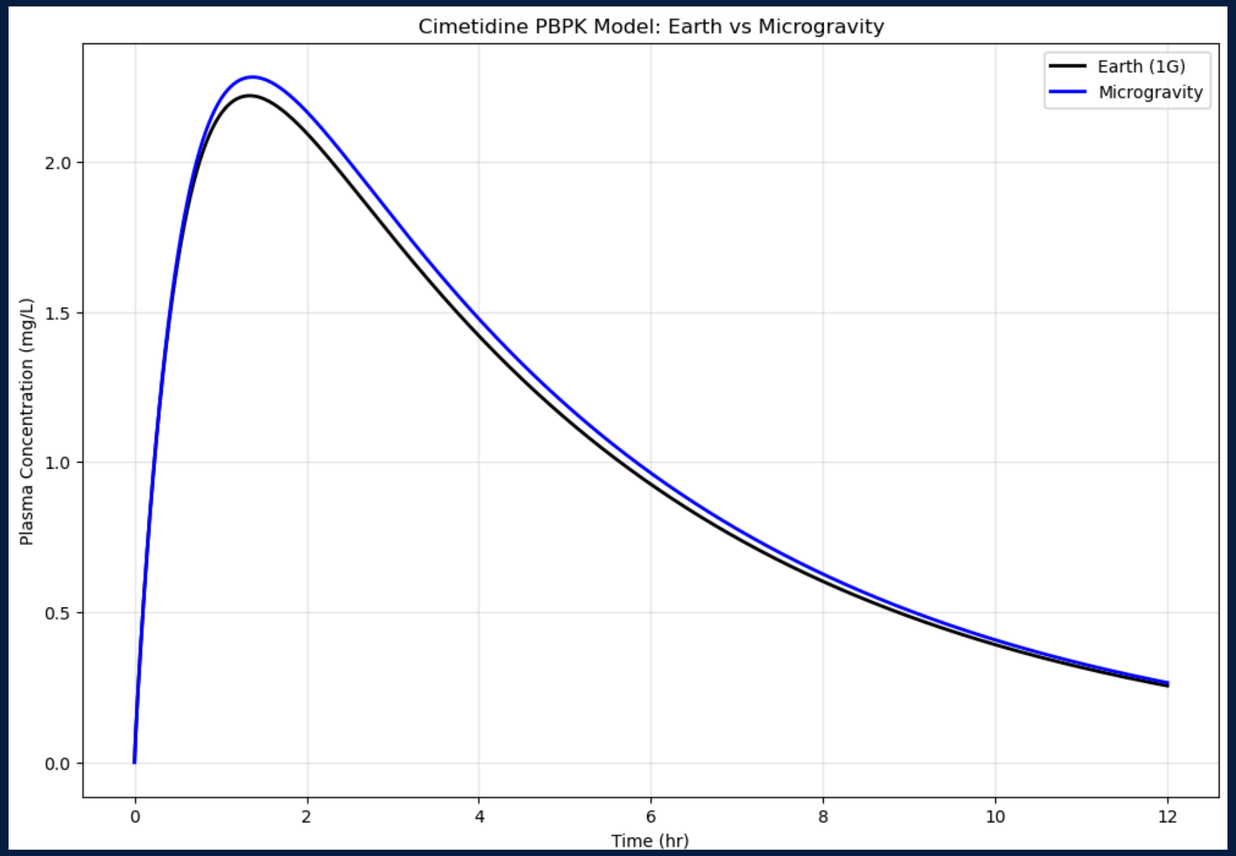
$$\frac{dA_{eliminated}}{dt} = (CL_{OCT2} + CL_{renal\_passive}) \cdot C_{plasma} + (CL_{CYP1A2} + CL_{CYP2C9} + CL_{CYP2D6}) \cdot C_{liver} + (CL_{biliary} + CL_{Pgp}) \cdot C_{liver}$$

ODE for Cimitidine

Gene Parameter Value Comparison

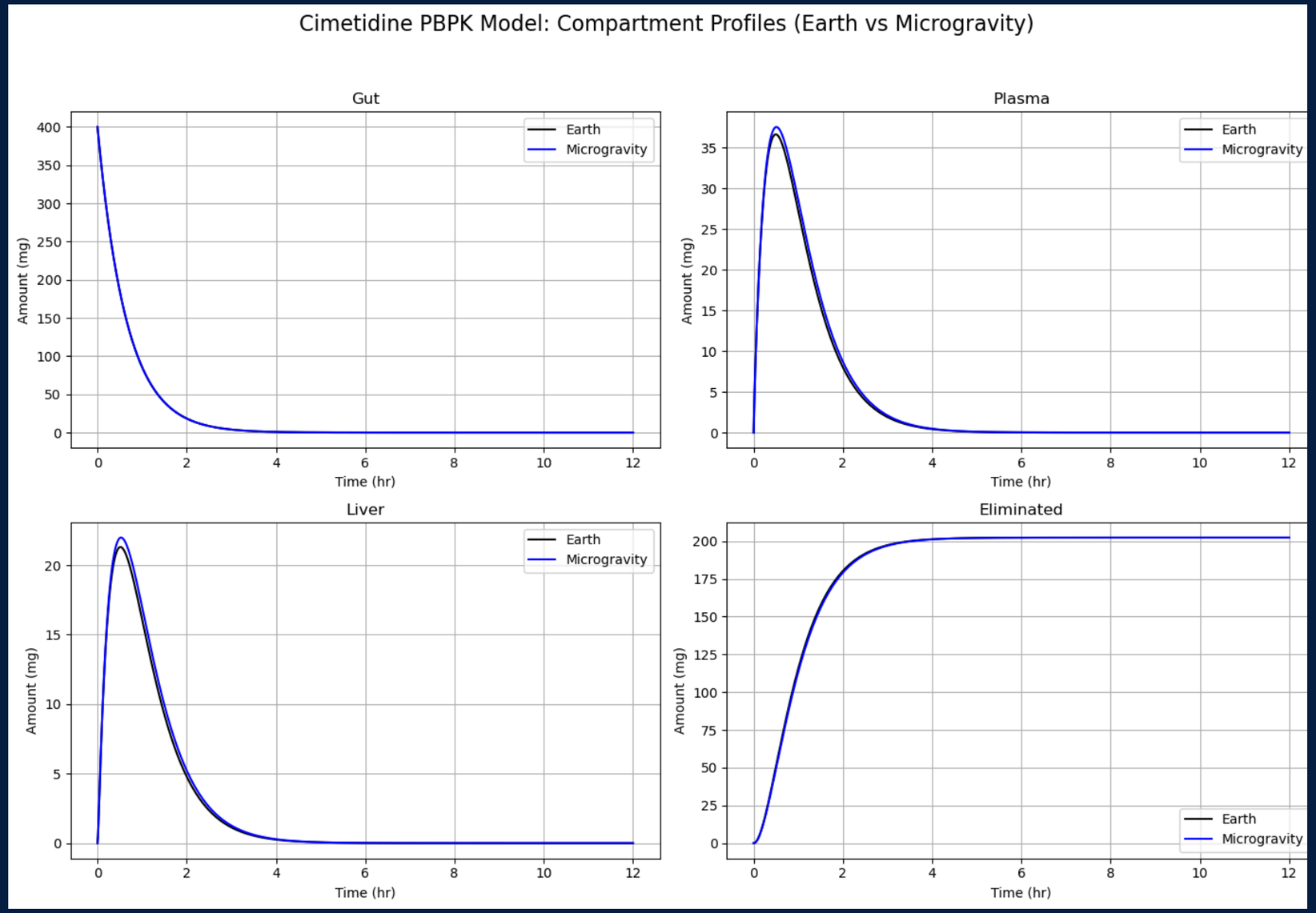


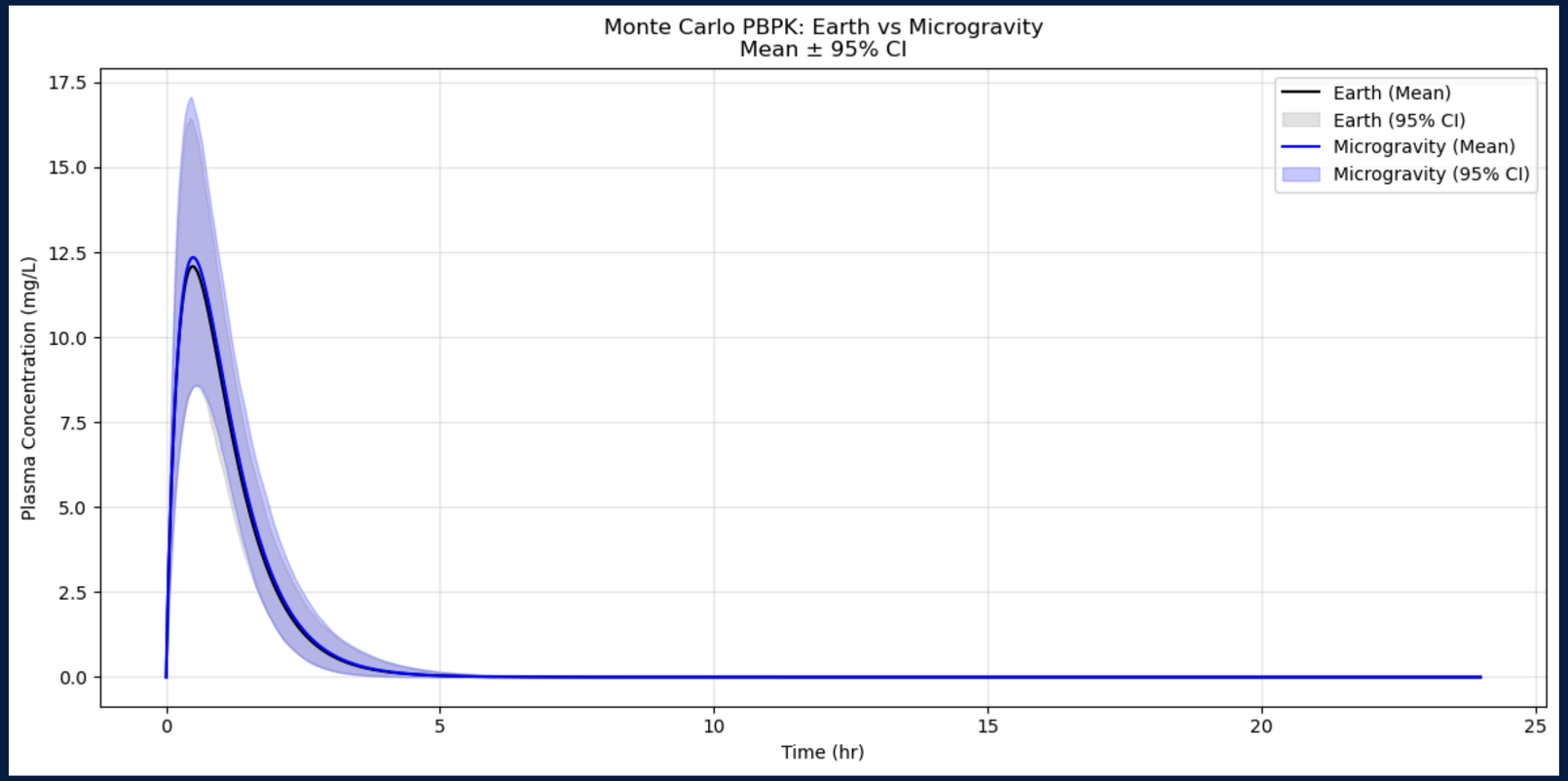




Gene	Normal	Microgravity	log2FC
Pgp	1.5000	1.5878	0.0821
CYP1A2	3.0000	2.5591	-0.2293
CYP2C9	2.0000	1.7540	-0.1893
CYP2D6	1.0000	1.0118	0.0169
OCT1	5.0000	4.9609	-0.0113
OCT3	2.0000	2.1229	0.0860
MATE1	2.0000	1.9773	-0.0164

Compartment level comparison in Earth VS Microgravity





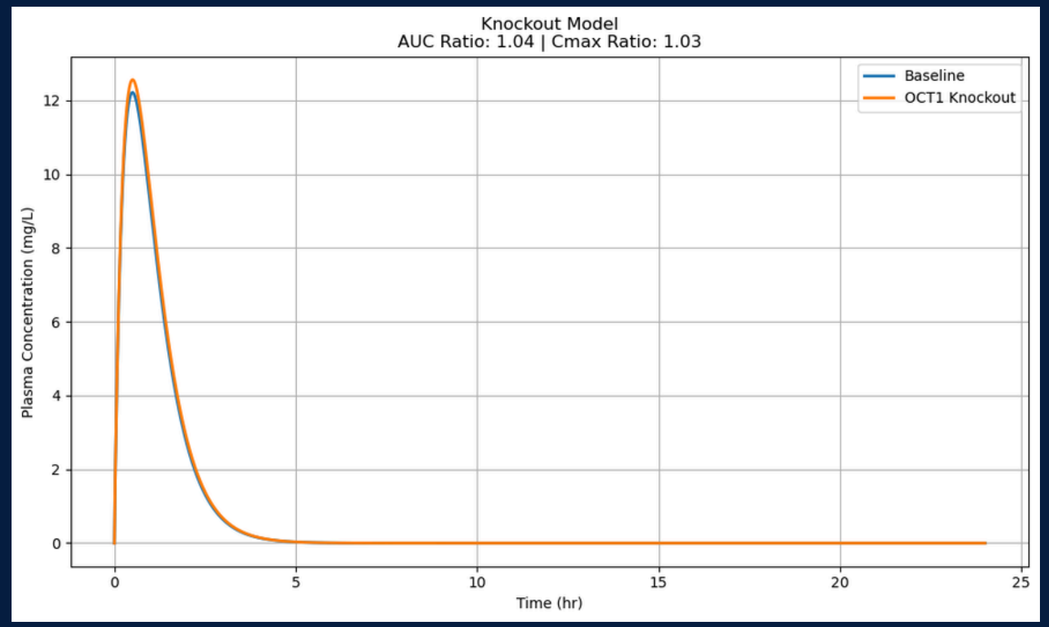
What we can deduce from the curve?

>The slight upward shift in the Microgravity curve shows that on average, cimetidine exposure (AUC) and peak concentration (Cmax) are a bit higher in microgravity.

What this means?

This means astronauts may have higher drug levels at the same dose.

Result for Cimetidine



The AUC ratio of 1.04 and Cmax ratio of 1.03 indicate that knocking out OCT1 (Organic Cation Transporter 1) results in a 4% increase in total drug exposure and a 3% increase in peak concentration

- Exposure (AUC)↑ ~3–5%
- Population mean AUC ratio: 1.040 ± 0.275
- Peak Concentration (Cmax)↑ ~2–6%
- Population mean Cmax ratio: 1.064 ± 0.362

- Mechanistic Drivers (logFC effects) ↓ CYP1A2 & CYP2C9 expression
- ↑ P-gp & OCT3 activity
- Net effect: slightly reduced clearance

- **Sensitivity Analysis**
- AUC most influenced by bioavailability (F)
- Cmax most influenced by absorption rate (ka)
- Moderate contributions from metabolic CLs (CYP1A2, CYP3A4, CYP2C9)

- **Clinical Implication**
- Small but consistent increases in exposure & peak concentration
- Recommendation: Monitor patients; adjust dosing for extended missions

OBJECTIVES ACHIEVED

01 Built a pharmacokinetic model for acetaminophen & Cimitidene using real-time dataset

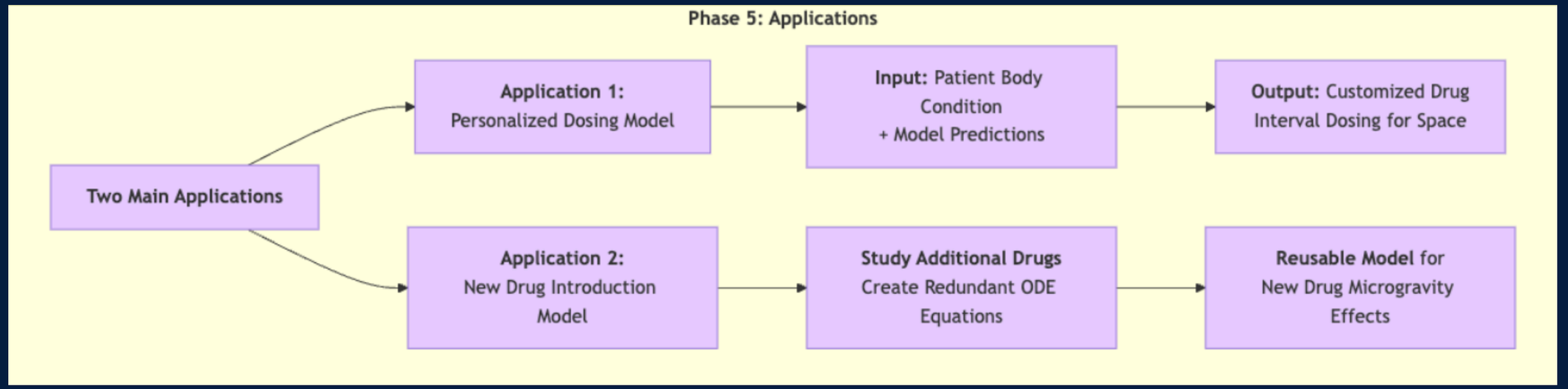
02 Found Curve for the Acetaminophen Drug testing (Plasma Concentration vs Time Graph) for our model Reference

03 Found Curve for the Cimitidene Drug testing (Plasma Concentration vs Time Graph) for our model

04 Filtering essential carriers from NASA OSDR dataset based on Transcriptome analysis of rodent and Humans under microgravity

05 Simulated the Microgravity conditions based on the changed Gene Parameters of APAP and Cimitidene

FUTURE SCOPE




Thank
you