

Model Documentation

Pharmacokinetics of Methamphetamine in Humans

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1 Model Objectives

- Develop a PK model for methamphetamine in humans

2 Data

Fig 2A in Mendelson (2006) was digitized using webplot digitizers. CSV was exported, column for dose was added 0.25 mg/kg and 0.5 mg/kg. Times in hours were rounded to two decimal places.¹

Table 1: Pharmacokinetic Data

Data	Filename	Source	PMID
Human PK Data	Fig2A_Mendelson_2006.csv	Mendelson 2006	17015058

3 Model Development

The model was developed by coding a one-compartment PK model in MRGsolve. The model was parameterized using literature values for clearance and volume of distribution, which were derived from noncompartmental analysis¹. The model was validated by simulating the model with the same dose and regimen as the observed data. Model predictions compared against observations are depicted in Figure 1 below. The model was then used to simulate various doses of methamphetamine in humans. The model then was applied to perform simulations of multiple ascending methamphetamine doses ranging from 0.03 to 3 mg/kg in humans. The results are shown in Figure 2 below.

3.1 Structure

One compartment PK model in MRGsolve

$$dA/dt = -CL/V \cdot A \quad (1)$$

$$C = A/V \quad (2)$$

3.2 Parameters

Table 2: Example Parameter Table

Parameter	Units	Value	Source	PMID
CL	0.257	L/h/kg	Literature	17015058
V	3.730	L/kg	Literature	17015058

3.3 Assumptions

None

4 Model Validation

Warning: package 'mrgsolve' was built under R version 4.3.1

Attaching package: 'mrgsolve'

The following object is masked from 'package:stats':

filter

```
-- Attaching core tidyverse packages ----- tidyverse 2.0.0 --
v dplyr      1.1.2      v readr      2.1.4
v forcats    1.0.0      v stringr    1.5.0
v lubridate  1.9.2      v tibble     3.2.1
v purrr      1.0.1      v tidyr      1.3.0
-- Conflicts ----- tidyverse_conflicts() --
x dplyr::filter() masks mrgsolve::filter(), stats::filter()
x dplyr::lag()     masks stats::lag()
i Use the conflicted package (<http://conflicted.r-lib.org/>) to force all conflicts to become
```

```
# Build model
model_1CM = mread("../code/1CM.cpp")
```

Building 1CM_cpp ... done.

```
model_2CM = mread("../code/2CM.cpp")
```

Building 2CM_cpp ... done.

```
# Define Parameters
params_1CM_human = list(BW = 70, TVVC = 3.73 * 1000, TVCL = 0.257 * 1000)
model_1CM_human = param(model_1CM, params_1CM_human)

params_2CM_human = list(BW = 70, TVVC = 3.73 * 1000, TVVP = 20, TVCL = 0.257 * 1000, TVQ = 10)
model_2CM_human = param(model_2CM, params_2CM_human)

# Define Dose
```

```

Human_BW_kg = 70
dose_025mgkg = 0.25
dose_25mg = dose_025mgkg * Human_BW_kg
dose_050mgkg = 0.5
dose_50mg = dose_050mgkg * Human_BW_kg

mg2ng = 1000000
dose_25e6ng = dose_25mg * mg2ng
dose_50e6ng = dose_50mg * mg2ng
rate = 0

# Define model, events, times, regimen
events_25mg = ev_expand(amt = dose_25e6ng, ii = 0, addl = 0, cmt = 1, rate = 0)
events_50mg = ev_expand(amt = dose_50e6ng, ii = 0, addl = 0, cmt = 1, rate = 0)
times = tgrid(0, 48, 0.01)

# Simulate model
sim_025mgkg = mrgsim(model_1CM_human, events_25mg, tgrid = times)
sim_050mgkg = mrgsim(model_1CM_human, events_50mg, tgrid = times)

# Convert to Long format (needed for plotting)
sim_025mgkg_long = convert_to_long_format(sim_025mgkg, compartments = "CP")
sim_050mgkg_long = convert_to_long_format(sim_050mgkg, compartments = "CP")

# Combine data and simulation
sim_025mgkg_long$Dose = "0.25 mg/kg"
sim_050mgkg_long$Dose = "0.50 mg/kg"
combined_data = rbind(sim_025mgkg_long, sim_050mgkg_long)

# Plot data
ggplot() +
  geom_point(data=data, aes(x = Time_h, y = PlasmaConc_ngmL, color = Dose_mgkg, group = Dose_mgkg)) +
  geom_line(data=combined_data, aes(x = time, y = Concentration, color = Dose, group = Dose_mgkg)) +
  labs(x = "Time (h)", y = "Plasma Concentration (ng/mL)") +
  theme_minimal()

```

Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
 i Please use `linewidth` instead.

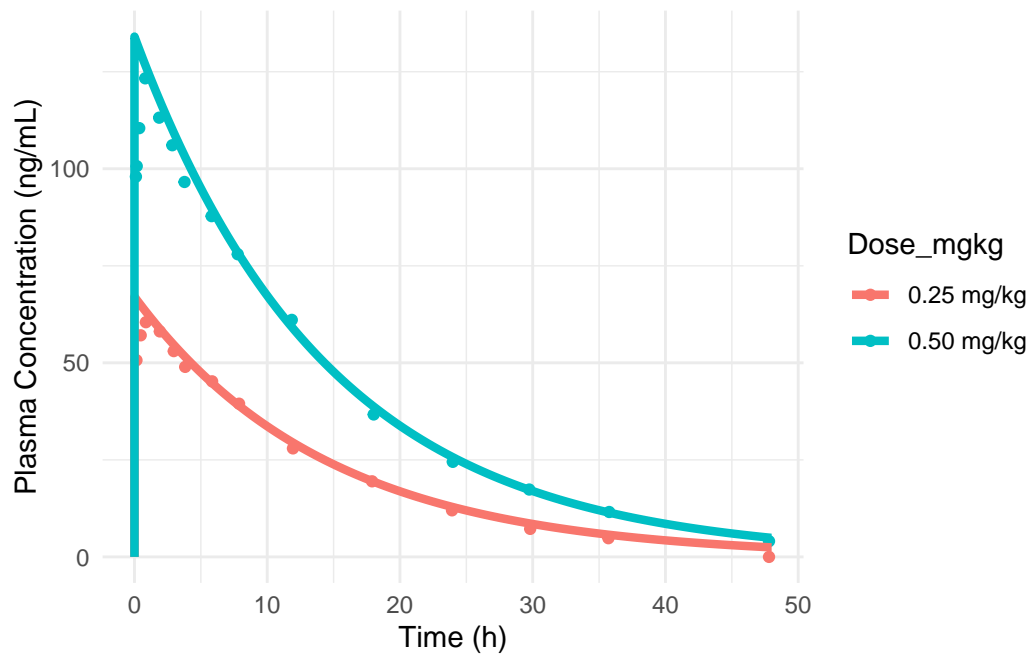


Figure 1: Methamphetamine Pharmacokinetics in Human

5 Model Application

5.1 Simulations of Methamphetamine Doses

```
# Define doses in mg/kg
dose_levels = c(0.03, 0.1, 0.3, 1, 3)
human_bw_kg = 70

# Function to run simulation for a given dose
run_simulation <- function(dose_mgkg) {
  dose_mg = dose_mgkg * human_bw_kg # Convert mg/kg to mg
  dose_ng = dose_mg * 1e6 # Convert mg to ng

  # Create an event object for the dose
  events = ev(amt = dose_ng, ii = 24, addl = 2, cmt = 1, rate = 0) # Assuming administration at 24h, 2 days, compartment 1, rate 0

  # Simulate
  sim_out = mrgsim(model_1CM_human, events, end = 72, delta = 0.1)

  # Convert to long format for plotting using the existing function
  sim_out_long <- convert_to_long_format(sim_out, compartments = "CP") %>%
    mutate(Dose = paste(dose_mgkg, "mg/kg"))

  return(sim_out_long)
}

# Run simulations for all doses
simulation_results = purrr::map_df(dose_levels, run_simulation)

# Plotting the results
ggplot(simulation_results, aes(x = time, y = Concentration, color = Dose, group = Dose)) +
  geom_line(size = 1.5) +
  scale_y_log10() +
  labs(x = "Time (hours)", y = "Plasma Concentration (ng/mL)") +
  theme_minimal() +
  scale_color_brewer(palette = "Set1")
```

Warning: Transformation introduced infinite values in continuous y-axis

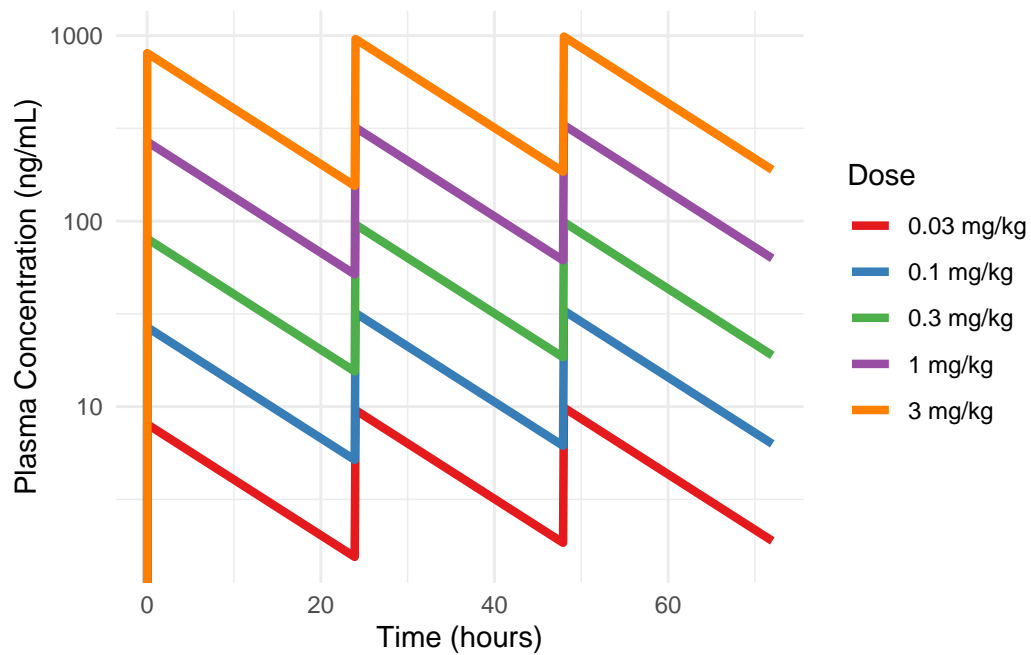


Figure 2: Predicted Methamphetamine Pharmacokinetics in Humans

5.2 Receptor Binding Model

6 Model Accessibility and Useability

- Model available in github repo: [Model Repo - Placeholder](#)

7 Acknowledgements

This report was generated using [Quarto](#), a scientific and technical publishing system built on Pandoc. The template used for this document is based on the *moDoc* template, which can be found at the following [GitHub repository](#).

8 References

1. Mendelson, J. *et al.* Human pharmacology of the methamphetamine stereoisomers. *Clinical Pharmacology & Therapeutics* **80**, 403–420 (2006).