Monte Carlo Pharmacokinetic/Pharmacodynamic (PK/PD) Simulation for Dose Target Attainment

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***Abstract*—A Monte Carlo simulation of a one-compartment, first-order absorption pharmacokinetic (PK) model was performed to quantify population variability and target attainment for a hypothetical oral antimicrobial regimen. Inter-individual variability (IIV) for clearance, central volume, and absorption rate constant was sampled from log-normal distributions for $n = 2000$ virtual subjects. Steady-state exposure metrics included $C_{\max}$, $AUC_{0-\tau}$, C_{trough}, and the percent of time above the minimum inhibitory concentration (%T>MIC). Results indicated robust target attainment for %T>MIC (median 100%, 5th–95th: 89.47–100.00%), supporting adequacy of the evaluated regimen under the modeled assumptions. This report summarizes model structure, parameterization, simulation design, and findings to ensure reproducibility and provide a foundation for future extensions.**

I. Introduction

Monte Carlo simulation (MCS) is widely used in pharmacometrics to propagate inter-individual variability (IIV) through pharmacokinetic/pharmacodynamic (PK/PD) models. Instead of single deterministic outputs, MCS produces distributions of exposure and response metrics, enabling probabilistic evaluation of regimen adequacy and dose optimization based on probability of target attainment (PTA).

II. Methods

A. Pharmacokinetic Model

A one-compartment model with first-order absorption and elimination was implemented. Following an oral dose D, the concentration-time profile at steady state over dosing interval τ is:

$$C(t) = \frac{FDk_a}{V(k_a - k)} \left(\frac{1 - e^{-k_a t}}{1 - e^{-k_a \tau}} - \frac{1 - e^{-kt}}{1 - e^{-k\tau}} \right), \quad t \in [0, \tau], \tag{1}$$

where F denotes bioavailability (assumed unity), k_a the absorption rate constant, $k = CL/V$ the elimination rate constant, CL the clearance, and V the apparent volume of distribution.

B. Parameter Distributions

Inter-individual variability was represented using log-normal distributions:

$$\log(CL) \sim \mathcal{N}(\mu_{CL}, \sigma^2_{CL}),$$
$$\log(V) \sim \mathcal{N}(\mu_V, \sigma^2_V),$$
$$\log(k_a) \sim \mathcal{N}(\mu_{k_a}, \sigma^2_{k_a}).$$

A single oral dosing regimen was simulated to steady state, and concentration profiles were computed over one dosing interval. The minimum inhibitory concentration (MIC) was set to 1.00 mg/L for %T>MIC determination.

C. Endpoints and Computations

For each virtual subject, the following PK/PD endpoints were derived:

- $C_{\max}$: maximum concentration within the interval
- $AUC_{0-\tau}$: area under the curve over the dosing interval
- C_{trough}: concentration immediately before next dose
- %T>MIC: percentage of time during which $C(t) > \text{MIC}$

Simulations were executed in Python using NumPy, Pandas, and Matplotlib. Summary statistics were exported to CSV and visualized using histograms.

III. Results

A. Exposure Distributions

Table I summarizes exposure metrics across 2000 virtual subjects.

TABLE I: PK/PD summary statistics (n=2000).

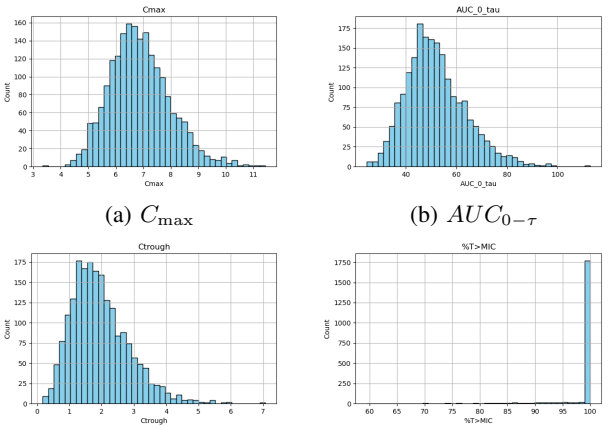
Metric	Median	5th pct	95th pct
$C_{\max}$ (mg/L)	6.78	5.22	8.79
$AUC_{0-\tau}$ (mg h/L)	50.25	35.15	73.57
C_{trough} (mg/L)	1.80	0.77	3.60
%T>MIC (%)	100.00	89.47	100.00

B. Visualization

Histograms of exposure distributions and representative steady-state profiles are shown in Figs. 1 and 2, respectively.

C. Interpretation

Simulations demonstrated moderate variability in $C_{\max}$ and $AUC_{0-\tau}$, primarily driven by variation in clearance and absorption rates. Nearly all simulated subjects achieved %T>MIC $\geq$ 90%, suggesting adequate pharmacodynamic coverage for time-dependent antimicrobial activity under modeled assumptions.



(a) $C_{\max}$ (b) $AUC_{0-\tau}$

(c) C_{trough} (d) %T>MIC

Fig. 1: Simulated distributions of exposure and pharmacodynamic metrics.

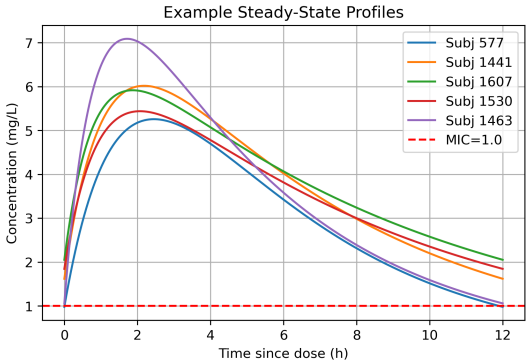


Fig. 2: Representative steady-state concentration–time profiles for five subjects (MIC = 1.00 mg/L, dashed).

IV. Discussion

Monte Carlo simulation offers an efficient framework for propagating uncertainty through PK/PD systems to generate distributions of exposure and PTA. The evaluated dosing regimen achieved complete PTA for most subjects, indicating limited risk of subtherapeutic exposure. Potential model extensions include covariate incorporation (body weight, renal function), multi-compartment models, or variable dosing intervals. Validation with observed clinical pharmacokinetic data would further enhance applicability.

V. Limitations

Model assumptions included fixed bioavailability, absence of residual unexplained variability, and a single MIC threshold. True patient heterogeneity and adherence factors were not represented.

VI. Reproducibility

All data and figures were generated using open-source Python libraries. Directory structure:

```
project/
    pkpd_monte_carlo.ipynb
    results/
        pkpd_sim_results.csv
        cmax_hist.png
        auc_hist.png
        ctrough_hist.png
        pctT_MIC_hist.png
    figures/
        profiles_examples.png
```

References

1) J. Gabrielsson and D. Weiner, *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*, 5th ed., CRC Press, 2016.
2) J. W. Mouton et al., "Time over MIC as a predictor of β-lactam efficacy," *Clin. Pharmacokinet.*, 2005.
3) E. I. Ette and P. J. Williams, *Pharmacometrics: The Science of Quantitative Pharmacology*, Wiley-Interscience, 2007.