Phase I PK/PD Analysis using the Two-Stage Approach

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Introduction

This document provides a comprehensive pharmacokinetic/pharmacodynamic (PK/PD) analysis using a nonlinear least squares method (two-stage approach). The source data were from the PhaseI/II study of drug candidate (RDX101) provided by the client that contains both PK measurements (plasma concentrations) and PD measurements (PCA).

Table 1. Number of PK and PD observations per subject (Only 10 displayed)

SUBJECTID	NO.PK.OBS	NO.PD.OBS
1	11	7
2	6	7
3	11	8
4	9	8
5	10	8
6	8	8
7	9	7
8	11	8
9	17	8
10	6	8

Exploratory Analyses

Figure 1. Plot concentration-time profiles by subject

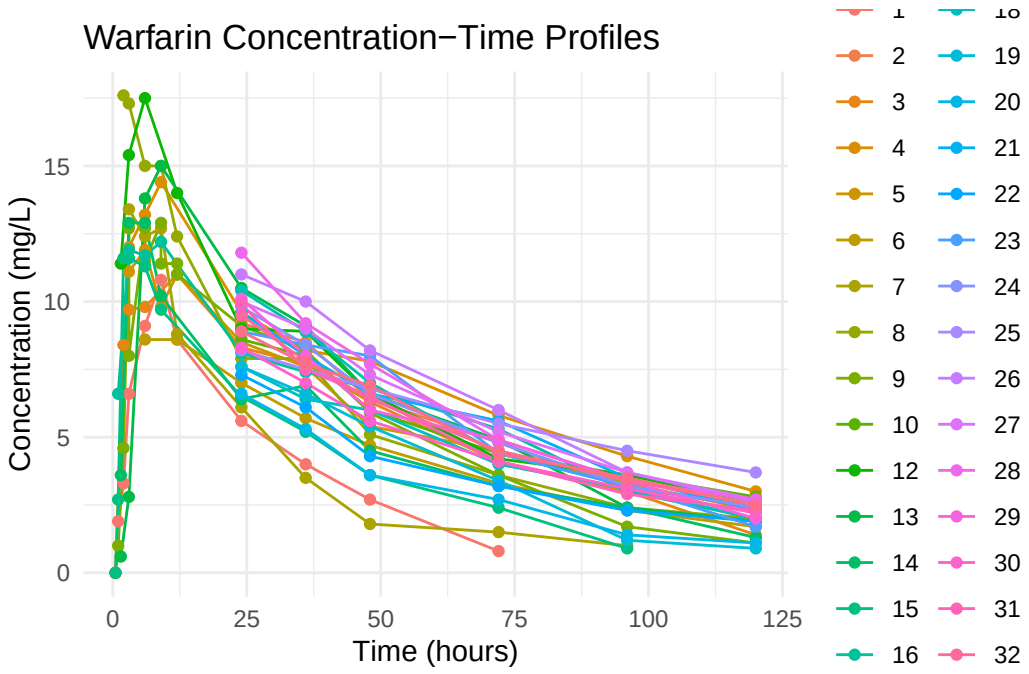


Figure 2. Concentration by dose

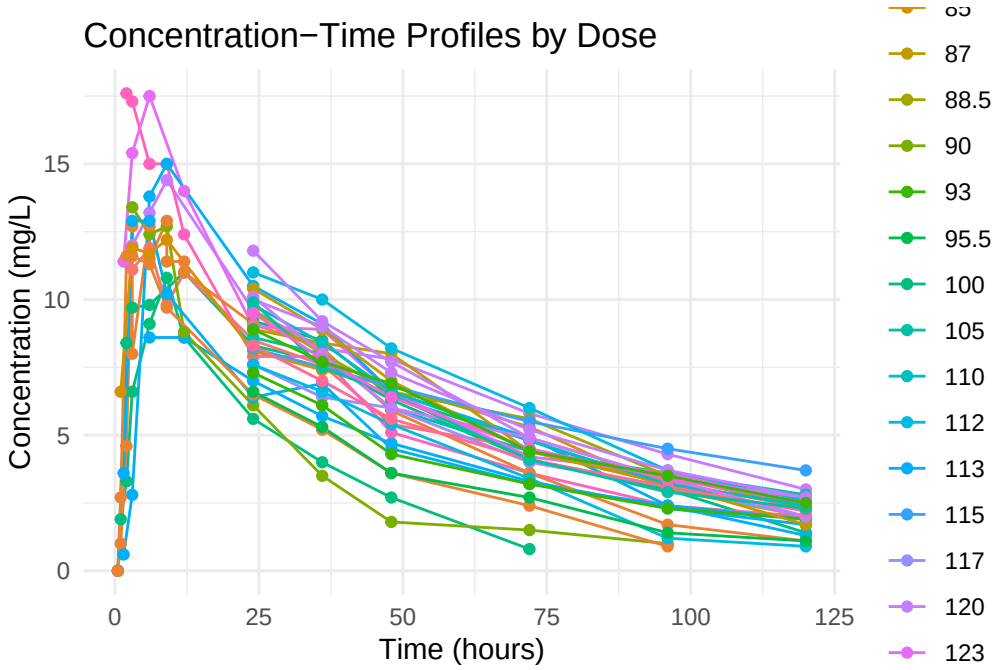


Figure 3. PD response-time profiles by subject

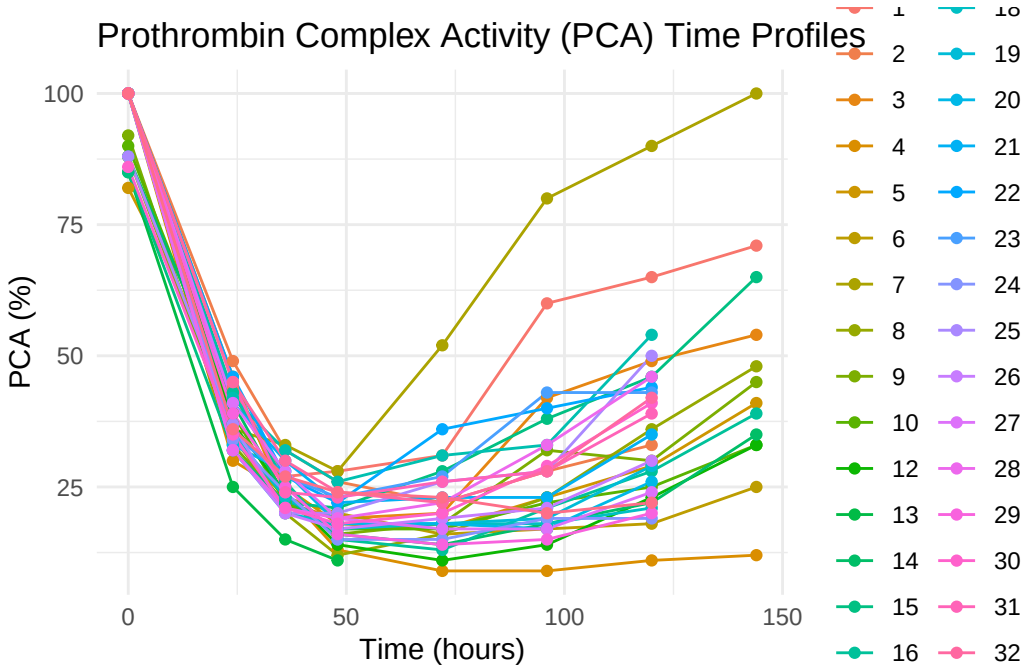
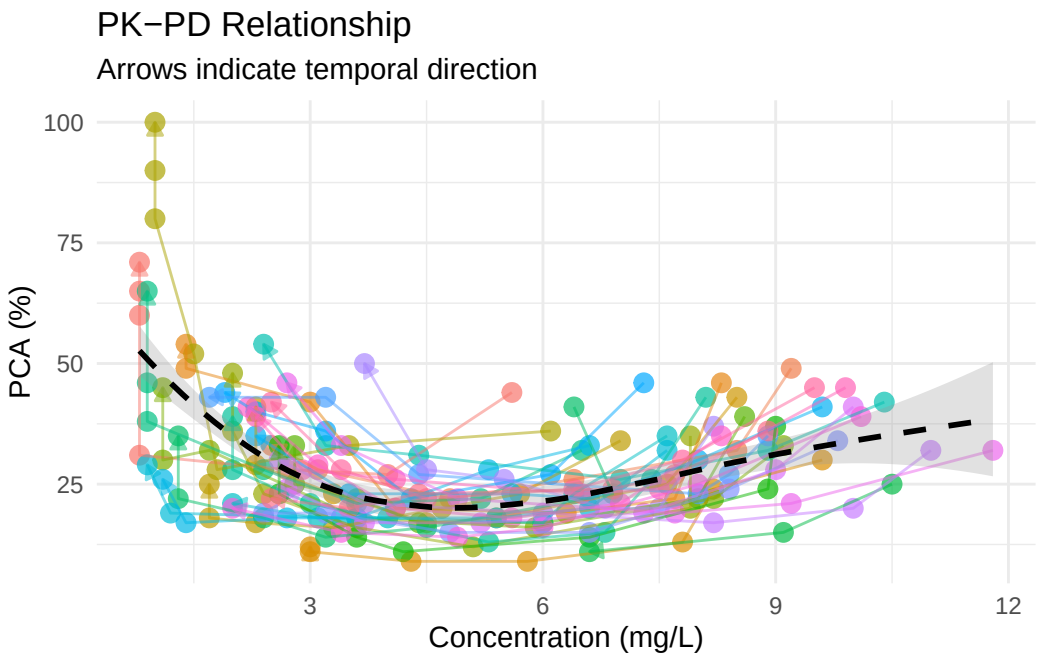


Figure 4. PK-PD Relationship Exploration



One-Compartment PK Model Development

1. First stage: Fit individual PK models for each subject
2. Second stage: Analyze population distribution of parameters

Fitting individual PK Model

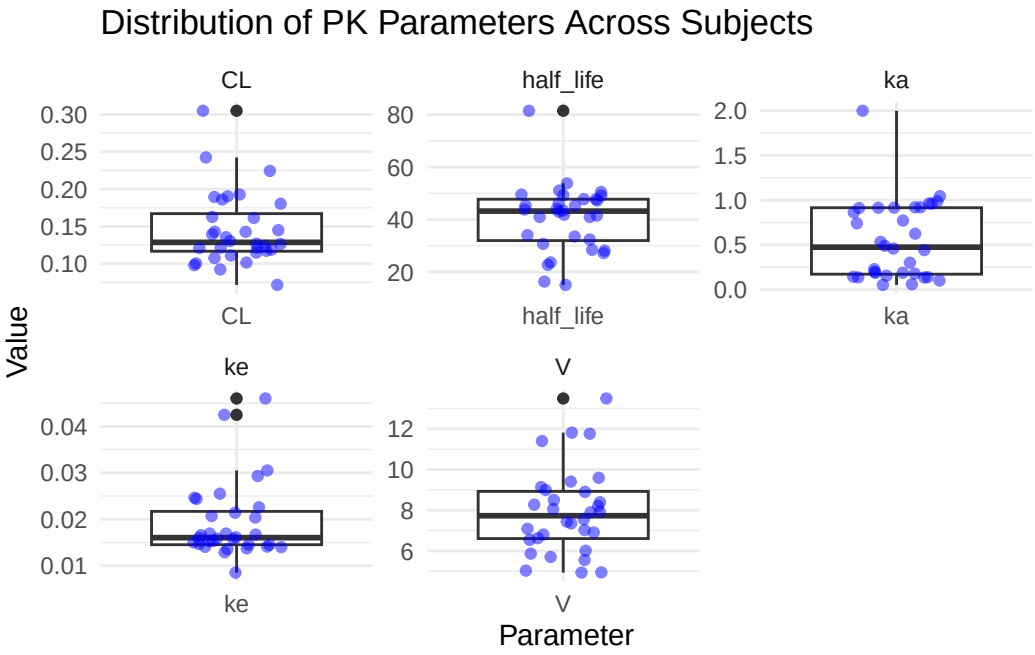
Table 2. Individual PK Model Fitting (Only 5 subjects displayed)

id	ka	ke	V	CL	half_life	AUC	Tmax	Cmax
1	0.19	0.05	6.63	0.30	15.06	327.97	9.94	9.55
2	0.13	0.02	7.92	0.12	45.23	823.34	18.30	9.53
3	0.46	0.02	8.06	0.13	44.03	788.14	7.62	11.00
4	0.62	0.01	8.21	0.11	49.55	1,044.40	6.23	13.39
5	0.99	0.01	4.94	0.07	47.78	836.66	4.34	11.40
6	0.44	0.02	11.40	0.18	43.81	626.60	7.83	8.76

Table 3. Population PK Parameters

parameter	mean	sd	median	min	max	percent
ka	0.55	0.44	0.47	0.05	2.00	
ke	0.02	0.01	0.02	0.01	0.05	
V	7.91	2.09	7.73	4.93	13.49	
half_life	40.50	12.87	43.22	15.06	81.50	
AUC	772.85	190.80	830.00	327.97	1,144.71	
CL	0.15	0.05	0.13	0.07	0.30	

Figure 5. Boxplots of parameter distributions



PK Model Evaluation

Figure 6. observed vs predicted across all subjects

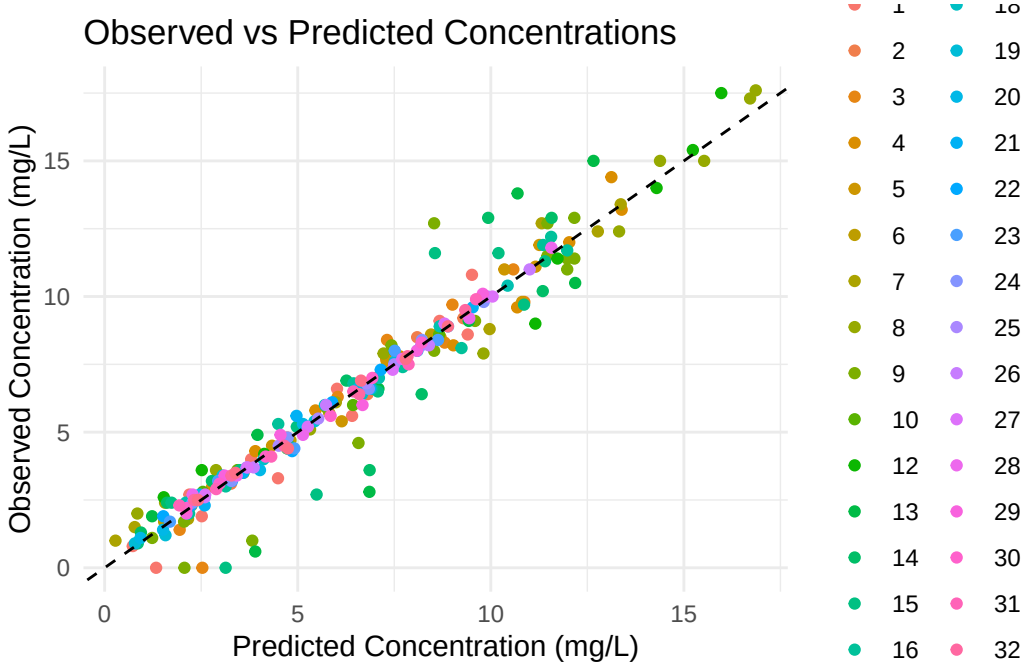


Figure 7. Time profiles for all subjects

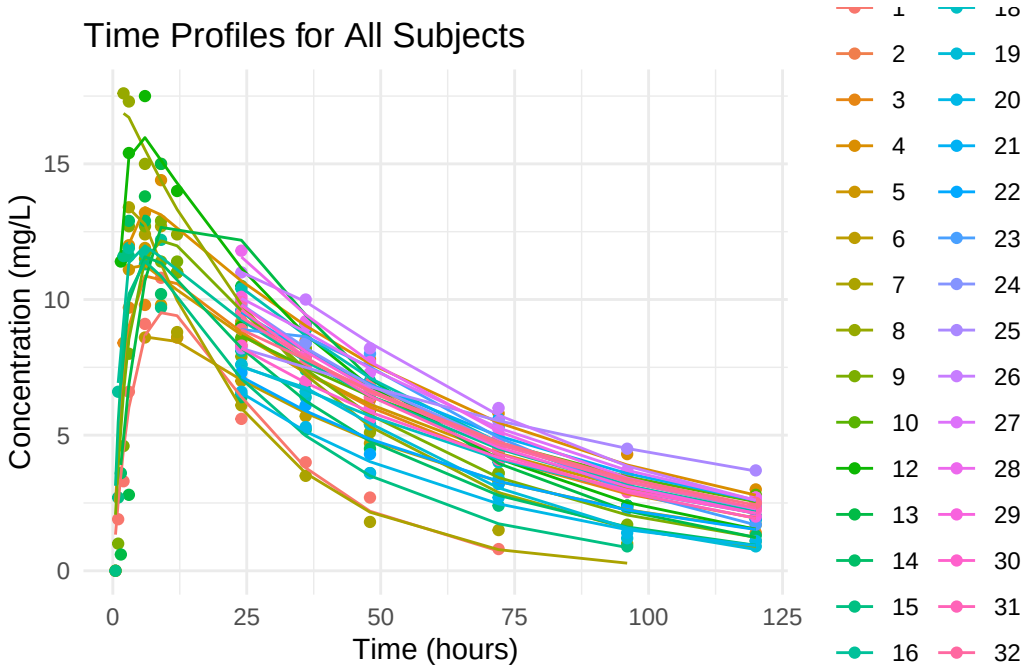


Figure 8. Plot residuals

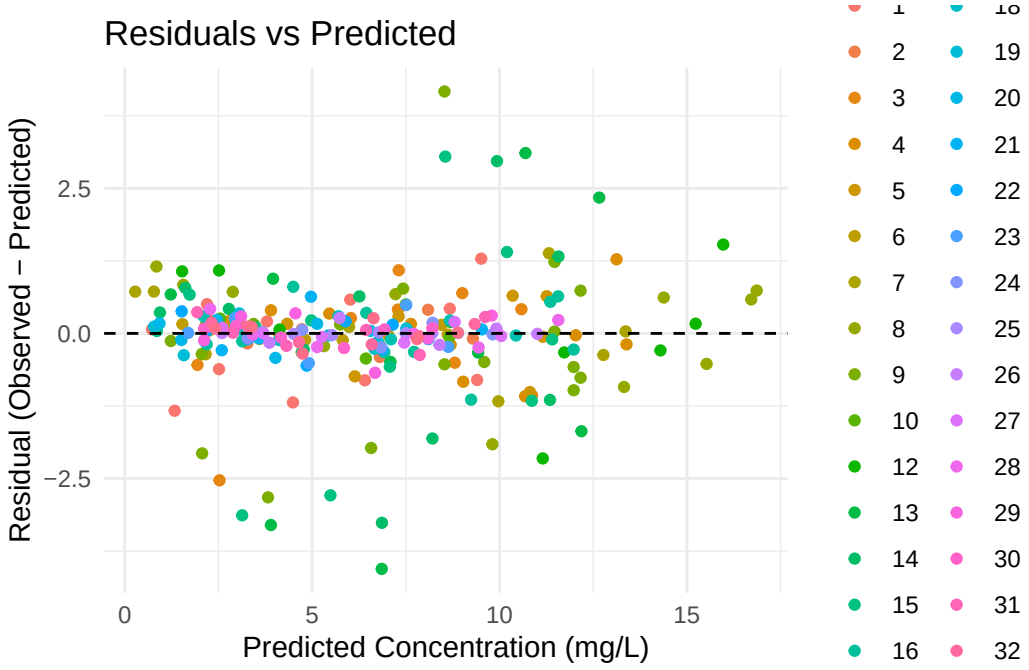


Figure 9. Plot smooth prediction curves

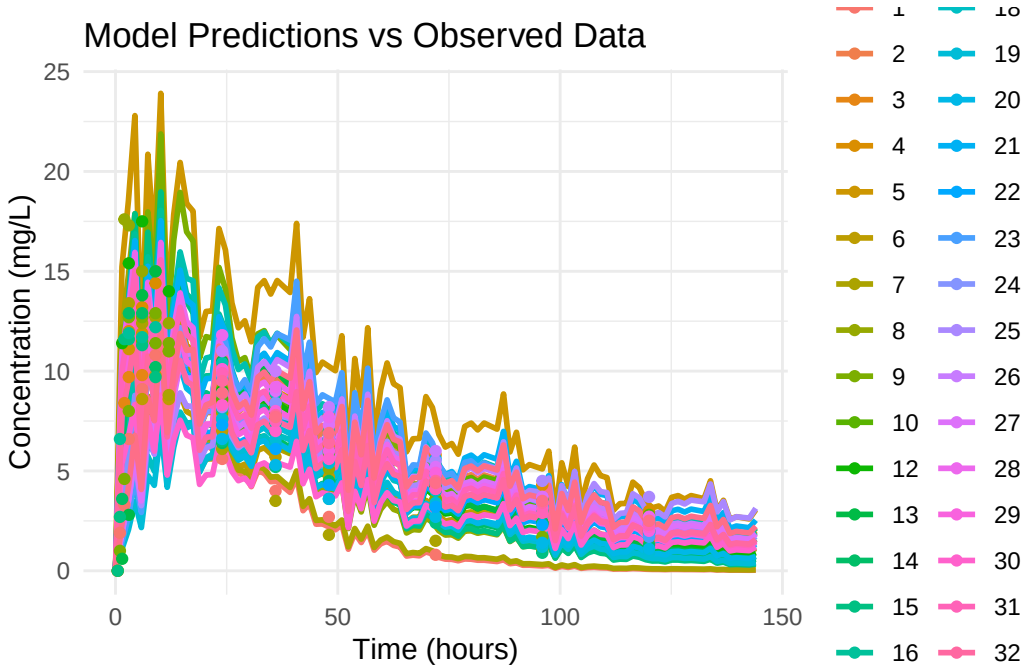


Figure 10. Individual Subject Plots

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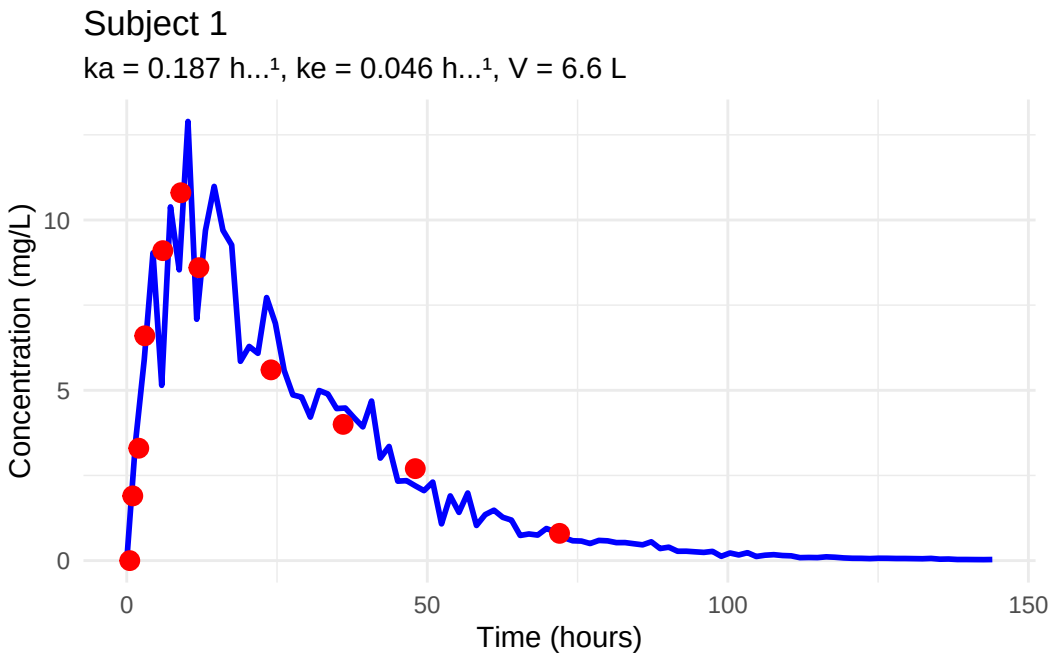

Subject 1
ka = 0.187 h...¹, ke = 0.046 h...¹, V = 6.6 L
Concentration (mg/L)
10
5
0
0
50
100
150
Time (hours)

PK/PD Relationship Analysis

Figure 11. Linking PK Predictions to PD Observations

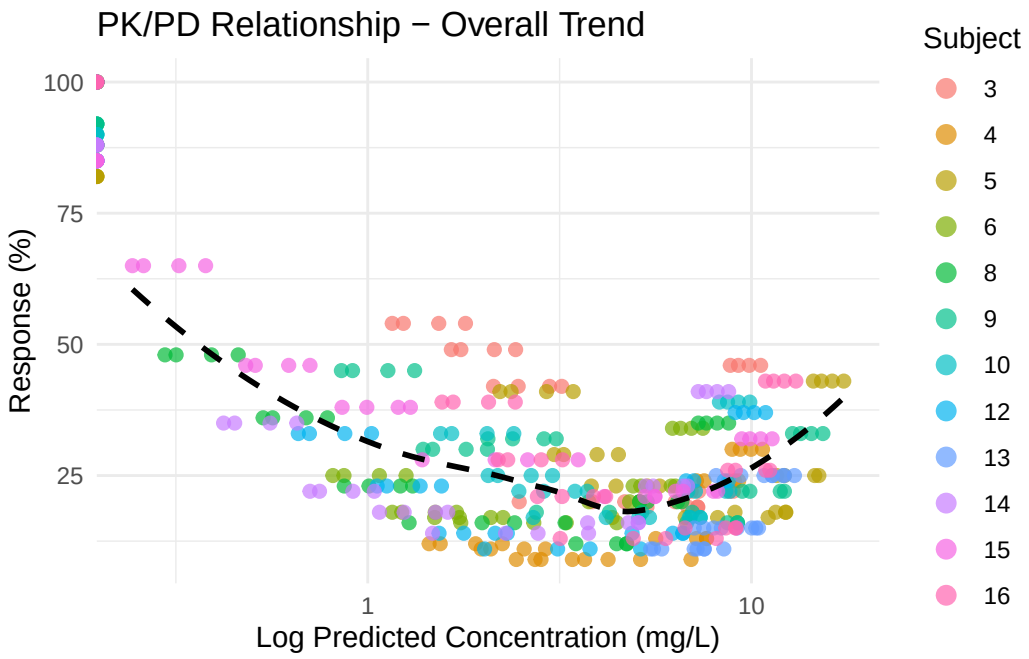
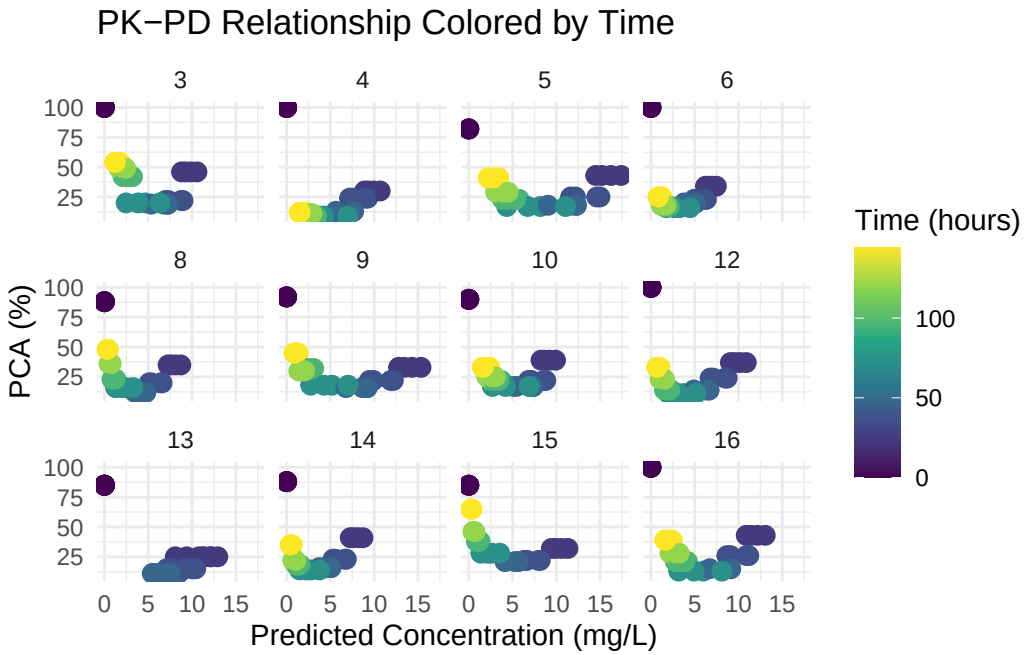


Figure 12. PK-PD relationship with time as a factor



Indirect Response PD Model

The PK/PD relationship shows evidence of hysteresis, indicating a delayed response. This is typical for the drug, which inhibits the synthesis of clotting factors. An indirect response model is appropriate for this mechanism.

Table 4. Summary of indirect response model

Table 1: Individual PD Parameter Estimates

	id	kin	kout	ic50	half_life_pd
kin	3	4.305	0.065	5.348	10.655
kin1	4	0.654	0.035	5.606	19.714
kin2	5	2.935	0.053	6.744	13.082
kin3	6	1.140	0.039	5.802	17.769
kin4	8	3.210	0.058	2.085	11.872
kin5	9	2.564	0.053	7.165	13.017
kin6	10	2.625	0.052	4.024	13.341
kin7	12	2.140	0.047	2.482	14.750

kin8	13	1.656	0.048	3.162	14.496
kin9	14	2.034	0.045	2.137	15.405
kin10	15	3.643	0.063	5.233	10.979
kin11	16	2.961	0.053	4.107	13.091

Parameter	Mean	SD	Median	Min	Max
kin	2.49	1.04	2.59	0.65	4.31
kout	0.05	0.01	0.05	0.04	0.07
ic50	4.49	1.76	4.67	2.08	7.16
half_life_pd	14.01	2.66	13.22	10.66	19.71

PD Model Evaluation

Figure 13. Plot observed vs predicted PCA

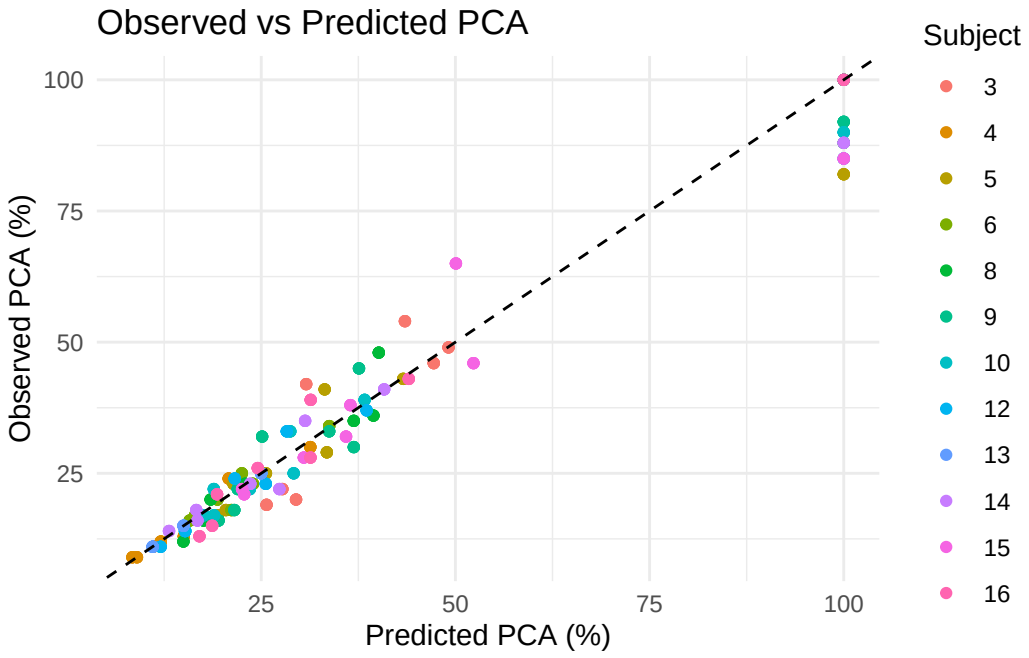


Figure 14. Plot time profiles for all subjects

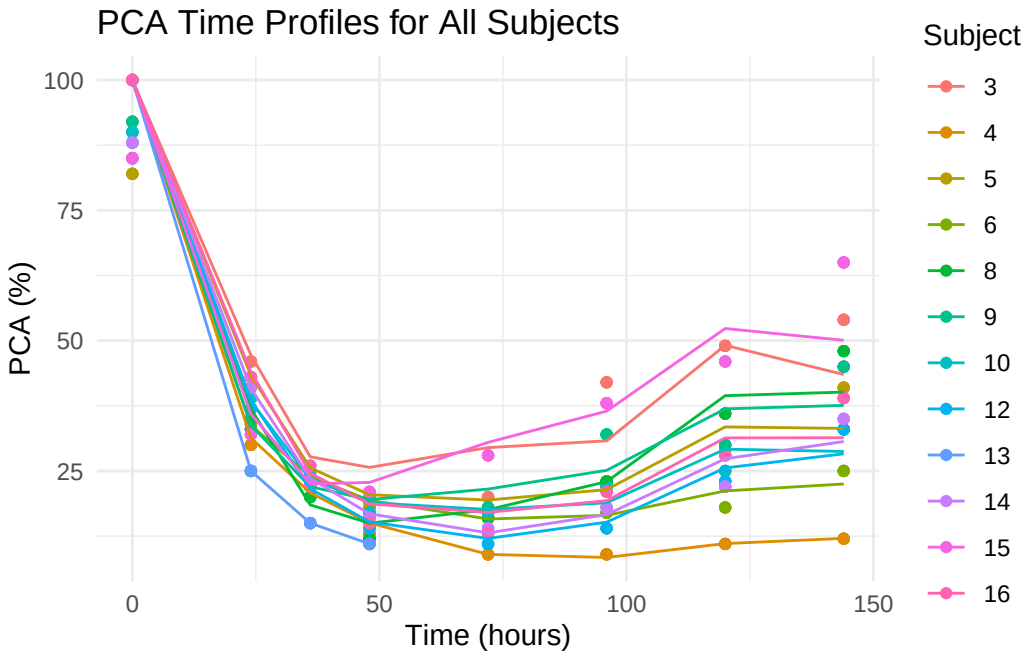
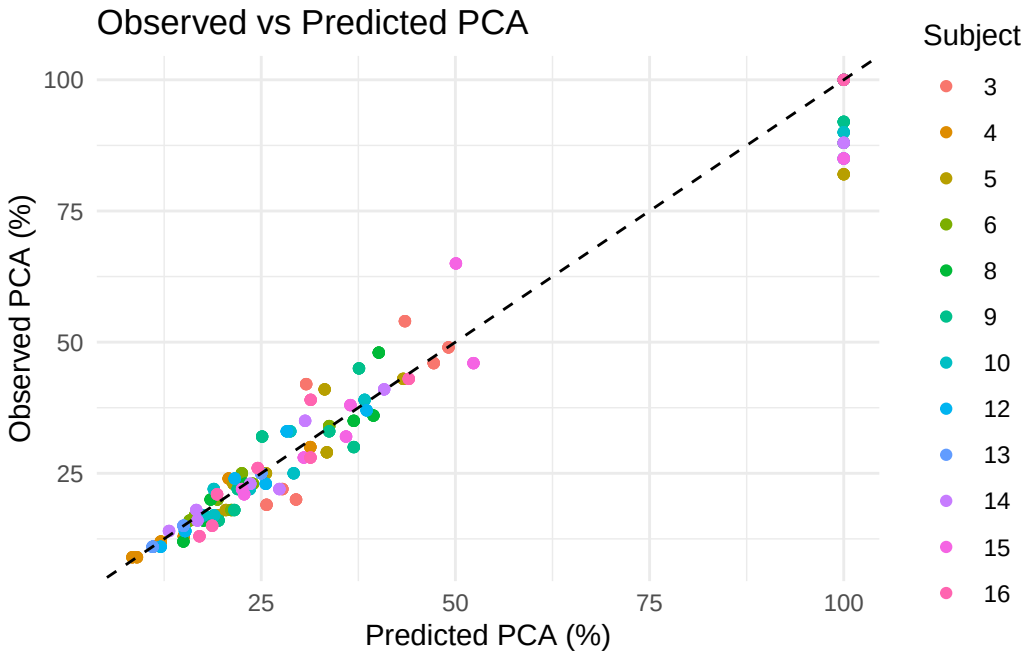


Figure 15. Plot residuals



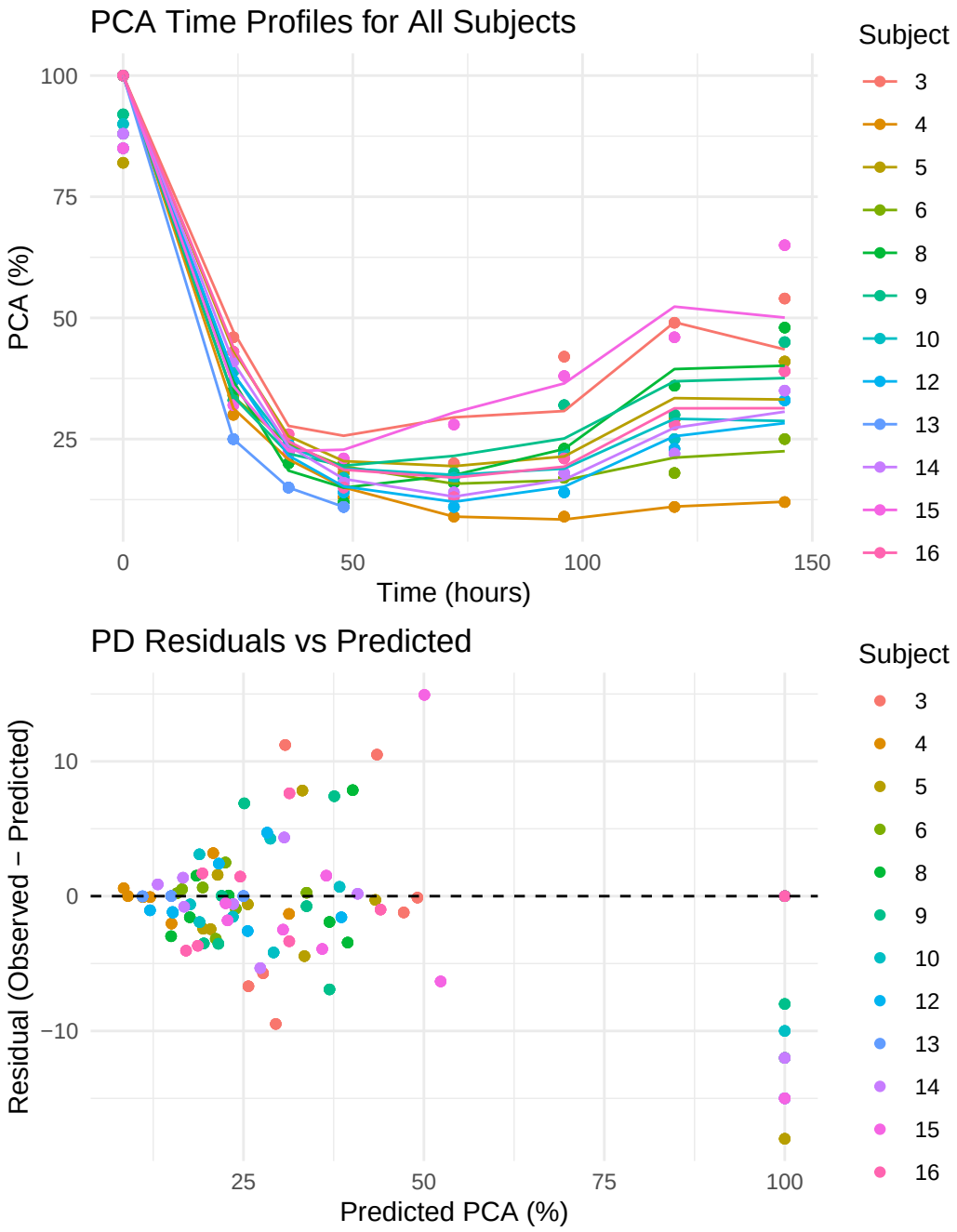


Figure 16. Individual Subject PD Plots

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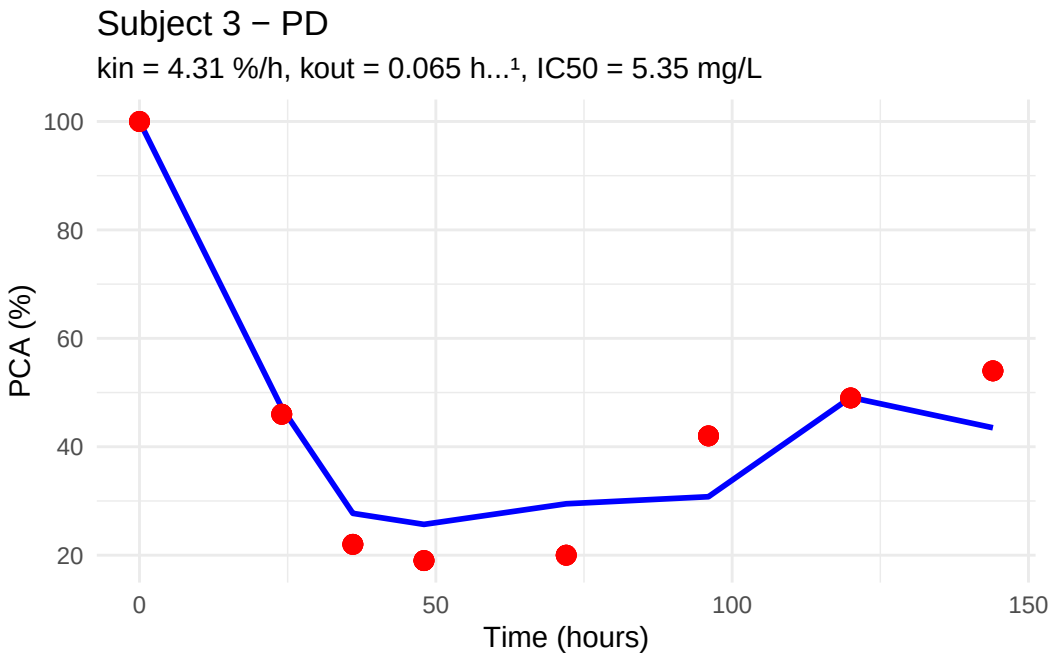


Integrated PK/PD Analysis

Combine findings from both the PK and PD analyses to gain a comprehensive understanding of the the drug system.

Figure 17. Parameter Correlations

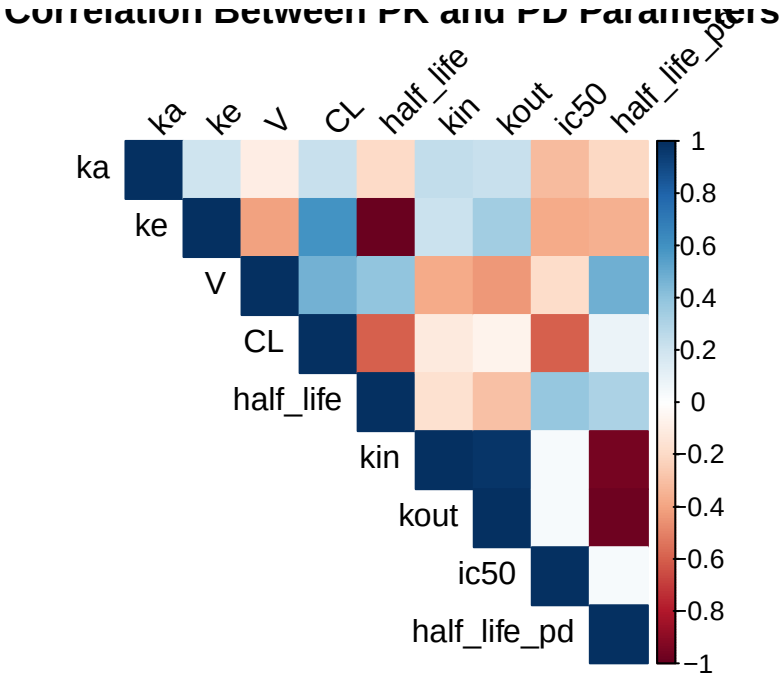


Table 2: PK/PD Half-life Ratios

id	half_life	half_life_pd	halflife_ratio
3	44.034	10.655	0.242
4	49.548	19.714	0.398
5	47.776	13.082	0.274
6	43.815	17.769	0.406
8	27.178	11.872	0.437
9	32.383	13.017	0.402
10	53.814	13.341	0.248
12	33.512	14.750	0.440
13	28.438	14.496	0.510
14	30.705	15.405	0.502
15	23.650	10.979	0.464
16	46.183	13.091	0.283

Simulations for Different Doses

Figure 18. Plot PK profiles for different doses by simulation

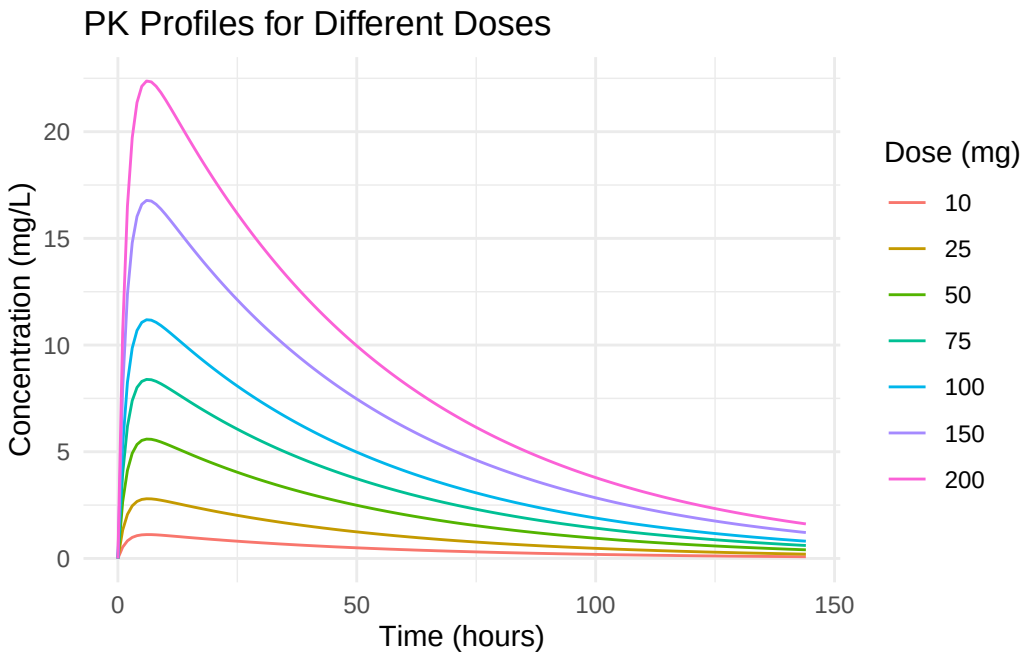


Figure 19. Plot PD profiles for different doses by simulation

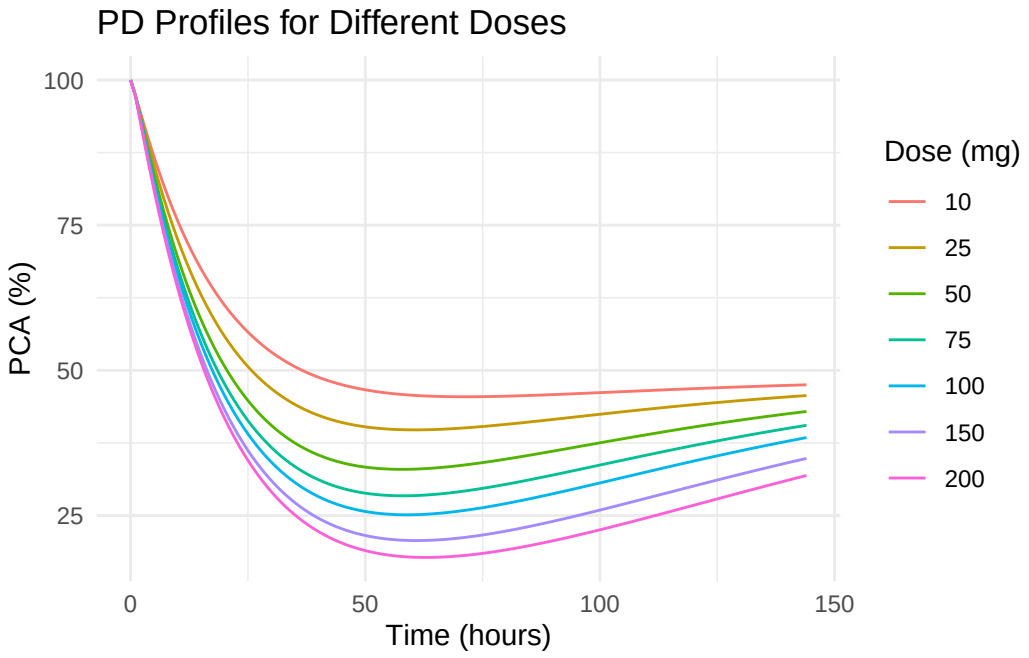
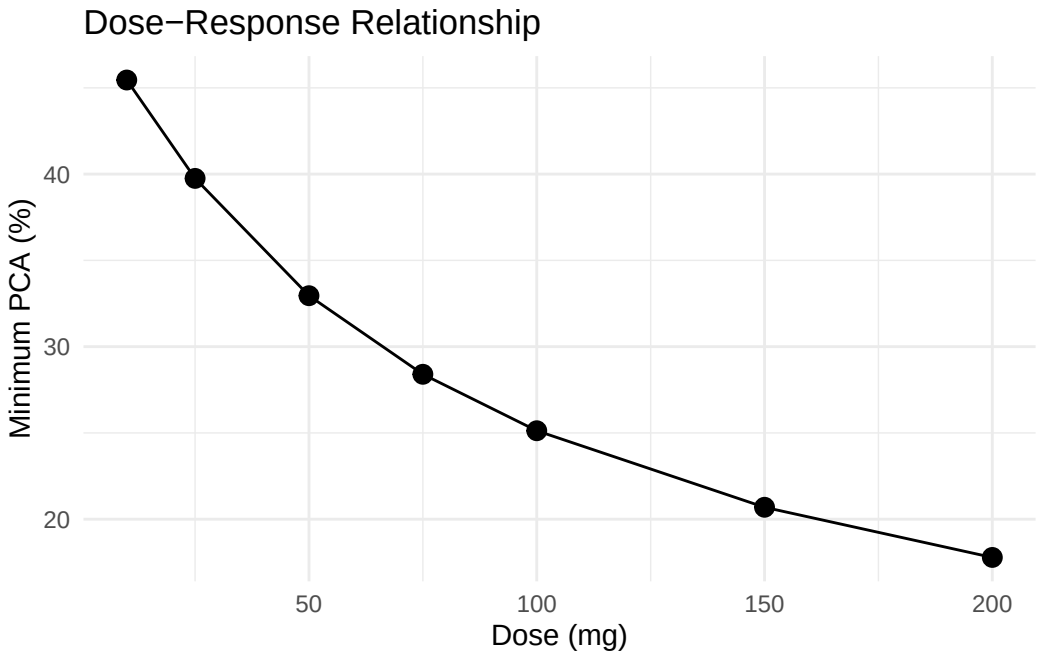


Table 6. PD metrics for each dose

Dose (mg)	Min PCA (%)	Time to Min PCA (hr)	Final PCA (%)	Duration Below 30% (hr)
10.0	45.5	71.0	47.5	0.0
25.0	39.8	61.0	45.7	0.0
50.0	33.0	58.0	42.9	0.0
75.0	28.4	58.0	40.5	34.0
100.0	25.1	59.0	38.4	60.0
150.0	20.7	61.0	34.8	88.0
200.0	17.8	63.0	31.9	105.0

Figure 20. Simulated dose-response curve



Optimal Dosing Regimen Selection

Table 7. Dose evaluation table

Dose (mg)	Min PCA (%)	Time to Min PCA (hr)	Final PCA (%)	Duration Below 30% (hr)
10	45.5	71.0	47.5	0.0
25	39.8	61.0	45.7	0.0
50	33.0	58.0	42.9	0.0
75	28.4	58.0	40.5	34.0
100	25.1	59.0	38.4	60.0
150	20.7	61.0	34.8	88.0
200	17.8	63.0	31.9	105.0

Figure 21 Find the optimal dose closest to target range

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Optimal dose(s) within target range: 25, 50, 75, 100, 150 mg
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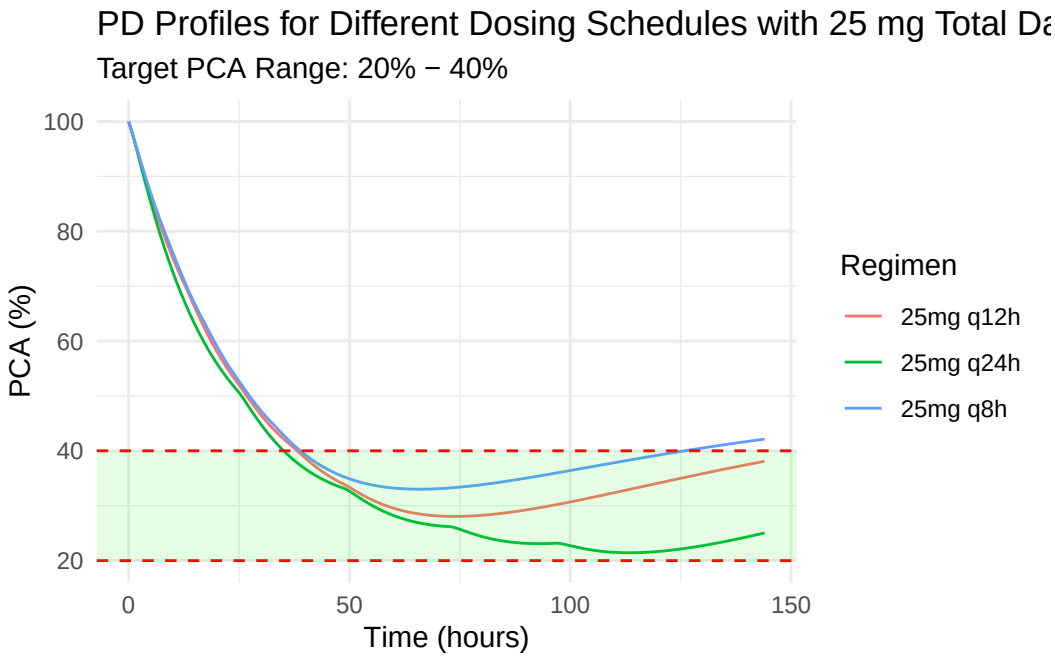

Table 3: Dosing Schedule Evaluation for 25 mg Total Daily Dose

regimen	min_PCA	mean_PCA	fluctuation	time_below_target	time_in_target	time_above_ta
25mg q12h	28.0	40.6	72.0	0	105	
25mg q24h	21.4	35.1	78.6	0	108	
25mg q8h	33.0	44.0	67.0	0	87	

Conclusions

Based on our comprehensive PK/PD analysis of the drug using the two-stage approach, we can draw the following conclusions:

1. **Pharmacokinetics**: the drug follows a one-compartment model with first-order absorption and elimination. The population mean values for key parameters are:

   - Absorption rate constant (ka): 0.551 h^{1}
   - Elimination rate constant (ke): 0.019 h^{1}
   - Volume of distribution (V): 7.9 L
   - Clearance (CL): 0.145 L/h
   - Elimination half-life: 40.5 h

2. **Pharmacodynamics**: The PD response (prothrombin complex activity, PCA) follows an indirect response model where the drug inhibits the input rate. The population mean values for key parameters are:

    - Input rate constant (kin): 2.49 %/h
    - Output rate constant (kout): 0.051 h ^{1}
    - IC50: 4.49 mg/L
    - Response half-life: 14 h

3. **PK/PD Relationship**: There is a clear hysteresis in the PK/PD relationship, indicating a delayed response. The PD effect typically lags behind the PK profile, with the PD half-life being longer than the PK half-life by a factor of approximately 0.4.

4. **Dose-Response Relationship**: Based on our simulations, doses between 25 and 150 mg provide the best balance of efficacy (maintaining PCA in the target range of 20-40%) and safety.

5. **Optimal Dosing Regimen**: For the optimal dose, a divided dosing regimen (BID or TID) provides a more stable PCA profile with less fluctuation compared to once-daily dosing, resulting in a higher percentage of time in the target range.

These findings provide valuable insights into the drug's PK/PD behavior and can inform dosing decisions in clinical practice. The two-stage approach, while simpler than a full population analysis, still captures the essential features of the system and provides reasonable parameter estimates.

References

1. Holford NH. Clinical pharmacokinetics and pharmacodynamics of the drug. Understanding the dose-effect relationship. Clin Pharmacokinet. 1986;11(6):483-504.

2. Jusko WJ, Ko HC. Physiologic indirect response models characterize diverse types of pharmacodynamic effects. Clin Pharmacol Ther. 1994;56(4):406-419.

3. Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications. 5th ed. Swedish Pharmaceutical Press; 2016.

4. Pinheiro JC, Bates DM. Mixed-Effects Models in S and S-PLUS. Springer; 2000.

5. Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. 1993;21(4):457-478.