Supplemental information

Neural-ODE for pharmacokinetics modeling

and its advantage to alternative machine learning

models in predicting new dosing regimens

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Figure S1. Comparison of Q1W and Q3W data of TDM1. **Related to Table 1 and Results.** a. The number of patients is bigger in Q3W than in Q1W. b. Total length of treatment. c. Number of PK records for each individual. d. Amount of dosing is higher in Q3W than in Q1W.
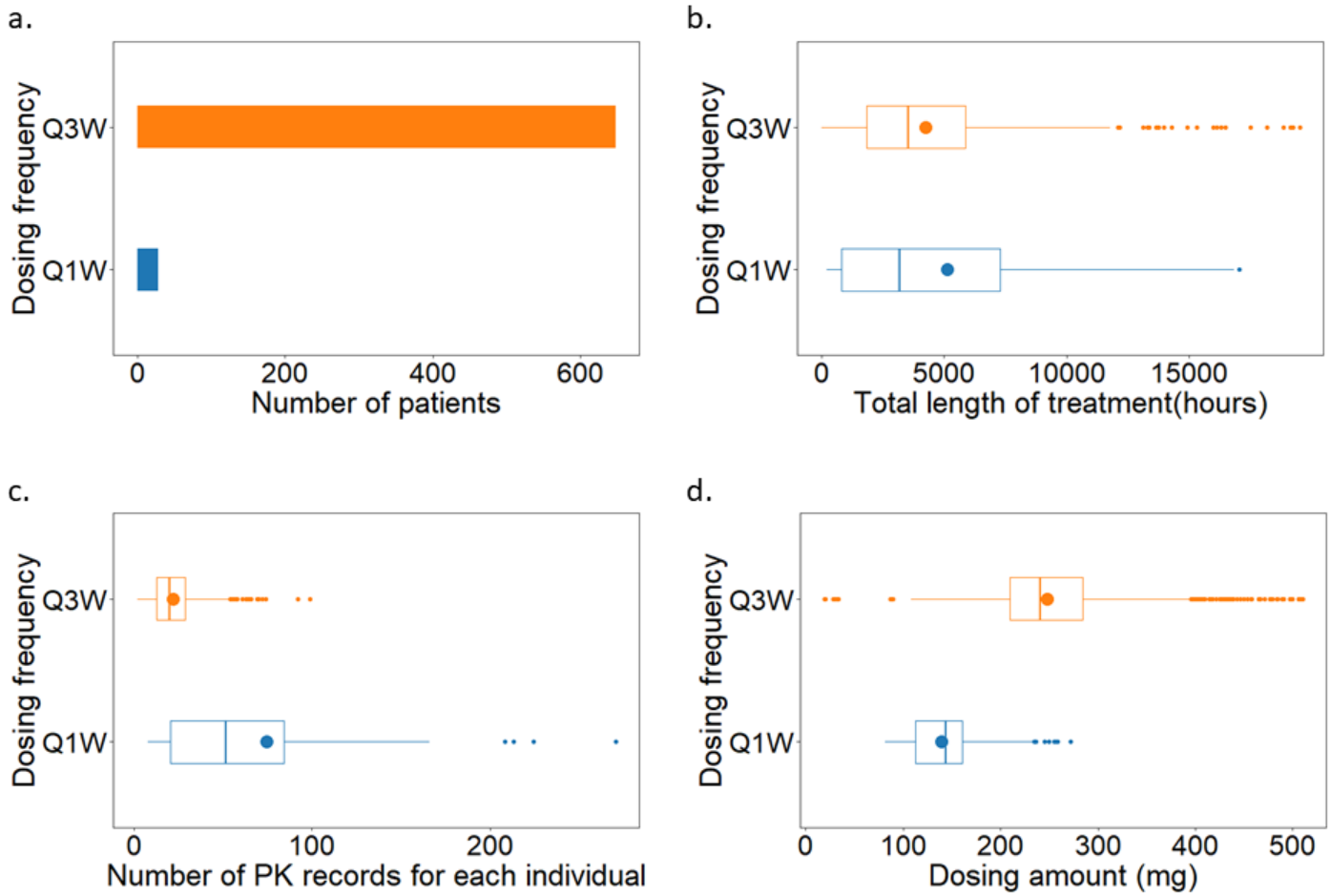
Figure S2. **Example of patient #5409**. **Related to Figure 4.** a. visualization of interpolated prediction points for patient #5409. b. we artificially stopped dosing after 2500 hours and used the trained models to predict PK values. c. we artificially stopped both dosing and TIME after 2500 hours for patient #5409 and used the trained models to predict PK values.

Figure S3. **Example of patient #5412. Related to Figure 4**. a. visualization of interpolated prediction points for patient #5412. b. we artificially stopped dosing after 2500 hours and used the trained models to predict PK values. c. we artificially stopped both dosing and TIME after 2500 hours for patient #5412 and used the trained models to predict PK values.
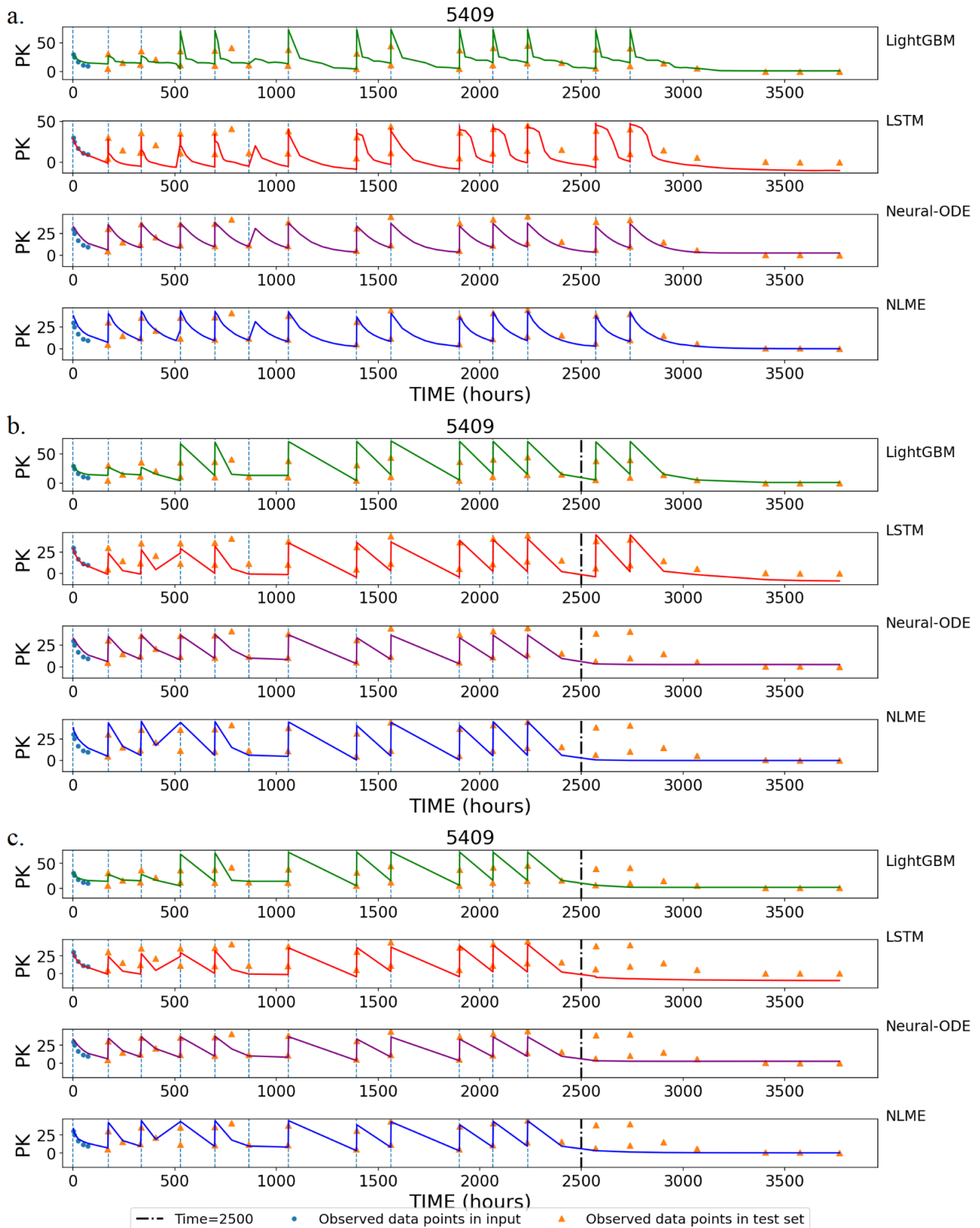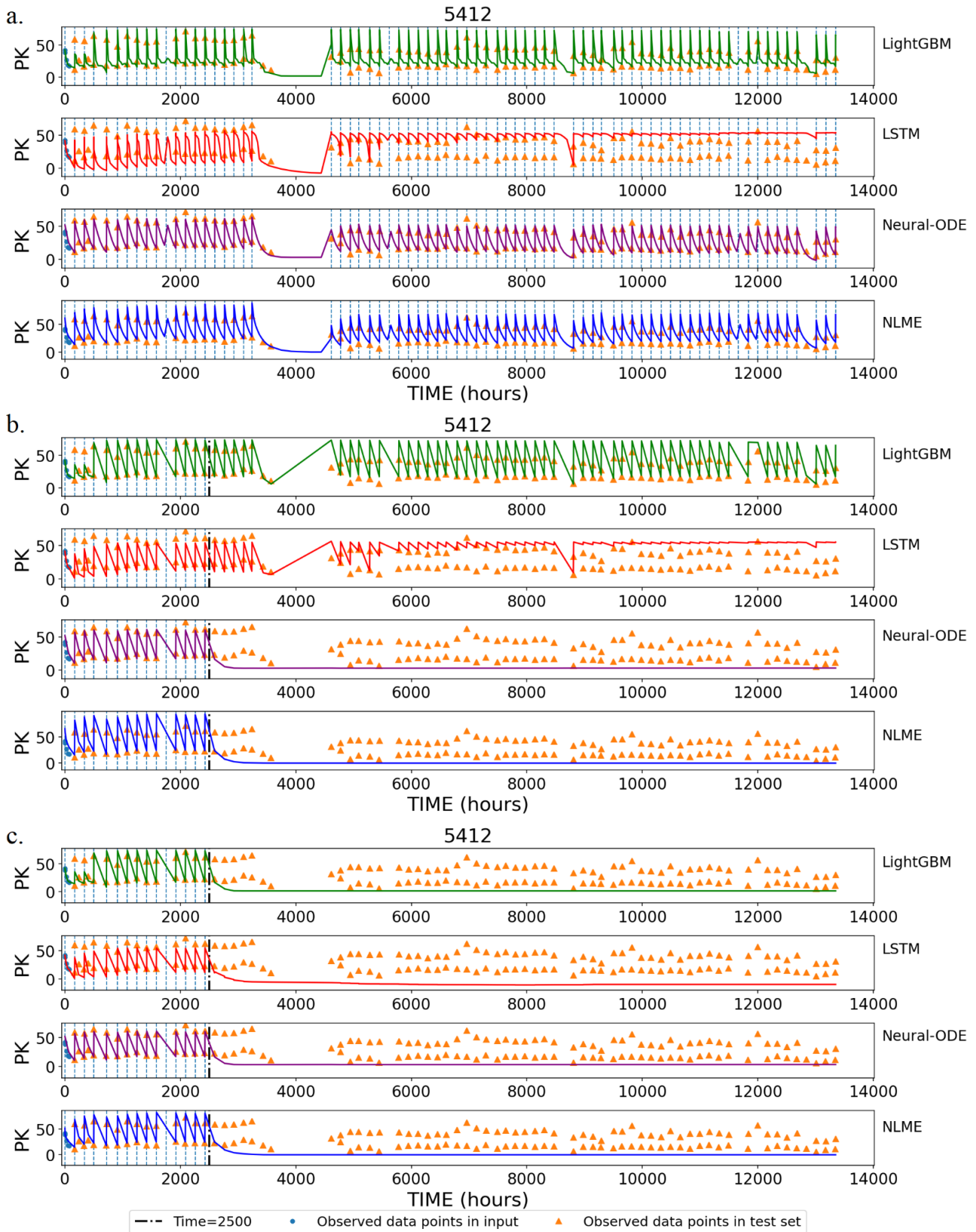
Figure S4. **Example of patient #5414. Related to Figure 4**. a. visualization of interpolated prediction points for patient #5414. b. we artificially stopped dosing after 2500 hours and used the trained models to predict PK values. c. we artificially stopped both dosing and TIME after 2500 hours and used the trained models to predict PK values.
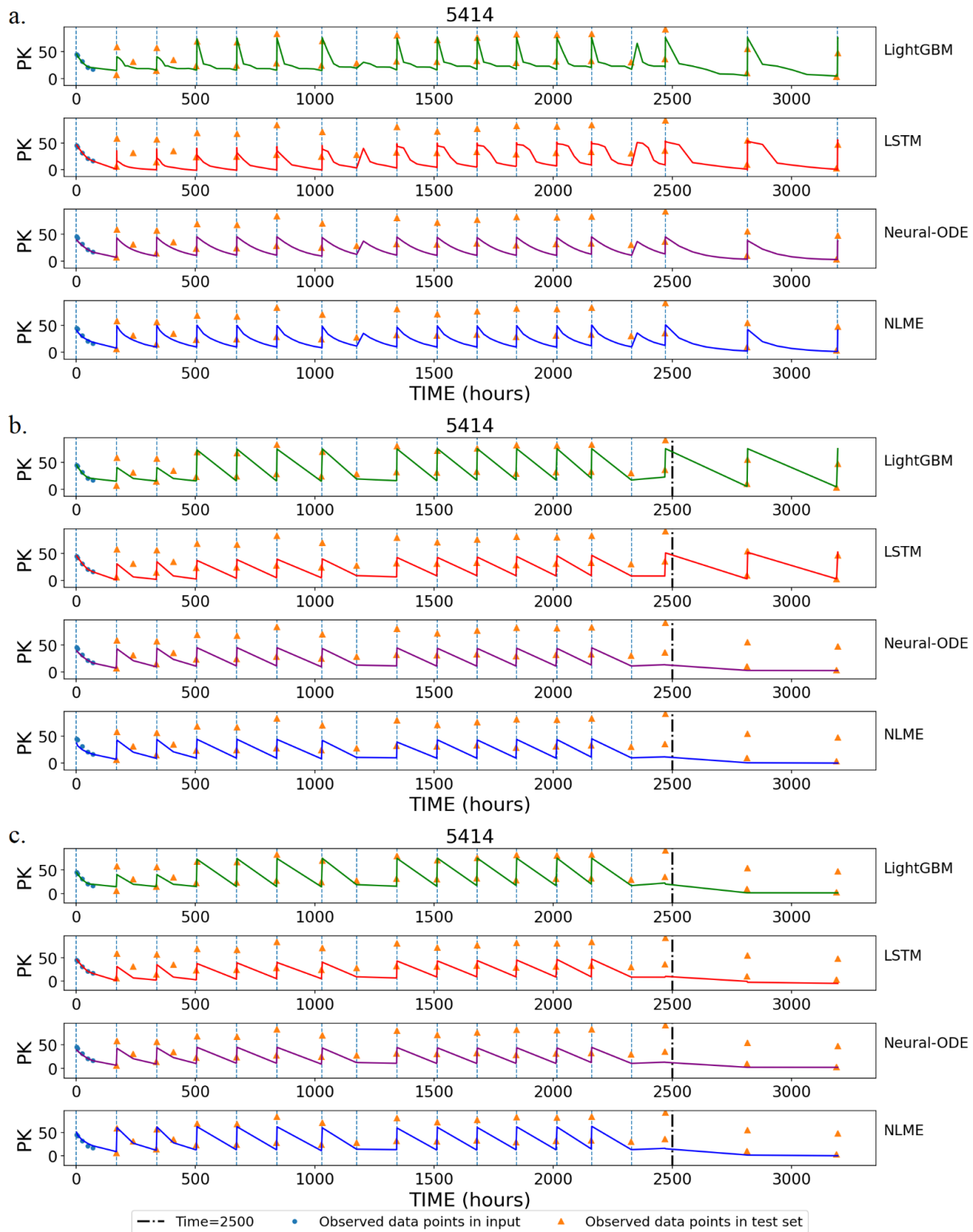

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Table S1. **Parameters used for initializing the NLME model. Related to Figure 3.**

Parameter	Parameter Description	Initial estimates	Boundaries(lower, upper; if defined)	
k_a	Absorption rate constant	1.14	--	--
CL	Elimination clearance	-3.57	-5	-1
Q	Distribution clearance	1.14	-1	3
V_2	Central volume of distribution	-0.454	-2	2
V_3	Peripheral volume of distribution	-2.87	-5	-1
ETA.k_a	Variability in k_a	0.1	--	--
ETA.CL	Variability in CL	0.1	--	--
ETA.Q	Variability in Q	0.1	--	--
ETA.V_2	Variability in V_2	0.1	--	--
ETA.V_3	Variability in V_3	2	--	--
σ	Additive residual error	0.1	--	--

Table S2. **Bootstrap hypothesis test p-values for cross-regimen model performances and five fold model performances. Related to Figure 3.**

	Models	RMSE	R2 score	Pearson's correlation
Cross-regimen bootstrap result	Neural-ODE vs. LightGBM	<1e-05	0.00014	<1e-05
	Neural-ODE vs. LSTM	0.00071	0.00206	<1e-05
	Neural-ODE vs. NLME	0.00011	0.00046	3e-05
Five fold bootstrap result	Neural-ODE vs. LightGBM	0.44788	0.42895	0.42302
	Neural-ODE vs. LSTM	0.69927	0.68677	0.80843
	Neural-ODE vs. NLME	<1e-05	<1e-05	<1e-05

Table S3. **NLME Model estimated parameters (cross-regimen model 1). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.28638	0.05825	4.5284	3.61967	3.22912	4.05745	98.67719	37.85645
tcl	-3.61554	0.01183	0.32731	0.0269	0.02629	0.02753	14.74115	47.38994
tv2	0.92935	0.01184	1.2736	2.53286	2.47478	2.5923	18.31932	27.59139
tv3	0.03275	0.06497	198.36617	1.03329	0.90975	1.17361	99.6739	50.30319
tq	-1.31828	0.1002	7.6009	0.2676	0.21988	0.32566	219.17092	49.89933
add.err	8.34765	NA	NA	8.34765	NA	NA	NA	NA

Figure S5. **VPC for cross-regimen model 1. Related to Figure 3.** Black points are original observations. Red line is the predicted median. Blue shaded areas represent intervals around 5th and 95th percentiles.

Table S4. **NLME Model estimated parameters (cross-regimen model 2). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.3263	0.05874	4.42924	3.76707	3.35738	4.22676	102.49442	37.84547
tcl	-3.61554	0.01154	0.31917	0.0269	0.0263	0.02752	13.50572	49.27309
tv2	0.93829	0.01083	1.15429	2.5556	2.50192	2.61043	17.85565	29.10447
tv3	0.10606	0.06145	57.935	1.11189	0.98573	1.2542	88.9007	51.81202
tq	-1.54266	0.10403	6.74325	0.21381	0.17437	0.26217	315.2457	49.06409
add.err	8.36423	NA	NA	8.36423	NA	NA	NA	NA

Figure S6. **VPC for cross-regimen model 2. Related to Figure 3.**

Black points are original observations. Red line is the predicted median. Blue shaded areas represent intervals around 5th and 95th percentiles.
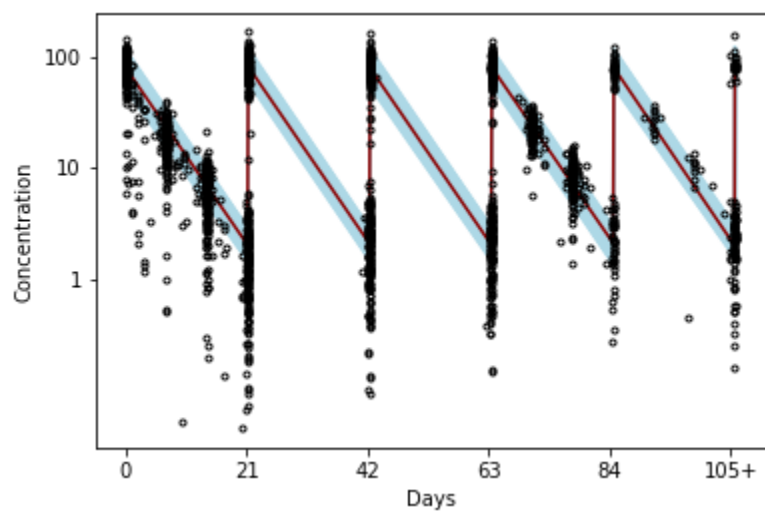
Table S5. **NLME Model estimated parameters (cross-regimen model 3). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.3855	0.06268	4.52432	3.9968	3.53473	4.51929	109.51242	38.98178
tcl	-3.61817	0.01178	0.32545	0.02683	0.02622	0.02746	14.4661	47.58632
tv2	0.94138	0.01101	1.16936	2.56351	2.5088	2.61942	18.39322	26.50099
tv3	-0.01032	0.06791	657.76323	0.98973	0.86638	1.13064	104.44421	50.70264
tq	-1.42984	0.09956	6.96319	0.23935	0.19692	0.29092	244.34299	51.73622
add.err	8.35516	NA	NA	8.35516	NA	NA	NA	NA

Figure S7. VPC for cross-regimen model 3. Related to Figure 3. Black points are original observations. Red line is the predicted median. Blue shaded areas represent intervals around 5th and 95th percentiles.
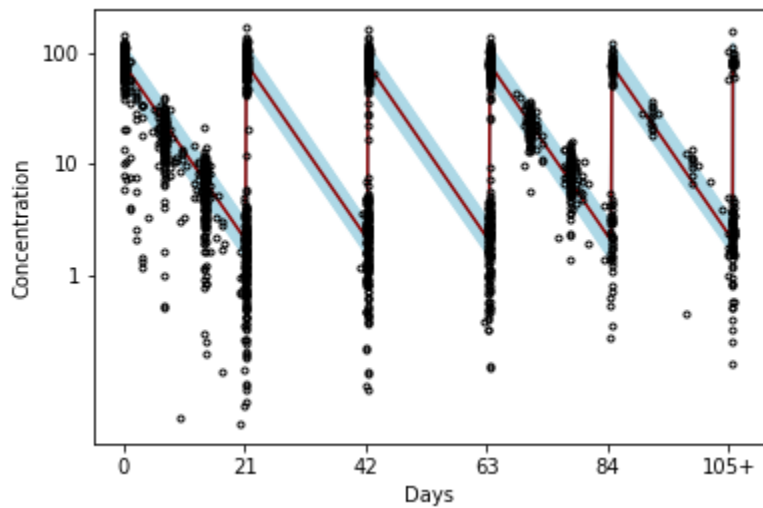
Table S6. **NLME Model estimated parameters (cross-regimen model 4). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.32319	0.06013	4.544	3.75537	3.3379	4.22505	103.01655	38.37446
tcl	-3.61565	0.01158	0.32025	0.0269	0.0263	0.02752	13.40369	49.10364
tv2	0.92985	0.01123	1.20789	2.53413	2.47896	2.59053	17.78989	29.10745
tv3	0.08205	0.06369	77.62073	1.08551	0.95812	1.22984	94.00857	50.02921
tq	-1.39766	0.10167	7.27401	0.24718	0.20252	0.30168	275.19279	48.48688
add.err	8.3583	NA	NA	8.3583	NA	NA	NA	NA

Figure S8. VPC for cross-regimen model 4. Related to Figure 3. Black points are original observations. Red line is the predicted median. Blue shaded areas represent intervals around 5th and 95th percentiles.
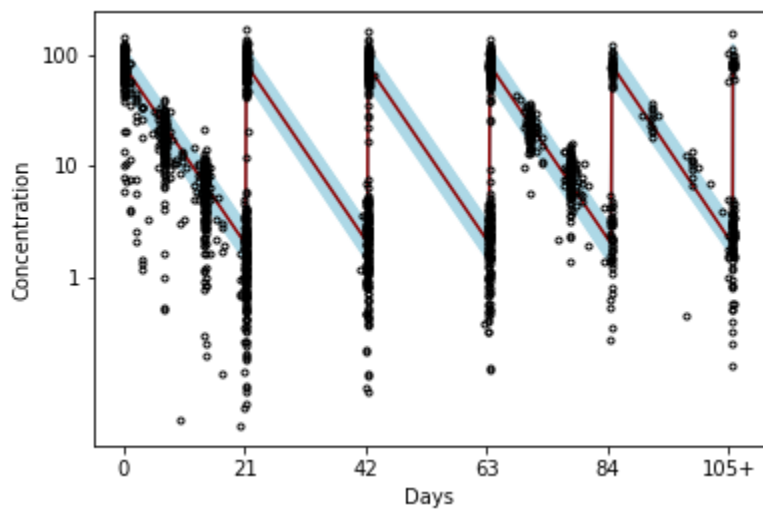
Table S7. **NLME Model estimated parameters (cross-regimen model 5). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.33949	0.05989	4.47133	3.81711	3.39432	4.29255	103.88998	38.135
tcl	-3.61674	0.0117	0.32355	0.02687	0.02626	0.02749	14.07063	48.55479
tv2	0.93604	0.01098	1.17268	2.54985	2.49558	2.60531	17.87464	28.67162
tv3	0.0567	0.06429	113.38385	1.05834	0.93304	1.20047	95.95689	50.72853
tq	-1.45731	0.10205	7.00234	0.23286	0.19065	0.28442	291.56843	49.26985
add.err	8.35534	NA	NA	8.35534	NA	NA	NA	NA

Figure S9. **VPC for cross-regimen model 5. Related to Figure 3.** Black points are original observations. Red line is the predicted median. Blue shaded areas represent intervals around 5th and 95th percentiles.
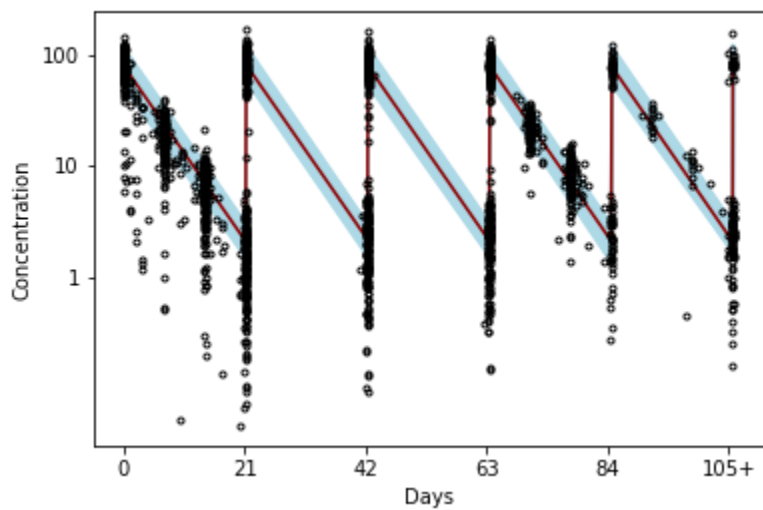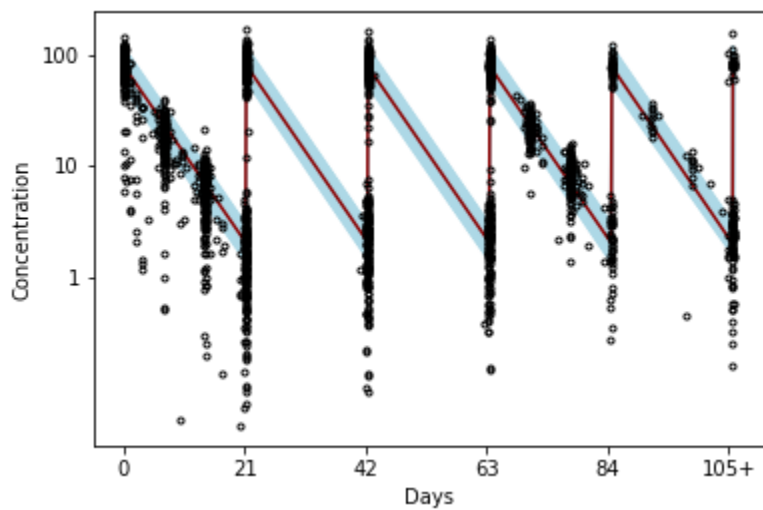
Table S8. **NLME Model estimated parameters (cross validation model 1). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.18049	0.05714	4.84074	3.25598	2.91099	3.64186	88.10342	34.72713
tcl	-3.5966	0.01382	0.38418	0.02742	0.02668	0.02817	19.70617	34.69762
tv2	0.92216	0.013	1.40938	2.51472	2.45147	2.5796	18.77901	27.67598
tv3	0.21533	0.06211	28.84469	1.24027	1.09811	1.40083	84.06165	48.52114
tq	-1.36935	0.10213	7.45837	0.25427	0.20814	0.31062	219.85211	47.00075
add.err	7.90541	NA	NA	7.90541	NA	NA	NA	NA

Table S9. NLME Model estimated parameters (cross validation model 2). Related to Figure 3.

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.17028	0.05645	4.82387	3.22289	2.88531	3.59996	88.9347	35.24532
tcl	-3.59631	0.01356	0.37718	0.02742	0.02671	0.02816	19.18691	34.75084
tv2	0.92295	0.01285	1.39215	2.51671	2.45412	2.58089	19.10322	27.35166
tv3	0.25358	0.06049	23.8536	1.28863	1.14456	1.45082	80.48276	49.30822
tq	-1.41438	0.09886	6.98958	0.24308	0.20026	0.29505	211.88197	47.2265
add.err	7.90681	NA	NA	7.90681	NA	NA	NA	NA

Table S10. **NLME Model estimated parameters (cross validation model 3). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.19894	0.05883	4.90654	3.3166	2.95543	3.72192	90.28141	35.86359
tcl	-3.60025	0.01384	0.38443	0.02732	0.02659	0.02807	20.11285	34.26278
tv2	0.91636	0.01349	1.47223	2.50017	2.43492	2.56716	18.9299	28.36956
tv3	0.14628	0.06557	44.82242	1.15752	1.01793	1.31625	92.35684	47.34783
tq	-1.25481	0.1032	8.22444	0.28513	0.23291	0.34905	217.40323	47.50185
add.err	7.89608	NA	NA	7.89608	NA	NA	NA	NA

Table S11. **NLME Model estimated parameters (cross validation model 4). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.16318	0.05724	4.92071	3.20009	2.8605	3.57999	88.98275	35.30937
tcl	-3.59655	0.01367	0.3802	0.02742	0.02669	0.02816	19.30622	35.39027
tv2	0.91698	0.01322	1.44204	2.50172	2.43771	2.5674	19.18084	27.807
tv3	0.24603	0.06179	25.11441	1.27894	1.13306	1.44359	80.95622	49.1023
tq	-1.34136	0.09824	7.32426	0.26149	0.21569	0.31702	202.78248	46.46734
add.err	7.90487	NA	NA	7.90487	NA	NA	NA	NA

Table S12. **NLME Model estimated parameters (cross validation model 5). Related to Figure 3.**

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)	Shrink(SD)%
tka	1.29017	0.06422	4.97761	3.63341	3.20369	4.12077	99.54151	36.16112
tcl	-3.60733	0.01285	0.35633	0.02712	0.02645	0.02782	17.11329	39.23065
tv2	0.93864	0.01203	1.28189	2.55651	2.49692	2.61751	18.04026	30.25982
tv3	0.20424	0.06031	29.52994	1.2266	1.08984	1.38051	76.11313	52.89438
tq	-1.56376	0.11394	7.286	0.20935	0.16745	0.26173	350.41384	46.51082
add.err	8.18695	NA	NA	8.18695	NA	NA	NA	NA