A machine learning approach to population pharmacokinetic modelling automation: Supplementary information

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Supplementary Tables

Supplementary Table 1. Extravascular model space features

Token number	Token	Values
1	Number of disposition compartments	0. 1 compartment 1. 2 compartments 2. 3 compartments
2	OMEGA V3 (2nd compartment volume)	0. Estimate OMEGA 1. Fix to CV=15%
3	OMEGA Q (intercompartmental clearance)	0. Estimate OMEGA 1. Fix to CV=15%
4	OMEGA V4 (3rd compartment volume)	0. Estimate OMEGA 1. Fix to CV=15%
5	Omegas Q2	0. Estimate OMEGA 1. Fix to CV=15%
6	OMEGA duration (Sequential 1st then 0 order absorption)	0. Estimate OMEGA 1. Fix to CV=15%
7	OMEGA duration (0 order absorption)	0. Estimate OMEGA 1. Fix to CV=15%
8	TLAG for 1st order absorption and sequential 1st the 0 order absorption	0. No time lag 1. Estimate time lag
9	TLAG2 for 0 order absorption	0. No time lag 1. Estimate time lag
10	Absorption model	0. 1st order absorption 1. Sequential 1st then 0 order absorption 2. 0 order absorption
11	Transient Compartments	0. 0 transient compartments 1. 2 transient compartments 2. 3 transient compartments 3. 4 transient compartments
12	Dose effect CL	0. No effect 1. Estimate effect
13	Dose effect V2	0. No effect 1. Estimate effect
14	Dose effect KA	0. No effect 1. Estimate effect
15	Dose effect V3	0. No effect 1. Estimate effect
16	Dose effect Q	0. No effect 1. Estimate effect
17	Error model	0. Combined 1. Proportional 2. Additive

Description of the model features selected by numerical model codes. Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), Q (intercompartmental clearance), V4 (volume of distribution for 2st peripheral compartment), TLAG (lag time).

Supplementary Table 2. Estimated model parameters for the top automatically discovered ribociclib model.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage	Penalty: Estimated values	Penalty: Relative error	Penalty: Shrinkage	Penalty: Total
THETA1	CL (L/h)	23.40	7%			0.00		0.00
THETA2	V2 (L)	244.38	11%			0.60		0.60
THETA3	Dose effect CL	-0.49	18%			7.50		7.50
THETA4	KA	0 (fix)	0%			0.00		0.00
THETA5	Additive error	3.42	19%			8.77		8.77
THETA6	Proportional error	0.22	3%			0.00		0.00
THETA7	V3 (L)	714.62	8%			0.00		0.00
THETA8	Q (L/h)	68.67	10%			0.00		0.00
THETA9	Dose effect V3	-0.61	17%			6.64		6.64
THETA10	Dose effect Q	-0.75	15%			5.24		5.24
THETA11	ALAG (h)	0.36	2%			0.00		0.00
THETA12	D (h)	3.47	2%			0.00		0.00
OMEGA(1,1)	CL	52%	8%	1.36	0.00	0.00		0.00
OMEGA(2,2)	V2	121%	8%	3.18	0.00	0.00		0.00
OMEGA(3,3)	KA	0% (fix)		0.00				0.00
OMEGA(4,4)	V3	53%	10%	18.53	0.00	0.00	0.00	0.00
OMEGA(5,5)	Q	61%	11%	19.46	0.00	0.00	0.00	0.00
OMEGA(6,6)	ALAG	10% (fix)	0%	13.98		0.00		0.00
OMEGA(7,7)	D	10% (fix)	0%	53.22		0.00		0.00

Estimated value penalties are provided for OMEGA estimates, THETA relative standard error, OMEGA relative standard error and OMEGA shrinkage. OMEGA estimates are provided as coefficient of variation (CV%). Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D (duration for zero order absorption). Q (intercompartmental clearance). ALAG (absorption lag time). KA is fixed to 0 for the 0-order absorption process and to avoid modification of THETA numbering. Total parameter estimate penalty = 28.15. Total parameter count penalty = 10 * 15 estimated THETA/OMEGA parameters. Penalty score = 28.15 + 150 = 178.15.

Supplementary Table 3. Estimated model parameters for the top automatically discovered camizestrant model.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage	Penalty: Estimated values	Penalty: Relative error	Penalty: Shrinkage	Penalty: Total
THETA1	CL (L/h)	62.40	4%			0.00		0.00
THETA2	V2 (L)	857.55	6%			0.00		0.00
THETA3	Dose effect CL	-0.17	23%			13.29		13.29
THETA4	Dose effect V2	-0.34	13%			3.39		3.39
THETA5	KA = KTR (h^{-1})	2.76	5%			0.00		0.00
THETA6	Additive error	1.01	25%			15.42		15.42
THETA7	Proportional error	0.32	2%			0.00		0.00
THETA8	V3 (L)	439.30	13%			3.45		3.45
THETA9	Q (L/h)	36.48	15%			4.53		4.53
OMEGA(1,1)	CL	40%	6%	3%	0.00	0.00		0.00
OMEGA(2,2)	V2	41%	10%	17%	0.00	0.00		0.00
OMEGA(3,3)	KA	56%	7%	13%	0.00	0.00	0.00	0.00
OMEGA(4,4)	V3	15% (fix)	0%			0.00		0.00
OMEGA(5,5)	Q	15% (fix)	0%			0.00		0.00

Estimated value penalties are provided for OMEGA estimates, THETA relative standard error, OMEGA relative standard error and OMEGA shrinkage. OMEGA estimates are provided as coefficient of variation (CV%). Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance). Parameters fixed and not estimated are marked by fix in parenthesis. Total parameter estimate penalty = 40.08. Total parameter count penalty = 10 * 12 estimated THETA/OMEGA parameters + 10 * 3 transit compartments. Penalty score = 40.08 + 150 = 190.08.

Supplementary Table 4. Estimated model parameters for the top automatically discovered osimertinib model.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage	Penalty: Estimated values	Penalty: Relative error	Penalty: Shrinkage	Penalty: Total
THETA1	CL (L/h)	13.84	3%			0.00		0.00
THETA2	V2 (L)	1101.20	4%			0.00		0.00
THETA3	KA = KTR (h^{-1})	1.70	4%			0.00		0.00
THETA4	Additive error	2.61	16%			5.70		5.70
THETA5	Proportional error	0.17	1%			0.00		0.00
OMEGA(1,1)	CL	53%	8%	1%	0.00	0.00		0.00
OMEGA(2,2)	V2	52%	10%	22%	0.00	0.00		0.00
OMEGA(3,3)	KA	48%	10%	31%	0.00	0.00	0.00	0.00

Estimated value penalties are provided for OMEGA estimates, THETA relative standard error, OMEGA relative standard error and OMEGA shrinkage. OMEGA estimates are provided as coefficient of variation (CV%). Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment). Total parameter estimate penalty = 5.7. Total parameter count penalty = 10 * 8 estimated THETA/OMEGA parameters + 10 * 4 transit compartments. Penalty score = 5.7 + 120 = 125.7.

Supplementary Table 5. Estimated model parameters for the top automatically discovered olaparib model.

Index	Name	Estimated value	Relative Standard Error	Shrinkage	Penalty: Estimated values	Penalty: Relative error	Penalty: Shrinkage	Penalty: Total
THETA1	CL (L/h)	5.21	3%			0.00		0.00
THETA2	V2 (L)	35.06	2%			0.00		0.00
THETA3	Dose effect V2	0.17	34%			27.78		27.78
THETA4	KA = KTR (h^{-1})	9.22	3%			0.00		0.00
THETA5	Additive error	0 (fix)						0.00
THETA6	Proportional error	0.36	1%			0.00		0.00
THETA7	V3 (L)	18.77	7%			0.00		0.00
THETA8	Q (L/h)	0.41	10%			0.28		0.28
OMEGA(1,1)	CL	55%	4%	2%	0.00	0.00		0.00
OMEGA(2,2)	V2	32%	8%	12%	0.00	0.00		0.00
OMEGA(3,3)	KA	60%	4%	5%	0.00	0.00	0.00	0.00
OMEGA(4,4)	V3	15% (fix)	0%	71%		0.00		0.00
OMEGA(5,5)	Q	190%	7%	29%	81.53	0.00	0.00	81.53

Estimated value penalties are provided for OMEGA estimates, , THETA relative standard error, OMEGA relative standard error and OMEGA shrinkage. OMEGA estimates are provided as coefficient of variation (CV %). Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Parameters fixed and not estimated are marked by fix in parenthesis. Total parameter estimate penalty = 109.59. Total parameter count penalty = 10 * 11 estimated THETA/OMEGA parameters + 10 * 4 transit compartments. Penalty score = 109.6 + 250 = 259.6.

Supplementary Table 6. Estimated model parameters for the top automatically discovered tezepelumab model.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage	Penalty: Estimated values	Penalty: Relative error	Penalty: Shrinkage	Penalty: Total
THETA1	CL (L/day)	0.21	4%			0		0
THETA2	V2 (L)	2.84	8%			0		0
THETA3	KA (/day)	0.44	6%			0		0
THETA4	Additive error	0 (fix)						0
THETA5	Proportional error	0.1	2%			0		0
THETA6	V3 (L)	3.6	5%			0		0
THETA7	Q (L/day)	6.04	11%			0.95		0.95
THETA8	D1 (days)	0.11	12%			1.95		1.95
OMEGA(1,1)	CL	39%	6%	1%	0	0		0
OMEGA(2,2)	V2	69%	3%	12%	0	0		0
OMEGA(3,3)	KA	56%	6%	7%	0	0	0	0
OMEGA(4,4)	V3	34%	8%	24%	0	0	0	0
OMEGA(5,5)	Q	15% (fix)	0%	82%		0		0
OMEGA(6,6)	D1	82%	15%	31%	0	0	0	0

Estimated value penalties are provided for OMEGA estimates, THETA relative error, OMEGA relative error and OMEGA shrinkage. OMEGA estimates are provided as coefficient of variation. Abbreviated terms used for apparent parameters, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance). Parameters fixed and not estimated are marked by fix in parenthesis. The subcutaneous bioavailability was fixed to 1 as no IV data was considered. Total parameter estimate penalty = 2.9. Total parameter count penalty = 10 * 12 estimated THETA/OMEGA parameters. Penalty score = 2.9 + 120 = 123.

Supplementary Table 7. Non-functional metrics for automatic model searches

Dataset	Number of participants	Number of observations	Average search time, hrs (standard deviation)	Average number of unique models tested (standard deviation)
Ribociclib (synthetic)	96	1,344	5.8 (0.8)	269 (83)
Camizestrant	184	2,709	46.0 (8.4)	275 (63)
Osimertinib	270	3,766	20.8 (5.6)	140 (63)
Olaparib	296	7,397	41.7 (12.8)	326 (104)
Tezepelumab	106	1,477	6.0 (1.0)	325 (82)

Non-functional metrics for model searches performed for each dataset. The average and standard deviation were measured across 5 repeat experiments. For each clinical dataset the number of participants and observations are given.

Supplementary Table 8. Overview of model searches performed without the estimated value penalty.

Dataset	Differences in structure to model discovered with full penalty	Abnormality observation
Ribociclib (synthetic)	+ IIV estimation V3, D1 + 0 order then 1st order with time lag	Abnormal relative error for OMEGA Ka >500%,
Camizestrant	+ IIV estimation V3, Q, D1 - 1st order absorption with 3 transient compartments + 0 order then 1st order absorption with time lag + Dose effect on Q	Abnormal variability estimate for OMEGA D1, CV% >700%.
Osimertinib	- 1 compartment + 2 compartments + IIV estimation V3 Q, D1 - 1st order absorption with 4 transient compartments + 0 then 1st order absorption with time lag + Dose effect on Cl, V3, and Q	Abnormal variability estimate for OMEGA V3, CV% >500%.
Olaparib	+ IIV estimation Q - 1st order with 4 transient compartments + 0 order then 1st order absorption with time lag + Dose effect on V3 & Q, - Combined error model + Proportional error model	Abnormally high CV% for OMEGA V3 >280%.
Tezepelumab	+ IIV estimation Q + With time lag on absorption + Dose effect on Cl, V3 and Q - Proportional error model + Combined error model	Estimated of OMEGA tend to 0 which causes numerical issues with the OFV calculation.

Top models discovered without the estimated value penalty where abnormal model structures were found for each dataset. Abbreviations: IIV (intraindividual variability), V3 (volume of distribution for 1st peripheral compartment), D1 (duration of 0 order absorption), Q intercompartmental clearance., Cl (clearance)

Supplementary Table 9. Parameter values for top ribociclib model discovered using AIC (model complexity) penalty only.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage
THETA1	CL	23.36	6.72%	
THETA2	V2	165.56	14.54%	
THETA3	Dose effect CL	-0.49	17.42%	
THETA4	KA	2.37	13.32%	
THETA5	Additive Error	2.09	129.82%	
THETA6	Proportional Error	0.22	4.20%	
THETA7	V3	705.49	7.85%	
THETA8	Q	81.58	10.24%	
THETA9	Dose effect V3	-0.62	14.93%	
THETA10	Dose effect Q	-0.67	16.56%	
THETA11	ALAG1	0.17	8.28%	
THETA12	D1	3.37	2.88%	
OMEGA(1,1)	CL	51.96%	8.12%	1%
OMEGA(2,2)	V2	161.61%	8.64%	3%
OMEGA(3,3)	KA	6.58%	564.36%	92%
OMEGA(4,4)	V3	49.54%	9.27%	16%
OMEGA(5,5)	Q	57.57%	11.23%	19%
OMEGA(6,6)	ALAG1	10.03%	0.00%	74%
OMEGA(7,7)	D1	8.13%	52.10%	59%

No estimated parameter penalties for biologically implausible parameters were included. An abnormal relative error >500% can be observed for OMEGA KA (rate constant). Abbreviated terms used, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance).

Supplementary Table 10. Parameter values for top camizestrant model discovered using AIC (model complexity) penalty only.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage
THETA1	CL	63.17	4%	
THETA2	V2	551.09	9%	
THETA3	Dose effect CL	-0.16	24%	
THETA4	Dose effect V2	-0.45	12%	
THETA5	KA	0.63	11%	
THETA6	Proportional error	0.77	28%	
THETA7	Additive error	0.31	2%	
THETA8	V3	797.91	9%	
THETA9	Q	78.68	11%	
THETA10	ALAG1	0.31	3%	
THETA11	D1	0.17	31%	
OMEGA(1,1)	CL	39%	5%	3%
OMEGA(2,2)	V2	36%	12%	34%
OMEGA(3,3)	KA	80%	11%	28%
OMEGA(4,4)	V3	55%	18%	55%
OMEGA(5,5)	Q	15%	0%	82%
OMEGA(6,6)	ALAG1	10%	0%	56%
OMEGA(7,7)	D1	707%	12%	29%

No estimated parameter penalties for biologically implausible parameters were included. Abnormal variability estimates for OMEGA D1 with coefficient of variation is >700%. Abbreviated terms used, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance).

Supplementary Table 11. Parameter values for top osimertinib model discovered using AIC (model complexity) penalty only.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage
THETA1	CL	13.72	3%	
THETA2	V2	542.27	13%	
THETA3	KA	0.70	30%	
THETA4	Additive error	3.58	12%	
THETA5	Proportional error	0.16	1%	
THETA6	V3	414.60	18%	
THETA7	Q	120.42	21%	
THETA8	ALAG1	0.58	9%	
THETA9	D1	3.03	6%	
OMEGA(1,1)	CL	54%	11%	2%
OMEGA(2,2)	V2	77%	26%	37%
OMEGA(3,3)	KA	536%	22%	33%
OMEGA(4,4)	V3	82%	18%	46%
OMEGA(5,5)	Q	71%	18%	67%
OMEGA(6,6)	ALAG1	10%	0%	68%
OMEGA(7,7)	D1	31%	16%	62%

No estimated parameter penalties for biologically implausible parameters were included. Abnormal variability estimate for OMEGA V3 with coefficient of variation is >500%. Abbreviated terms used, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance).

Supplementary Table 12. Parameter values for top olaparib model discovered using AIC (model complexity) penalty only.

Index	Name	Estimated Value	Relative Standard Error	Shrinkage
THETA1	CL	4.59	4%	
THETA2	V2	2.43	8%	
THETA3	Dose effect CL	0.68	16%	
THETA4	Dose effect V2	0.24	81%	
THETA5	KA	0.27	3%	
THETA6	Additive error	0.01	6%	
THETA7	Proportional error	0.30	1%	
THETA8	V3	65.08	15%	
THETA9	Q	3.30	6%	
THETA10	Dose effect V3	-3.06	13%	
THETA11	ALAG1	0.20	1%	
THETA12	D1	0.04	25%	
OMEGA(1,1)	CL	63%	6%	6.25%
OMEGA(2,2)	V2	90%	8%	21.64%
OMEGA(3,3)	KA	48%	18%	28.09%
OMEGA(4,4)	V3	283%	7%	19.35%
OMEGA(5,5)	Q	72%	12%	23.29%
OMEGA(6,6)	ALAG1	41%	0%	33.85%
OMEGA(7,7)	D1	426%	9%	20.68%

An abnormal OMEGA value (>280% coefficient of variation) is observed for OMEGA V3. Abbreviated terms used, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance).

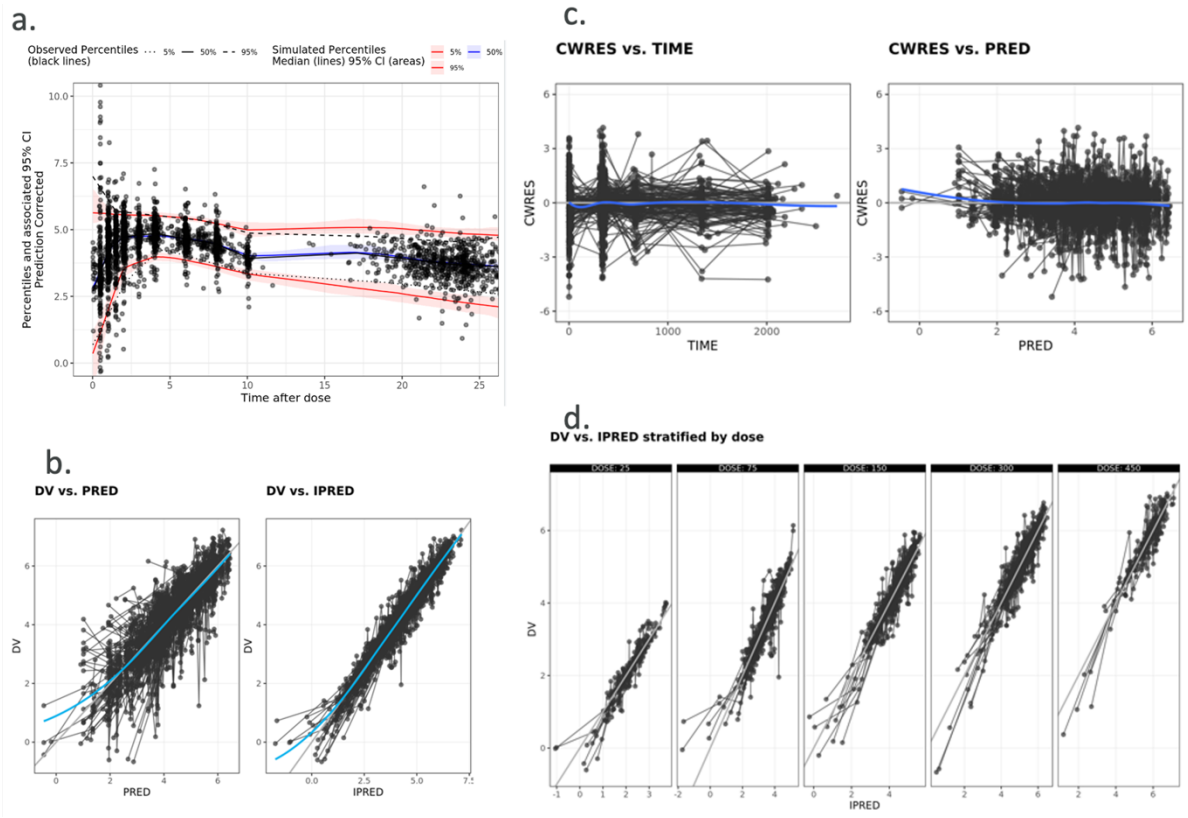
Supplementary Table 13. Results from model searches using random local initialisation.

Dataset	Δ Model structure	Δ Fitness	N observation local only	Number of models tested local	Δ models tested	Search time local (hours)	Δ time (hours)
Ribociclib (synthetic)	-	0	2	276	-7	6	0
Olaparib	-	0	4	253	87	30	12
Tezepelumab	-	0	4	278	48	5.5	0.5
Camizestrant	- 2 compartments + 1 compartment - 1st order absorption with 3 transient compartments + 1st order absorption with 4 transient compartments - Dose effect on Cl and V2 + Dose effect on V2	-93	5	142	138	30	16
Osimertinib	- 1 compartment + 2 compartments - 1st order oral absorption with 4 transient compartments + 1st order absorption with 3 transient compartments	5	1	197	-58	24	-3

Observations from model searches using local search only with random initialisation. The Δ fields present a comparison to the top model found using both the global and local search. For the fitness, number of models tested and time the delta is calculated as global+local performance – local performance so in all cases -ve scores indicate global+local is best and +ve if local only is best. Abbreviated terms used, CL (clearance), KA (absorption rate constant), V2 (volume of distribution for central compartment), V3 (volume of distribution for 1st peripheral compartment), D1 (duration for zero order absorption). Q (intercompartmental clearance).

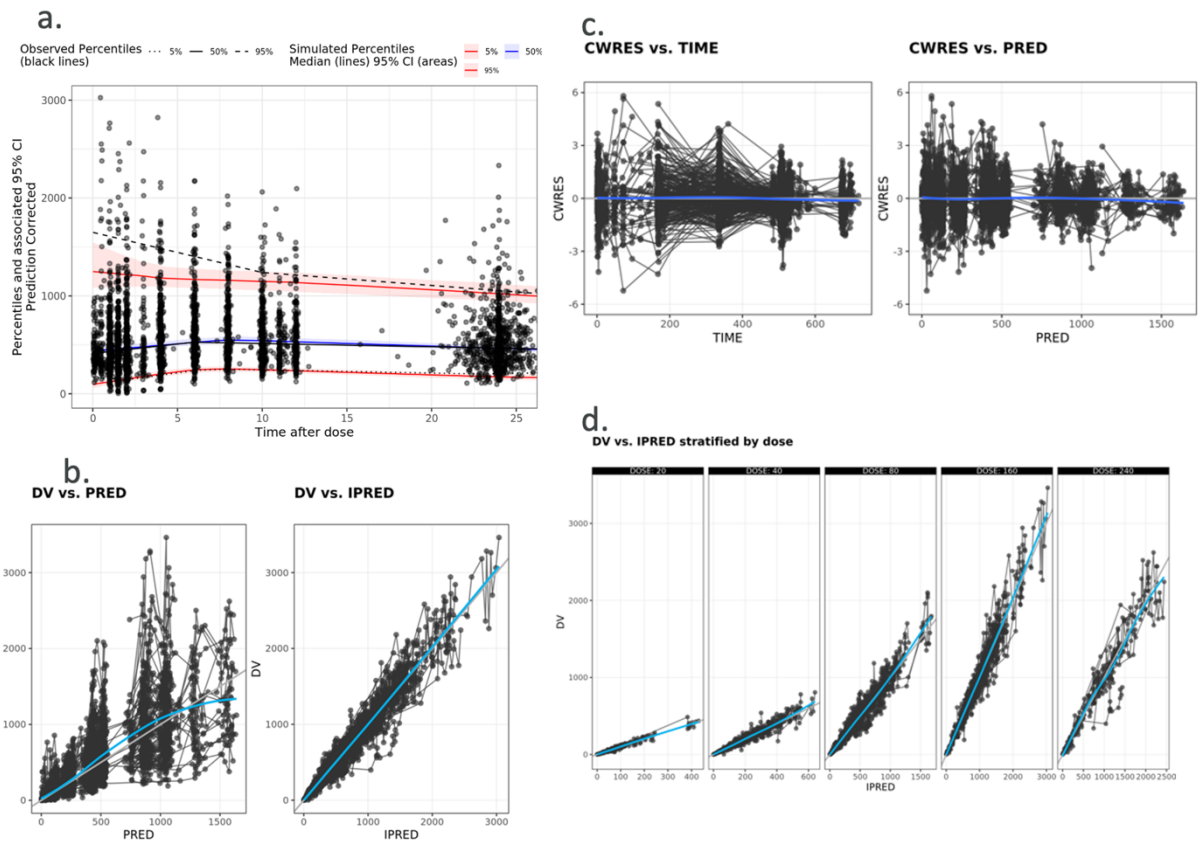
Supplementary Figures

Supplementary Figure 1. Model validation for the top automatically discovered camizestrant model.



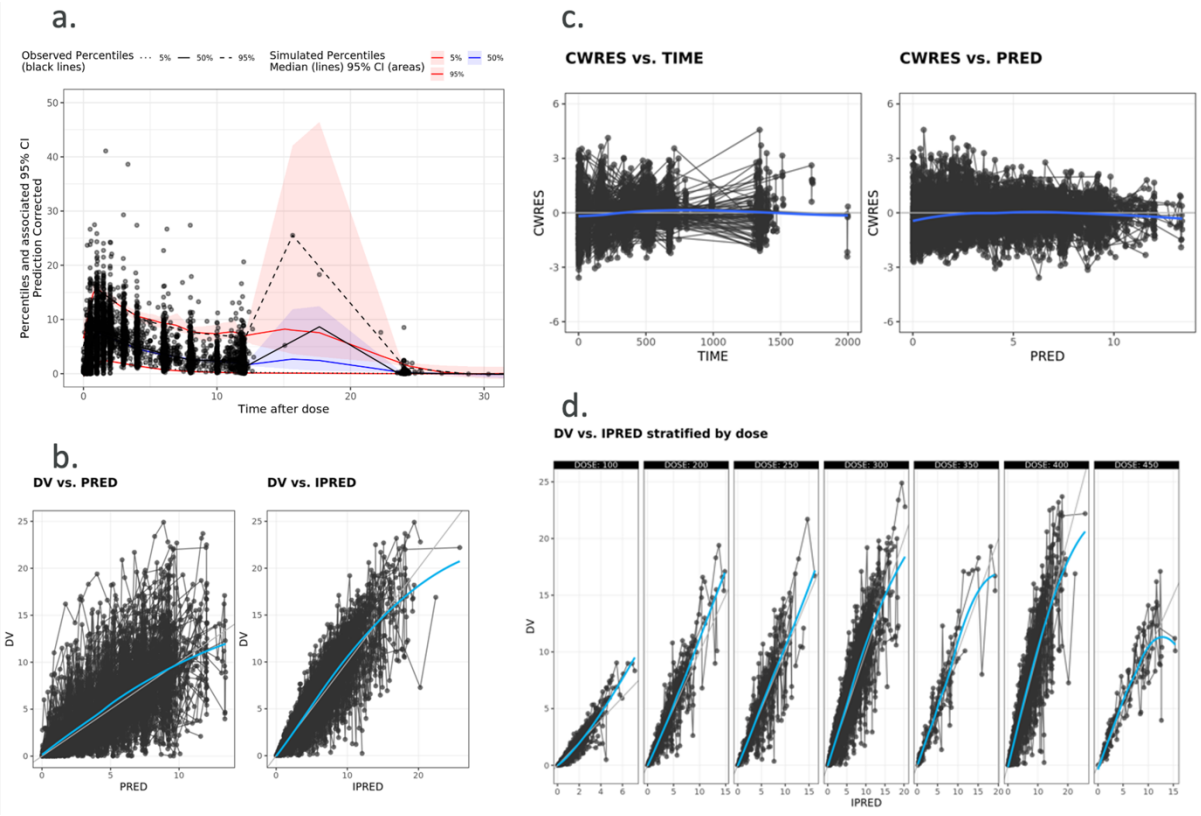
(a) visual predictive check for 200 simulated runs, the simulated concentration values for the 5th, 50th and 95th percentiles are given in coloured lines and the areas around the lines describe the 95% confidence intervals of the corresponding percentiles of the simulations. The black lines (dotted, solid and dashed) indicate the percentiles of the observations. (b) shows the observed concentration values (DV) vs. the population (PRED) and individual predictions (IPRED). (c) shows the residual error over time and simulated population prediction. (d) shows observations vs. individual predictions stratified by dose.

Supplementary Figure 2. Model validation for the top automatically discovered osimertinib model.



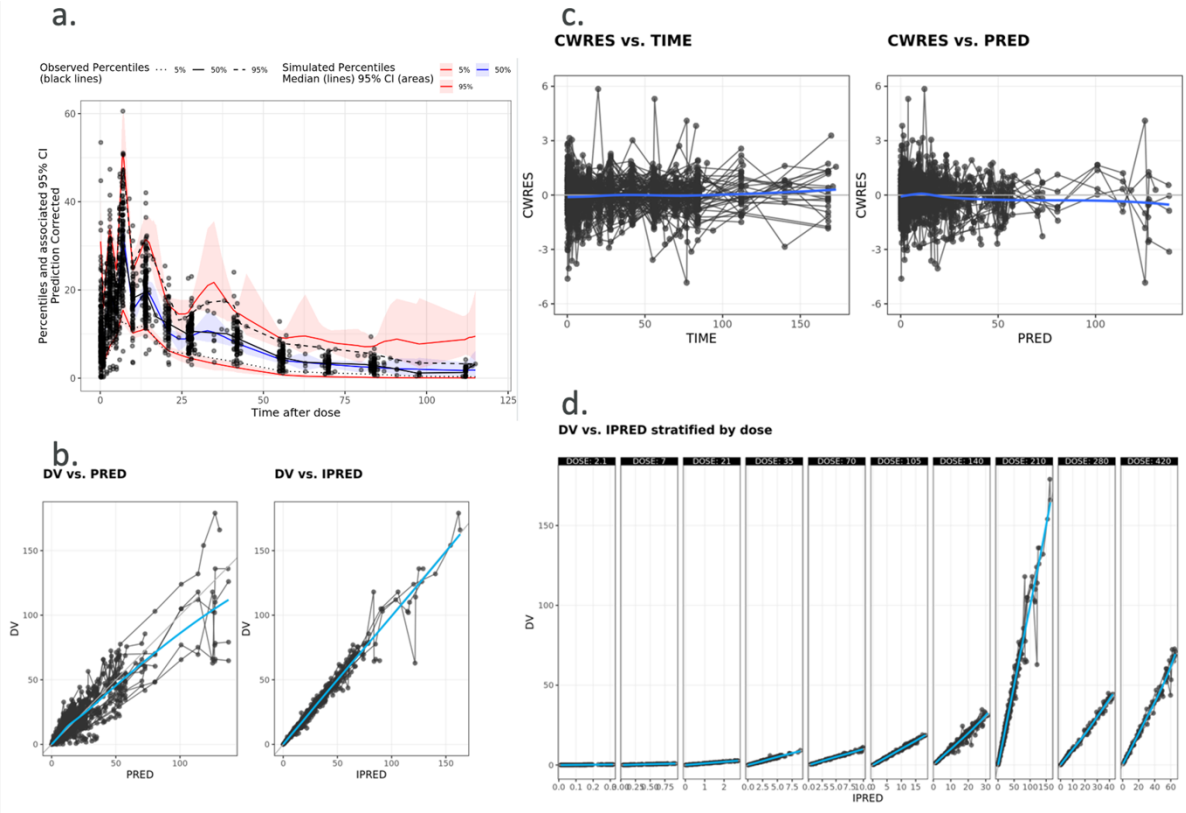
(a) visual predictive check for 200 simulated runs, the simulated concentration values for the 5th, 50th and 95th percentiles are given in coloured lines and the areas around the lines describe the 95% confidence intervals of the corresponding percentiles of the simulations. The black lines (dotted, solid and dashed) indicate the percentiles of the observations. (b) shows the observed concentration values (DV) vs. the population (PRED) and individual predictions (IPRED). (c) shows the residual error over time and simulated population prediction. (d) shows observations vs. individual predictions stratified by dose.

Supplementary Figure 3. Model validation for the top automatically discovered olaparib model



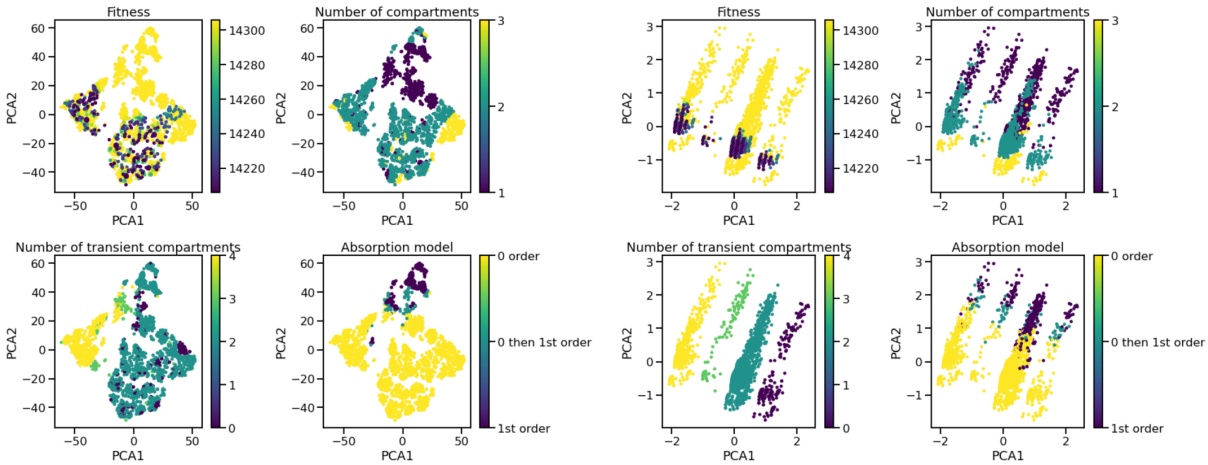
(a) visual predictive check for 200 simulated runs, the simulated concentration values for the 5th, 50th and 95th percentiles are given in coloured lines and the areas around the lines describe the 95% confidence intervals of the corresponding percentiles of the simulations. The black lines (dotted, solid and dashed) indicate the percentiles of the observations. (b) shows the observed concentration values (DV) vs. the population (PRED) and individual predictions (IPRED). (c) shows the residual error over time and simulated population prediction. (d) shows observations vs. individual predictions stratified by dose.

Supplementary Figure 4. Model validation for the top automatically discovered tezepelumab model.



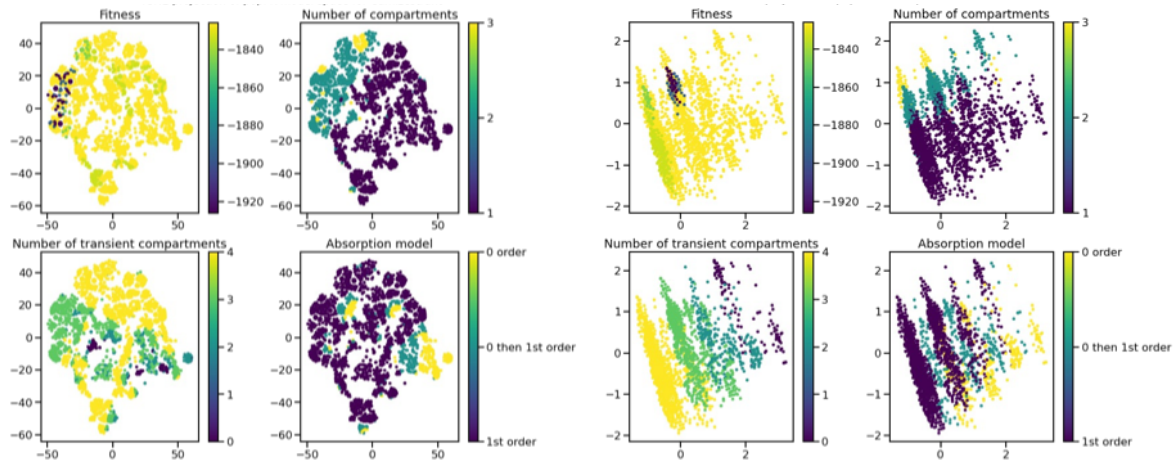
(a) visual predictive check for 200 simulated runs, the simulated concentration values for the 5th, 50th and 95th percentiles are given in coloured lines and the areas around the lines describe the 95% confidence intervals of the corresponding percentiles of the simulations. The black lines (dotted, solid and dashed) indicate the percentiles of the observations. (b) shows the observed concentration values (DV) vs. the population (PRED) and individual predictions (IPRED). (c) shows the residual error over time and simulated population prediction. (d) shows observations vs. individual predictions stratified by dose.

Supplementary Figure 5. 2D visualisations of the models explored during 5 ribociclib model searches.



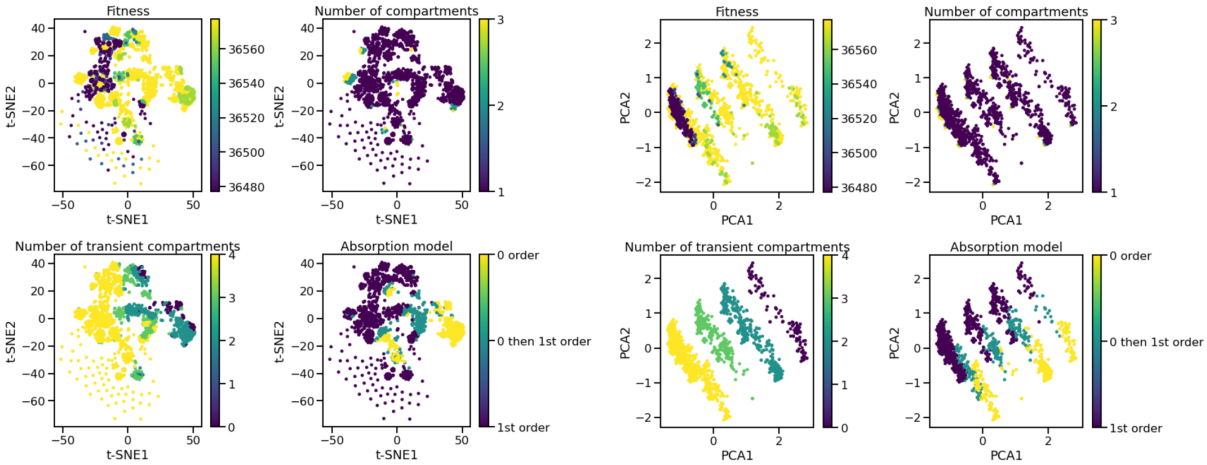
Visualisation of models explored in ribociclib model search. Dimension reduction of feature vectors performed using TSNE (left) and PCA (right). The colour scale denotes overall fitness, number of compartments, absorption model and number of transient compartments in each plot (in clockwise direction).

Supplementary Figure 6. 2D visualisations of the models explored during 5 camizestrant model searches.



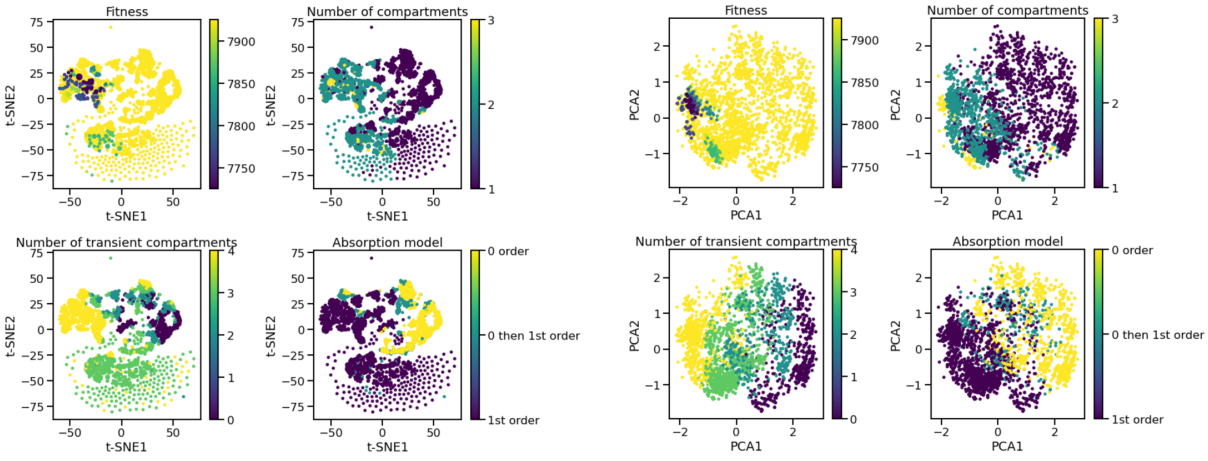
Visualisation of models explored in camizestrant model search. Dimension reduction of feature vectors performed using TSNE (left) and PCA (right). The colour scale denotes overall fitness, number of compartments, absorption model and number of transient compartments in each plot (in clockwise direction).

Supplementary Figure 7. 2D visualisations of the models explored during 5 osimertinib model searches.



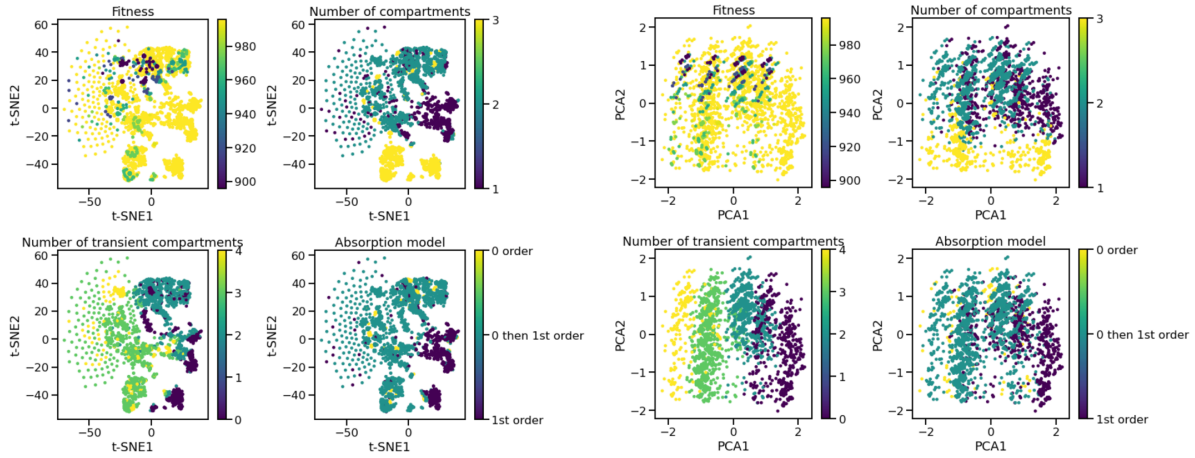
Visualisation of models explored in osimertinib model search. Dimension reduction of feature vectors performed using t-SNE (left) and PCA (right). The colour scale denotes overall fitness, number of compartments, absorption model and number of transient compartments in each plot (in clockwise direction).

Supplementary Figure 8. 2D visualisations of the models explored during 5 olaparib model searches.



Visualisation of models explored in olaparib model search. Dimension reduction of feature vectors performed using TSNE (left) and PCA (right). The colour scale denotes overall fitness, number of compartments, absorption model and number of transient compartments in each plot (in clockwise direction).

Supplementary Figure 9. 2D visualisations of the models explored during 5 tezepelumab model searches.



Visualisation of models explored in olaparib model search. Dimension reduction of feature vectors performed using TSNE (left) and PCA (right). The colour scale denotes overall fitness, number of compartments, absorption model and number of transient compartments in each plot (in clockwise direction).

Supplementary methods

Count of unique model configurations

Some tokens were active only under specific conditions. For instance, the token determining whether to estimate the inter-individual variability (IIV) for the 2nd compartment was used exclusively when the model consisted of 2 or 3 compartments. Due to the conditional activation of these nested tokens, a single model configuration could correspond to multiple feature vectors, resulting in many-to-one relationships between feature vectors and model configurations. This led to a total of 12,672 unique models within the search space.

The number of unique models could be determined by using the template and token file to map the conditions under which nested tokens were activated. While all tokens referenced in the template are active across every model, additional nested tokens become active based on the number of compartments and the absorption model specified. A mapping of the nested tokens that are active under various compartment and absorption model configurations is provided in the table below.

Condition	Nested tokens activated
Template (Always active)	- Dose effect CL - Dose effect V2 - Dose effect Ka - Error model
Compartment = 1	- No additional activated tokens
Compartment = 2	- OMEGA V3 - OMEGA Q - Dose effect V3 - Dose effect Q
Compartment = 3	- OMEGA V3 - OMEGA Q - OMEGA V4 - OMEGA Q2
Absorption = 1st order oral absorption	- Tlag - Transit compartments
Absorption = Sequential 1st then 0 order oral absorption	- OMEGA duration - Tlag
Absorption = 0 order oral absorption	- OMEGA duration - Tlag

As the model search space featured only a single level of hierarchy with just two features affecting which nested tokens were activated, it was possible to complete this analysis manually. Unique models for each compartment / absorption model configuration could be calculated as a product of the number possible values for the activated tokens. As there were 9 subgroups and only 1 level of hierarchy it was possible to do this calculation by hand. The calculation of unique model counts for each subgroup is given below.

1 compartment / 1st order
Active tokens: Tlag (2 values), transit compartments (4 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), Error model (3 values)
Unique models: 2 * 4 * 2 * 2 * 2 * 3 = 192

1 compartment / Sequential 0 then 1st order
Active tokens: Omega duration (2 values), Tlag (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 3 = 96

1 compartment / 0 order
Active tokens: Omega duration (2 values), Tlag (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 3 = 96

2 compartment / 1st order
Active tokens: Omega V3 (2 values), Omega Q (2 values), Tlag (2 values), transit compartments (4 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), V3 dose effect (2 values), Q dose effect (2 values), Error model (3 values)
Unique models: 2 * 2 * 2 * 4 * 2 * 2 * 2 * 2 * 2 * 3 = 3072

2 compartment / Sequential 0 then 1st order
Active tokens: Omega V3 (2 values), Omega Q (2 values), Omega duration (2 values), Tlag (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), V3 dose effect (2 values), Q dose effect (2 values), error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 3 = 1536

2 compartment / 0 order
Active tokens: Omega V3 (2 values), Omega Q (2 values), Omega duration (2 values), Tlag (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), V3 dose effect (2 values), Q dose effect (2 values), error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 3 = 1536

3 compartment / 1st order
Active tokens: Omega V3 (2 values), Omega Q (2 values), Omega V4 (2 values), Omega Q2 (2 values), Tlag (2 values), transit compartments (4 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), Error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 2 * 4 * 2 * 2 * 2 * 3 = 3072

3 compartment / Sequential 0 then 1st order
Active tokens: Omega duration (2 values), Tlag (2 values), Omega V3 (2 values), Omega Q (2 values), Omega V4 (2 values), Omega Q2 (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), Error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 3 = 1536

3 compartment / 0 order
Active tokens: Omega duration (2 values), Tlag (2 values), Omega V3 (2 values), Omega Q (2 values), Omega V4 (2 values), Omega Q2 (2 values), Cl dose effect (2 values), V2 dose effect (2 values), Ka dose effect (2 values), Error model (3 values)
Unique models: 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 2 * 3 = 1536

The total number of unique models in the space could then be calculated as the sum of possible models across each configuration.

Total unique models:
192 + 96 + 96 + 3072 + 1536 + 1536 + 3072 + 1536 + 1536 = 12,672

Updated versions of the model space will remove Ka dose dependency from the template file which leads to the possibility to combine the Ka dose dependence with 0 order models creating invalid model structures. As these configurations were not highly ranked for any of the datasets it was not considered an issue that these model configurations existed within the space.