
Table of Contents

1.	Chapter 1 – General Principles	1
1.1	Introduction	1
1.2	Basic Concepts	1
1.3	Why Model the Data	2
1.4	The Art of Successful Modeling	4
1.5	How to Use This Book	7
2.	Chapter 2 – Pharmacokinetic Concepts	11
2.1	Background	11
2.2	One Compartment Models	12
2.2.1	Intravenous bolus administration	12
2.2.2	Constant rate infusion	21
2.2.3	Integration of clearance and volume	25
2.2.4	Extravascular administration	28
2.2.5	Estimation of absorption parameters from first-order input	33
2.2.6	Estimation of absorption parameters from zero-order input	40
2.2.7	What lies behind the apparent absorption rate constant?	42
2.2.8	Estimation of bioavailability	43
2.2.9	How does input to the plasma compartment vary?	45
2.2.10	Multiple dosing	46
2.2.11	Absorption from multiple sites	49
2.2.12	Conclusions for extravascular dosing	50
2.3	Plasma and Urine Data	51
2.3.1	Basic renal physiology	51
2.3.2	Derivation of equations	51
2.3.3	Analysis of urinary excretion data	54
2.3.4	Estimation of bioavailability from urinary data	62
2.4	Multi-Compartment Models	63
2.4.1	Catenary and mammillary models	63
2.4.2	Intravenous bolus administration	65
2.4.3	Reparameterization of the two-compartment model	73
2.4.4	Constant rate infusion	80
2.4.5	Extravascular administration	82
2.4.6	Plasma and urine data	84
2.5	Clearance Concepts	86
2.5.1	Derivation of clearance	86
2.5.2	Extraction	87
2.5.3	Impact of route of administration	93
2.5.4	<i>In vitro/in vivo</i> comparisons of clearance	95
2.5.5	Hepatic clearance models	100
2.5.6	Additional reading	104
2.6	Turnover	105
2.6.1	Background	105

2.6.2	Introduction to turnover of proteins, peptides and antibodies	110
2.6.3	Turnover of immunoglobulins	112
2.6.4	Turnover of hormones - Estradiol	114
2.6.5	Comparison of models	116
2.6.6	Turnover of body temperature	118
2.6.7	Feedback	123
2.7	Nonlinear Systems – Capacity, Time, Flow and Binding	125
2.7.1	What causes nonlinearity and how is it assessed?	125
2.7.2	Nonlinear kinetics – Capacity	128
2.7.2.1	Bolus input - Capacity limited elimination	132
2.7.2.2	Constant rate input - Capacity limited elimination	132
2.7.2.3	First order input - Capacity limited elimination	133
2.7.2.4	Conclusions on capacity limited elimination	133
2.7.3	Nonlinear kinetics – Time	134
2.7.3.1	Background	134
2.7.3.2	Turnover of induction	135
2.7.3.3	Heteroinduction – Pentobarbital induction of nortriptyline	139
2.7.3.4	Autoinduction	142
2.7.4	Nonlinear kinetics – Flow	145
2.7.5	Nonlinear kinetics – Binding	145
2.7.6	Nonlinear drug metabolite models	153
2.7.7	Ethanol combines capacity, time and flow dependencies	157
2.8	Non-Compartmental Analysis	161
2.8.1	Non-compartmental <i>versus</i> regression analysis	161
2.8.2	Computational methods – Linear trapezoidal rule	162
2.8.3	Computational methods – Log-linear trapezoidal rule	164
2.8.4	Strategies for estimation of λ_z	167
2.8.5	Pertinent pharmacokinetic estimates	169
2.8.6	Issues related to steady state	173
2.8.7	Metabolite kinetics	177
2.8.8	When half-life is short relative to input time	179
2.9	How to Assess Exposure	181
2.9.1	What do we mean by exposure?	181
2.9.2	The case(s) for abandoning dose	181
2.9.3	Exposure based on total concentrations	186
2.9.4	Exposure based on unbound concentrations	189
2.9.5	Conclusions on exposure	191
2.10	Inter-Species Scaling	193
2.10.1	When and why do we extrapolate data across species?	193
2.10.2	What is allometry?	195
2.10.3	Allometric equations	196
2.10.4	Time scales differ between different species	206
2.10.5	Estimation of parameters	208
2.10.6	The elementary Dedrick plot	209
2.10.7	The complex Dedrick plot	212
2.10.8	Integration of concepts	215

2.10.9	Physiological variables of 11 animal species and man	216
2.10.10	Allometric scaling of turnover parameters	220
2.10.11	General conclusions about exposure and scaling	222
2.11	Additional Reading	223
3.	Chapter 3 – Pharmacodynamic Concepts	225
3.1	Background	225
3.2	Definitions	227
3.3	Law of Mass Action	228
3.4	Receptor Binding Models	233
3.4.1	Saturation studies	233
3.4.2	Displacement studies	234
3.5	Pharmacodynamic Models	236
3.5.1	Background	236
3.5.2	Linear effect-concentration model	237
3.5.3	Log-linear effect-concentration model	238
3.5.4	Ordinary E_{max} model	239
3.5.5	Sigmoid E_{max} model	243
3.5.6	Composite E_{max} model	247
3.5.7	Multiple binding site model	250
3.6	Interaction Models	251
3.6.1	Competitive antagonism	251
3.6.2	Noncompetitive antagonism	251
3.6.3	General empirical dynamic model for two drugs	252
3.6.4	Enantiomer interaction models	253
3.6.5	Additional sigmoidal models	254
3.6.6	Kinetics of pharmacological responses	255
3.6.7	Area under the response-time curve	260
3.7	Turnover Models – Reversible Drug Effects	261
3.7.1	Background	261
3.7.2	Model taxonomy	263
3.7.3	Model characteristics	271
3.7.4	Initial parameter estimates	273
3.7.5	Model behavior	278
3.7.6	Model extensions	281
3.8	Turnover Models – Irreversible Drug Effects	282
3.8.1	Simple irreversible action – Cell killing	283
3.8.2	Cell growth coupled with cell killing	284
3.8.3	Minimum inhibitory concentration	287
3.9	Effect Compartment (Link) Models	289
3.9.1	Background	289
3.9.2	One-compartment models	291
3.9.3	Two-compartment models	294
3.9.4	Integration of time into the Hill equation	295
3.9.5	Alternative parameterizations	296
3.9.6	Some literature examples and simulations	297
3.9.7	Problems and pitfalls	299

3.10	Dose-Response-Time Models	301
3.10.1	Background	301
3.10.2	Miotic data	302
3.10.3	Acetylcholinesterase turnover	304
3.10.4	Antinociception	307
3.10.5	Body temperature	308
3.10.6	Turnover of antipsychotic effects – Disease modeling	310
3.10.7	Conclusions about dose-response-time data modeling	311
3.11	Tolerance and Rebound Models	312
3.11.1	Background	312
3.11.2	Systems analysis	316
3.11.3	Time dependent attenuation of parameters	316
3.11.4	Antagonistic metabolite model	319
3.11.5	Tolerance compartment model	320
3.11.6	Counteracting mechanisms	321
3.11.7	Feedback and rebound	322
3.11.8	Simple negative feedback on turnover rate	324
3.11.9	Negative feedback via a moderator	325
3.11.10	Negative feedback via a moderator and level of response	329
3.11.11	Simulation of feedback via a moderator	331
3.11.12	Pool model – Unidirectional flow	333
3.11.13	Pool model – Bidirectional flow	336
3.11.14	Comparisons with other models	339
3.11.15	Modeling of cocaine response-time data	340
3.11.16	Some thoughts about tolerance and dependence models	343
3.12	Baseline Models	345
3.12.1	Constant <i>versus</i> variable baseline models	345
3.12.2	Oscillating turnover rates	347
3.13	Transduction Models	350
3.14	Synergistic Effects Modeled by Turnover Functions	353
3.15	Synergistic Effects Modeled by Hyperbolic Functions	356
3.16	Logistic Response Models	357
3.17	Additional Reading	360
4.	Chapter 4 – Parameter Estimation	361
4.1	Background	361
4.2	Linear and Nonlinear Models	362
4.3	Criteria for Best Fit – Minimization Methods	364
4.3.1	Ordinary, weighted and extended least squares methods	364
4.3.2	Generalized least squares method	366
4.4	Considerations in the Choice of Weights	368
4.4.1	Why weight?	368
4.4.2	Constant absolute error	369
4.4.3	Poisson error	370
4.4.4	Constant relative error – Proportional error	370
4.4.5	Graphical estimation of weights	372

4.5	Application of Least Squares to Linear Models	374
4.6	Application of Least Squares to Nonlinear Models	375
4.6.1	Background	375
4.6.2	Random search methods	377
4.6.3	Stripping or peeling methods	377
4.6.4	Linearization methods	379
4.6.5	Simplex methods	382
4.7	Constraints on the Parameter Space	383
4.8	Estimating Functions of Parameters	384
4.9	Validation of Software	386
4.9.1	What do we mean by software validation?	386
4.9.2	Computer systems validation	387
4.9.3	Testing of user models	388
5.	Chapter 5 – Modeling Strategies	389
5.1	Background	389
5.2	Plot and Explore Data	390
5.2.1	Understand your experimental data better	390
5.2.2	Pooling of data	391
5.2.3	Transformation for exploration	393
5.2.4	Transformation for fitting	395
5.2.5	Normalizing data	397
5.3	How Complicated a Model?	399
5.3.1	How many parameters?	399
5.3.2	How do we specify the model?	400
5.3.3	Combining several sources of data for modeling	404
5.3.4	Parameter identifiability	405
5.3.5	Ability to estimate parameters	408
5.4	Obtaining Initial Estimates	409
5.4.1	Graphical methods and linear regression	410
5.4.1.1	Kinetic data	410
5.4.1.2	Dynamic steady state data	413
5.4.1.3	Dynamic non-steady state data	413
5.4.1.4	Dynamic repeated dose data	418
5.4.2	Convolution and deconvolution analysis	422
5.4.2.1	Background	422
5.4.2.2	Theory	424
5.4.2.3	Oral solution <i>versus</i> tablet	427
5.4.2.4	Transdermal input	428
5.4.2.5	Drug and metabolite data	428
5.4.2.6	Bidirectional drug flux	431
5.4.3	When all else fails	432
5.5	Selection of the Minimization Algorithm	433
5.6	Iterations	434
5.7	Assessing the Goodness-of-Fit	438
5.7.1	Analyzing the residuals	438
5.7.2	Graphical presentation of residuals	441

5.7.3	Pure error <i>versus</i> lack of fit	446
5.7.4	Parameter estimates – Accuracy	448
5.7.5	Parameter estimates – Precision	450
5.7.6	Correlation between observed and predicted values	451
5.7.7	Correlation between parameters	452
5.7.8	Condition number	456
5.8	Discrimination Between Rival Models	456
5.8.1	F test	457
5.8.1.1	Background	457
5.8.1.2	The ordinary E_{max} <i>versus</i> the sigmoid E_{max} model	458
5.8.1.3	The ordinary E_{max} <i>versus</i> the linear response model	459
5.8.1.4	The hepatic distributed <i>versus</i> parallel tube model	459
5.8.2	Akaike and Schwarz criteria	460
5.9	Outliers	461
5.10	A Checklist for Assessing Goodness-of-Fit	462
5.11	Additional Reading	463
6.	Chapter 6 – Design Elements	464
6.1	Background	464
6.2	Tools for Experimental Design	465
6.2.1	Delta function	465
6.2.2	Variance inflation factor	466
6.2.3	Partial derivatives	469
6.2.4	Sensitivity analysis	474
6.3	General Design Issues of Kinetic/Dynamic Studies	476
6.3.1	Bolus, infusion and first-order input	477
6.3.2	Nonlinear kinetics	481
6.3.3	Design of toxicokinetic studies	483
6.3.4	Dynamic studies – Baseline	486
6.3.5	Acute <i>versus</i> chronic dosing	488
	Pharmacokinetic and Pharmacodynamic Applications	490
	Pharmacokinetic Applications	491
PK1	One-compartment iv bolus dosing	491
PK2	One-compartment oral dosing	508
PK3	One-compartment 1 st and 0-order input	517
PK4	One-compartment oral dosing	523
PK5	One-compartment iv plasma/urine I	535
PK6	One-compartment iv plasma/urine II	543
PK7	Two-compartment iv bolus dosing	551
PK8	Two-compartment distribution models	559
PK9	Two-compartment model testing	571
PK10	Simultaneous fitting of iv/po data	577
PK11	Two-compartment repeated po dosing	585
PK12	Intravenous and oral dosing	593
PK13	Bolus plus constant rate infusion	599
PK14	Multi-compartment model oral dosing	605
PK15	Toxicokinetics I	615

PK16	Two-compartment iv plasma/urine	622
PK17	Nonlinear kinetics – Capacity I	628
PK18	Ethanol kinetics – Capacity II	634
PK19	Metabolite kinetics – Capacity III	650
PK20	Nonlinear kinetics – Capacity IV	666
PK21	Nonlinear kinetics – Heteroinduction	676
PK22	Nonlinear kinetics – Autoinduction	684
PK23	Nonlinear kinetics – Flow I	691
PK24	Nonlinear kinetics – Flow II	698
PK25	Two-compartment plasma and urine analysis with rate and ARE plots	708
PK26	Toxicokinetics II – Multiple dose data	713
PK27	Toxicokinetics III – Repeated dose safety study	718
PK28	Allometry – Elementary Dedrick plot	723
PK29	Allometry – Complex Dedrick plot	729
PK30	Turnover I – Sc dosing of hormone	739
PK31	Turnover II – Iv dosing of hormone	743
PK32	Turnover III – Nonlinear disposition	750
PK33	Transdermal input and kinetics	759
PK34	Reversible metabolism	764
PK35	Bayesian model – Digoxin	772
PK36	Time controlled drug delivery	777
PK37	<i>In vitro/in vivo</i> extrapolation I	780
PK38	<i>In vitro/in vivo</i> extrapolation II	788
PK39	Two-compartment plasma data – Experimental design issues	796
PK40	Enterohepatic recirculation	803
PK41	Multiple intravenous infusions – NCA <i>versus</i> regression	808
PK42	Saturable absorption via transporters	814
PK43	Multiple absorption routes	823
PK44	Estimation of inhibitory constant K_i by means of SNLR	828
PK45	Toxicokinetics IV – Study Simulation	837
PK46	Long infusion and short half-life	839
PK47	Plasma protein binding modeling	844
PK48	One-compartment Michaelis-Menten kinetics-Drug&metabolite in urine	851
PK49	<i>In vitro</i> enzyme kinetics Reaction product measurement	857
PK50	Analysis of multiple subject profiles – Two-compartment plasma data	862
PK51	Multi-compartment drug/metabolite	865
PK52	Impact of disease on r-hSOD kinetics	873
PK53	Kinetics of a large molecule	883
	Pharmacodynamic applications	888
PD1	Receptor binding models. Part I – One- and two-site models	888
	Part II – Specific and non-specific binding	
PD2	One and two-site receptor binding	895
PD3	Inhibitory I_{max} model	902
PD4	Turnover model 1 – Bolus dosing	917
PD5	Turnover model 2 – Iv infusions	933
PD6	Turnover model 3 – Turnover <i>versus</i> link modeling	941
PD7	Turnover model 4 – Iv infusions	954
PD8	Turnover models 2 and 3	962
PD9	Turnover model 1 - Repeated dosing I	970
PD10	Turnover models 1 and 4 – Iv infusions	980
PD11	Sigmoidal models	989

PD12	Tolerance I – Single <i>iv</i> dosing	1000
PD13	Tolerance II – Repeated <i>iv</i> infusions	1009
PD14	Feedback modeling – Cortisol/ACTH	1019
PD15	Oscillating response	1028
PD16	Turnover model – Irreversible action	1034
PD17	Composite model I – I_{max}	1039
PD18	Composite model II – E_{max} / I_{max}	1042
PD19	Enantiomer interaction	1048
PD20	Effect compartment I – <i>Iv</i> bolus	1055
PD21	Effect compartment II – Oral dosing	1061
PD22	Effect compartment III – <i>Iv</i> infusion	1067
PD23	Logistic regression I – Single stimulus	1076
PD24	Logistic regression II – Multiple stimuli	1081
PD25	Dose-response-time analysis I	1086
PD26	Dose-response-time analysis II – Irreversible response	1093
PD27	Dose-response-time analysis III	1109
PD28	Dose-response-time analysis IV	1118
PD29	Synergy via hyperbolic functions	1127
PD30	Incomplete response data	1131
PD31	Consecutive escalating infusions – Safety data	1137
PD32	Scaling PD and PK data – Efficacy	1143
PD33	Turnover of anti-psychotic response	1151
PD34	Agonist/antagonist interaction model	1158
PD35	Transduction modeling	1165
PD36	Turnover of asymmetric baseline	1173
PD37	Multiple binding site model	1178
PD38	Turnover model 1 - Repeated dosing II	1181
PD39	Turnover model of synergistic effects	1186
PD40	Operational model of agonism	1193
PD41	Receptor on/off rate model	1198
PD42	Pool model of antipolytic effect	1206
	References	1212
	Symbols and Definitions	1236
	Index	1244
