Interspecies population modeling of pharmacokinetic data available at the end of drug discovery

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Introduction

- Forecasting human PK from preclinical data
  - getting human PK data is expensive (~5-10 M$)
  - many existing methods, but all with low predictive power
- Yet Another Method?
  - allometric nonlinear mixed effects
  - model all species simultaneously
    - H. Boxenbaum. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. J.Pharmacokinet.Biopharm. 10 (2):201-227, 1982.
    - V. F. Cosson, E. Fuseau, C. Efthymiopoulos, and A. Bye. Mixed effect modeling of sumatriptan pharmacokinetics during drug development. I: Interspecies allometric scaling. J.Pharmacokinet.Biopharm. 25 (2):149-167, 1997.
    - K. Jolling, J. J. Perez Ruixo, A. Hemeryck, A. Vermeulen, and T. Greway. Mixed-effects modelling of the interspecies pharmacokinetic scaling of pegylated human erythropoietin. Eur.J.Pharm.Sci. 24 (5):465-475, 2005.
    - T. Martin-Jimenez and J. E. Riviere. Mixed-effects modeling of the interspecies pharmacokinetic scaling of oxytetracycline. J.Pharm.Sci. 91 (2):331-341, 2002
  - extensive datasets used, sometimes including human
    - but: limited data available at the end of discovery

=> explore application in early stage

Dataset

- anonymous compound
  - human PK data not yet available
- in vivo PK experiments
  - 4 species: mouse, rat, dog, monkey
  - approx. 10 timepoints, n=2/3 per dosing route
  - mouse: terminal sample, n=26, n=2/timepoint, 6/7 timepoints per route
  - routes: iv + oral
- body weight available as individual covariate in all but mouse
  - practical procedures different for mouse at the time

(nonmem V; PsN 1 for bootstraps)

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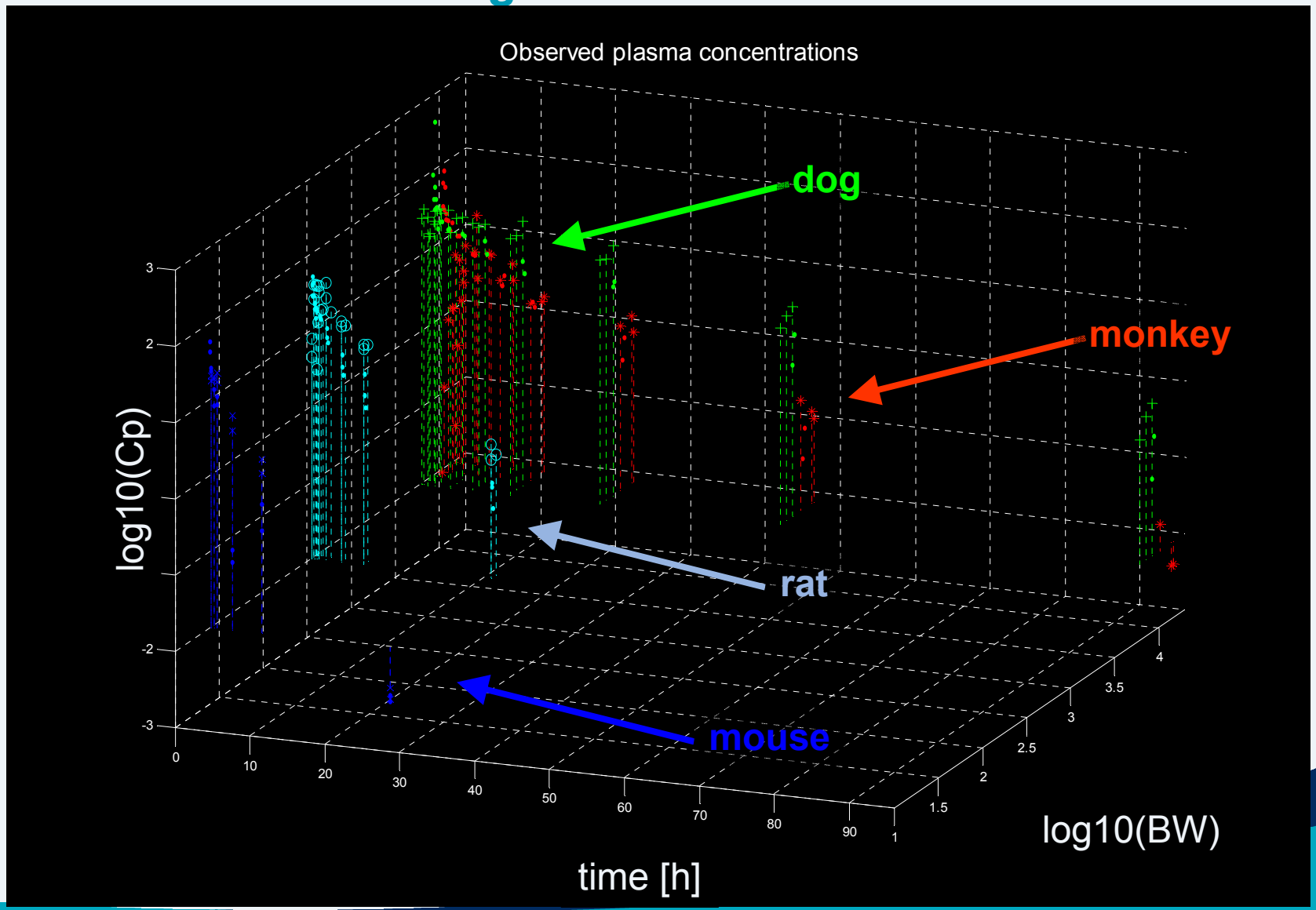
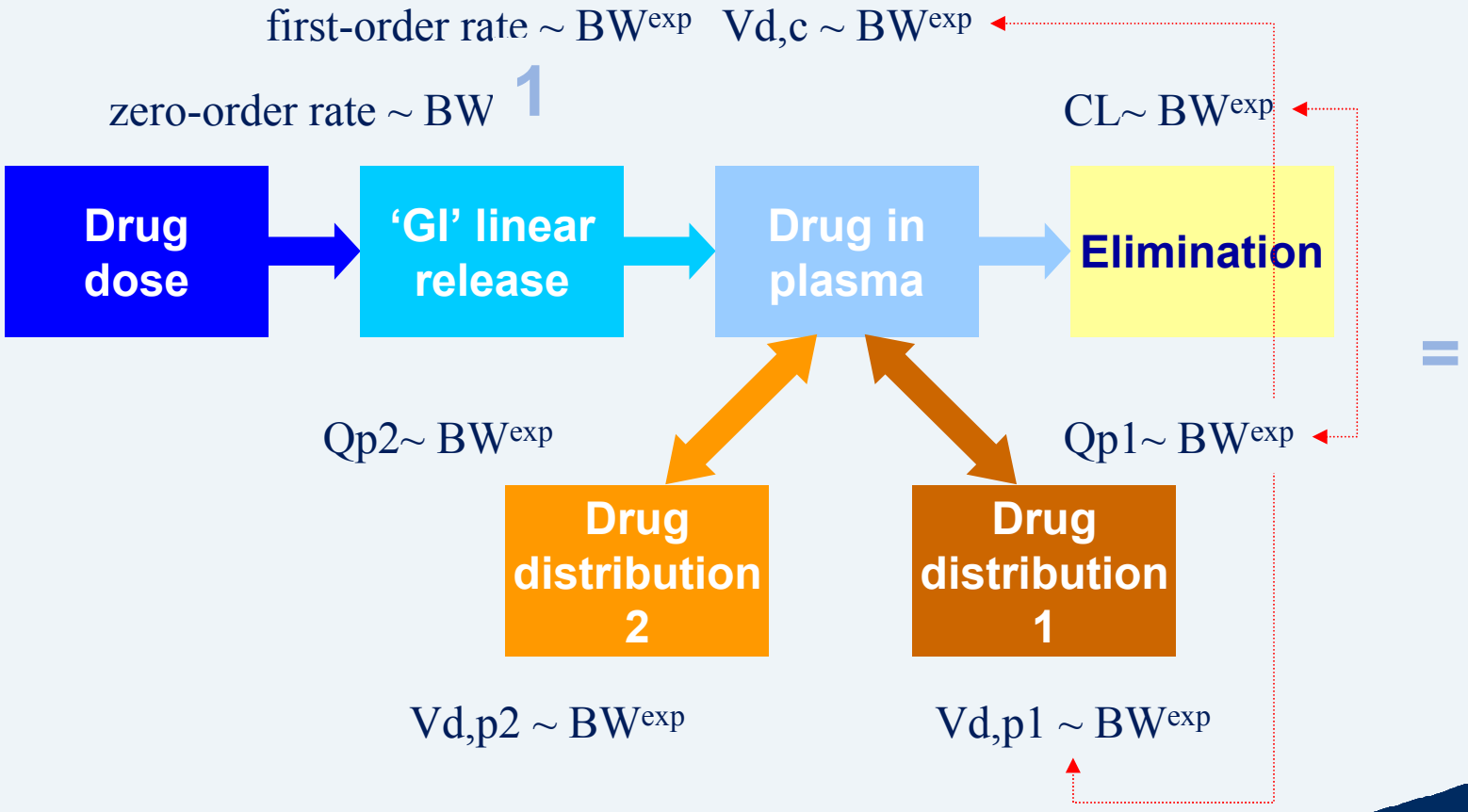
Dataset – oral dosing



Drug model – multiple species



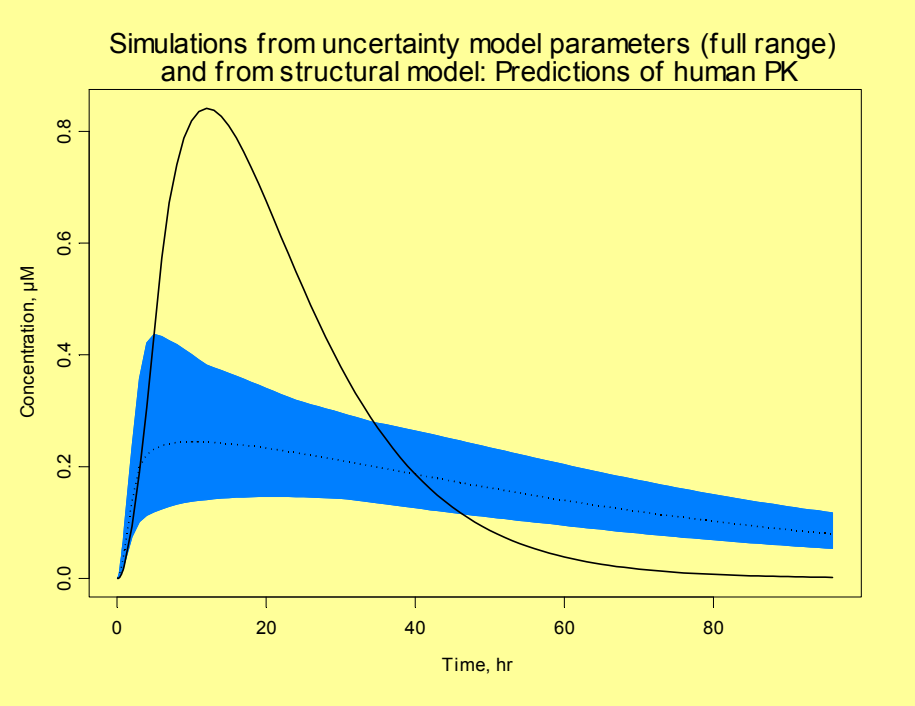
Overview model building steps [1]

numbers refer to objective function value

- compartmental fit per species
  - mouse, dog: 2-compartmental; rat, monkey: 3-compartmental
- combined compartmental fit
  - first stage: 1-compartmental: 1327; 2-comartmental: 1167
  - absolute amounts: 2-compartmental: 702; 3-compartmental: 671 {thusfar no successful term.}
- monkey is different
  - zero-order absorption + monkey[Fbio-oral bioavailability]: 515 {succesfull with covar}
  - zero-order absorption + monkey[Fbio,Ka,Cl]: 400 {cond.n. ~100 with all exps}
- actual body weights, collapse allometric exponents
  - D1[no allometric exponent]: 432
  - ClsVs[exponents collapsed]: 442
  - D1[no exponent] + mouse[2-compartmental]: 426
  - D1[no exponent] + mouse[2-compartmental] +ClQV12[collapsed] + V3[no exponent] + monkey[Fbio,Cl]: 378
- mixed effects
  - Eta[Fbio,Cl,V]: 321 {no covariance step}
  - Eta[Fbio,Cl] + FO: 318
  - Eta[Fbio,Cl] + FOCE INT + tweak: 352
  - Eta[Fbio,Cl] + FO + V3[exponent]: 315 {slightly improved covar. matrix cond.n. ~ 1000}
  - Eta[Fbio,Cl] + FO + D1V3[exponent]: 313

Overview model building steps [2]

- bootstrapping of Eta[Fbio,Cl] + FO + V3[exponent] model
  - instable: almost no covariance steps, parameters confidence intervals including zero, bimodal distribution
- simulations from covariance matrix of estimates
  - mean and range of simulations is **far from population predicted**!



Overview model building steps [3]

numbers refer to objective function value

- conclusion (after checks):
  assumption of multivariate normal distribution violated
  - (up to here, ~250 model runs)

- remediation: specify thetas as lognormal
  - (Eta[Fbio,Cl] + FO + V3[exp]) + logtransform: 315->309
  - +FOCE INT: 346 {no covar step}
  - +monkey[Q3]: 293
  - +monkey[Q3,add+non-monkey] + non-diagonal Omega: 290 {corr 0.944 Q3/V2}
  - +FOCE INT +monkey[Q3,add+non-monkey,reparFbio] {cond.n. ~ 10000
    + LTQ3=LTQ3e+LTV2: 335 ugly hack, but it works}
  - idem, FOCE: 288 {cond.n. ~ 10000}
- FOCE INT model selected
  - objective function not comparable (?) across methods
  - structural bias FOCE without INT
    - (but individiual predictions *better* without INT)
    - purpose is prediction of mean, not of population

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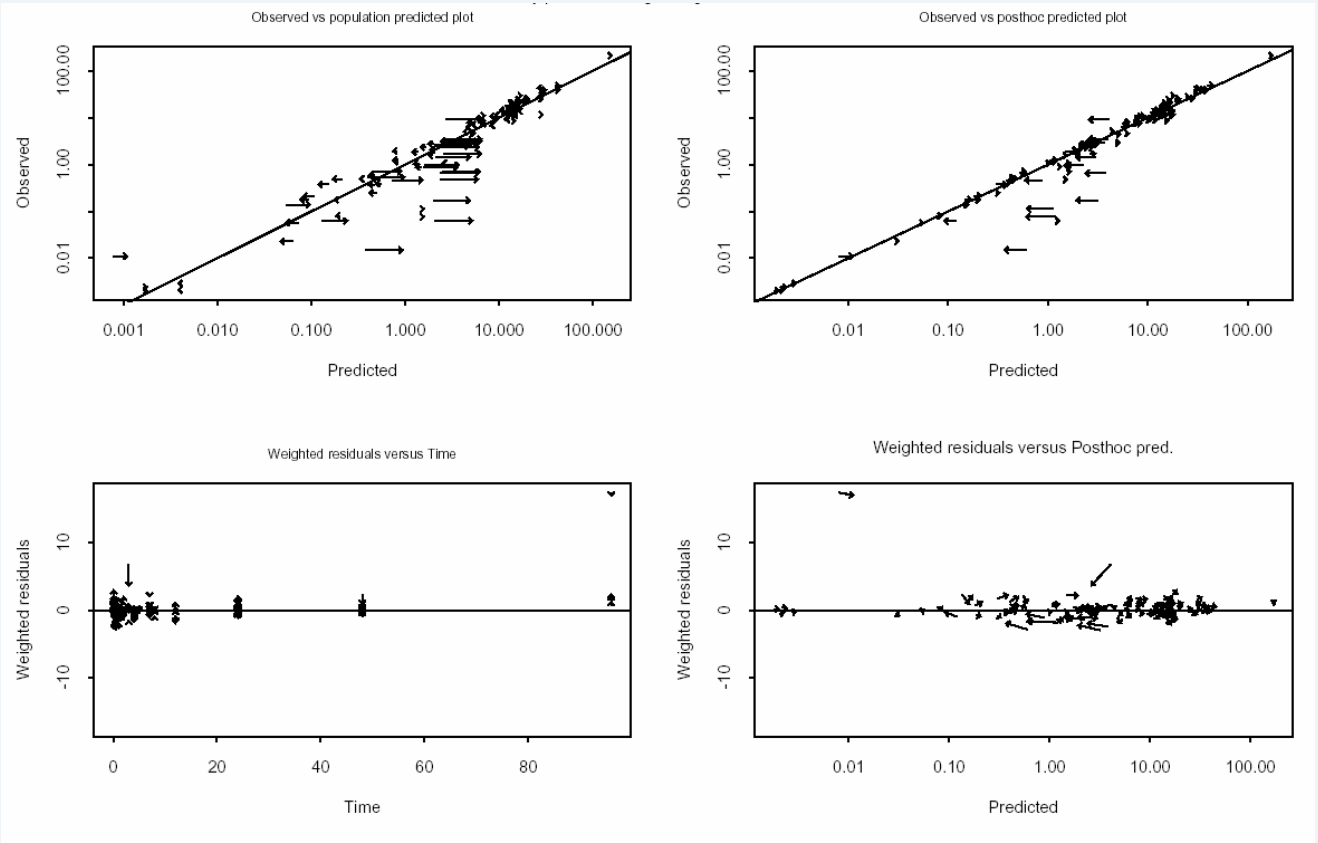
Overview model building steps [4]

- graphical comparison FOCE INT to FOCE (>5% difference in posthoc pred)



Characterisation final model

- bootstrap
  - still unstable (10% succesful covar; 60% succesful runs)
  - but ...
    - bimodality largely disappeared (shoulder-like)
    - 4 standard errors larger than 0.69 on log scale (expKa,D1,monkQ3) (etas including zero)
- simulations from covariance matrix of estimates
  - mean of simulations coincides with population prediction
- condition number ~ 10000
  - one correlation higher than 0.9: 0.92 between Q4 and V4
- allometric exponent clearance rather extreme
  - ~ 0.5 instead of ~0.75

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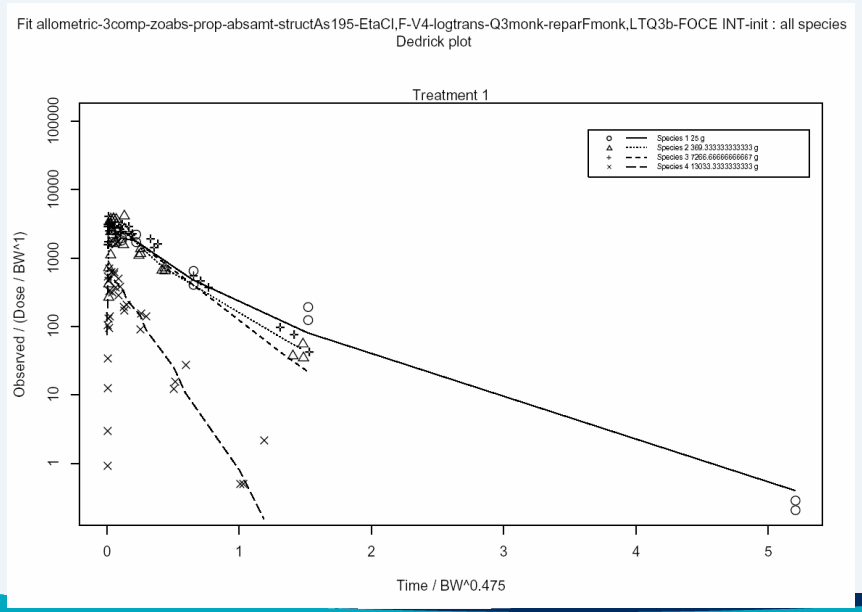
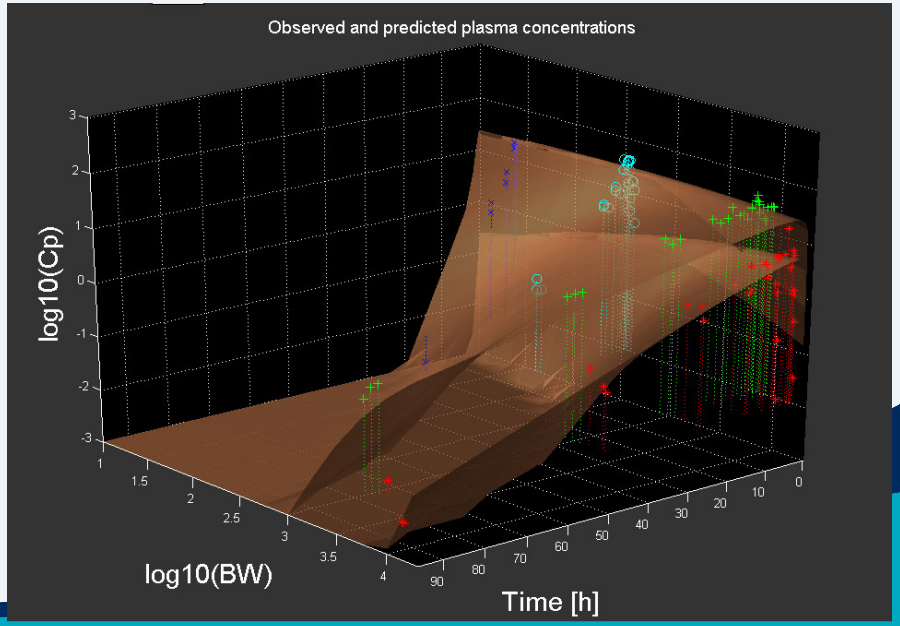
Conclusion

- allometric nonlinear mixed effects modeling also possible with limited PK datasets available at the end of drug discovery
- resource requirements too large (~ 0.1 FTE) for routine application

Discussion points

- violation of multivariate normality assumption justifiable?
  - as explanation of difference between theta prediction and median of simulation
- graphical comparison FOCE w/o INT
- explicit correlation V2 and Q3
- alternative to Dedrick plot

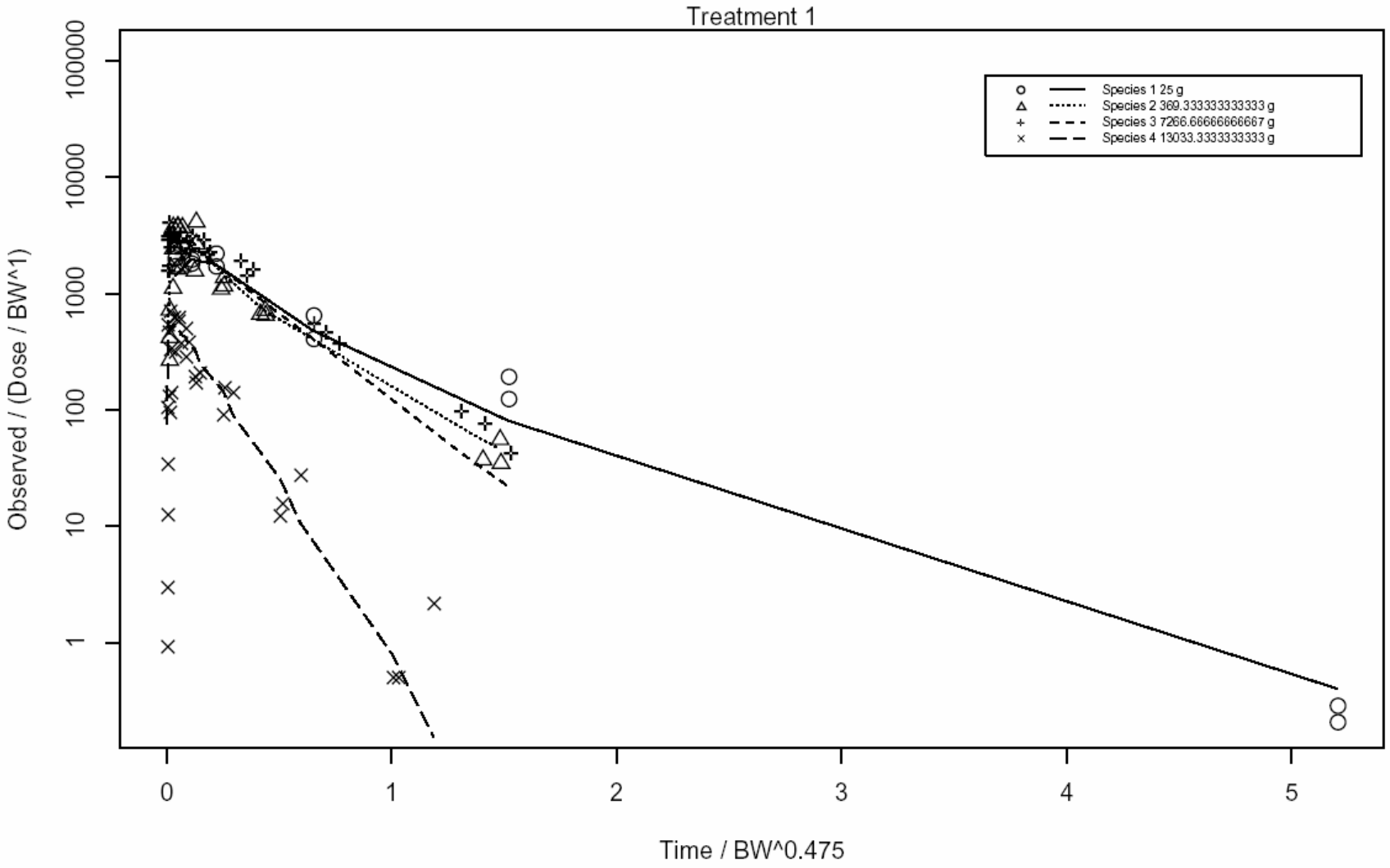


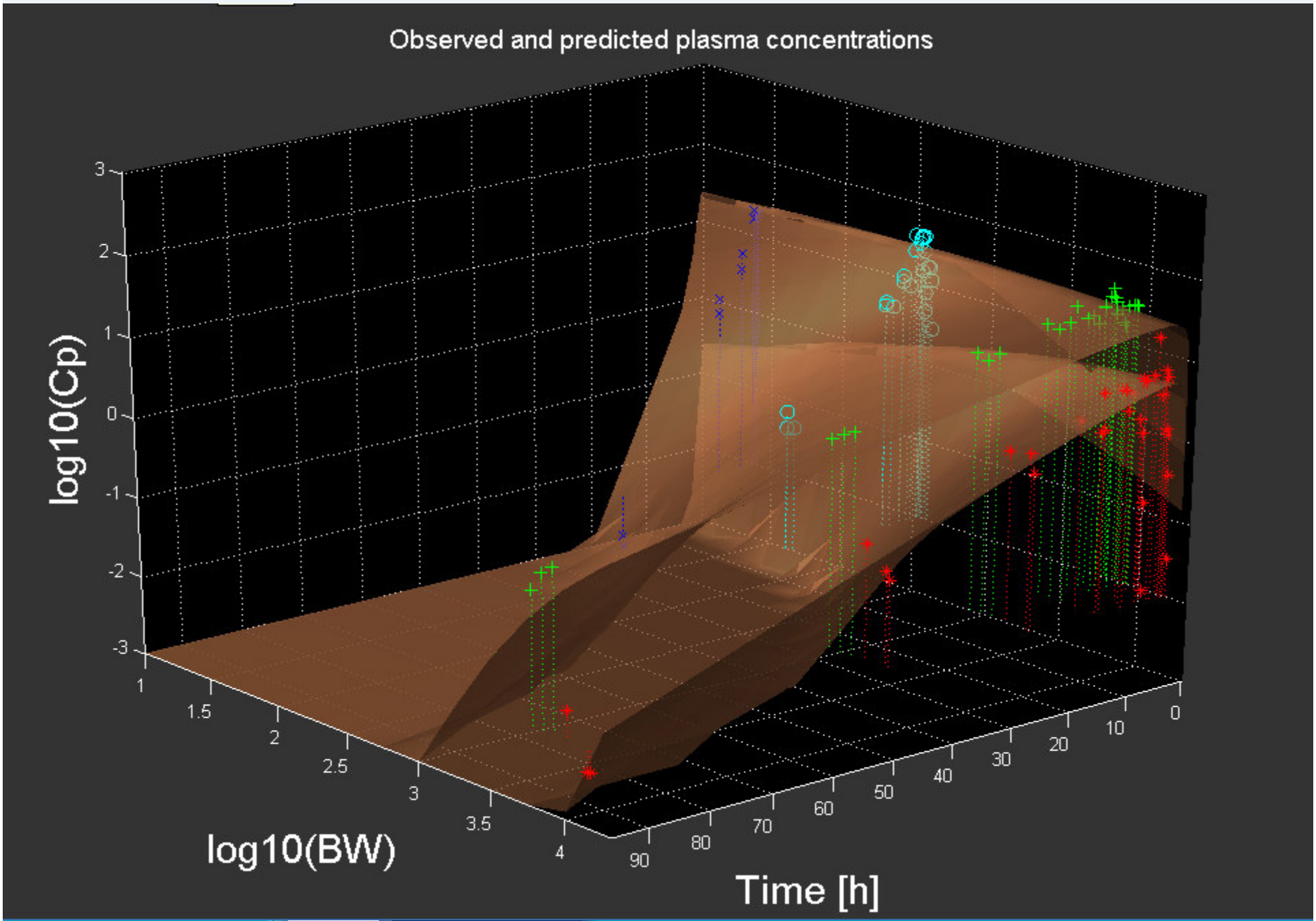


Backup slides

- Dedrick plot
- 3D with model
- standard GOF plots

Fit allometric-3comp-zoabs-prop-absamt-structAs195-EtaCl,F-V4-logtrans-Q3monk-reparFmonk,LTQ3b-FOCE INT-init : all species
Dedrick plot




Observed and predicted plasma concentrations
log10(Cp)
3
2
1
0
-1
-2
-3
log10(BW)
1
1.5
2
2.5
3
3.5
4
Time [h]
0
10
20
30
40
50
60
70
80
90

Allometric model FOCE with interaction
Outliers removed with threshold: 5