Setting the scene

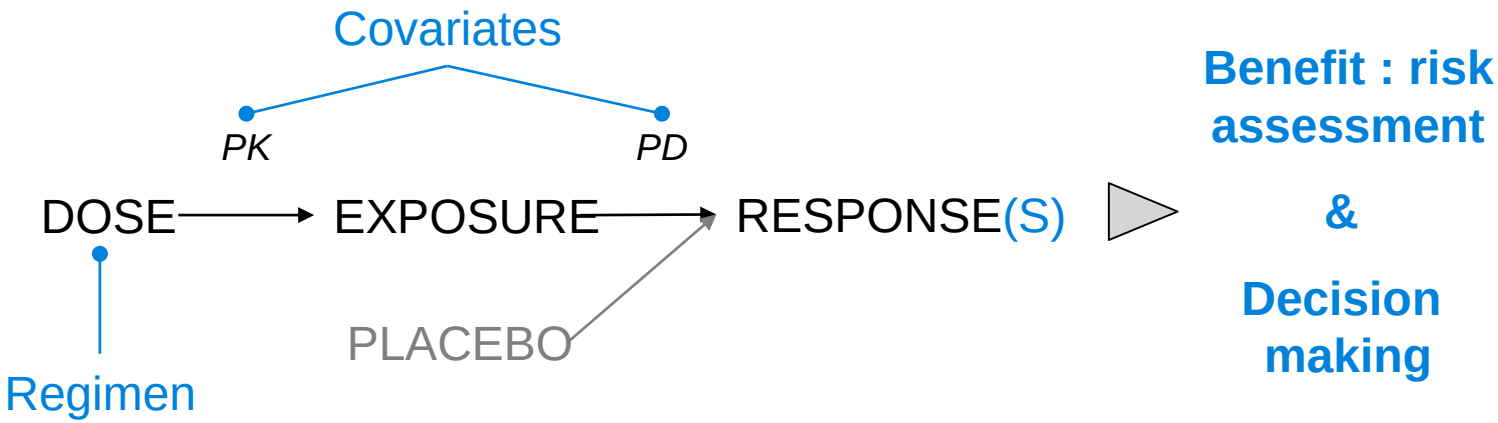
Clinical Pharmacology

Science that studies the characteristics, effects, reactions and uses of drugs. Notes: it spans from FiH to market access.

To describe these relationships, we use models.

Aims of Clinical Pharmacology

"The right dose for the right patient"



To describe this, we use deterministic models

To support this, we use statistic models

Pharmacometrics as a discipline

‘Pharmacometrics’[1] has emerged as a discipline thanks to the introduction of a new tool designed to address the *specifics needs* of clinical pharmacology.

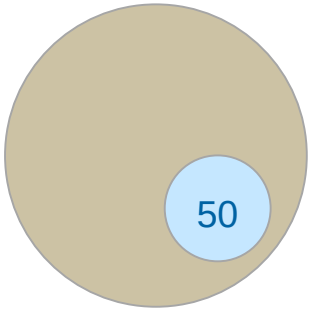
NONMEM was created in the 70’s by L. Sheiner and S. Beal.

- Bottom-up approach (using prior knowledge)
  ⇨ towards more mechanistic models
- Parameter estimates are conditional to the observed data
  ⇨ more Bayesian than frequentist – *in spirit*
- ODE, non-linear **longitudinal** mixed-effects models
  ⇨ PK and disease (progression) modeling

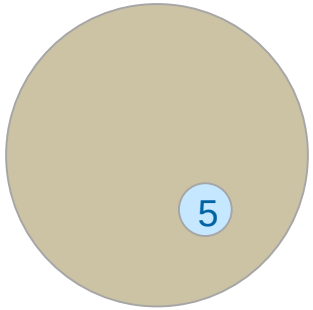
[1]Word used for the 1st time in *JPKPD* in 1982.

Pharmacometrics in the OrgCharts

Roche (PMx⊂CP)

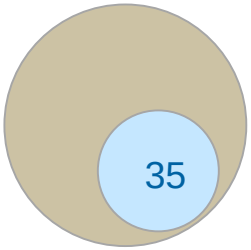


Novartis (PMx⊂Stat)



Sanofi (PMx⊂Stat)

GSK (CPMS)

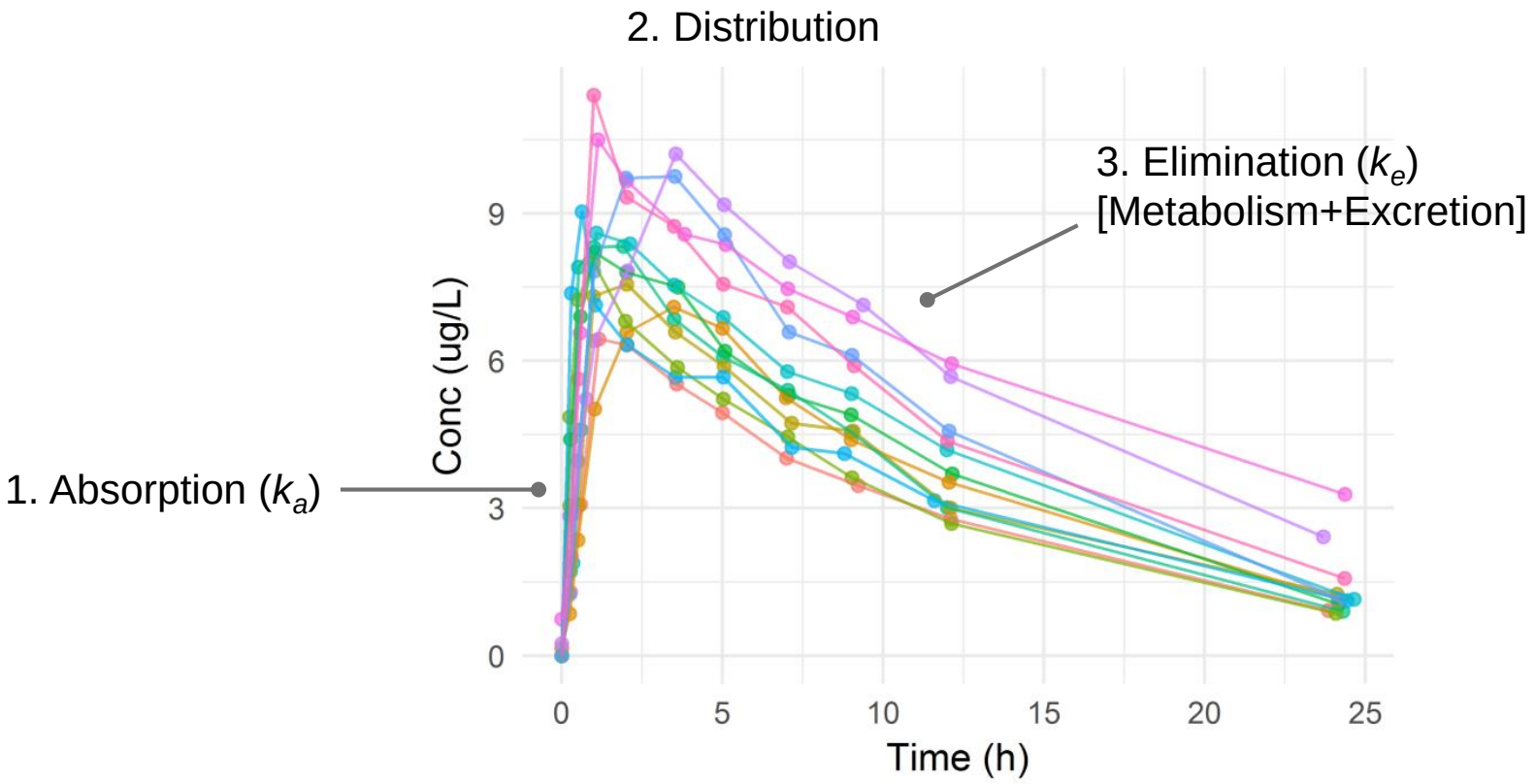


J&J (PMx⊂Stat)

AZ (PMx⊂CP)

Theophylline: *the* PK model example

Serum concentrations of the drug theophylline are measured in 12 subjects over a 25-hour period after oral administration[1].



[1]Pinheiro and Bates (1995).

Theophylline: a PK model example

Deterministic (a.k.a. structural) model

$$\begin{cases} \dfrac{dM}{dt} = k_a A - k_e M & M(0) = 0 \\ \dfrac{dA}{dt} = -k_a A & A(0) = D \end{cases}$$

$A(t)$ is the amount of drug at absorption site (*e.g.* vein)

Concentration at t:

$$m(t) = \frac{M}{V} = \frac{k_a D}{V(k_a - k_e)}\left[\exp(-k_e t) - \exp(-k_a t)\right]$$

$$k_e = \frac{CL}{V}$$

CL: clearance

V: volume of distribution

Theophylline: a PK model example

Statistical model

Based on the observations, we estimate the typical values of $\theta = (k_a, CL, V)$ and how they vary in the population of subjects.

$$Y_{ij} = m(t_{ij}, \theta_i) + \varepsilon_{ij} \qquad \varepsilon_{ij} \sim N(0, \sigma^2)$$

$$m(t, \theta_i) = \frac{k_{ai} D_i}{V_i (k_{ai} - \frac{CL_i}{V_i})} \left[\exp(-\frac{CL_i}{V_i} t) - \exp(-k_{ai} t) \right]$$

$$k_{ai} = \exp(\theta_1 + \eta_{1i})$$

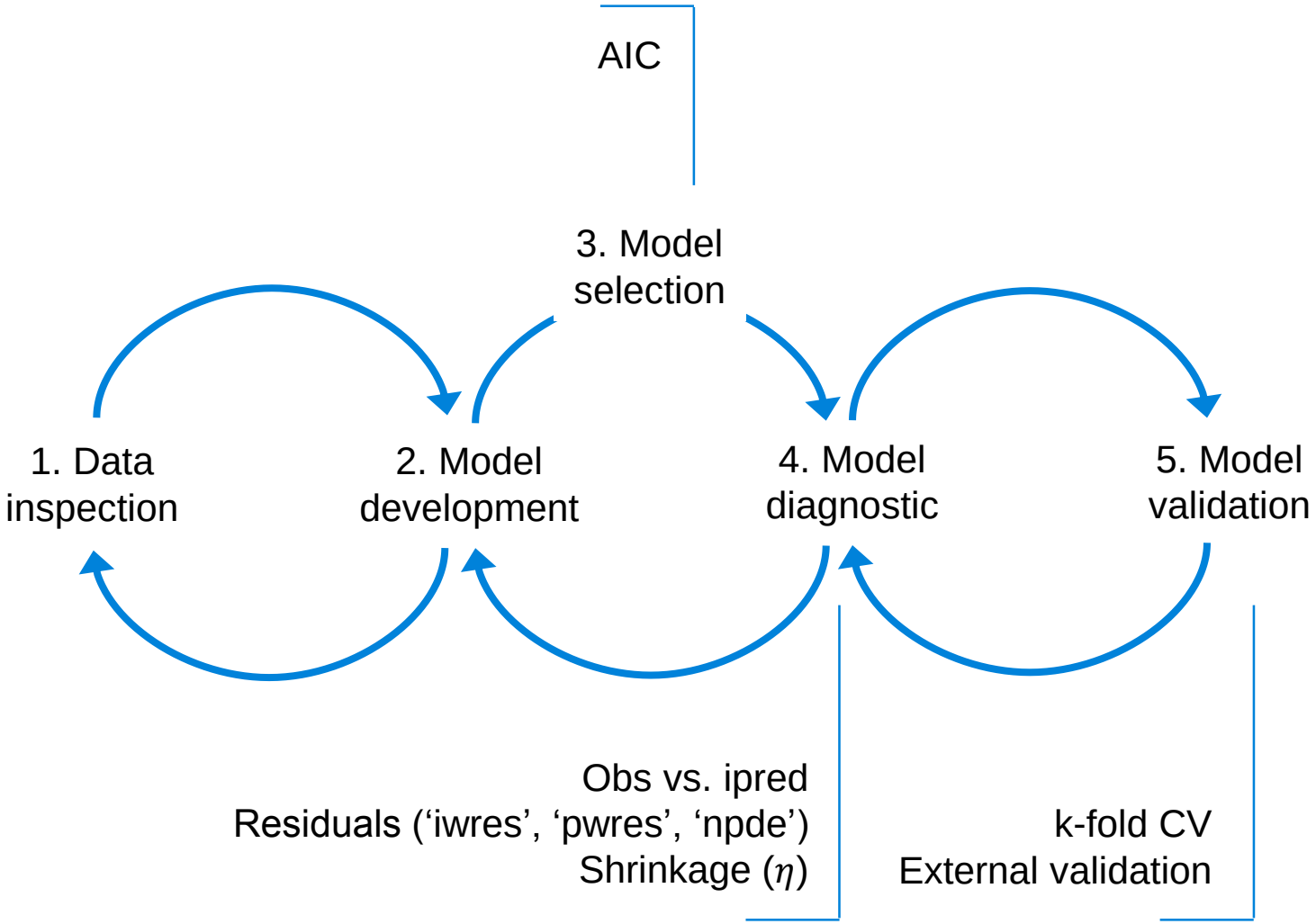
$$V_i = \exp(\theta_2 + \eta_{2i})$$

$$CL_i = \exp(\theta_3 + \eta_{3i})$$

$$\eta_i \sim MVN(0, \Omega)$$

Enforced positivity,
log-normal distribution

Model building



R packages to fit NLME (ODE) models

Package	nlmeODE	FME
Likelihood estimation	2-steps likelihood approxim[1]: - Penalized non-linear least squares (PNLS) - Linear mixed-effect (LME)	MCMC sampling
Main authors	J. Pinheiro, D. Bates, C. Tornøe[2]	K. Soetaert, T. Petzoldt[3]
Maintenance	Minimal (2004)	Active (2016)
Model diagnostics	Basic	Very basic
Model validation	None	None

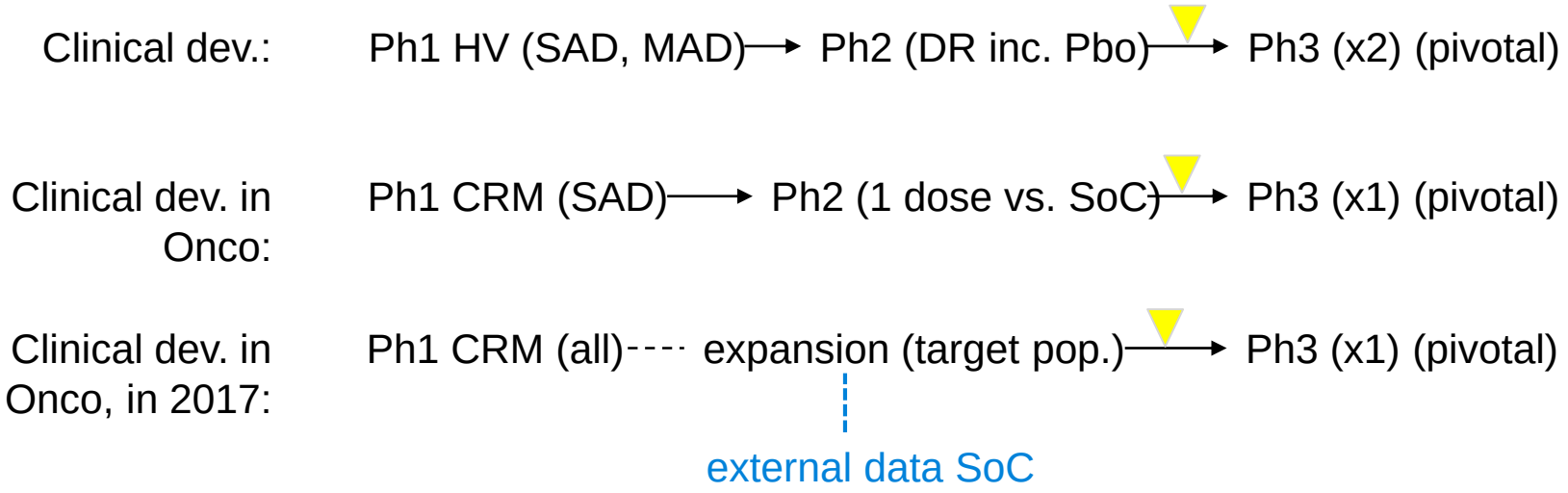
Solution 1: Work out the analytical solution of the ODE and use R packages with better GoF/model qualification suit (*e.g.* nlme, saemix[4])

Solution 2: Use other tools (*e.g.* Monolix, NONMEM)

[1]Lindstrom and Bates (1990) Biometrics; [2]Tornoe *et al*. (2004) CMPB; Soetaert and Petzoldt (2010) JSS;
[4]Comets *et al.* (2011) PAGE meeting.

ITT5

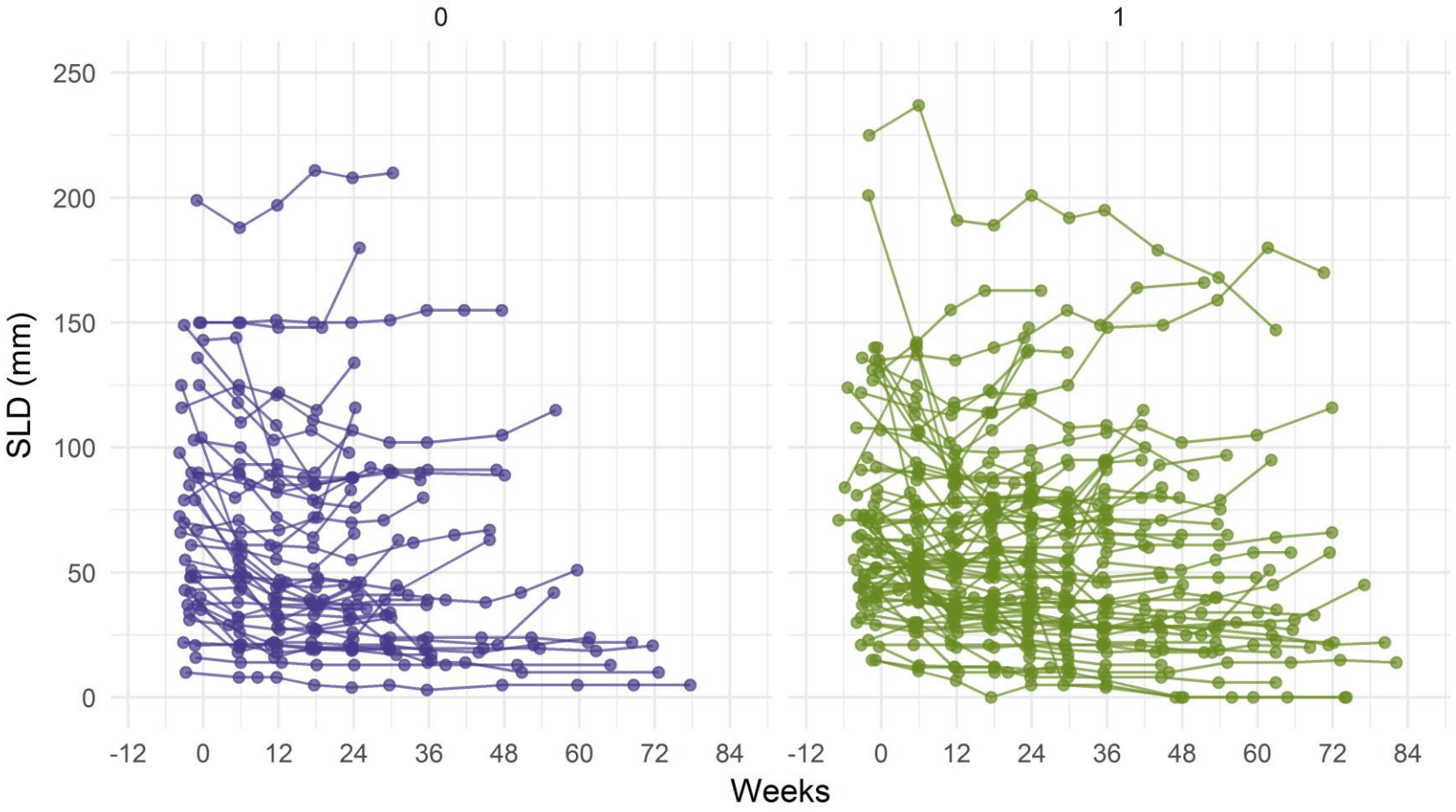
Motivation: Clin dev in Oncology



In solid tumors, decision to initiate Ph3 activities are typically based on tumor size data.

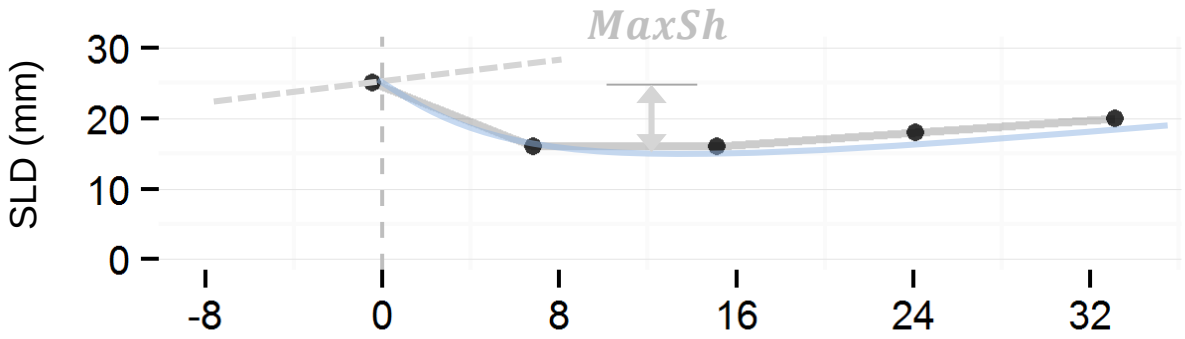
▼ Key investment point

Tumor size (SLD) data



Tumor size dynamics

$$\frac{dY}{dt} = aY - bY \cdot \exp(-\lambda t) \quad (1)$$



- Tumor size ratio at a given date or Maximum shrinkage
- Time to (re)growth or time below threshold
- Resistance and/or Tumor growth rate
- TS at baseline

Tumor size dynamics – structural models[1]

(1) $Y(t) = Y_0 \cdot \exp(-dt) + gt$

(2) $Y(t) = Y_0 \cdot (\exp(-dt) + \exp(gt) - 1)$

(3) $Y(t) = Y_0 \cdot \exp(-dt) + gt + ht^2$

(4) $\frac{dY}{dt} = a - bY \Leftrightarrow Y(t) = \frac{b}{a} + \left(Y_0 - \frac{b}{a}\right) \cdot \exp(at)$

(5) $\frac{dY}{dt} = aY \cdot (Y_0 b - Y)$

(6) $\frac{dY}{dt} = aY - bY \cdot \exp(-\lambda t)$

(7) $\frac{dY}{dt} = aY \cdot \log\left(\frac{\theta}{Y}\right) - bY \cdot \exp(-\lambda t)$

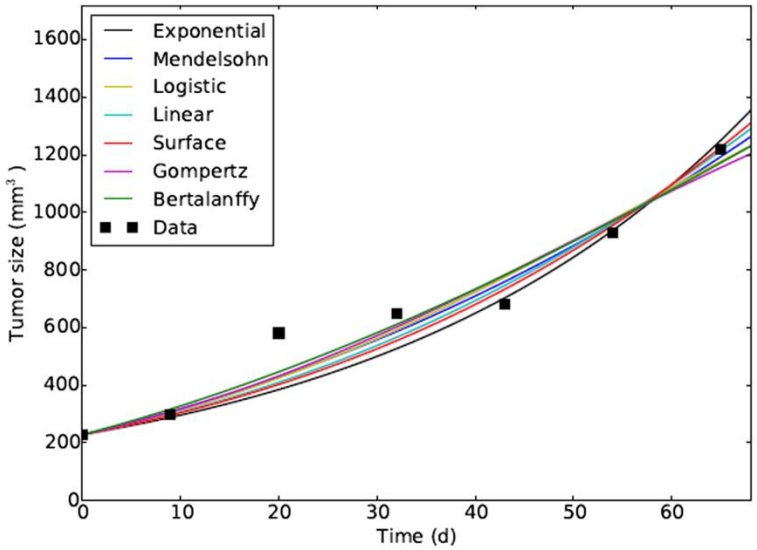
Depending on random effects two (or more) different models may have similar 'performance' (AIC, diagnostic tools).

Yet, these models may lead to different predictions (in particular *w.r.t.* IIV).

Which model should be retained?

[1]Ribba *et al*. (2014) CPT:PSP.

Illustration (1/2) - Murphy *et al*. (2016)[1]



Model	a	b	c	SSR	AIC_C
Exponential	0.0262 /d			54900	69.8
Mendelsohn	0.286 /d	0.616		35100	73.6
Logistic	0.0370 /d	2000 mm^3		39800	74.5
Linear	58.7 mm^3/d	1690 mm^3		41200	74.8
Surface	0.265 mm/d	506 mm^3		44000	75.2
Gompertz	0.279 /d	13900 mm^3	12000 mm^3	40100	88.6
Bertalanffy	0.306 mm/d	0.0119 /d		33700	73.3

Various models lead to AIC within a 4 points range.

[1]Murphy et al. (2016) *BMC Cancer*, 16:163.

Illustration (2/2) - Murphy *et al*. (2016)[1]

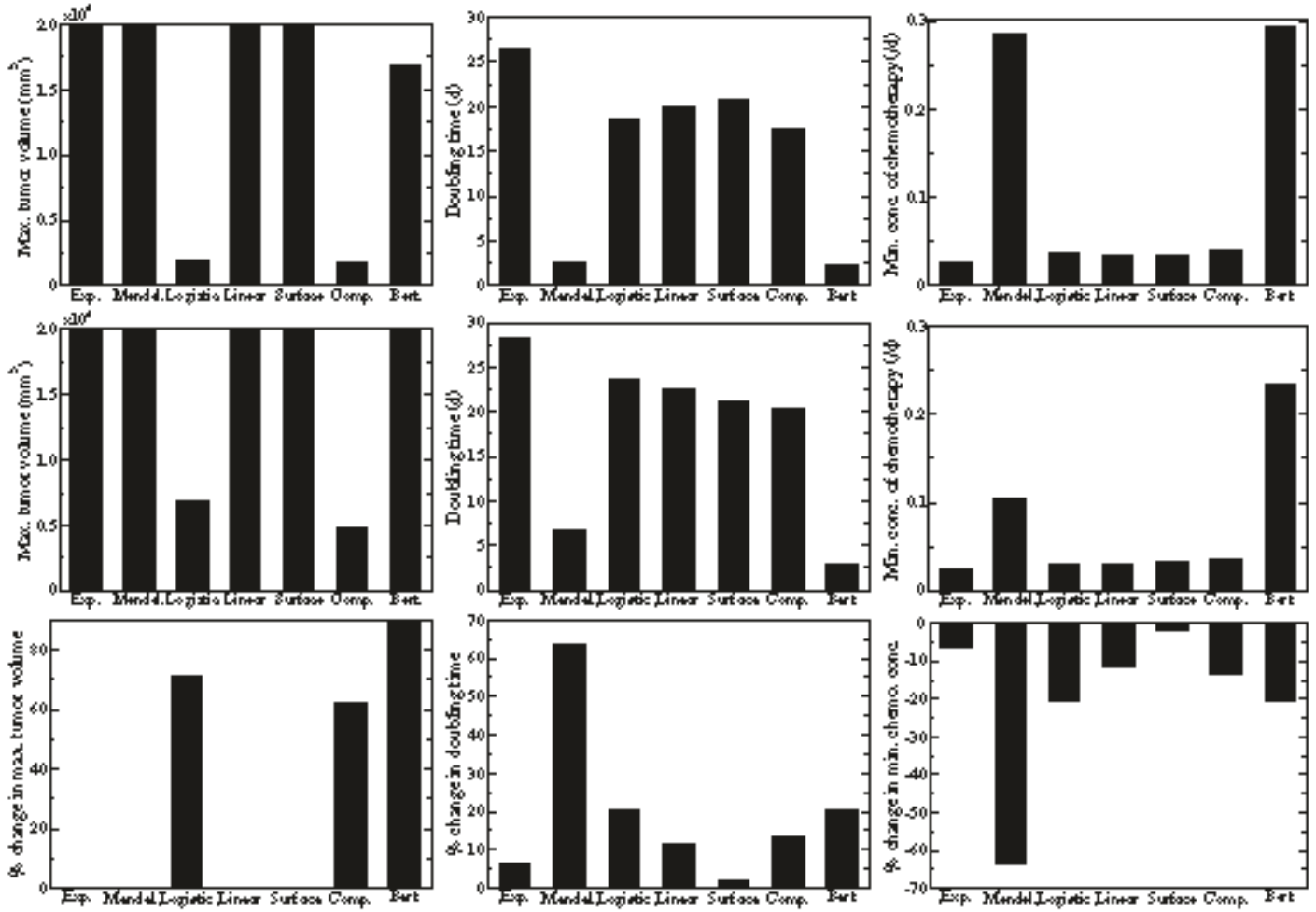


Fig. 4 Estimates of clinically important measurements. Model predictions of the maximum tumor volume (*left*), doubling time (*center*), and minimum concentration of chemotherapy needed for eradication (*right*) based on parameter estimates from the half (*top row*) or the full (*center row*) Worschech data set. The bottom row shows the percent change in each of the predictions when the full data set is used rather than the truncated data set.

[1]Murphy et al. (2016) *BMC Cancer*, 16:163.

Doing now what patients need next