Modeling Drug Effects and Resistance Development on Tumor Growth Dynamics

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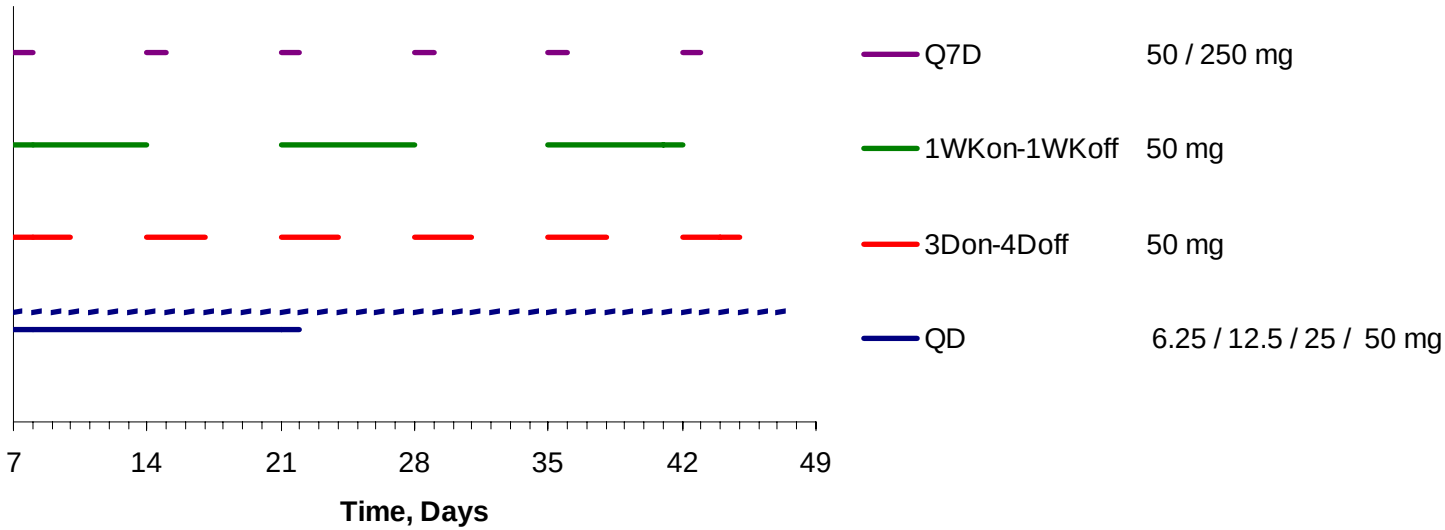
PHARMACEUTICAL RESEARCH & DEVELOPMENT

Outline

- Xenograft data used
- Simeoni and KPD model
- PKPD model implementation
- Results and simulations
- Conclusions

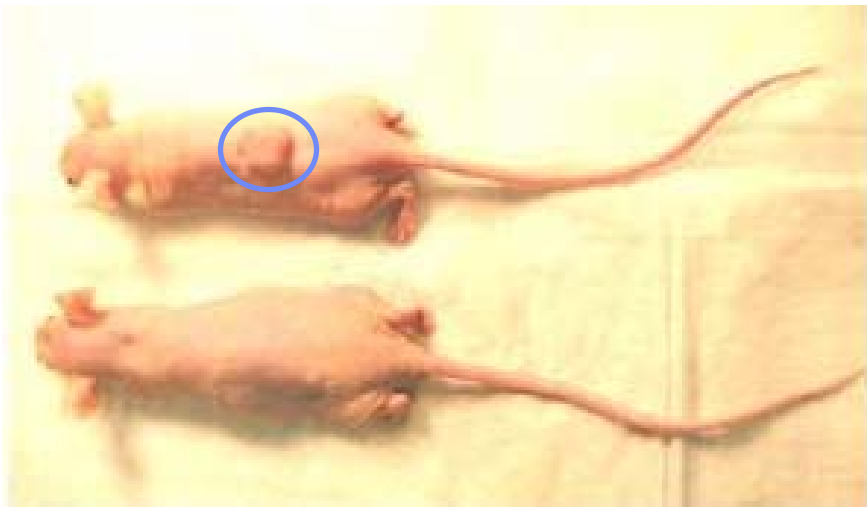
Tumor Xenograft data

- Overall sample size
  - Animals: 347 (nude mice)
  - Measurements: 1729
- Tumor inoculation on day 0 (U-87MG glioblastoma)
- First dose and observations at day 7 or day 9
- Oral Dosing Regimens:



Animal model used

- Animal model
  - Human tumor xenograft animal model:
    - human tumor lines
    - implanted in nude mice
  - Measure tumor weight/volume

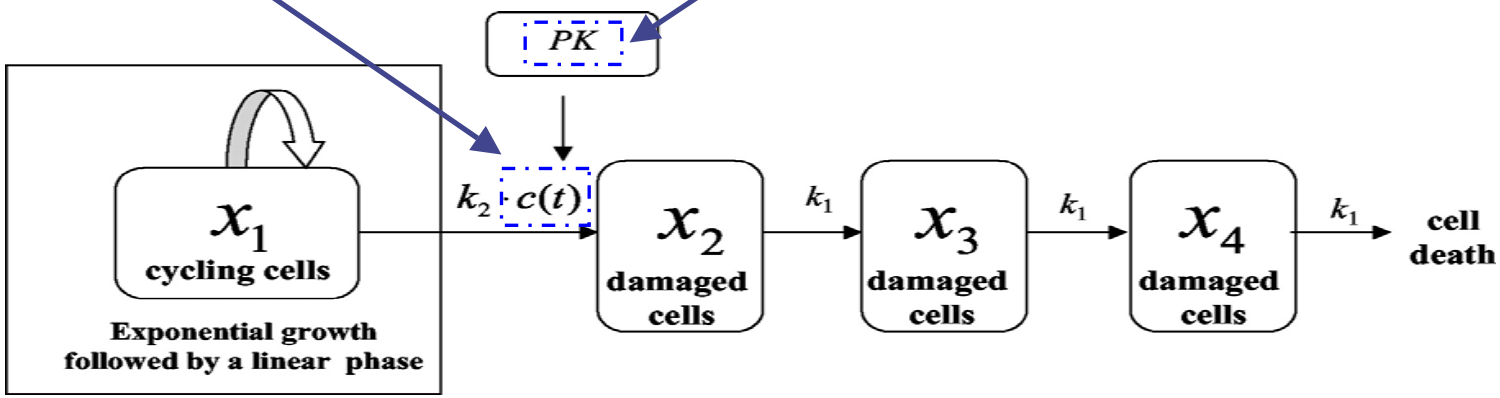


PKPD model used

- Model published by Simeoni. [1]
  - Mechanistic model
  - Allows:
    - Re-use in other anti-tumor compounds
    - Link: dosing - tumor growth
  - Adaptations to the model

Resistance term

KPD model [2]

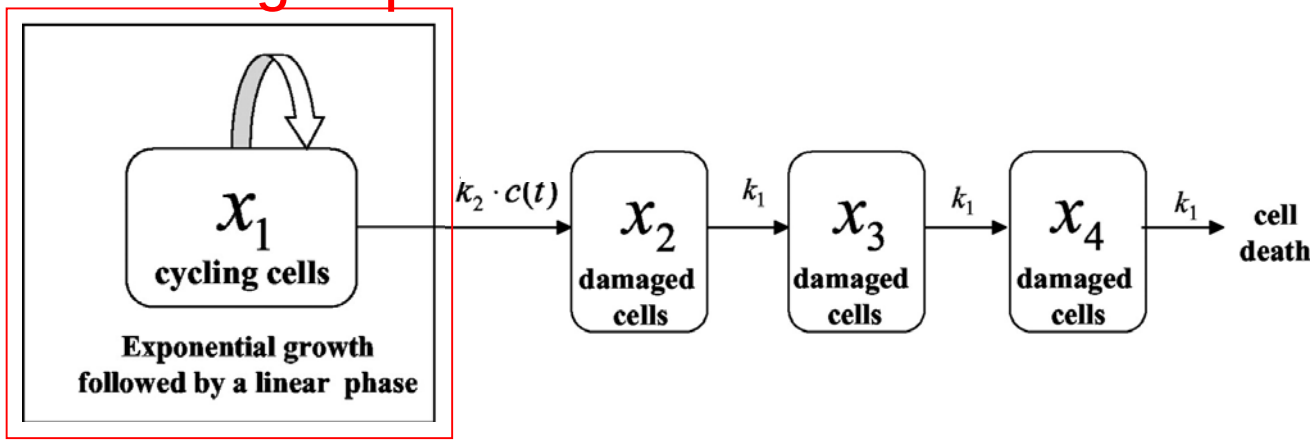


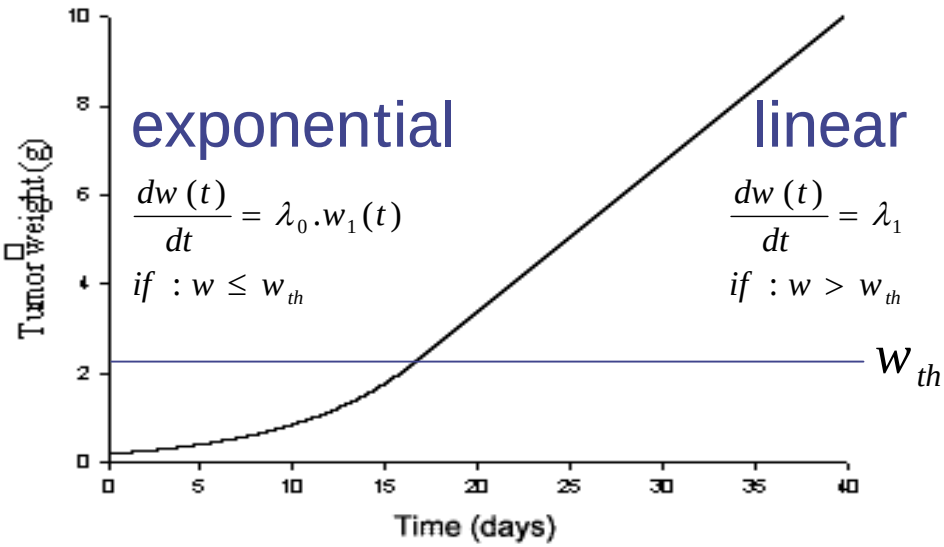
[1] Simeoni et al. CANCER RESEARCH, 2004

[2] Jacqmin et al. JPKPD, 2007

Simeoni model

Control group

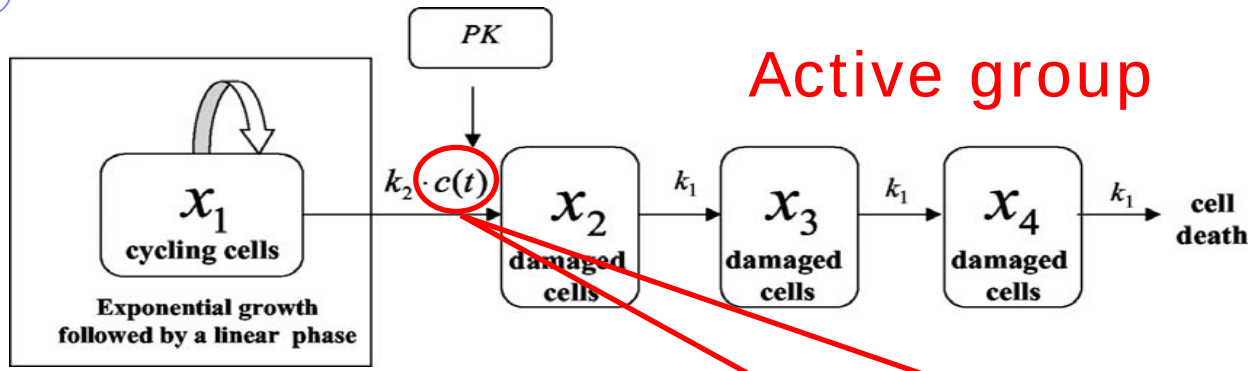




$$\frac{dw(t)}{dt} = \frac{\lambda_0 \cdot w(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\Psi}\right]^{1/\Psi}}$$

$$w(0) = w_0$$

Simeoni model (cont.)



$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\Psi}\right]^{1/\Psi}} - k_2 \cdot c(t) \cdot x_1(t)$$

$$\frac{dx_2(t)}{dt} = k_2 \cdot c(t) \cdot x_1(t) - k_1 \cdot x_2(t)$$

$$\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)]$$

$$\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)]$$

- KPD model used
- Resistance equation

Simeoni endpoints

- At equilibrium:

$$\frac{\lambda_0 . x_1(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}.w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 . c(t) . x_1(t) = 0$$

- Threshold Concentration for Tumor Eradication (TCTE):

$$TCTE = \frac{\lambda_0}{k_2}$$

- Threshold Dose Rate for Tumor Eradication PKPD (TDRTE):

$$TDRTE = \frac{\lambda_0}{k_2} \cdot CL$$

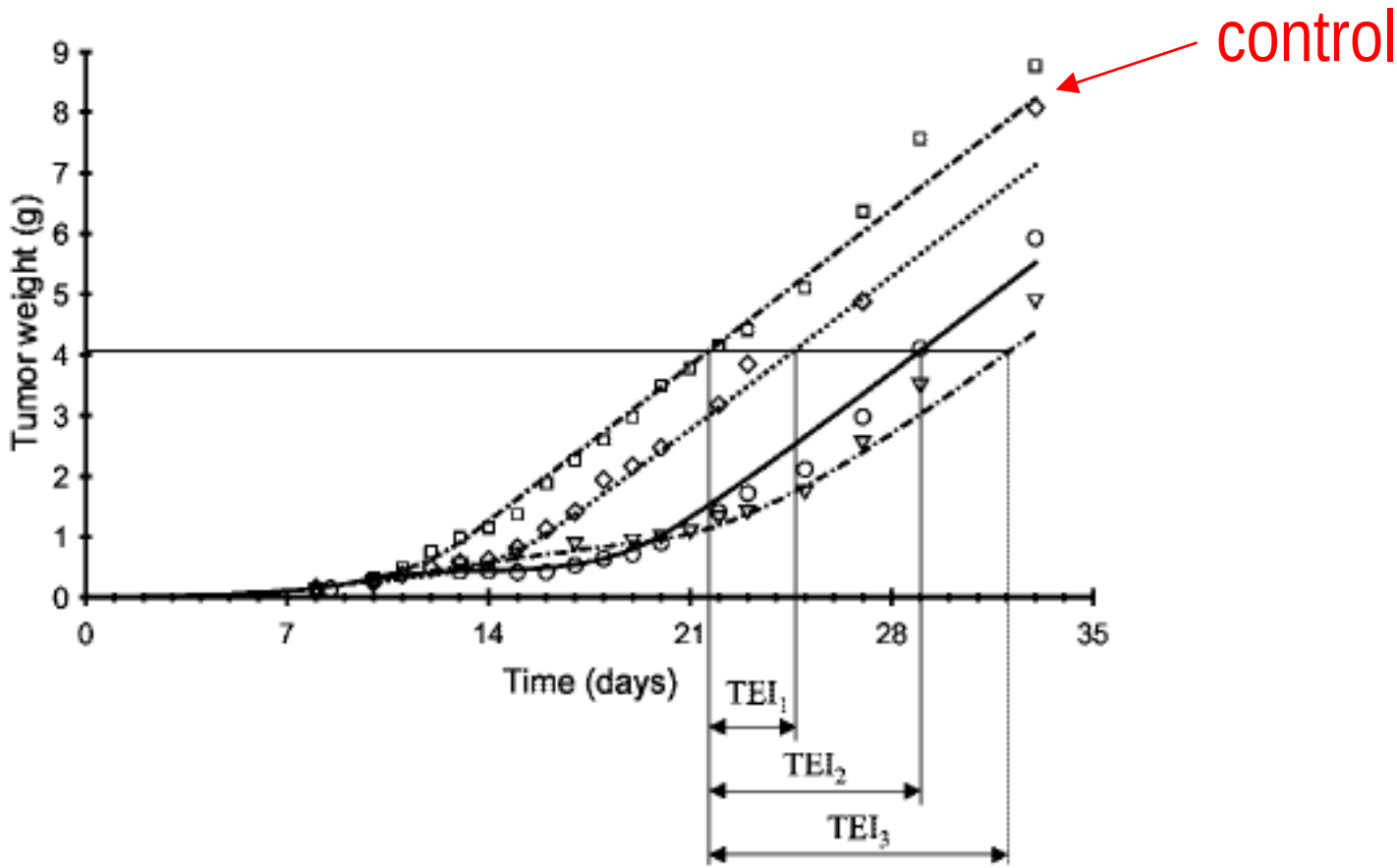
- Threshold Dose Rate for Tumor Eradication KPD (TDRTE):

$$TDRTE = \frac{\lambda_0 . k_{PD}}{k_2}$$

Kpd=CL/V

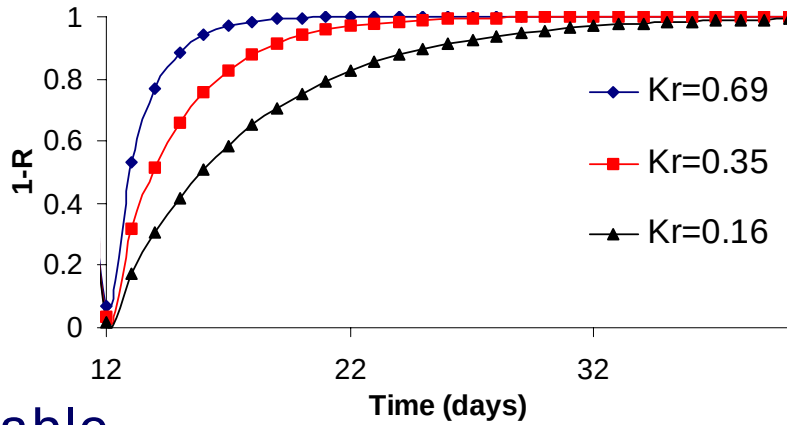
Simeoni endpoints (cont.)

Time Efficacy Index during linear growth:



Implementation of the model

- Population approach of the model:
  - One model amongst the different dosing regimens
- Resistance term incorporated
  - If $t \leq t_{lag}$: no resistance
  - If $t > t_{lag}$: $R = \exp^{-k_r.(t-t_{lag})}$

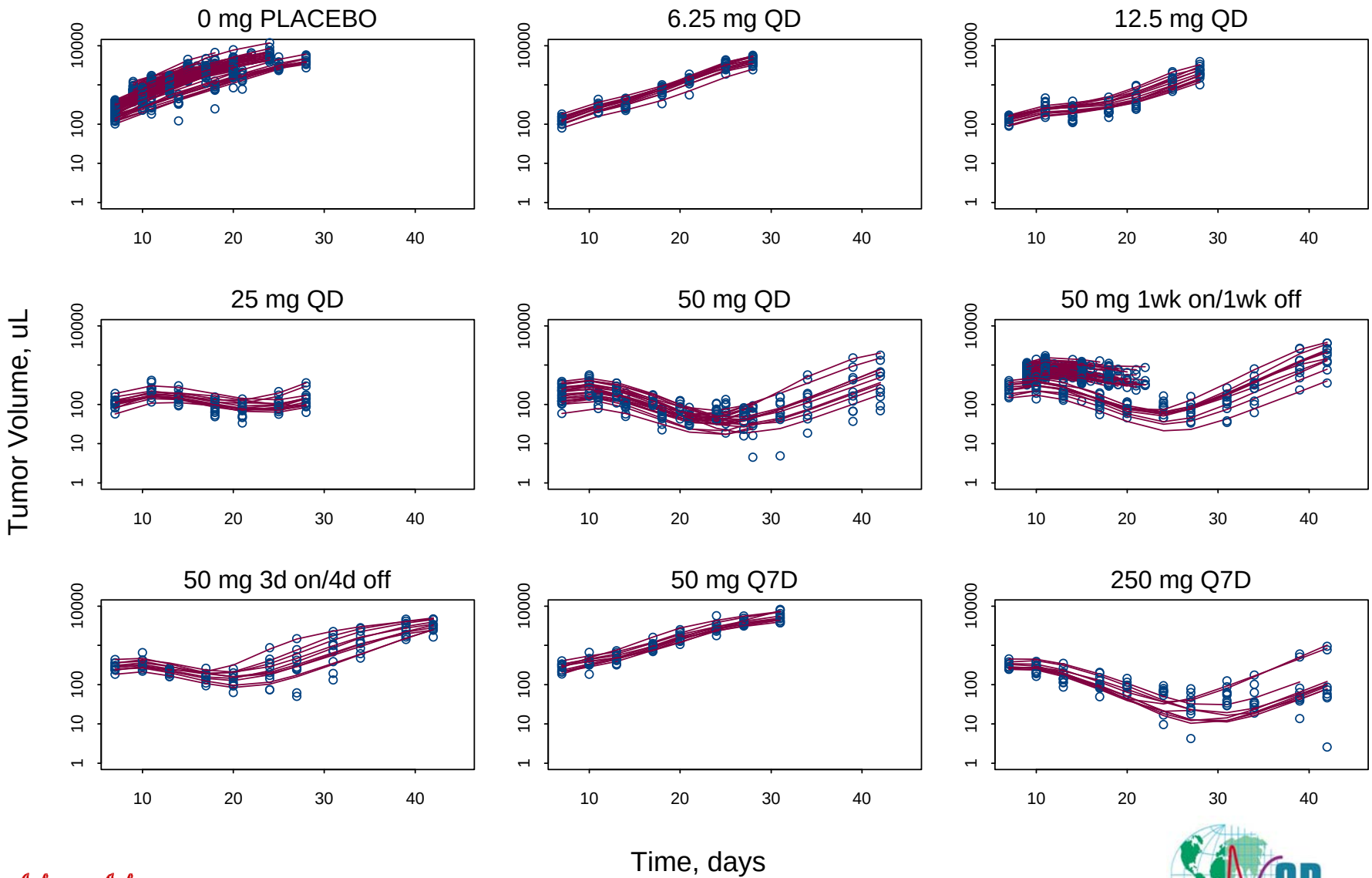


- KPD model
  - Very limited PK of mice available
  - PK in the rats non-linear

dose → A → K_{pd}

=> Growth rate decreased by: K_2 . K_{pd} . R . X(1)

Individual predictions - oral dosing



Parameters estimates : U87GM-cells

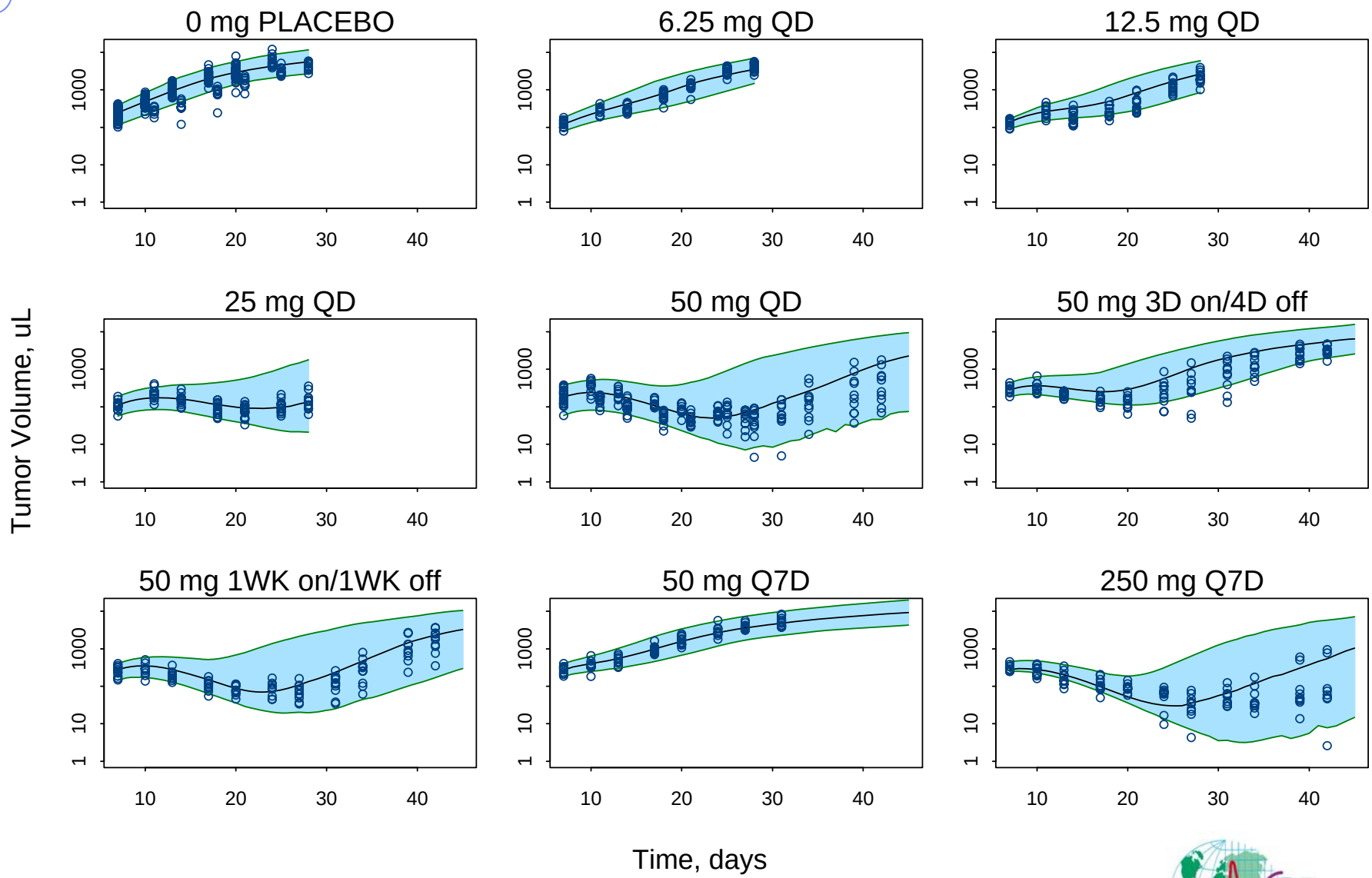
	Mean	SE	BAV
λ_0 (day^{-1})	0.23	5%	17%
λ_1 ($\mu L.day^{-1}$)	323	2%	45%
k_1 (day^{-1})	0.389	6%	9%
k_2 ($day^{-1}.mg^{-1}$)	0.021	10%	/
k_{PD} (day^{-1})	0.993	14%	90%
T_{Lag} (day)	11.9	3%	/
k_R (day^{-1})	0.78	54%	52%

- Threshold Daily Dose for Tumor Eradication:
  11 mg (95% CI: 9 - 12 mg)
- Average time for a cell to die (n/k1):
  8 days (n the number of damage stages)

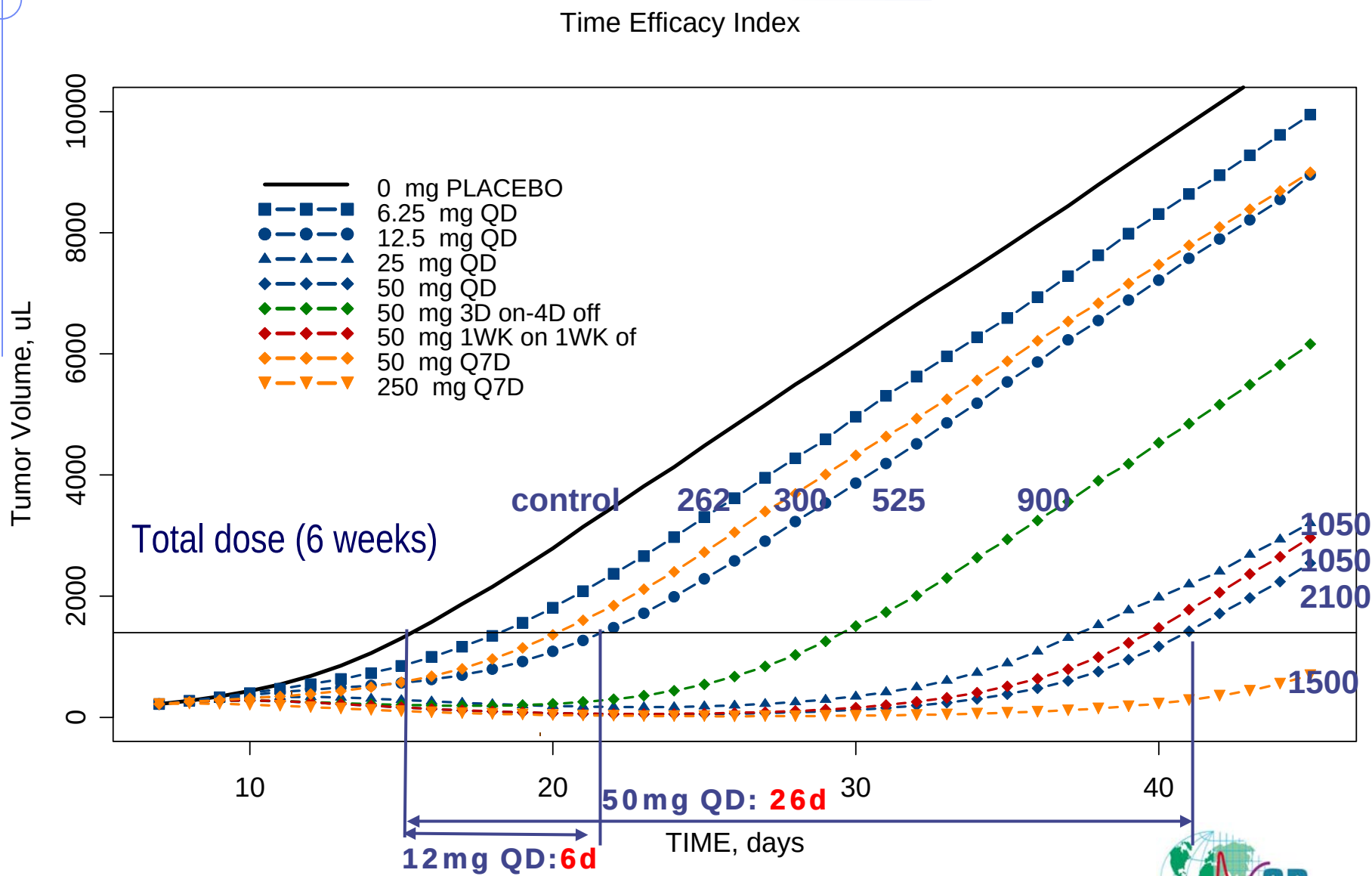
BAV: Between Animal Variability

SE: Standard Error on the estimate

Visual predictive check

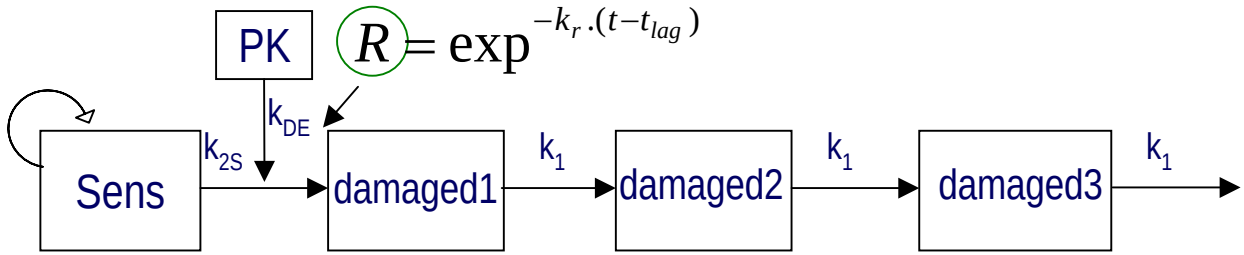


Time-efficacy index

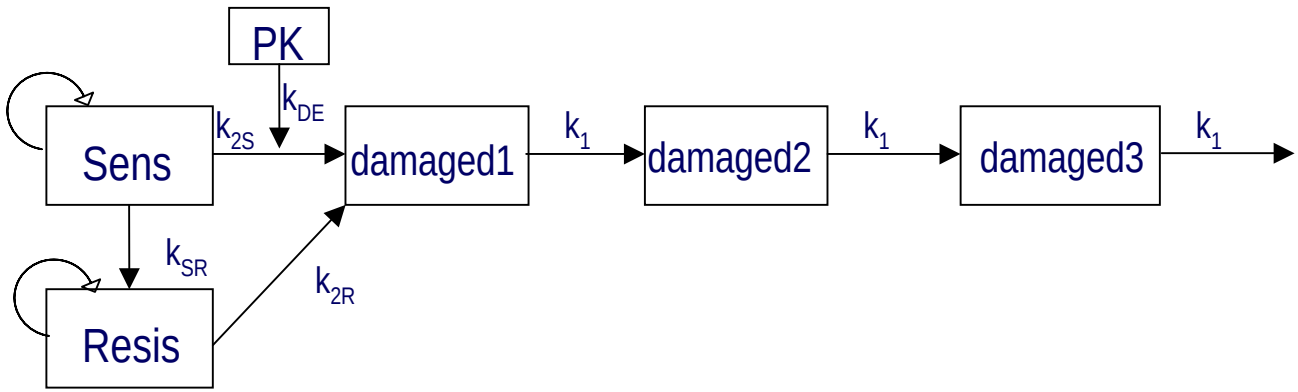


Comparison resistance models

- Empirical resistance



- Mechanistic resistance



Conclusions

- Data is very well described by the model
- KPD model can be used in absence of PK data
- Useful parameters can be derived:
  - Time efficacy index
  - Effective dose (if no resistance)
  - Time when resistance shows up
  - Time needed for a cell to die
- Model will be used to optimize future experiments