


**Tumor Growth Inhibition Models**

PD43



## Overview

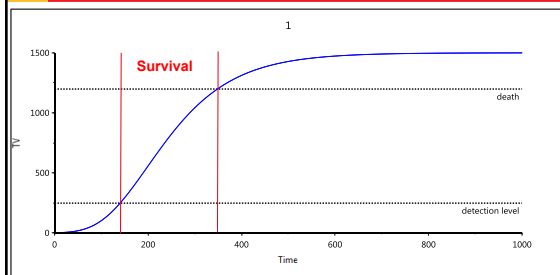
- Tumor Growth Modeling
- Preclinical models
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  - Modeling Strategy
  - Models of Tumor Growth/Kill
    - Gompertz
    - Simeoni
    - Jumbé
- Demo
- Summary
- Q&A
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  - NONMEM-2-PML

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## Tumor Growth Modeling: Survival



Gompertz:  $TV = TV_0 \cdot e^{\frac{A}{\alpha}(1 - e^{-\alpha t})}$

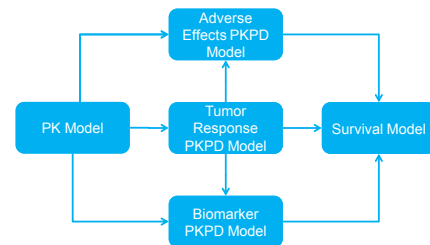
$TV_0$ : Initial Tumor Volume  
 $A$ : initial growth rate constant  
 $\alpha$ : deceleration rate constant

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## Tumor Growth Modeling: Clinical Scenario

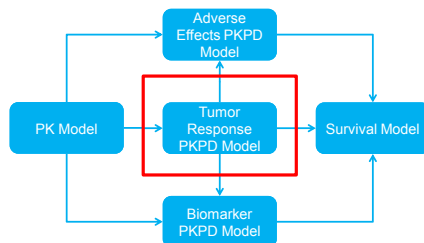


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## Focus of our Session: Tumor Response PKPD



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## Preclinical Scenario: Xenografts

- Xenograft models are in vivo models to establish antitumor activity of compounds in drug discovery process
  - Human tumor fragments are subcutaneously implanted into the flank of nude or severe combined immunodeficient mice
  - Xenograft mice develop human solid tumors
  - Once the tumors have reached a predefined size (~100-300 mm<sup>3</sup>), the mice are randomized to different treatment groups (one placebo group)
  - Doses are given and tumor size is measured over a period of time
- Tumor dimensions are measured with caliper
  - Tumor volume estimated from length and width

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## Preclinical Models: Typical Modeling Strategy

- Pharmacokinetics
  - Only Satellite PK measurements in study
  - PK part is frozen in PK/PD model
- Tumor dynamics is modeled in two stages
  - Tumor aggressiveness and resistance estimated on control group
  - Drug induced decay estimated on all treatment groups
    - Rank order compounds on antitumor potency
    - Sensitivity analysis performed on PD parameters
- Simulations
  - Testing of new dose levels and regimens
  - Eventually scale to first dose in human

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## Models of Tumor Growth/Kill: Objective

- Characterize tumor growth/kill using three different models:
  - Gompertz - TGI
  - Simeoni
  - PD43: Jumble
- Find estimates for:
  - Tumor growth rate
  - Tumor kill rate

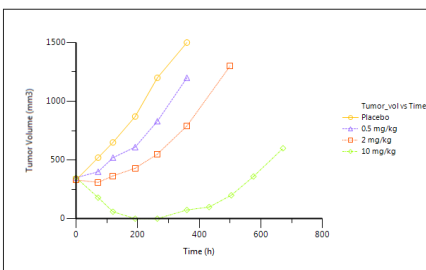
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## PK32: Exploratory Data Analysis

- Linear plot of tumor volume versus time



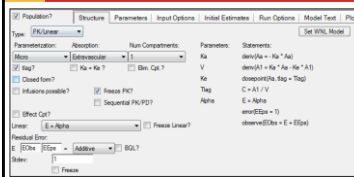
Gibaldi &amp; Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 3rd Edition, Swedish Pharmacology Press (2015)

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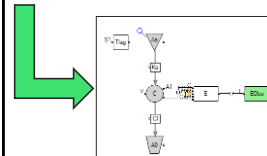
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## Building Gompertz Model: Built-in Options



Need to change effect equation



No changes in graphical model

```

dE/dt = E * (alpha - beta * ln(E/E0))
dE/dt = E * (alpha - beta * ln(E/E0)) - gamma * C(t) * E
dE/dt = E * (alpha - beta * ln(E/E0)) - gamma * C(t) * E

```

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## Building Gompertz Model - textual

$$\frac{dE}{dt} = E \cdot \left( \alpha - \beta \cdot \ln \left( \frac{E}{E_0} \right) \right)$$

Gompertz model

$$decay = \gamma \cdot C(t) \cdot E$$

Drug induced decay

$$\frac{dE}{dt} = E \cdot \left( \alpha - \beta \cdot \ln \left( \frac{E}{E_0} \right) \right) - \gamma \cdot C(t) \cdot E$$

combined model

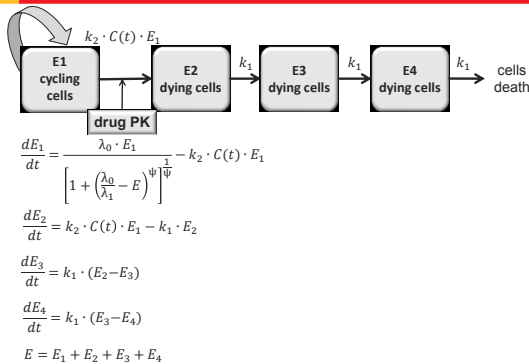
```

test()
## EE Model: EE
deriv(dE) = E * (alpha - beta * ln(E/E0))
deriv(dC) = Ka * Aa - Ka * Aa * A1
C = A1 / V
dcomp(dAa, tlag*tlag, lsdosim = AaDose)

## Tumor Growth Inhibition Model: EE
# Gompertz Equation with drug induced decay
deriv(dE) = E * (alpha - beta * ln(E/E0)) - gamma * C * E
# Initial tumor volume
E0 = 300

## Fixed effects for the PK model - all parameters frozen
frozen(dE) = 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 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1846, 1847, 1848, 1849, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 
```

## Simeoni Model



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## Simeoni Model in PML

```

test() {
  ## PK Model ##
  deriv(Aa = Ka * Aa)
  deriv(A1 = Ka * Aa - Ka * A1)
  C = A1 / V
  dosepoint(Aa, tlag=tlag, idosewr = AaDose)

  ## SE Model ##
  pai = 20
  E = E1 + E2 + E3 + E4
  Inh = (1 + (lambda0/E/lambda1)^pai)^(1/pai)
  deriv(E1 = lambda0 * E1 / Inh - k2 * C * E1)
  deriv(E2 = k2 * C * E1 - k1 * E2)
  deriv(E3 = k1 * (E2 - E3))
  deriv(E4 = k1 * (E3 - E4))
  sequence(E1 = E0)
  error(RSqr = 1)
  observe(RDx = E + Epa)

  ## secondary parameters
  secondary(R0=lambda0/lambda1)
  secondary(Q0=lambda0/K1)
  deriv(ADC=C)
  TEI=k2*ADC/lambda0

  ## fixed effects for PK model - all frozen ##
  fixed(Wa(freeze) = c(, 4.0485, ))
  fixed(V(freeze) = c(, 2.561, ))
  fixed(Wa(freeze) = c(, 0.1439, ))
  fixed(tlag(freeze) = c(, 0.8464, ))

  ## fixed effects for SE model ##
  fixed(lambda0 = c(0, 0.5, ))
  fixed(lambda1 = c(0, 5, ))
  fixed(E0 = c(0, 340, ))
  fixed(K1 = c(0, 0.05, ))
  fixed(K2 = c(0, 0.2, ))

  # segment to switch between exponential and linear growth
  # tumor volume is sum of tumor volumes from all compartments
  # inhibition function - denominator part
  # de for compartment of proliferating cells
  # de for first transit compartment of damaged cells
  # de for second transit compartment
  # de for third transit compartment
  # initialize tumor
  # residual error initially set to 1
  # additive residual error model for effect
}

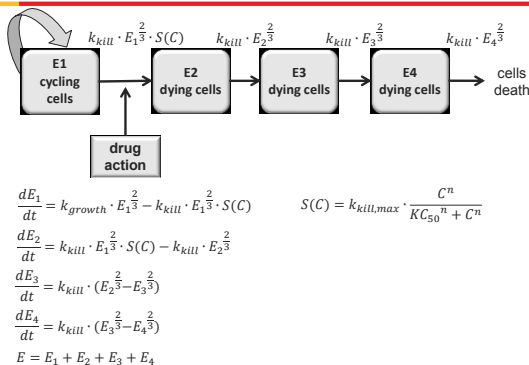
```

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## PD43: Jumbe Model



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## PD43: Jumbe Model in PML

```

test() {
  ## PK Model ##
  deriv(Aa = Ka * Aa)
  deriv(A1 = Ka * Aa - Ka * A1)
  Cp = A1 / V
  dosepoint(Aa, tlag=tlag)

  ## SE Model ##
  Inh = Wmax * (Cp / (KC50 + Cp))
  # Effect should be positive or 0
  E1max(E1,0)
  E2max(E2,0)
  E3max(E3,0)
  E4max(E4,0)
  deriv(E1 = (Rgrow - Inh * Kkill) * E1^(2/3))
  deriv(E2 = (Inh * Kkill * E1^(2/3) - Kkill * E2^(2/3)))
  deriv(E3 = (Kkill * E2^(2/3) - Kkill * E3^(2/3)))
  deriv(E4 = (Kkill * E3^(2/3) - Kkill * E4^(2/3)))
  E = E1 + E2 + E3 + E4
  sequence(E1 = E0)
  error(RSqr = 1)
  observe(RDx = E + Epa)

  ## fixed effects for PK model - all frozen
  fixed(Wa(freeze) = c(, 0.0485, ))
  fixed(V(freeze) = c(, 2.561, ))
  fixed(Wa(freeze) = c(, 0.1439, ))
  fixed(tlag(freeze) = c(, 0.8464, ))

  ## fixed effects for SE model ##
  fixed(Rgrow = c(, 0.01, ))
  fixed(Kkill = c(, 0.1, ))
  fixed(Wmax = c(, 5, ))
  fixed(KC50 = c(, 350, ))
  fixed(E0 = c(, 340, ))

  ## secondary parameters ##
  secondary(TIC = Rgrow * KC50/Kkill * Wmax - Rgrow)

  # tumor static mean drug level
}

```

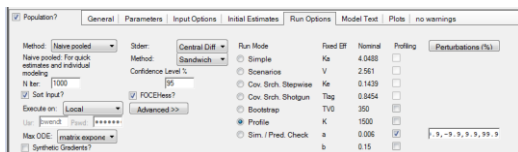
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## Initial Estimates for either model

- Use Initial Estimates Tab
- You can derive initial estimates from sensitivity analysis:
  - Switch to Population mode
  - Go to Run Options Tab
  - Select Profile as Run Mode:



- Enter Perturbations (%), e.g. -99.9, -99, -9, 9, 99, 999

Gastrén and Weiner, Pharmacokinetic and Pharmacodynamic Analysis - Concepts and Applications, 9th Edition, Swedish Pharmacology Press (2015)

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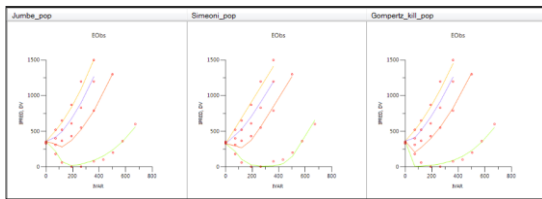
Demo

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## PD43: Results



	Name	InitCode	Loglik	AIC	BIC	nlparm	nlObs	nlSub	SpdChkUsage	Condition
1	Jumble_pop	3	-149.2567	288.51394	318.75775	4	29	4	0	10294317
2	Simeoni_pop	1	-154.8928	308.19462	328.39629	6	29	4	0	10294317
3	Gompertz_pop	3	-159.41237	329.22638	359.46286	5	29	4	0	10294317

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## PD43: Results

Parameter	Name		
	Gompertz_kill	Simeoni	Jumble
E0	361.828	324.308	357.601
a	0.005		
lambda0		0.018	
Kgrow			0.036
g	0.191		
k2		0.339	
Kmax			14.142
k1		0.030	
Kdall			0.172
stdev0	59.440	49.144	41.587
b	0.002		
lambda1		3.021	
KC50			1.605

- Initial Tumor Volume
- Exponential growth rate constant
- Drug-induced decay rate constant
- Transit rate constant
- Residual error

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## PK43: Summary

- Tumor Growth/Kill Models
  - Gompertz
    - Classic equation
    - Empirical
      - Single growth phase: exponential
      - Drug effects the total tumor volume
      - Drug induced decay expressed by proportional factor
  - Simeoni
    - Widely used
    - Semi-mechanistic
      - Two different growth phases: exponential and linear
      - Differentiates proliferating cells from dying ones
      - Drug induced decay expressed by proportional factor
  - Jumble
    - Semi-mechanistic
      - Single growth phase: exponential
      - Differentiates proliferating cells from dying ones
      - Drug induced decay expressed with saturable function

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Questions?



## New PML Library: NONMEM-2-PML

- <https://support.certara.com/forums/forum/35-nlme-nonmem-model-comparisons/>

Model Comparison	Created	Replies	Views
NONMEM to Phoenix Model Interface and comparison with NONMEM	12 Jan 2017	2 replies	10 views
PK 2 compartment multiple IV bolus Phoenix and CL	12 Jan 2017	2 replies	10 views
PK 2 compartment oral with Disease State covariate on V and CL	12 Jan 2017	2 replies	10 views
PK 2 compartment IV bolus RGL, Laplace	12 Jan 2017	2 replies	10 views
PK 2 compartment IV bolus First and Second FOCE	12 Jan 2017	2 replies	10 views
PK 2 compartment IV bolus First and Second FOCE	12 Jan 2017	2 replies	10 views
PK 1 Compartment Mixed First Order and Zero Order input	12 Jan 2017	2 replies	10 views

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## New PML Library: NONMEM-2-PML

Home → Support → Certara Forums → Certara Forums → NLME-NONMEM model comparisons

**PK 2 compartment oral with Disease State covariate on V and CL**  
Started by Christopher Mehl, Apr 04 2017 09:10 PM

Please log in to reply

No replies to this topic

Christopher Mehl  
Member  
17 posts

Posted 04 April 2017 - 09:10 PM

This is a PK 2 compartment oral with a covariate relationship between both Volume and Clearance, and a categorical covariate disease state. Disease State is a 3 level covariate (0,1 and 2) linked to both V and CL. The model is fit using First Order Conditional Estimation (FOCE).

For model translation information, refer to the attached slide deck. The model is run in both NLME and NONMEM in the attached Phoenix project file.

NONMEM to NLME Translation PK 2comp Oral Disease State on V and CL FOCE.pdf 1.7MB 1 download

ZComp\_Oral\_Disease\_State\_Effect\_on\_V\_CL\_FOCE.phnxproj 5.8MB 1 download

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## Coming up...

### Modeling PK/PD Systems with Distributed Delays

**Speaker(s):** Wojciech Krzyzanski

**Date:** May 16, 2017

**Time:** 11 am EST

**Duration:** 1 hour



### Modeling Inhibition of Enzyme Activity by Means of Turnover

Construction of a mechanistic turnover model

April 27, 2017 | 10am EST

*Presenter: Chris Mehl*

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## Coming up...



### Modeling Inhibition of Enzyme Activity by Means of Turnover

Construction of a mechanistic turnover model

April 27, 2017 | 10am EST

*Presenter: Chris Mehl*



### Effect Compartment fit to infusion

Model response-time data with a one-compartment model

May 11, 2017 | 10am EST

*Presenter: Bernd Wenzel*



### Turnover Model 1: IV Bolus Dosing

Model response-time data with a one-compartment model

June 8, 2017 | 10am EST

*Presenter: Chris Mehl*



### Turnover Model 4: IV Infusions

Apply a turnover model to multiple IV dosing response data

June 22, 2017 | 10am EST

*Presenter: Bernd Wenzel*



### Turnover Model 1: Repeated Dosing

Apply a turnover model to repeated IV dosing response data

July 13, 2017 | 10am EST

*Presenter: Chris Mehl*



### Dose-response-time Analysis: IV

Analyze dose-response-time data with an instantaneous effect model

July 27, 2017 | 10am EST

*Presenter: Bernd Wenzel*



### Transduction Modeling: Assessment of Number of Transit Compartments

Analyze a transduction rate limited response time course

August 10, 2017 | 10am EST

*Presenter: Dan Wister*

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