

Transduction Modeling – Assessment of Number of Transit Compartments



Semiphysiological Model for the Time Course of Leukocytes after Varying Schedules of 5-Fluorouracil in Rats¹

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ABSTRACT

Models of leukopenia after chemotherapy are mainly empirical. To increase the derived models' potential of mechanistic understanding and extrapolation, more physiologically based models are being developed. To date, presented models cannot characterize the often-observed rebound of leukocytes. Therefore, a model able to describe the transient decrease and rebound in leukocytes was developed. Three different dosing regimens of 5-fluorouracil were given to rats. One group received a single dose of 127 mg/kg. The other two groups received two and three injections of 63 mg/kg and 49 mg/kg, respectively, with a 2-day interval. Leukocyte counts were followed for 23 to 25 days after the first dose. Plasma concentrations were determined by high-performance liquid chromatography. Population pharmacokinetic and pharmacodynamic models were developed using NONMEM. 5-Fluorouracil showed one-compartment disposition with capacity-limited

elimination. The 49-mg/kg dose injected on three occasions produced the lowest leukocyte count (28% of baseline) and the most prominent rebound of the schedules, despite the fact that the fractionated regimens produced only 52 to 56% of the area under the concentration-time curve from time 0 to infinity in the single-dose group. The final semiphysiological model included two 5-fluorouracil-sensitive and two -insensitive transit compartments as well as a compartment of circulating leukocytes. Second order rate constants from the transit compartments and a negative feedback from the circulating leukocytes to the input of the first sensitive compartment characterized the pronounced changes in leukocyte counts. A posterior predictive check as well as predictions into a new data set showed that our model could well predict the schedule-dependent leukopenic effects of 5-fluorouracil.

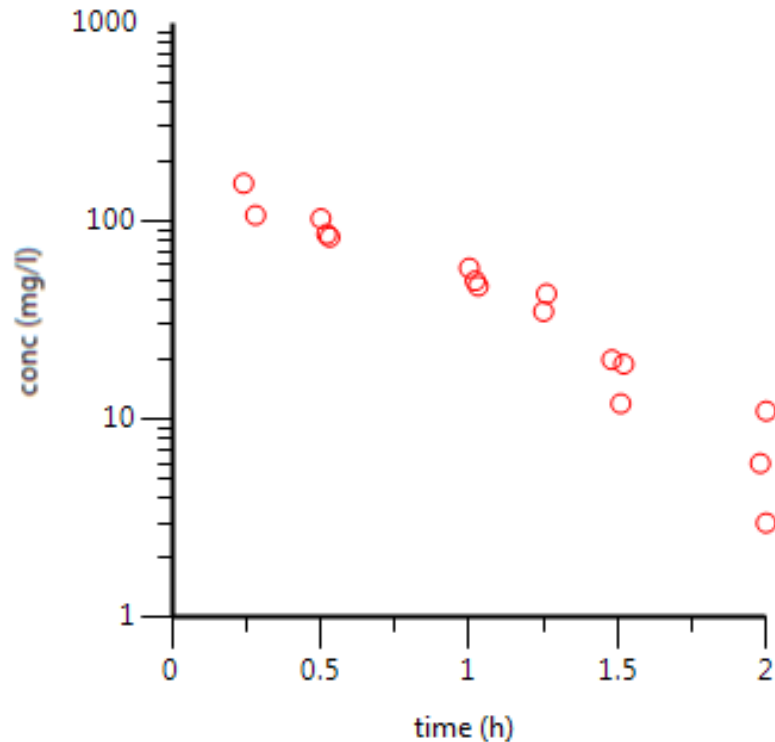
Friberg, Lena E., et al. "Semiphysiological model for the time course of leukocytes after varying schedules of 5-fluorouracil in rats." *Journal of Pharmacology and Experimental Therapeutics* 295.2 (2000): 734-740.

Problem Description

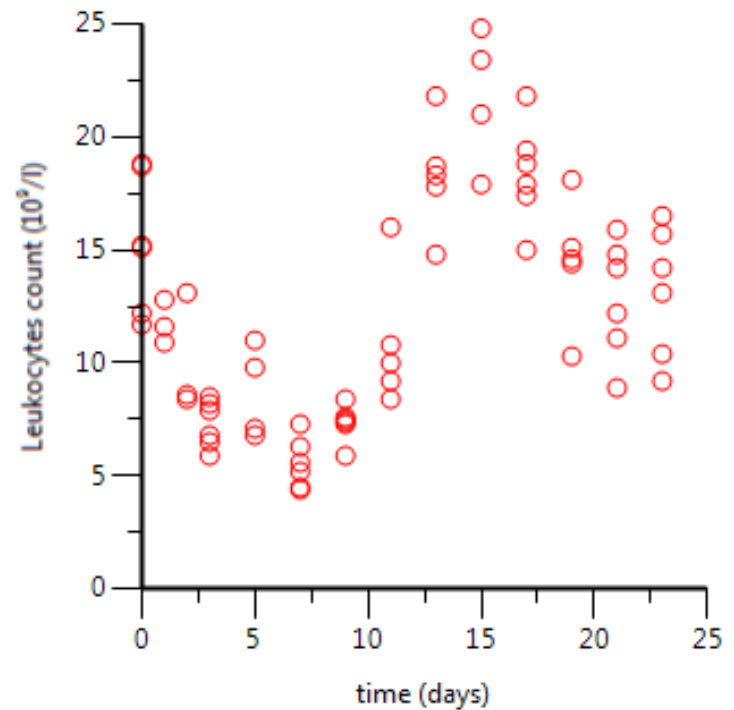
- PK Data:
 - 24 rats were randomized into three treatment groups and one control group with six rats in each group.
 - This exercise focusses on single group
 - Received a single 5-FU injection of 127 mg/kg on average on day 0
 - Blood samples were drawn in a sampling interval of 15 to 120 min after the injection.
- PD Data:
 - Blood samples for determination of number of leukocytes were collected at baseline (1 day before the first injection), on the day after the first injection (day 1) in half of the rats, on day 2 in the other half of the rats, and then in all rats every other day from day 3 to 23 or 25. Then the leukocytes were considered to have returned to baseline.

Exploratory Data Analysis

PK Data



PD Data



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

Modeling Delays: Review

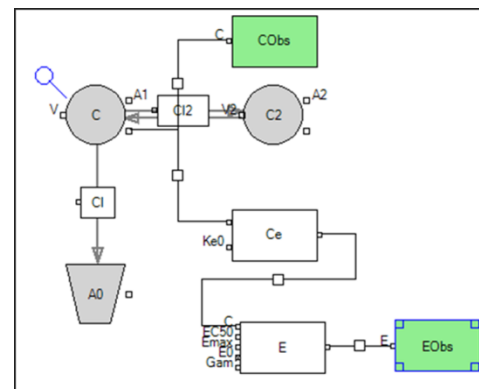


Effect Compartment III: IV infusion

Model response-time data with a link-model

May 11, 2017 | 10am EST

Presenter: Bernd Wendt

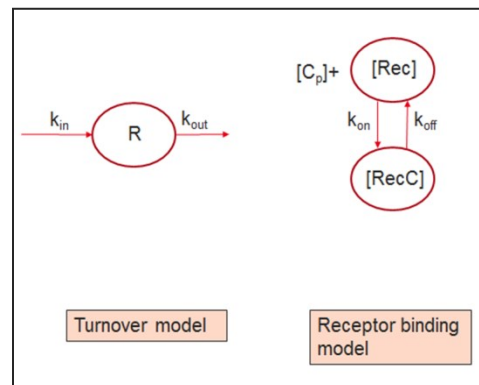


Analysis and Comparison of Link, Turnover and Receptor Binding Models

Fit a link-, turnover- and receptor binding model to data

March 16, 2017 | 10am EST

Presenter: Dan Weiner

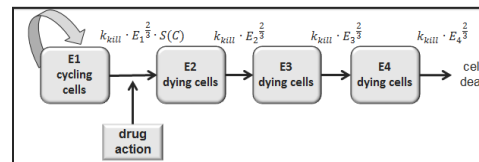


Analysis of a Tissue Growth/Kill Model

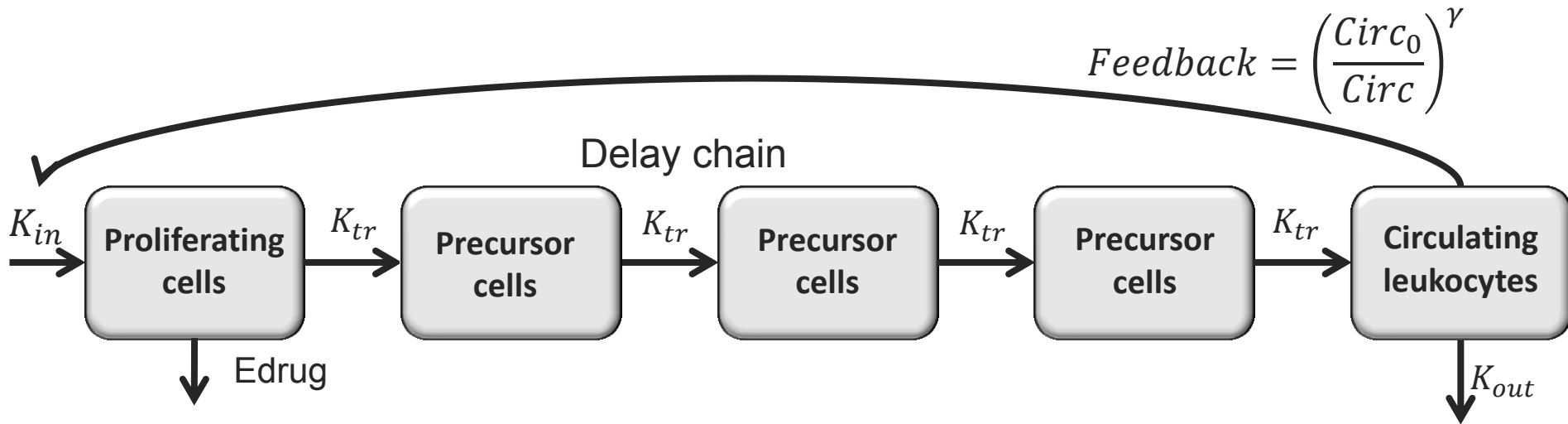
Analyze a tumor cell kill model after acute dosing

April 13, 2017 | 10am EST

Presenter: Bernd Wendt



Semiphysiologic model with Transit Compartments



$$\frac{dProl}{dt} = K_{in} \cdot Prol \cdot (1 - Edrug) \cdot \left(\frac{Circ_0}{Circ}\right)^\gamma - K_{tr} \cdot Prol$$

$$Edrug = Slope \cdot C$$

$$\frac{dTr_1}{dt} = K_{tr} \cdot (Prol - Tr_1)$$

$$\frac{dTr_2}{dt} = K_{tr} \cdot (Tr_1 - Tr_2)$$

$$\frac{dTr_3}{dt} = K_{tr} \cdot (Tr_2 - Tr_3)$$

$$\frac{dCirc}{dt} = K_{tr} \cdot Tr_3 - K_{out} \cdot Circ$$

Friberg Model in PML

```
test(){
  deriv(A1 = - Vmax * C / (Km + C))
  deriv(Prol = Kin*Prol* (1- Edrug) *(Circ0/Circ)^gam - Ktr * Prol)
  deriv(Tr1 = Ktr * (Prol - Tr1))
  deriv(Tr2 = Ktr * (Tr1 - Tr2))
  deriv(Tr3 = Ktr * (Tr2 - Tr3))
  deriv(Circ = Ktr*Tr3 - Kout*Circ)
  dosepoint(A1)
  C = A1 / V
  FB=(Circ0/Circ)^gam
  Edrug = Slope*C
  error(Eps = 0.1)
  observe(EObs = Circ * (1 + Eps))
  # Initialization of transit compartments
  sequence{Circ=Circ0}
  sequence{Tr1=Circ0}
  sequence{Tr2=Circ0}
  sequence{Tr3=Circ0}
  sequence{Prol=Circ0}
  # fixed effects with PK frozen
  fixef(V(freeze) = c(0, 0.814622, ))
  fixef(Km(freeze) = c(0, 95.5578, ))
  fixef(Vmax(freeze) = c(0, 179.066, ))
  fixef(Circ0 = c(, 15, ))
  fixef(Kin = c(0,1, ))
  fixef(Kout = c(0, 1,))
  fixef(gam = c(0,0.3,))
  fixef(Ktr = c(0, 1,))
  fixef(Slope = c(0,0.01,))
}
```

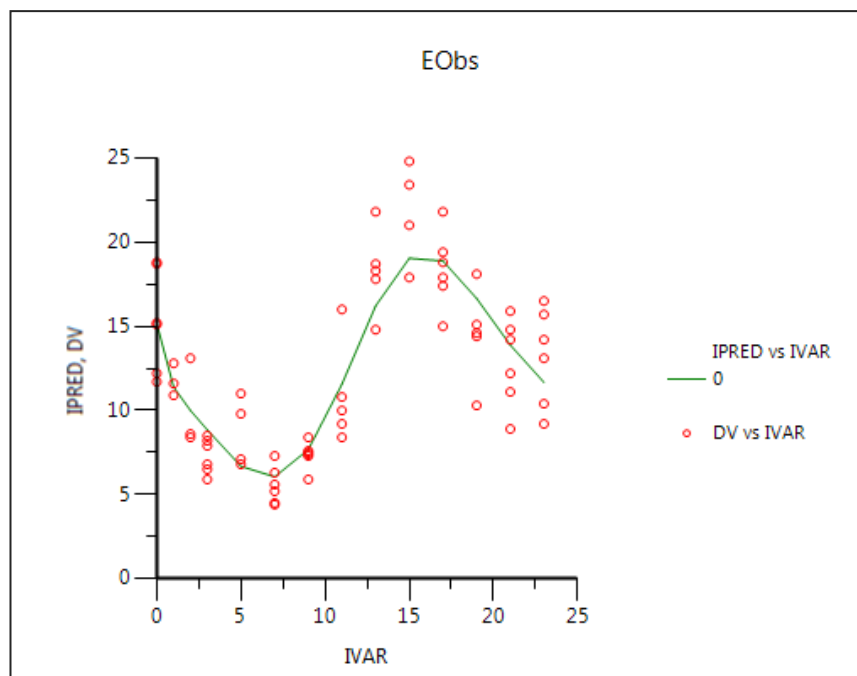
1-compartment IV Bolus with non-linear elimination
amount of proliferating cells
amount of cell in 1st transit compartment
ditto for 2nd transit compartment
ditto for 3rd compartment
amount of circulating cells
IV Bolus dose
convert amounts in concentrations
Feedback loop

initial estimate of error 10%
multiplicative residual error model



Demo

Transduction Modeling: Results



	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	V	0.814622		0	0	0.814622	0.814622	0
2	Km	95.5578		0	0	95.5578	95.5578	0
3	Vmax	179.066		0	0	179.066	179.066	0
4	Circ0	15.1496		1.2238872	8.078677	12.704593	17.594607	37.441
5	Kin	0.798249		0.095304774	11.939229	0.60785493	0.98864307	0.28395
6	Kout	1.29009		0.10966768	8.5007775	1.0710026	1.5091774	0.33175
7	gam	0.366059		0.053625554	14.649429	0.25892914	0.47318886	0.11024
8	Ktr	0.851206		0.077252832	9.0756916	0.696875	1.005537	0.18439
9	Slope	0.00862431		0.00079835456	9.2570253	0.0070294059	0.010219214	1.4244E-05
10	stdev0	0.206946		0.018095027	8.7438399	0.17079686	0.24309514	

Transduction Modeling: Summary

- Implemented Friberg Model
 - linear PK/PD relationship
 - semiphysiologic
 - transit compartments to mimic cell maturation
 - feedback mechanism
- Determine number of transit compartments
 - no big differences between 2-4 transit compartments
 - 3 transit compartments shows best fit

Questions?



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PML School

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Coming up...



2017

August

summer break

September

summer break

October

2 Webinars

November

2 Webinars

December

2 webinars

Coming up...

- Model examples suggested by the users
 - Please send me your suggested models, literature references or ideas to
 - bernd.wendt@certara.com
 - We can help you develop or refine models for live presentation at the PML School
 - You can either fill a PML School webinar on your own or we can cover for you
- New Topic: NONMEM to PML Comparisons
 - Popular Models using NONMEM software
 - 1:1 translation into Phoenix Modeling Language
 - Setup and run NONMEM models in Phoenix
 - Setup and Run same model in Phoenix NLME
 - Compare Results