

## Receptor & Target-Binding Models: Practice

### Aim of analysis

To develop a mechanism-based pharmacokinetic model where receptor-binding influences the time-course of plasma drug concentrations.

### Study design and background

A study was conducted to assess the pharmacokinetics of recombinant human vascular endothelial growth factor (rhVEGF), a novel angiogenic agent, in patients with coronary artery disease (Eppler et al. *Clin Pharmacol Ther.* 2002 72:20). Two groups of patients received 4 hour IV infusions at rates of either 27 or 79 pmole/kg/hr. Blood samples were collected at 0.5, 2, 3, 4, 4.083, 4.25, 4.5, 5, 6, 8, and 10 hrs after starting the infusion regimen.

### Preliminary data information

The drug was found to be well described by a modified target-mediated pharmacokinetic model (Mager and Jusko. *J Pharmacokinetic Pharmacodyn.* 2001 28:507). Drug in the central compartment is subject to non-saturable and reversible non-specific distribution, direct elimination defined by a linear first-order rate constant, and saturable, irreversible specific-binding with its pharmacological receptor. Once formed, the drug-receptor complex is degraded according to a linear first-order rate constant.

### Data analysis

Data analysis methodology is provided for WinNonlin (Pharsight, Mountain View, CA).

### Modeling Process

- ✓ It is assumed that an initial preliminary analysis has been conducted and rough initial estimates have been obtained. The two articles cited above may be consulted for further discussion of both concepts.

## Tabulated Data

Time (h)	rhVEGF Concentration (pM)	
	107 pmoles/kg/hr	316 pmoles/kg/h
0.5	5.6	36.6
2	14.8	67.2
3	17.1	77
4	17.9	89.3
4.083	9.4	59.8
4.25	3.6	43.3
4.5	2.1	32.3
5	0.7	19.9
6	0.25	5.9
8	--	0.5
10	--	0.25

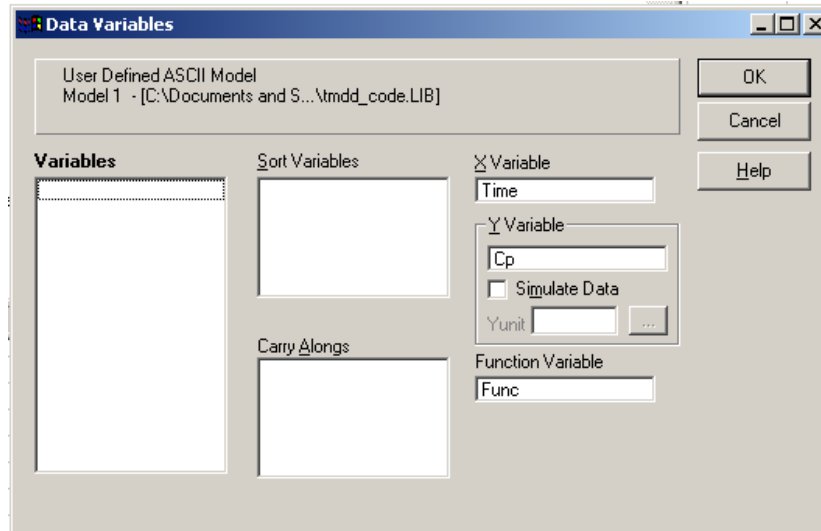
## Data File

	Time (hr)	Cp (pmol/L)	Func	D	E
1	0.5	5.6	1		
2	2	14.8	1		
3	3	17.1	1		
4	4	17.9	1		
5	4.083	9.4	1		
6	4.25	3.6	1		
7	4.5	2.1	1		
8	5	0.7	1		
9	6	0.25	1		
10	0.5	36.6	2		
11	2	67.2	2		
12	3	77	2		
13	4	89.3	2		
14	4.083	59.8	2		
15	4.25	43.3	2		
16	4.5	32.3	2		
17	5	19.9	2		
18	6	5.9	2		
19	8	0.5	2		
20	10	0.25	2		
21					

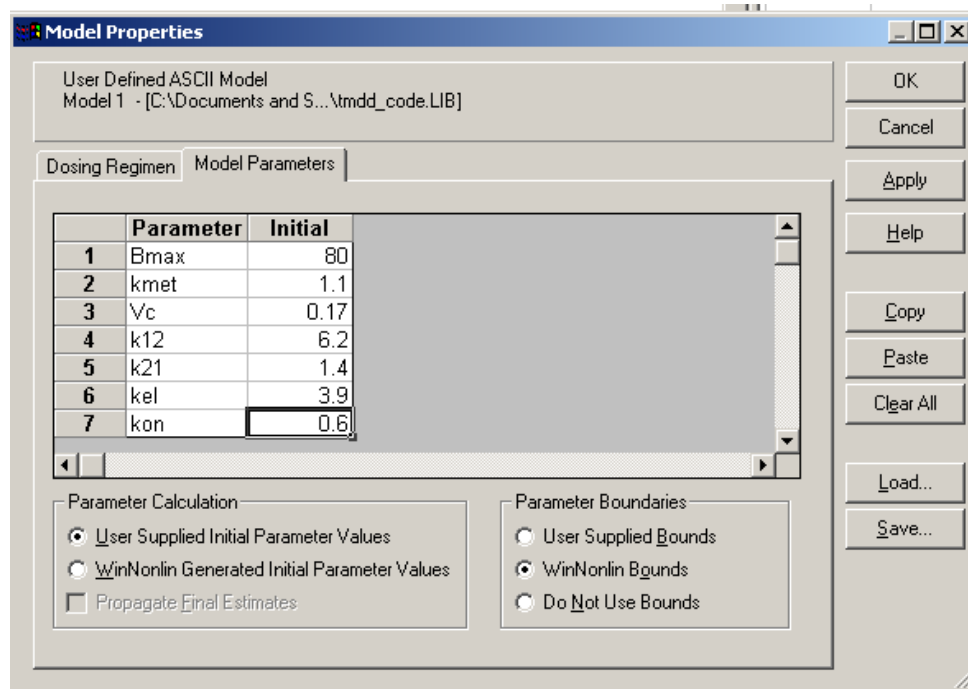
## WinNonlin Model Code

```
MODEL
remark *****
remark Model: Eppler et al. Clin Pharmacol Ther. 72:20 (2002)
remark Description: Target-Mediated PK of VEGF
remark Coded by: Donald E. Mager, PharmD, PhD
remark Purpose: ACCP PK/PD Workshop September 16, 2006
remark *****
remark - define model-specific commands
COMMANDS
NFUNCTIONS 2
NDERIVATIVES 6
NPARAMETERS 7
PNAMES 'Bmax', 'kmet', 'Vc', 'k12', 'k21', 'kel', 'kon'
NSECONDARY 0
END
remark - define temporary variables
TEMPORARY
T = X
Tinf = 4
END
remark - define differential equations starting values
START
Z(1) = 0
Z(2) = 0
Z(3) = 0
Z(4) = 0
Z(5) = 0
Z(6) = 0
END
remark - define differential equations
DIFFERENTIAL
remark - units of Ko = pmol/kg/hr
IF T < Tinf THEN
    Ko1=27
    Ko2=79
ELSE
    Ko1=0
    Ko2=0
ENDIF
DZ(1)= Ko1/Vc-(k12+kel)*Z(1)+k21*Z(2)-kon*Z(1)*(Bmax-Z(3))
DZ(2)= k12*Z(1)-k21*Z(2)
DZ(3)= kon*Z(1)*(Bmax-Z(3))-kmet*Z(3)
DZ(4)= Ko2/Vc-(k12+kel)*Z(4)+k21*Z(5)-kon*Z(4)*(Bmax-Z(6))
DZ(5)= k12*Z(4)-k21*Z(5)
DZ(6)= kon*Z(4)*(Bmax-Z(6))-kmet*Z(6)
END
remark - define algebraic functions
remark - Output units = pM, but could be converted to other
remark - units in the following functions
FUNCTION 1
F= Z(1)
END
FUNCTION 2
F= Z(4)
END
remark - define any secondary parameters
remark - end of model
EOM
```

## Data Variables



## Model Properties



## Model Options

The screenshot shows the 'Model Options' dialog box with the 'Weight' tab selected. The window title is 'Model Options'. The main area contains the following options:

- User Defined ASCII Model  
Model 1 - [C:\Documents and S...\tmdd\_code.LIB]
- Output Options | **Weight** | Title | PK Settings | Units
- Weights On File in Column (with a dropdown menu)
- Observed to Power n (with a text input field)
- Pre-Selected Scheme (with a dropdown menu showing '1/Y')
- Predicted to Power n (with a text input field)
- No Scaling of Weights

Buttons on the right side: OK, Cancel, Apply, Help.

The screenshot shows the 'Model Options' dialog box with the 'PK Settings' tab selected. The window title is 'Model Options'. The main area contains the following options:

- User Defined ASCII Model  
Model 1 - [C:\Documents and S...\tmdd\_code.LIB]
- Output Options | Weight | Title | **PK Settings** | Units
- Minimization: Gauss-Newton (Levenberg and Hartley) (dropdown menu)
- Transpose Final Parameter Table
- Increment for Partial Derivatives: 0.001 (text input)
- Meansquare: (text input)
- Number of Predicted Values: (text input)
- Iterations: 50 (text input)
- Convergence Criteria: 0.0001 (text input)
- Model Size: 4 (text input)

Buttons on the right side: OK, Cancel, Apply, Help.

## Workbook Output

Workbook - [C:\Documents and...\tmdd\_output.pwo]

A8

	Parameter	Units	Estimate	StdError	CV%	UnivarCI_Lower	UnivarCI_Upper	PlanarCI_Lower	PlanarCI_Upper
1	BMAX		59.735032	19.915138	33.34	16.711017	102.759047	-29.289013	148.759077
2	KMET		1.370895	0.344232	25.11	0.627228	2.114562	-0.167879	2.909669
3	VC		0.199238	0.033825	16.98	0.126164	0.272312	0.048035	0.350441
4	K12		4.808008	1.272866	26.47	2.058149	7.557867	-0.881921	10.497936
5	K21		1.281466	0.180346	14.07	0.891852	1.671079	0.475289	2.087643
6	KEL		3.315554	0.553859	16.70	2.119016	4.512092	0.839712	5.791395
7	KON		0.825498	0.335123	40.60	0.101510	1.549486	-0.672557	2.323553
8									
9									

Final Parameters / Non-Transposed Final Parameters / Correlation Matrix

Workbook - [C:\Documents and...\tmdd\_output.pwo]

F1

	Function	Item	Value	D
1	1	CSS	402.269	
2	1	WCSS	80.2201	
3	1	SSR	11.834	
4	1	WSSR	1.49345	
5	1	S	0.864133	
6	1	DF	2	
7	1	CORR_(OBS,PRED)	0.9973	
8	2	WT_CORR_(OBS,PRED)	0.9938	
9	2	CSS	9714.5	
10	2	WCSS	714.683	
11	2	SSR	35.4511	
12	2	WSSR	1.47683	
13	2	S	0.607625	
14	2	DF	4	
15	All	CORR_(OBS,PRED)	0.9982	
16	All	WT_CORR_(OBS,PRED)	0.9993	
17	All	TSSR	47.2852	
18	All	TWSSR	2.97028	
19	All	TOT_S	0.477999	
20	All	TOT_DF	13	
21		AIC	35.77314	
22		SBC	42.74327	
23				

Diagnostics / Differential Equ

## Chart Output

