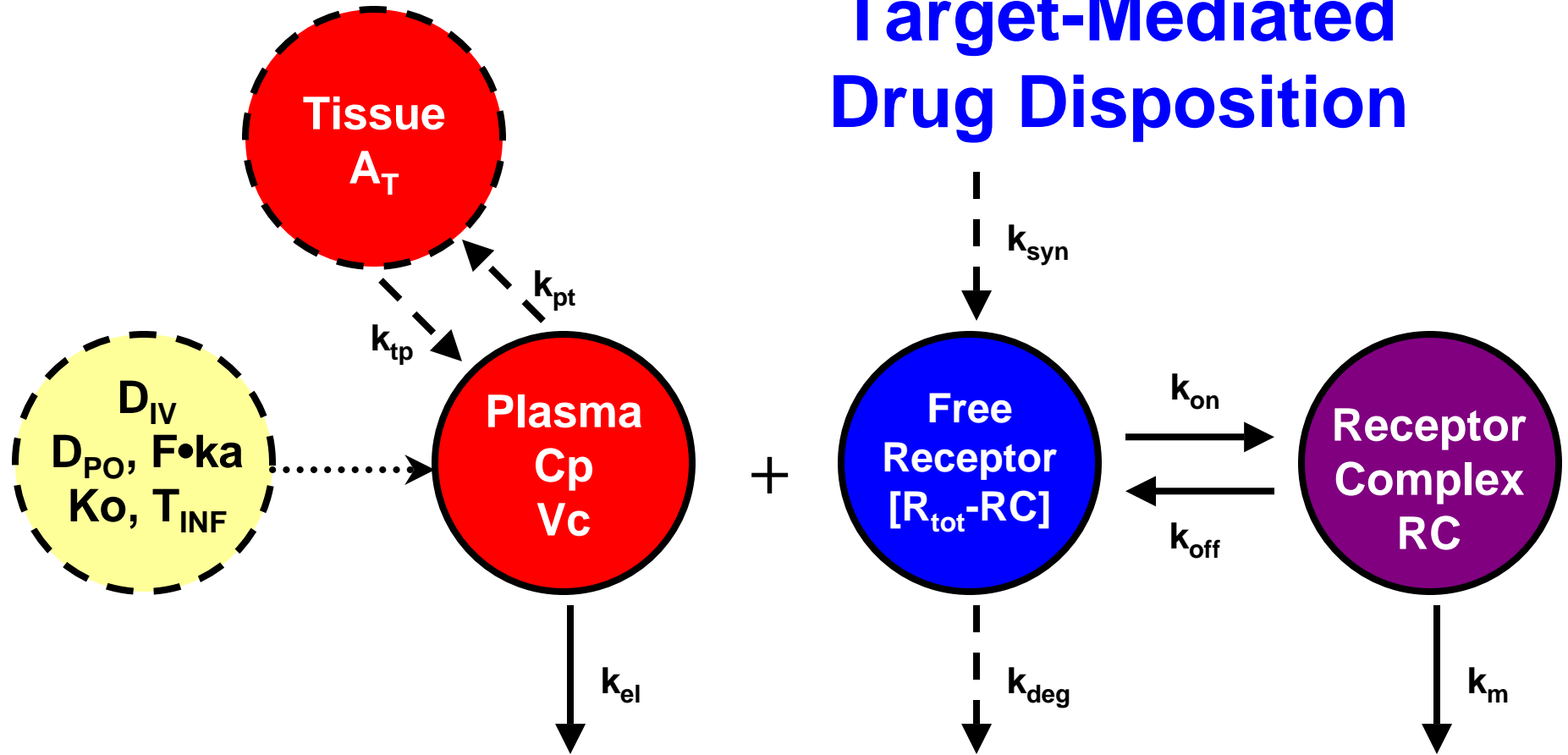


Receptor & Target-Binding Models: Practice

**ACCP Workshop in PK/PD Modeling
September 16, 2006 Cambridge, MA**

**Donald E. Mager, Pharm.D., Ph.D.
Department of Pharmaceutical Sciences**

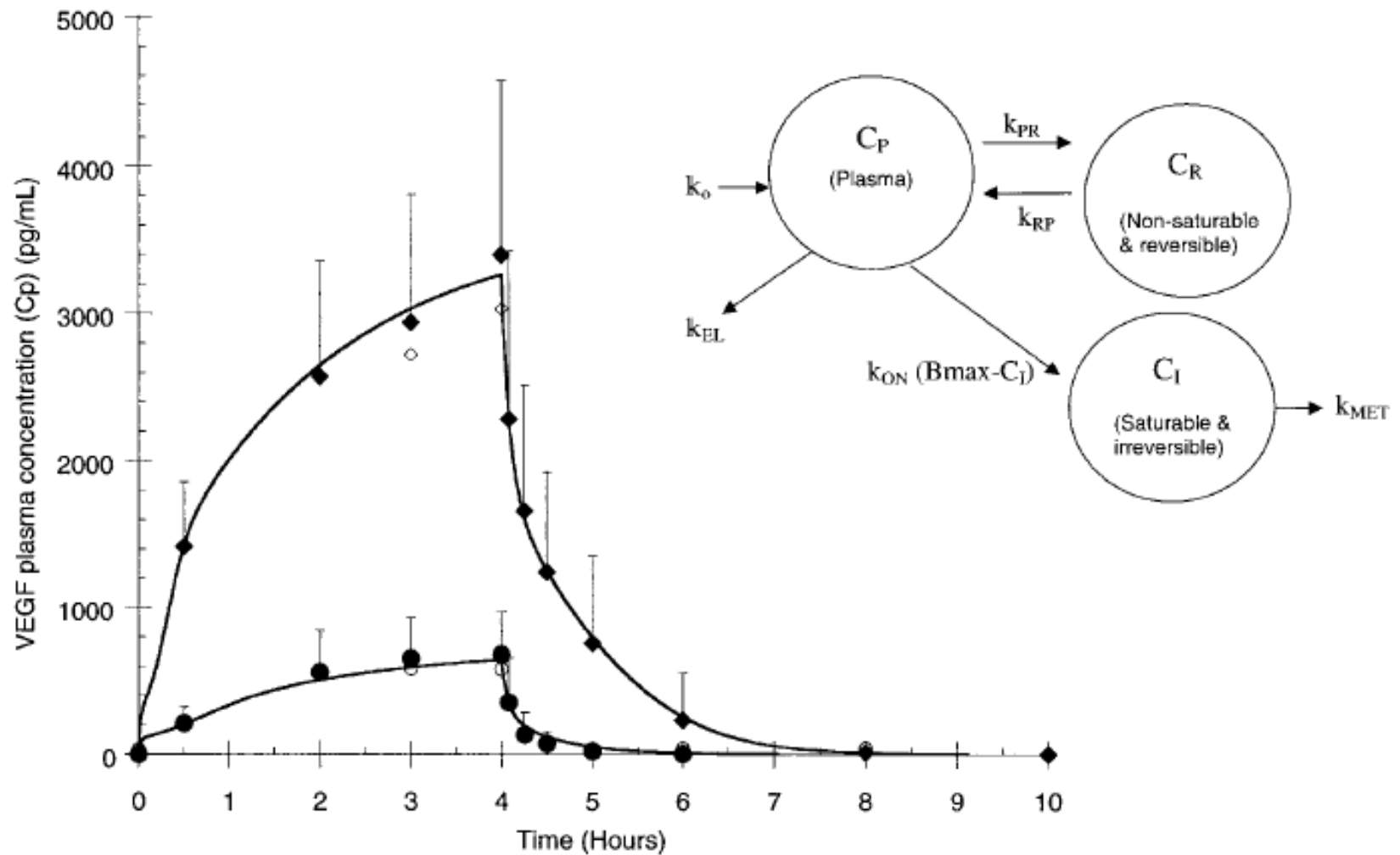
Target-Mediated Drug Disposition



$$\frac{dC_p}{dt} = In(t) - (k_{el} + k_{pt}) \cdot C_p + k_{tp} \cdot \frac{A_T}{V_c} - k_{on} \cdot (R_{tot} - RC) \cdot C_p + k_{off} \cdot RC$$

$$\frac{dRC}{dt} = k_{on} \cdot (R_{tot} - RC) \cdot C_p - (k_{off} + k_m) \cdot RC$$

Vascular Endothelial Growth Factor

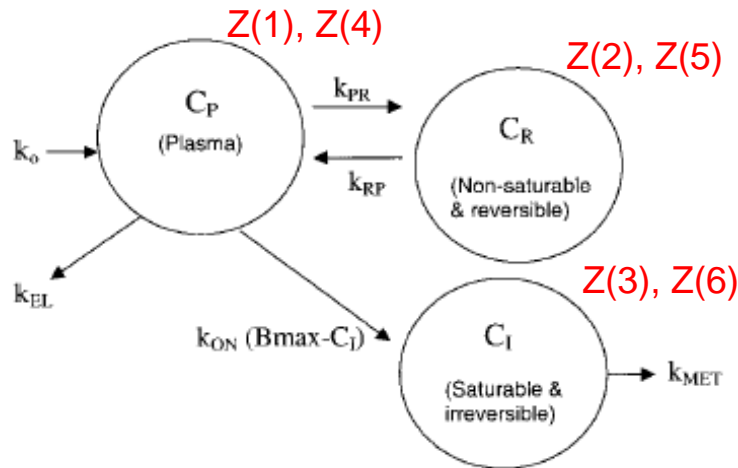


WinNonlin Code

```

Model 1
remark *****
remark Developer: Donald E. Mager
remark Model Date: 2006
remark Model Version: 1.0 Eppler et al. Model
remark *****
remark
remark - define model-specific commands
COMMANDS
NFUN 2
NDER 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
DIFF
remark - Ko units = pmole/kg/hr
IF T < Tinf THEN
    Ko1=27
    Ko2=79
ELSE
    Ko1=0
    Ko2=0
ENDIF

DZ(1)= Ko1/Vc-(k12+kcl)*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+kcl)*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
FUNC 1
F= Z(1)
END
FUNC 2
F= Z(4)
END
remark - define any secondary parameters
SECO
END
remark - end of model
EOM

```

Eppler et al. *Ibid.*

Initial Parameter Estimates

Model Properties

User Defined ASCII Model
Model 1 - [C:\Documents and S...\tmdd_code.LIB]

Dosing Regimen | Model Parameters

	Parameter	Initial
1	Bmax	80
2	kmet	1.1
3	Vc	0.17
4	k12	6.2
5	k21	1.4
6	kel	3.9
7	kon	0.6

Parameter Calculation

- User Supplied Initial Parameter Values
- WinNonlin Generated Initial Parameter Values
- Propagate Final Estimates

Parameter Boundaries

- User Supplied Bounds
- WinNonlin Bounds
- Do Not Use Bounds

Buttons: OK, Cancel, Apply, Help, Copy, Paste, Clear All, Load..., Save...

See Appendices in Mager and Jusko. Ibid.

Weighting

The image shows a software dialog box titled "Model Options" with a standard Windows-style title bar (minimize, maximize, close buttons). The main content area is divided into tabs: "Output Options", "Weight", "Title", "PK Settings", and "Units". The "Weight" tab is currently selected and highlighted with a dotted border. Inside this tab, there are four radio button options and one checkbox. The first two are "Weights On File in Column" (with an empty dropdown menu) and "Observed to Power n" (with an empty input field). The next two are "Pre-Selected Scheme" (with a dropdown menu containing "1/Y") and "Predicted to Power n" (with an empty input field). At the bottom of the tab is a checkbox labeled "No Scaling of Weights". To the right of the dialog box, there are five buttons: "OK", "Cancel", "Apply", and "Help", arranged vertically.

Model 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
[]

Observed to Power n
[]

Pre-Selected Scheme
[1/Y]

Predicted to Power n
[]

No Scaling of Weights

OK
Cancel
Apply
Help

Final Parameter Estimates

Workbook - [C:\Documents and...\tmdd_output.pwo]

A8

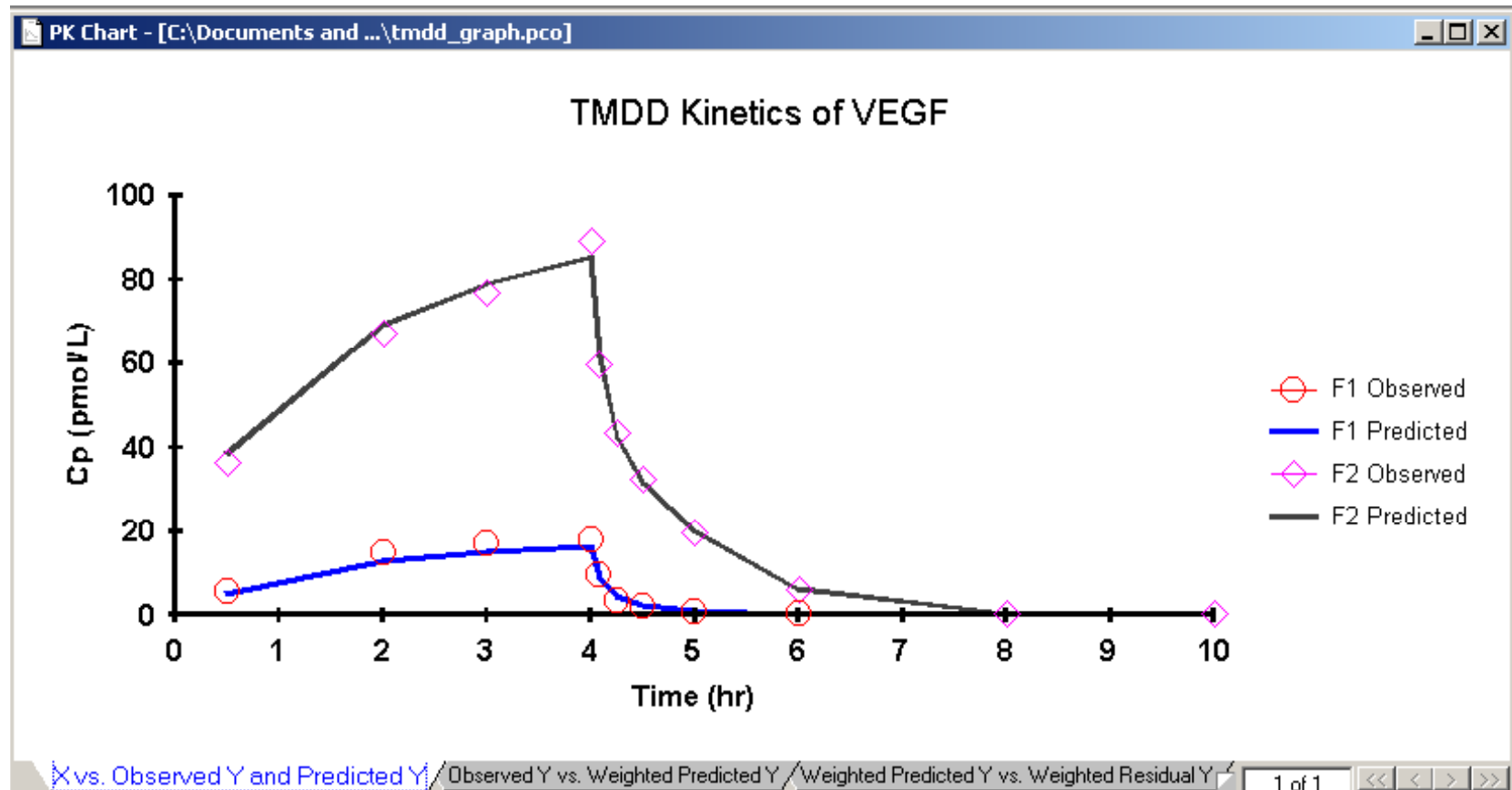
	Parameter	Units	Estimate	StdError	CV%	UnivarCI_Lower	UnivarCI_Upper	PlanarCI_Lower	PlanarCI_Upper
1	BMAX		59.735032	19.915138	33.34	16.711017	102.759047	-29.289013	148.759077
2	KMET		1.370895	0.344232	25.11	0.627228	2.114562	-0.167879	2.909669
3	VC		0.199238	0.033825	16.98	0.126164	0.272312	0.048035	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

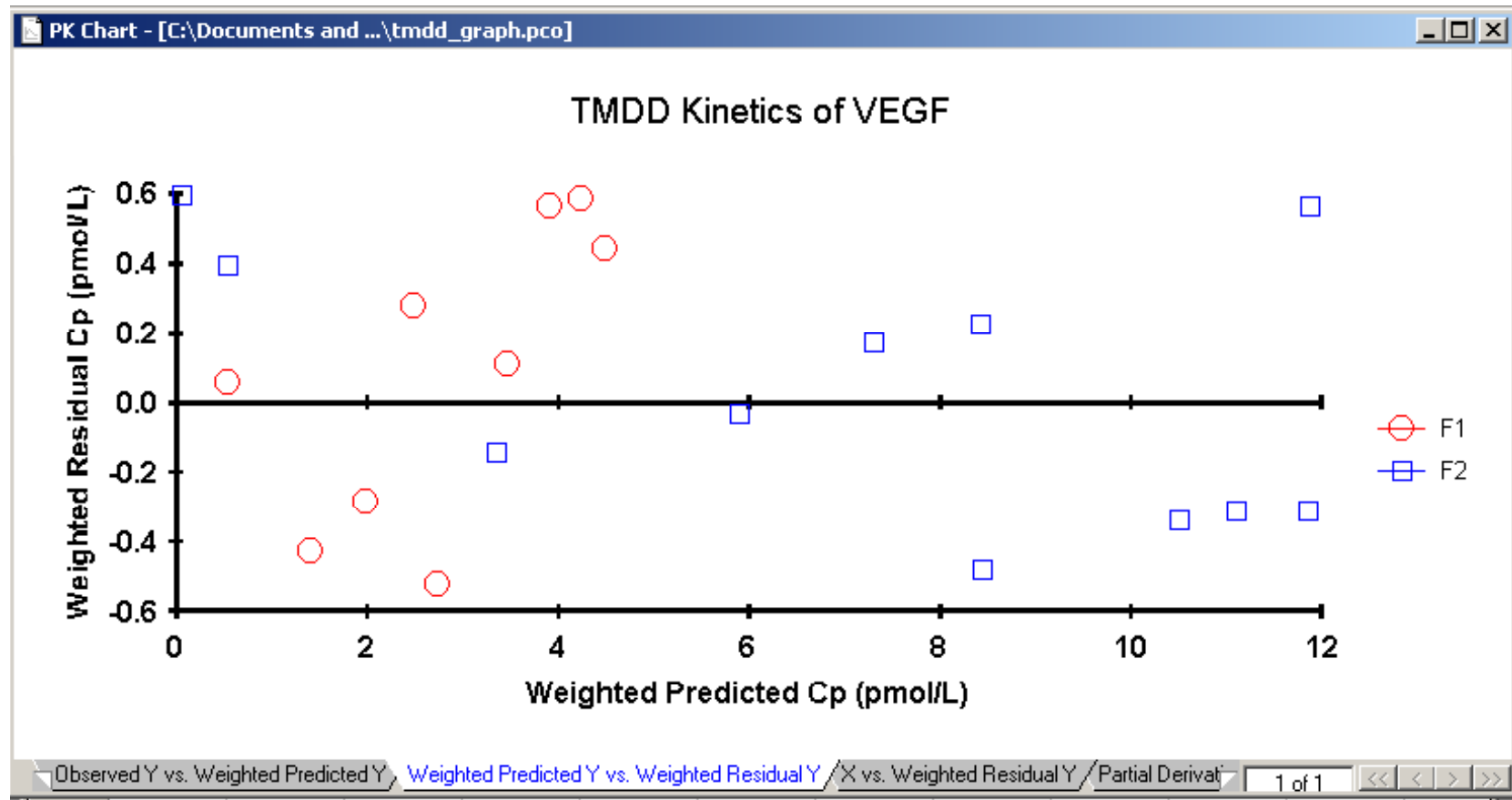
Table V. Pharmacokinetic results from the compartmental analysis of the VEGF plasma concentration data after a 4-hour intravenous infusion on day 3*

Parameter	Estimate	Standard error	%CV	95% Confidence interval	
				Lower	Upper
Volume (L/kg)	0.171	0.021	12.1	0.127	0.215
k_{PR} (h^{-1})	6.18	1.3	20.5	3.49	8.88
k_{RP} (h^{-1})	1.42	0.22	15.3	0.961	1.89
k_{EL} (h^{-1})	3.89	0.48	12.4	2.86	4.92
k_{ON} ($pmol/L^{-1} \cdot h^{-1}$)	0.559	0.25	44.6	0.028	1.09
k_{MET} (h^{-1})	1.16	0.28	24.3	0.561	1.76
B_{max} (pmol/L)	79.6	17	21.3	43.5	116

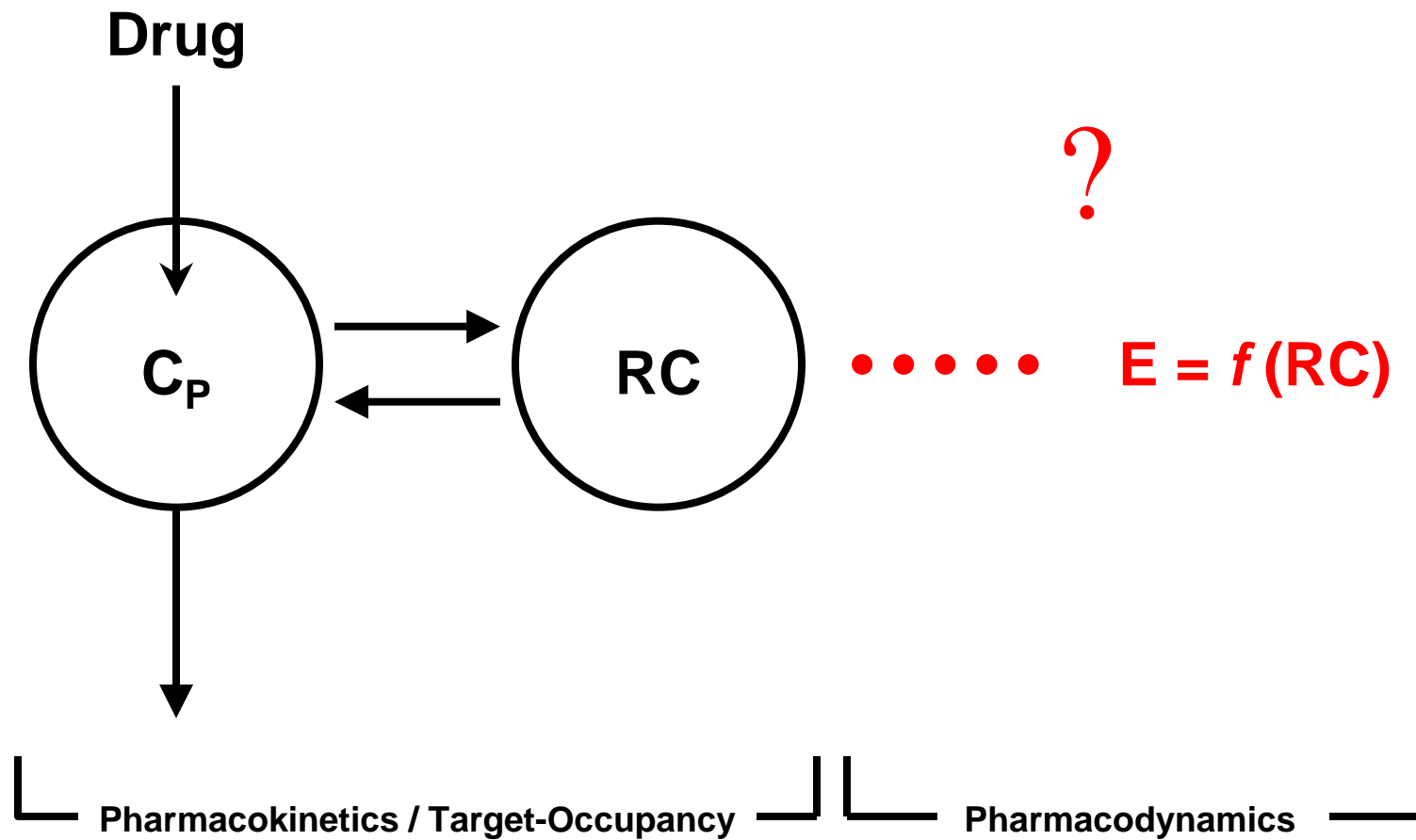
Fitted Profiles



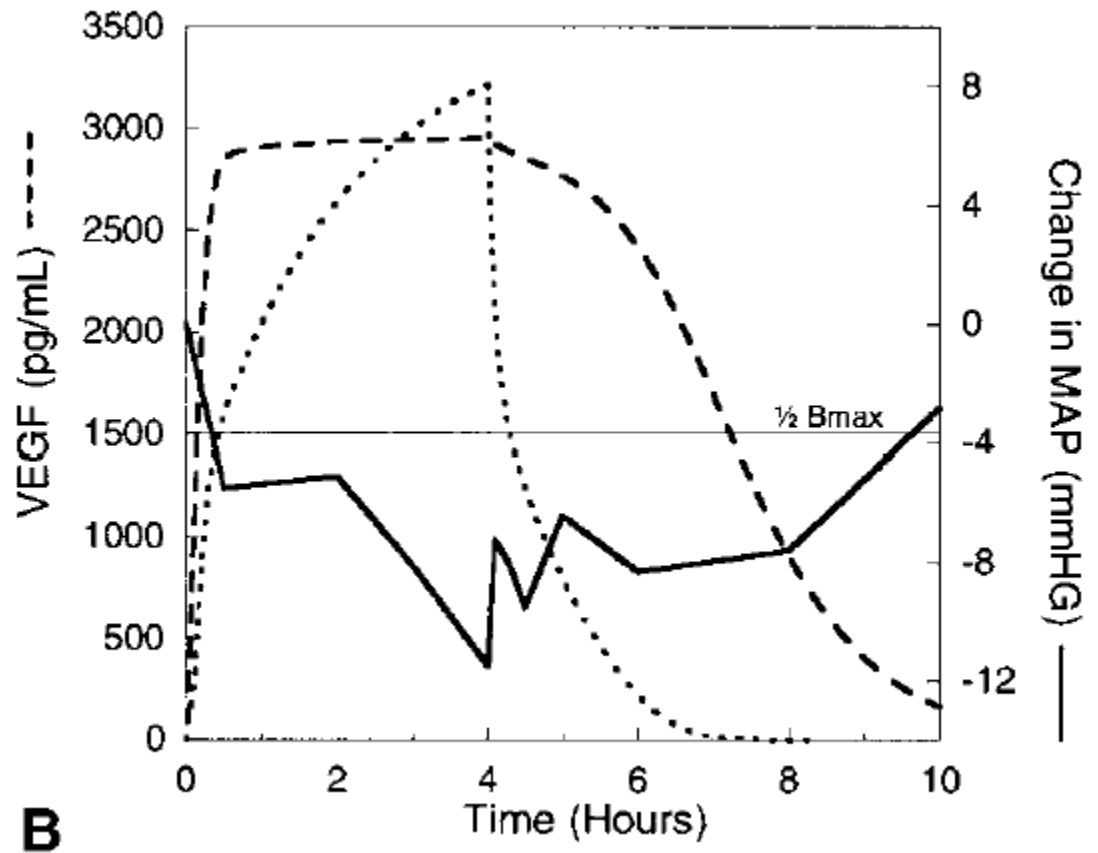
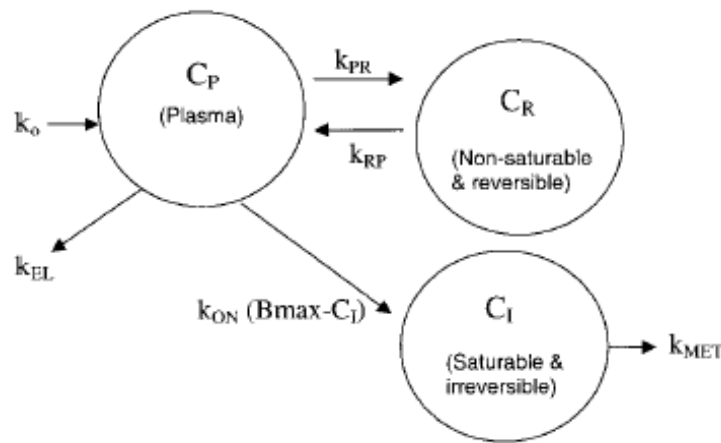
Weighted Residuals



Target-Mediated Drug Disposition: Pharmacodynamic Implications



Vascular Endothelial Growth Factor Hemodynamic Effects



Eppler et al. *Ibid.*