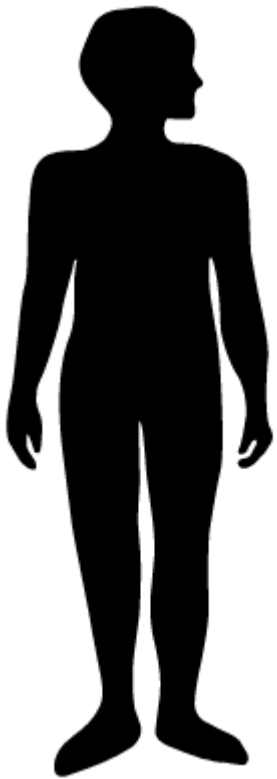


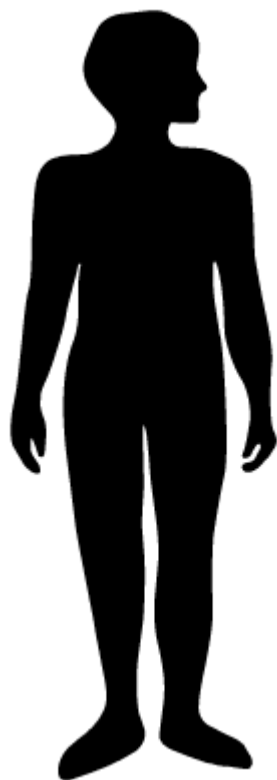
*POPULATION
PHARMACOMETRICS
MODELS, METHODS & TOOLS
(A VERY QUICK OVERVIEW...)*

*MARC LAVIELLE
INRIA SACLAY, POPIX*

Introduction to PKPD modeling



Introduction to PKPD modeling



warfarin



anticoagulant used
in the prevention
of thrombosis

Introduction to PKPD modeling



Pharmacokinetics:

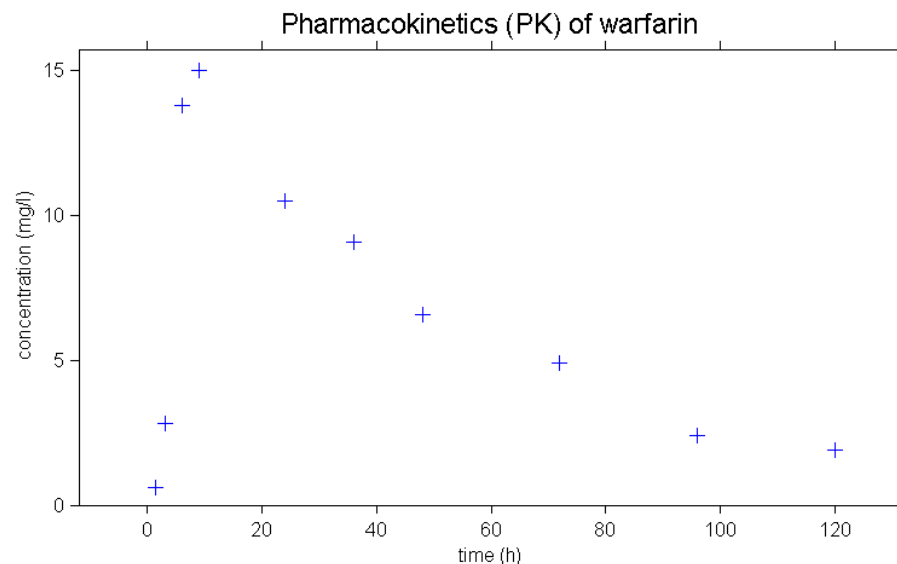
what the body does
to the drug

Absorption

Distribution

Metabolism

Excretion



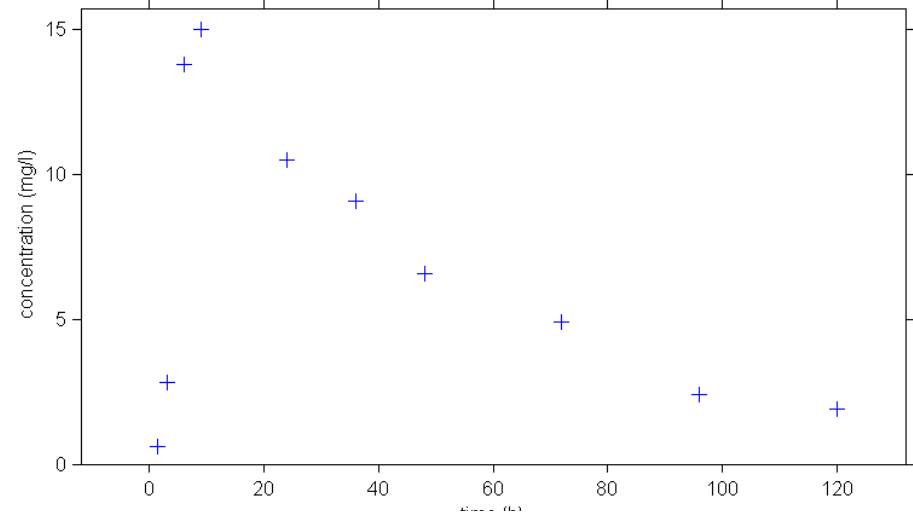
Introduction to PKPD modeling



Pharmacokinetics:

what the body does
to the drug

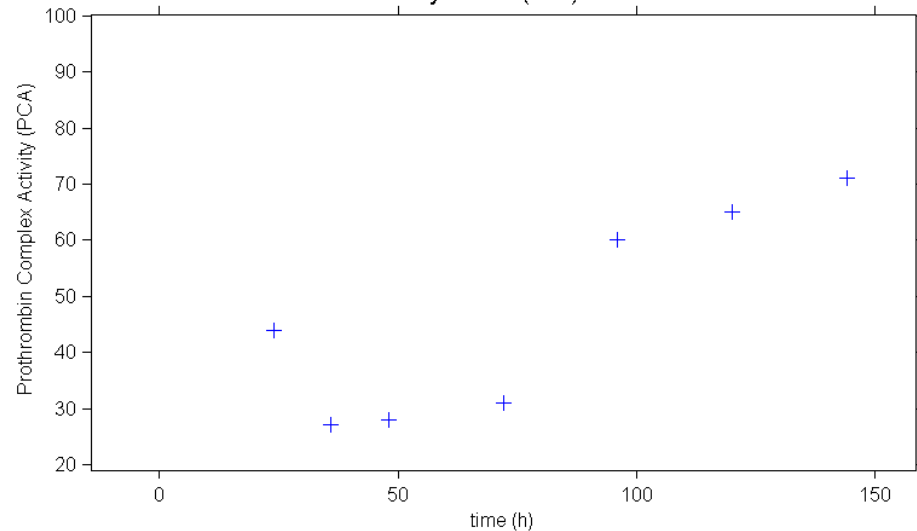
Pharmacokinetics (PK) of warfarin



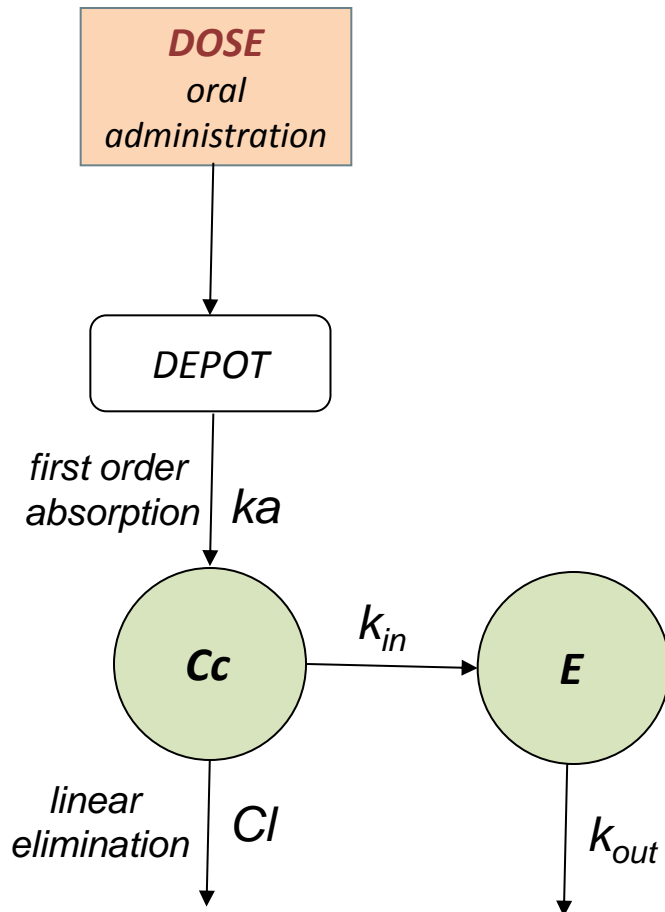
Pharmacodynamics:

what the drug does
to the body

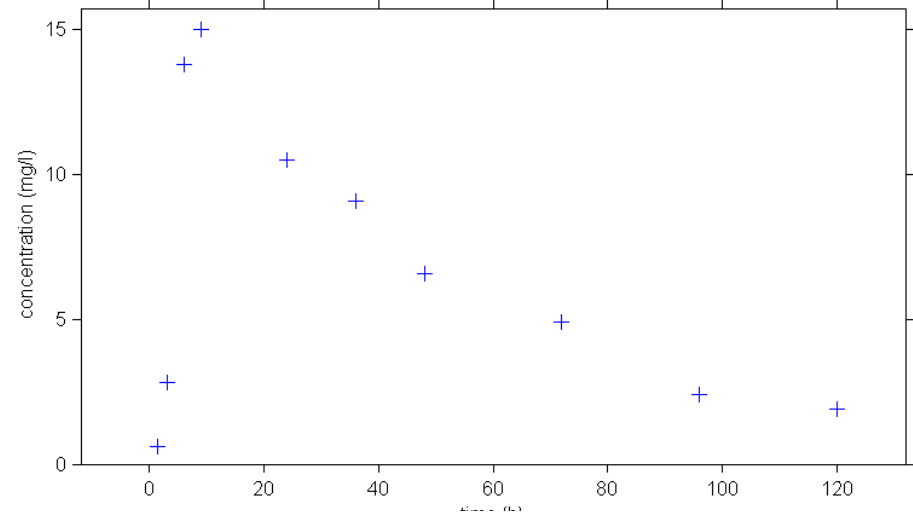
Pharmacodynamic (PD) of warfarin



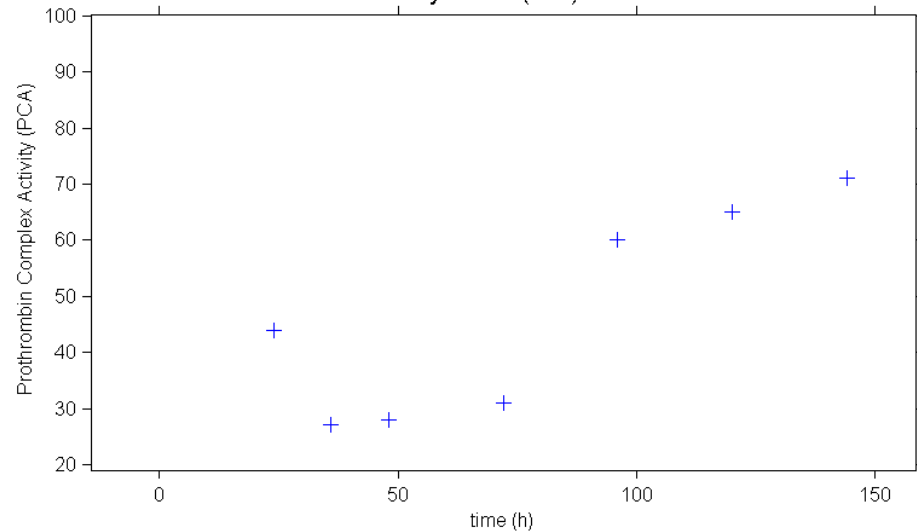
Introduction to PKPD modeling



Pharmacokinetics (PK) of warfarin



Pharmacodynamic (PD) of warfarin



Introduction to PKPD modeling

$$\begin{aligned}\frac{d}{dt}A_d(t) &= -k_a A_d(t) \\ \frac{d}{dt}A_c(t) &= k_a A_d(t) - (Cl/V) A_c(t) \\ \frac{d}{dt}E(t) &= -k_{in} \left(1 - I_{max} \frac{C_c(t)}{IC_{50} + C_c(t)} \right) - k_{out} E(t) \\ C_c(t) &= A_c(t)/V \\ E_0 &= k_{in}/k_{out}\end{aligned}$$

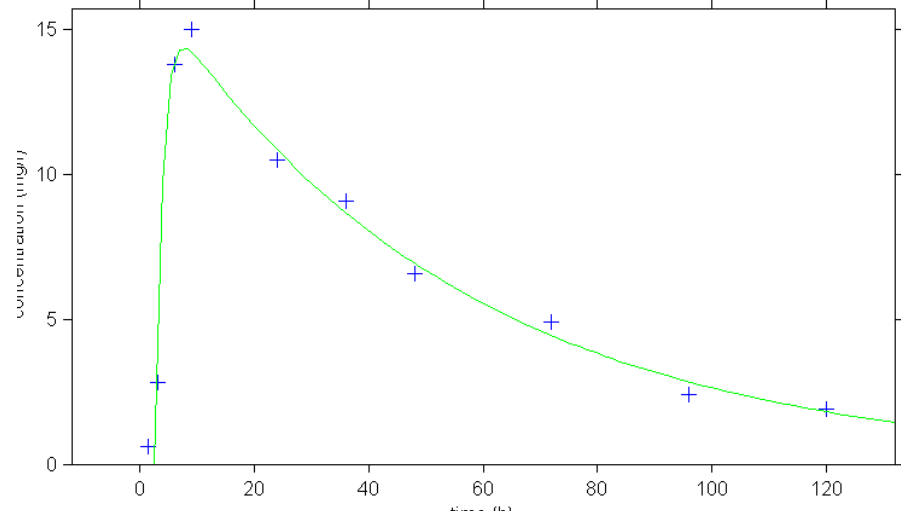
$C(t)$: predicted concentration

$E(t)$: predicted effect

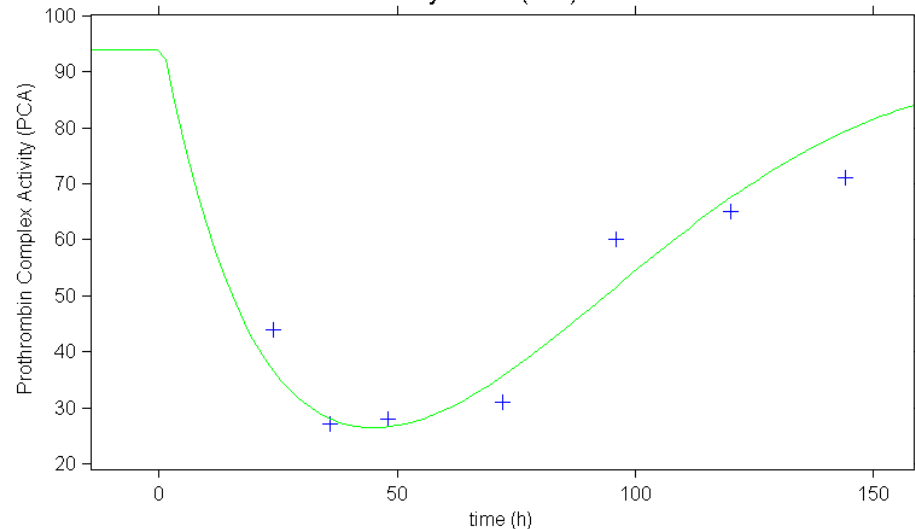
PKPD parameters:

$k_a, V, Cl, I_{max}, k_{in}, k_{out}, IC_{50}$

Pharmacokinetics (PK) of warfarin

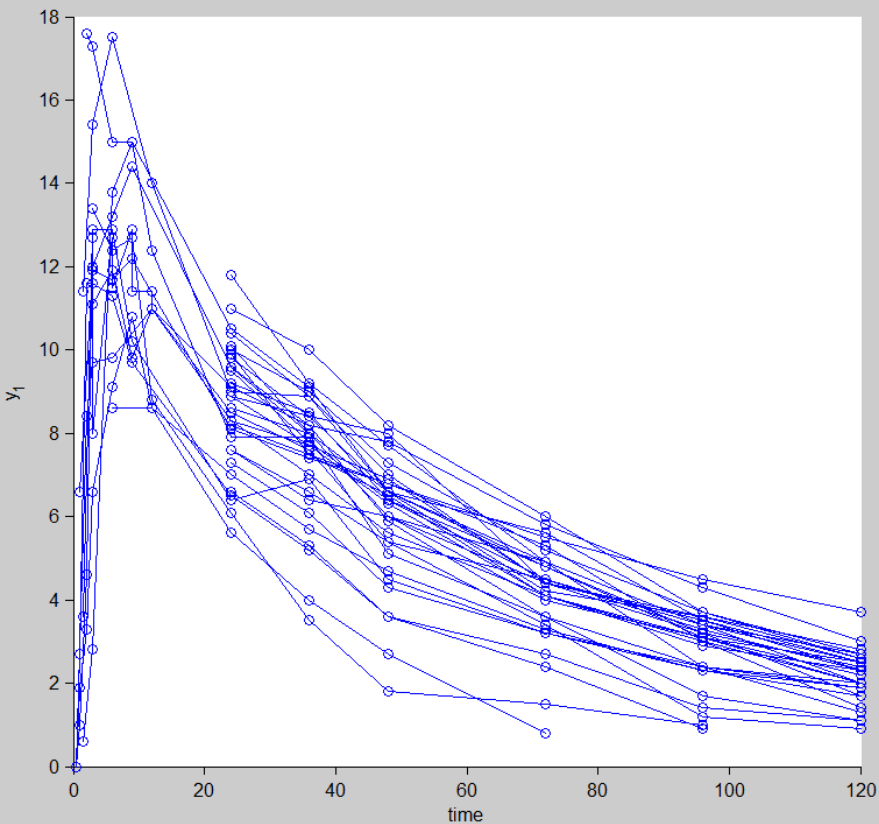


Pharmacodynamic (PD) of warfarin

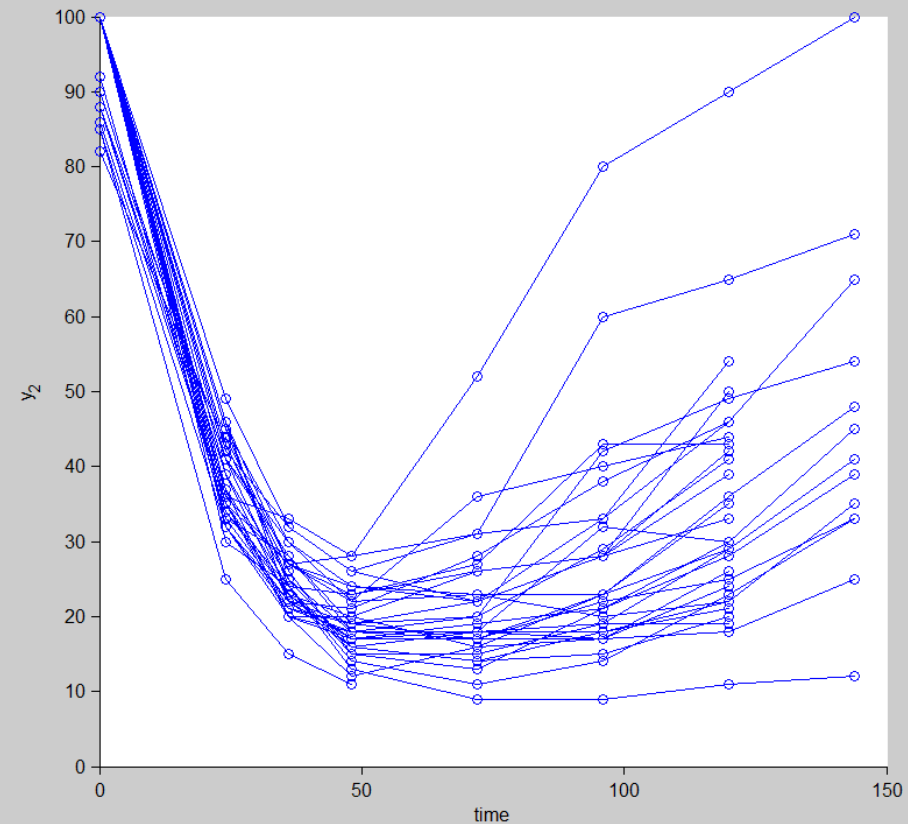


Introduction to the population approach

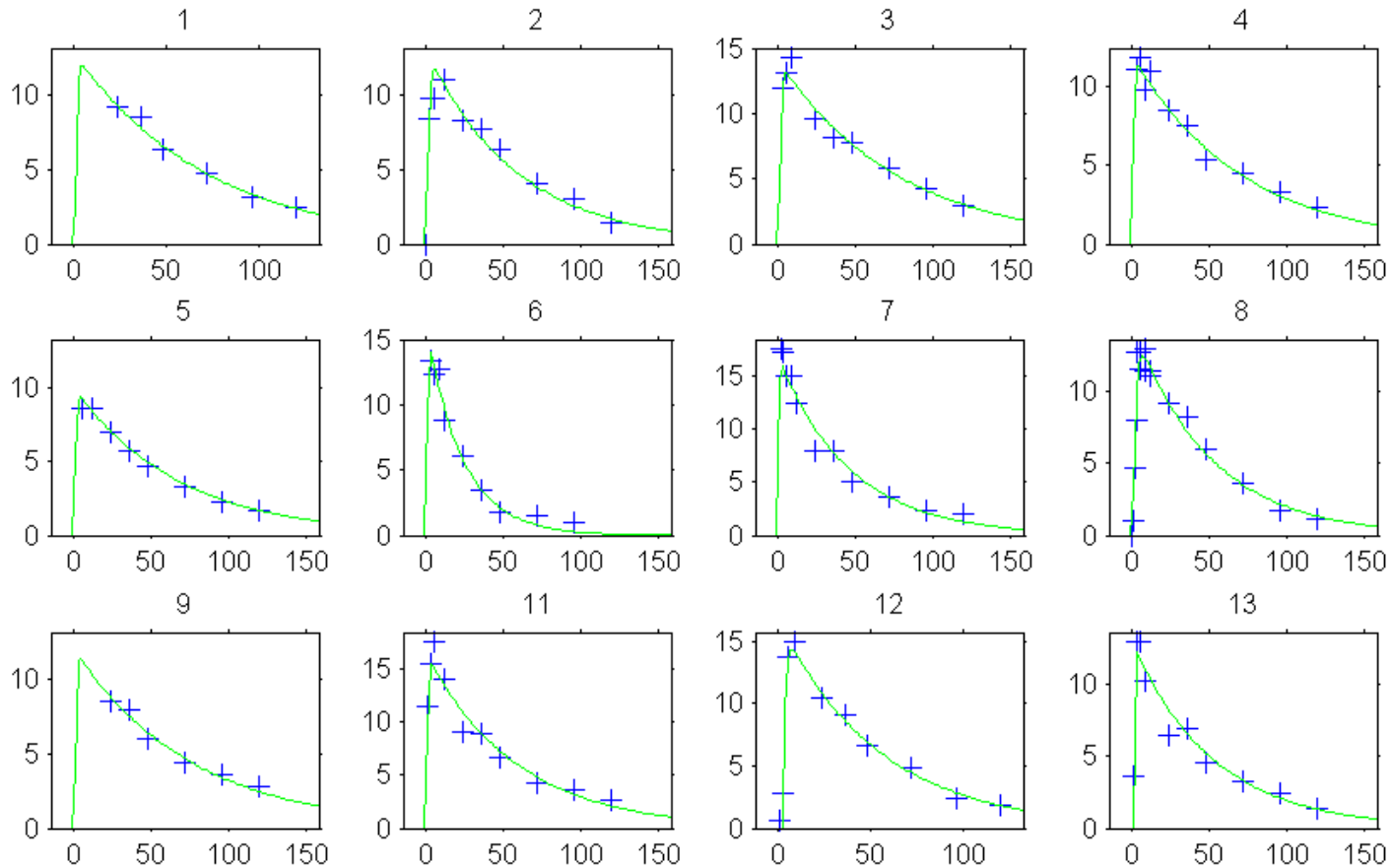
Total number of subjects: 32
Average number of doses per subject: 1.00
Total/Average/Min/Max numbers of observations: 251 7.84 6 17



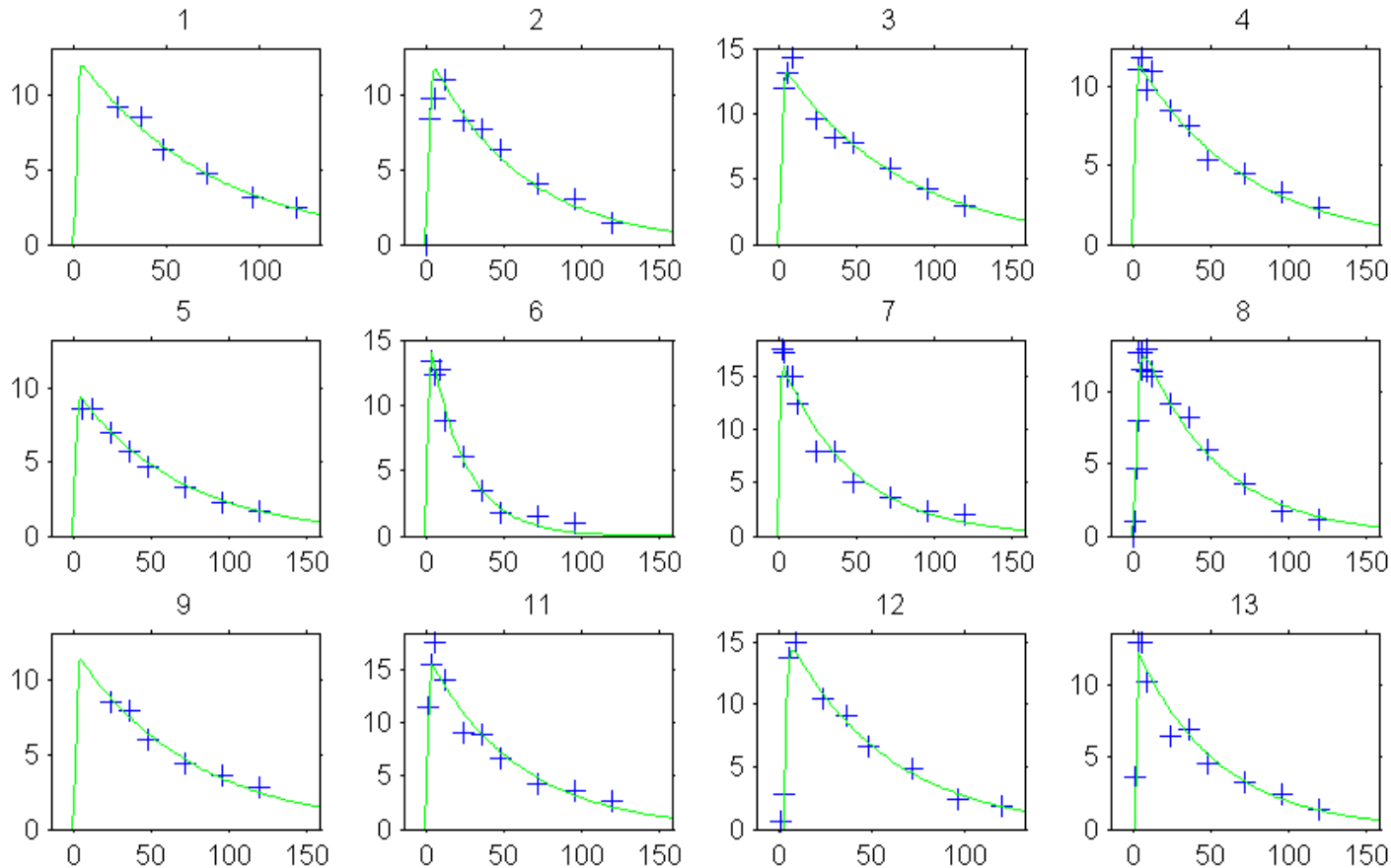
Total number of subjects: 32
Total/Average/Min/Max numbers of observations: 232 7.25 4 8



Introduction to the population approach



Introduction to the population approach



Model = pharmacological model + statistical model

Introduction to the population approach

- N subjects
- $y_i = (y_{ij}, 1 \leq j \leq n_i)$: measurements for subject i (observed)

$$y_i \sim h(\cdot; \psi_i)$$

- ψ_i : individual parameters for subject i (not observed)

$$\psi_i \sim \pi(\cdot; \theta)$$

- θ : population parameters of the model (unknown)

Some tasks to perform

$$y_i \sim h(\cdot, \psi_i)$$

$$\psi_i \sim \pi(\cdot; \theta)$$

1 Model exploration

- sensitivity analysis,
- visual exploration,

2 Parameter estimation

- population parameters θ ,
- Fisher Information matrix,
- individual parameters (ψ_i) ,

3 Model evaluation

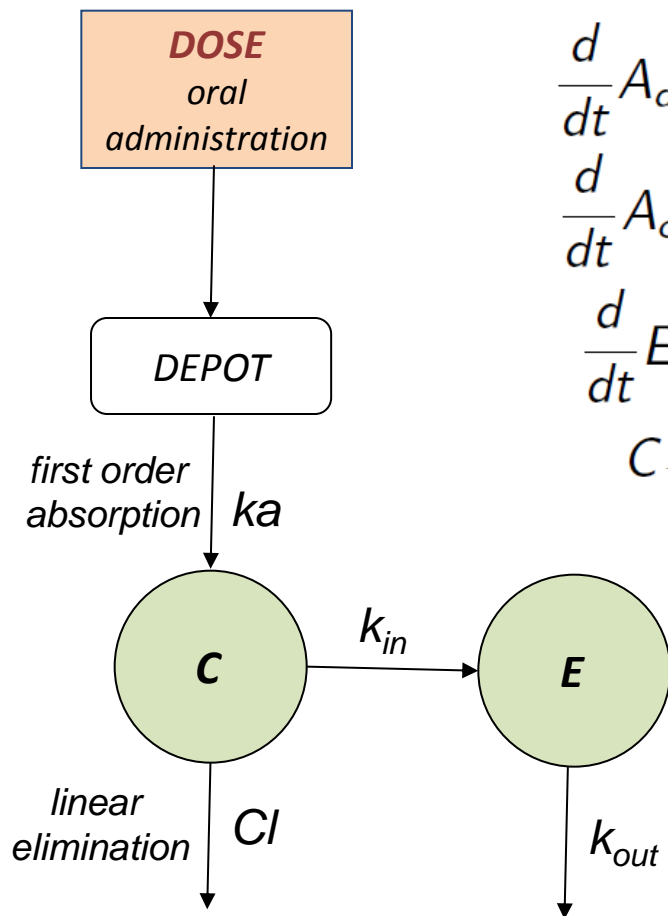
- model diagnostic,
- model selection,

4 Simulation

- clinical trial simulation

Some tools for PKPD modeling

A PKPD model



$$\frac{d}{dt}A_d(t) = -k_a A_d(t)$$

$$\frac{d}{dt}A_c(t) = k_a A_d(t) - (Cl/V) A_c(t)$$

$$\frac{d}{dt}E(t) = -k_{in} \left(1 - I_{max} \frac{C_c(t)}{IC_{50} + C_c(t)} \right) - k_{out} E(t)$$

$$C_c(t) = A_c(t)/V$$

$$E_0 = k_{in}/k_{out}$$

$C(t)$: predicted concentration

$E(t)$: predicted effect

PKPD parameters:

$k_a, V, Cl, I_{max}, k_{in}, k_{out}, IC_{50}$

MLXTran: a new modeling language

[LONGITUDINAL]

input = {ka, V, Cl, I_{max}, IC₅₀, k_{in}, k_{out}}

EQUATION:

$$\text{ddt_Ad} = -k_a * \text{Ad}$$

$$\text{ddt_Ac} = k_a * \text{Ad} - \text{Cl}/V * \text{Ac}$$

$$\text{Cc} = \text{Ac}/V$$

$$\text{E_0} = k_{in}/k_{out}$$

$$\text{ddt_E} = k_{in} * (1 - I_{max} * \text{Cc} / (\text{IC}_{50} + \text{Cc})) - k_{out} * \text{E}$$



MLXTran: a new modeling language

[LONGITUDINAL]

input = {ka, V, Cl, I_{max}, IC₅₀, k_{in}, k_{out}}

EQUATION:

$$\text{ddt_Ad} = -k_a * \text{Ad}$$

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$$\text{E_0} = k_{in}/k_{out}$$

$$\text{ddt_E} = k_{in} * (1 - I_{max} * \text{Cc} / (\text{IC}_{50} + \text{Cc})) - k_{out} * \text{E}$$

[INDIVIDUAL]

input = {V_{pop}, Cl_{pop}, omega_V, omega_{Cl}}

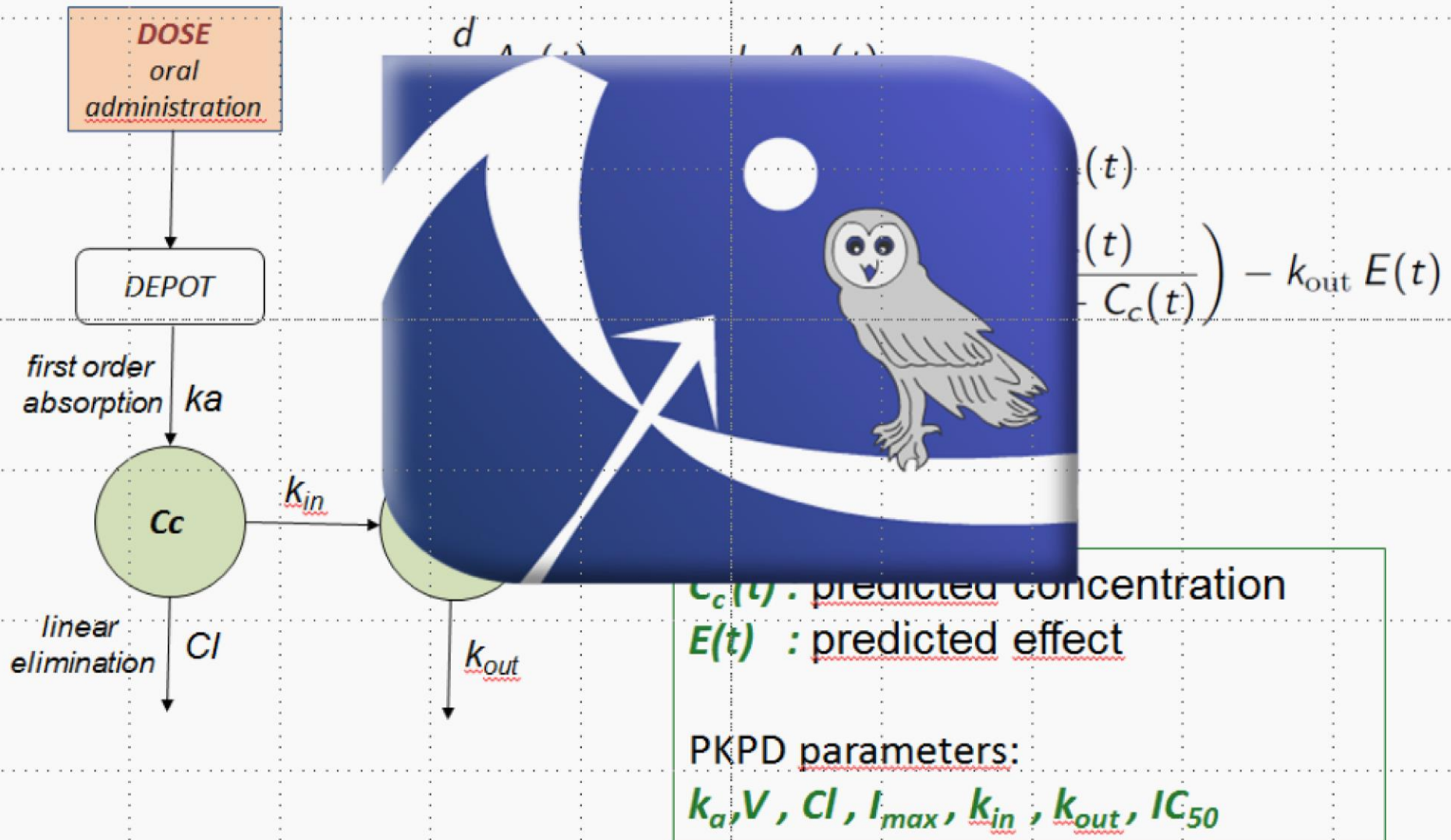
DEFINITION:

V = {**distribution**=lognormal, **reference**=V_{pop}, **sd**=omega_V}

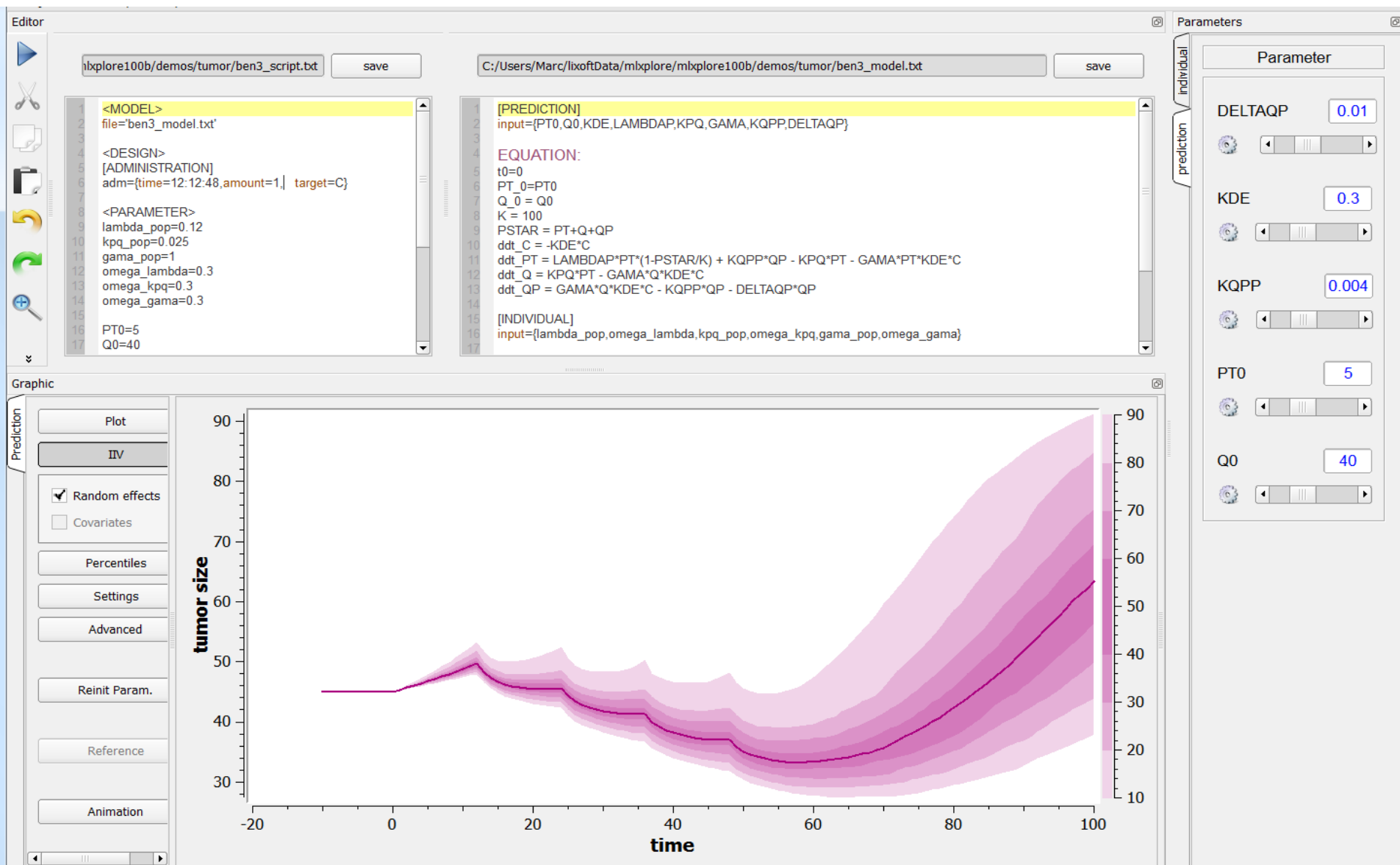
Cl = {**distribution**=lognormal, **reference**=Cl_{pop}, **sd**=omega_{Cl}}



MLXPlore: a graphical software for the exploration and visualization of complex models



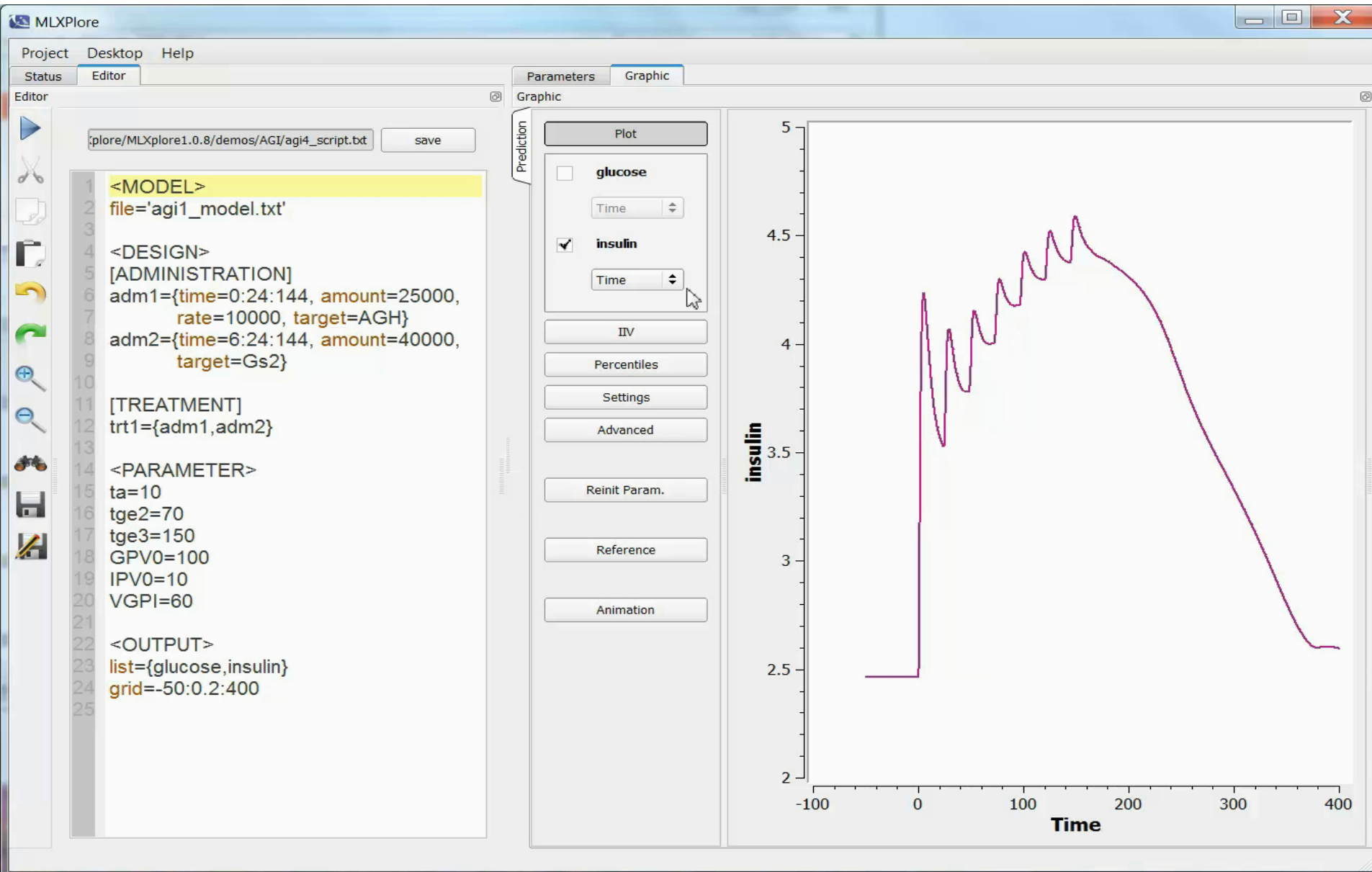
Tumor growth model



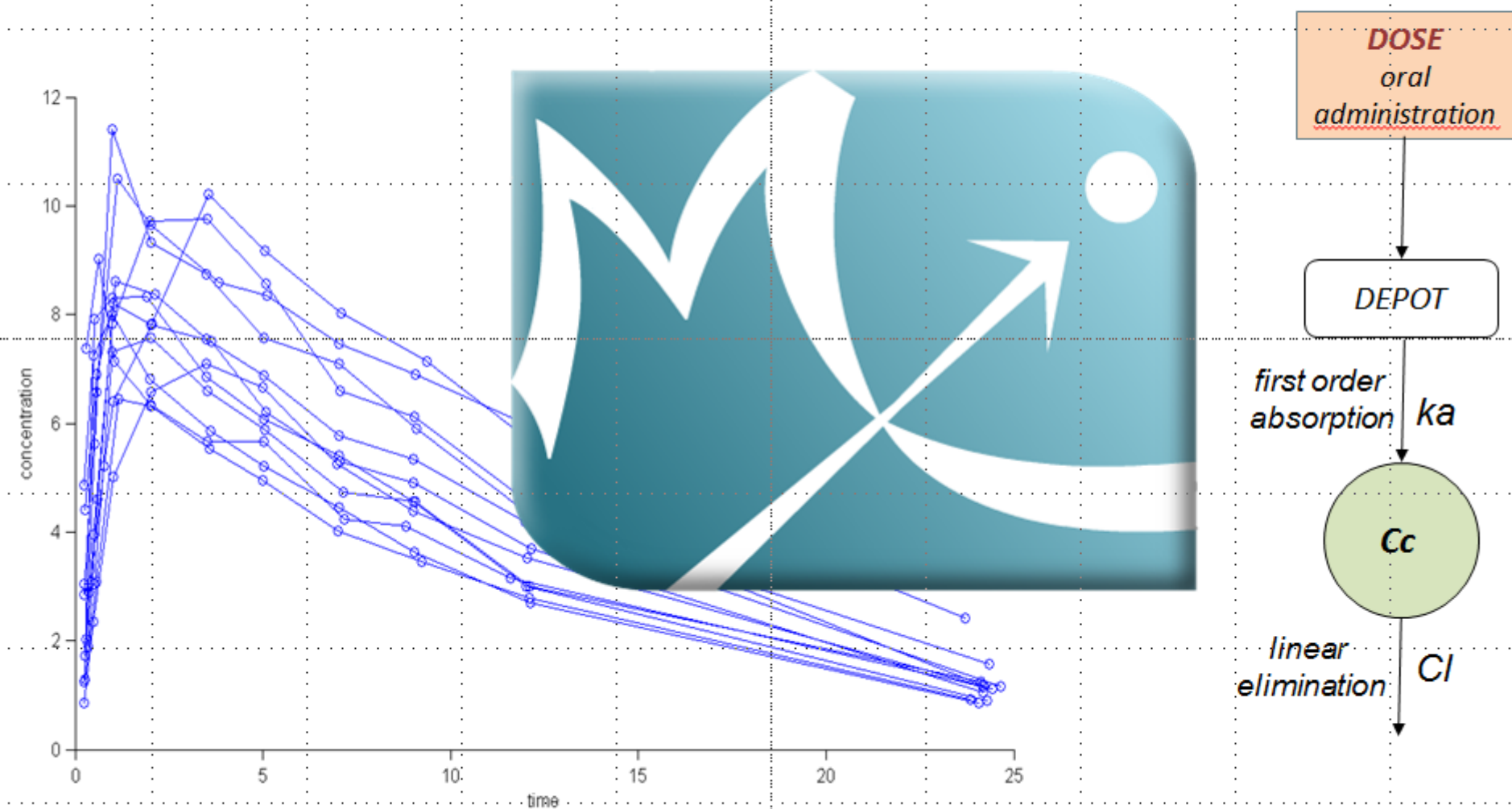
Glucose insulin model

[PREDICTION] input={ta,tge2,tge3,GPV0,IPV0,VGPI}	Q GK=10.1 Q GP=15.1 Q GPN=0.5 TB=2.1 TGP=5.0 Taul=25 TauGamma=65 rBGU=70 rBCU=10 rGGU=20 rBPGU=35 rBHGP=155 rBHGU=20 GPI=AGPI/VGPI MIHGP_0=1 MIHGU_0=1 f_0=0 VGamma=9930 rMGammaC=910 VInc=9.930 rMIncC=0.14 Taulnc=25 IncG_0=0 Alnc_0=0 IB0=IPV0/(1-FPIC) IH0=IB0 IL0=(IH0/QIL)*(QIH-QIP*(1-FPIC)-QIK*(1-FKIC)-QIB) IPN0=(IH0/QIPN)*(QIH/(1-FLIC)-QIA-QIG-(1-FPIC))/(1-FLIC)*QIP-QIB/(1-FLIC)-QIK*(1-FKIC))/(1-FLIC)) IK0=IH0*(1-FKIC) IPI0=(1-(TIP*FPIC*QIP)/(VIPI*(1-FPIC)))*IPV0 IG0=IH0 IH=AIH/VIH IB=AIB/VIH IL=AIL/VIL IG=AIG/VIG IK=AIK/VIK IPV=AIPV/VIPV IPI=AIPV/VIPV IPN=AIPN/VIPN rLIC=FLIC*(QIA*IH+QIG*IG+QIPN*IPN) rKIC=FKIC*QIK*IH rPIC=IPI/((1-FPIC)/(FPIC*QIP)-TIP/VIPI) AIH_0=IH0*VIH ddt_AIH=QIB*IB+QIL*IL+QIK*IK+QIP*IPV-QIH*IH INH=IH/IH0 AIB_0=IB0*VIB ddt_AIB=QIB*(IH-IB) AIL_0=IL0*VIL ddt_AIL=QIA*IH+QIG*IG-QIL*IL+QIPN*IPN-rLIC INL=IL/IL0 AIG_0=IG0*VIG	ddt_AIG=QIG*(IH-IG) AIK_0=IK0*VIK ddt_AIK=QIK*(IH-IK)-rKIC AIPV_0=IPV0*VIPV ddt_AIPV=QIP*(IH-IPV)+(VIPI/TIP)*(IPI-IPV) AIPV_0=IPI0*VIPI ddt_AIPV=(VIPI/TIP)*(IPV-IPI)-rPIC rBPIR=IH0*(QIH/(1-FLIC)-QIA-QIG-(1-FPIC))/(1-FLIC)*QIP-QIB/(1-FLIC)-QIPN-QIK*(1-FKIC))/(1-FLIC)) AIPN_0=IPN0*VIPN IIPV=log(IPV) IIH=log(IH) GH0=GPV0+rBPGU/QGP GBV0=GH0-rBGU/QGB GBI0=GBV0-rBGU*TB/VGBI GPI0=GPV0-rBPGU*TGP/VGPI GK0=GH0 GG0=(GH0-rGGU/QGG) GPN0=GH0 GL0=(1/QGL)*(QGA*GH0+QGG*GG0+QGP N*GPN0+rBHGP-rBHGU) x0=GH0^(3.267)/(131.87^(3.267)+5.932*(GH0^(3.024))) y0=x0^(1.1141) GH=AGH/VGH GBV=AGBV/VGBV GBI=AGBI/VGBI GG=AGG/VGG GPN=AGPN/VGPN GL=AGL/VGL GK=AGK/VGK GPV=AGPV/VGPV MlinfHGP=1.2088-1.138*tanh(1.669*(INL-0.8885)) MlinfHGU=2.0*tanh(0.549*INL) MGHGP=1.425-1.406*tanh(0.6199*(GL/GL0-0.4969)) MGHGU=5.6648+5.6589*tanh(2.4375*((GL/GL0)-1.48)) MGPGU=GPI/GPI0 MIPGU=7.035+6.51623*tanh(0.33827*((IPI/IP0)-5.82113)) ddt_MIHGP=(MlinfHGP-MIHGP)/Taul ddt_MIHGU=(MlinfHGU-MIHGU)/Taul rHGU=MGHGU*MIHGU*rBHGU rPGU=MGPGU*rBPGU*MIPGU AGH_0=GH0*VGH ddt_AGH=QGB*GBV+QGL*GL+QGK*GK+QGP*GPV-QGH*GH-rBCU GNH=GH/GH0 AGBV_0=GBV0*VGBV AGBI_0=GBI0*VGBI ddt_AGBV=QGB*(GH-GBV)- ((AGB*GPV)*(QGB*GPV)) ddt_AGG=rOGA3 + rOGA2 + QGG*(GH-GG)-rGGU AGPN_0=GPN0*VGPN ddt_AGPN=QGPN*(GH-GPN) AGL_0=GL0*VGL AGK_0=GK0*VGK if GK<0 rKGE=0 elseif GK<460 rKGE=71+71*tanh(0.011*(GK-460)) else rKGE=-330+0.872*GK end ddt_AGK=QGK*(GH-GK)-rKGE AGPV_0=GPV0*VGPV ddt_AGPV=QGP*(GH-GPV)- (VGPI/TGP)*(GPV-GPI) AGPI_0=GPI0*VGPI ddt_AGPI=(VGPI/TGP)*(GPV-GPI)- rPGU IGPV=log(GPV) IGH=log(GH) MG=2.93-2.10*tanh(4.18*(GNH-0.61)) MI=1.31-0.61*tanh(1.06*(INH-0.47)) AGammaN_0=VGamma GammaN=AGammaN/VGamma ddt_AGammaN=rMGammaC*(MG*MI-GammaN) Inc=Alnc/VInc ddt_IncG=IncG/Taulnc ddt_Alnc=IncG/Taulnc-rMIncC*Inc X=GH^(3.267)/(131.87^(3.267)+5.932*(GH^(3.024))) Y=X^(1.1141)+phi1*Inc I_0=x0 PP_0=y0 ddt_PP=alpha*(Y-PP) ddt_I=beta*(X-I) Qi=(K*Imb0+gam*y0)/(M1*y0+K) Imb_0=Qi ddt_Imb=K*(Imb0-Imb)+gam*PP- (M1*Y+M2*max(0,X-I))+phi2*Inc)*Imb S=(M1*Y+M2*max(0,X-I))+phi2*Inc)*Imb SBGH=(M1*y0)*Qi rPIR=(S/SBGH)*rBPIR ddt_AIPN=QIPN*(IH-IPN)+rPIR MGamma0HGP=2.7*tanh(0.388*GammaN) MGammaHGP=MGamma0HGP-f ddt_f=((MGamma0HGP-1)/2-f)/TauGamma rHGP=MGHGP*MIHGP*MGammaHGP*rBHGP
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Glucose-insulin model



MONOLIX: a platform of reference for model based drug development



Running a **MLXTran** model from MATLAB or R

[LONGITUDINAL]

input = {ka, V, Cl, I_{max}, IC₅₀, k_{in}, k_{out}}

EQUATION:

$$\text{ddt_Ad} = -k_a \cdot \text{Ad}$$

$$\text{ddt_Ac} = k_a \cdot \text{Ad} - \text{Cl}/V \cdot \text{Ac}$$

$$\text{Cc} = \text{Ac}/V$$

$$\text{E_0} = k_{in}/k_{out}$$

$$\text{ddt_E} = k_{in} \cdot (1 - I_{max} \cdot \text{Cc} / (\text{IC}_{50} + \text{Cc})) - k_{out} \cdot \text{E}$$

[INDIVIDUAL]

input = {V_{pop}, Cl_{pop}, omega_V, omega_{Cl}}

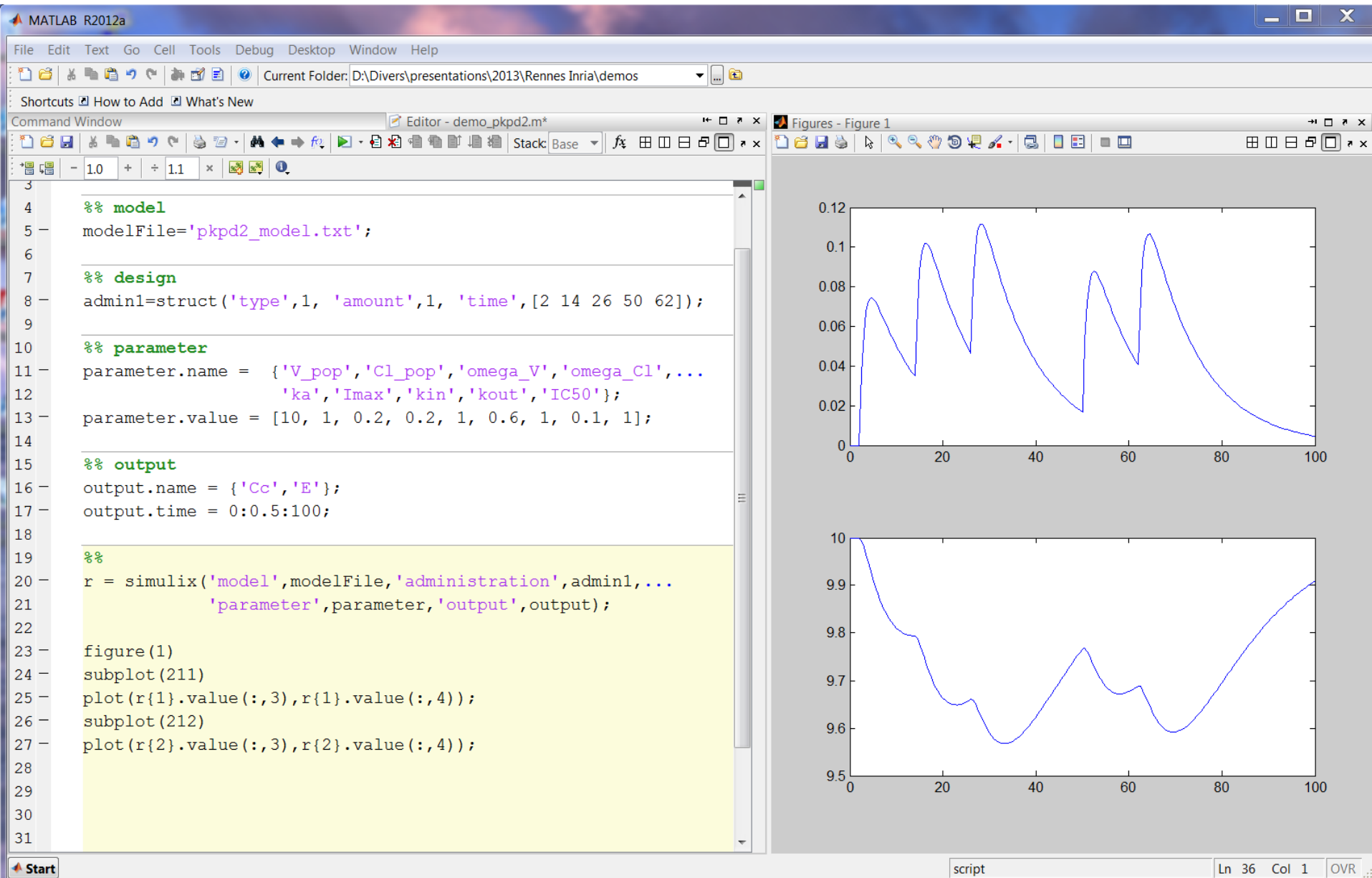
DEFINITION:

V = {**distribution**=lognormal, **reference**=V_{pop}, **sd**=omega_V}

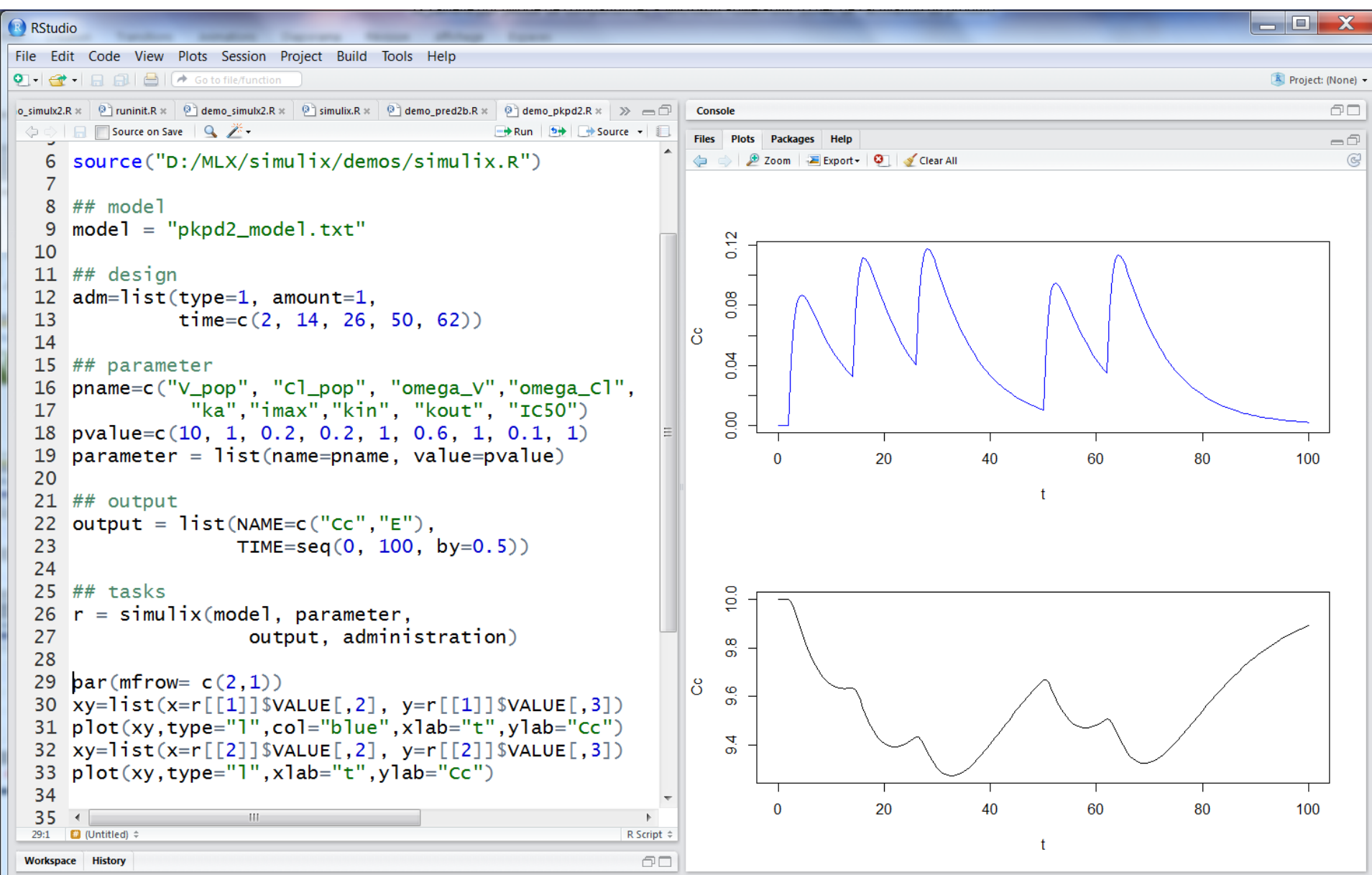
Cl = {**distribution**=lognormal, **reference**=Cl_{pop}, **sd**=omega_{Cl}}



Running a MLXTran model from MATLAB



Running a **MLXTran** model from R studio



MLXTran

- Continuous data model
 - ODEs based model
 - PK & PKPD model (dynamical system)
- Categorical data model
- Count data model
- Survival data model



Some links

Get Monolix &
MLXPlore on the
LIXOFT website



<http://lixoft.net>

WikiPopix: a wiki
about the mixed
effects models for the
population approach



<https://wiki.inria.fr/popix>