Estimation of the Area-Under-the-Curve of Mycophenolic Acid using population pharmacokinetic and multi-linear regression models simultaneously.

Michał J. Figurski & Leslie M. Shaw

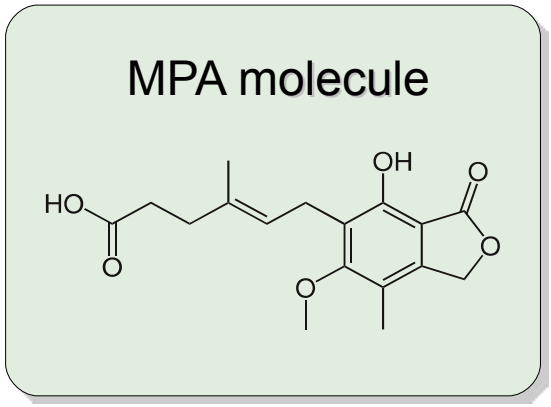
Biomarker Research Laboratory
University of Pennsylvania, Philadelphia, PA.

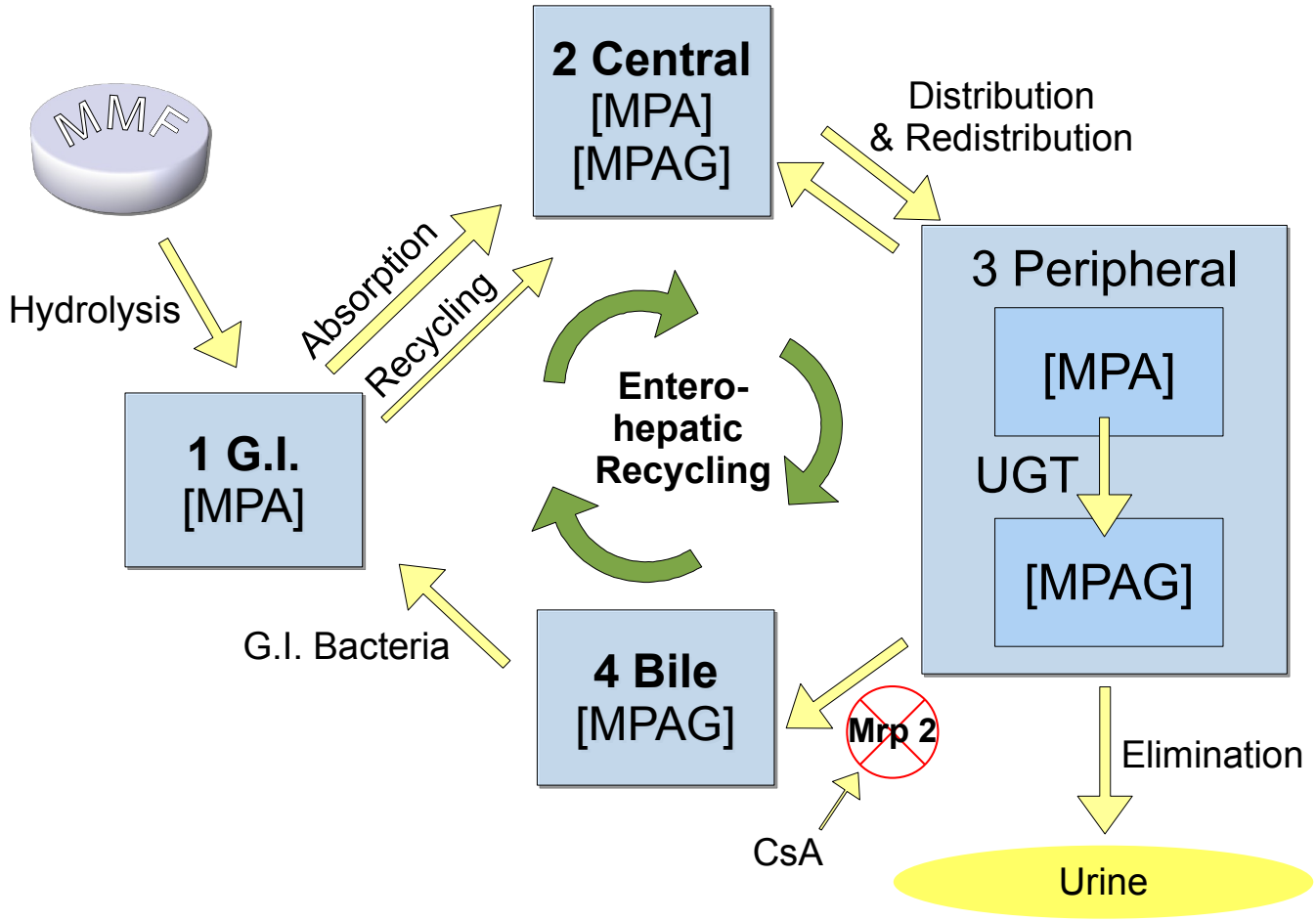
Presentation overview

- Introduction
  - The drug and the problem (2 slides)
  - Concepts of Pharmacokinetics and Therapeutic Drug Monitoring (5 slides)
- Model development
  - Overview of the data (1 slide)
  - Multi-linear regression & population PK models (4 slides)
- AUC Monitoring Study
  - Study overview (5 slides)
- The Script
  - Snippets of the code (4 slides)
- Future plans
- Acknowledgments

Introduction

The drug: Mycophenolic Acid (MPA)





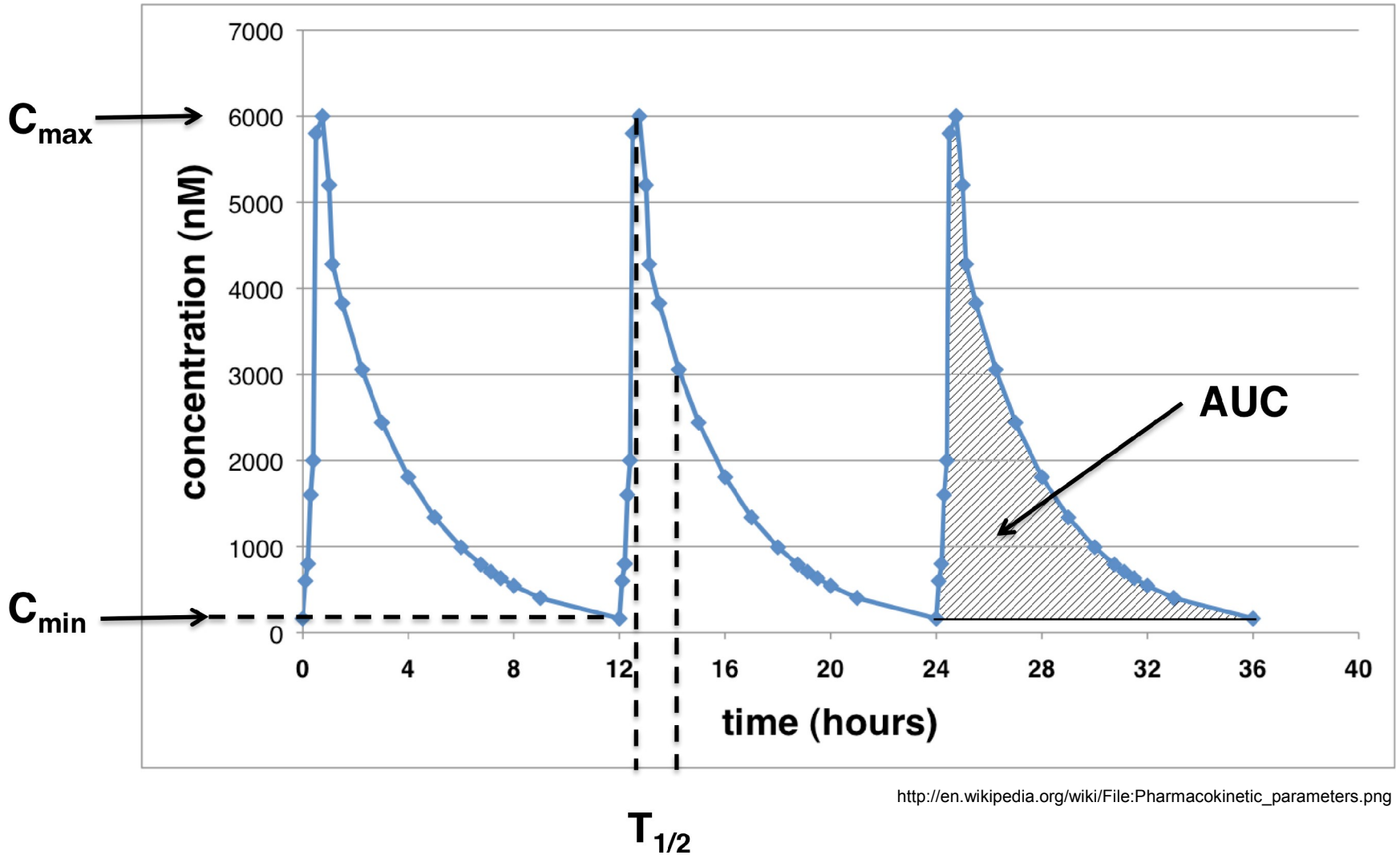
From:

L.M. Shaw, M. Figurski, M.C. Milone, J. Trofe, R.D. Bloom. *Therapeutic drug monitoring of mycophenolic acid*. Clin J Am Soc Nephrol. 2007, 2(5):1062-72

Exposure?

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Introduction
The concept of AUC

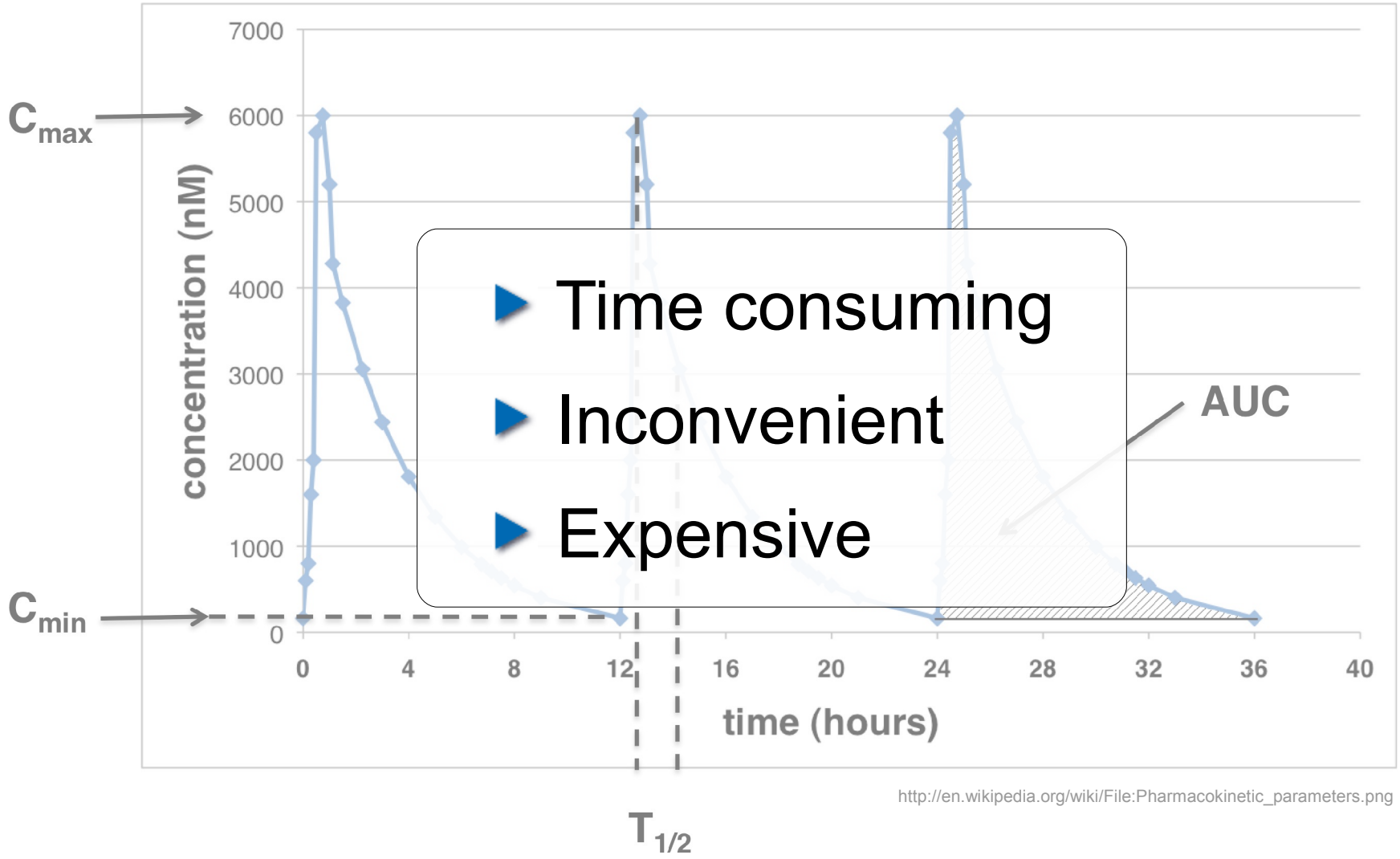


http://en.wikipedia.org/wiki/File:Pharmacokinetic_parameters.png

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Introduction

The concept of AUC

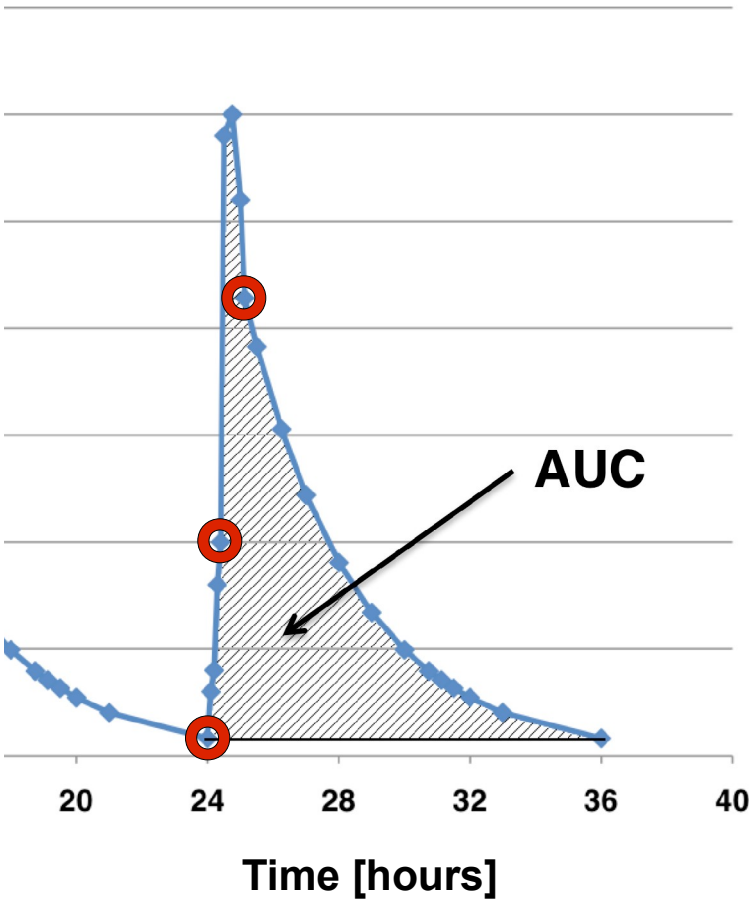


- Time consuming
- Inconvenient
- Expensive

http://en.wikipedia.org/wiki/File:Pharmacokinetic_parameters.png

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Introduction
Limited Sampling Strategy (LSS)



Predict AUC based on a few, selected time-points.

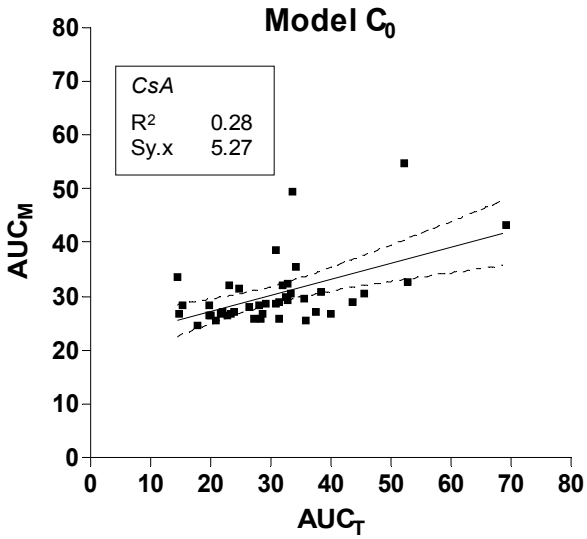
Introduction

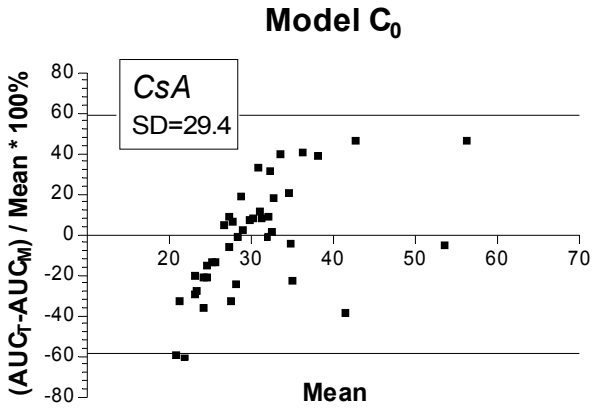
Methods of LSS: Multi-Linear Regression (MLR)

- Multiple models in the simple form:

$$AUC = \alpha_0 + \alpha_1 \cdot C_1 + \alpha_2 \cdot C_2 + \alpha_3 \cdot C_3$$

- Fit by **`glm`** in a loop, best models selected based on predictive performance
- Restriction: the same protocol must be followed

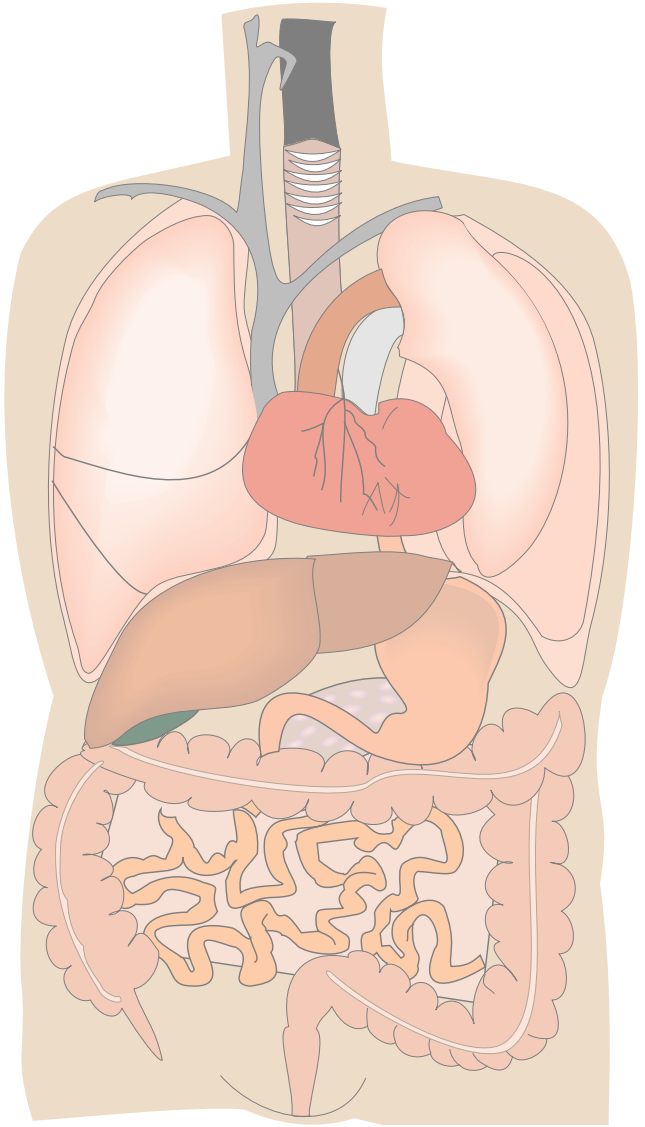




From:

M.J. Figurski, A. Nawrocki, M.D. Pescovitz, R. Bouw, L.M. Shaw, *Development of a predictive limited sampling strategy for estimation of mycophenolic acid AUC in patients receiving concomitant Sirolimus or Cyclosporine*. Ther Drug Monit, 2008, 30(4), 445-55.

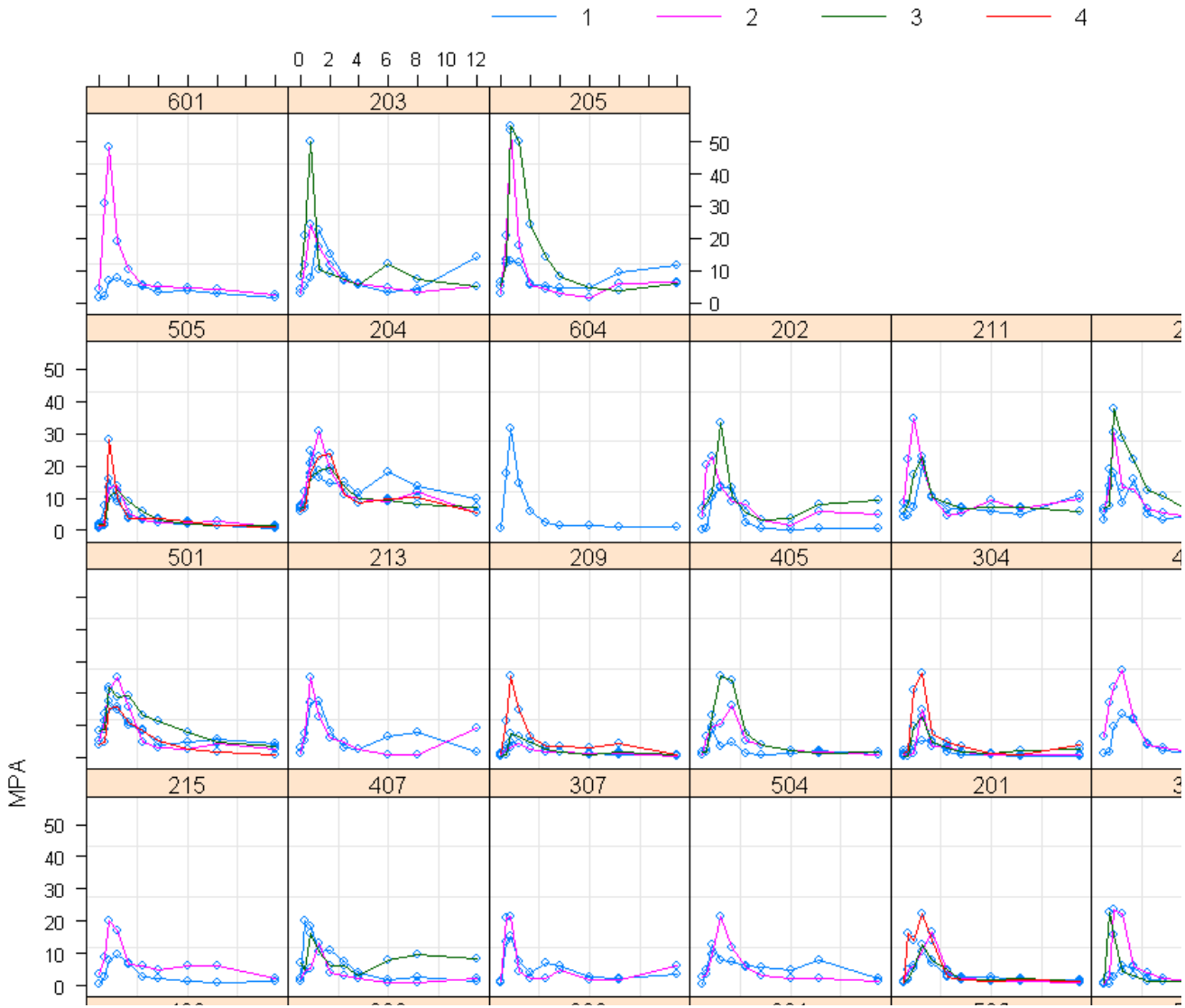
- Physiology-based models
- Form: differential equations, fit by nonlinear mixed effects method
- **NONMEM** software package is generally used for model development.
- More flexible than MLR
- Laborious model development
- Cost of license



http://www.openclipart.org/detail/596

Model development

Data snippet



M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Model development

SAS MLR code snippet

Macro with "proc glm" for developing actual models

```
...

%macro analyze (data=,model=,mod=,name=);  *INITIALIZING MACRO ANALYZE**;
title "Testgroup:  &data.   Model:  &model";
proc glm data=&data;   **START OF PROGRAM THAT I NEED TO RUN ALL TEST GROUPS THROUGH**;
model auc_t = &model;  **SPECIFY MODEL WITH MODEL STATEMENT**;
ODS OUTPUT FitStatistics=fittemp ParameterEstimates=soltemp;

**Store the data in a temporary dataset;
data fittemp;
length label $30;
length group $20;
length model $15;
set fittemp;
label = "&name";
group = "&data";
model = "&mod";
run;

**Add it (stack) to the results dataset;
data fit;
set fit fittemp;
run;

data soltemp;
length label $30;
length group $20;
length model $15;
set soltemp;
label = "&name";
group = "&data";
model = "&mod";

data solution;
set solution soltemp;
run;

%mend analyze;

data fit; **Initialize the dataset, so the 1st row is not lost;
Run;

...
```

<u>Results published in:</u>

M.J. Figurski, A. Nawrocki, M.D. Pescovitz, R. Bouw, L.M. Shaw, *Development of a predictive limited sampling strategy for estimation of mycophenolic acid AUC in patients receiving concomitant Sirolimus or Cyclosporine*. Ther Drug Monit, 2008, 30(4), 445-55

Model development

NONMEM Pop-PK model code snippet

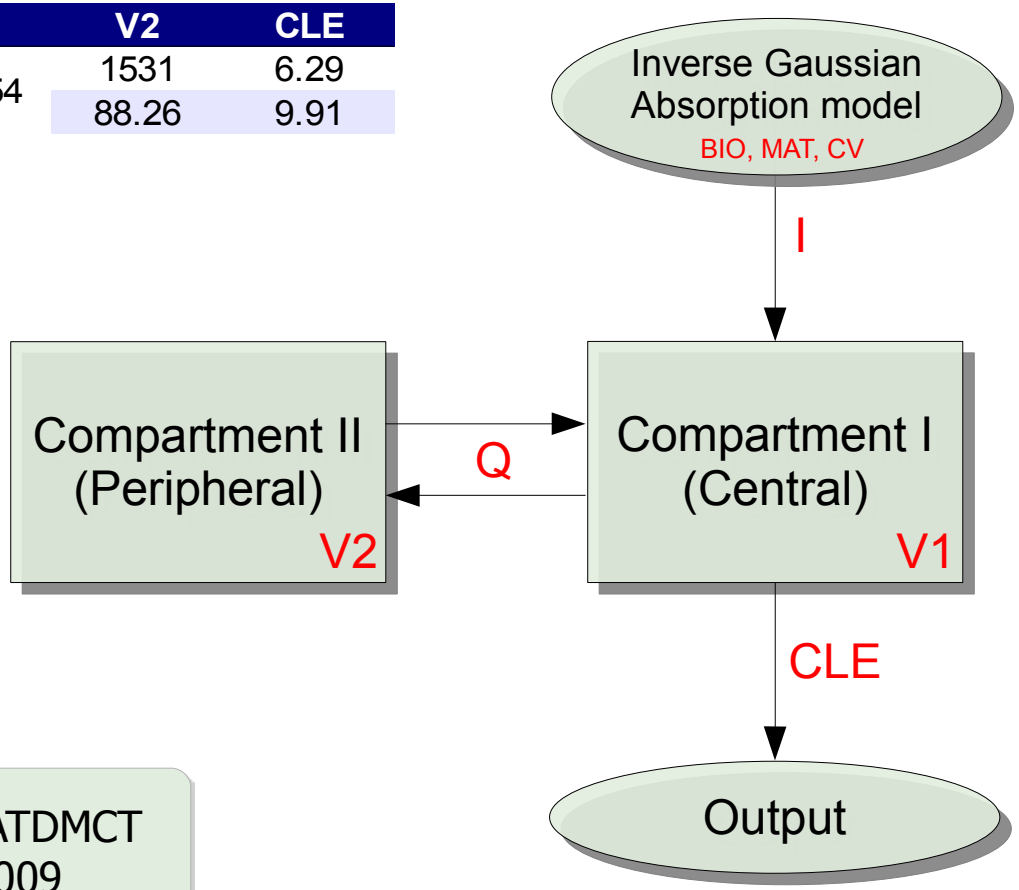

```
$PK
        GEN = (SEX +1)**THETA(12)                       ;Gender

        BIO = THETA(1)*EXP(ETA(1))                      ;Inverse Gaussian absorption model
        MAT = THETA(2)*EXP(ETA(2))
        CV  = THETA(3)*EXP(ETA(3))

        V1   = THETA(6)*EXP(ETA(6))                     ;Central Volume
        CLD  = THETA(7)*EXP(ETA(7))                     ;Disposition Clearance

        IF (TRTI.EQ.0) THEN                             ;SRL arm
           BIO2 = 0.35*BIO
           MAT2 = THETA(4)*EXP(ETA(4))
           CV2  = THETA(5)*EXP(ETA(5))
           V2   = THETA(8)*EXP(ETA(8))                  ;Peripheral Volume
           CLE  = THETA(9)*EXP(ETA(9))*GEN              ;Elimination Clearance
        ELSE                                            ;CsA arm
           BIO2 = 0
           MAT2 = 1
           CV2  = 1
           CLE  = THETA(10)*EXP(ETA(10))*GEN            ;Elimination Clearance
           V2   = THETA(11)*EXP(ETA(11))                ;Peripheral Volume
        ENDIF

        K12  = CLD/V1                                   ;Calculations of microconstants
        K21  = CLD/V2
        K10  = CLE/V1

$DES
        IF (AMT.GT.0) THEN                              ;Obtain and store DOSE for calculation of I
          D = AMT
        ENDIF

        IF (T.EQ.0) THEN
          I1 = 0
          I2 = 0
        ELSE
          FA1= MAT/(6.28*T*T*T*CV*CV)                   ;Compute absorption rate at TIME
          FA2= FA1**0.5
          FA3= (MAT-T)*(MAT-T)/(2*CV*CV*MAT*T)
          I1 = BIO*D*FA2*EXP(-FA3)
          FA21= MAT2/(6.28*T*T*T*CV2*CV2)               ;Compute absorption rate at TIME (second Gauss)
          FA22= FA21**0.5
          FA23= (MAT2-T)*(MAT2-T)/(2*CV2*CV2*MAT2*T)
          I2 = BIO2*D*FA22*EXP(-FA23)
        ENDIF

        DADT(1) = A(2)*K21 + I1 - (A(1)*K12 + A(1)*K10)     ;Central compartment: absorption & recycling
        DADT(2) = A(1)*K12 + I2 - A(2)*K21                  ;Peripheral compartment
```

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Model development

Final population PK model

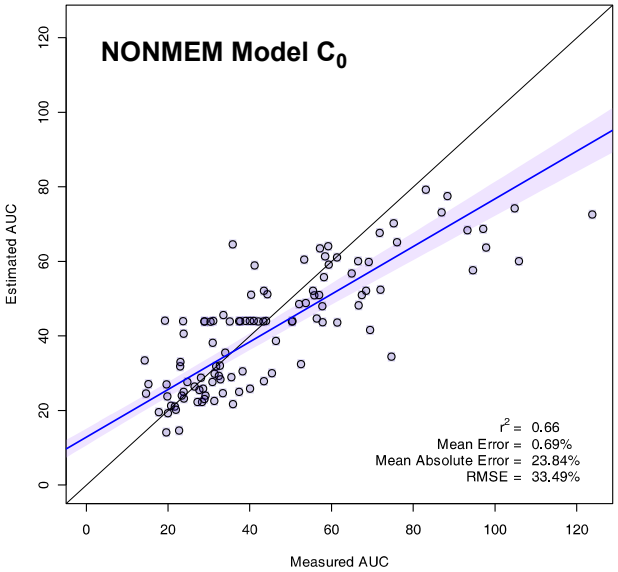
	MAT	CV	V1	Q	V2	CLE
SRL	0.73	0.59	20.94	12.54	1531	6.29
CsA					88.26	9.91

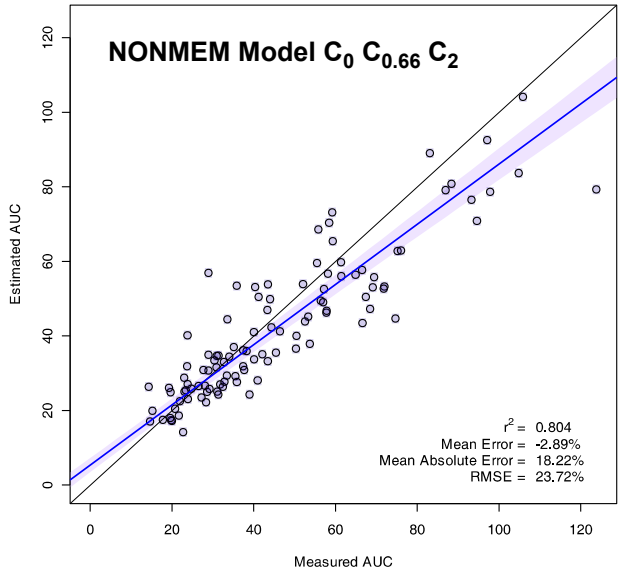


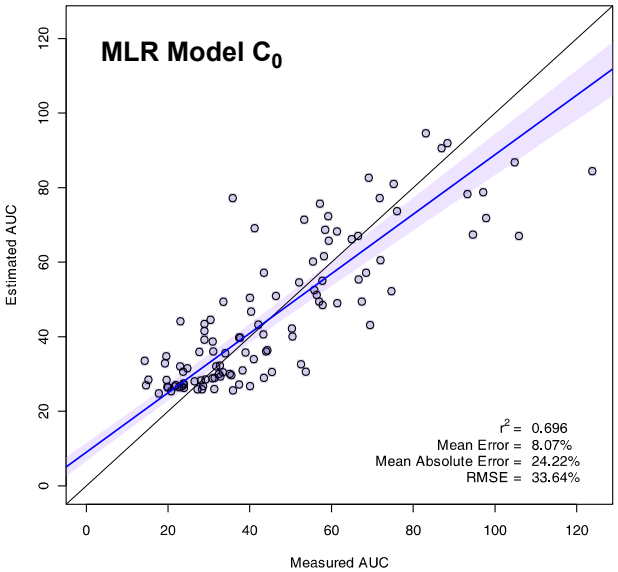
Results presented as a poster at IATDMCT conference in Montreal, Canada, 2009

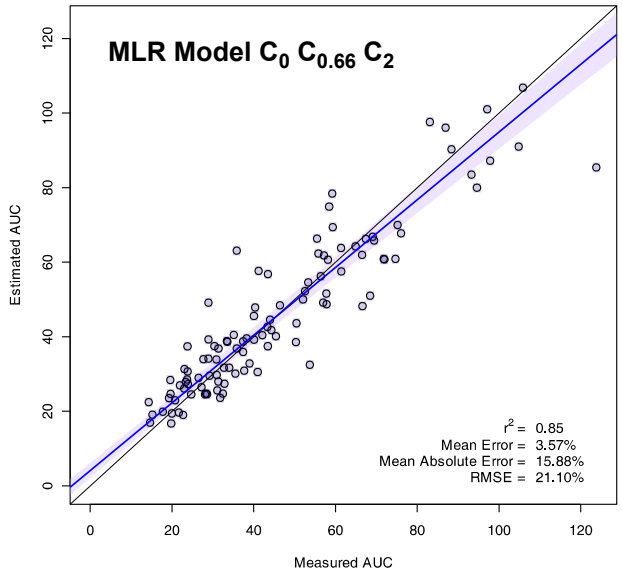
Model development

Comparing Pop-PK to MLR method for AUC prediction





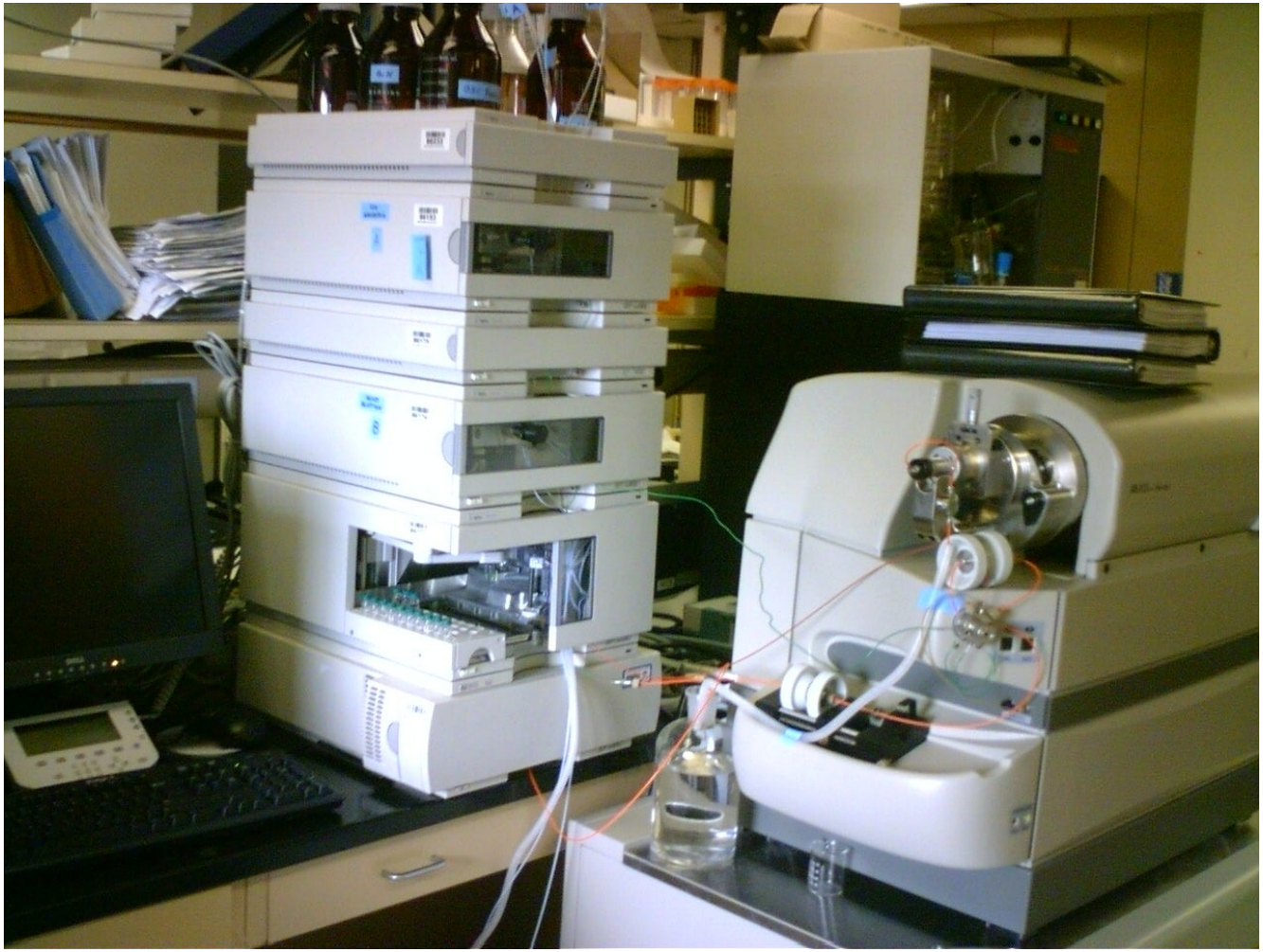




M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

Therapeutic Drug Monitoring

The laboratory



AUC Monitoring Study

Utilizing both: MLR and Pop-PK methods

LEGACY HEA

This form is to be compl
changes to the protocol, c
from related studies or adv

Principal Investigator:
Co-Investigator: Ahmed Z

Title: *AUC Monitoring of*

THE PROJECT HAS BE
☒ Protocol Modification

☒ Consent Form Modification

☐ Other (specify): Addition of co-investigator and patient consenter, Ahmed Zikri, PharmD

Does the change affect subject participation (e.g. procedures, risks, costs, etc.)
YES ☐
NO ☒

If yes, do subjects previously entered need to be notified of major changes?
YES ☐
NO ☐

BRIEF SUMMARY OF PROPOSED CHANGE (S) (or attach sponsor's summary):

This study to date demands the use of brand name CellCept®, as all historical data on which this study is based occurred in an era when generic options for mycophenolate mofetil (MMF) were not in

Fragment of a protocol page

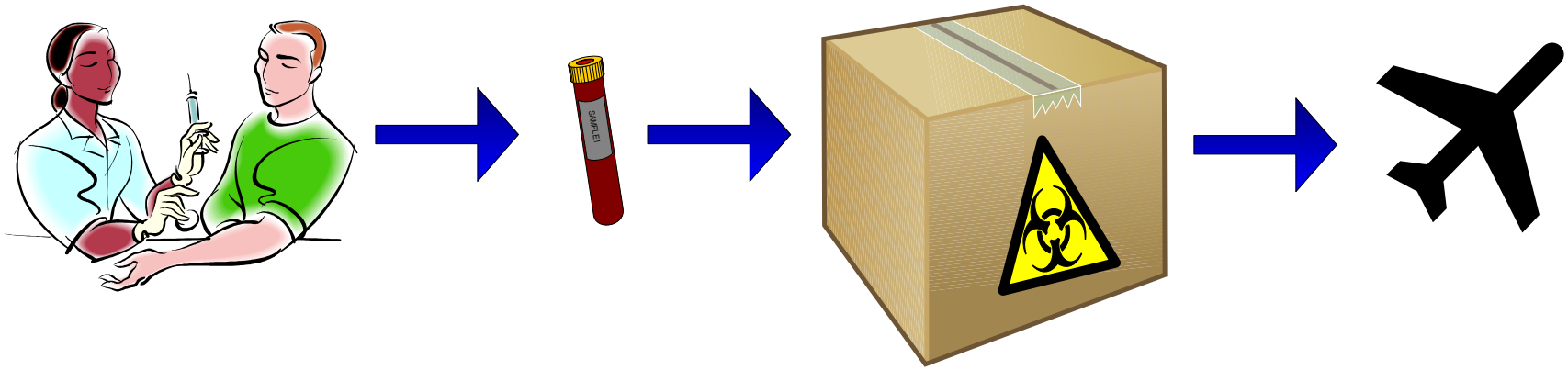
Study done in cooperation between:

- Legacy Health System, Portland, OR, and
- Biomarker Research Lab, University of Pennsylvania, Philadelphia, PA

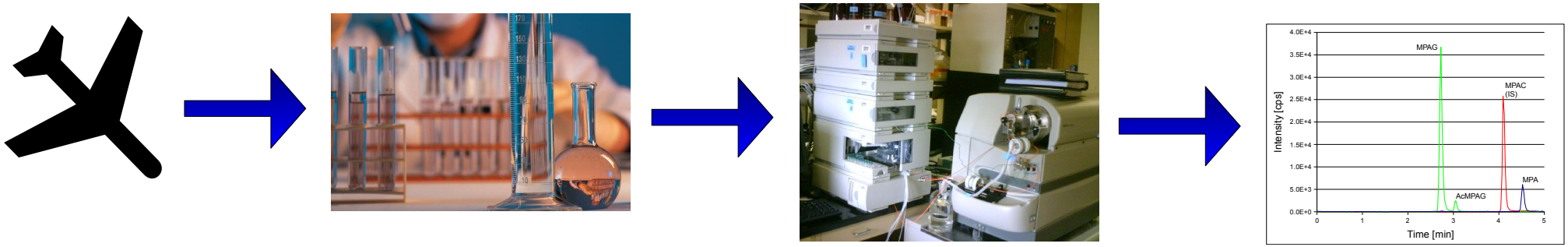
AUC Monitoring Study

Overview of study procedures

Portland:



Philadelphia:

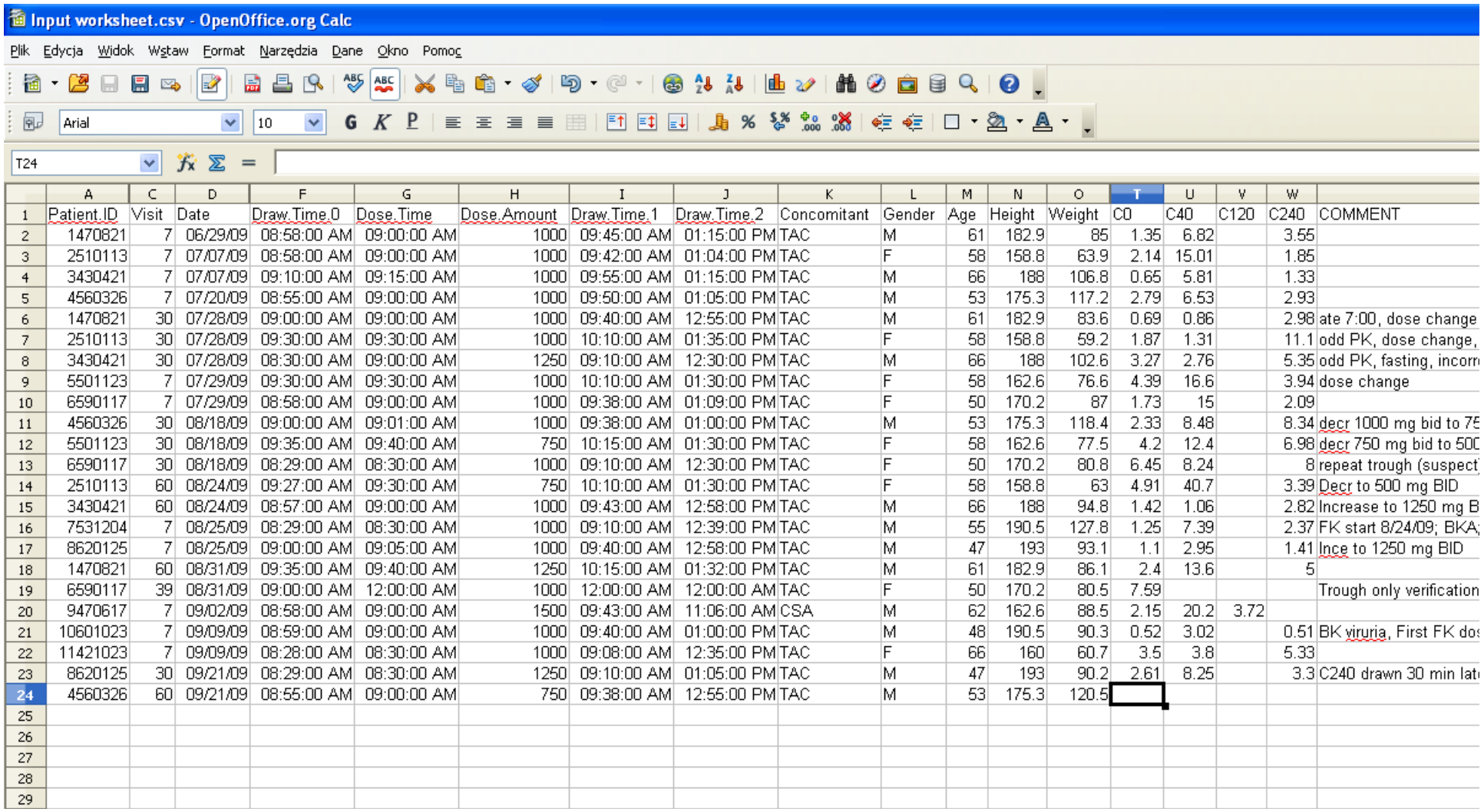


Less than 24 hours turn-around time

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

AUC Monitoring Study

Data entry



Input worksheet.csv - OpenOffice.org Calc

Plik Edycja Widok Wstaw Format Narzędzia Dane Okno Pomoc

Arial 10

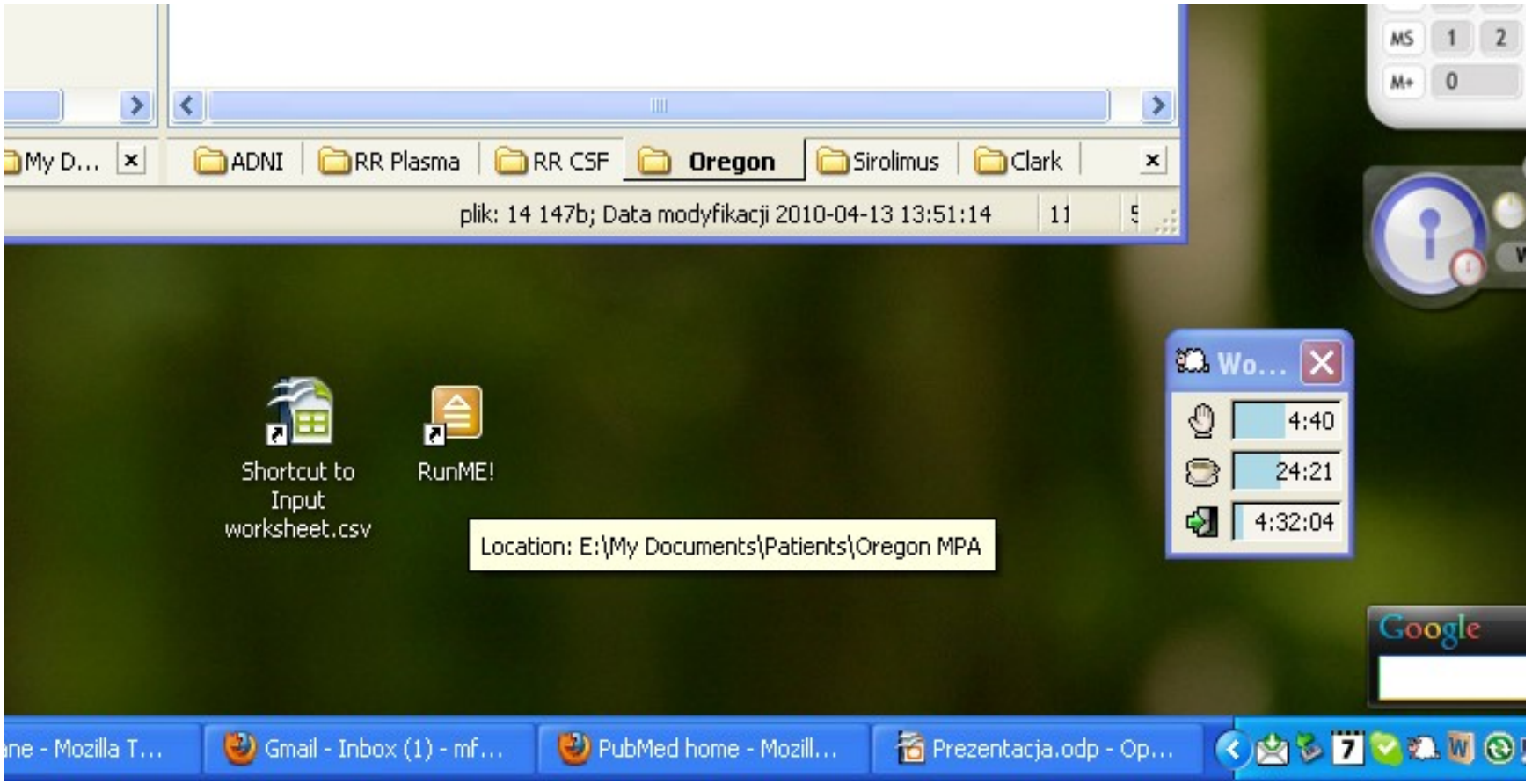
T24

	A	C	D	F	G	H	I	J	K	L	M	N	O	T	U	V	W	
1	Patient.ID	Visit	Date	Draw.Time.0	Dose.Time	Dose.Amount	Draw.Time.1	Draw.Time.2	Concomitant	Gender	Age	Height	Weight	C0	C40	C120	C240	COMMENT
2	1470821	7	06/29/09	08:58:00 AM	09:00:00 AM	1000	09:45:00 AM	01:15:00 PM	TAC	M	61	182.9	85	1.35	6.82		3.55	
3	2510113	7	07/07/09	08:58:00 AM	09:00:00 AM	1000	09:42:00 AM	01:04:00 PM	TAC	F	58	158.8	63.9	2.14	15.01		1.85	
4	3430421	7	07/07/09	09:10:00 AM	09:15:00 AM	1000	09:55:00 AM	01:15:00 PM	TAC	M	66	188	106.8	0.65	5.81		1.33	
5	4560326	7	07/20/09	08:55:00 AM	09:00:00 AM	1000	09:50:00 AM	01:05:00 PM	TAC	M	53	175.3	117.2	2.79	6.53		2.93	
6	1470821	30	07/28/09	09:00:00 AM	09:00:00 AM	1000	09:40:00 AM	12:55:00 PM	TAC	M	61	182.9	83.6	0.69	0.86		2.98	ate 7:00, dose change
7	2510113	30	07/28/09	09:30:00 AM	09:30:00 AM	1000	10:10:00 AM	01:35:00 PM	TAC	F	58	158.8	59.2	1.87	1.31		11.1	odd PK, dose change,
8	3430421	30	07/28/09	08:30:00 AM	09:00:00 AM	1250	09:10:00 AM	12:30:00 PM	TAC	M	66	188	102.6	3.27	2.76		5.35	odd PK, fasting, incorr
9	5501123	7	07/29/09	09:30:00 AM	09:30:00 AM	1000	10:10:00 AM	01:30:00 PM	TAC	F	58	162.6	76.6	4.39	16.6		3.94	dose change
10	6590117	7	07/29/09	08:58:00 AM	09:00:00 AM	1000	09:38:00 AM	01:09:00 PM	TAC	F	50	170.2	87	1.73	15		2.09	
11	4560326	30	08/18/09	09:00:00 AM	09:01:00 AM	1000	09:38:00 AM	01:00:00 PM	TAC	M	53	175.3	118.4	2.33	8.48		8.34	decr 1000 mg bid to 75
12	5501123	30	08/18/09	09:35:00 AM	09:40:00 AM	750	10:15:00 AM	01:30:00 PM	TAC	F	58	162.6	77.5	4.2	12.4		6.98	decr 750 mg bid to 500
13	6590117	30	08/18/09	08:29:00 AM	08:30:00 AM	1000	09:10:00 AM	12:30:00 PM	TAC	F	50	170.2	80.8	6.45	8.24		8	repeat trough (suspect
14	2510113	60	08/24/09	09:27:00 AM	09:30:00 AM	750	10:10:00 AM	01:30:00 PM	TAC	F	58	158.8	63	4.91	40.7		3.39	Decr to 500 mg BID
15	3430421	60	08/24/09	08:57:00 AM	09:00:00 AM	1000	09:43:00 AM	12:58:00 PM	TAC	M	66	188	94.8	1.42	1.06		2.82	Increase to 1250 mg B
16	7531204	7	08/25/09	08:29:00 AM	08:30:00 AM	1000	09:10:00 AM	12:39:00 PM	TAC	M	55	190.5	127.8	1.25	7.39		2.37	FK start 8/24/09; BKA;
17	8620125	7	08/25/09	09:00:00 AM	09:05:00 AM	1000	09:40:00 AM	12:58:00 PM	TAC	M	47	193	93.1	1.1	2.95		1.41	Ince to 1250 mg BID
18	1470821	60	08/31/09	09:35:00 AM	09:40:00 AM	1250	10:15:00 AM	01:32:00 PM	TAC	M	61	182.9	86.1	2.4	13.6		5	
19	6590117	39	08/31/09	09:00:00 AM	12:00:00 AM	1000	12:00:00 AM	12:00:00 AM	TAC	F	50	170.2	80.5	7.59				Trough only verification
20	9470617	7	09/02/09	08:58:00 AM	09:00:00 AM	1500	09:43:00 AM	11:06:00 AM	CSA	M	62	162.6	88.5	2.15	20.2	3.72		
21	10601023	7	09/09/09	08:59:00 AM	09:00:00 AM	1000	09:40:00 AM	01:00:00 PM	TAC	M	48	190.5	90.3	0.52	3.02		0.51	BK viruria, First FK dos
22	11421023	7	09/09/09	08:28:00 AM	08:30:00 AM	1000	09:08:00 AM	12:35:00 PM	TAC	F	66	160	60.7	3.5	3.8		5.33	
23	8620125	30	09/21/09	08:29:00 AM	08:30:00 AM	1250	09:10:00 AM	01:05:00 PM	TAC	M	47	193	90.2	2.61	8.25		3.3	C240 drawn 30 min lat
24	4560326	60	09/21/09	08:55:00 AM	09:00:00 AM	750	09:38:00 AM	12:55:00 PM	TAC	M	53	175.3	120.5					
25																		
26																		
27																		
28																		
29																		

M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

AUC Monitoring Study

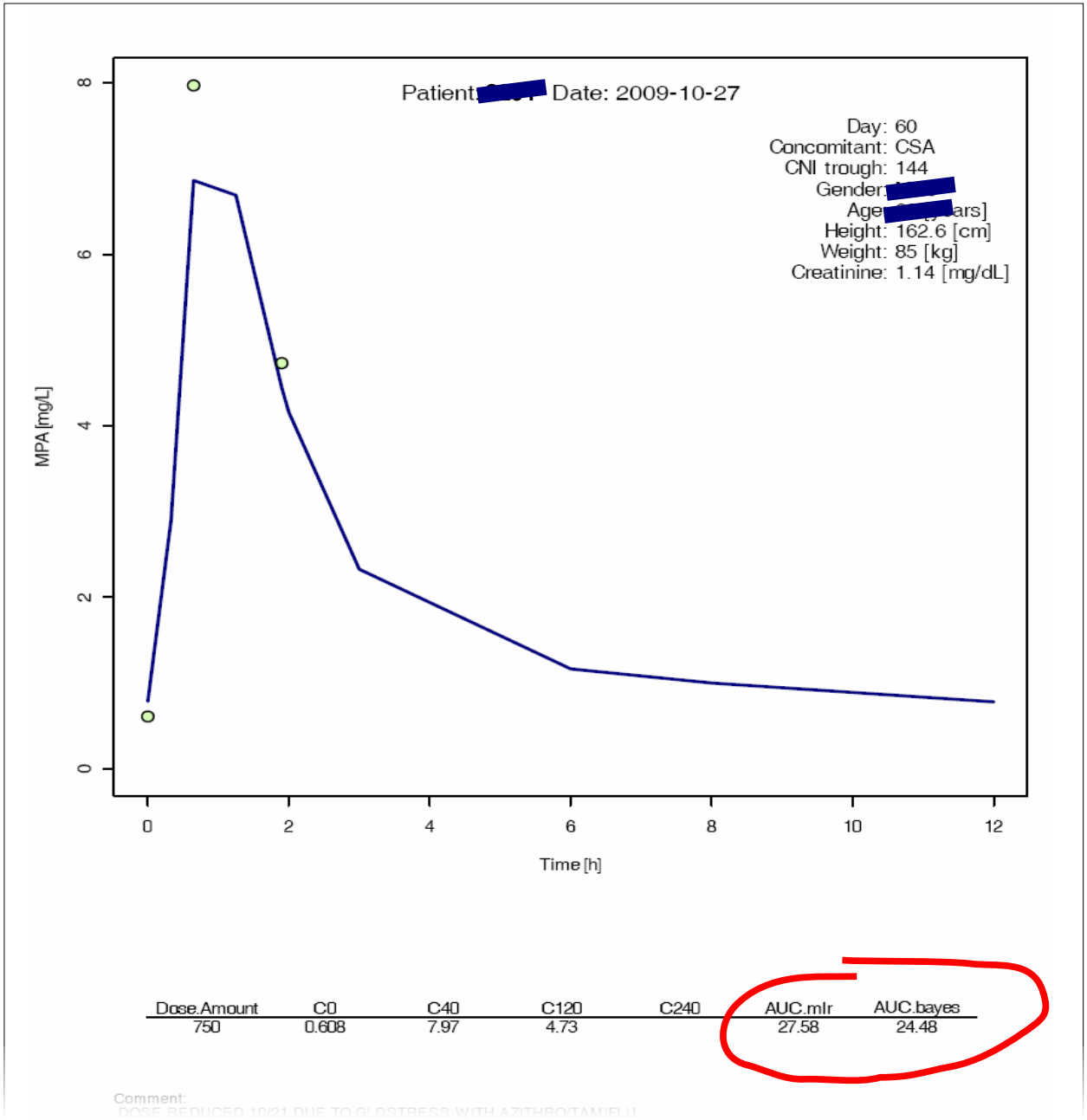
Starting the script



M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

AUC Monitoring Study

Example report page with AUC results



M.J. Figurski & L.M. Shaw, Biomarker Research Laboratory, University of Pennsylvania, Philadelphia, PA.

The Script
Code snippets 1/4

The click-able batch file

```
"C:\Program Files\R\R-2.9.2\bin\Rterm" --vanilla <"E:\My Documents\Patients\Oregon MPA\Oregon MPA.txt"
```

The R script

```
# ********************************** Load data ************************************ #

ore      = read.csv("E:\\My Documents\\Patients\\Oregon MPA\\Input worksheet.csv")

# ******************************** Type conversions ******************************** #

ore$Date = as.Date(as.character(ore$Date), "%m/%d/%y")

for (i1 in 1:nrow(ore)) {
    ore[i1,"DT.1"] = (difftime(strptime(as.character(ore[i1,"Dose.Time"]), format= "%I:%M:%S %p"),
        strptime(as.character(ore[i1,"Draw.Time.1"]), format= "%I:%M:%S %p")))[[1]]/(-60)
    ore[i1,"DT.2"] = (difftime(strptime(as.character(ore[i1,"Dose.Time"]), format= "%I:%M:%S %p"),
        strptime(as.character(ore[i1,"Draw.Time.2"]), format= "%I:%M:%S %p")))[[1]]*(-1)
    }

# ******************************** Calculate MLR AUC ******************************** #

ore$AUC.mlr = ifelse(toupper(ore$Concomitant)!="CSA", {
    ifelse(is.na(ore$C240),10.19 + 7.15 * ore$C0 + 0.80 * ore$C40 + 2.05 * ore$C120,
        8.31 +  5.91 * ore$C0 + 0.79 * ore$C40 + 5.86 * ore$C240) } ,
        10.43 +  1.47 * ore$C0 + 1.06 * ore$C40 + 1.65 * ore$C120)

ore$AUC.bayes = NA
```

Load the data

Calculate the MLR AUC

NONMEM dataset preparation

```
# *************** Prepare dataset for NONMEM (Model LSS-A6-M8-LOG-AI-S) *************** #

ore.n = matrix(nrow=0, ncol=15)
for (i1 in 1:nrow(ore)) {
    ore.c = c(0,ore[i1,"C0"], 0, ore[i1,"C40"], 0, ifelse(is.na(ore[i1,"C120"]),0,ore[i1,"C120"]), 0,
        ifelse(is.na(ore[i1,"C240"]),0,ore[i1,"C240"]),0,0,0)
    ore.t = c(0,0,0.33,ore[i1,"DT.1"],1.25,ifelse(is.na(ore[i1,"C120"]),2,ore[i1,"DT.2"]),3,
        ifelse(is.na(ore[i1,"C240"]),2,ore[i1,"DT.2"]),6,8,12)
    for (i2 in 1:length(ore.t)) {
    ore.n = rbind(ore.n, c(paste(trunc(ore[i1,"Patient.ID"]/1000000),ore[i1,"Visit"],sep="."),
        ore[i1,"Patient.ID"], round(ore.t[i2],3), round(ore.t[i2]+ore[i1,"Visit"]*24,3), ore[i1,"Visit"],
        ifelse(i2==1, round(ore[i1,"Dose.Amount"]/0.4335/2.306805, 2),0), ifelse(i2==1,1,0),
        ifelse(i2==1,12,0), ore.c[i2]/0.320/2.306805, ifelse(toupper(ore[i1,"Concomitant"])=="TAC",0,1),
        ore[i1,"Age"], ore[i1,"Height"], ore[i1,"Weight"], ifelse(ore[i1,"Gender"]=="M",0,1),
        ifelse(i2==1,1, ifelse(ore.c[i2]==0,2,0))))
        }
    }
```

Followed by setting of column names, sorting, format conversions and log of DV.

Set-up the data structure

Invoke the NONMEM run

```
# Assign the drive letter K to the working folder and save the data
system("cmd /c subst K: \"E:\\My Documents\\NONMEM\"")
write.table(ore.n, "K:/MData/OREGON/DATAFILES/MPAoLOGs.csv", row.names=F, col.names=F, sep=",", dec=".")

# Set working area and execute nonmem - will result in a crash, but output is prepared
setwd("K:\\MData\\OREGON\\WORKING\\")
shell("nmfe6 control.LSS-A6-M8-LOG-AI-S.txt output.txt", wait=T, mustWork=NA, ignore.stderr=T)
```

Call to a modified “nmfe6.bat”

Call the second script

```
source("E:\\My Documents\\Patients\\Oregon MPA\\AUCs.txt", local=F)
```

Calculate the AUCs from NONMEM simulation results

```
library(caTools)
library(Cairo)
library(plotrix)

# Read file
ore.run = read.table("AllRecords.txt", skip=1, header=T)

# Exponentiate and convert to mg/L
ore.run$eDV  = exp(ore.run[,"IPRE"])*0.320
ore.run$eDVT = exp(ore.run[,"DV"])*0.320
ore.run[ore.run$DV==0,"eDVT"] = NA

# Get rid of dosing records and get list of patients
ore.run = ore.run[ore.run$AMT==0,]
ore.ids = unique(ore.run$ID)
ore$IDS = as.numeric(paste(trunc(ore$Patient.ID/1000000),ore$Visit,sep="."))

# Calculate AUCs
for (i1 in 1:length(ore.ids)) ore[ore.ids[i1]==ore$IDS,"AUC.bayes"] =
   round(trapz(ore.run[ore.run$ID==ore.ids[i1],"TIME"], ore.run[ore.run$ID==ore.ids[i1],"eDV"]),2)
ore$AUC.mlr = round(ore$AUC.mlr,2)

# Save data table
ore$DT.1 = ore$DT.2 = ore$HPLC = NULL
write.csv(ore, "E:\\My Documents\\Patients\\Oregon MPA\\Output worksheet.csv", row.names=F)
```

This does the AUC calculation

Prepare the report file

```
# Plot the data along with fit
CairoPDF(file = "E:\\My Documents\\Patients\\Oregon MPA\\Report.pdf", width = 8.5/1.3,
    height = 11/1.3, onefile = TRUE, title = "R Graphics Output", paper = "letter")

    layout(matrix(c(1,1,1,1,1,1,2,2), 4, 2, byrow = TRUE))
    for (i1 in 1:length(ore.ids)) {
        dat  = ore.run[ore.run$ID==ore.ids[i1],c("TIME","eDV","eDVT")]
        dmax = max(dat[,2:3], na.rm=T)

        plot(dat[,1:2], type="l", xlab= "Time [h]", ylab= "MPA [mg/L]", col= "navyblue",
            lwd=1.5, ylim=c(0, dmax))
        points(ore.run[ore.run$ID==ore.ids[i1],c("TIME","eDVT")], pch=21, bg="#aaff6677",
            cex=1.2)
        text(6, 0.99*dmax, paste( "Patient: ", ore[ore$IDS==ore.ids[i1] ,"Initials"],
            ", Date: ", ore[ore$IDS==ore.ids[i1] ,"Date"], sep=""), adj=c(0.5,0.5), cex=1.3)
        text(10.5, 0.95*dmax, paste( "Dose:\n", "Concomitant:\n", "CNI trough:\n", "Gender:\n", "Age:\n",
            "Height:\n", "Weight:\n"), cex = 1.1, adj=c(1,1))
        text(10.6, 0.95*dmax, paste( ore[ore$IDS==ore.ids[i1] ,"Visit"], "\n",
            ore[ore$IDS==ore.ids[i1], "Concomitant"], "\n", ore[ore$IDS==ore.ids[i1],
            "CNI.trough"], "\n", ifelse(ore[ore$IDS==ore.ids[i1] ,
            "Gender"]=="M", "Male","Female"), "\n", ore[ore$IDS==ore.ids[i1] ,"Age"],
            " [years]\n",  ore[ore$IDS==ore.ids[i1] , "Height"], " [cm]\n",
            ore[ore$IDS==ore.ids[i1] ,"Weight"], " [kg]\n", ore[ore$IDS==ore.ids[i1] ,"SCr"],
            " [mg/dL]\n", sep = ""), cex = 1.1, adj=c(0,1))
        plot.new()
        a.tab=ore[ore$IDS==ore.ids[i1] ,c("Dose.Amount","C0","C40","C120","C240","AUC.mlr",
            "AUC.bayes")]
        addtable2plot(0,0.5,data.frame(a.tab), xjust=0, yjust=1, hlines=T, cex=1)
        mtext(paste("Comment:\n", ore[ore$IDS==ore.ids[i1] ,"COMMENT"]), side=1, line=0, adj=0, cex=0.5)
        }

dev.off()
shell.exec("E:\\My Documents\\Patients\\O
```

Plot simulated profile line

Add raw data points

Add table of results

Future plans

- Translate the Pop-PK model to R (*nlmeODE*)
  - At this stage: able to predict C_{max}
  - Poor prediction of C_0 and AUC
  - Problems with convergence
- Get rid of NONMEM
- Add simple GUI
  - File/folder selection
  - Model selection, if more than one available

Acknowledgments

- University of Pennsylvania (Philadelphia, PA):
  - Leslie M. Shaw, PhD (laboratory director)
  - Michał J. Figurski, PhD (project manager)
    contact: figurski@mail.med.upenn.edu
  - Leona B. Fields, BSc
  - Teresa Waligórska, MSc
- Legacy Health System (Portland, OR)
  - Ian Doyle, PharmD (PI of the study)
  - Ahmed Zikri, PharmD
- Parts of the project (model development) were sponsored by Roche