Optimal Sampling

Determining the 'Best' Time to Collect Samples

Objectives

- Understand the Idea of Optimal Sampling
- Understand the Graphical, Numerical and Analytical Methods of Determining Optimal Sampling Times

Why Optimal Sampling

- Samples Scarce
  - Needle stick - pain
  - Indwelling cannula - Patient sick
  - Blood loss
- Assay
  - Cost
  - Time required
- With Limited Data we want the Best Estimates of Parameter Values

Optimal Sampling

- Gives a Single Time per Parameter
  - Based on Known Model and Parameter Values
    e.g. kel = 0.2 hr^{-1} use t = 5 hr
    [IV Bolus - One compartment]
- Use a Range of Parameter Values
  - When Values not Exact Use a Range of Sample Times - Choose Extreme of Range for More Points
    e.g. kel = 0.1 — 0.3 hr^{-1} use t = 10 and 3.3 hr as well as 5 hr
    [IV Bolus - One compartment]

Optimal Sampling

- How did I get the time values in the previous slide
- A number of approaches
  - Graphical
  - Analytical
  - Numerical

Graphical Approach

- One Compartment Model - IV Bolus

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

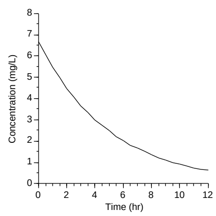
- Time for Best Values for kel and V

Graphical Approach

- Simulate Data using Known Model and Model Parameters
- Adjust One Parameters (at a time) by a Small Amount (± 1, 5, 10%) in Both Directions
- Plot (ΔCp/ΔParameter) versus Time to Determine Time of Maximum Change, Maximum Sensitivity

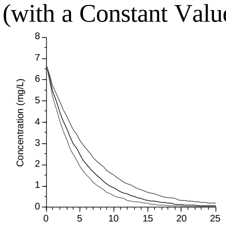
Graphical Approach

- Concentration versus Time



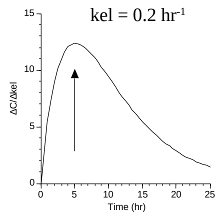
Graphical Approach

- Vary kel (with a Constant Value of V)



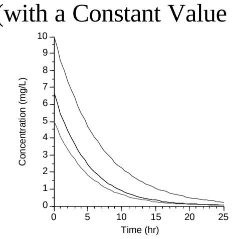
Graphical Approach

- Vary kel (with a Constant Value of V)



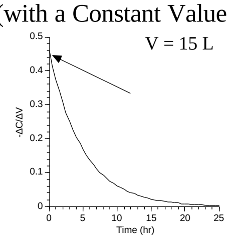
Graphical Approach

- Vary V (with a Constant Value of kel)



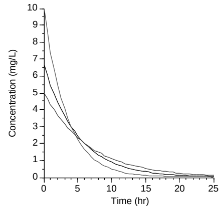
Graphical Approach

- Vary V (with a Constant Value of kel)



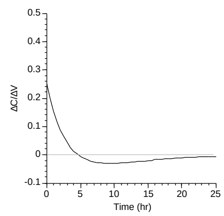
Graphical Approach

- Vary V (with a Constant Value of Cl)



Graphical Approach

- Vary V (with a Constant Value of Cl)



Analytical Approach

- Differentiate Cp versus Parameter, P_i, to Determine dCp/dP_i
- Differentiate dCp/dP_i versus Time to Determine $d^2Cp/dt.P_i$
- Set $d^2Cp/dt.P_i$ equal to 0 to Find the Time for the Maximum Value of dCp/dP_i
- Solve for Time

Analytical Approach

- One Compartment - IV Bolus Dose

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

$$\frac{dCp}{dkel} = -\frac{t \bullet Dose}{V} \bullet e^{-kel \bullet t}$$

$$\frac{d^2Cp}{dkel \bullet dt} = \boxed{(t \bullet kel - 1)} \bullet \frac{Dose}{kel} \bullet e^{-kel \bullet t} \boxed{= 0}$$

$$t = \frac{1}{kel} = \frac{1}{0.2} = 5hr$$

Analytical Approach

- One Compartment - IV Bolus Dose

$$Cp = \frac{Dose}{V} \bullet e^{-kel \bullet t}$$

$$\frac{dCp}{dV} = -\frac{Dose}{V^2} \bullet e^{-kel \bullet t}$$

$$\frac{d^2Cp}{dV \bullet dt} = \frac{Dose}{V^2 kel} \bullet \boxed{e^{-kel \bullet t} = 0}$$

$$t \quad -\infty \text{ hr}$$

$$\text{Practical Limit } t = 0 \text{ hr}$$

Numerical Approach

- Use ADAPT II, Sample Module
  - Define the Model
  - Enter the Parameter Values
  - Review Output

ADAPT II - Sample

- Define Model

Differential Equation

```
c      p(1) is kel
c
       xp(1) = -p(1)*x(1)
```

$$\frac{dX_1}{dt} = -kel \cdot X_1$$

Output Equation

```
c      p(2) is V
c
       Y(1) = x(1)/p(2)
```

$$Cp = X_1 / V$$

Weighting Equation

```
c      pv(1) is Power term
c
       v(1) = y(1)**pv(1)
```

$$Wt = 1/Var = 1/Cp^b$$

ADAPT II - Sample

- Weighting - Equal Wt (b = 0)

Sample Time	Initial Value	Final Value
Time(1)	1.000	0.4439E-08
Time(2)	10.00	4.996

Model Parameter Values used in the Design Calculations:

System Parameter	Value	"Expected" CV (%)
kel	.2000	43.47
V	15.00	15.02
IC(1)	.0000E+00	Fixed

ADAPT II - Sample

- Weighting - 1/Val (b = 1)

Sample Time	Initial Value	Final Value
Time(1)	1.000	0.1000E-01
Time(2)	10.00	10.00

Model Parameter Values used in the Design Calculations:

System Parameter	Value	"Expected" CV (%)
kel	.2000	56.21
V	15.00	38.85
IC(1)	.0000E+00	Fixed

ADAPT II - Sample

- Weighting - 1/Val^2 (b = 2)

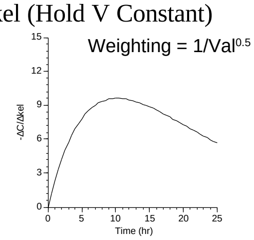
Sample Time	Initial Value	Final Value
Time(1)	1.000	0.1000E-01
Time(2)	10.00	24.00

Model Parameter Values used in the Design Calculations:

System Parameter	Value	"Expected" CV (%)
kel	.2000	29.55
V	15.00	100.1
IC(1)	.0000E+00	Fixed

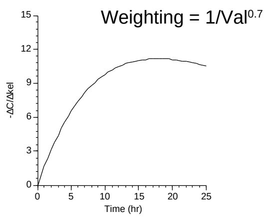
Graphical Approach

- Vary kel (Hold V Constant)



Graphical Approach

- Vary kel (Hold V Constant)



ADAPT II - Sample

- Another Example - Oral Administration

Differential Equations

```
xp(1) = -p(1)*x(1)
xp(2) =  p(1)*x(1) - p(2)*x(2)
```

Output Equation

```
y(1) = x(2)/p(3)
```

Weighting Equation

```
v(1) = y(1)**pv(1)

Psym(1) = 'ka'
Psym(2) = 'kel'
Psym(3) = 'V/F'

PVsym(1) = 'Power Term'
```

ADAPT II - Sample

- Another Example - Oral Administration

Sample Time	Initial Value	Final Value
Time(1)	1.000	0.5714
Time(2)	5.000	2.354
Time(3)	10.00	7.856

Model Parameter Values used in the Design Calculations:

System Parameter	Value	"Expected" CV (%)
ka	1.500	30.17
kel	.2000	27.69
V/F	15.00	15.72
IC(1)	.0000E+00	Fixed
IC(2)	.0000E+00	Fixed

Optimal Sampling for Model Selection

- Use the Program DESIGN
- Define both Models
- Run the Program
- Output Gives the Best Time to Distinguish Between Models

DESIGN

- Output - One Compartment Model

```
 RESID VAR 1    PARAMETERS FOR MODEL 1
   .20818      11.951      .54549
 STD. DEVS. =  1.4909     0.82943E-01
                  12.5%       15.2%
 DEPENDENCIES  .83773      .83773
 FINAL LAMBDA = 0.10000E-03   DEGREES OF FREEDOM =  4
ITERATIONS =   1

 FIT DETAILS FOR THE MODEL 1
----------------------------

       X           Y         YFIT       RESIDUAL     Z-RESIDUAL
   1.0000      7.1700      6.9262      .24376         15.856
   2.0000      3.4600      4.0142     -.55415        -36.045
   4.0000      1.5600      1.3483      .21170         13.770
   6.0000      .92000      .45288      .46712         30.384
   9.0000      .48000     0.88159E-01  .39184         25.488
   12.000      .24000     0.17162E-01  .22284         14.495
```

DESIGN

- Output - Two Compartment Model

```
RESID VAR 2    PARAMETERS FOR MODEL 2
 0.23635E-03  15.842      1.3120      3.6454      .22751
STD. DEVS. =  .30922     0.35855E-01  .13744     0.62182E-02
                 2.0%        2.7%        3.8%        2.7%
DEPENDENCIES  .98729      .99688      .99611      .97987
FINAL LAMBDA = 0.10000E-05   DEGREES OF FREEDOM =  2
 ITERATIONS =   3

FIT DETAILS FOR CURRENT BEST MODEL: MODEL 2 (NEXT BEST IS MODEL 1)
-------------------------------------------------------------------

      X           Y         YFIT       RESIDUAL     Z-RESIDUAL
  1.0000      7.1700      7.1697     0.27275E-03   0.17741E-01
  2.0000      3.4600      3.4616    -0.16046E-02   -.10437
  4.0000      1.5600      1.5506     0.93634E-02    .60905
  6.0000      .92000      .93697    -0.16974E-01   -1.1041
  9.0000      .48000      .47056     0.94417E-02    .61414
  12.000      .24000      .23774     0.22639E-02    .14725
```

DESIGN

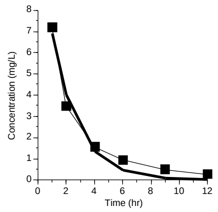
- Output - Combined

```
LIKELIHOODS:     MODEL1      MODEL2
               0.000000    1.000000

L(2)/L(1)              =  0.6833E+09
LN(L(2)/L(1))          =   20.34
CONFIDENCE IN MODEL 2  =  100.0%                PERFORM NEXT
                                              EXPERIMENT AT X
T(MAX) MODEL 2 =    0.4286E-01 AT X =     1.000
                                                VALUE
                                            INDICATED BELOW FOR:
T(MAX) MODEL 1 =     1.285     AT X =     1.000
D0(MAX)        =    0.1689E-03 AT X =     12.00-- MODEL
                                                DISCRIMINATION
E(MAX)         =     1.000     AT X =     1.000-- PARAMETER
                                                ESTIMATION
W1 =    .0000    , W2 =    1.000
C(MAX)         =     1.000     AT X =     1.000-- COMBINED
                                                REQUIREMENT
```

DESIGN

- Output Plot



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