Identifiability

Can you support your model with the data that you have?

Objective

- To understand the problem of model identifiability
- To recognize some common examples and types of identifiability problems
- To use some of the techniques that could be used to recognise identifiability problems

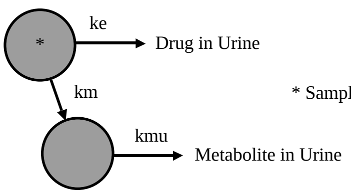
Chapter Outline

- Definitions
- Examples
- Numerical Approaches
- Analytical Approaches

Definitions

- Identifiability Problem: Can the Model Parameters be Estimated Accurately with the Data Provided
- Identifiable Parameters
  - Effect the value of the data and can be estimated
- Nonidentifiable Parameters
  - Effect the value of the data but cannot be estimated
- Nonobservable Parameters
  - Don’t have an influence on the data

Definitions - Parameters



* Sampled Component of the Model

V, kel	Identifiable
ke, km	Nonidentifiable
kmu, Vm	Nonobservable

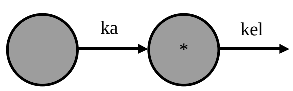
Definition - Identifiability

- Global
  - Not affected by dose, scale
- Local
  - Dependent on dose or scale

Examples: Problems caused by:

- Too many parameters
- Poor sample site selection
- Poor selection of dose levels
- Poor selection of sample times

Example - Too Many Parameters



$$Cp = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left\{ e^{-kel \bullet t} - e^{-ka \bullet t} \right\}$$

* Sampled Component of the Model

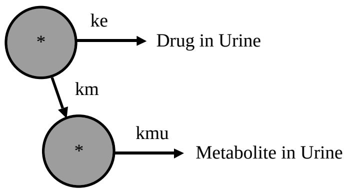
Example - Too Many Parameters

$$Cp = \frac{F \bullet Dose \bullet ka}{V \bullet (ka - kel)} \bullet \left\{ e^{-kel \bullet t} - e^{-ka \bullet t} \right\}$$

Constants: Dose

Parameters: ka
kel
V } V/F
F

Example - Sample Site Selection



* Sampled Component of the Model

Example - Sample Site Selection

Dose = 100 mg, V = 10 L, kmu = 0.5 hr^{-1}, ke = 0.1 hr^{-1}, km = 0.2 hr^{-1}, Vm = 20 L.

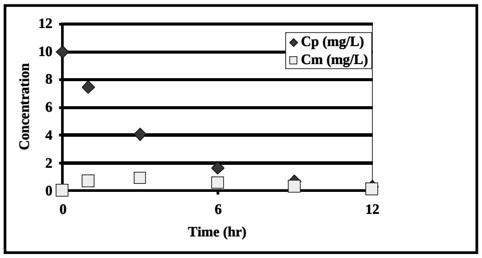
Time (hr)	Cp (mg/L)	Cm (mg/L)	U (mg)
0.0	10.0	0.0	0.0
1.0	7.41	0.671	8.64
3.0	4.07	0.917	19.8
6.0	1.65	0.578	27.8
9.0	0.672	0.280	31.1
12.0	0.273	0.124	32.4

Example - Sample Site Selection

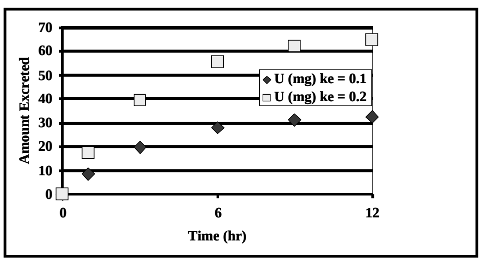
Dose = 100 mg, V = 10 L, kmu = 0.5 hr^{-1}, ke = 0.2 hr^{-1}, km = 0.1 hr^{-1}, Vm = 10 L.

Time (hr)	Cp (mg/L)	Cm (mg/L)	U (mg)
0.0	10.0	0.0	0.0
1.0	7.41	0.671	17.3
3.0	4.07	0.917	39.6
6.0	1.65	0.578	55.6
9.0	0.672	0.280	62.2
12.0	0.273	0.124	64.8

Example - Sample Site Selection



Example - Sample Site Selection



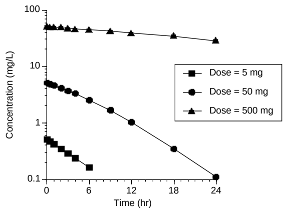
Example - Dose Level Selection

- Michaelis-Menten

$$\frac{dCp}{dt} = -\frac{Vm \cdot Cp}{Km + Cp}$$

- Low Dose
- High Dose

Example - Dose Level Selection

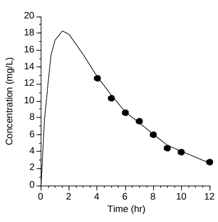


Example - Sample Time Selection

- One Compartment - Oral Administration

$$Cp = \frac{F \bullet ka \bullet Dose}{V \bullet (ka - kel)} \bullet \left\{ e^{-kel \bullet t} - e^{-ka \bullet t} \right\}$$

Example - Sample Time Selection



Numerical Approach

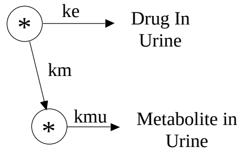
- Empirical
- Using IDENT

Empirical Approach

- Method
  - Simulate Model
  - Sample Sites and Times
  - Use Many Sample Times
  - Refit Simulated Data

Empirical Approach

The Model



Empirical Approach

The Data

Time (hr)	[Drug] mg/L	[Metabolite] mg/L
.0000	10.00	.0000
1.000	7.408	.6714
1.500	6.376	.8263
2.000	5.488	.9046
2.500	4.723	.9293
3.000	4.065	.9171
4.000	3.011	.8293
5.000	2.231	.7052
6.000	1.652	.5775
7.000	1.224	.4613
8.000	.9071	.3620
9.000	.6720	.2804
10.00	.4978	.2152
11.00	.3688	.1639
12.00	.2732	.1242

Empirical Approach

Results

** FINAL PARAMETER VALUES ***

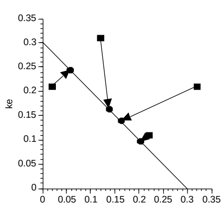
#	Name	Value	S.D.	C.V. %
1)	ke	.24967	0.113E-04	0.45E-02
2)	km	0.50369E-01	0.590E-05	0.12E-01
3)	kmu	.49999	0.639E-04	0.13E-01
4)	V1	10.000	0.319E-03	0.32E-02
5)	V2	5.0369	.000	.00

AIC = -404.6 Final WSS = 0.6186E-06
R-squared = 1.000 Correlation Coeff = 1.000

Generally very good CV%, but .00 for V2 a worry

Empirical Approach

Results



Multiple Starting Points - Multiple Answers!!

Empirical Approach

- Michaelis-Menten Example

Dose Level - 500 mg

** FINAL PARAMETER VALUES ***

#	Name	Value	S.D.	C.V. %
1)	Vm Elim	10.000	0.155E-03	0.16E-02
2)	Km Elim	50.007	0.682E-02	0.14E-01
3)	V	10.000	0.293E-05	0.29E-04

AIC= -225.6Final WSS = 0.8723E-10
R-squared = 1.000 Correlation Coeff = 1.000

Empirical Approach

- Michaelis-Menten Example

Dose Level - 5 mg

** FINAL PARAMETER VALUES ***

#	Name	Value	S.D.	C.V. %
1)	Vm Elim	95.938	688.	7.2E02
*** WARNING *** FINAL PARAMETER VALUE CLOSE TO UPPER LIMIT				
2)	Km Elim	500.00	0.361E+04	7.2E02
*** WARNING *** FINAL PARAMETER VALUE CLOSE TO UPPER LIMIT				
3)	V	10.063	0.477E-01	.47

AIC = -61.39 Final WSS = 0.6591E-04
R-squared = .9993 Correlation Coeff = .9999

Empirical Approach

- Sample Time Example

** FINAL PARAMETER VALUES ***

#	Name	Value	S.D.	C.V.%
1)	ka	1.0953	.685	63.
2)	kel	.19752	0.132E-01	6.7
3)	V	10.691	.673	6.3

AIC = -15.63Final WSS = 0.6694E-01
R-squared = .9992 Correlation Coeff = .9977

Using IDENT

- Define Model
- Run IDENT
- Interpret Results

Using IDENT

- Specify Model

```
c
c      theta(1) = ke
c      theta(2) = km
c      theta(3) = kmu
c
c      y(i) = amount in compartment i
c
       dydx(1) = -(theta(1) + theta(2))*y(1)
       dydx(2) = theta(1)*y(1)
       dydx(3) = theta(2)*y(1) - theta(3)*y(3)
       dydx(4) = theta(3)*y(3)
```

Using IDENT

- Program Output (Concise)

NON-IDENTIFIABLE PARAMETERS:

2	1	5
km	ke	Vm

IDENTIFIABLE PARAMETERS:

3	4
kmu	V

Analytical Approach

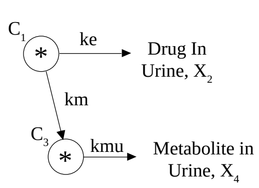
- Laplace Transform
- Taylor Series

Laplace Transform

- Less Complex Method
- Doesn’t work if Parameters Vary with Time
- Doesn’t work with Non-linear Systems (MM)

Laplace Transform

- The Model



Laplace Transform

- If you measure C_1

$$\frac{dX_1}{dt} = -(ke + km) \cdot X_1$$

$$s \cdot \bar{X}_1 - Dose = -(ke + km) \cdot \bar{X}_1$$

$$\bar{X}_1 (s + ke + km) = Dose$$

$$\bar{X}_1 = \frac{Dose}{(s + ke + km)}$$

$$\bar{C}_1 = \frac{Dose}{V_1} \cdot \frac{1}{(s + ke + km)}$$

$$C_1 = \frac{Dose}{V_1} \cdot e^{-(ke+km)\cdot t}$$

Since we know D, the intercept gives us V_1

From this root we can calculate kel = ke + km but not ke or km alone

Laplace Transform

- If you measure C_3

$$\frac{dX_3}{dt} = km \cdot X_1 - kmu \cdot X_3$$

$$s \cdot \bar{X}_3 = km \cdot \bar{X}_1 - kmu \cdot \bar{X}_3$$

$$\bar{C}_3 = \frac{D}{V_3} \cdot \frac{km}{(s + ke + km) \cdot (s + kmu)}$$

Although we know D we cannot separate km from V_3

Still no luck!

We can get kmu from this root

Laplace Transform

- Finally, measuring X_4

$$\frac{dX_4}{dt} = kmu \cdot X_3$$

$$s \cdot \bar{X}_4 = kmu \cdot \bar{X}_3$$

$$\bar{X}_4 = \frac{km \cdot kmu \cdot D}{s \cdot (s + ke + km) \cdot (s + kmu)}$$

Since we know D and kmu we can get km from the intercept [2]

Now we can get ke from this root (we now know km) [3]

[1] We know kmu (again) from this root

Taylor Series

- Determination Involves the Development of Successive Derivatives
- More Cumbersome
- More General Application

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