More Laplace Transforms

Back-transforming without Tables
Multicompartment Models
Convolution

Laplace Back Transform

✓ Objective
- Use the general fraction theorem, i.e. the fingerprint method*
- Understand the limitations of the method
- Extend the method to multicompartment models
- Use the convolution method

* Benet, L.Z. and Turi, J.S. 1971. "Use of the General Partial Fraction Theorems for Obtaining Inverse Laplace Transforms in Pharmacokinetic Analysis", J. Pharm. Sci., 60: 1593-1594

General Equation

$$L^{-1}\left\{\frac{N(s)}{D(s)}\right\} = \sum_{i=1}^{i=n} \frac{N(\lambda_i)}{D(\lambda_i)} \bullet e^{\lambda \bullet t}$$

s domain on the left ---> t domain on the right

Requirements

$$L^{-1}\left\{\frac{N(s)}{D(s)}\right\} = \sum_{i=1}^{i=n} \frac{N(\lambda_i)}{D(\lambda_i)} \bullet e^{\lambda \bullet t}$$

- ✓ The denominator [D(s)] has a higher power in s than the numerator [N(s)]
- ✓ The denominator has no repeated factors in s

Procedure

- ✓ Check Requirements
- ✓ Determine Roots in Denominator
- ✓ Write Back Transform using fingerprint Method for each Root
  - Take each root in turn
  - Cover the corresponding s term and replace remaining s with the root
  - Multiply by $e^{root \bullet t}$

Example - 1

$$\bar{X} = \frac{F \bullet Dose \bullet ka}{(s + ka) \bullet (s + kel)}$$

Note that the denominator has power of 2 in s and no repeat terms

Consider denominator as:

(s+ka)•(s+kel) = 0

Roots or solutions are -ka and -kel

Example 1 - Root 1

$$\frac{F \bullet Dose \bullet ka}{(s+ka) \bullet (s+kel)}$$

First root is -ka

$$\frac{F \bullet Dose \bullet ka}{(s+ka) \bullet (s+kel)}$$

$$\frac{F \bullet Dose \bullet ka}{(-ka+kel)} \bullet e^{-ka \bullet t}$$

Example 1 - Root 2

$$\frac{F \bullet Dose \bullet ka}{(s+ka) \bullet (s+kel)}$$

Second root is -kel

$$\frac{F \bullet Dose \bullet ka}{(s+ka) \bullet (s+kel)}$$

$$\frac{F \bullet Dose \bullet ka}{(-kel+ka)} \bullet e^{-kel \bullet t}$$

Putting It Together - 1

$$\frac{F \bullet Dose \bullet ka}{(-ka+kel)} \bullet e^{-ka \bullet t} \qquad \frac{F \bullet Dose \bullet ka}{(-kel+ka)} \bullet e^{-kel \bullet t}$$

$$\frac{F \bullet Dose \bullet ka}{(-ka+kel)} \bullet e^{-ka \bullet t} + \frac{F \bullet Dose \bullet ka}{(-kel+ka)} \bullet e^{-kel \bullet t}$$

OR

$$\frac{F \bullet Dose \bullet ka}{(ka-kel)} \bullet \left[e^{-kel \bullet t} - e^{-ka \bullet t}\right]$$

Another Example - 2

$$\overline{X} = \frac{k0}{s \cdot (s + kel)}$$

Note that again the denominator has power of 2 in s and no repeat terms

Consider denominator as:

s•(s+kel) = 0

Roots or solutions are 0 and -kel

Example 2 - Root 1

$$\frac{k0}{s \cdot (s + kel)}$$

First root is 0

$$\frac{k0}{s \cdot (s + kel)}$$

$$\frac{k0}{(0 + kel)} \cdot e^{-0}$$

Example 2 - Root 2

$$\frac{k0}{s \cdot (s + kel)}$$

Second root is -kel

$$\frac{k0}{s \cdot (s + kel)}$$

$$\frac{k0}{-kel} \cdot e^{-kel \cdot t}$$

Putting It Together - 2

$$\frac{k0}{(0+kel)} \bullet e^{-0} \qquad \frac{k0}{-kel} \bullet e^{-kel \bullet t}$$

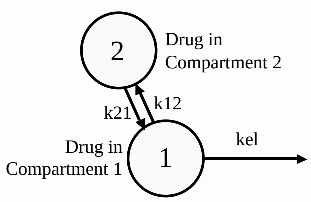
$$\frac{k0}{kel} + \frac{k0}{-kel} \bullet e^{-kel \bullet t}$$

OR

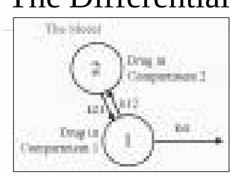
$$\frac{k0}{kel} \bullet \left[1 - e^{-kel \bullet t}\right]$$

Multicompartment Models

The Model



The Differential Equations



$$\frac{dX_1}{dt} = k21 \bullet X_2 - k12 \bullet X_1 - kel \bullet X_1$$

$$\frac{dX_2}{dt} = k12 \bullet X_1 - k21 \bullet X_2$$

Take Laplace of the Equations

$$\frac{dX_1}{dt} = k21 \cdot X_2 - k12 \cdot X_1 - kel \cdot X_1$$
$$\frac{dX_2}{dt} = k12 \cdot X_1 - k21 \cdot X_2$$

$$s \cdot \bar{X}_1 - X_1(0) = k21 \cdot \bar{X}_2 - k12 \cdot \bar{X}_1 - kel \cdot \bar{X}_1$$
$$s \cdot \bar{X}_2 - X_2(0) = k12 \cdot \bar{X}_1 - k21 \cdot \bar{X}_2$$

Since $X_1(0)$ = Dose and $X_2(0) = 0$

$$\bar{X}_2 = \frac{k12 \cdot \bar{X}_1}{(s + k21)}$$

Substitute and Rearrange

$$s \cdot \bar{X}_1 - X_1(0) = k21 \cdot \bar{X}_2 - k12 \cdot \bar{X}_1 - kel \cdot \bar{X}_1$$
$$\bar{X}_2 = \frac{k12 \cdot \bar{X}_1}{(s + k21)}$$

$$s \cdot \bar{X}_1 - \text{Dose} = \frac{k21 \cdot k12 \cdot \bar{X}_1}{(s + k21)} - (k12 + kel) \cdot \bar{X}_1$$

$$s \cdot \bar{X}_1 + (k12 + kel) \cdot \bar{X}_1 - \frac{k21 \cdot k12 \cdot \bar{X}_1}{(s + k21)} = \text{Dose}$$

$$\bar{X}_1 \cdot [s \cdot (s + k21) + (k12 + kel) \cdot (s + k21) - k21 \cdot k12] = \text{Dose} \cdot (s + k21)$$

$$\bar{X}_1 \cdot [s^2 + s \cdot (k21 + k12 + kel) + k21 \cdot kel] = \text{Dose} \cdot (s + k21)$$

Notice the similarity with

$$[s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = (s + \alpha) \cdot (s + \beta)$$

Getting close now

$$\bar{X}_1 \cdot [s^2 + s \cdot (k21 + k12 + kel) + k21 \cdot kel] = \text{Dose} \cdot (s + k21)$$

Notice the similarity with

$$[s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = (s + \alpha) \cdot (s + \beta)$$

If $(\alpha + \beta) = k21 + k12 + kel$

and $\alpha \cdot \beta = k21 \cdot kel$

$$\bar{X}_1 \cdot [s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = \text{Dose} \cdot (s + k21)$$
$$\bar{X}_1 \cdot (s + \alpha) \cdot (s + \beta) = \text{Dose} \cdot (s + k21)$$
$$\bar{X}_1 = \frac{\text{Dose} \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)}$$

Third Example

$$\overline{X}_1 = \frac{Dose \bullet (s + k21)}{(s+\alpha)\bullet(s+\beta)}$$

The denominator has a power of 2 in s and no repeat terms. Note the numerator has a power of 1 in s

Considering the denominator:

$$(s + \alpha)\bullet(s + \beta) = 0$$

Roots or solutions are -α and -β

Example 3 - Root 1

$$\overline{X}_1 = \frac{Dose \bullet (s + k21)}{(s+\alpha)\bullet(s+\beta)}$$

First root is -α

$$\frac{Dose \bullet (s + k21)}{(s+\alpha)\bullet(s+\beta)}$$

$$\frac{Dose \bullet (k21 - \alpha)}{(\beta - \alpha)} \bullet e^{-\alpha \bullet t}$$

Example 3 - Root 2

$$\overline{X}_1 = \frac{Dose \bullet (s + k21)}{(s+\alpha)\bullet(s+\beta)}$$

Second root is -β

$$\frac{Dose \bullet (s + k21)}{(s+\alpha)\bullet(s+\beta)}$$

$$\frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

Putting It Together - 3

$$\frac{Dose \bullet (k21 - \alpha)}{(\beta - \alpha)} \bullet e^{-\alpha \bullet t} \qquad \frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

$$\frac{Dose \bullet (\alpha - k21)}{(\alpha - \beta)} \bullet e^{-\alpha \bullet t} + \frac{Dose \bullet (k21 - \beta)}{(\alpha - \beta)} \bullet e^{-\beta \bullet t}$$

OR

$$Cp = A \bullet e^{-\alpha \bullet t} + B \bullet e^{-\beta \bullet t}$$

where $A = \frac{Dose \bullet (\alpha - k21)}{V_1 \bullet (\alpha - \beta)}$

and $B = \frac{Dose \bullet (k21 - \beta)}{V_1 \bullet (\alpha - \beta)}$

Convolution

- ✓ A method of obtaining the Laplace equation
- ✓ Use parts from known models to create new equations for new models
- ✓ Based on*:

$$\overline{X}_i = in_{roa} \bullet out_i$$

* Benet, L.Z.1972. "General Treatment of Linear Mammillary Models with Elimination from any Compartment as Used in Pharmacokinetics", J. Pharm. Sci., 61: 536-541

The parts

In_{roa}			
$\frac{k0}{s}$	IV Infusion - One Compartment	$\frac{k0}{s} \bullet \frac{1}{(s + kel)}$	$\frac{1}{(s + kel)}$
Dose	IV Bolus - Two Compartment	$\frac{Dose \bullet (s + k21)}{(s + \alpha) \bullet (s + \beta)}$	$\frac{(s + k21)}{(s + \alpha) \bullet (s + \beta)}$
$\frac{F \bullet Dose \bullet ka}{(s + ka)}$	Oral - One Compartment	$\frac{F \bullet Dose \bullet ka}{(s + ka) \bullet (s + kel)}$	$\frac{1}{(s + kel)}$

An Example

- ✓Oral Administration - Two Compartment Model

Oral

$$\frac{F \cdot Dose \cdot ka}{(s + ka)}$$

Two Compartment

$$\frac{(s + k21)}{(s + \alpha) \cdot (s + \beta)}$$

Oral Two Compartment

$$\frac{F \cdot Dose \cdot ka \cdot (s + k21)}{(s + ka) \cdot (s + \alpha) \cdot (s + \beta)}$$