More Laplace Transforms

Back-transforming without Tables
Multicompartment Models
Convolution

Laplace Back Transform

Objective
- Use the general fraction theorem, i.e. the fingerprint method\footnote{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}
- Understand the limitations of the method
- Extend the method to multicompartment models
- Use the convolution method

\[ L^{-1}\left\{ \frac{N(s)}{D(s)} \right\} = \sum_{i=1}^{n} \frac{N(\lambda_i)}{D(\lambda_i)} \cdot e^{\lambda_i t} \]

s domain on the left \(\rightarrow\) t domain on the right
Chapter 7

Requirements

\[ \mathcal{L}^{-1}\left\{ \frac{N(s)}{D(s)} \right\} = \sum_{i=1}^{n} \frac{N(\lambda_i)}{D(\lambda_i)} \cdot e^{\lambda_i t} \]

- 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 \(e^{\text{root} t}\)

Example - 1

\[ x = \frac{F \cdot \text{Dose} \cdot \text{ka}}{(s + \text{ka}) \cdot (s + \text{kel})} \]

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

Consider denominator as:

\[ (s+\text{ka}) \cdot (s+\text{kel}) = 0 \]

Roots or solutions are \(-\text{ka}\) and \(-\text{kel}\)
Example 1 - Root 1

\[ \frac{F \cdot \text{Dose} \cdot ka}{(s + ka)(s + kel)} \]

First root is -ka

\[ \frac{F \cdot \text{Dose} \cdot ka}{(s + ka)(s + kel)} \cdot e^{-ka \cdot t} \]

Example 1 - Root 2

\[ \frac{F \cdot \text{Dose} \cdot ka}{(s + ka)(s + kel)} \]

Second root is -kel

\[ \frac{F \cdot \text{Dose} \cdot ka}{(s + ka)(s + kel)} \cdot e^{-kel \cdot t} \]

Putting It Together - 1

\[ \frac{F \cdot \text{Dose} \cdot ka \cdot e^{-ka \cdot t}}{(s + ka)(s + kel)} \]

\[ \frac{F \cdot \text{Dose} \cdot ka \cdot e^{-kel \cdot t}}{(s + ka)(s + kel)} \]

\[ \frac{F \cdot \text{Dose} \cdot ka \cdot e^{-ka \cdot t}}{(s + ka)(s + kel)} \cdot e^{-kel \cdot t} \cdot e^{-ka \cdot t} \]

OR

\[ \frac{F \cdot \text{Dose} \cdot ka}{(ka - kel) \cdot [e^{-ka \cdot t} - e^{-kel \cdot t}]} \]
Another Example - 2

\[ X = \frac{k_0}{s(s+k_0)} \]

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

Consider denominator as:

\[ s(s+k_0) = 0 \]

Roots or solutions are 0 and -k_0

Example 2 - Root 1

First root is 0

\[ \frac{k_0}{s(s+k_0)} \]

\[ \frac{k_0}{(0+k_0)}e^{-0} \]

Example 2 - Root 2

Second root is -k_0

\[ \frac{k_0}{s(s+k_0)} \]

\[ \frac{k_0}{-k_0}e^{-k_0t} \]
Putting It Together - 2

\[
\frac{k_0}{(0 + k_{el})} e^{-kt} - \frac{k_0}{k_{el}} e^{-k_{el}t} = \frac{k_0}{k_{el}} \left[ 1 - e^{-k_{el}t} \right]
\]

OR

\[
\frac{k_0}{k_{el}} e^{-k_{el}t} - \frac{k_0}{k_{el}} e^{-k_{el}t} = \frac{k_0}{k_{el}} \left[ 1 - e^{-k_{el}t} \right]
\]

Multicompartment Models

The Model

Drug in Compartment 2

Drug in Compartment 1

\(k_{el}\)

\(k_{21}\)

\(k_{12}\)

The Differential Equations

\[
\begin{align*}
\frac{dX_1}{dt} &= k_{21} X_2 - k_{12} X_1 - k_{el} X_1 \\
\frac{dX_2}{dt} &= k_{12} X_1 - k_{21} X_2
\end{align*}
\]
Take Laplace of the Equations

\[ s \cdot X_1 - X_1(0) = k_{21} \cdot X_1 - k_{12} \cdot X_2 - k_{el} \cdot X_1 \]
\[ s \cdot X_2 - X_2(0) = k_{12} \cdot X_1 - k_{21} \cdot X_2 \]

Since \( X_1(0) = \text{Dose} \) and \( X_2(0) = 0 \)

\[ X_1 = \frac{k_{12} \cdot X_1}{s + k_{21}} \]

Substitute and Rearrange

\[ s \cdot X_1 - \text{Dose} = \frac{k_{21} \cdot k_{12} \cdot X_1}{s + k_{21}} - (k_{12} + k_{el}) \cdot X_1 \]
\[ s \cdot X_1 + (k_{12} + k_{el}) \cdot X_1 - \frac{k_{21} \cdot k_{12} \cdot X_1}{s + k_{21}} = \text{Dose} \]
\[ X_1 \cdot [s+(s+k_{21}) + (k_{12} + k_{el}) (s + k_{21}) - k_{21} \cdot k_{12}] = \text{Dose} \cdot (s + k_{21}) \]

Notice the similarity with
\[ [s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = (s + \alpha) \cdot (s + \beta) \]

Getting close now

If \( \alpha + \beta = k_{21} + k_{12} + k_{el} \)
and \( \alpha \cdot \beta = k_{21} \cdot k_{el} \)

\[ X_1 \cdot [s^2 + s \cdot (\alpha + \beta) + \alpha \cdot \beta] = \text{Dose} \cdot (s + k_{21}) \]
\[ X_1 \cdot (s + \alpha) \cdot (s + \beta) = \text{Dose} \cdot (s + k_{21}) \]
\[ X_1 = \frac{\text{Dose} \cdot (s + k_{21})}{(s + \alpha) \cdot (s + \beta)} \]
Third Example

\[ x_i = \frac{Dose \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)} \]

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:

\[(s + \alpha) \cdot (s + \beta) = 0\]

Roots or solutions are \(-\alpha\) and \(-\beta\)

Example 3 - Root 1

\[ x_i = \frac{Dose \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)} \]

First root is \(-\alpha\)

\[ \frac{Dose \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)} \]

\[ \frac{Dose \cdot (k21 - \alpha)}{(\beta - \alpha)} \cdot e^{-\alpha \cdot t} \]

Example 3 - Root 2

\[ x_i = \frac{Dose \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)} \]

Second root is \(-\beta\)

\[ \frac{Dose \cdot (s + k21)}{(s + \alpha) \cdot (s + \beta)} \]

\[ \frac{Dose \cdot (k21 - \beta)}{(\alpha - \beta)} \cdot e^{-\beta \cdot t} \]
Putting It Together - 3

\[
\begin{align*}
\text{Dose} \times (k21 - \beta) \cdot e^{-\alpha t} + \text{Dose} \times (k21 - \beta) \cdot e^{-\beta t}
\end{align*}
\]

OR

\[
C_p = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t}
\]

where

\[
A = \frac{\text{Dose} \times (\alpha - k21)}{V \cdot (\alpha - \beta)}
\]

and

\[
B = \frac{\text{Dose} \times (k21 - \beta)}{V \cdot (\alpha - \beta)}
\]

Convolution

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

\[
X_i = \text{in}_{\text{in}} \cdot \text{out}_i
\]


The parts

<table>
<thead>
<tr>
<th>( \text{In}_{\text{in}} )</th>
<th>( \text{Dose} \times k0 )</th>
<th>( \text{Dose} \times (s + k21) )</th>
<th>( \text{Dose} \times (s + \alpha) \cdot (s + \beta) )</th>
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<td>( \frac{1}{s + k0} )</td>
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An Example

Oral Administration - Two Compartment Model

Oral

\[
F \cdot \text{Dose} \cdot k_a \cdot \frac{1}{(s + k_a)}
\]

Two Compartment

\[
\frac{1}{(s + k_{21})} \cdot \frac{1}{(s + \alpha) \cdot (s + \beta)}
\]

Oral Two Compartment

\[
\frac{F \cdot \text{Dose} \cdot k_a \cdot (s + k_{21})}{(s + k_a) \cdot (s + \alpha) \cdot (s + \beta)}
\]