Application of Stochastic Deconvolution in IVIVC Development

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*Disclaimer: The views expressed in this presentation are those of the author and do not reflect the opinion nor the policy of the FDA.
Presentation Overview

• Background
• How is Stochastic Deconvolution Applied?
• Proof of Principle using Simulated PK Data
• IVIVC Example using Clinical PK Data
• Conclusions and Future Goals

Figures, comments and ideas presented in these slides are taken primarily from the following publications:


What is Stochastic Deconvolution?

• A parameter estimation method / diagnostic tool used to inform on a mapping function for level A IVIVC development.

• Based on a system of ODEs representative of compartmental PK.

• The absorption coefficient \((k_a)\) is expressed as a mixed effect.

• The random effect on \(k_a\) is modeled as a Wiener Process*.

• Embedded in a nonlinear mixed effects population-PK formalism.

* Wiener Process: a stochastic process characterized by statistically stationary and independent increments that are normally distributed, continuous in time, have an expected value of zero, and a variance representative of the process noise.
What Benefits does it offer?

- A modeling option when complete mechanistic knowledge of the system dynamics is not available.
- Not limited to linear, time-invariant (LTI) systems.
- No need for reference treatment to determine the UIR.
- Mathematically rigorous framework for addressing variability.
- Can support two-stage deconvolution and one-stage convolution approaches.
What Limitations can it have?

• Parameter estimation may be inconclusive due to underlying model-data complexity.
  - No or poor convergence
  - Parameter identifiability issues
  - Uniqueness of solutions

• Blood draw sampling times may be inadequately distributed for ER treatments in order to determine system characteristics (V, CL).
How is it applied?
How is it applied?

• Structural parameters $V_1$ and $k_e$: mixed effects with assumed log-normal distribution.

$$V_1 = \theta_{V_1} \cdot e^{\eta_1}; \quad k_e = \theta_{k_e} \cdot e^{\eta_{ke}}$$

• Absorption rate coefficient is modeled as a mixed effect.

$$k_a(t) = \theta_{k_a} \cdot e^{\sum \eta_{ka}(t)}$$

• Random walk for $\eta_{ka}$ at any given time is the sum of all random effects up to and including that time.

$$\sum \eta_{ka}(t) = \sum_{t_i \leq t} \eta_{ka}(t_i)$$

$$\eta_{ka}(t_i) = w_i \cdot \sqrt{(t_i - t_{i-1})}$$

• $w_i \sim N(0, \sigma_w^2)$. Variance $\sigma_w^2$ assumed to be constant.
How is it applied?

• The data are combined for a given subject to include all formulation treatments \((FID)\).

\[ t_{RAT} = (FID - 1) \times \text{WashOutTime} + t \]

• Between the observation times the random walk on \(k_a\) is held fixed and the compartmental PK ODEs are solved.

• Specification of an error model to build the likelihood function.

• A maximum likelihood estimate criterion is employed to solve the NLME system.

• To-be-estimated parameters: \(\theta_{V_1}, \theta_{k_e}, \theta_{k_a}, \text{all } \eta_{k_a}(t), \eta_{V_1}, \eta_{k_e}, \sigma_{V_1}^2, \sigma_{k_e}^2, \sigma_{k_a}^2, \text{and residual error of error model.}\)

• Calculations performed with Phoenix/WinNonlin 6.4 using Phoenix model object coupled to custom PML code.
Example: Proof of Principle

- Consider 3 types of PK systems kinetics.
  - Linear, time-invariant (LTI)
  - Nonlinear based on Michaelis-Menten clearance (MM)
  - Time variant: Enterohepatic circulation (EHC).

- Specify an *a priori* known absorption profile.

- Define 12 subjects with respective $V$ and CL (based on a log-normal distribution).

- Apply 1-compartment PK specified as identifiable underlying model.

- Use stochastic deconvolution on simulated $C_p(t)$ data to determine if specified (known) absorption profile can be recovered.
Example: Proof of Principle
Example: Proof of Principle

<table>
<thead>
<tr>
<th>FID = 1</th>
<th>FID = 2</th>
<th>FID = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Graph for FID = 1" /></td>
<td><img src="image2" alt="Graph for FID = 2" /></td>
<td><img src="image3" alt="Graph for FID = 3" /></td>
</tr>
</tbody>
</table>

- $k_a [h^{-1}] / F_{abs} [-]$
- $0.0$ to $1.5$
- Time after Dose [h]: $0$ to $60$

Legend:
- $F_{abs}$ BL
- $F_{abs}$ SD
- $K_E$ BL
- $K_e$ SD

XID: 3, 7, 12
Example: Proof of Principle

<table>
<thead>
<tr>
<th>FID = 1</th>
<th>FID = 2</th>
<th>FID = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph 1" /></td>
<td><img src="image2.png" alt="Graph 2" /></td>
<td><img src="image3.png" alt="Graph 3" /></td>
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<tr>
<td><img src="image4.png" alt="Graph 4" /></td>
<td><img src="image5.png" alt="Graph 5" /></td>
<td><img src="image6.png" alt="Graph 6" /></td>
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<tr>
<td><img src="image7.png" alt="Graph 7" /></td>
<td><img src="image8.png" alt="Graph 8" /></td>
<td><img src="image9.png" alt="Graph 9" /></td>
</tr>
</tbody>
</table>

**Baseline**

**Stoch.Decon.**

Time after Dose [h]

www.fda.gov
Example: IVIVC

- ER tablet formulation approved by the FDA.
- Drug release rate controlled by coating thickness applied after compression stage.
- Linear PK over a dose range of 100-400 mg.
- Highly water soluble. IR formulation has an absolute BA ≈75%.

4-way, 4 treatment, randomized, single-dose (100 mg), fasting, cross-over study involving 16 healthy adult volunteers. 1 week washout.

USP 1 apparatus at 75 rpm in 0.1N HCl (N=12). Drug release showed very weak pH and dissolution medium dependence.
Example: IVIVC

Does stochastic deconvolution work with real data?

Scenarios considered for stochastic deconvolution to calculate $F_{abs}$:

1. Using a single compartment PK framework and in vivo data from the IR and all ER treatment arms to inform on the estimation of the model’s structural parameters ($k_a$, $V_1$, and $k_e$).

2. Same as scenario 1, but using in vivo data just from the ER treatment arm (i.e. reference formulation data withheld).

3. Same as scenario 1 but using a 2-compartment PK framework ($k_{12}$, and $k_{21}$ modeled as fixed effects).

4. Same as scenario 3 but using in vivo data just from the ER treatment arm (i.e. reference formulation data withheld).

Solution also sought using numerical deconvolution for comparison.
Example: IVIVC
Example: IVIVC

Formulation: Fast

Formulation: Medium

Formulation: Slow

$F_{abs}$ [%]

Time after Dose [h]

$C_p$ [ng/ml]

Time after Dose [h]
### Example: IVIVC

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Parameter</th>
<th>Observed</th>
<th>( \text{Percent Prediction Error (%PE)} = \left( \frac{\text{Predicted} - \text{Observed}}{\text{Observed}} \right) \times 100 )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD_1PK_IR</td>
</tr>
<tr>
<td><strong>Fast</strong></td>
<td>( AUC_{\text{last}} )</td>
<td>2787</td>
<td>-11.2</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td>168</td>
<td>-8.7</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
<td>( AUC_{\text{last}} )</td>
<td>2716</td>
<td>-11.1</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td>128</td>
<td>-0.85</td>
</tr>
<tr>
<td><strong>Slow</strong></td>
<td>( AUC_{\text{last}} )</td>
<td>2301</td>
<td>-0.64</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td>103</td>
<td>15.5</td>
</tr>
<tr>
<td>( \langle</td>
<td>%PE</td>
<td>\rangle )</td>
<td>( AUC_{\text{last}} )</td>
</tr>
<tr>
<td></td>
<td>( C_{\text{max}} )</td>
<td></td>
<td>8.4</td>
</tr>
</tbody>
</table>
Conclusions and Future Goals

- Stochastic deconvolution’s predictive accuracy was verified under simulated conditions with a known absorption rate and an identifiable PK model.
- Simulated PK systems falling outside classical numerical deconvolution’s scope were successfully handled.
- The stochastic deconvolution scenarios, as well as numerical deconvolution, yielded very similar results with respect to the IVIVC validation.
- Encouraging results could be achieved with stochastic deconvolution without recourse to IR data.
- Future work will look at systems where numerical deconvolution is known to fail to produce a predictive IVIVC.
Acknowledgments

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Back Up slides
Classical Deconvolution

• Inverse of convolution:

\[ C(t) = \int_0^t g(t - \tau)f(\tau)d\tau \Rightarrow f(t) = L^{-1}\left\{\frac{C(s)}{g(s)}\right\} \]

• Ill-conditioned problem. Indirect methods used to calculate \( f(t) \)
Constitutive Equations without EHC

\[
F_{\text{abs}}(t) = \alpha F_{\text{diss}}(t_{\text{vito}}) \begin{cases}
    t_{\text{vito}} = \beta t \\
    F_{\text{diss}}(t_{\text{vito}}) = F_{\text{diss,}} \left[1 - \exp \left(-\frac{(t_{\text{vito}})^b}{T_{\text{diss}}} \right) \right]
\end{cases}
\]

Absorption profile

Baseline estimation, IVIVC prediction

Stoch Decon estimation

\[
\frac{dA_a}{dt} = \begin{cases}
    -D \frac{dF_{\text{abs}}}{dt} \\
    -k_a A_a
\end{cases}
\]

For Michaelis-Menten example

\[
C_1(t) = \frac{A_1(t)}{V_1}
\]

\[
CL = \frac{V_m}{(C_1 + K_m)}
\]

For 1-compt, \( k_{12} = k_{21} = 0 \)
Constitutive Equations with EHC

\[ F_{rel}(t) = \alpha F_{diss}(t_{vitro}) \]

\[ F_{diss}(t_{vitro}) = F_{diss,\infty} \left[ 1 - \exp \left( - \left( \frac{t_{vitro}}{T_{diss}} \right)^b \right) \right] \]

Release profile

Baseline estimation

\[ \frac{dA_s}{dt} = -D \frac{dF_{rel}}{dt} \]

Stoch Decon estimation

\[ \frac{dA_a}{dt} = \begin{cases} 
- \frac{dA_s}{dt} - k_a A_a + f_g k_g A_g \\
- k_a A_a 
\end{cases} \]

\[ \frac{dA_1}{dt} = k_a A_a - k_e A_1 \]

\[ \frac{dA_g}{dt} = f_b k_e A_1 - f_g k_g A_g \]
Parameters for Weibull Dissolution Distribution

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Form ID (FID)</th>
<th>$F_{diss,\infty}$</th>
<th>$\bar{T}_{diss}$</th>
<th>$b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>[-]</td>
<td>[-]</td>
<td>[-]</td>
<td>[h]</td>
<td>[-]</td>
</tr>
<tr>
<td>Fast</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Medium</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Slow</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

Parameters for EHC model data generation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_a$ [h$^{-1}$]</td>
<td>2</td>
</tr>
<tr>
<td>$k_g$ [h$^{-1}$]</td>
<td>4</td>
</tr>
<tr>
<td>$f_b$ [-]</td>
<td>0.5</td>
</tr>
<tr>
<td>$f_g(t)$ [-]</td>
<td>$\begin{cases} 0 &amp; t &lt; 24, t &gt; 26 \ 1 &amp; 24 \leq t \leq 26 \end{cases}$</td>
</tr>
</tbody>
</table>
Simulated Fabs vs Time Profiles, LTI & MM

Simulated Fabs vs Time Profiles, EHC
Concentration–time profiles for all subjects receiving FID = 2 based on the PK models LTI, MM, and EHC
Sensitivity of fraction absorbed using stochastic deconvolution ($F_{abs}$ SD) for LTI kinetics subject to various random walks. Points denote the baseline result ($F_{abs}$ BL).
Numerical (dots) and stochastic (line) deconvolution using the same UIR parameters as input.
Constitutive Equations for IVIVC-Predicted PK

- Assume linear IVIVC model with constant time scaling:
  \[ F_{\text{abs}}(t) = A_S F_{\text{diss}}(T_S t) \]

- Rate of drug loss from the absorption compartment:
  \[
  \frac{d\bar{A}_a}{dt} = -D A_s T_s F_{\text{diss,\infty}} \frac{b}{T_{\text{diss}}} \left( \frac{T_s t}{T_{\text{diss}}} \right)^{b-1} e^{-\left(\frac{T_s t}{T_{\text{diss}}}\right)^b}
  \]

- Mass transfer relationship for the peripheral compartment:
  \[
  \frac{d\bar{A}_1}{dt} = -\frac{d\bar{A}_a}{dt} - \bar{k}_e \bar{A}_1 - \theta_{k_{12}} \bar{A}_1 + \theta_{k_{21}} \bar{A}_2, \text{ where } \bar{k}_e = \exp\left[\frac{1}{N} \sum_{i=1}^{N} \ln(k_{e,i})\right]
  \]

- \( \bar{k}_e \) is the log-mean (or geometric mean) of the post-hoc estimates of subject elimination rate coefficients.

- Mass transfer relationship for the peripheral compartment:
  \[
  \frac{d\bar{A}_2}{dt} = \theta_{k_{12}} \bar{A}_1 - \theta_{k_{21}} \bar{A}_2
  \]

- Averaged IVIVC-predicted plasma concentration:
  \[
  \bar{C}_1(t) = \frac{\bar{A}_1(t)}{\bar{V}_1}, \bar{V}_1 = \exp\left[\frac{1}{N} \sum_{i=1}^{N} \ln(V_{1,i})\right]
  \]
## PK Parameters (Standard Errors) and Shrinkages

<table>
<thead>
<tr>
<th>Scenario</th>
<th>$V_1$ or $V_{ss}$ (CV%)</th>
<th>$k_e$ (CV%)</th>
<th>Shrinkage [-]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[L]</td>
<td>[h$^{-1}$]</td>
<td>$\eta_V$</td>
</tr>
<tr>
<td>1. SDcon: 1 Comp PK with IR</td>
<td>332 (3%)</td>
<td>0.12 (6.6%)</td>
<td>0.22</td>
</tr>
<tr>
<td>2. SDcon: 1 Comp PK without IR</td>
<td>324 (0.8%)</td>
<td>0.10 (0.9%)</td>
<td>0.54</td>
</tr>
<tr>
<td>3. SDcon: 2 Comp PK with IR</td>
<td>335 (1.1%)</td>
<td>0.14 (1.6%)</td>
<td>0.17</td>
</tr>
<tr>
<td>4. SDcon: 2 Comp PK without IR</td>
<td>354 (1.1%)</td>
<td>0.11 (1.1%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>