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:

Kakhi and Chittenden, J Pharm Sci. 102:4433–4443, 2013

Kakhi et al. J Pharm Sci. 2017 DOI: 10.1016/j.xphs.2017.03.015 [In Press].

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.*

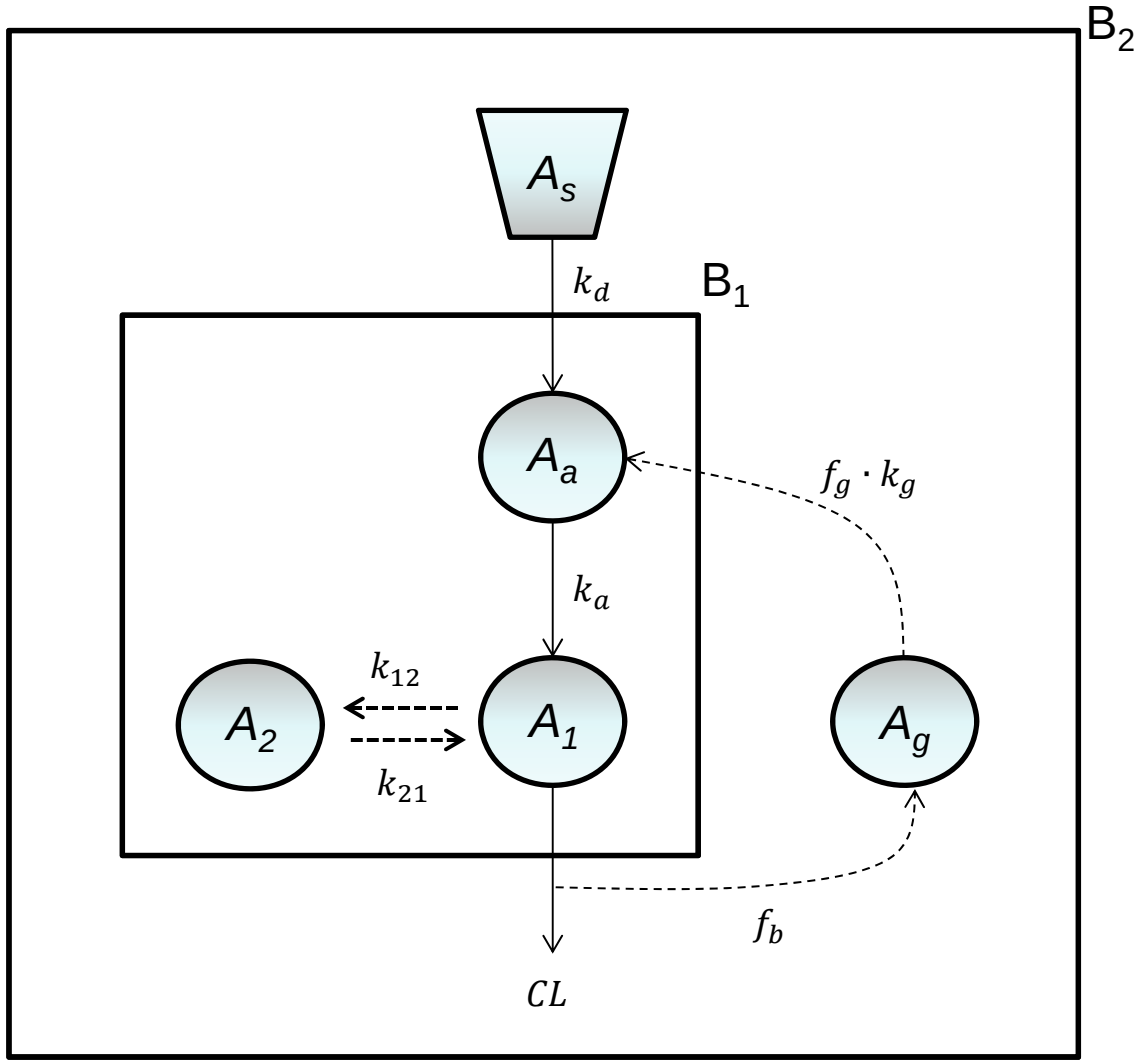
What Benefits does it offer?

- 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.

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

- Absorption rate coefficient is modeled as a mixed effect.

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

- Random walk for η_{k_a} at any given time is the sum of all random effects up to and including that time.

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

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

- $w_i \sim N(0, \sigma_w^2)$. Variance σ_w^2 assumed to be constant.

How is it applied?

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

$$t_{RAT} = (FID - 1) * \text{WashOutTime} + t$$

- 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: θ_{V_1}, θ_{k_e}, θ_{k_a}, all $\eta_{k_a}(t)$, η_{V_1}, η_{k_e}, $\sigma^2_{V_1}$, $\sigma^2_{k_e}$, σ^2_w, 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 Cp(t) data to determine if specified (known) absorption profile can be recovered.

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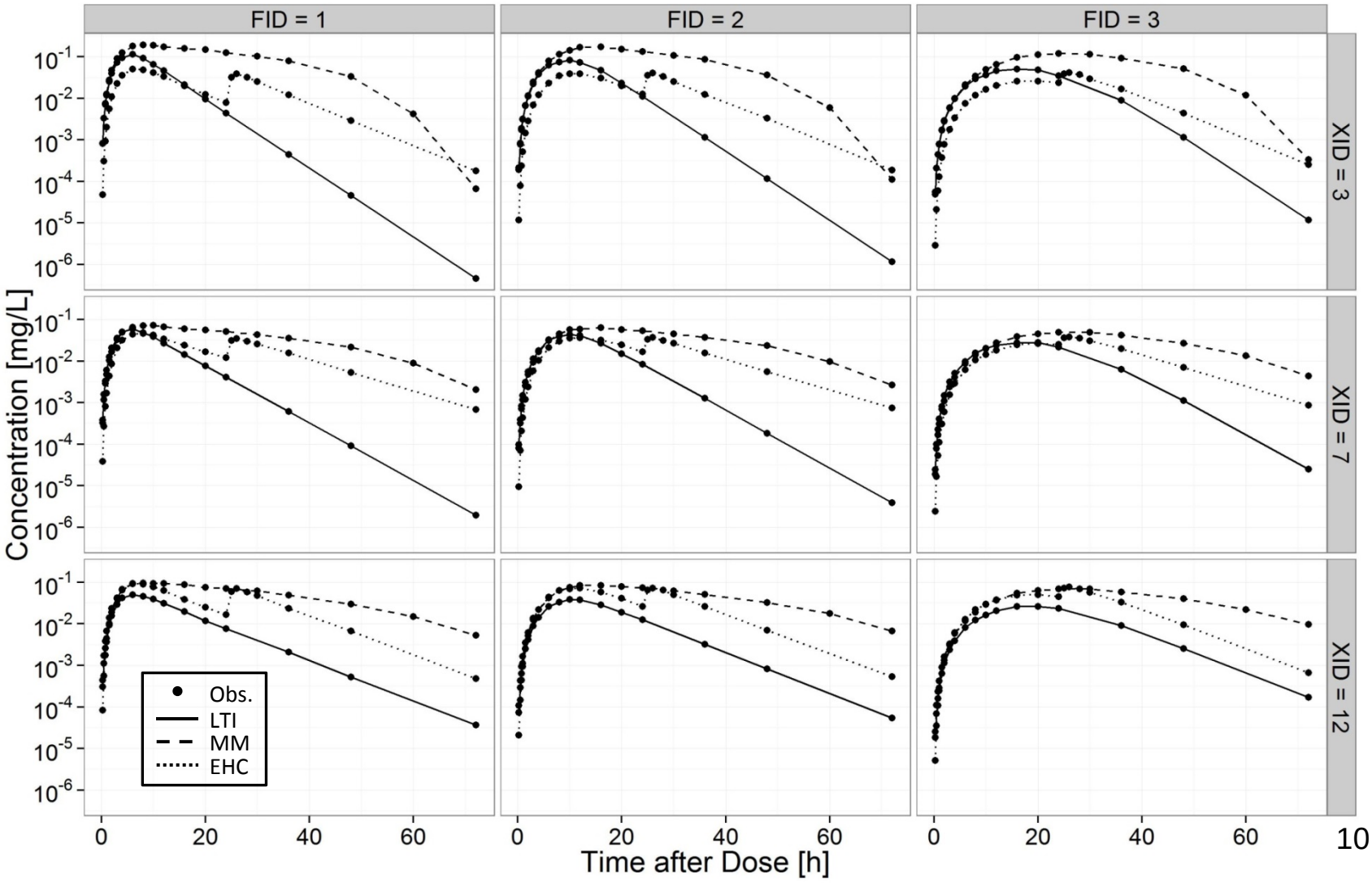
Example: Proof of Principle



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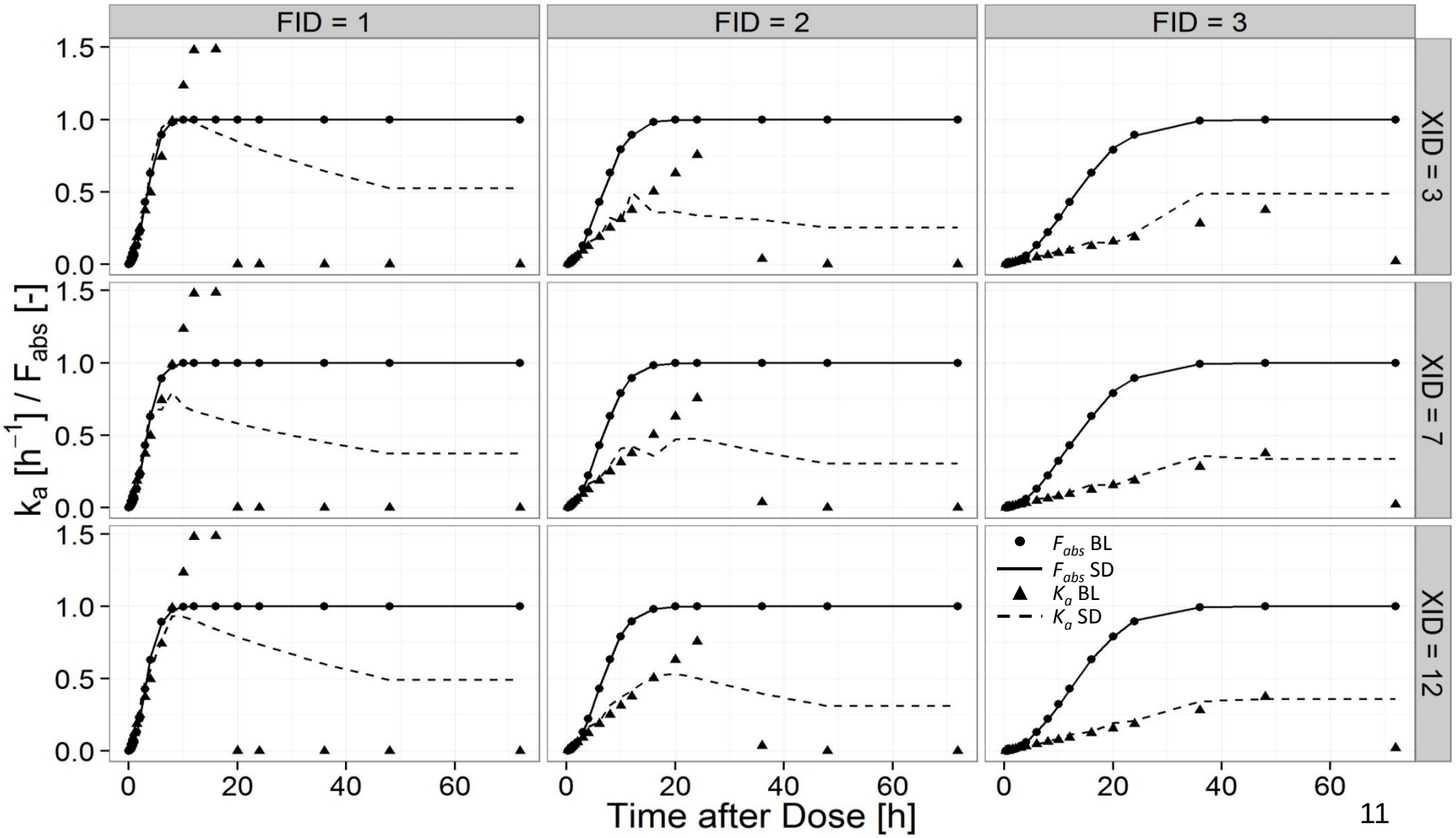
Example: Proof of Principle



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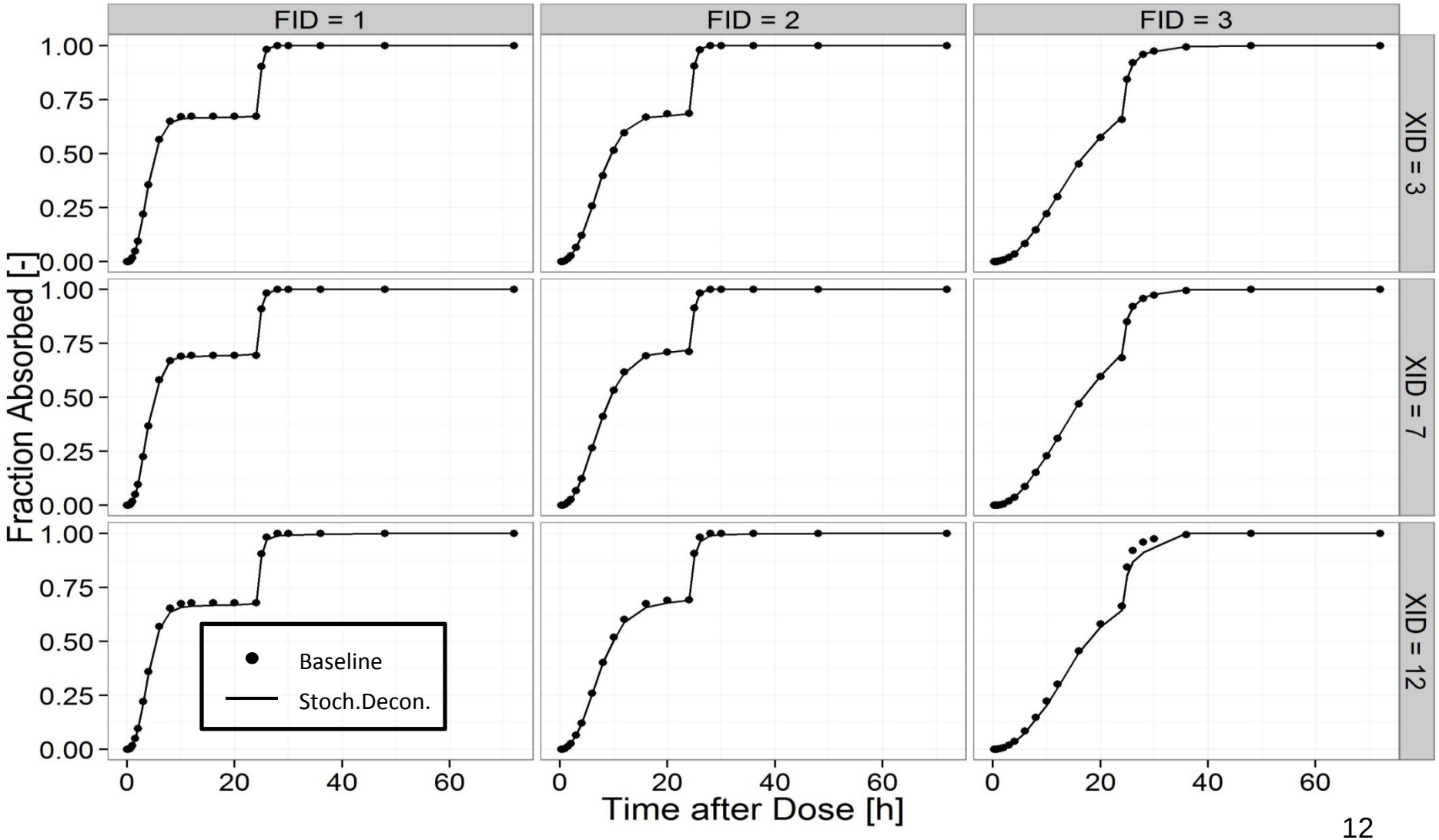
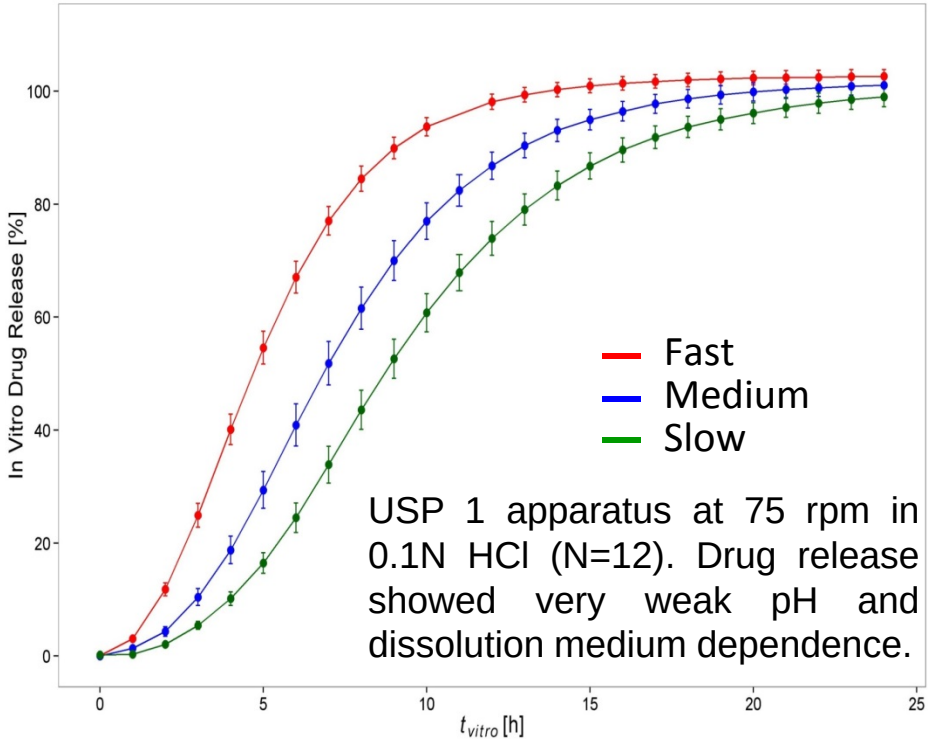
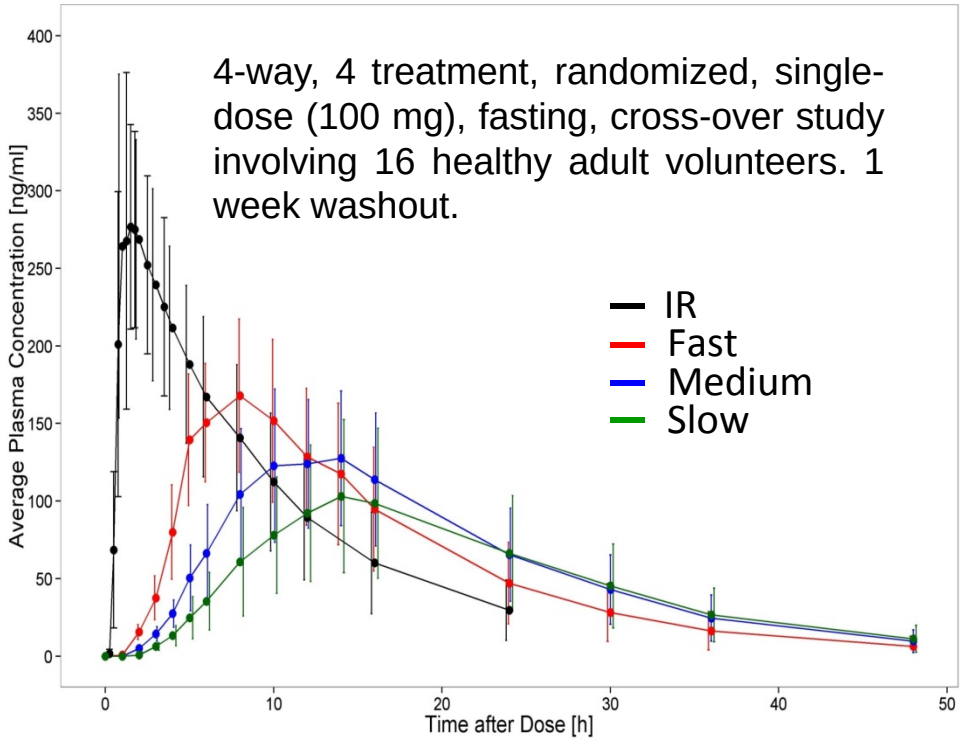
Example: Proof of Principle



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%.

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.

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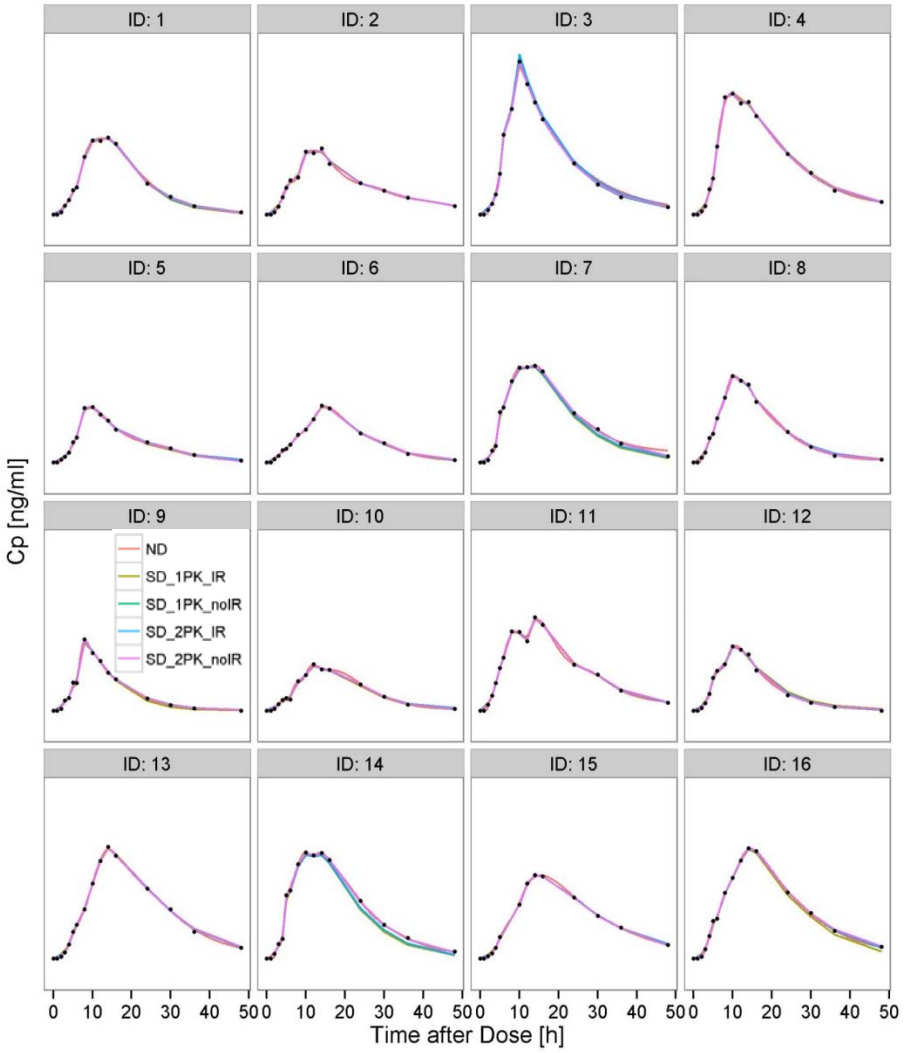
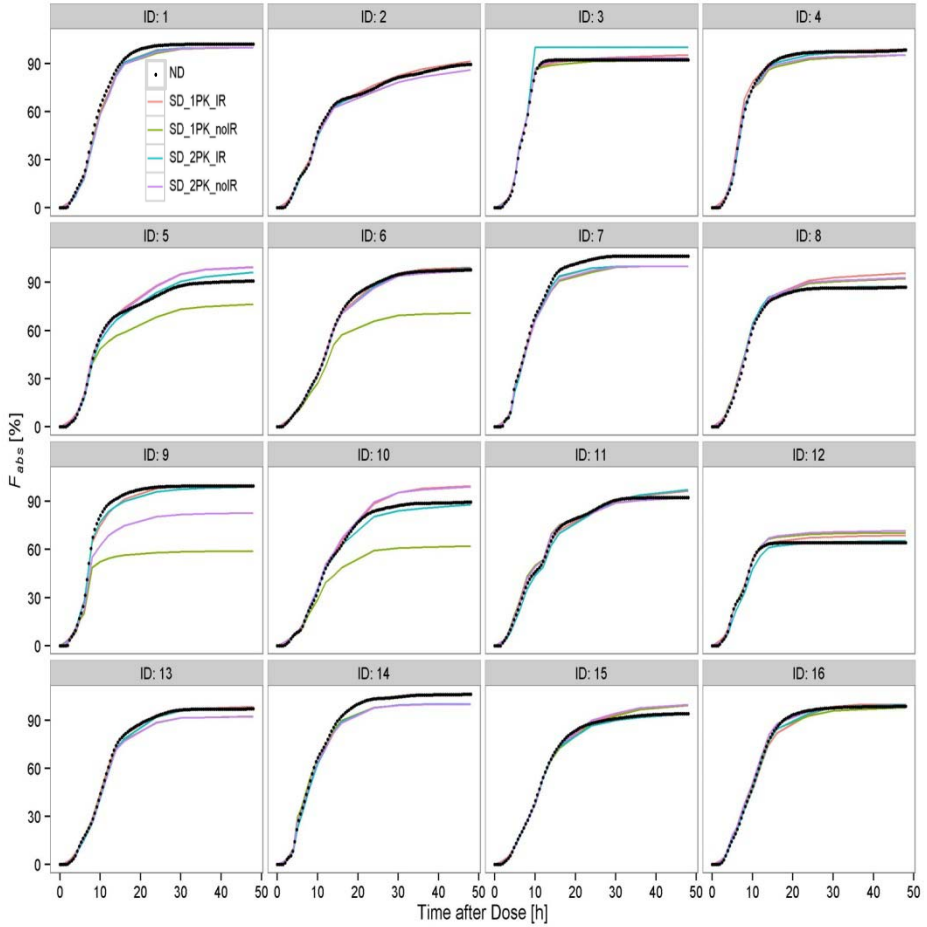
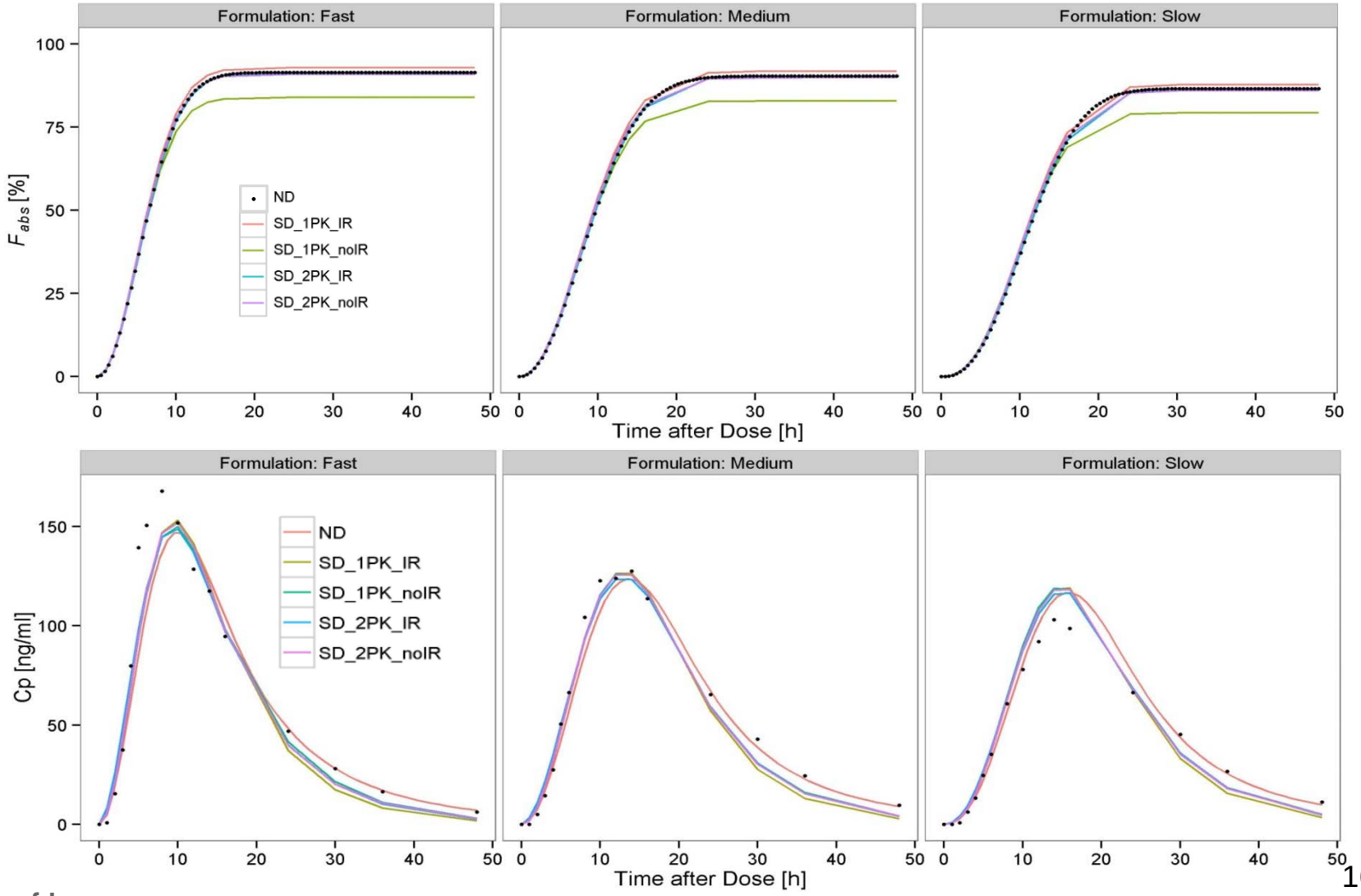
Example: IVIVC





Example: IVIVC



Example: IVIVC

Formulation	Parameter	Observed	Percent Prediction Error (%PE) = $\left(\frac{\text{Predicted}-\text{Observed}}{\text{Observed}}\right) \times 100$				
			SD_1PK_IR	SD_1PK_noIR	SD_2PK_IR	SD_2PK_noIR	ND
Fast	AUC_{last}	2787	-11.2	-8.8	-9.3	-9.2	-3.4
	C_{max}	168	-8.7	-10.7	-11.5	-9.5	-12.6
Medium	AUC_{last}	2716	-11.1	-8.6	-9.2	-9.2	-3.9
	C_{max}	128	-0.85	-1.0	-3.1	-1.3	-3.3
Slow	AUC_{last}	2301	-0.64	2.2	1.4	1.5	7.2
	C_{max}	103	15.5	15.4	13.0	14.9	13.1
$\langle\lvert\%PE\rvert\rangle$	AUC_{last}		7.6	6.6	6.7	6.6	4.8
	C_{max}		8.4	9.0	9.2	8.6	9.6

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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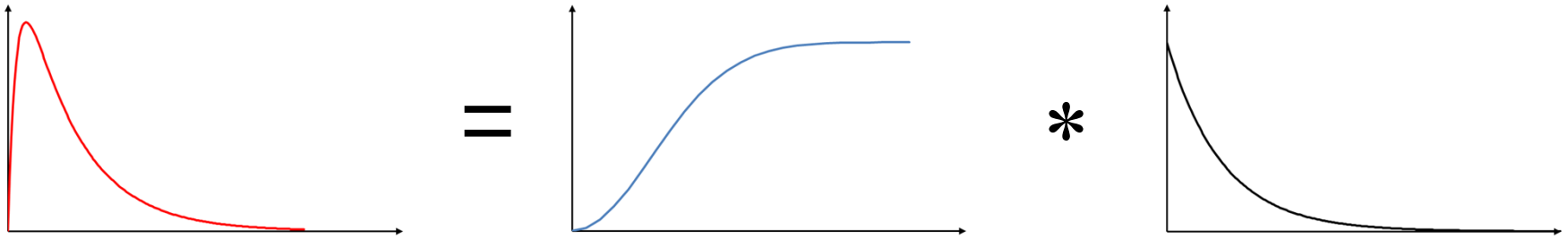
Back Up slides

Classical Deconvolution



Concentration
Output

Absorption
Input

Distribution/Elimination
UIR

- Inverse of convolution:

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

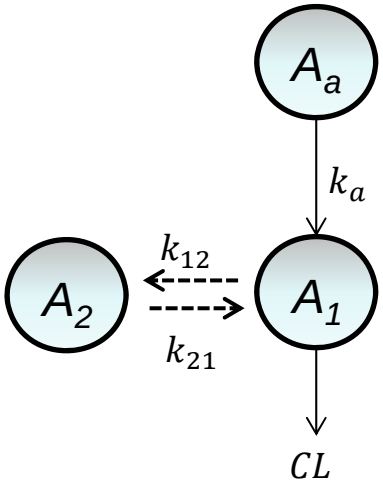
- Ill-conditioned problem. Indirect methods used to calculate $f(t)$

Constitutive Equations without EHC

$$F_{abs}(t) = \alpha F_{diss}(t_{vitro}) \begin{cases} t_{vitro} = \beta t \\ F_{diss}(t_{vitro}) = F_{diss,\infty}\left[1 - \exp\left(-\left(\frac{t_{vitro}}{\bar{T}_{diss}}\right)^{b}\right)\right] \end{cases}$$

Absorption profile

$$\frac{dA_a}{dt} = \begin{cases} -D\dfrac{dF_{abs}}{dt} & \text{Baseline estimation, IVIVC prediction} \\ -k_a A_a & \text{Stoch Decon estimation} \end{cases}$$



$$\frac{dA_1}{dt} = k_a A_a - k_e A_1 - k_{12} A_1 + k_{21} A_2$$

$$\frac{dA_2}{dt} = k_{12} A_1 - k_{21} A_2$$ For 1-compt, $k_{12} = k_{21} = 0$

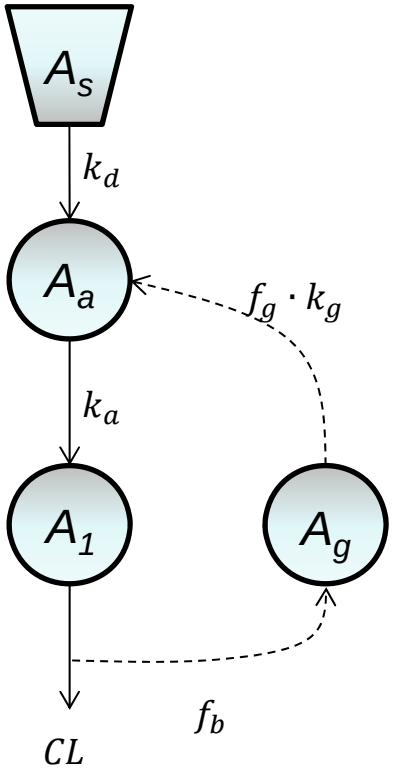
$$C_1(t) = \frac{A_1(t)}{V_1}$$

$$CL = \frac{V_m}{(C_1 + K_m)}$$ For Michaelis-Menten example

Constitutive Equations with EHC

$$F_{rel}(t) = \alpha F_{diss}(t_{vitro}) \begin{cases} t_{vitro} = \beta t \\ F_{diss}(t_{vitro}) = F_{diss,\infty}\left[1 - \exp\left(-\left(\frac{t_{vitro}}{\bar{T}_{diss}}\right)^{b}\right)\right] \end{cases}$$

Release profile



$$\frac{dA_s}{dt} = -D\frac{dF_{rel}}{dt}$$

Baseline estimation

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

Baseline estimation

Stoch Decon estimation

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

$$\frac{dA_g}{dt} = f_b k_e A_1 - f_g k_g A_g$$

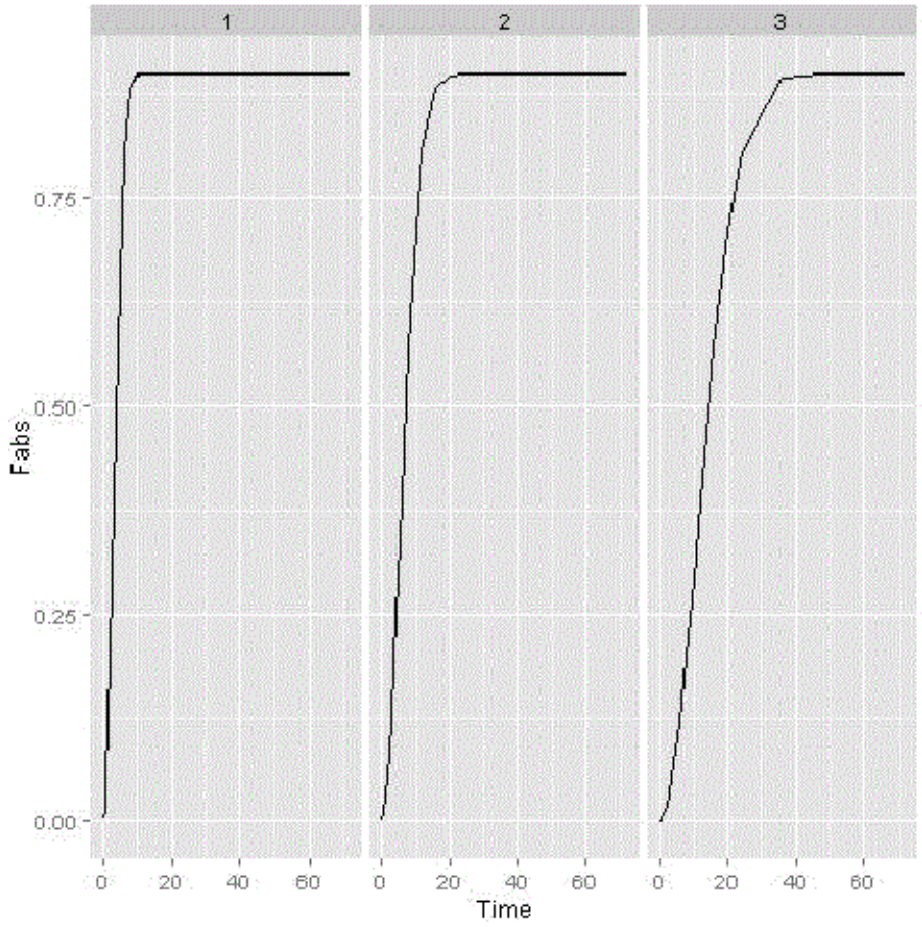
Parameters for Weibull Dissolution Distribution

Formulation	**Form ID (*FID*)**	$F_{diss,\infty}$	$\overline{T}_{diss}$	b
[–]	[–]	[–]	[h]	[–]
Fast	1	1	2	2
Medium	2	1	4	2
Slow	3	1	8	2

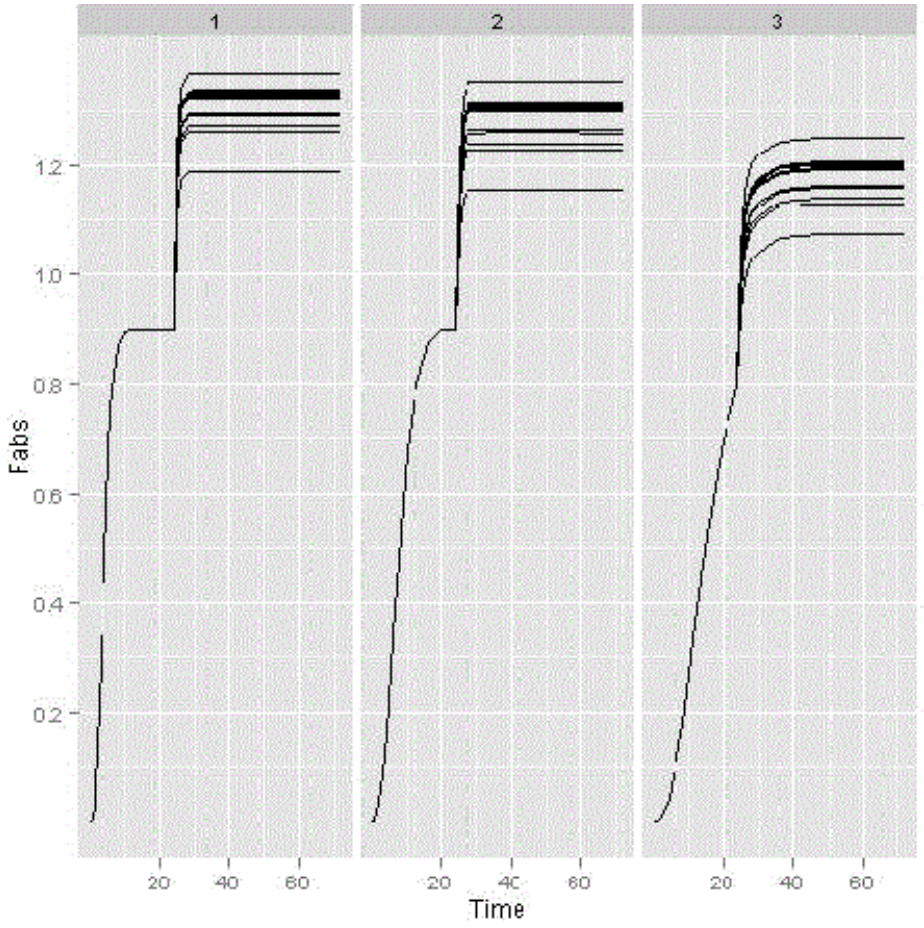
Parameters for EHC model data generation

Parameter	**Value**
k_a [h^{-1}]	2
k_g [h^{-1}]	4
f_b [–]	0. 5
$f_g(t)$ [–]	$\begin{cases} 0 & t < 24, t > 26 \\ 1 & 24 \leq t \leq 26 \end{cases}$

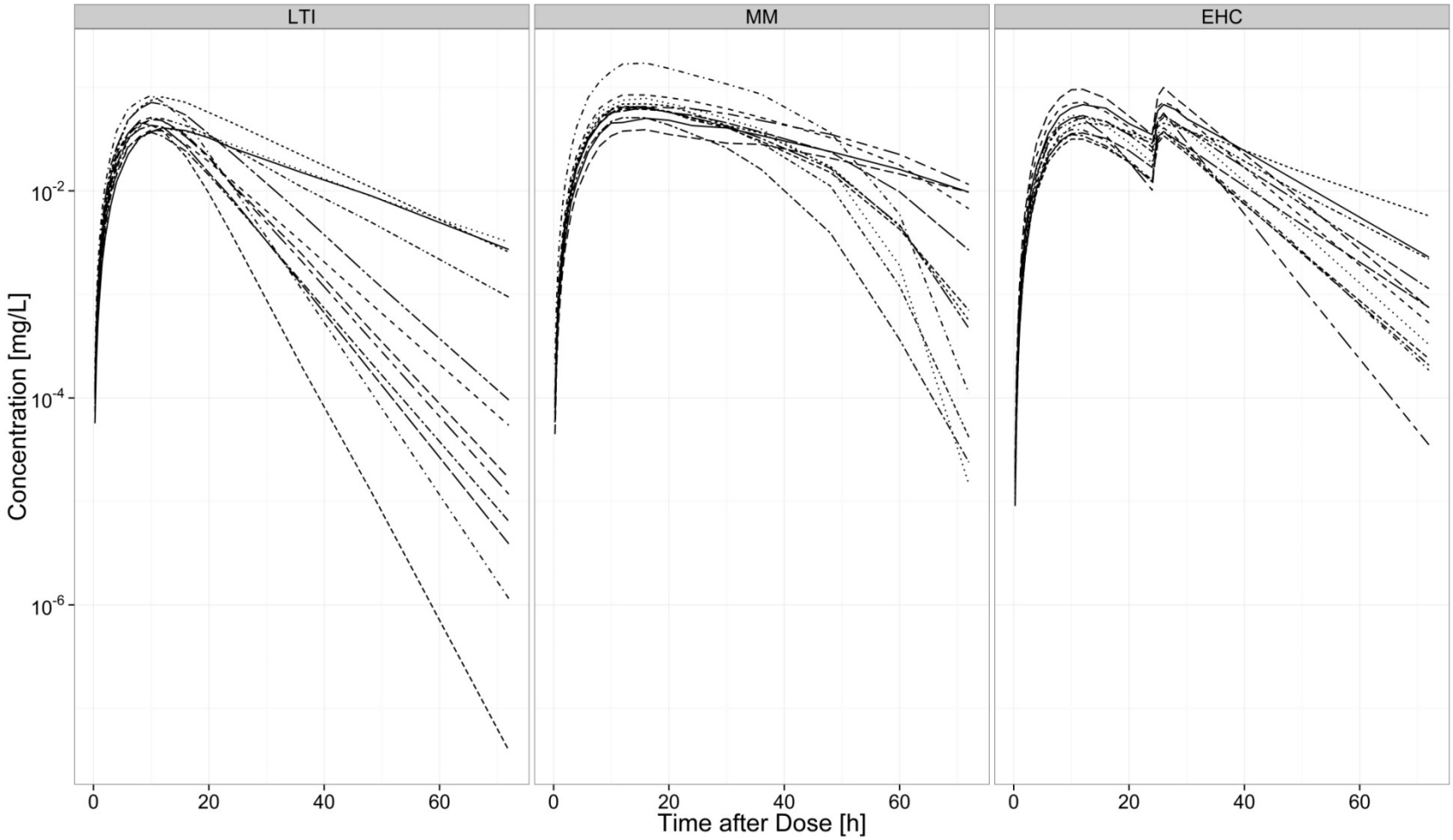
Simulated Fabs vs Time Profiles, LTI & MM



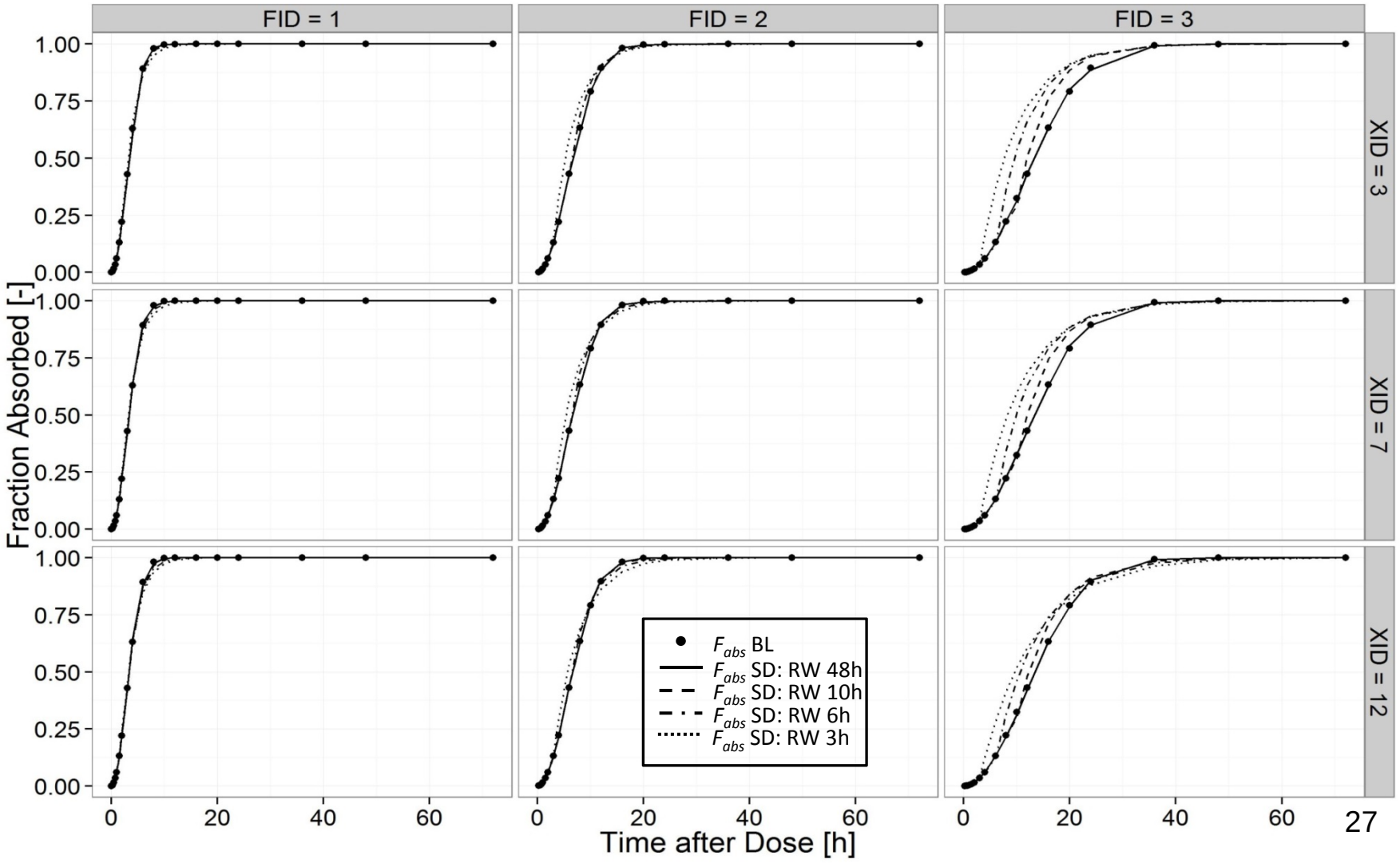
Simulated Fabs vs Time Profiles, EHC



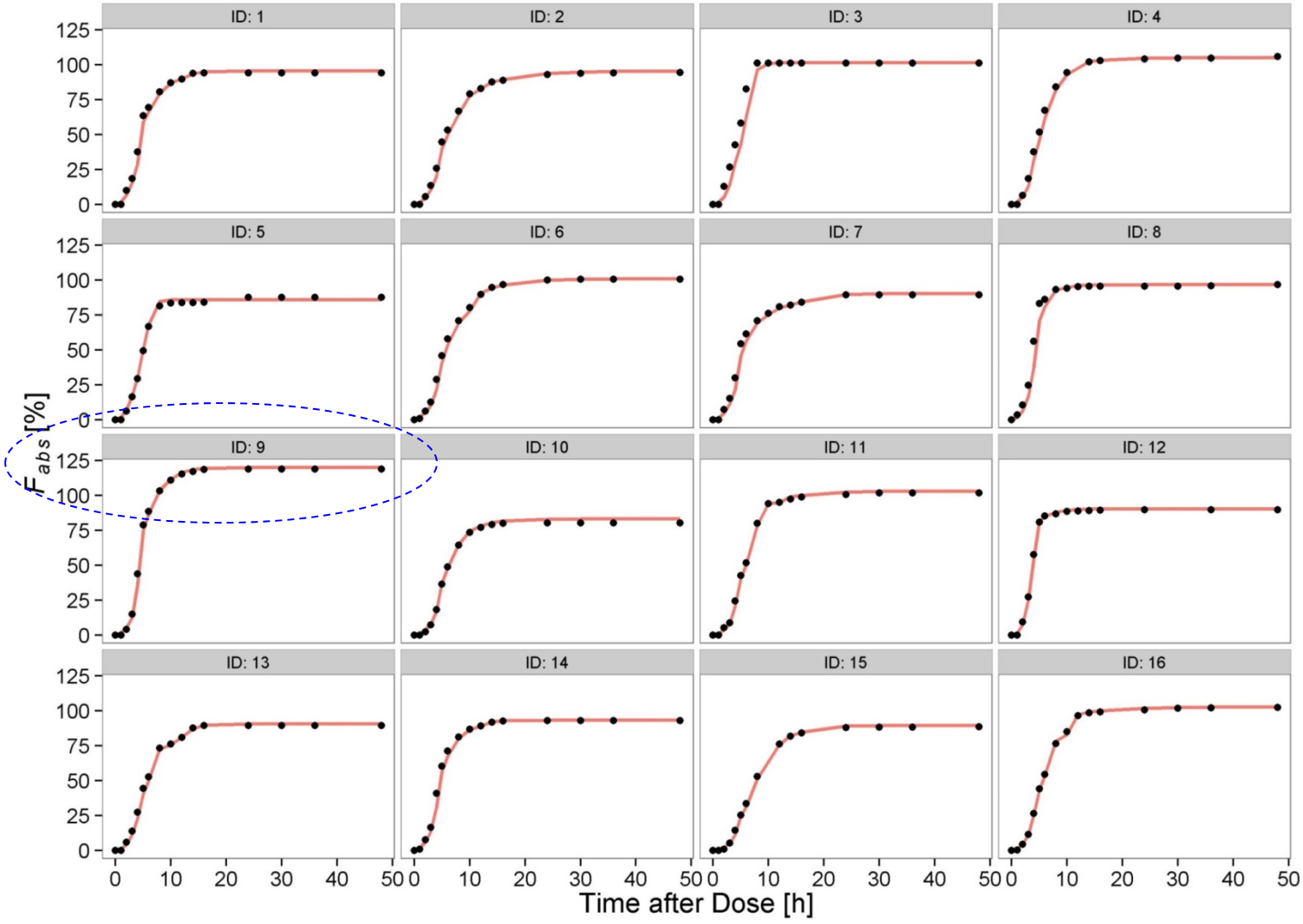
Concentration–time profiles for all subjects receiving FID = 2 based on the PK models LTI, MM, and EHC



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:

$$\bar{F}_{abs}(t) = A_s \, F_{diss}(T_s \, t)$$

- Rate of drug loss from the absorption compartment:

$$\frac{d\bar{A}_a}{dt} = -D \, A_s \, T_s \, F_{diss,\infty} \frac{b}{\bar{T}_{diss}} \left(\frac{T_s \, t}{\bar{T}_{diss}} \right)^{b-1} e^{-\left(\frac{T_s \, t}{\bar{T}_{diss}} \right)^b}$$

$$\frac{d\bar{A}_1}{dt} = -\frac{d\bar{A}_a}{dt} - \widetilde{k_e} \, \bar{A}_1 - \theta_{k_{12}} \, \bar{A}_1 + \theta_{k_{21}} \bar{A}_2, \text{ where } \widetilde{k_e} = \exp\left[\frac{1}{N} \sum_{i=1}^{N} \ln\left(k_{e,i}\right) \right]$$

- $\widetilde{k_e}$ 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:

$$\bar{C}_1(t) = \frac{\bar{A}_1(t)}{\widetilde{V_1}}, \; \widetilde{V_1} = \exp\left[\frac{1}{N} \sum_{i=1}^{N} \ln\left(V_{1,i}\right) \right]$$

PK Parameters (Standard Errors) and Shrinkages

Scenario	V_1 or V_{ss} (CV%) [L]	k_e (CV%) [h^{-1}]	Shrinkage [-]		
			η_V	η_{Ke}	ε
1. SDcon: 1 Comp PK with IR	332 (3%)	0.12 (6.6%)	0.22	0.021	0.21
2. SDcon: 1 Comp PK without IR	324 (0.8%)	0.10 (0.9%)	0.54	0.73	0.37
3. SDcon: 2 Comp PK with IR	335 (1.1%)	0.14 (1.6%)	0.17	0.32	0.32
4. SDcon: 2 Comp PK without IR	354 (1.1%)	0.11 (1.1%)	0.41	0.08	0.41