Solutions to non-ideal reference data: Stochastic Deconvolution

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6 November 2014

Motivation

- Start from assumption that we are interested in the absorption profile
  - Want to IVIVC
  - Examine formulation performance
- What do we do when we can't apply standard deconvolution:
  - No unit impulse response
  - Nonlinear processes
  - Time-varying PK (e.g. enterohepatic recirculation, enzyme induction)

What's wrong with numerical deconvolution?

- Nothing! If it's applicable use it.
- Often don't have correct data to use deconvolution
  - No unit impulse (IV or IR data) collected.
    - No UIR means we can't characterize the PK model
  - No individual UIR (maybe from literature or another study)
    - Introduces bias
- Or deconvolution isn't applicable:
  - nonlinearity in clearance
  - complicated PK model (largely a limitation in the tools)
  - time varying PK model

Modeling as an alternative

- Removes most limitations
  - We can easily model nonlinearity, time-varying, etc…
  - Can combine data across subjects and studies
- We have a framework for comparing options (likelihood, etc.)
- Need some proposal for functional form of absorption
  - Can work really well if we guess correctly
  - Can introduce a lot of bias if we guess poorly
  - Imposes our prior belief into the analysis
  - May be over-parameterized or, if not, not flexible enough
- Maybe we can specify something really flexible

Proposal for a flexible absorption function

- What if instead of saying absorption must have some form, say it could have almost *any form*
- Continuous random processes
  - Basically attribute noise in absorption phase of profile to time-varying k_a
  - Allows for absorption rate to be almost any value, but
  - Constrains it to be most likely somewhere

Wiener Process

The Wiener Process is a random walk $W(t)$ with:

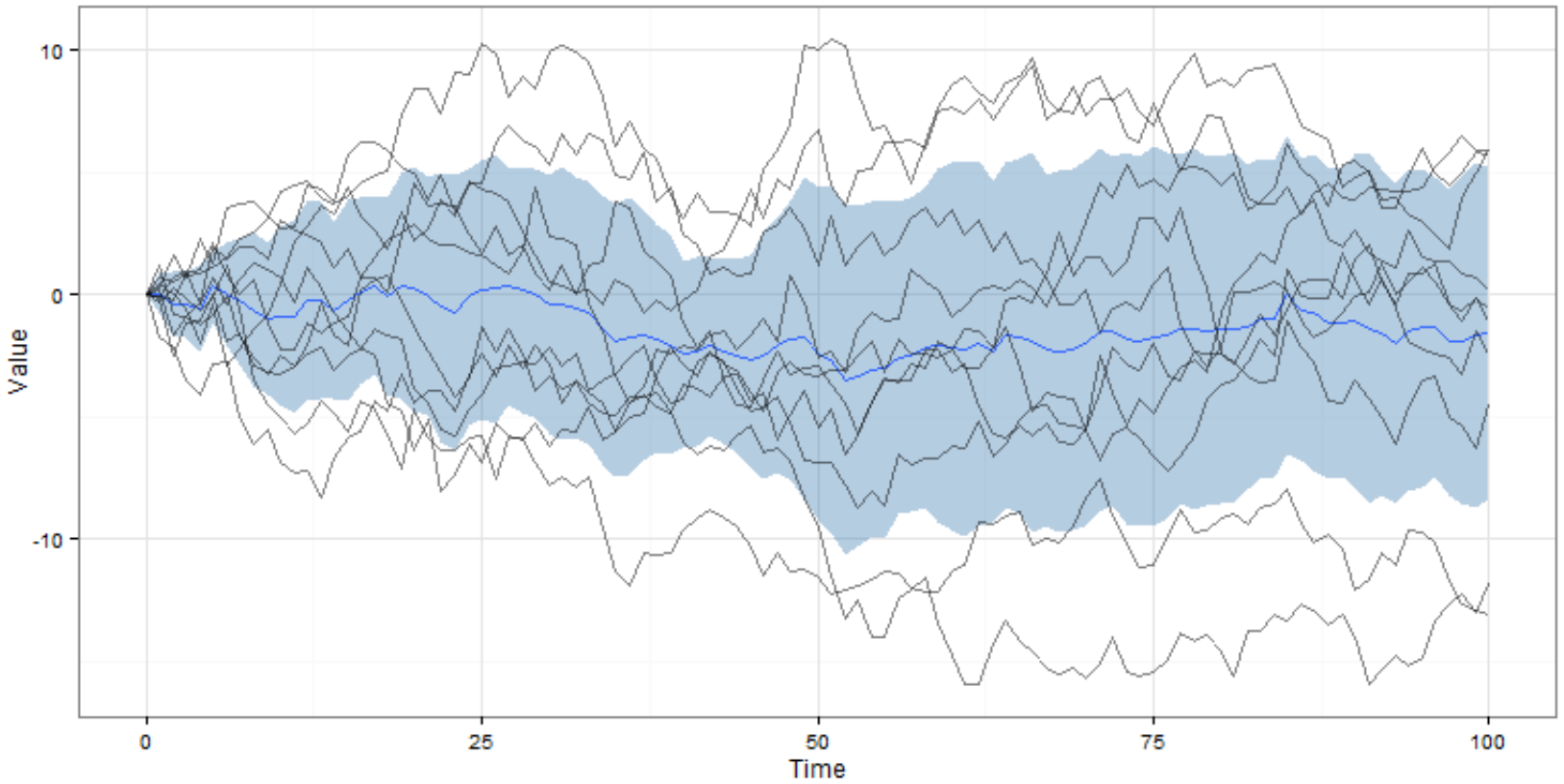
- initial value: $W(0) = 0$
- expected value: $E[W(t)] = 0$
- value is a sum of independent, normally distributed increments
  - $W(t) - W(s) \sim N(0, t - s), \quad \text{for } 0 \leq s \leq t$
  - that is the variance is proportional to Δtime

Wiener Process in Action

Number of samples: 10

Line opacity : 0.5

Displaying: Process



Modeling a Wiener Process

Given that the Wiener Process, W, is either directly or indirectly observed over a set $T = \{t_1, t_2, t_3, \cdots\}$, define:

$$W(T_i) = \sum_{t \leq T_i} w_i, \quad w_i \sim N(0, (T_i - T_{i-1})\sigma^2)$$

The increments of W, w_i, are independent and can be transformed to identically distributed normal variables:

$$w_i = (T_i - T_{i-1})^{\frac{1}{2}} \eta_i, \quad \eta_i \sim N(0, \sigma^2)$$

Then attach W to an observed or latent variable (like k_a):

$$\log(k_a) = \theta_{\log k_a} + W(T_i)$$

Solve a mixed effects model using appropriate tools.

How does it work?

- The observed data carry information about the parameters
  - Early points have a lot of information about k_a
  - Later points have a lot of information about k_e
- w_i are adjusted to better fit the absorption phase
- As drug is fully absorbed, k_a becomes less influential on the fit
- If the terminal phase is sampled well enough k_e can be estimated
- A population approach can be used to help ground parameter values
  - k_e and V would have *likely* values and tend towards those
- Can try different PK models

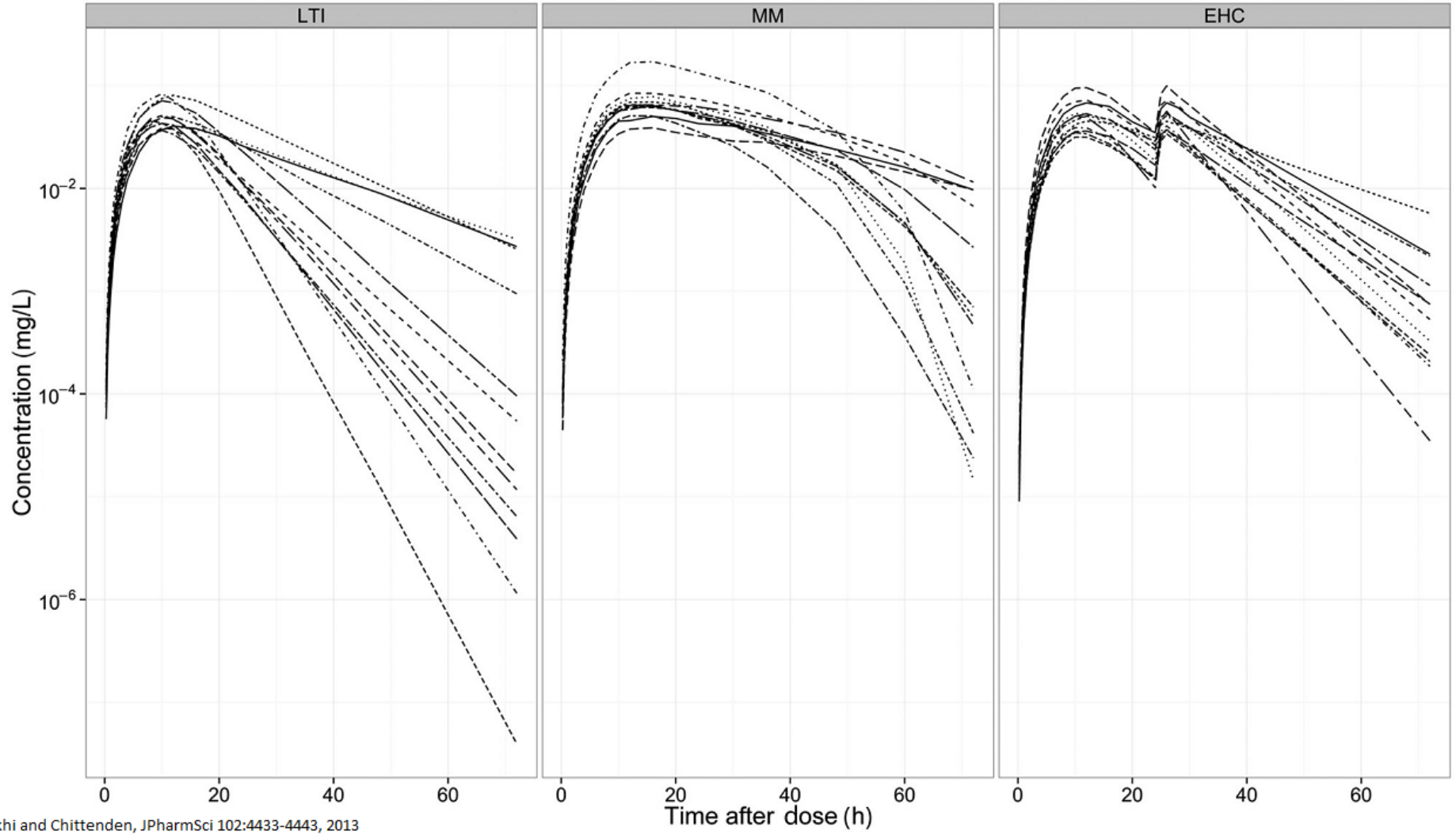
How well does it work?

Modeling of Pharmacokinetic Systems Using Stochastic Deconvolution
Kakhi and Chittenden; JPharmSci 102:4433-4443, 2013

- Evaluated the performance of stochastic deconvolution on three simulated datasets:
  - Linear time-invariant (LTI)
  - Michaelis-Menten elimination
  - Enterohepatic circulation (EHC)
- Common features:
  - three formulations (fast, medium, slow)
  - inter-subject variability in PK parameters

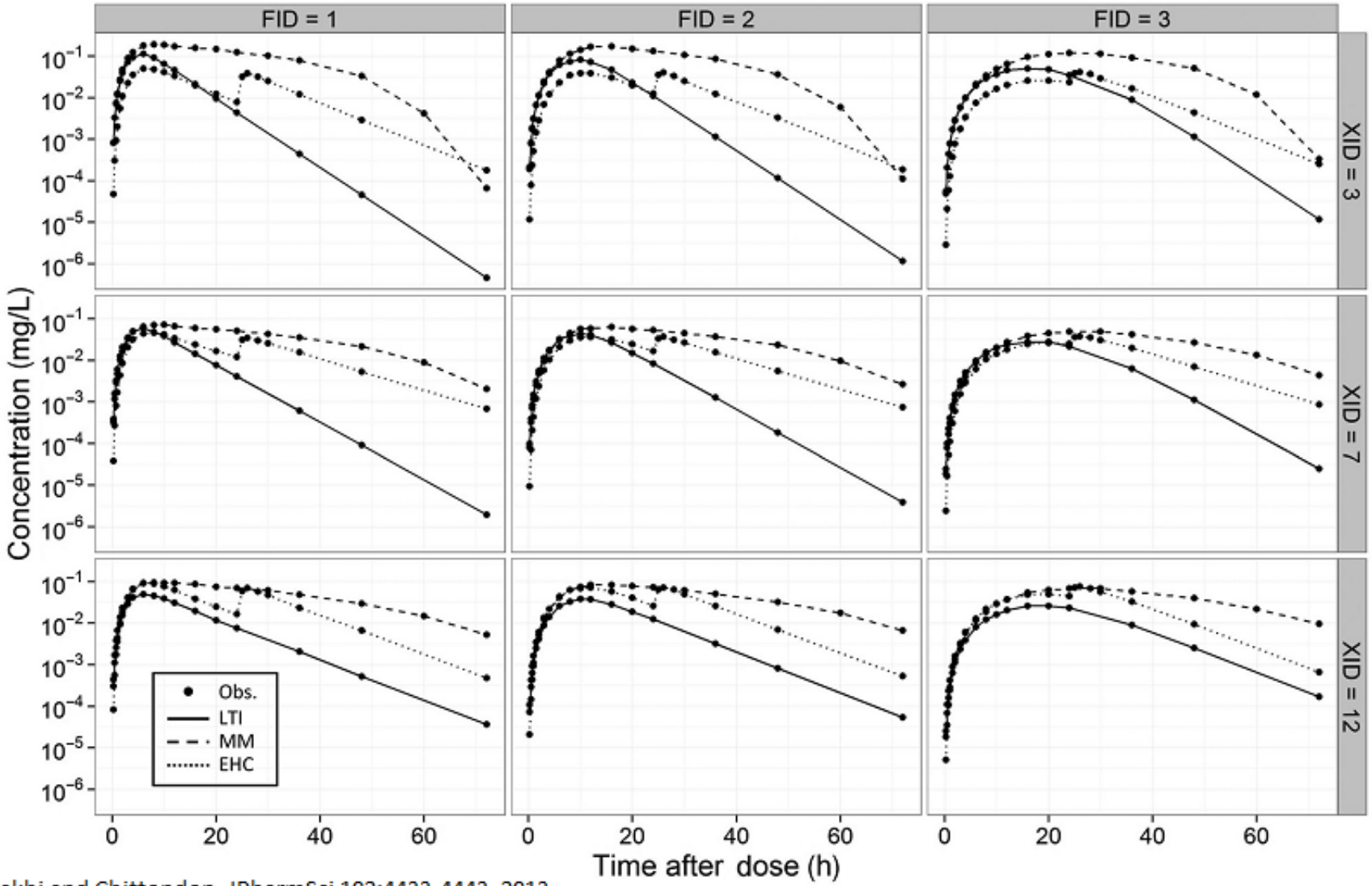
Note: We (ab)use the term "deconvolution" here to signify that we're trying to recover the input process.

Simulated data



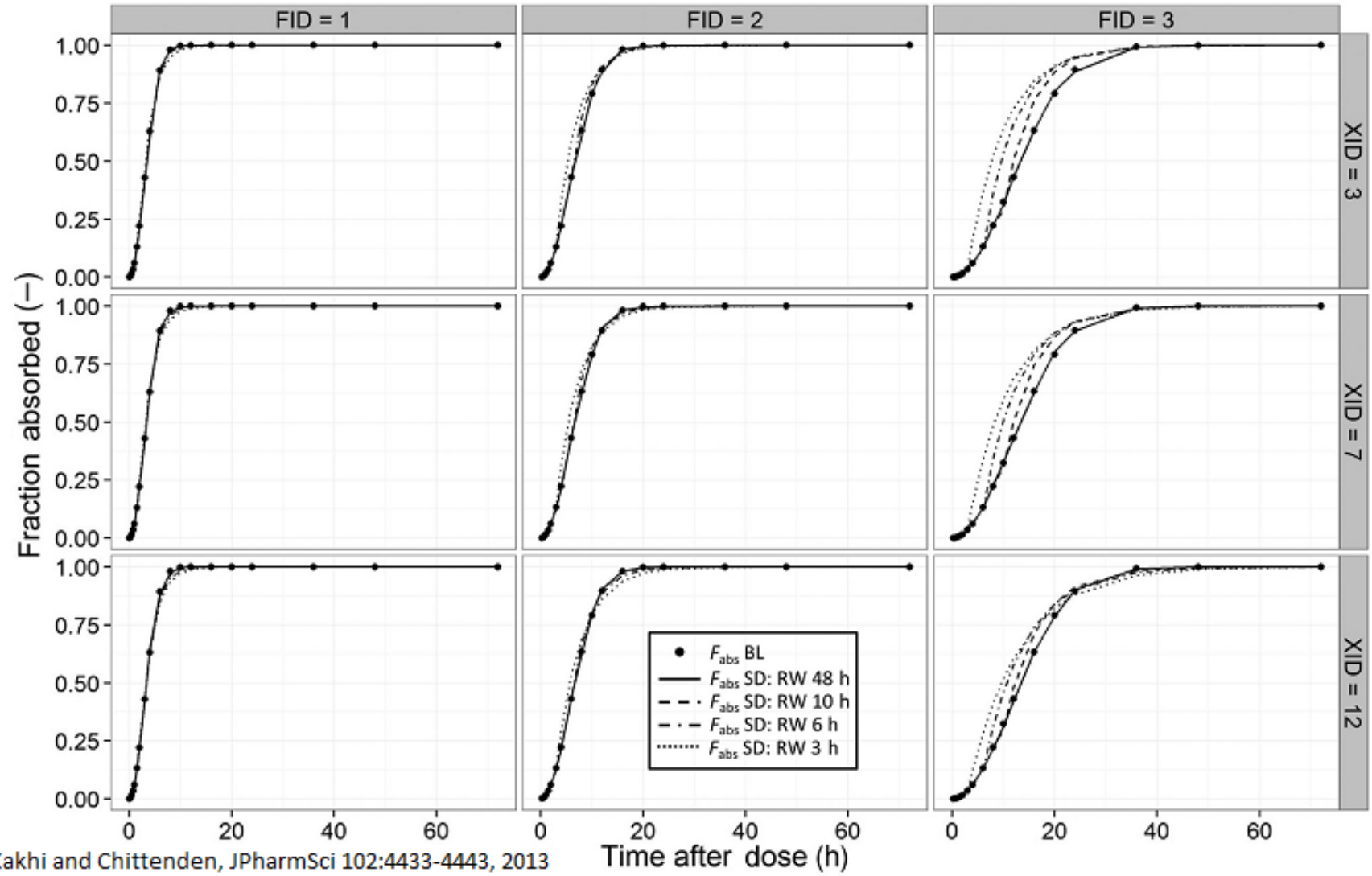
Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

The data are well estimated



Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

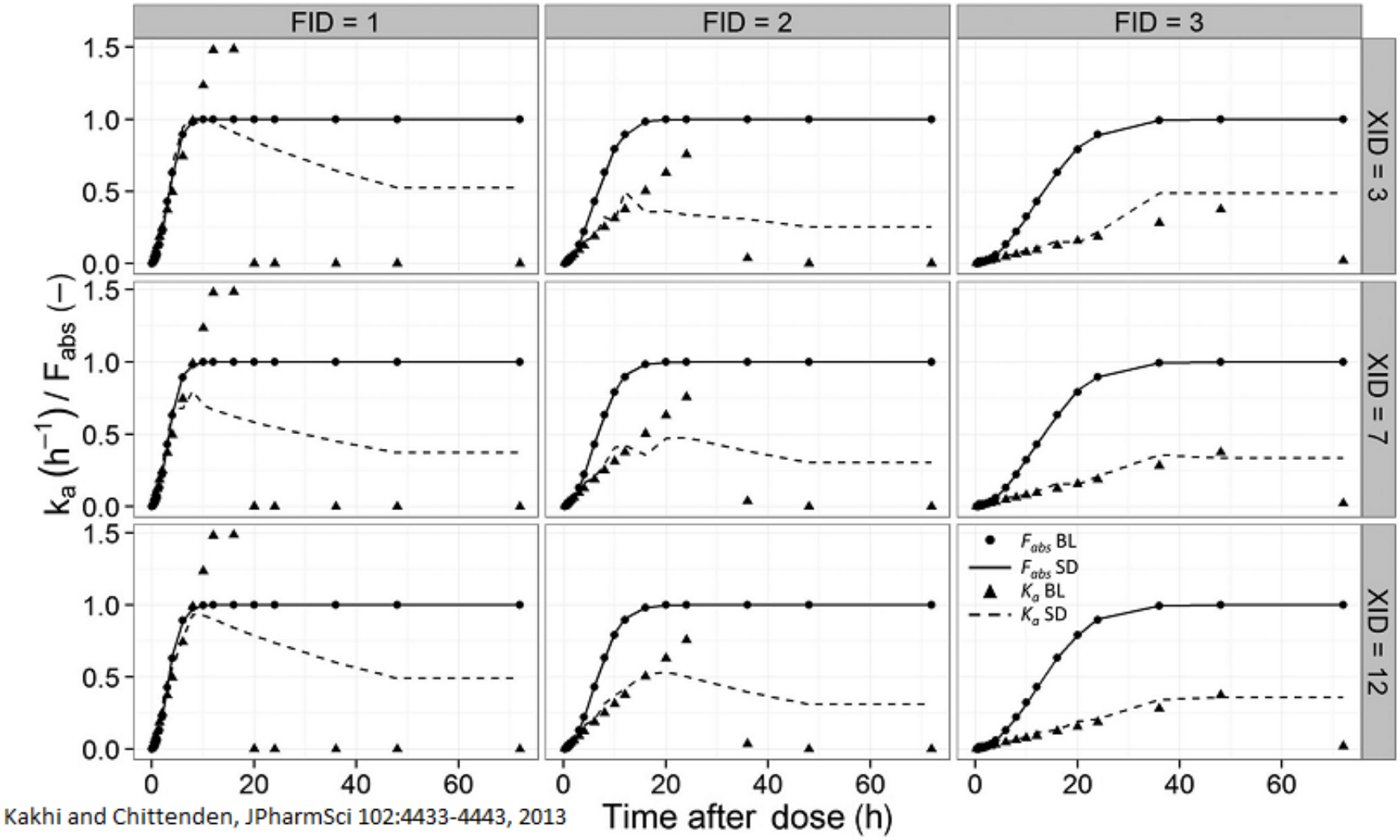
Estimated absorption profiles (LTI)



Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

Multiple profiles show the effect of truncating the random walk.

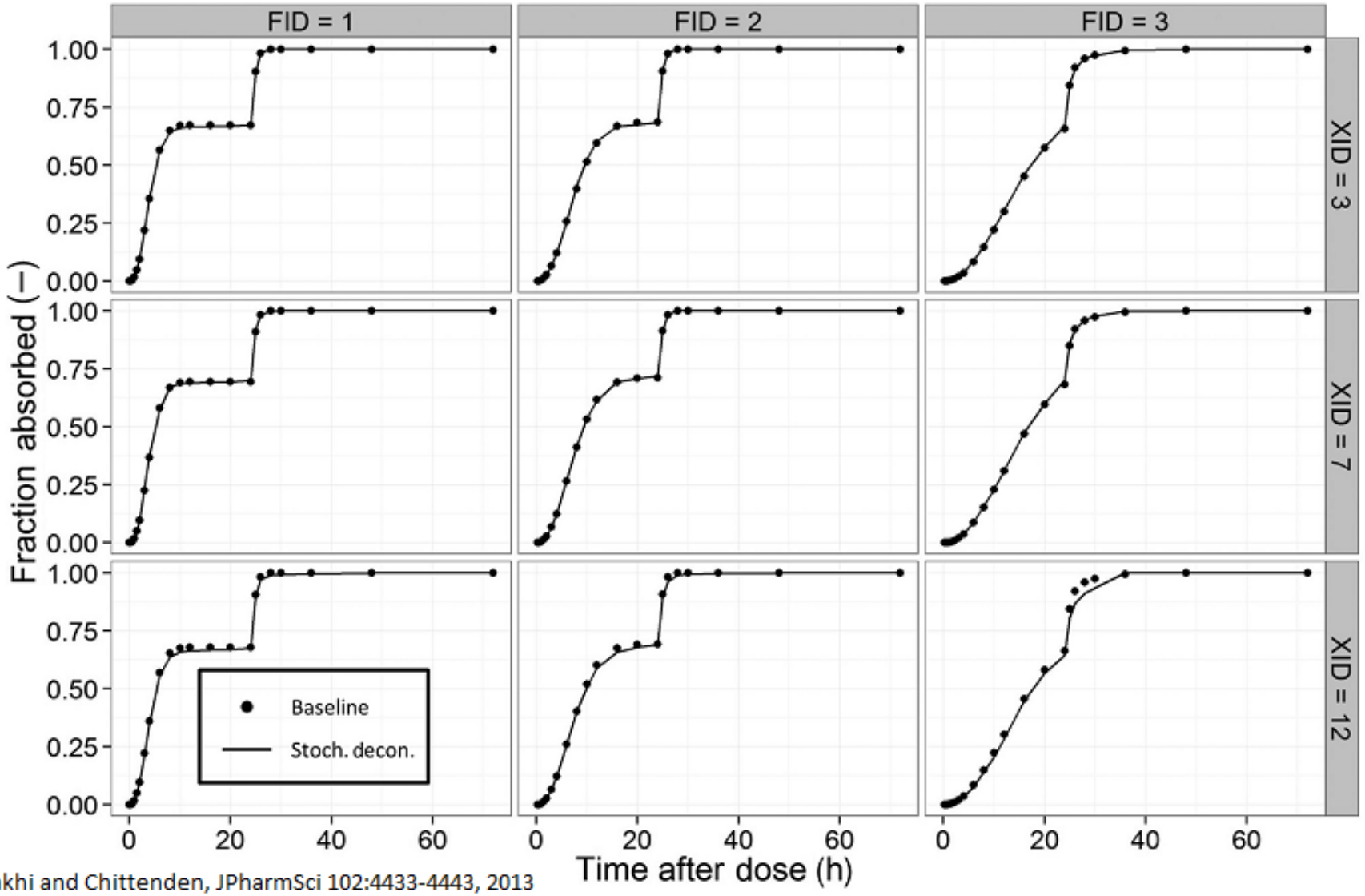
Estimated k_a profiles (LTI)



Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

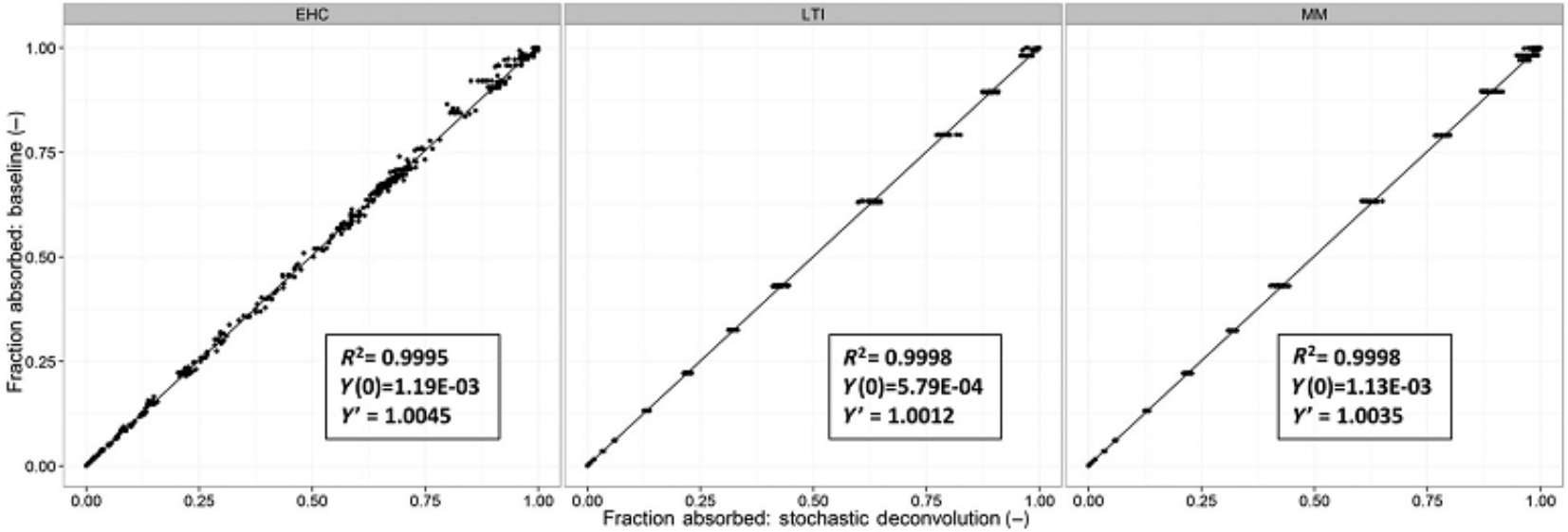
Note: Baseline k_a is continuous vs. estimated stepwise process

Second peak in EHC is identified



Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

Overall performance



Kakhi and Chittenden, JPharmSci 102:4433-4443, 2013

- High correlation between known and estimated absorption.
- Additional scatter in known EHC absorption due to variability in PK model.

Conclusion

- A random process model can identify time varying k_a
- Time varying k_a can estimate complicated absorption profiles
- Allows "deconvolution" in cases where it is not otherwise applicable
- The process can be applied across multiple subject/studies

Applications and Future work

- This methodology has already been used in practice
  - Not just for identifying absorption, but also to evaluate other time-varying parameters (e.g. clearance).
  - Gain insights to use for refining models.
  - Bypass detailed absorption model yet get good estimates of the other parameters (e.g. V, CL, post-hocs).
- There is some similarity between this approach and SDE (filtering approaches)
  - SDE modeling in NONMEM is still tricky. Stochastic deconvolution is more accessible.
  - Compare Stochastic Deconvolution and SDE approaces.