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Population pharmacokinetic modeling of total and unbound docetaxel plasma concentrations in cancer patients with poor liver function

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Outline

1. Docetaxel
2. Data
3. Modeling methods
4. Results
5. Problems/questions from modeling

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Docetaxel

- A taxane with significant anti-tumor activity used in chemotherapy treatment.

Main problem with docetaxel – patients with poor liver function

- FDA: Do not dose (EU: Reduce dose by 25%)
  - Due to unpredictable PK
  - Increased risk of dose-limiting toxicity (neutropenia)

- **Better dosing strategies are needed for poor liver function patients!**

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Docetaxel PK

R. Bruno *et al*., *J. PKPD,* 1996:

- 3-compartment model
- $CL = BSA\ (\theta_1 + \theta_2\, AAG + \theta_3\, AGE)(1 - \theta_4\, HEP12)$
- Based on total concentrations of drug

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Main objective

Better dosing strategies for patients with poor liver function

- Develop a *clinically useful* population PK model to describe *and predict* docetaxel (especially CL) that incorporates unbound concentration measurements, liver function and CYP3A activity.

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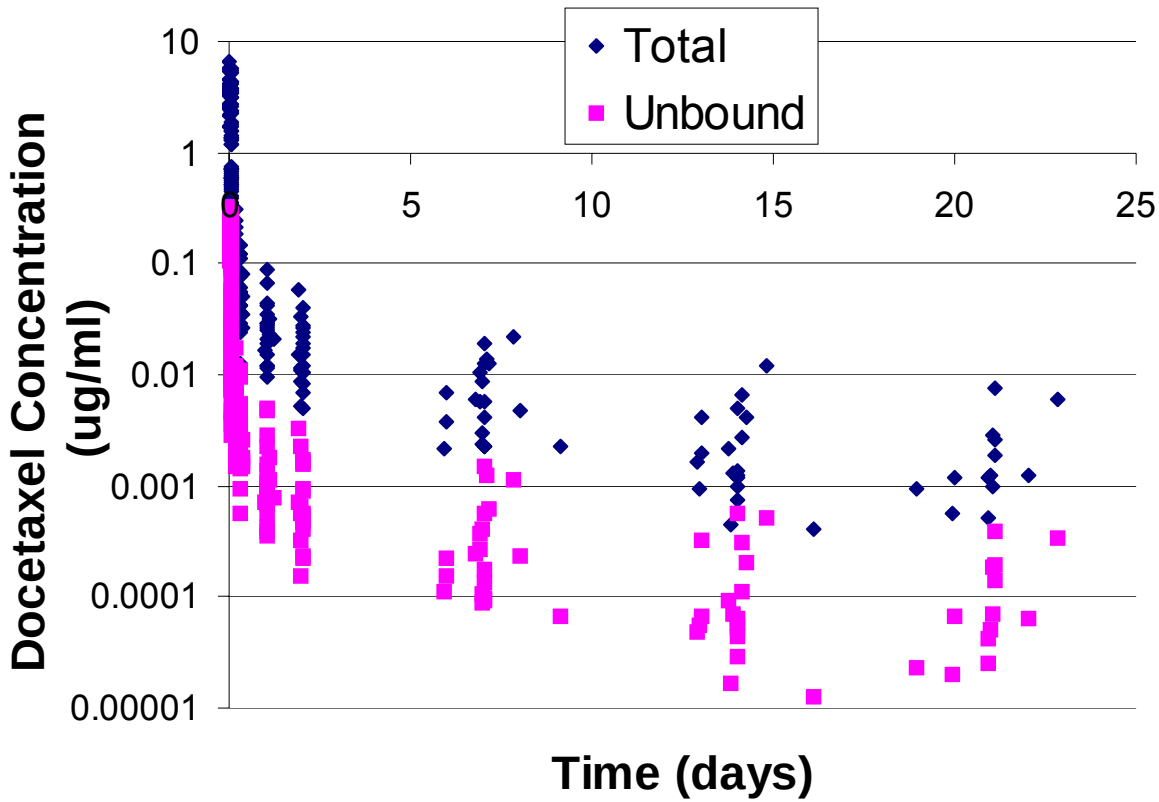
The data



- PK from 21 patients with poor liver function
- Similar data from 50 patients with normal liver function
- Liver function based on AST/ALT, ALPHOS, bilirubin
- CYP3A activity – Erythromycin Breath Test (ERMBT)
- Doses: 40 – 75 mg/m^2 Docetaxel in 1-hour infusion

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Modeling methods

- Developed separate models for normal and poor liver function patients. Both had:
  - 4-compartment model
  - A binding model including AAG as a covariate
  - Block(3) structure of IIV (covariance)
  - Same structure of residual error (incl. L2 & IIV)

- Poor precision of estimates in poor liver function group
  - Low number of patients (21)
  - Complexity of model

- Next combined models for the two groups
  - More information on parameters similar between the two groups.

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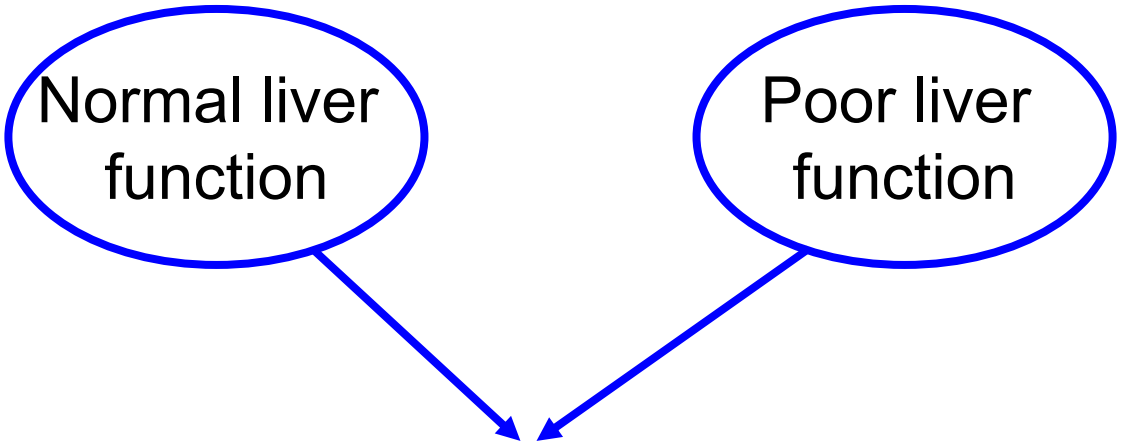
Problem:
How do we combine the two models?



Structural →	Combine binding…other parts?
IIV →	Combine etas: SE's for poor liver function model high
Covariates (?) →	Mechanistically, should both groups have the same covariates?
Residual error →	Some terms similar in size

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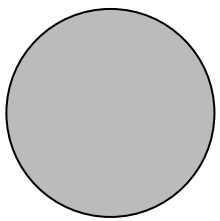
Two strategies for combining models:

‘**Bottom up**’ model building strategy

- Begin with one model and add components when the two groups are different

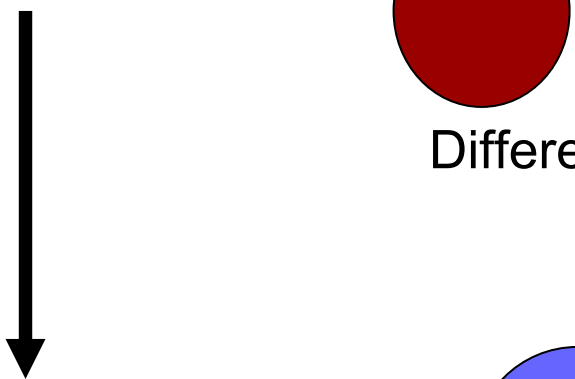
‘**Top down**’ model building strategy

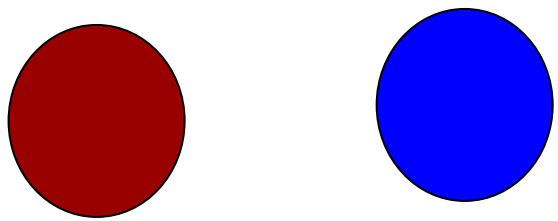
- Begin with two models and remove components when the two groups are the same



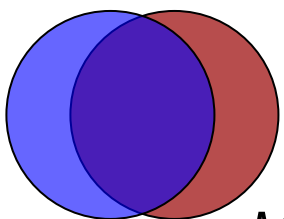
Same θ’s, η’s, ε’s

Initial model

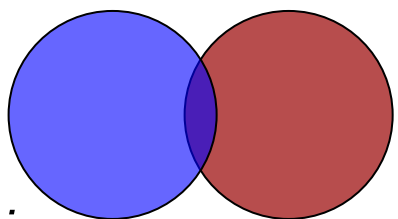




Different θ’s, η’s, ε’s



Final model



May not be the same for both strategies

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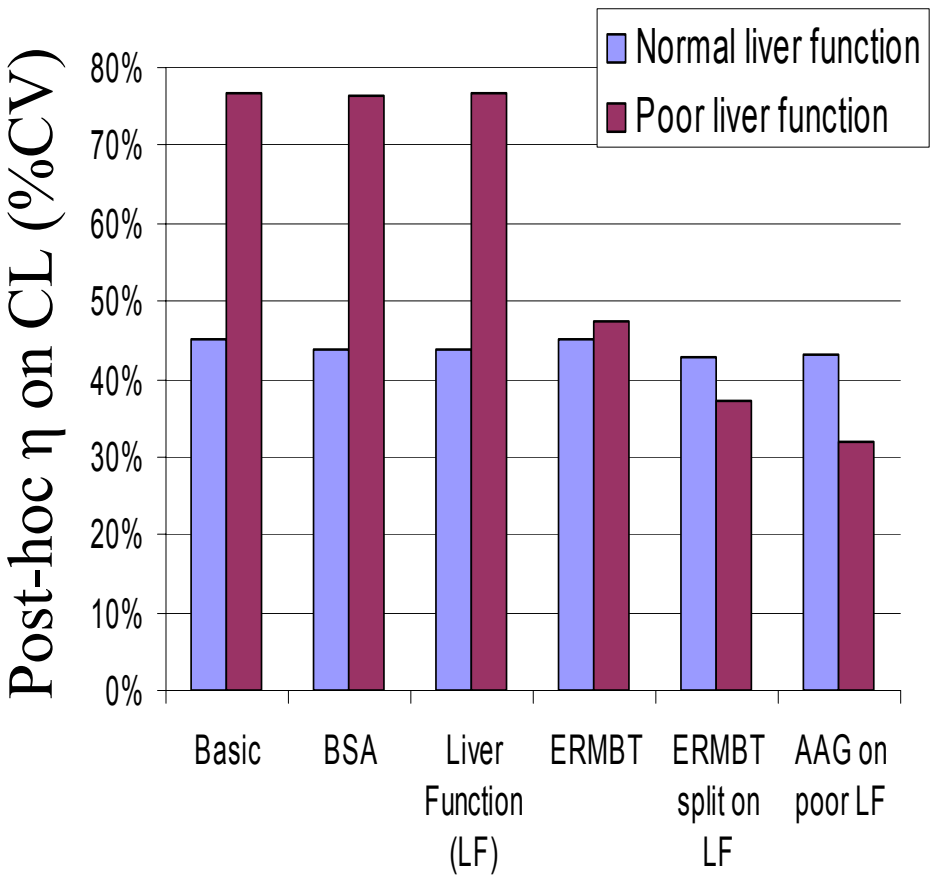
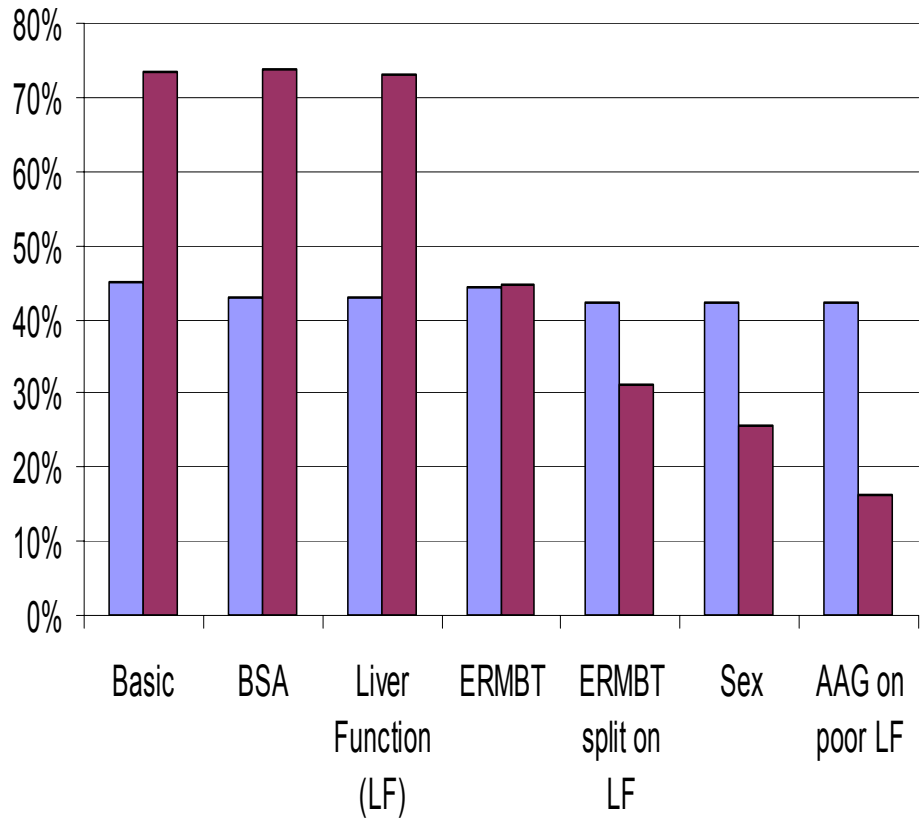
Results: Unexplained variability in CL

‘Bottom up’ model building method



‘Top down’ model building method



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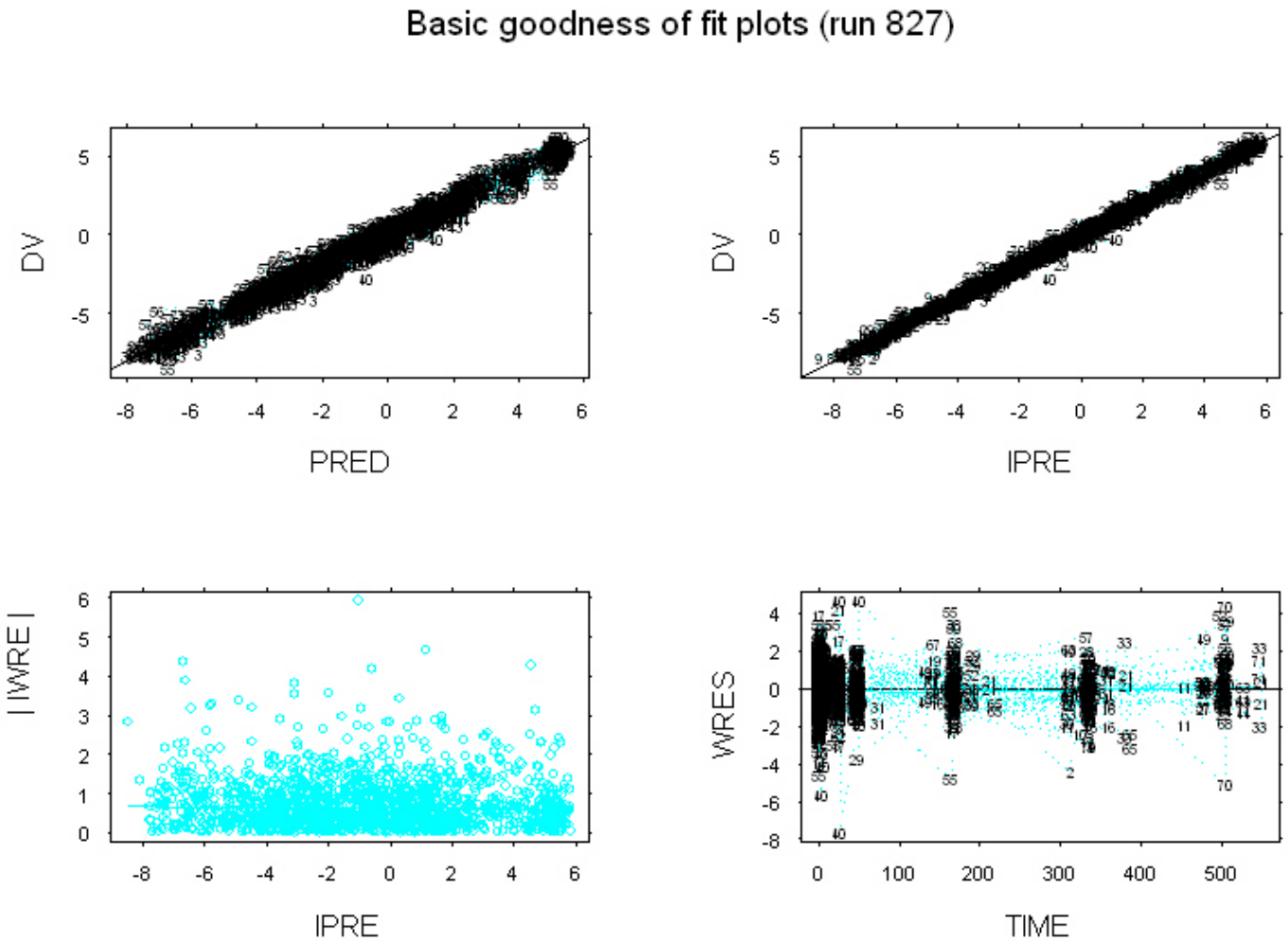
Results: G.O.F. for 'Bottom Up' model building strategy



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Results

Significant reduction in CL variability using ERMBT and liver function for both model building strategies (‘bottom up’ and ‘top down’)

We chose the model from the ‘bottom up’ strategy.

- Odd correlation properties with the ‘top down’ strategy
- Conservative: Smaller amount of data in poor liver function group, higher variance prediction

Covariates in CL

- Good liver function: BSA, ERMBT(1)
- Poor liver function: BSA, ERMBT(2), AAG

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Modeling questions

Where to begin?

(Based on poor parameter estimates?)