Information synthesis from literature sources

Bayesian analysis of a simulated patient dataset, using prior information from normal volunteers and from another patient group

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Outline

- **Information synthesis from literature sources**
  - ***WHY***
    - **To address important aspects of drugs' PK (& PD)**
    - **A single source of info. often *cannot* achieve this**
  - ***HOW***
    - **Bayesian approach (using WinBUGS)**
- **Bayesian analysis & reporting**
  - **Subjectivity : *Subjectivity is not a weakness***
  - ***Important !!!***
    - ***Good coverage* of realistic prior believes**
    - ***Purpose* of an analysis**

Good Bayesian analysis

(mixed effects modelling perspective)

- **Good frequentist approach *plus***
- **Accurate prior elicitation from credible sources**
- **Exchangeability of priors & datasets**
  - **Similarity of important quantities**
- **Realistic sensitivity analyses**

Case study

Fluconazole (anti-fungal): primarily renally cleared

Prior – *PK studies*

Toon et al. (UK, 1990)

Shiba et al. (Japan, 1990)

Berl et al. (US, 1995)

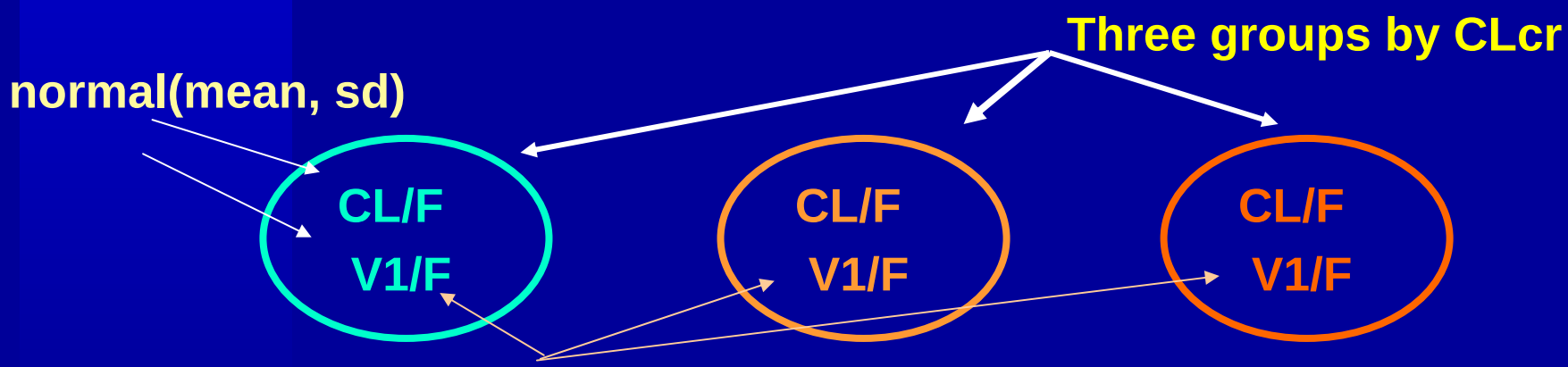
Data (simulated) – *HIV, AIDS PK*

McLachlan et al. (Australia, 1996)

Toon *et al.* *(UK, 1990)*

- **Parallel; Single 50 mg oral dose**
- **Four groups of 5 by CLcr (Male/Female: 8/12)**
  - **> 70 *ml/min***
  - **20 – 70 *ml/min***
  - **< 20 *ml/min*; haemodialysis**
- **Densely sampled**
- **Summary info:**
  - **Mean + SD of observations (a plot)**
  - **Mean + SD of estimated CL/F and V1/kg/F per each renal group**

Toon *et al.* *model 1*



V1/F = V1/kg/F × weight (mixture, p = 0.4)

male = Norm(78, 10)
female = Norm(62, 10)

- ***From another source***
  - –Fixed proportional intra. subject variability
  - –Fixed mean + variability of Ka

Toon *et al.* *model 2*

Model 2 CL

Mixture normal for CL (model 1)

- Mean trend

Pro: accurate

Con: extrapolation

- Plus variability

Pro: extrapolation

Con: a lesser quality representation of the present dataset

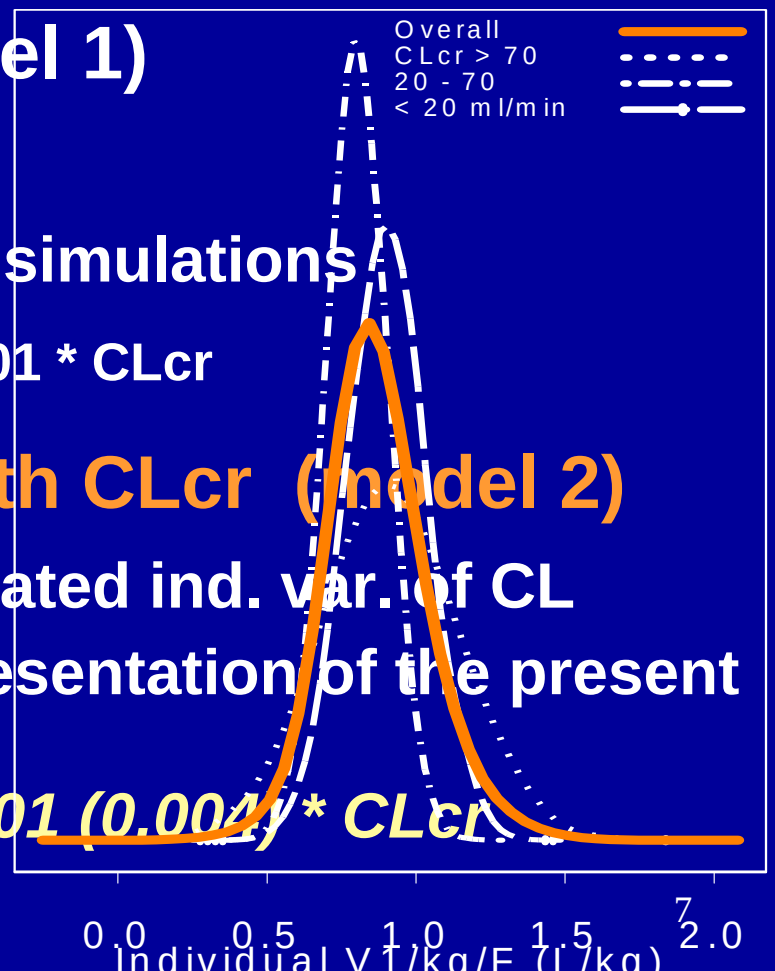
Univariate normal for CL with CLcr (model 2)

- Identified through simulations

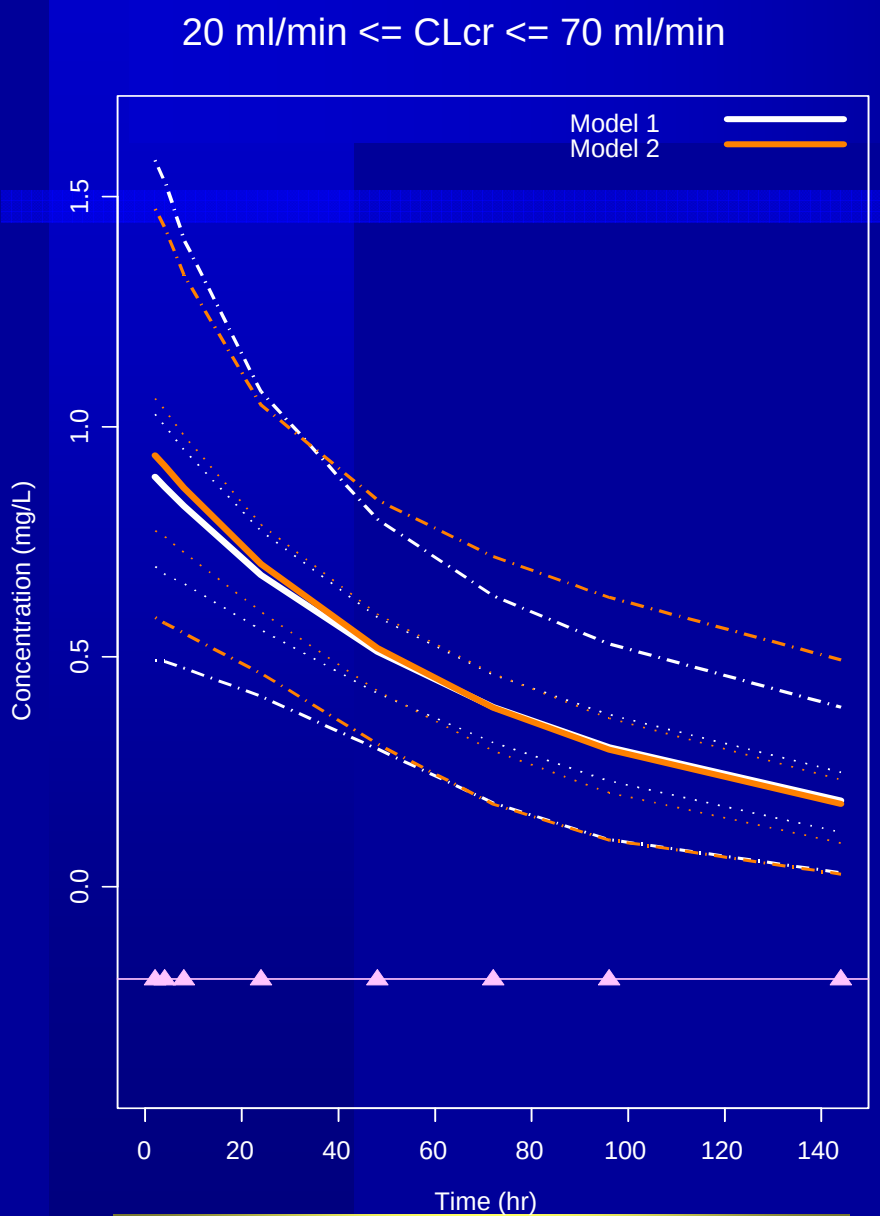
CL/F = 0.24 + 0.01 * CLcr

- Considering estimated ind. var. of CL in Toon's

CL/F = 0.24 (SD: 0.02) + 0.01 (0.004) CLcr*



Model 2 vs. Model 1: 95 % credible plasma conc. intervals



- **Comparison:**

  Model 2 vs. Model 1

- **Similarity:**

  Box's generalised significant test

  $2\,\mathrm{Min}(P(y_{obs} < y_{pred}),\ 1 - P(y_{obs} < y_{pred}))$

  ≈ two sided p-value

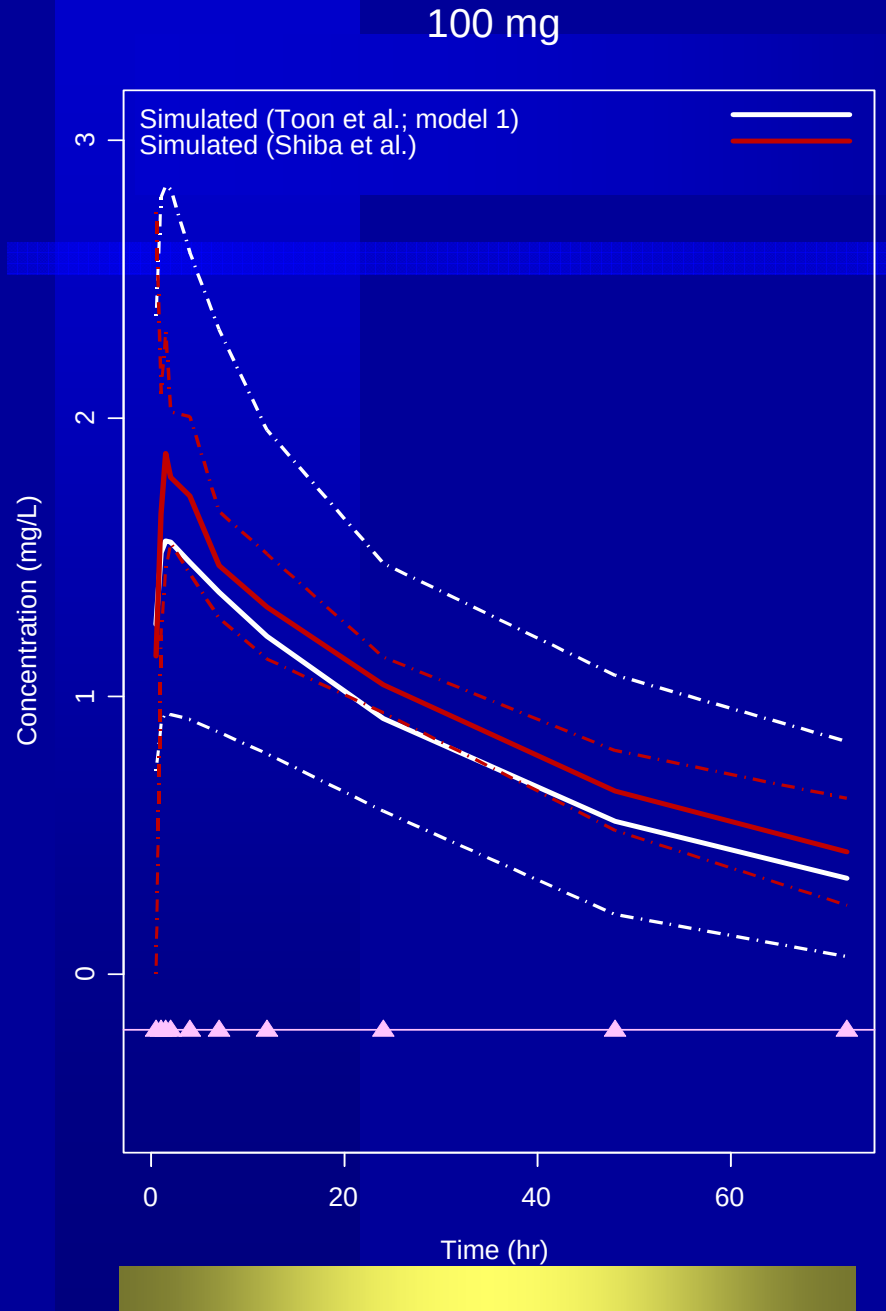
- ***For individual points***

- ***Overall stat. = 0.95***

Shiba *et al*. *(Japan, 1990)*

- **Crossover study**
- **Single 25/ 50/ 100 mg oral dose (& some IV)**
- **8 healthy male volunteers**
- **Densely sampled**
- **Summary info:**
  - **Mean + SD of observations (*a table*)**
  - **Mean + SD of estimated CL/F and V1/F per each dosing group**
  - **Weight info.**

Toon's model 1 vs. Shiba's data summary (95 % intervals)



- **Comparison:**

  Simulations from Toon's model 1 (CLcr > 70ml/min)

  vs.

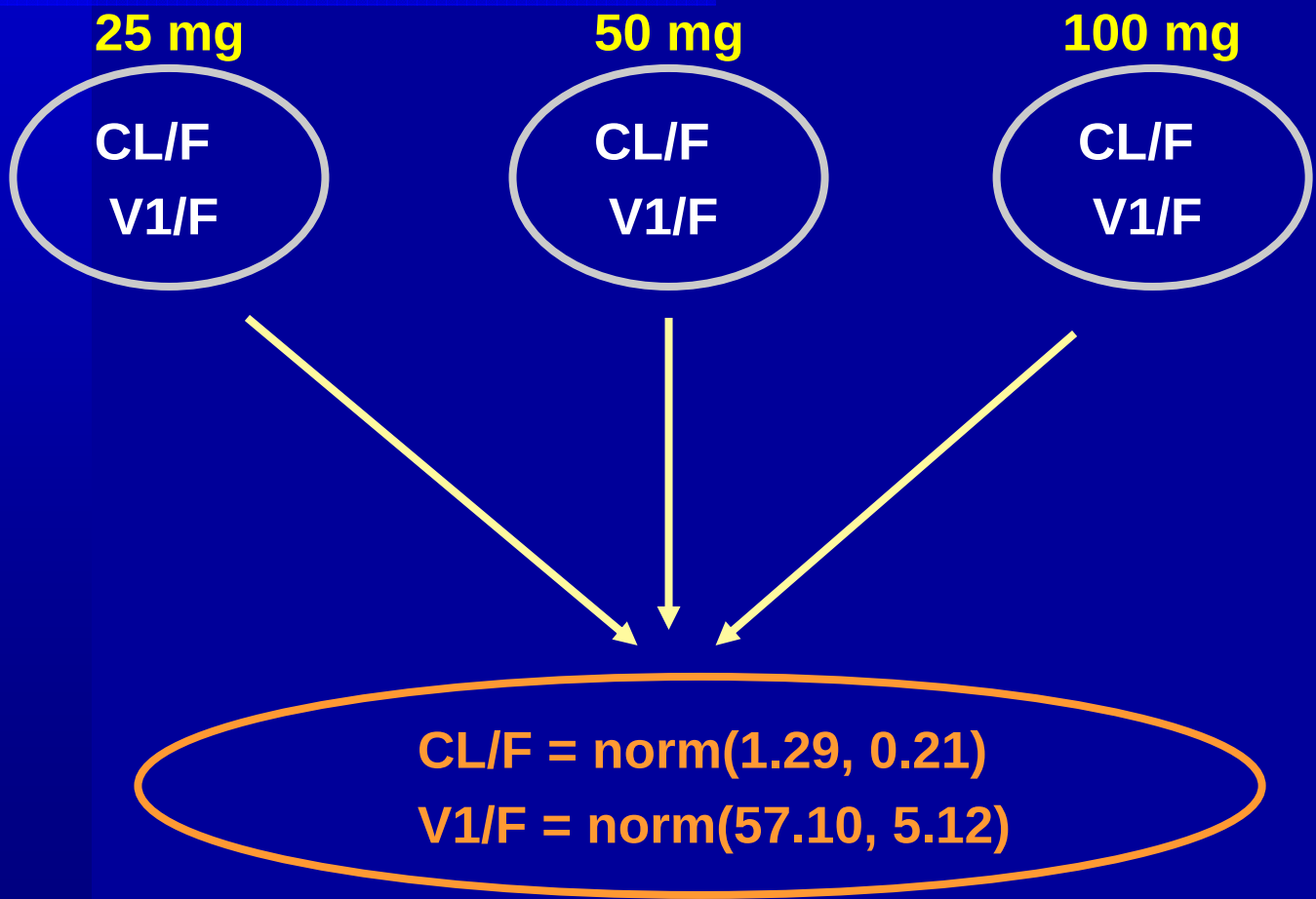
  Simulations from Shiba's data summary (normal volunteers)

- **Similarity (*exchangeability*)**

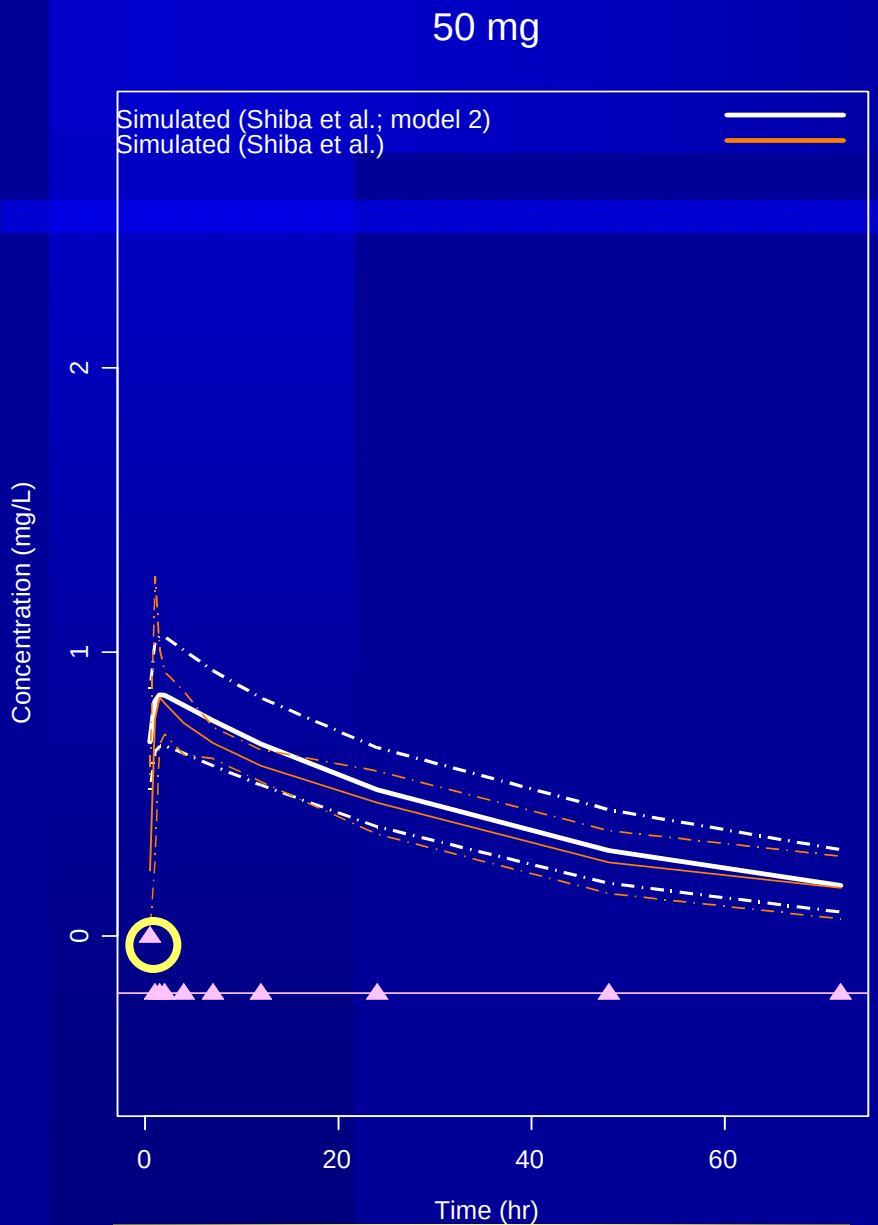
  - ***For individual points***

  - ***Overall Box's stat. = 0.71***

Shiba *et al*. *model 2*



Shiba's *model 2* vs. Shiba's data summary (95 % intervals)



- **Comparison:**

  Simulations from Shiba's model 2

  vs.

  Simulations from Shiba's data summary

- **Similarity**

  - ***For individual points***

  - ***Overall Box's stat. = 0.96***

Berl *et al.* *(Australia,1995)*

- **Multiple daily dose study**
- **Four groups of 10 by CLcr *(mainly male)***
  - **> 50 ml/min (*in reality > 70* ≡ Toon's); (400, 200)**
  - **20-50 ml/min (loading/maintenance: 200, 100)**
  - **< 20 ml/min (100, 50); haemodialysis**
- **Densely sampled**
- **Summary info**
  - **Mean + SD of observations (plots)**

Berl *et al*.

- **Berl's vs. Toon's: exchangeable**
- **Can Berl's results be composed as a parametric prior?**
  - **CL/F (mean, sd), V1/F (mean, sd) cannot be obtained solely from Berl's article**
  - **Model to mimic Berl's results – too many assumptions**
  - **Still provides important information**

Case study

Fluconazole *(anti-fungal)*

Objectives

1, To find out whether PK (non HIV, AIDS; *prior*) ≈ PK (HIV, AIDS; *McLachlan*)?

2, If PK (prior) ≈ PK (McLachlan), what are the consequences of *likely prior believes + McLachlan's?*

Toon et al. (UK, 1990)

Shiba et al. (Japan, 1990)

Berl et al. (US, 1995)

parametric priors

semi-parametric prior

+

McLachlan et al. (1996)

McLachlan *et al.* (1996)

Objectives

1, Pop. PK in HIV and AIDS

2, Dosing recommendation

Study 1

Two datasets simulated

Prospectively based on Study 1

Densely sampled

Up to 3 oral dose levels + IV

Study 2

100 subjects

Steady State

1 obs. per subject

50 – 800 mg oral doses

Sim. Data generation

- **2 simulated datasets**
  - ***Model 1*: No covariate, study 1 structure**

    ≡ McLachlan's results (P-Pharm)

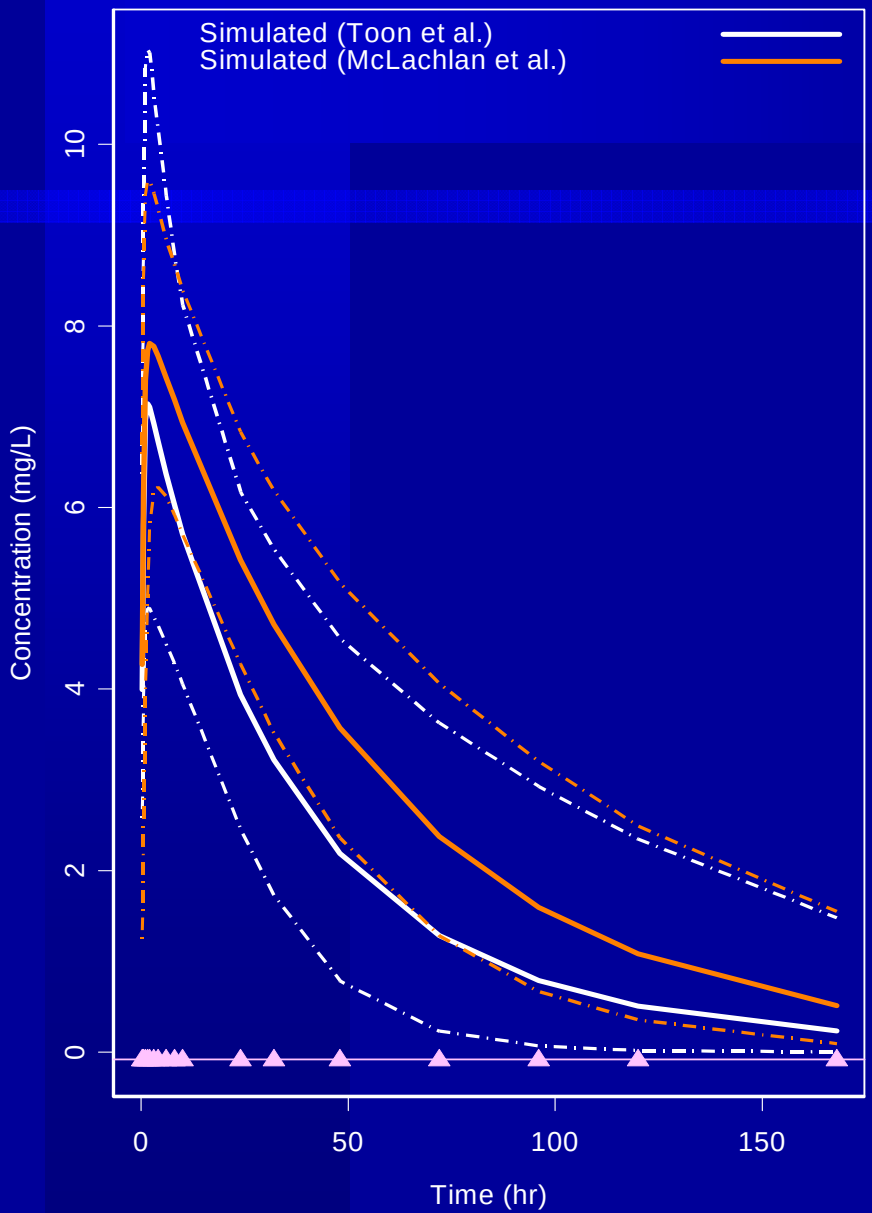
  - ***Model 2*:**

    CL vs. additive CLcr, study 1 structure

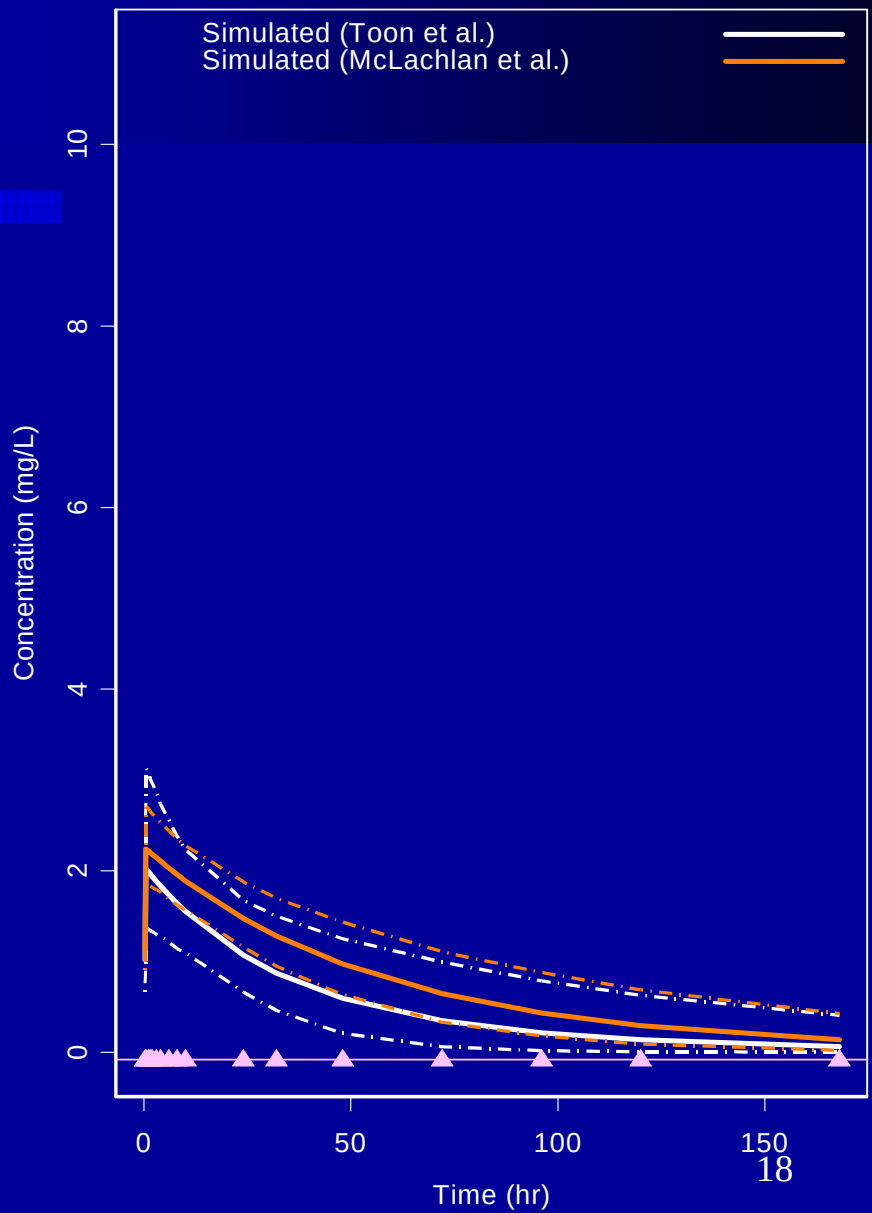
    ≈ McLachlan's results (P-Pharm)

Model 1 simulations vs. Toon's model 1: exchangeable (Box: 0.41)

400 mg Oral



100 mg IV



Prior adjustment

model 1

Data

Scenario 4: up-weighted CL & V1 (Toon)

CL, var (σ^2/n: unit var. / artificial sample size)

Model 1

Analyses

Scenario 1: Data & Non-informative prior

Scenario 2: Data & Informative prior (Toon & Shiba)

Scenario 3: Data & Informative prior (Toon)

Scenario 4: Data & informative prior (Toon & Shiba)

Toon: up-weighted CL & V1

- Data (crossover):
  - 1/ 34.6 (pop. & ind.)
  - ($\approx 3 \times (n_{real} : 13)$)
- Toon (parallel):
  - -CrCL > 70 ml/min group only (model 1)
  - -V1/F adjusted for weight (42-88 kg)
  - -CL/F, V1/F → CL, V1
  - 1/ 5.4
  - ($\approx 1 \times (n_{real} : 5)$) → n = 3×5
- Shiba (crossover):
  - -Model 2 (combined)
  - -CL/F, V1/F → CL, V1
  - 1/ 25
  - ($\approx 3 \times (n_{real} : 8)$)

Toon et al. (UK, 1990)

Shiba et al. (Japan, 1990)

Prior

Results

model 1

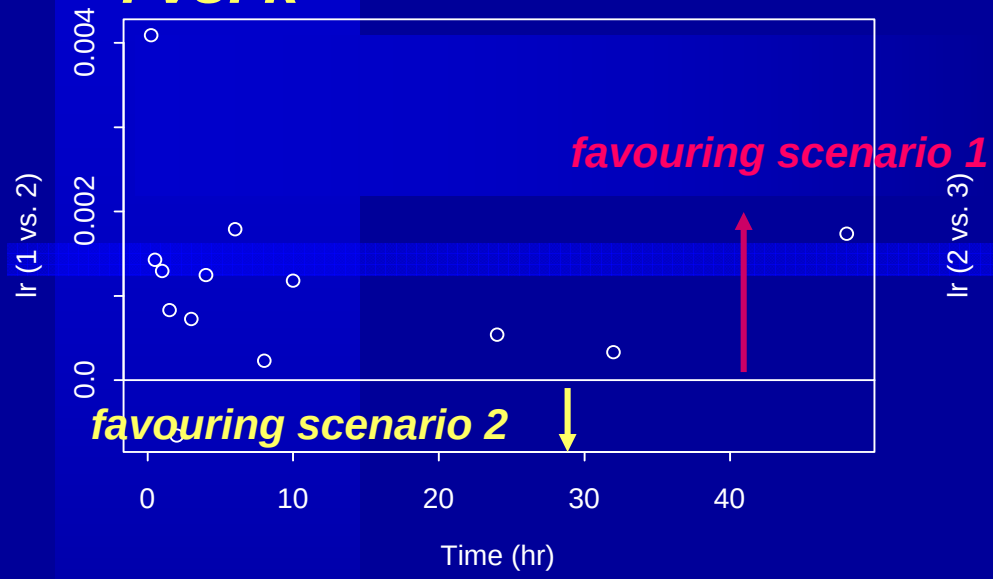
	Sce.1 Non-informative	Sce.2 Informative (Toon & Shiba)	Sce.3 Informative (Toon)	Sce.4 Informative (up-weighted Toon)
PPC (χ^2)	0.5	0.51	0.51	0.5
F	0.91 (0.01)	0.91 (0.01)	0.91 (0.01)	0.91 (0.01)
CL (L/hr)	0.93 (0.05)	0.96 (0.06)	0.97 (0.06)	0.95 (0.04)
V1 (L)	44.11 (0.92)	46.11 (1.55)	46.41 (1.79)	45.28 (1.17)
Ka – Ke (1/hr)	3.21 (0.40)	3.22 (0.41)	3.21 (0.40)	3.22 (0.39)

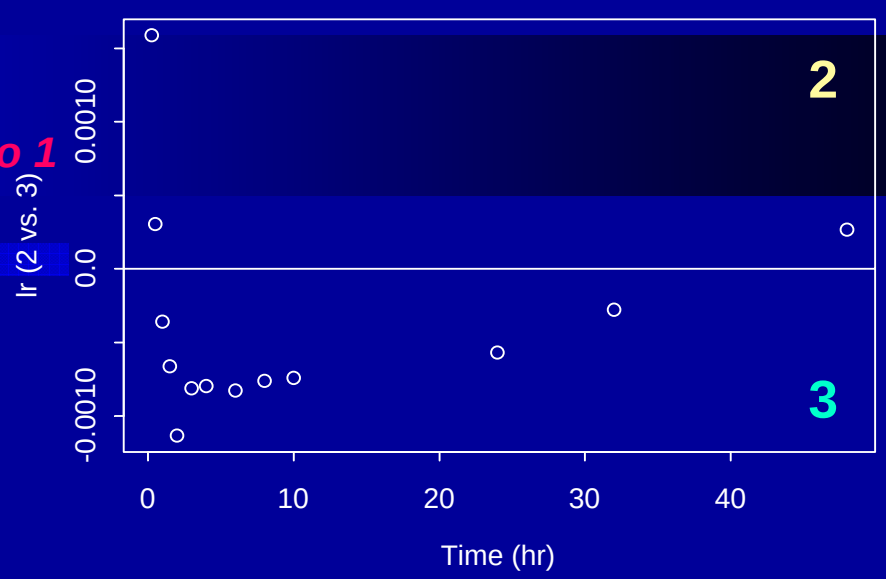
Results

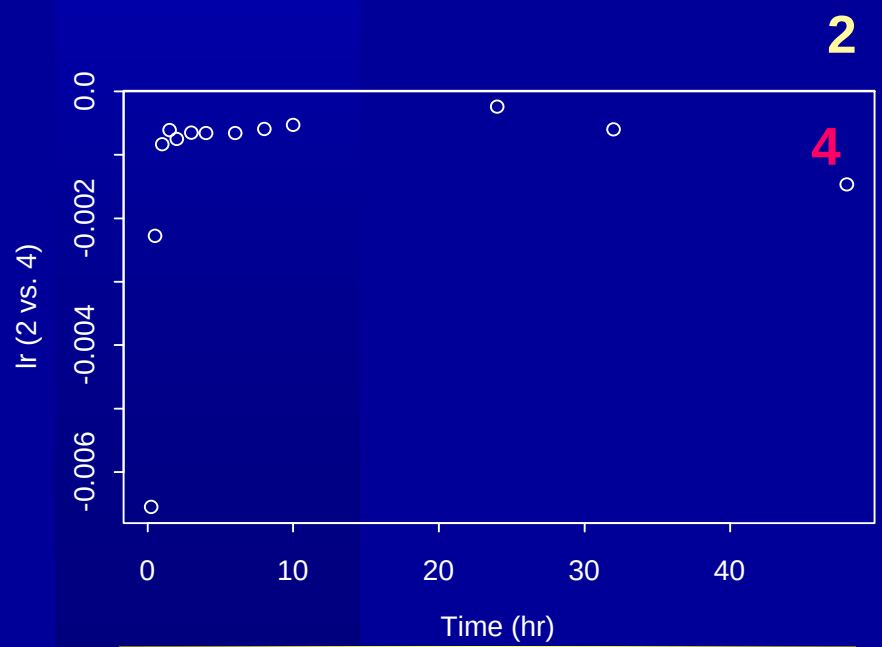
model 1

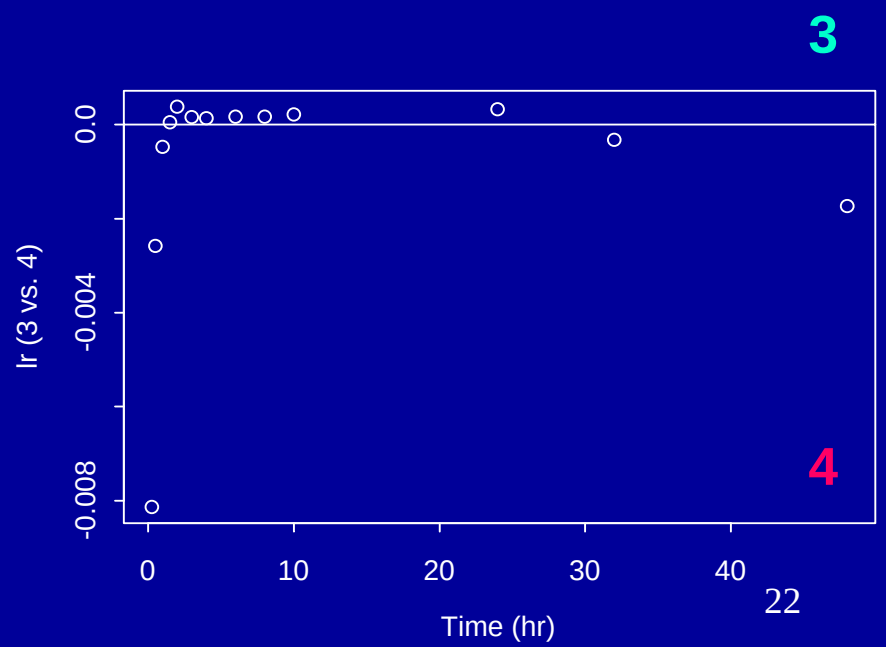
Ind.SD	Sce.1 Non-informative	Sce.2 Informative (Toon & Shiba)	Sce.3 Informative (Toon)	Sce.4 Informative (up-weighted Toon)
F	0.03 (0.02)	0.04 (0.01)	0.04 (0.01)	0.04 (0.01)
CL (L/hr)	0.19 (0.05)	0.22 (0.04)	0.24 (0.05)	0.15 (0.02)
V1 (L)	2.94 (0.80)	6.12 (0.81)	7.50 (1.22)	4.29 (0.40)
Ka – Ke (1/hr)	1.32 (0.36)	1.33 (0.37)	1.32 (0.36)	1.32 (0.36)
Resid.SD	0.11 (0.00)	0.11 (0.00)	0.11 (0.00)	0.11 (0.00)

$lr_{i\ vs.\ k} = log_{10}CPO_i - log_{10}CPO_k$ (CPO = conditional predictive ordinates)



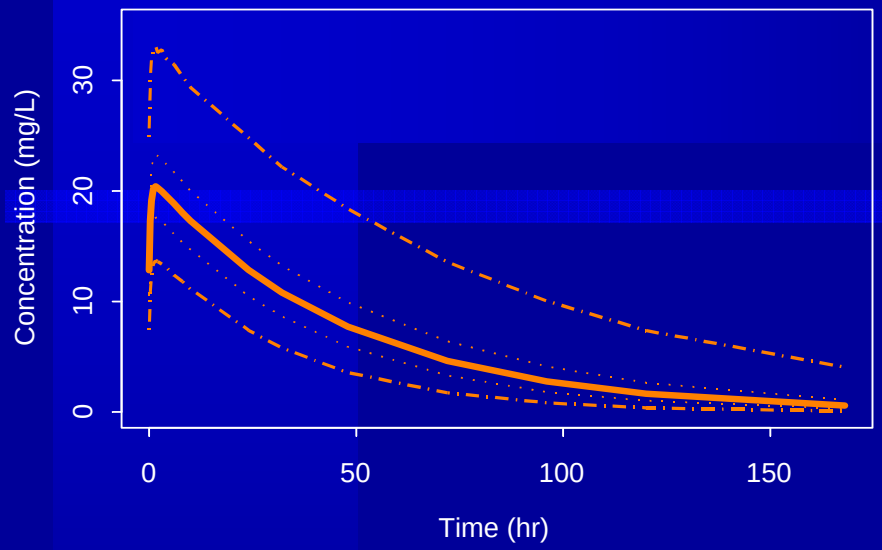




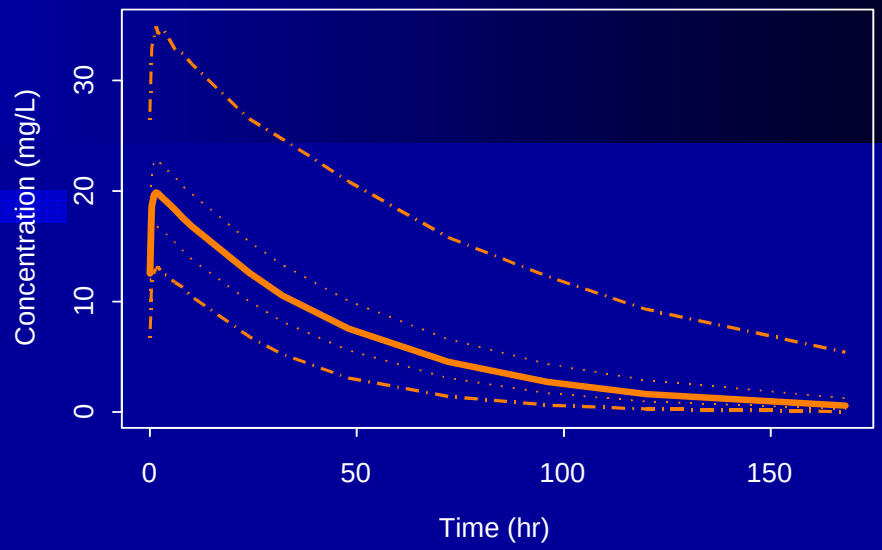


Predictions (95% credible intervals; after the last steady-state dose)

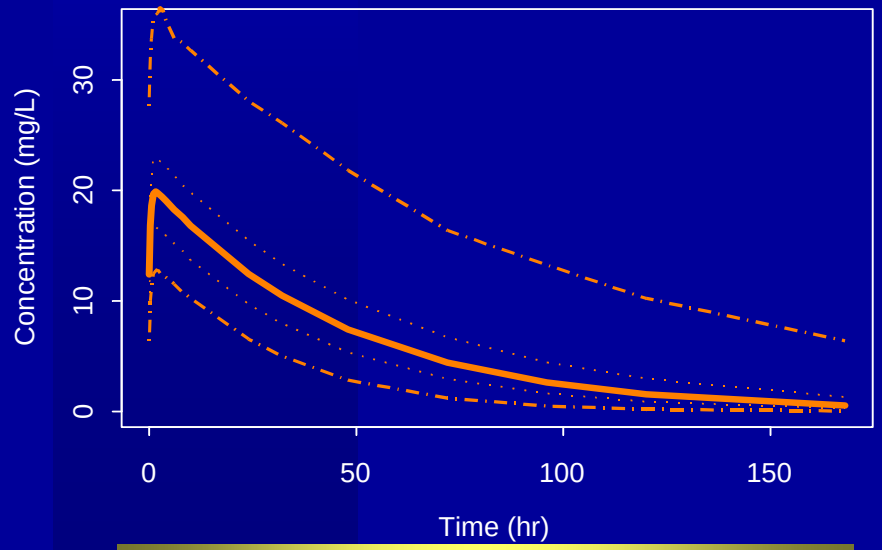
400 mg oral; **scenario 1**



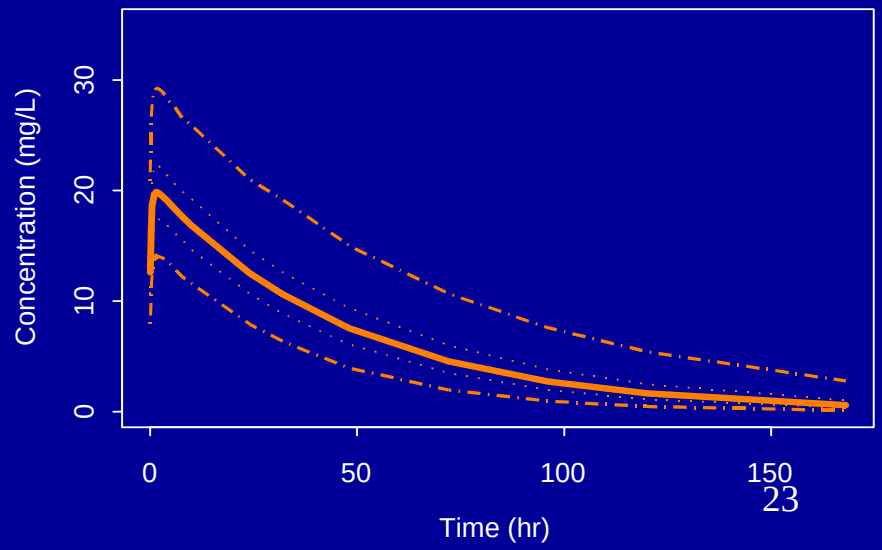
400 mg oral; **scenario 2**



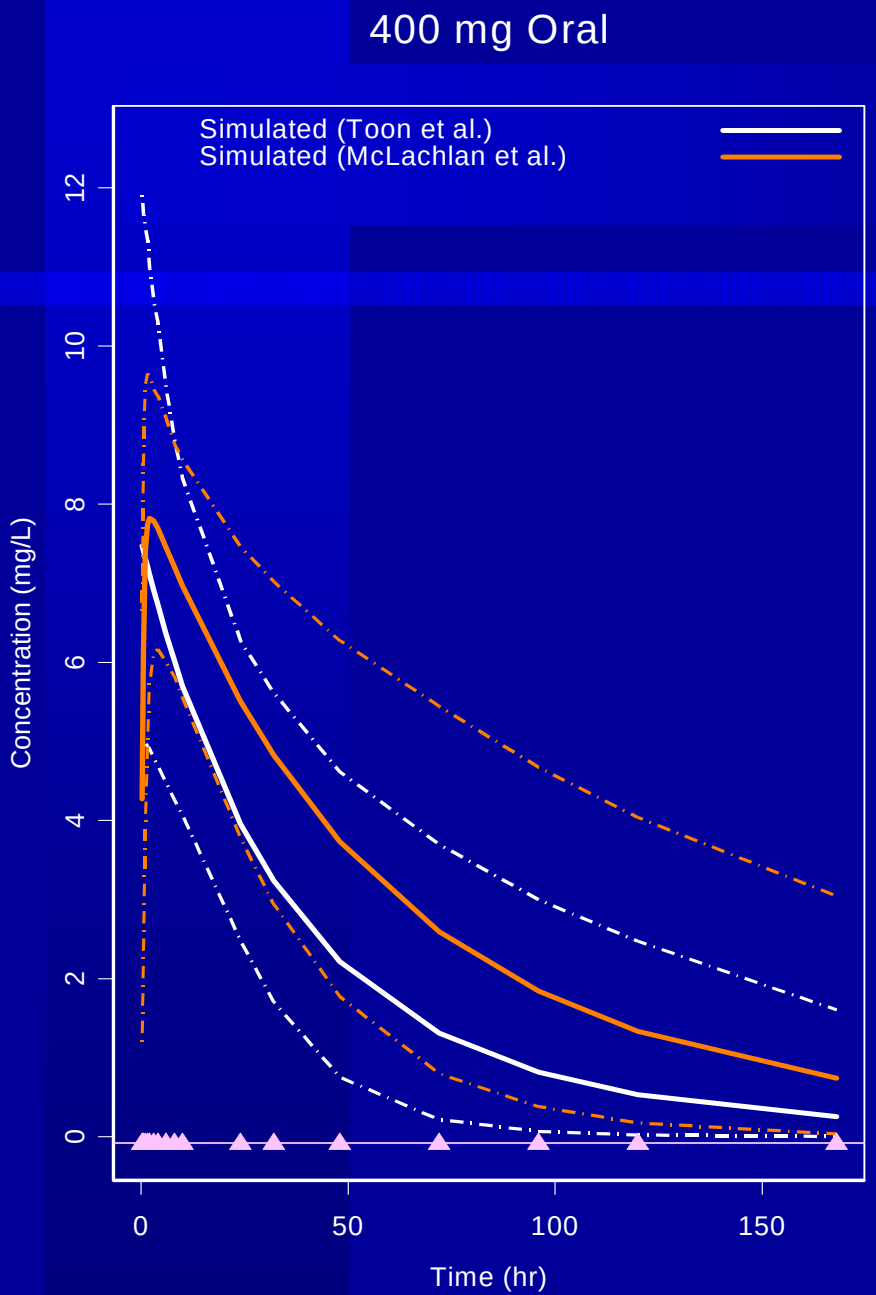
400 mg oral; **scenario 3**

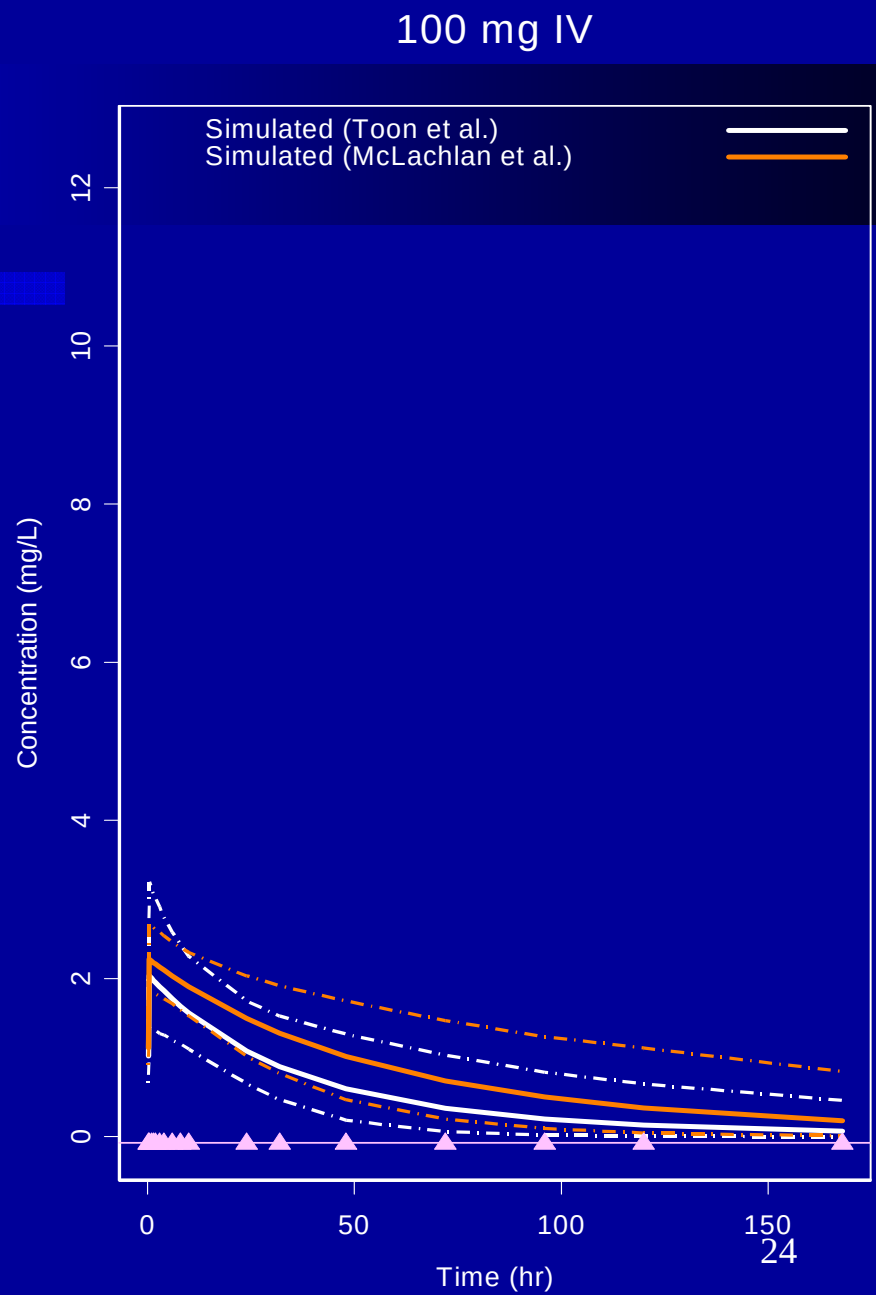


400 mg oral; **scenario 4**



Model 2 simulations vs. Toon's model 1: exchangeable (Box: 0.48)





Prior adjustment

model 2

$CL_i = baseline + slope * CLcr_i$

Data

Scenario 3: up-weighted base SD for CL & V1

Model 2

CL (σ^2/n: unit var. / adjusted sample size)

- Data, base (CLcr > 80 ml/min): n = 13
- Toon, base: n = 10.5
- Data, slope: m = 13
- Toon, slope: n = 69.5

Analysis

Scenario 1: Data & Non-informative prior

Scenario 2: Data & Informative prior (Toon & Shiba)

Scenario 3: Data & Informative prior (Toon)

up-weighted base SD for CL, & V1

$(\approx 1 \times (m_{real} : 13))$

$(\approx 1 \times m_{real}) \rightarrow n = 5 \times 13$

Scenario 4: Data & informative prior (Toon)

up-weighted base SD for CL, & V1

$(\approx 1 \times (m_{real} : 13))$

$(\approx 5 \times m_{real})$

changed Pop. var. : Ind. var. ratio; Pop. ↑

Scenario 4: up-weighted base SD for CL, & V1

All 3 CrCL groups with CL or (model 2)

Combined (model 2)

Pop. var. increased by 2 fold → Ind. var. reduced accordingly

Toon et al. (UK, 1990)

Shiba et al. (Japan, 1990)

Prior

Conclusion

- **Bayesian approach for information synthesis**
  - **Why synthesising information?**
    - **A single source of information is often not enough**
  - **Why Bayesian?**
    - **Through a prior, one's belief can be elicited in a open quantitative manner**
- **Key issues:**
  - **Clear, logical elicitation of prior information**
  - **Good coverage of likely prior believes**