Population based pharmacometrics in clinical oncology and haematology

- Concepts and recent advances

ESOP 29th January 2010 **Mikkel Krogh-Madsen**, MSc pharm, PhD student

Population based pharmacometrics

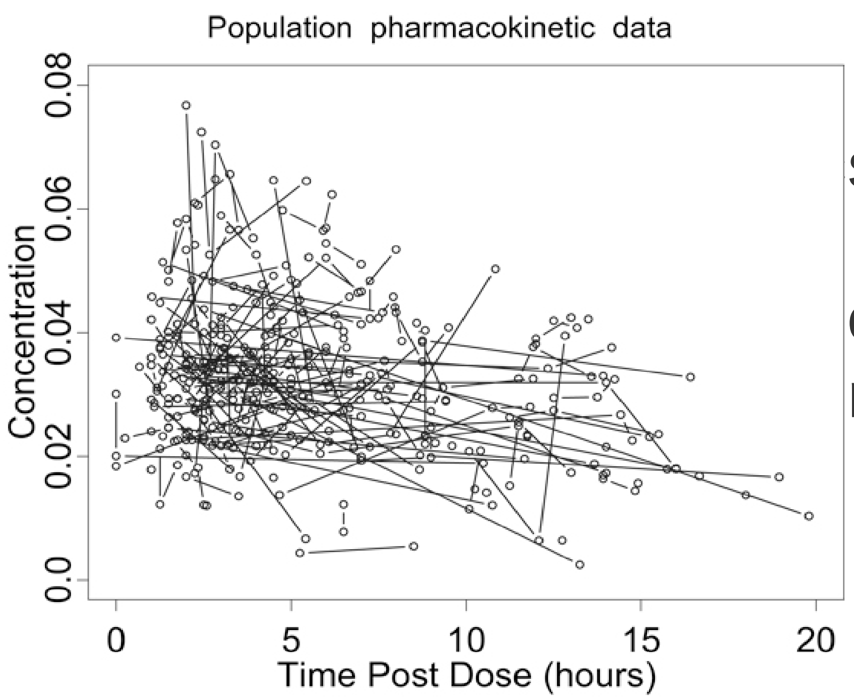
Population based:

The stu ates of
variabili ıs among
individu ɔatient
populat ɘlevant
doses o

- patients - not healthy volunteers
- population - not individuals
- variability - potentially explained, not just described

1. FDA, 1999

Population based pharmacometrics



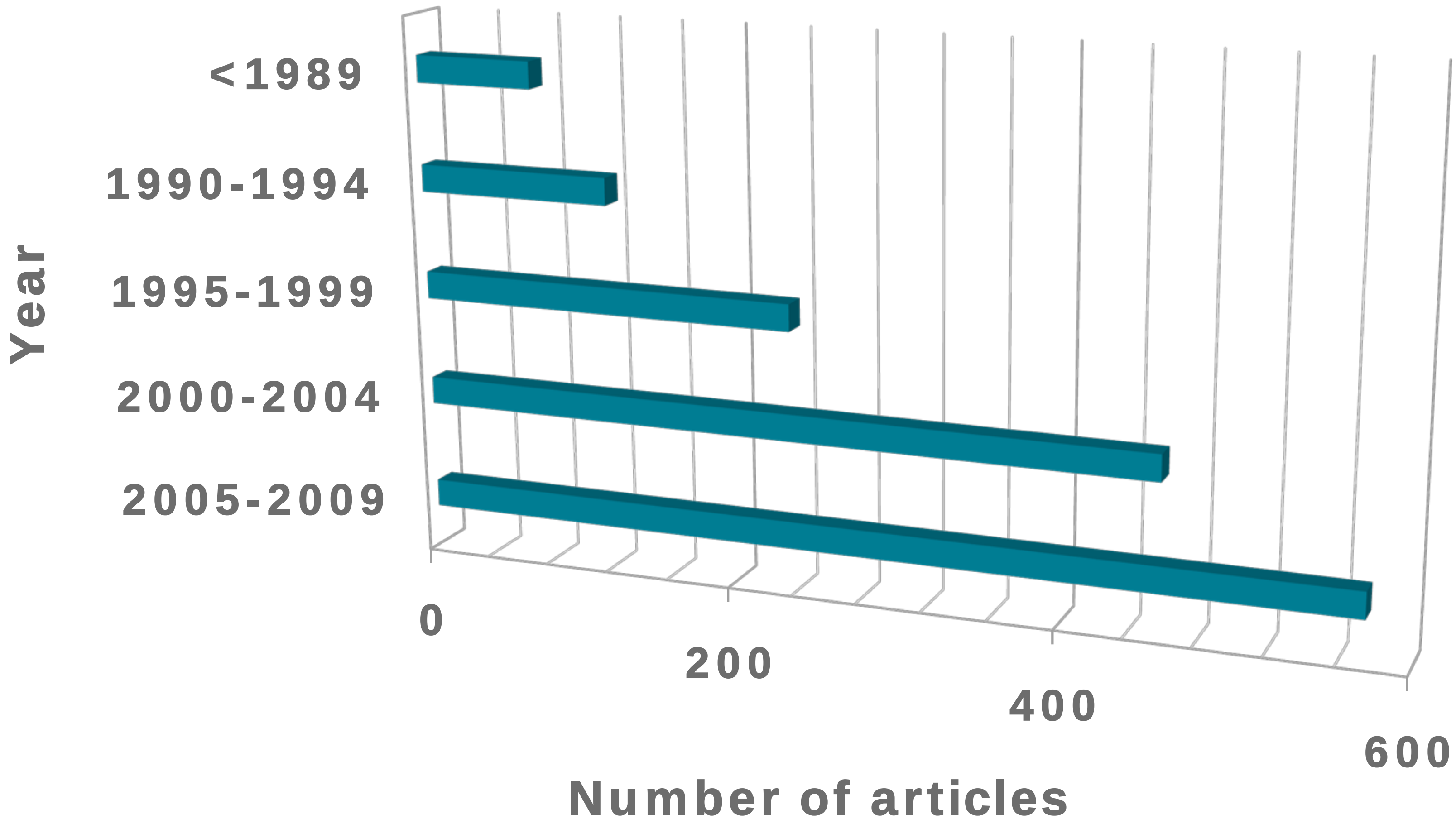
s, pharmacodynamics
mathematical
esentations ("models")
ment and observed

Figure from Nedelman JR, *AAPS Journal*. 2005; 7(2): E374-E382

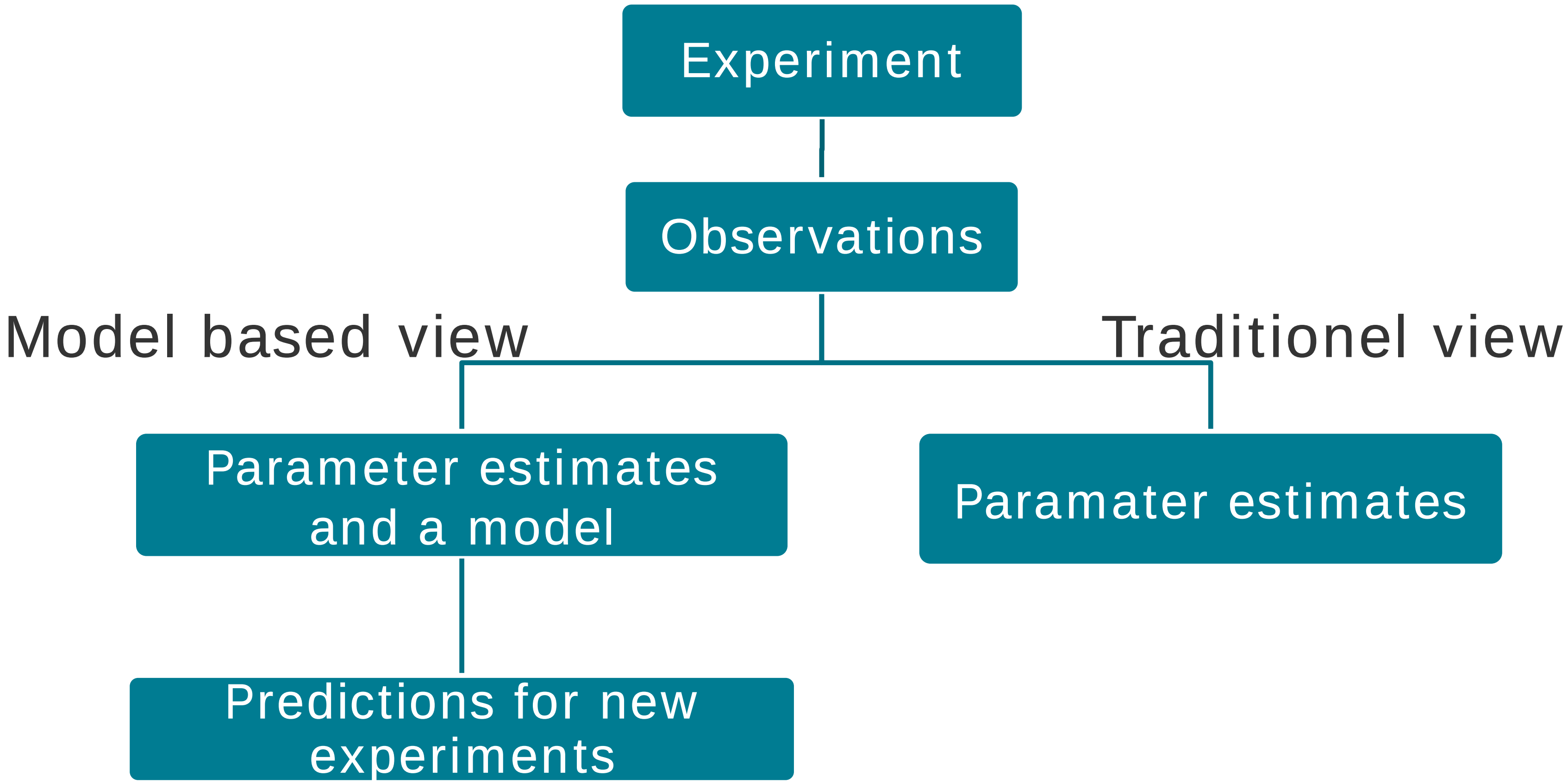
- Description of the underlying system that makes the curve (a model).

2. Grasela TH et al, *AAPS Journal*. 2007; 9(1): E84-E91

PubMed search: population pharmacokinetics AND cancer



Population based pharmacometrics



Quantitative <u>and</u> predictive tool

Population based pharmacometrics

- Some advantages of population modeling:
  - One model is a more natural (or true) representation of current knowledge than *n* models.
  - Better mechanistic (physiological) understanding.
  - ...es and
  -
- P... put to use for:
  - ...ples per subject)
  -

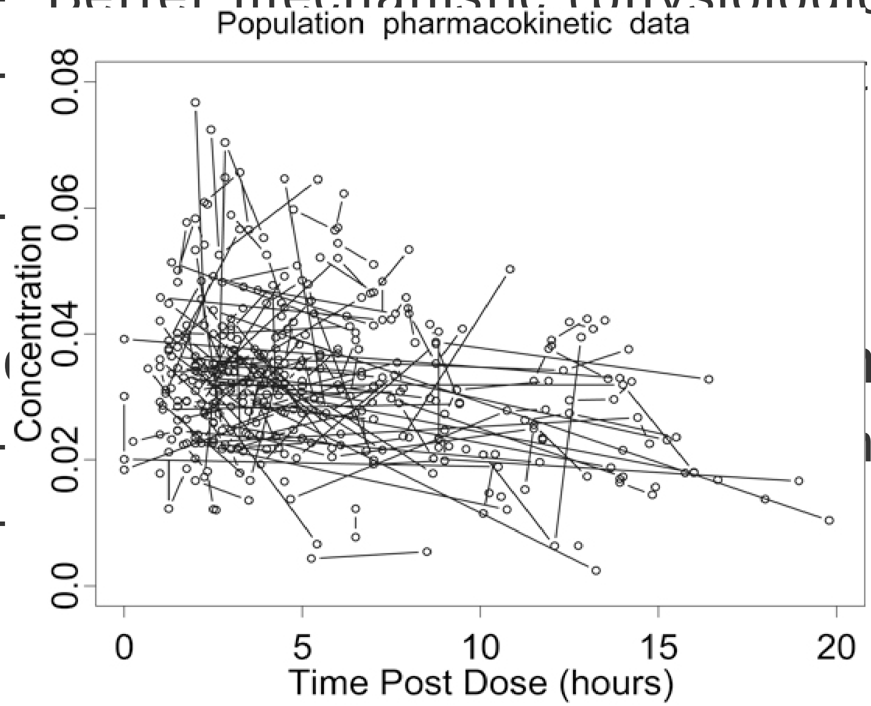


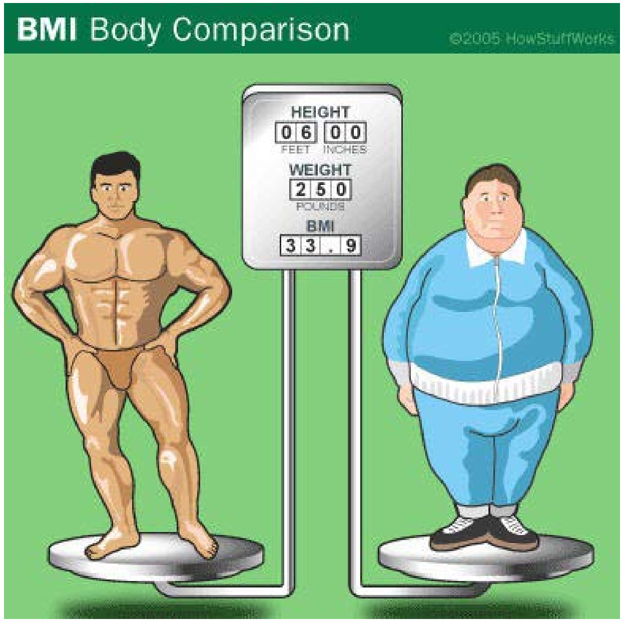
Figure from Nedelman JR, *AAPS Journal*. 2005; 7(2): E374-E382

The model components

- Structural model:
  - One/two compartment
  - Zero/first order absorption
- Statistical model
  - Between subject variability
  - Between occasion variability
  - Residual variability
- Co-variate model
  - Relationship between parameters and co-variates.

Co-variates

- Weight
- Height
- Age
- Sex
- Organ function
- Concomitant medication
- Genetics
- ...



Purpose of including co-variates

- Increase predictive performance
- Identify patient sub-groups
- Increase mechanistic interpretation of the model

A few pit-falls

- Random sampling times?
  - Optimal experimental design.
- Correlation of co-variates?
  - Bias from unknown concomitant co-variates.
  - Understand the properties of your co-variates. Consider: ”Sex and age” vs ”creatinine clearance”

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

For a drug with hepatic clearance - which is then the significant co-variate to include in the final model?

Example 1: Imatinib in GI stromal tumors[3]

- Q: Is there a relationship between plasma levels of imatinib and clinical benefit in GIST?

- Population PK of imatinib (Glivec®).
- 400 or 600 mg daily (peroral).
- 4 blood samples on day 1 and 29.

3. Demetri GD et al, *Journal of Clinical Oncology*. 2009; 27(19): 3141-3147

Example 1: Imatinib in GI stromal tumors[3]

High inter-patient variability:

	Mean	SD	CV%
CL/F (L/h)	8.01	4.88	60.9
V/F (L)	157	87.6	55.8

$$TVCL = 8.18 \cdot (albumin/38.3)^{1.66} \cdot (WBC/[7 \cdot 10^9])^{-0.418}([L/h])$$

$$TVV = (168 + 58.5 \text{ on day } 28) \cdot (albumin/38)^{1.66} \cdot (WBC/[7 \cdot 10^9])^{-0.418}[L]$$

3. Demetri GD et al, *Journal of Clinical Oncology*. 2009; 27(19): 3141-3147

Example 1: Imatinib in GI stromal tumors[3]

- Models for CL and for V

- Imatinib trough levels at steady state were associated with clinical benefit.

$$C_{min,N} = \frac{D}{V} \times \left(\frac{1 - e^{-Nk\tau}}{1 - e^{-k\tau}} \right) \times e^{-k\tau} \qquad k = \frac{CL}{V}$$

- Further studies of plasma level monitoring is needed.

3. Demetri GD et al, *Journal of Clinical Oncology*. 2009; 27(19): 3141-3147

Example 2: Myelotoxicity of the BEACOPP regimen in Hodgkin's lymphoma[4]

- Q: What is the role of PK in individual toxicity with BEACOPP?

- Population PK of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone.
- Administered relative to body surface area.
- 3 plasma samples on day 1 of the first 3 cycles of therapy.

4. Wilde S et al, *Clinical Pharmacokinetics*. 2007; 45(4): 319-333

Example 2: Myelotoxicity of the BEACOPP regimen in Hodgkin's lymphoma[4]

$$\Delta platelet = -304 + 207 \cdot BSA - 5.20 \cdot ETOPEAK - 1644 \cdot DCL \text{ (-55 for the 1 st cycle)}$$

- Model explains 37% of the inter-individual variability in platelet counts.

4. Wilde S et al, *Clinical Pharmacokinetics*. 2007; 45(4): 319-333

Example 2: Myelotoxicity of the BEACOPP regimen in Hodgkin's lymphoma[4]

$$\Delta platelet = -304 + 207 \cdot BSA - 5.20 \cdot ETOPEAK - 1644 \cdot DCL \text{ (-55 for the 1st cycle)}$$

- Etoposide peak plasma concentration
- Individual CYP3A4 activity (DCL).

- Standardise infusion times
- CYP3A4 phenotyping

4. Wilde S et al, *Clinical Pharmacokinetics*. 2007; 45(4): 319-333

Population based pharmacometrics

”All models are wrong, but some are useful”

George E. P. Box (1987)

Thank you for your attention!