Bayesian POP-PK analysis of exposure data from a Phase IIb clinical trial

Henry Pertinez, Leon Aarons

Centre for applied Pharmacokinetic Research, School of Pharmacy and Pharmaceutical sciences, The University of Manchester

E-mail: henry.pertinez@postgrad.manchester.ac.uk

1. Introduction

- **Bayesian methods** for fitting hierarchical models to POP-PK data are often considered in **contrast** to the **maximum likelihood methods** employed by widely used software such as NONMEM.
- In a Bayesian approach, **parameters** of a mathematical model are considered as **probability distributions**, P(θ), which reflect the degree of uncertainty of the parameter value.
- In a modelling exercise there is also **data**, y, which is described by a likelihood function (the mathematical model)
- In a Bayesian analysis, we attempt to assess how the **data** should change our opinion as to what the **parameter distributions** are, in other words…
- …the **prior** parameter distributions are updated to **posterior** distributions via the influence of the data (***Fig. 1***).

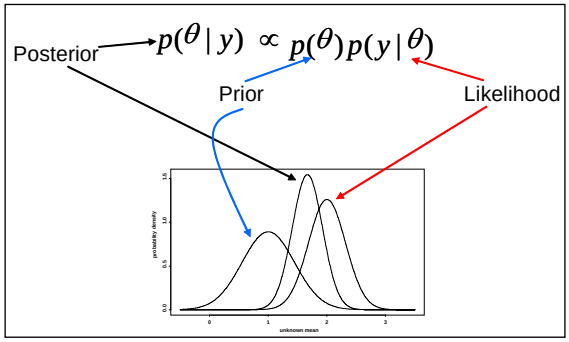

Fig. 1

- Mathematically, this is achieved in the WinBUGS software package through direct sampling from the Bayesian network of posterior distributions using a specialised **Markov Chain Monte Carlo (MCMC)** algorithm called the **Gibbs sampler**.

2. Modelling context

- Efforts are ongoing to model the PK of "drug X" in a physiologically based manner in animal and human.
- The available **human PK datasets** amenable to physiologically based modelling (i.e. containing exposure data for key tissues as well as plasma) are **sparse and variable in nature** and demand a mixed effects (POP-PK) approach to make fullest use of them
- An empirical modelling exercise was therefore undertaken to:
  - provide the best descriptions of the available human data amenable to PBPK modelling
  - **provide forcing functions** for use in an open loop PBPK paradigm.
- Prior to analysis of the phase IIb data, richly sampled data from phase I clinical trials of "drug x" was modelled using a POP-PK approach to enable model selection.

3. Initial empirical modelling

- Data from phase I clinical trials was modelled using a POP-PK approach with an **empirical 3-compartment, mammillary** model in WinBUGS, using uninformative priors, analysing IV infusion, PO single dose and PO multiple dosing regimes in a single run ***(Fig. 2)***.

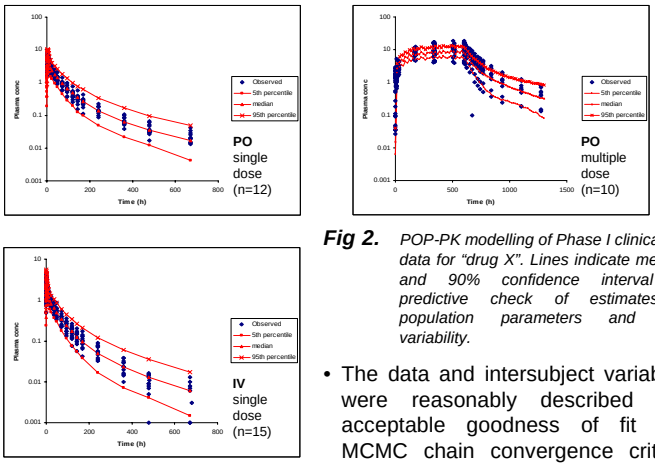

Fig 2. *POP-PK modelling of Phase I clinical trial data for "drug X". Lines indicate median, and 90% confidence interval for predictive check of estimates of population parameters and their variability.*

- The data and intersubject variability were reasonably described and acceptable goodness of fit and MCMC chain convergence criteria were achieved

4. Initial modelling of phase IIb dataset

- Initial efforts to model a longer timecourse, sparsely sampled Phase II dataset encountered difficulties.
- A **simulation of the longer timecourse study**, using the 3-compartment model parameters obtained from the analysis of the earlier phase I studies offered some explanation (***Fig. 3***).

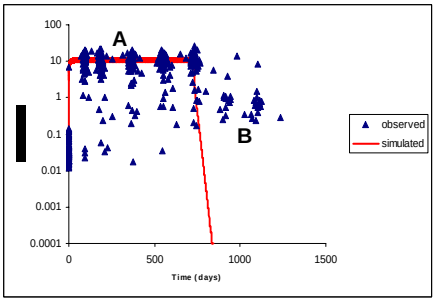

Fig 3.

Simulation of phase IIb study timecourse using parameters obtained from analysis of earlier phase studies.

***A** = steady state exposure during dosing period*

***B** = longer term exposure after dosing period*

- **Steady state exposure** during the dosing period (***Fig 3***. region **A**) is **reasonably well described** using the earlier study parameters indicating Cl_{tot} is broadly similar in the two datasets.
- However there is **strong evidence for a 4th, extended phase** visible only **in the longer timecourse study** (***Fig 3***. region **B**) making a relatively minor contribution to the overall AUC.
- It is of particular interest to describe this extended terminal phase accurately, especially if long term predictions of exposure are required.
- **Reconciling** the two datasets given their different timescales proves **difficult with a standard POP-PK approach**: the richly sampled, short timecourse datasets contain information for the initial 3 phases but lack information on the fourth, and vice versa for the sparsely sampled, long timecourse dataset.

5. Initial Bayesian analysis of phase IIb dataset

- In a Bayesian analysis of the phase IIb data, **prior information** for the parameters describing the **3-compartment PK** shown in the earlier phase studies (Cl, Q12, Q13, V1, V2, V3) can be **carried forward** into a **4-compartment analysis of the longer timecourse**, Phase II study.

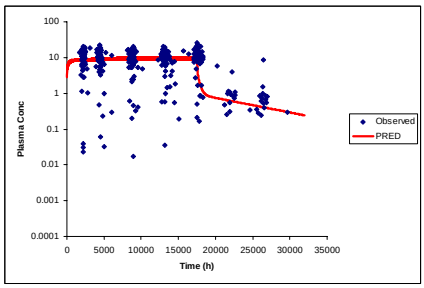

Fig 4.

Initial results from a 4 compartment model fitting to a phase II Strontium exposure dataset using informative priors.

- The **initial results** of the Bayesian analysis are **satisfactory**, providing a description of the phase IIb dataset that captures the long terminal phase seen on this timescale and remains consistent with earlier data modelling.
- **Problems remain with the convergence** of the sampling chains in this analysis. Some issues were resolved using the **WinBUGS 'CUT' function** to allow the data from phase II dataset only to update the parameters related to the 4th phase (i.e. V4 and Q4 in macro parameterisation) and various **other options are being investigated to improve the convergence of the chains** (e.g. incorporation of a background level of Strontium into the model, censoring of data that reflects non-compliance with the dosing regimen etc.).